Edison investment research

Targeting soft tissue sarcoma

Pharma & biotech

CytRx's investment case effectively rests on the successful development and commercialisation of its lead programme, aldoxorubicin, for advanced soft tissue sarcoma (STS). Backed by a strong balance sheet, encouraging Phase I/II data, and positive FDA feedback, we expect CytRx to advance its pipeline through major value inflection points in 2013. Positive data for aldoxorubicin (STS, pancreatic cancer) and tamibarotene (lung cancer) in 2013 could drive a re-rating of CytRx shares, closing the gap between the current market cap ($65m) and our base-case valuation ($120m).

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/11	0.3	(21.8)	(0.11)	0.0	N/A	N/A
12/12e	0.1	(20.4)	(0.86)	0.0	N/A	N/A
12/13e	0.1	(21.8)	(0.71)	0.0	N/A	N/A

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

Aldoxorubicin…a more active, less toxic doxorubicin

Aldoxorubicin is a tumour-targeted conjugate of doxorubicin, a widely used chemotherapy for solid and haematologic cancers. It is doxorubicin attached to an acid-sensitive linker, which binds to circulating albumin following intravenous injection and then releases doxorubicin in acidic tumour tissues. Preclinical data show that aldoxorubicin enhances the anti-tumour activity of doxorubicin but lacks its dose-limiting heart toxicity (cardiotoxicity). A 19-patient Phase I/II trial in advanced STS showed promising efficacy and no acute cardiotoxicity at doses equal to 3.5x the maximum doxorubicin dose.

Advanced STS is the gateway indication

We anticipate FDA agreement (SPA grant) on the Aldoxorubicin Phase III study in second-line STS during Q213 and trial initiation around mid-2013. There is a strong rationale for targeting relapsed/refractory STS patients: positive Phase I/II data; doxorubicin is indicated for STS; competition is limited; unmet need is high; and a clear regulatory pathway. In 2013, we expect further aldoxorubicin Phase II data in front-line STS (Q313) and third-line pancreatic cancer (Q313) to support the product's favourable risk/benefit profile and broad commercial potential.

Tamibarotene Phase II lung cancer data in Q413

Phase IIb results for tamibarotene (a novel oral retinoid) in first-line advanced non-small cell lung cancer (NSCLC) are expected in Q413. Tamibarotene is a more potent version of all-trans retinoic acid (ATRA), which increased survival in NSCLC patients in a Phase II study. The tamibarotene Phase IIb study recently passed an interim safety analysis and is on track to complete enrolment in Q113.

Valuation: Risk-adjusted NPV of $120m

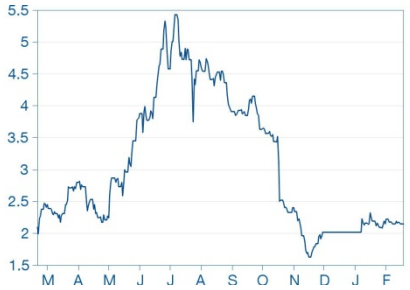
We value CytRx at $120m, or $4.00 per share, based on a risk-adjusted NPV analysis of key pipeline programmes (aldoxorubicin, tamibarotene) plus net cash. This base-case valuation, which offers clear upside to the current share price, assumes a conservative 40% probability of success on aldoxorubicin in second-line STS. Positive programme newsflow (SPA grant, front-line STS data) would unwind this risk adjustment and increase our valuation by c 28%. Further upside potential exists from positive tamibarotene data (c 18%) and out-licensing deals on the pipeline.

CytRx is a research client of Edison Investment Research Limited

19 February 2013

Price	$2.15
Market cap	$65m
Shares in issue	30.4m
Free float	82%
Code	CYTR
Primary exchange	NASDAQ

Share price performance



%	1m	3m	12m
Abs	(1.8)	31.9	2.4
Rel (local)	(3.1)	12.6	(11.0)
52-week high/low		$5.5	$1.6

Business description

CytRx is a US biopharmaceutical company focused on oncology. Lead programme, aldoxorubicin is Phase III-ready for STS and in a Phase II study for pancreatic cancer. Tamibarotene is in Phase II trial for NSCLC, while Bafetinib has completed a Phase II study in B-CLL and could be partnered.

Next events

Aldoxorubicin SPA	Q213
Aldoxorubicin Phase III start in second-line STS	Q213
Aldoxorubicin Phase II data in first-line STS	Q313
Tamibarotene Phase II data in first-line NSCLC	Q413

Analysts

Michael Aitkenhead +44 (0)20 3077 5736
Robin Davison +44 (0)20 3077 5737
healthcare@edisoninvestmentresearch.co.uk

Investment summary

Company description: Targeted cancer therapies

CytRx is a US biopharmaceutical company focused on the development of cancer therapies. The company's key pipeline programmes are aldoxorubicin (formerly INNO-206), which will shortly enter a pivotal Phase III study for the second-line treatment of STS, and tamibarotene, which is in a Phase IIb trial for NSCLC. The third candidate, bafetinib, has generated positive Phase II data in B-cell chronic lymphocytic leukaemia (B-CLL) and could be partnered for future development. CytRx gained these oncology assets through its acquisition of Innovive Pharmaceuticals in 2008. With this transaction, CytRx transformed itself into a development-stage cancer company. The company's previous lead programme in CNS disease, arimoclomol, was hit with an FDA clinical hold order in 2007 during a Phase IIb trial in amyotrophic lateral sclerosis (ALS). The hold was lifted in late-2009 and arimoclomol (plus other non-core assets) were sold to Orphazyme ApS in 2011 in a deal worth up to $120m.

