EDISON

Trillium Therapeutics

Initiation of coverage

A novel immunotherapy approach targeting CD47

Pharma & biotech

Trillium's lead candidate, SIRPaFc, is an antibody-like fusion protein that blocks the activity of CD47, and thereby impedes a 'do not eat signal' expressed on several cancers including acute myeloid leukaemia (AML), which otherwise spares them from phagocytosis by the immune system. A Phase I AML study is planned to start in H215 and, with C$27.9m net cash as of 30 September 2014, Trillium is funded through this study's completion. While still several years away from possible commercialisation, SIRPaFc's immunotherapy mode of action could be applicable to multiple haematological and solid tumour types, potentially leading to well over $1bn in peak sales.

Year end	Revenue (C$m)	PBT* (C$m)	EPS* (C$)	DPS (C$)	P/E (x)	Yield (%)
12/12	0.0	(1.1)	(1.70)	0.0	N/A	N/A
12/13	0.0	(3.7)	(2.69)	0.0	N/A	N/A
12/14e	0.0	(10.6)	(2.50)	0.0	N/A	N/A
12/15e	0.0	(11.8)	(2.73)	0.0	N/A	N/A

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

CD47 targeting yields benefits in preclinical models

Animal studies by Trillium and the Weissman group at Stanford show that CD47 is over-expressed in several tumour types, including AML, and that blocking CD47 can cause tumour shrinkage. IND-enabling studies are underway and Trillium plans to start a Phase I AML study in H215.

SIRPaFc potentially differentiated vs anti-CD47 mAbs

While Celgene and the Weissman group are developing monoclonal antibodies against CD47, SIRPaFc is a fusion protein with a differentiated binding profile that could potentially provide a safety advantage. Trillium presented data showing that while SIRPaFc binds similarly well to CD47-presenting AML cells as several commercial anti-CD47 mAbs, it binds much less efficiently to human red blood cells (hRBCs), unlike anti-CD47 mAbs. This could result in superior pharmacokinetics or a lower risk of hRBC toxicity, but this will be better understood as the different CD47-targeting agents advance in clinical development.

Financials: Funded through Phase I studies

With C$27.9m net cash (30 September 2014), Trillium has sufficient funds to complete Phase I studies of its novel SIRPaFc immunotherapy approach. While Trillium is initially focusing on AML, given CD47's wide expression in different tumour types and that other onco-immunotherapies (eg CTLA-4 or PD-1 inhibitors) target multiple indications, we estimate that SIRPaFc could potentially also be applicable across several cancer types. Trillium is already actively conducting preclinical work to explore SIRPaFc advancement in other haematological indications and solid tumours.

9 January 2015

Price	**C$14.75**
Market cap (common shares only)	**C$63m**
	C$1.18/US$1
Net cash (C$m) at Q314	27.9
Basic shares in issue (post-consolidation)	4.27m
Free float	97%
Code	TR/TRIL
Primary exchange	TSX
Secondary exchange	NASDAQ

Share price performance

%	1m	3m	12m
Abs	71.7	100.7	5.7
Rel (local)	68.0	103.6	(0.4)
52-week high/low	C$20.4		C$6.5

Business description

Trillium Therapeutics is a Canadian pharmaceutical company developing cancer therapeutics targeting immune-regulatory pathways that tumour cells exploit to evade the host immune system. Lead candidate SIRPaFc targets CD47 and is planned to start Phase I in AML in H215.

Next events

Q414 results	March 2015
Start patient dosing in Phase I SIRPaFc study	Q415

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Edison profile page

Investment summary: Immunotherapy using CD47

Company description: Focus on CD47 to target cancer

Trillium Therapeutics is a Toronto-based firm developing oncology therapeutics. Its lead programme, SIRPaFc, targets an immune-regulatory pathway exploited by tumour cells to evade the host immune system. SIRPaFc is an antibody-like fusion protein that blocks the activity of CD47, a molecule that is up-regulated on cancer cells in acute myeloid leukaemia (AML) and other tumours. Trillium also has rights to a human monoclonal antibody (mAb) that blocks CD200, an immunosuppressive molecule overexpressed by many hematopoietic (blood cell related) and solid tumours. In April 2013, the firm (then operating under the name Stem Cell Therapeutics, or SCT) merged with a then privately-held firm called Trillium Therapeutics. The combined firm retained the management team and lead development assets (SIRPaFc programme) of the private entity, and in June 2014 changed its corporate name to Trillium Therapeutics.

Exhibit 1: Trillium Therapeutics' product pipeline

Product	Description	Stage
TTI-621 (SIRPaFc)	Oncology including acute myeloid leukaemia	Preclinical
TTI-622 (SIRPaFc)	Cancer (combination therapy)	Preclinical
CD200 Monoclonal antibody	Cancer	Preclinical (on hold)

Source: Edison Investment Research

Sensitivities: Clinical efficacy and partnerships

The key sensitivities for investors will be the success of SIRPaFc in clinical development, and subsequently the ability to monetise this candidate on attractive economic terms. As with all drug development programmes, there are risks associated with unfavourable outcomes in clinical trials or longer-than-expected timing to completion, success of eventual competitors and a dependence on potential and actual commercial partners.