Valuation: Risk-adjusted NPV of $120m

We value CytRx at $120m, or $4.00 per share, based on a risk-adjusted NPV analysis using a 12.5% discount rate. Our rNPV model includes aldoxorubicin (second-line STS indication) and tamibarotene (first-line NSCLC) and year-end 2013 net cash of $15.7m. Our valuation represents significant upside to CytRx's current market capitalisation of $65m and $2.15 share price. We value the pipeline products using prudent assumptions about their probability of success, launch date, pricing, commercialisation and market penetration. We currently attribute no value to aldoxorubicin in first-line STS (data Q313), other solid tumour indications, or potential licensing agreements on the pipeline, so these represent pure upside to our forecasts and valuation.

Sensitivities: Front-line STS results in Q313

CytRx is exposed to the usual biotech company development risks, the unpredictable outcomes of clinical trials, regulatory decisions, success of competitors, financing and commercial risks. In particular, aldoxorubicin has been tested in a limited number of patients (66 total) in Phase I/II studies. While results are encouraging, the small dataset makes it difficult to call the outcome of future clinical studies. CytRx has attempted to mitigate clinical and development risks by targeting second-line STS as the pathway to registration: the doxorubicin component is already indicated for STS; positive aldoxorubicin Phase I/II data in relapsed/refractory STS patients; few competitors and high unmet medical need; and there is a clear regulatory pathway. The key near-term sensitivity is results of the aldoxorubicin Phase II study versus doxorubicin in front-line STS, where headline data (Q313) are expected shortly after initiation (mid-2013) of the second-line Phase III study. Positive front-line data favouring aldoxorubicin would increase our confidence in the second-line opportunity and could drive a significant re-rating in CytRx's valuation. Conversely, negative data would eliminate the first-line indication and, in our view, could call into question the second-line opportunity.

Financials: Cash runway into late-2014

CytRx had cash and short-term investments of $22.5m as of 30 September 2012 and a nine-month operating cash burn of $13.5m. However, CytRx subsequently raised $21.4m from an underwritten public offering in October 2012. We estimate the company has, in the absence of licensing deals or exercise of warrants from a 2011 financing (potentially raising $28.7m), a cash runway into late-2014.

Outlook

CytRx's investment case effectively rests on the successful development and commercialisation of its lead programme, aldoxorubicin, for advanced STS. Backed by a strong balance sheet, limited but encouraging Phase I/II data, and positive FDA feedback, we expect CytRx to advance its pipeline through major value inflection points in 2013. Positive data for aldoxorubicin (STS, pancreatic cancer) and tamibarotene (lung cancer) in 2013 could drive a re-rating of CytRx shares.

Exhibit 1: CytRx's R&D pipeline

Product	Indication	Stage	Notes
Aldoxorubicin	Second-line STS	Phase III ready	Anticipate Phase III initiation, under SPA, during Q213.
Aldoxorubicin	First-line STS	Phase IIb	Headline results (Response rates, PFS) in Q313.
Aldoxorubicin	Third-line pancreatic cancer	Phase IIa	Preliminary data (Response rates, Disease control rate) in mid-2013.
Tamibarotene	First-line advanced NSCLC	Phase IIb	Headline results (Response rates, PFS) during Q313.
Bafetinib	Relapsed/refractory B-CLL	Phase IIa complete	Initial activity in B-CLL; CytRx seeking licensing partner.

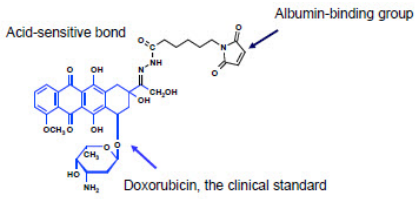
Source: Edison Investment Research

Aldoxorubicin: Targeting STS

Tumour-targeted doxorubicin conjugate

Aldoxorubicin (formerly INNO-206) is a tumour-targeted conjugate of the anticancer agent doxorubicin. Essentially, the drug is doxorubicin attached to an acid-sensitive linker (called EMCH). Following intravenous (IV) administration, aldoxorubicin's EMCH linker covalently binds to circulating albumin (the major protein in blood plasma) and then releases doxorubicin selectively at the tumour site by passive targeting. Preclinical and initial clinical data suggest that this novel mechanism enhances doxorubicin's anti-tumour activity and improves the overall toxicity profile.

Exhibit 2: Structure of aldoxorubicin



Source: CytRx

Aldoxorubicin comprises three parts - a doxorubicin molecule, an acid-sensitive bond (hydrazone linker) and an albumin-binding group (maleimide moiety) (see Exhibit 2). Following IV injection, the maleimide portion covalently binds, rapidly and selectively, to the cysteine-34 residue of endogenous albumin.[1] Aldoxorubicin then circulates in an albumin-bound form, which is highly stable, a small volume of distribution and low clearance compared to free doxorubicin.[2] Exploiting albumin as a drug carrier has two theoretical advantages: it provides passive drug targeting by leveraging the preferential uptake of albumin by tumour cells and it could minimise drug deposition in sensitive, off-target tissues such as the heart. Once albumin-bound aldoxorubicin reaches the tumour, the slightly acidic environment (in extracellular tissues or intracellularly in endosomal/lysosomal compartments) cleaves the acid-sensitive linker and releases free doxorubicin directly into the tumour.

1 Katz et al, J Control Release 2011;10:1-25.
2 Kratz F, Expert Opin Investig Drugs 2007;16(6):1-11.

Doxorubicin is a highly potent anthracycline chemotherapy used to treat a wide variety of solid and haematologic cancers, including breast and ovarian carcinoma, STS, lymphoma and certain leukaemias. However, its efficacy is limited by a dose-dependent cardiotoxicity, which can cause irreversible heart failure. The risk of developing heart failure relates to the cumulative dose of 'free' doxorubicin, with a sharp increase in prevalence for total doses >450mg/m^2. However, impaired cardiac function can occur at even lower cumulative doses, with declines in left ventricular ejection fraction (LVEF) seen at total doses >350mg/m^2. As such, treatment duration with doxorubicin is limited to six cycles of 60-75mg/m^2 due to the risk of progressive cardiotoxicity.[3]

The toxicity that doxorubicin exhibits in cardiac cells (cardiomyocytes) is related to free radical formation caused by doxorubicin metabolism. This leads to cardiomyocyte death or dysfunction, which ultimately results in left ventricular dysfunction and heart failure. As a result, liposomal formulations of doxorubicin (J&J's Doxil/Caelyx, Teva's Myocet) were developed to decrease the circulating concentration of free doxorubicin, thereby sparing cardiomyocytes, and result in selective uptake by tumour cells. Use of Doxil, a PEGylated liposomal doxorubicin, reduces the risk of cardiotoxicity, even at doses >500mg/m^2. Production problems have resulted in a shortage of Doxil since October 2011. However, a recently approved generic is expected to help resolve this issue.

Albumin-based drug delivery – a validated approach

Albumin is the most abundant protein in the body, with approximately 500g distributed between the blood, lymphatic system and the extracellular and intracellular compartments. One of its key functions is to transport poorly water soluble molecules such as fatty acids, steroids and drugs. Under conditions of cellular stress, such as inflammation or malignancy, albumin is taken up by cells as a source of amino acids and energy.[4] An extensive body of research has shown preferential uptake of albumin (and other macromolecules) by tumour tissue, including data from preclinical experiments and clinical studies. In experimental animals with solid tumours, radioactively and fluorescently labelled albumin was specifically taken up by tumours.[5] Human studies have also shown preferential uptake of albumin into tumour tissue.[6]

The preferential uptake of albumin by solid tumours forms the basis of two distinct drug development strategies: coupling low-molecular weight drugs to endogenous albumin (CytRx's aldoxorubicin) and the encapsulation of drugs with exogenous albumin (Celgene's Abraxane). Abraxane, an albumin-paclitaxel nanoparticle, is approved for the treatment of metastatic breast cancer, advanced NSCLC. In addition, the drug recently extended survival in patients with metastatic pancreatic cancer. Abraxane posted global was $427m in 2012, an increase of 11% year-on-year.

Phase I study: Initial anti-tumour activity and acceptable safety

The primary objective of this prospective, open-label, dose-escalation Phase I study was to establish the maximum tolerated dose (MTD) of aldoxorubicin in patients with advanced cancers.[7] Secondary objectives included general toxicity, pharmacokinetics and anti-tumour activity. A total of 41 patients (including four sarcoma) received aldoxorubicin every 21 days for up to six cycles, at doses of 27mg/m^2 to 460mg/m^2 (equivalent to 20mg/m^2 to 340mg/m^2 of doxorubicin). Results confirmed the MTD as 460mg/m^2, due to the high frequency (c 50%) of grade 3 adverse events (haematologic toxicity, mucositis). A lower dose of 350mg/m^2 was therefore recommended for future studies; at this dose, haematologic toxicity (grade 1-2) and mucositis (grade 1-2) were the most common AEs. Importantly, no cardiac toxicity (heart failure, left ventricular impairment) was seen at any dose. Finally,

3 Nielsen et al, Sarcoma 2000;4:31-35.
4 Frei E, Diabetology & Metabolic Syndrome 2011;3:11.
5 Stehle et al, Anticancer drugs 1997;8:677-685.
6 Kremer et al, Neurosurgery 2009;64:53-60.
7 Unger et al, Clin Cancer Res 2007;13(16):4858-4865.

of 30 patients evaluable for tumour response, 15 (50%) had stable disease, three (10%) had partial remission – including one PR in a patient with advanced STS – and 12 (40%) had progressive disease.

Lead indication: Phase III-ready for STS

Phase Ib/II study in advanced STS

A Phase Ib/II study evaluated the safety, MTD and initial efficacy of aldoxorubicin in 25 patients with advanced solid tumours – including 21 with metastatic STS - who had failed previous chemotherapy. The Phase Ib portion of the study recruited 13 patients into one of three ascending dose cohorts of aldoxorubicin – 230, 350, or 450mg/m^2 – given every 21 days for up to eight consecutive cycles. This determined the MTD as 350mg/m^2 (260mg/m^2 of doxorubicin equivalents) or 3.5x the dose of standard doxorubicin (60-75mg/ m^2). The Phase II part enrolled another 12 patients at the MTD in order to evaluate the preliminary efficacy (objective tumour responses) of aldoxorubicin. Patients were periodically assessed for signs of cardiac dysfunction using multi-gated radionucleotide angiography (MUGA) or cardiac ultrasound scans.