Financials: Funded through Phase I study

Trillium had C$27.9m net cash as of 30 September 2014, and the cash burn rate in 9m14 was C$5.6m. We expect the burn rate to increase when Trillium commences a Phase I AML study in H215. We expect Trillium's funds on hand to last until the completion of this study, which we believe will be in late 2016 or early 2017. We expect Trillium will require C$40m in financing between 2016 and mid-2018 to further SIRPaFc development through Phase II studies. At this early stage, we show the financing as long-term debt, acknowledging that in reality it could also be achieved through an equity issue or via licensing agreements. We expect a SIRPaFc out-licensing transaction will occur after the completion of Phase II trials.

Outlook: Targeting CD47 is the priority

Trillium Therapeutics' development priority is its anti-CD47 cancer immunotherapy compound, SIRPaFc. Trillium raised C$33m in December 2013 from a group of US healthcare investors, with all of this capital dedicated to the anti-CD47 programme.

Overview of CD47

CD47 (Cluster of Differentiation 47) is a transmembrane immunoglobulin superfamily cell-surface protein (CSP) that interacts with membrane integrins and binds ligands thrombospondin-1 (TSP-1) and signal-regulatory protein alpha (SIRPa). CD47 is widely expressed on human cell surfaces and

has been found to be over-expressed in many different tumour cells.[1,2] CD47 is involved in many areas, including cardiovascular physiology and immunology. Two major functions include:

1. The interaction of CD47 with SIRPa present on the surfaces of phagocytic cells (those capable of phagocytosis,[3] such as certain white blood cells including macrophages), whereby CD47 effectively sends a 'do not eat' signal to suppress phagocytosis (thereby sparing CD47-presenting targets of clearance or removal). As CD47 is widely expressed in the majority of normal tissues, its role in regulating phagocytosis is believed to be widespread.[4]
2. CD47 functions as a signalling receptor when bound to TSP-1, as it can then modulate factors affecting cellular viability and resistance to stress, which are relevant in cardiovascular disease.

SIRPaFc believed to block CD47 'do not eat signal'

As CD47 overexpression can allow tumours to resist innate immune system activity by evading phagocytosis[3] (thereby allowing tumour survival), a therapeutic strategy would be to target CD47. SIRPaFc is an antibody-like fusion protein biologic that binds to CD47. SIRPaFc is believed to block CD47 from interacting with SIRPa and thus block the survival mechanism whereby cells with high-CD47 membrane expression evade phagocytosis by macrophages. Hence, SIRPaFc is believed to activate macrophages to kill both bulk cancer cells (BCCs), as well as cancer stem cells (CSCs),[5] which are both believed by Trillium and other researchers to have high CD47 expression. Trillium believes that by also being active against CSCs, SIRPaFc can potentially lead to a longer-lasting cancer remission from treatment (vs existing therapies) in the targeted cancer indications.

Weissman group's studies show CD47 implication in cancers

Irving L Weissman's research group at Stanford University (no relationship with Trillium) has long studied CD47's potential role in cancer. It found that multiple tumour cell lines express increased levels of CD47 (compared to their normal cell counterparts) and that CD47 overexpression plays a large role in tumour survival, notably in AML. Multiple samples of AML cancer stem cells had higher CD47 expression than their normal counterparts.[6] Human studies also found that increased CD47 expression predicted worse overall survival in three independent cohorts of adult AML patients (of 285, 242, and 137 patients).[6]

The group also showed that certain anti-CD47 mAbs in in-vitro and in-vivo (mouse) studies were capable of blocking the CD47-SIRPa interaction, leading to increased phagocytosis of AML CSCs by macrophages. The administration of a blocking anti-human CD47 antibody to mice engrafted with primary human AML and acute lymphoblastic leukaemia (ALL) cells led to tumour elimination in both the peripheral blood and bone marrow, including cases of long-term remissions[6]. Lower tumour burden using blocking anti-CD47 antibodies was also found in in vitro and/or in vivo studies for human non-Hodgkin lymphoma (NHL), multiple myeloma (MM), bladder cancer and breast cancer.[4, 6] At a 2014 American Association for Cancer Research (AACR) special conference on pancreatic cancer, research by Krampitz et al showed that tumour samples from 39 patients with

[1] Expert Opin Ther Targets. 2013 January; 17(1): 89–103.

[2] Elevated CD47 expression has been reported in a variety of cancers including renal and prostate carcinoma, multiple myeloma (MM), T-cell acute lymphoblastic leukaemia (ALL), oral squamous cell carcinoma, human acute myeloid leukaemia-associated eukemia stem cells , bladder carcinoma cells, glioma and glioblastoma.

[3] A progress by which a phagocytic cell engulfs a targeted foreign particle or material, forming an internal vesicle, which is then digested.

[4] Curr Opin Immunol. 2012 April; 24(2): 225–232.

[5] According to the stem cell model for cancer development, cancer stem cells (CSCs) are a small pool of self-renewing cells that can differentiate into all the cell types found in a cancer sample. The theory suggests that CSCs must be eliminated in order to eradicate the tumour, or 'cure' the cancer, and that many conventional anti-cancer therapies can kill bulk cancer cells (and thereby shrink tumours) but not CSCs, which can eventually lead to relapses or metastasis.