A total of 19 patients (including 13 with STS) received aldoxorubicin at the MTD, with over half completing at least eight cycles (median 8, range 2-8). Baseline characteristics suggest a representative population of advanced patients: predominately leiomyosarcoma (smooth muscle tumour), median age of 56 years; male-to-female ratio of 0.9; and median of two previous chemotherapy regimens. Seven patients had received previous anthracycline chemotherapy (doxorubicin, liposomal doxorubicin or epirubicin) with the remaining six receiving a variety of other agents (ie ifosfamide, gemcitabine, avastin).

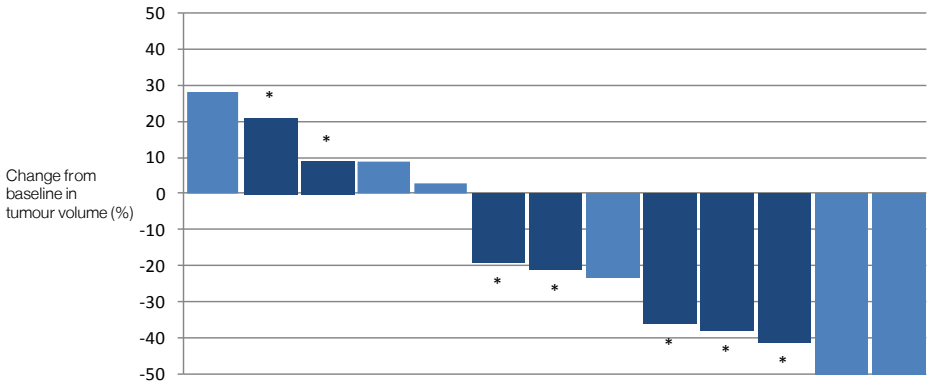
Results showed partial responses in five (39%) and stable disease in seven (54%) patients, equating to a clinical benefit (PR + SD) in 12 (92%) of the 13 evaluable patients (see Exhibit 3). Notably, five patients previously failing anthracyclines (doxorubicin, Doxil, epirubicin) showed a clinical benefit, including three partial responses (Exhibit 4). Estimated median PFS in the STS cohort was 6.4 months.

Exhibit 3: Aldoxorubicin Phase I/II study – efficacy in advanced STS patients

Efficacy end point	Number of evaluable patients (%)
Complete response (CR)	0 (0)
Partial response (PR)	5 (39)
Stable disease (SD)	7 (54)
Clinical benefit	12 (93)
Progressive disease	1 (7)
Progression-free survival (PFS)	6.4 months (median), 1-11 months (range)

Source: CytRx presentation, CTOS meeting 2012

Exhibit 4: Aldoxorubicin Phase Ib/II study – best response of STS patients



Source: CytRx. Note: *Indicates previous therapy with anthrcycline (doxorubicin, epirubicin, or Doxil).

With the caveat that cross-trial comparisons are not scientifically valid, aldoxorubicin's efficacy in this small study compares favourably with historical response rates (12-18%), clinical benefit (60-70%) and PFS (4-5 months) seen with doxorubicin in the front-line setting (Exhibit 5). It also compares favourably with GSK's Votrient (pazopanib) in the second-line setting, which showed a 4% response rate and 4.6-month PFS in a similar patient population (ie advanced STS patients failing previous chemotherapy). Comparing aldoxorubicin with Phase II data for the developmental-stage drugs (palfisofamide, TH-302) is difficult, as these were primarily first-line patients, administered in combination with doxorubicin and included patients (TH-302) with locally advanced disease. Acknowledging these caveats, response rates and PFS benefits for all three drugs appear comparable.

Exhibit 5: Efficacy results for approved and key Phase III drugs in STS

Product (company)	Setting	Treatment regimen	Study	No. (n)	Median PFS (mths)	CR (%)	PR (%)	SD (%)	Clinical benefit (%)	Reference
Aldoxorubicin (CytRx)	**Second/third-line**	**Monotherapy**	**Phase I/II**	**13**	**6.4**	**0**	**39**	**54**	**93**	**Chawla et al, ASCO 2011**
Doxorubicin	First-line	Mono	Phase IV	167	4.3	7	18	45	70	Nielsen et al, Sarcoma 2000
Doxorubicin	First-line	Mono	Phase IV	314	4.0	2	12	50	64	Nielsen et al, Sarcoma 2000
Doxorubicin	First-line	Mono	Phase IV	455	4.6	0	13	46	59	EORTC 62012, ESMO 2012
Votrient (GSK)	**Second-line**	**Mono**	**Phase III**	**369**	**4.6**	**0**	**4**	**nd**	**-**	**Prescribing information**
Palifosfamide (Ziopharm)	First/second-line	Combo with doxorubicin	Phase II	62	7.8	0	23	nd	-	PICASSO study, ASCO 2010
TH-302 (Threshold)	First-line	Combo with doxorubicin	Phase I/II	91	6.7	2	34	48	84	Phase II, CTOS 2012

Source: CytRx, Sarcoma Journal, CTOS, ESMO, ASCO, GSK. Note: CR=complete response, PR=partial response, SD=stable disease.

The safety population included all 19 patients treated at the 350mg/m^2 dose. Patients received a median of six cycles (range 1-8) equating to a cumulative aldoxorubicin dose of 2,100mg (1,500mg of doxorubicin equivalents). The drug was well tolerated at this dose with at least 50% of patients completing eight cycles and, thus, receiving a cumulative dose of 2800mg/m^2 (2000mg/m^2 of doxorubicin equivalents), which is over 3.5x the peak cumulative dose of standard doxorubicin.

The key drug-related adverse event was haematological toxicity, with 16 reported events of grade 3 or 4 neutropenia (see Exhibit 6). While most episodes were transient and resolved before subsequent cycles, either with or without G-CSF therapy (most patients received one dose), there were three cases of febrile neutropenia and two cases of sepsis. With the majority of patients experiencing at least one neutropenic episode, the c 80% incidence of grade 3/4 events on aldoxorubicin appears high relative to doxorubicin monotherapy (40-50%) or doxorubicin/ifosfamide combination therapy (46%).[8], [9] Based on our discussions with leading sarcoma physicians at the ESMO 2012 conference, the apparent increase in bone marrow suppression may relate to the higher total dose of doxorubicin equivalents administered to patients. Moreover, aldoxorubucin's mechanism of action (acid-sensitive hydrazone linker) coupled with the slightly more acidic environment of bone marrow (pH=7.38) than other organs (blood pH=7.42) may lead to preferential release of doxorubicin in this tissue.[10]

Physicians we spoke to agreed that future clinical studies of alodoxorubicin should include close haematological monitoring and, potentially, regular use of G-CSF to limit neutropenic episodes. Indeed, ongoing clinical studies of aldoxorubicin (front-line STS, third-line pancreatic cancer) permit the use of prophylactic G-CSF to reduce the incidence and/or severity of neutropenia.

[8] Nielsen et al, Sarcoma 2000;4:31-35.
[9] EORTC 62012 trial results, ESMO 2012.
[10] Miettinen et al, Journal of Translational Medicine 2012;10:66.

Exhibit 6: Aldoxorubicin Phase I/II study – haematologic adverse events

Event	Grade 3: Number (%)	Grade 4: Number (%)
Neutropenia	4 (21%)	12 (63%)
Febrile neutropenia	0 (0%)	1 (20%)
Thrombocytopenia	5 (26%)	
Worsening anaemia	5 (26%)	

Source: CTOS 2012

Cardiac safety data in this admittedly small cohort is consistent with preclinical data and raised no concerns (see Exhibit 7). No cases of cardiac toxicity were reported. However, two patients showed mild declines in left ventricular ejection fraction (LVEF), which could relate to the margin of error seen with MUGA/ultrasound scans. The one patient with reported LVEF <55% entered the study with a baseline value of 50% (normal range for LVEF is 55-70%).

Exhibit 7: Aldoxorubicin Phase Ib/II study – cardiac safety

End point	Evaluable patients (n=19) (%)
Subjects with >10% decrease in LVEF	2 (11%)
Subjects with >10% increase in LVEF	5 (26%)
Subjects with <55% expected value for LVEF	1 (5%)

Source: CTOS 2012

Pivotal Phase III study in second-line STS – expected to start Q213

In our view, the Phase Ib/II data provides a clear rationale for advancing aldoxorubicin into a pivotal study as second-line chemotherapy for advanced STS. Following a positive FDA meeting in Q412, CytRx filed a Special Protocol Assessment (SPA) for its planned Phase III trial in the second-line setting. As a reminder, an SPA agreement with the FDA states that the proposed trial design, end points and planned analysis are acceptable for regulatory submission. We anticipate an SPA grant by Q213, which should trigger Phase III initiation shortly thereafter.

While details of the SPA filing have not been disclosed, we expect recent pivotal studies in STS – Votrient, ombrabulin, TH-302, palifosfamide – to inform the aldoxorubicin Phase III protocol. We anticipate a randomised, double-blind, comparative design recruiting c 400 locally advanced or metastatic STS patients who are relapsed/refractory to front-line chemotherapy, including doxorubicin. We view PFS as the likely primary outcome measure, based on the precedent of GSK's Votrient (full FDA and EMA approval on PFS), with RR and overall survival (OS) as secondary measures. A potential comparator, Votrient, was approved for second-line STS based on modest efficacy (4.6 months PFS, 4% response rates, 12.6 months OS). Initial aldoxorubicin data in similar patients (6.4 months PFS, 39% RR) compares favourably with these results. We model a two-year study duration with initiation in Q213, completion of recruitment in H214 and headline PFS data in H215. We project US and EU regulatory submissions in late 2015 with FDA and EMA approvals in H216. Finally, we expect orphan drug status designation in both territories.

Phase II study in front-line STS – headline data Q313

Headline results from the aldoxorubicin Phase IIb study in front-line STS are expected in Q313. The randomised (2:1), open-label, multicentre study is comparing aldoxorubicin 350mg/m^2 (260mg/m^2 of doxorubicin equivalents) head-to-head with doxorubicin (75mg/m^2) in 105 subjects with metastatic or locally advanced disease, who have not received chemotherapy. Both drugs will be administered every three weeks for up to six cycles. The primary end point is PFS with secondary measures including response rates, OS and safety – preliminary data in Q313 will include PFS and tumour responses.