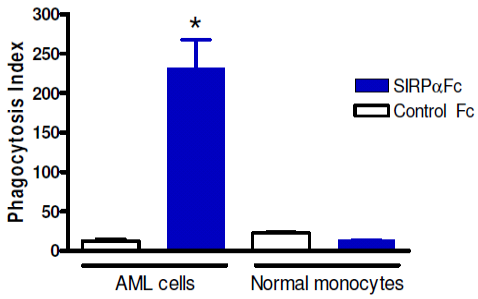
[6] Cell. 2009 Jul 23; 138(2): 286-99.

pancreatic neuroendocrine tumours and from 39 patients with pancreatic ductal adenocarcinoma had high CD47 expression and that the Stanford anti-CD47 antibody Hu5F9 caused tumour regression (when the tumours were transplanted into mice) for both types of pancreatic cancer.[7] The Weisman group published that CD47-blockage mediated cancer cell phagocytosis can initiate an anti-tumour cytotoxic T-cell immune response (increase in activated cytotoxic CD8+ cells, which would then mobilise their own immune attack against the cancer cells).[8] Hence, targeting CD47 may also promote the activation of the adaptive immune system response against tumour cells.

Trillium approach uses a fusion protein ligand instead of mAb

Instead of using mAbs, Trillium's approach targets CD47 using a modified version of the SIRPa ligand, fused to an Fc region of an immunoglobulin. SIRPaFc binds to CD47 and blocks its interaction with SIRPa. SIRPaFc would target both BCCs and CSCs, operate through macrophages (and the innate immune system) and potentially exert downstream effects on the adaptive immune system as well. In-vitro and in-vivo studies using AML patient cell samples show that SIRPaFc enables macrophages to kill AML tumour cells while sparing normal cord blood- or peripheral blood-derived mononuclear cells (monocytes).

Exhibit 2: Preclinical data showing SIRPaFc mediated phagocytosis in AML cells, but sparing normal cells



Source: Trillium Therapeutics

Trillium demonstrated that this SIRPaFc displays anti-leukaemic activity in an in-vivo AML xenograft model (xenotransplantation of human AML tumour cells into immuno-deficient mice), as the treatment significantly reduces the leukaemic burden in the bone marrow and impairs disease dissemination.

Immunotherapy approach to treating cancer gaining momentum

While traditional chemotherapy often aims to kill cancer cells by arresting their cellular division, immunotherapies (such as SIRPaFc) seek to stimulate the host immune system to target and kill cancer cells. Immunotherapy gained validation when ipilimumab (Yervoy, BMS) was approved by the FDA in 2011 for metastatic melanoma; ipilimumab enhances cytotoxic T-cell activity against cancer cells through blockage of Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), a protein receptor that normally downregulates the immune system. Merck's pembrolizumab (Keytruda, approved in 2014 by the FDA in metastatic melanoma) and BMS's nivolumab (a Phase III melanoma candidate) each block the Programmed Cell Death, or PD-1, receptor, and aim to strengthen anticancer T-cell activity by blocking cancer cells' ability to bind PD-1 (which would suppress T-cell activity). Innate Pharma's lirilumab (partnered with BMS) also seeks to promote immune activity against cancer, but instead of affecting T-cells, it blocks an inhibitory signal in NK (Natural Killer) cells.

[7] www.ascopost.com/ViewNews.aspx?nid=16233.

[8] Proc Natl Acad Sci U S A. 2013 Jul 2; 110(27): 11103-8.

Can targeting CD47 provoke off-target effects?

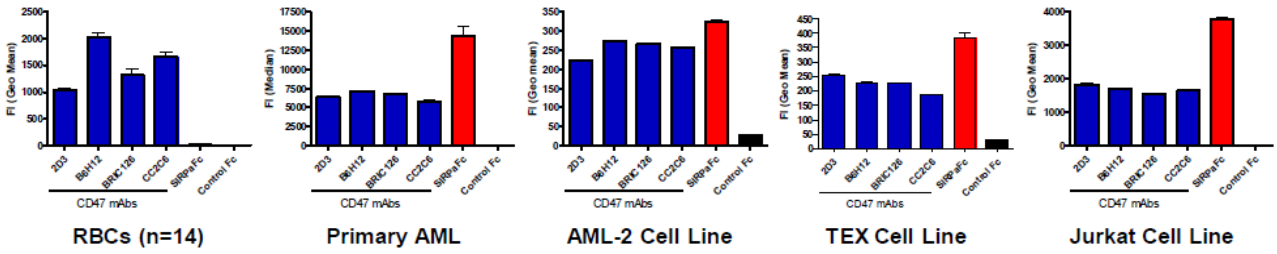
As CD47 is widely expressed on most normal tissues at low levels,[4] there are concerns that targeting the CD47-SIRPa pathway could provoke adverse events. Weissman's group found that its anti-CD47 antibody selectively eliminates tumour cells, but not their normal counterparts, and that the administration of anti-mouse CD47 antibodies to wild-type mice for weeks did not result in any severe toxicity. Similarly, Trillium found that in vitro, SIRPaFc enables macrophages to kill AML tumour cells but spares normal cord blood- or peripheral blood-derived mononuclear cells.