Single-agent doxorubicin is the current standard-of-care in first-line STS (4.6 month PFS), but this could shift if Phase III data are positive for Ziopharm's palifosfamide (Q113) and/or Threshold's TH-302 (H115). Both agents are being tested in combination with doxorubicin. As such, we expect CytRx's

development strategy in front-line STS to be informed by both the aldoxorubicin Phase II readout and competitor Phase III data. We envisage three possible outcomes:

- Positive aldoxorubicin, negative competitor(s) – this would eliminate key late-stage competitors and, hence, could trigger an aldoxorubicin Phase III study in front-line STS.
- Positive aldoxorubucin data, positive competitor(s) data – a decision to progress aldoxorubicin into Phase III as front-line therapy would depend, in our view, on the drug's efficacy/safety relative to both doxorubicin and competitors. This scenario also raises the possibility of a Phase III study of aldoxorubicin in combination with TH-302 or palifosfamide.
- Negative aldoxorubicin, positive competitor(s) – this would eliminate the first-line opportunity for aldoxorubicin. Moreover, if the drug is less effective and/or more toxic than doxorubicin, it may also raise questions about the second-line opportunity – would patients failing first-line doxorubicin then respond to second-line aldoxorubicin? Countering this is the observation that five anthracycline-treated patients subsequently responded to aldoxorubicin in the Phase Ib/II trial.

Supportive Phase I studies ongoing

CytRx is running two additional Phase I studies of aldoxorubicin, which are designed to better understand the drug's activity in man and, thus, support future regulatory and licensing activities:

- Pharmacokinetic (PK) study – an open-label Phase I trial to investigate standard PK parameters and safety in 12 patients with advanced solid tumours. Doses of 230mg/m^2 or 350mg/m^2 will be given every three weeks for up to eight cycles. Expected completion in Q313.
- MTD combination study – an open-label Phase Ib trial to investigate the safety and MTD of aldoxorubicin and doxorubicin combination therapy in 18 patients with advanced solid tumours. Subjects will receive aldoxorubicin (175, 240 and 320mg/m^2) plus half the standard dose of doxorubicin (35mg/m^2). Expected completion in Q213. The rationale for combining aldoxorubicin and doxorubicin at half their MTDs is preclinical data (ovarian and pancreatic models) showing similar anti-tumour activity to single-agent aldoxorubicin and potentially better safety/tolerability.

Exhibit 8: STS background

What is STS?	Soft tissue sarcomas are malignant cancers of connective tissue. They arise from mesenchymal cells, which normally give rise to a variety of soft tissues including muscle, cartilage, fat, tendons, nerves and blood vessels. As such, STS can occur virtually anywhere in the body including the limbs (c 40%), trunk (c 40%), and head/neck (c 20%). While there are over 50 different subtypes of STS, the most common among US adults are leiomyosarcoma (smooth muscle, 21%), undifferentiated pleiomorphic sarcoma (unknown origin, 15%) and liposarcoma (fat, 13%). A recent European study mirrors this with the most common subtypes including sarcoma 'not otherwise specified' (36%), leiomyosarcoma (smooth muscle, 24%) and liposarcoma (fat tissue, 12%).
Incidence/ prevalence	STS are a rare group of tumours, accounting for around 1% of all cancers and 2% of cancer-related mortality. The median age of diagnosis is 50 years and the international incidence rates range from two to five cases per 100,000 per year. In the US, an estimated 11,280 new STS were diagnosed in 2012, with almost 4,000 deaths. In Europe, there are approximately 23,400 new cases per year in the EU27 countries. In total, we estimate that 35,000 cases of STS are diagnosed annually in the US and EU. One estimate suggests that 23,000 patients in the US (9,000) and EU (14,000) currently receive front-line chemotherapy for metastatic disease.
Treatment outline	Initial treatment for STS includes surgical resection of the primary tumour and adjuvant radiotherapy. While this achieves local control and is potentially curative, up to 40% of patients experience local recurrence or metastatic disease. These patients are treated with sequential chemotherapies with the goal of palliation. Advanced STS patients face a poor prognosis, with median survival around 12 months and two-year survival rates approaching 30%. Chemotherapy remains the backbone of therapy for advanced STS. Approved treatments include first-line doxorubicin (cytotoxic chemotherapy) and second-line pazopanib (GSK's Votrient), although imatinib (Novartis's Gleevec) is indicated for specific STS subtypes (GIST and dermatofibrosarcoma).
Front-line chemotherapy for advanced STS	Single-agent doxorubicin is the 'gold standard' first-line therapy for advanced STS, despite offering modest improvements in response rates (13-25%), PFS (4-5 months) and median OS (c 12 months). Moreover, as noted earlier, doxorubicin is associated with significant side effects including haematological toxicity (35-50% grade 3 or 4 neutropenia) and dose-dependent cardiotoxicity. Combining doxorubicin with other agents (usually ifosfamide) shows higher tumour responses and PFS than single-agent doxorubicin, but no OS improvement and greater toxicity. This was confirmed by the EORTC 62012 study, where combination therapy (doxorubicin + ifosfamide) improved PFS versus doxorubicin (7.4 vs 4.6 months; p=0.002) but showed no OS benefit (two-year OS: 31% vs 28%, p=0.06). Moreover, combo therapy had more adverse events (neutropenia: 46% vs 14%, anaemia: 14% vs 5%).
Second-line chemotherapy for advanced STS	In 2012, GSK's Votrient (pazopanib) received FDA and EMA approval for second-line STS. Results of the 369-patient Phase III PALETTE study showed modest improvements in response rates (4% vs 0%) and PFS (4.6 vs 1.6 months) versus placebo but no significant impact on OS (12.6 vs 10.7 months). Moreover, side effects caused dose interruption in 58% of patients, dose reduction in 38% and cessation in 14%. In 2007, Zeltia's Yondelis (trabectedin) gained EMA 'exceptional circumstances' approval for second-line STS, based on a 27% reduction in the risk of disease progression for advanced patients dosed every three weeks (time to progression 3.8 months) versus weekly (TTP 2.1 months). Median OS with q3weekly dosing was 13.9 months. However, most Yondelis-treated patients experienced side effects and c 10% had serious adverse events. Clearly, there is high unmet need for new agents to treat advanced STS with improved efficacy and fewer side effects.

Source: Edison Investment Research

Competitive landscape of STS drug development

Advanced STS is a challenging indication, as evidenced by the recent termination of two late-stage programmes (Sanofi's ombrabulin, Merck's ridaforolimus) due to marginal efficacy. This leaves a limited number of novel chemotherapeutic agents in Phase III development (Exhibit 9). Near-term readouts for Ziopharm's palifosfamide (PFS data, Q113) and Threshold's TH-302 (interim PFS analysis, mid-2013) are directly relevant to CytRx, as both could inform CytRx's plans for aldoxorubicin in front-line STS.

Exhibit 9: Competing STS therapies in Phase III development

Product (company)	Setting	Population	Design	Expected readout	Notes
Palifosfamide (Ziopharm)	First-line	Metastatic	Pali + Dox vs Dox; PFS primary end point, followed by OS	Q113	No SPA agreement. Powered to show three-month improvement in PFS. Headline PFS data Q113.
TH-302 (Threshold)	First-line	Locally advanced, unresectable or metastatic	TH-302 + Dox vs Dox; OS primary end point	H115	SPA agreement with FDA. Powered to show 40% improvement in OS. Interim PFS futility analysis mid-2013, interim OS analysis end-2013/early-2014, final OS data early-2015.
Eribulin (Eisai)	Second-line	Locally advanced, unresectable or metastatic L-sarcoma	Eribulin vs Dacarbazine; OS primary end point	H115	L-sarcoma is liposarcoma or leiomyosarcoma; failed first-line anthrcycline.
Trabectedin (Zeltia/J&J)	Second-line	Locally advanced, unresectable or metastatic L-sarcoma	Trabectedin vs Dacarbazine; OS primary end point	H114	L-sarcoma subtypes only; failed first-line anthracycline.

Source: Threshold Pharma, Zeltia, Ziopharm, Clinicaltrials.gov

Ziopharm's palifosfamide – headline PFS data in late-Q113

Palifosfamide is an active metabolite of ifosfamide, a DNA alkylating agent that crosslinks DNA to impede DNA replication. The randomised PICASSO Phase II study evaluated doxorubicin +/- palifosfamide in 62 patients with locally advanced or metastatic STS (mix of first- and second-line patients). The combination showed higher responses (23% vs 9%), 3.4-month PFS benefit (7.8 vs 4.4 months; HR 0.43) and an uptick in two-year OS (40% vs 30%). Grade 3 or 4 AEs included neutropenia and raised creatinine, which were reportedly similar across treatment arms. Headline PFS results from the PICASSO III Phase III study in front-line STS are expected in Q113. PICASSO III is evaluating doxorubicin +/- palifosfamide in 420 metastatic patients and is powered to show a three-month PFS benefit. Although PICASSO III is not under SPA, Ziopharm anticipates accelerated approval based on PFS data, with final OS data required for full approval. While Votrient was approved for second-line STS based on a three-month PFS benefit, there is no regulatory precedent for PFS in the front-line setting. Moreover, the EORTC 62012 study (see above) showed a 2.8-month PFS benefit for ifosfamide plus doxorubicin, no increased survival and greater toxicity. As such, we remain cautious on the approval prospects for palifosfamide in STS.

Threshold's TH-302 – interim PFS futility analysis in mid-2013

TH-302 is a hypoxia-targeted prodrug of bromoisophosphamide mustard (Br-IPM) that is activated in hypoxic (low oxygen) regions of solid tumours, which are generally located distant from tumour blood vessels. Under hypoxic conditions, TH-302 is reduced and Br-IPM released to alkylate tumour cell DNA. Doxorubicin has poor tissue penetration and targets well-oxygenated (normoxic) tumour adjacent to tumour vessels.[11] Thus, combining doxorubicin with TH-302 could lead to improved efficacy by targeting both normoxic and hypoxic regions of STS tumours.

In a dose-escalation, single-arm Phase I/II front-line study, 91 patients with locally advanced (18%) or metastatic disease (82%) received initial TH-302 plus doxorubicin (induction therapy); 48 patients then continued on single-agent TH-302 (maintenance therapy). In the entire cohort, combination therapy

11 Minchinton et al, Nat Rev Cancer 2006;6(8):583-92.

delivered a response rate of 36%, PFS of 6.7 months, and median OS of 21.5 months.[12] Patients continuing on maintenance showed improved PFS of 8.2 months and median OS of 22.5 months. Finally, the combination was well tolerated with limited haematoxicity (20% grade 3 or 4 neutropenia), manageable skin toxicity (rash) and no additive cardiotoxicity.

Initiated in Q311, the pivotal Phase III study in first-line STS is evaluating TH-302 plus doxorubicin (followed by TH-302 maintenance) versus doxorubicin alone in 450 patients with metastatic or locally advanced disease. The trial, which is under SPA, is powered to show a 40% improvement in OS. An interim PFS futility analysis (113 events) is anticipated in mid-2013 and, assuming trial continuation, the next hurdle is an interim OS analysis (175 events) around end-2013. Positive interim OS data could trigger an early regulatory filing, although there is a high hurdle for statistical significance. The more likely scenario, in our view, is trial continuation to final OS data (323 events) in early-2015.