Both groups hypothesise that one way that CD47-blockage selectively eliminates tumour cells while sparing normal cells could be that while an anti-CD47 treatment blocks a negative phagocytic signal, a positive phagocytic stimulus may still be needed for the phagocytosis action to occur. The selective phagocytosis of tumour cells (and sparing of normal cells) would be supported by the expression of a pro-phagocytic signal(s) on tumour cells that are absent on normal cells. Weissman's group found that human haematologic and solid tumours expressed the pro-phagocytic signal calreticulin (CRT) on the cell surface, whereas normal counterparts did not[4] and that anti-CD47 mediated phagocytic potency was correlated with CRT expression on target cells.[4]

SIRPaFc could have lower RBC binding vs anti-CD47 mAbs

As CD47 is well expressed on circulating human red blood cells (hRBCs), agents that bind CD47 present on hRBCs could potentially provoke increased phagocytosis of such cells and thus undesired haematological toxicity risk (eg, anaemia). The CD47 expression on hRBCs can possibly also act as a large 'antigen sink' for potential therapies targeting CD47 (ie, increasing the amount of drug needed to reach targeted sites). To this end, Trillium presented data at the 2014 AACR meeting showing that SIRPaFc binds very poorly to human red blood cells (hRBCs), particularly in comparison to several commercial anti-CD47 mAbs and proprietary CD47-blocking agents. This binding difference appeared to be hRBC-specific, as SIRPaFc and the tested anti-CD47 mAbs bound similarly to (CD47-presenting) AML and other T lymphocyte cell lines.

Exhibit 3: Binding difference is RBC-specific – both bind similarly to AML and other CD47+ cells



Source: Trillium poster presented at 2014 AACR meeting

The relative sparing on CD47-binding on hRBC by SIRPaFc could lead to it being a superior CD47-targeting therapeutic to competing approaches given a possibly reduced likelihood of hRBC sink effects (thus leading to potentially improved pharmacokinetics) and for causing hRBC toxicities. Altogether, these binding differences and the lack of pro-phagocytic signals (eg, CRT) in non-cancerous cells increase the chance for a positive therapeutic window whereby SIRPaFc preferentially kills cancer cells vs healthy cells.

Initially targeted SIRPaFc indication – AML

SIRPaFc is initially being developed as a therapy to target BCCs and CSCs in AML patients following conventional chemotherapy. The choice to target AML is for several reasons: in addition to the preclinical work compiled in this model, AML is one of the first tumour types where CSCs were identified[9] (a presumed differential advantage of anti-CD47 treatment is that it can also target CSCs as well as BCCs) and CSC frequency/gene expression has been shown to be highly correlated with mortality risk in AML patients. Trillium began IND-enabling studies for SIRPaFc in H213, and is currently completing additional preclinical studies (including mouse tumour studies and additional pharmacology studies). Contract manufacturing for the SIRPaFc programme proteins has been secured to develop product for the formal GLP (Good Laboratory Practice) toxicology studies (expected to start in early 2015 and finish by mid-2015). The firm expects to start a Phase I safety and tolerability trial in H215.

High unmet need in AML, particularly among older population

AML is the most common type of acute leukaemia in adults, with approximately 19,000 new cases diagnosed a year in the US[10] and about 26,000 in Europe.[11] AML is a malignancy of myeloblast cells (within the myeloid line of blood cells), and leads to the rapid growth of abnormal WBCs that accumulate in the bone marrow and interfere with normal haematopoeisis (blood cell production). AML incidence increases with age (AML is uncommon before age 45). Most AML patients receive induction chemotherapy as the initial treatment, with the most common initial treatment consisting of (anthracycline class chemotherapeutic) daunorubicin and/or cytarabine (an antimetabolite chemotherapeutic). Induction therapy leads to a remission in 60-70% of cases, although relapses are common, which are treated either with chemotherapy/radiation or haematopoetic stem cell transplantation. Nonetheless, the five-year AML survival rate is about 25%, although it falls below 15% in patients over 65 and is approximately 50% in patients under 45.[12] Survival rates also vary based on the cytogenic subtype of disease (characterisation of specific chromosomal anomalies in leukaemic cells). Given the low five-year survival rate, particularly in the older population, there is much unmet need for new therapies.

Trillium examining SIRPaFc in other tumours

Beyond AML, SIRPaFc could be applicable to other cancers. CD47 blockade has shown efficacy in other haematological malignancies including acute lymphoblastic leukaemia, diffuse large cell B lymphoma and Burkitt's lymphoma xenograft models,[13,14] and elevated CD47 expression has also been observed in chronic lymphocytic leukaemia, mantle cell lymphoma and MM. In terms of solid tumours, high CD47 messenger RNA (mRNA) expression is also associated with poor clinical outcomes (ie more aggressive disease) in ovarian cancer, glioma and glioblastoma.[15] The charts below of different patient cohorts show shorter survival times in those with higher CD47 expression.

[9] Research conducted by Dr John Dick (currently a Trillium collaborator) at the University of Toronto.

[10] Data from American Cancer Society.

[11] Eur J Cancer. 2012 Nov; 48(17): 3,257-66.

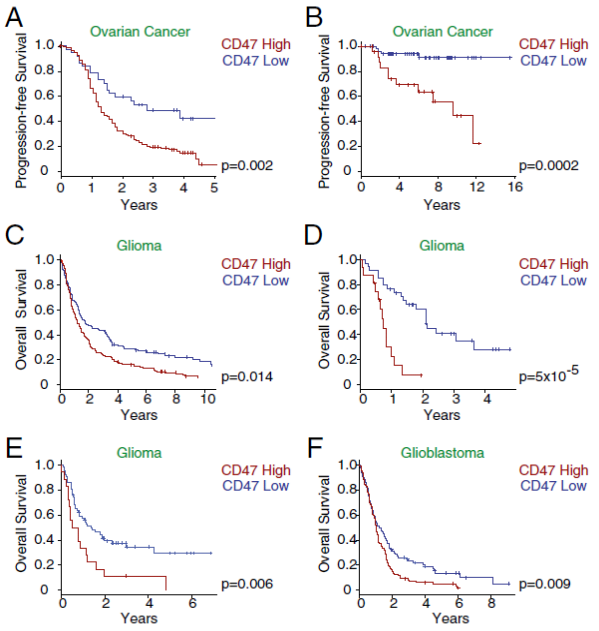
[12] Data from Cancer Research UK (http://www.cancerresearchuk.org/cancer-help/type/aml/treatment/statistics-and-outlook-for-acute-myeloid-leukaemia) and American Cancer Society 2014 (http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf).

[13] Chao et al. 2010 Cell 142: 699.

[14] Chao et al. 2011 Cancer Res 71: 1374.

[15] Willingham et al. 2012 PNAS 109: 6662.

Exhibit 4: Increased levels of CD47 mRNA expression were correlated with decreased probability of progression-free survival in numerous cancers



Source: Adapted from: Willingham et al. 2012 PNAS 109:6662

CD47 antibody blockade was found to be efficacious in human xenograft/xenotransplantation models of solid tumours, including bladder, ovarian, glioblastoma and bladder cancer, leading to inhibition of tumour growth or improved survival compared to control mice.[15]

Trillium in August 2014 entered into a collaboration with academic investigators at the University of Western Ontario (London, Ontario) to explore the therapeutic potential of SIRPaFc, in a variety of solid and other liquid tumour models. We estimate that Trillium is seeking to build preclinical data that can lead to future trials in solid tumours.

SIRPaFc variants for monotherapy and combination therapy

Inhibition of the CD47-SIRPa pathway can potentially provide therapeutic utility in combination therapy. One strategy would be to combine the CD47-targeting agent with a therapeutic antibody that stimulates immune Fc receptor-mediated responses, such antibody-dependent cell-mediated cytotoxicity (ADCC), to increase tumour cell killing. Hence, combination therapy can stimulate target phagocytosis by both blocking a negative signal (CD47) and delivering a positive signal. The combination of an anti-CD47 antibody with the anti-CD20 antibody rituximab (Rituxan) led to synergistic elimination and curing of mice engrafted with human lymphoma cells.[13] An anti-SIRPa antibody also potentiated the ADCC mediated by anti-Her2/Neu antibody trastuzumab (Herceptin) in breast cancer cells.[16] These studies suggest that targeting the CD47-SIRPa pathway can be combined with other Fc-receptor activating antibodies to augment treatment efficacy. Combination of anti-CD47 therapy and chemo-radiation therapy could also be explored.

Trillium is currently developing two distinct SIRPaFc fusion proteins, TTI-621 and TTI-622. Both compounds contain the same SIRPa region (and bind to CD47 equally) but differ in their Fc regions. TTI-621 uses a IgG1 immunoglobulin 'tail', which binds with high affinity to Fc receptors on phagocytic cells (eg macrophages) and thereby can promote activation of such cells (and increased resulting phagocytic activity). TTI-622 uses an IgG4 'tail', which binds with lower affinity to these activating Fc receptors.

[16] Zhao et al. 2011 PNAS 108: 18342.

In-vivo studies showed that TTI-621 was more potent in terms of tumour xenograft shrinkage than TTI-622, suggesting that its stronger Fc affinity contributed to the therapeutic effect, but it also found that TTI-622 generated fewer adverse reactions. Trillium assumes that in a combination therapy setting, particularly with a biological antibody that stimulates effector Fc functions (eg, rituximab) there is less of a need or benefit for the SIRPaFc molecule to provide additional Fc activation and generate the potentially increased toxicity-risk (versus a variant that uses an IgG4 tail). Hence, Trillium is planning to develop TTI-621 (with the stronger Fc activation) for monotherapy, following AML debulking by conventional chemotherapy. TTI-622 is intended to be used in combination with other targeted anti-cancer treatments, such as monoclonal antibodies. Trillium's current pre-IND development work involves both compounds and both are currently planned to be ready for IND filings by Q315.

Stanford group, Celgene, others also targeting CD47

The Weissman group is developing an anti-CD47 antibody (Hu5F9-G4) as a potential cancer drug, and started in August 2014 a 36-patient Phase I safety study (NCT02216409) in patients with advanced solid tumours. Results are expected in August 2017. The California Institute for Regenerative Medicine[17] is one of the study sponsors, and the trial is designed to determine the maximum tolerated dose (MTD) and optimal dosing regimen of the anti-CD47 antibody.

Celgene (NASDAQ: CELG) confirmed when it reported Q214 results in July 2014 that it is developing anti-CD47 antibodies in-licensed from privately held InhibRx; Celgene in 2012 acquired an option and licence to an antibody programme covering a then-undisclosed target (now confirmed as CD47) with upfront and milestone payments potentially exceeding US$500m (in addition to potential sales royalties). Celgene disclosed that it intends to bring the CD47 antibody to the IND-stage by year-end 2014, which we believe indicates it plans to start Phase I studies in 2015. Privately-held Novimmune SA is developing NI-1701, a bi-specific antibody that seeks to block CD47 while also having a Fab targeting arm that is selective for CD19 (an antigen more highly expressed in tumours), although this is currently in discovery stages.

Exhibit 5: Competitors developing anti-cancer compounds targeting CD47

Company name	Description	Development stage
Weissman group (Stanford)	Anti-CD47 monoclonal antibody	Phase I
Celgene/InhibRx	Anti-CD47 monoclonal antibody	Preclinical/Pre-IND
Novimmune SA	Anti-CD47 and CD19 Bi-specific antibody	Discovery

Source: Edison Investment Research

Outside of CD47, other projects are being investigated for AML and could extend the competitive landscape and raise the bar needed for SIRPaFc to be successful. Namely, Ambit Biosciences' (NASDAQ: AMBI) quizartinib (an FMS-like tyrosine kinase 3, or FLT3, inhibitor) started a 326-patient Phase III trial in relapsed/refractory AML patients with the FLT3-ITD mutation in April 2014. Boehringer Ingelheim's volasertib (a polo-like kinase 1 inhibitor) is being tested in combination with cytarabine in a 660-pt Phase III AML (NCT01721876) trial. Novartis's midostaurin (a multi-targeted kinase inhibitor) is in Phase III development for FLT3-mutated AML. Cyclacel's (NASDAQ: CYCC) sapacitabine (an oral nucleoside analogue that impedes DNA synthesis) is being studied in a 450-pt Phase III trial in elderly AML patients. Agios Therapeutics' (NASDAQ: AGIO) reported in August 2014 that its AG-221 (an isocitrate dehydrogenase-2, or IDH2, inhibitor) showed objective responses in 14 out of 25 evaluable AML patients with an IDH2 mutation (which occur in up to 15-20% of AML patients) in an ongoing Phase I trial. Sunesis's (NASDAQ: SNSS) vosaroxin (an anticancer quinolone derivative) was recently reported as unsuccessful in its 711-pt Phase III study in combination with cytarabine in patients with relapsed or refractory AML.

[17] www.cirm.ca.gov/our-progress/awards/clinical-investigation-humanized-anti-cd47-antibody-targeting-cancer-stem-cells.

Anti-CD200 programme on the shelf for now

Trillium developed a human mAb that blocks the activity of CD200, an immunosuppressive molecule believed to be employed by many tumour cell types to evade immune attack. Trillium believes that CD200 is over-expressed in many different forms of haematological and solid tumours, and this over-expression correlates with more rapid disease progression. Trillium's anti-CD200 antibodies have promoted anti-tumour activity in a human tumour xenograft model. This programme is ready to enter a formal pre-clinical programme, but has been suspended internally since mid-2013 due to a prioritisation of existing resources towards the SIRPaFc programme.

Market potential considerations

The bulk of SIRPaFc preclinical data and of Trillium's R&D efforts have concentrated on AML, yet given the preclinical data on CD47-targeting already shown by the Weissman group, we believe CD47 inhibition can potentially be applicable to cancers other than AML as well. Given that the mechanistic pathways used in other cancer immunotherapies (such as ipilimumab, pembrolizumab and nivolumab) are believed to be applicable to multiple forms of cancer, we expect that SIRPaFc (TTI-621 and/or TTI-622) could eventually be approved in multiple oncology indications.

For AML, we assume that a Phase I SIRPaFc monotherapy study will start patient recruitment and dosing in Q415. We estimate trial completion in late 2016 or early 2017, and that a Phase II programme will then be completed by H218, leading to a Phase III programme, and then market approval and launch in 2021. We expect the compound will be developed internally until the end of Phase II development, after which an out-licensing or sale transaction will be sought. However, potentially lucrative licensing transactions with double-digit royalty opportunities in the oncology/immuno-oncology space are also possible at earlier development stages, and below we highlight a sample of recent deals in the space.

Exhibit 6: Selected comparable early to mid-stage oncology licensing transactions

Licensor	Licensee	Year	Stage at signing	Upfront (US$m)	Potential milestones (US$m)	Royalties (%)	Licensor obtains
Medivation	CureTech	2014	Phase II	5	330	Between 4-11%	Global rights to pidilizumab, an anti-PD-1 monoclonal antibody
Merck	Ablynx	2014	Preclinical	27	2,300	Tiered	Global rights to nanobody candidates directed toward immune checkpoint modulators
Roche	New Link Genetics	2014	Phase I	150	1,000	Double-digit	Global rights to NLG919, an IDO pathway (immune checkpoint) inhibitor
Tesaro	AnaptysBio	2014	Preclinical	17	324	Single-digit	Rights to antibody programmes targeting PD-1, TIM-3 and LAG-3, all immuno-oncology related checkpoint receptors
Roche	Inovio Pharma	2013	Preclinical	10	413	Up-to double-digit	DNA-based vaccines INO-5150 (for prostate cancer) and INO-1800 (hepatitis B) and use of vaccine delivery technology
Cell Therapeutics	S*Bio	2012	Phase I/II	15	132.5	Single-digit	Pacritinib, a selective JAK2 and FLT3 inhibitor, for haematological cancers
Amplimmune	GSK	2010	Preclinical	23	485	Double-digit	Global rights to PD-1 inhibitor, AMP-224, and potential next generation products targeting PD-1
Bayer	Ardea Biosciences	2009	Phase I/II	35	407	Double-digit	RDEA119, a mitogen-activated ERK kinase (MEK) inhibitor for the treatment of cancer, and follow-on compounds
Median				20	410		

Source: Company reports, BioCentury

For AML, assuming an initial average annual net treatment price of US$80,000 per patient in the US and US$72,000 in Europe, a target market as 19,000 newly diagnosed AML patients per year in the US and 26,000 in Europe, and 25% peak US market share (20% in Europe), we estimate peak sales of US$950m in AML alone. We reiterate that we expect SIRPaFc to be developed for other cancers as well, and thus approvals in other solid tumours (eg breast or ovarian) or haematological (eg MM or myelodysplastic syndromes) cancers can provide markedly higher total sales potential

for SIRPaFc. Trillium indicates that the first SIRPaFc patents expire in 2029, hence we expect over eight years of market exclusivity for this product.

Trillium's rights to SIRPaFc have been licensed from the University Health Network and the Hospital for Sick Children (both based in Toronto). The licensors will be entitled to single-digit royalties on commercial sales (if Trillium or a prospective acquirer commercialises SIRPaFc) or, if Trillium out-licenses the product, 20% of any sublicensing revenues on the first C$50m of sublicensing revenues received, and 15% thereafter. This transaction structure provides a greater retention of SIRPaFc economics to Trillium if it retains this asset (rather than out-licensing it).

Sensitivities

Advancement of SIRPaFc to Phase I trials and beyond should de-risk the programme. The pipeline indication expansion of SIRPaFc to other tumours can also provide further upside, as can the realisation of development partnerships for the CD200 mAb.

Drug development risk. Prospective cancer treatments have a high hurdle rate to reach approval, including lengthy and costly development programmes and high rates of failure. On the plus side, a 2013 study by DiMasi et al.[18] found that oncology investigational drugs for haematological indications (such as AML) have markedly higher success rates than drugs targeting solid tumours.

Competition considerations. The potential emergence of alternate AML therapies, or in particular alternate CD47-targeting treatments, could affect the commercial prospects of SIRPaFc, particularly if those candidates can demonstrate superior clinical efficacy or reach the market more quickly. SIRPaFc's potential advantage vs anti-CD47 mAbs is that it may have less hRBC toxicity risk, but this will be further elucidated as clinical study data is generated.

Partnership/transactional risk. The timing for SIRPaFc development will depend on Trillium's ability to secure a development partner or acquirer at favourable terms, as we do not expect it to independently develop or fund SIRPaFc at Phase III. Commercial success will also depend on the marketing capabilities of the potential partner.

Financing risk. Trillium has limited sources of non-dilutive funding and challenges in obtaining funding on desirable terms for future studies (after the Phase I AML trial) could lead to programme delays or unfavourable dilution to equity holders.

Financials

In December 2013, Trillium raised gross proceeds of C$33m through a private placement. As of 30 September 2014, Trillium had C$27.9m net cash (C$28.3m cash and marketable securities, offset by C$0.4m debt), and the cash burn rate in 9m14 was C$5.6m, although we expect it to increase when the firm starts a Phase I AML study in H215. We expect Trillium's funds on hand to last until the completion of this Phase I study, which we believe will be late 2016 or early 2017. We expect Trillium will require C$40m in financing between 2016 and mid-2018 to further SIRPaFc development through Phase II studies. As per usual Edison policy, we anticipate this raise will be in the form of debt financing. Trillium completed a 30-for-one reverse stock split in November 2014, in preparation for its NASDAQ listing. Our fully diluted (FD) post-split common share count of 8.84m shares is based on the 4.27m listed (post-split) basic shares outstanding as of 30 September 2014, and includes the addition of 2.48m from preferred share conversion (74.3m preferred shares convertible one-for-30 into common shares) and 2.10m shares through the cash-neutral exercise (using the treasury method) of outstanding in-the-money options and warrants.

[18] DiMasi JA, Reichert JM, Feldman L, Malins A. Clin Pharmacol Ther. 2013 Sep; 94(3): 329-35.

Exhibit 7: Financial summary

C$000	2012	2013	2014e	2015e	2016e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
General & Administrative	(466)	(962)	(2,688)	(1,661)	(1,694)
Research & Development	(617)	(2,688)	(8,203)	(10,500)	(15,000)
EBITDA	(1,083)	(3,650)	(10,891)	(12,161)	(16,694)
Depreciation	(4)	(16)	(47)	(82)	(106)
Amortisation	(2)	(633)	(562)	(230)	(120)
Operating Profit (before exceptionals)	(1,090)	(4,299)	(11,500)	(12,473)	(16,920)
Exceptionals	0	0	0	0	0
Other	0	0	0	0	0
Operating Profit	(1,090)	(4,299)	(11,500)	(12,473)	(16,920)
Net Interest	28	10	371	426	163
Profit Before Tax (norm)	(1,060)	(3,657)	(10,567)	(11,816)	(16,637)
Profit Before Tax (FRS 3)	(1,062)	(4,289)	(11,129)	(12,047)	(16,757)
Tax	0	0	0	0	0
Profit After Tax and minority interests (norm)	(1,060)	(3,657)	(10,567)	(11,816)	(16,637)
Profit After Tax and minority interests (FRS 3)	(1,062)	(4,289)	(11,129)	(12,047)	(16,757)
Average Number of Shares Outstanding (m)	0.6	1.4	4.2	4.3	4.4
EPS - normalised (C$)	(1.70)	(2.69)	(2.50)	(2.73)	(3.78)
EPS - normalised and fully diluted (C$)	(1.70)	(2.69)	(2.50)	(2.73)	(3.78)
EPS - (IFRS) (C$)	(1.71)	(3.16)	(2.63)	(2.79)	(3.81)
Dividend per share (C$)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	3	1,582	737	646	661
Intangible Assets	3	1,473	482	251	131
Tangible Assets	0	109	256	394	530
Current Assets	1,565	33,505	25,879	14,963	19,250
Short-term investments	0	527	505	505	505
Cash	1,375	32,457	24,653	13,738	18,025
Other	190	522	720	720	720
Current Liabilities	(185)	(733)	(264)	(264)	(264)
Creditors	(185)	(733)	(264)	(264)	(264)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	0	(446)	(364)	(364)	(20,364)
Long term borrowings	0	(446)	(364)	(364)	(20,364)
Other long term liabilities	0	0	0	0	0
Net Assets	1,382	33,908	25,988	14,981	(716)
CASH FLOW					
Operating Cash Flow	(1,350)	(2,492)	(8,831)	(11,122)	(15,634)
Net Interest	28	10	371	426	163
Tax	0	0	0	0	0
Capex	0	(34)	(194)	(220)	(242)
Acquisitions/disposals	0	(648)	0	0	0
Financing	0	34,030	966	0	0
Net Cash Flow	(1,322)	30,865	(7,688)	(10,915)	(15,713)
Opening net debt/(cash)	66,087	(1,375)	(32,537)	(24,795)	(13,879)
HP finance leases initiated	0	0	0	0	0
Other	68,784	297	(54)	0	0
Closing net debt/(cash)	(1,375)	(32,537)	(24,795)	(13,879)	1,833

Source: Edison Investment Research. Note: We assume C$20m illustrative long-term debt financing in 2016.

Contact details	Revenue by geography
Trillium Therapeutics Inc. 96 Skyway Avenue Toronto, Ontario, Canada M9W 4Y9 +1 416.595.0627 www.trilliumtherapeutics.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2011-15e	N/A	ROCE 14e	N/A	Gearing 14e	N/A	Litigation/regulatory	●
EPS 2013-15e	N/A	Avg ROCE 2011-15e	N/A	Interest cover 14e	N/A	Pensions	○
EBITDA 2011-15e	N/A	ROE 14e	N/A	CA/CL 14e	N/A	Currency	○
EBITDA 2013-15e	N/A	Gross margin 14e	N/A	Stock days 14e	N/A	Stock overhang	○
Sales 2011-15e	N/A	Operating margin 14e	N/A	Debtor days 14e	N/A	Interest rates	○
Sales 2013-15e	N/A	Gr mgn / Op mgn 14e	N/A	Creditor days 14e	N/A	Oil/commodity prices	○

Management team

President and CEO: Niclas Stiernholm	Chief Financial Officer: James Parsons
Dr Stiernholm served as president and CEO of the company (then named Stem Cell Therapeutics) upon the completion of its merger in April 2013 with private company Trillium Therapeutics. He joined Trillium from YM BioSciences where he was executive vice president and chief scientific officer. Dr Stiernholm began his industry career as a member of Allelix Biopharmaceuticals' business development office. He currently serves on the boards of AvidBiologics and Vasomune Therapeutics. He received his PhD in immunology from the University of Toronto, where he also completed his postdoctoral training.	Mr Parsons has over 25 years of financial management experience, which includes a significant background in the life sciences industry. His past involvement in the sector includes roles with Amorfix Life Sciences Ltd, DiaMedica Inc, Trillium Therapeutics Inc and YM BioSciences Inc. Mr. Parsons serves on the board of Sernova Corp where he chairs the audit committee. He has a master of accounting degree from the University of Waterloo and is a Chartered Professional Accountant and a Chartered Accountant.
Chief Scientific Officer: Bob Uger	**Vice President, Drug Development: Penka Petrova**
Dr Uger has been chief scientific officer at the company since the completion of its merger with private company Trillium Therapeutics. Dr Uger oversees both internal product development and external research discovery programmes. He also acts as the firm's scientific liaison with respect to global collaborations with academic and hospital research scientists. Dr Uger was previously vice-president, research & development at Trillium Therapeutics (private company). He joined Trillium from Aventis Pasteur where he was a senior research scientist involved in cancer vaccine research. He received his PhD in immunology from the University of Toronto.	Dr Petrova is responsible for managing the company's formal drug development efforts, including all outsourced activities to contract manufacturers and contract research organisations. She also heads the firm's cell biology group and oversees all in vivo studies. Dr Petrova was previously director, drug development at Trillium Therapeutics (private company). She joined Trillium from Prescient Neuropharma in 2003, where she held a research scientist position. Dr Petrova received her PhD in microbiology from Saarland University in Saarbruecken, Germany, where she also conducted her postdoctoral studies.

Principal shareholders	(%)
Austin W Marxe and David M Green Special Situations Funds	9.3
Merlin Biomed Group LLC	9.3
Opaleye LP	7.7

Companies named in this report

Agios Therapeutics, Ambit Biosciences, BMS, Boehringer Ingelheim, Celgene, Cyclacel, Innate Pharma, Merck, Novartis, Novimmune, Sunesis

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