STS market opportunity – modelling Aldoxorubicin peak sales of $425m

We model a 2016 launch for Aldoxorubicin in second-line STS and peak sales of $425m in US and EU by 2021. Our timeline assumes Phase III start in H113, completion of recruitment in H214 and headline PFS results in H115. Provided the data are positive, we anticipate US and EU regulatory submissions in mid-2015, FDA and EMA approvals in H116 and launches in H216.

We estimate that around 32,000 patients across the US (12,000) and Europe (20,000) are treated annually for front-line advanced STS (metastatic or locally advanced disease). With virtually all patients failing front-line therapy, we assume the addressable second-line population (relapsed/refractory patients) is of similar size. We model a 50% peak penetration of the second-line STS population in both the US and EU. This assumes that aldoxorubicin shows a superior risk/benefit profile to Votrient and, as such, becomes the preferred second-line option.

We conservatively assume that Aldoxorubicin is priced at c $5000 per month, which is higher than GSK's Votrient (Federal Supply Schedule price of $4,100 per month).We assume that aldoxorubicin will launch in Europe at $3,750 per month, or c 75% of the US price. Based on aldoxorubicin Phase Ib/II data, we assume that patients receive an average of six cycles spread across four months. Finally, we assume that CytRx out-licenses US and EU rights during Phase III development, with the company receiving a 20% royalty on net sales in both markets. However, our forecasts do not include potential upfront payments and commercial/development milestones from a licensing agreement.

Potential follow-on indication: Pancreatic cancer

Exploratory Phase II study in third-line setting

Initiated in Q212, a pilot Phase II study is evaluating aldoxorubicin in patients with advanced pancreatic cancer. The open-label study will enrol 27 subjects with metastatic, locally advanced or unresectable pancreatic ductal carcinoma (PDA) who have failed both gemcitabine and fluoropyrimidine-based chemotherapy (ie fluorouracil). These patients have an extremely poor prognosis, with PFS and OS of around 13 and 20 weeks, respectively, following second-line chemotherapy. The study's primary end point is Objective Response Rate (CR + PR), with secondary measures including Disease Control Rate (CR + PR + SD), PFS and safety. We anticipate headline data around mid-2013.

The rationale for aldoxorubicin in advanced pancreatic cancer is based on research showing preferential uptake of albumin by pancreatic cancer cells. Perhaps the strongest support for this approach comes from results of the Phase III MPACT study of Abraxane (an albumin-bound formulation of paclitaxel), which increased survival in combination with gemcitabine.

12 TH-302 Phase II poster, CTOS 2012.

Treatment paradigm of pancreatic cancer

Pancreatic cancer is a lethal disease and remains one of the most resistant cancers to traditional therapies (surgery, radiotherapy, chemotherapy). It is rarely curable and has a five-year survival rate of less than 4%. The majority of tumours (c 80%) are malignant adenocarcinomas of ductal epithelium and very few (c 2%) are benign. In the US, pancreatic cancer is the tenth most common site of cancer (c 3% of cases) but the fourth leading cause of cancer death (c 6% of all cancer-related deaths). In 2013, an estimated 45,000 individuals in the US will be diagnosed and 38,500 will die from the disease.

Most patients are either locally advanced (c 25%) or metastatic (c 50%) at the time of diagnosis. In these patients, systemic chemotherapy provides a limited survival benefit (Exhibit 10). Recommended first-line options include gemcitabine monotherapy (Eli Lilly's Gemzar), gemcitabine-based combination therapy (ie gemcitabine + erlotinib) or the FOLFIRINOX regimen (5-FU, leucovorin, oxaliplatin and irinotecan). In metastatic disease, gemcitabine plus erlotinib (Roche's Tarceva) showed a small increase in OS (6.4 months) versus gemcitabine (6.0 months) but higher toxicity. More recently, a European Phase III study showed better OS with FOLFIRINOX (11.1 months) than gemcitabine (6.8 months), but with a significantly higher incidence of adverse events.

Competitive landscape of pancreatic cancer drug development

There a number of novel therapies in late-stage development for advanced pancreatic cancer (see Exhibit 10). Two gemcitabine-based combinations – Celgene's Abraxane, AB Science's masitinib – recently reported positive Phase III data and could receive regulatory approval(s) in 2013 (Exhibit 10).

Exhibit 10: Efficacy of approved and late-stage agents for pancreatic cancer

Product/ regimen	Stage	Study	Setting	Treatment regimen	Median OS benefit (months)	One-year survival (%)	Hazard Ratio
Gemcitabine (Eli Lilly)	Market	Phase III	First-line	Gem vs 5-FU	1.5 (5.7 vs 4.2)	18% vs 2%	-
Erlotinib (Roche)	Market	Phase III	First-line	Erl + Gem vs Gem	0.4 (6.4 vs 6.0)	23% vs 19%	0.81
FOLFIRINOX	Market	PRODIGE	First-line	FOLF vs Gem	4.8 (11.1 vs 6.8)	48% vs 20%	0.57
Abraxane (Celgene)	Registration	MPACT	First-line	Abr + Gem vs Gem	1.8 (8.5 vs 6.7)	35% vs 22%	0.72
Masitinib (AB Science)	Registration	Phase III	First-line	Mas + Gem vs Gem	2.7 (8.1 vs 5.4) *	32% vs 18%	0.61
TH-302 (Threshold)	Phase III	Phase IIb	First-line	Gem + TH-302 vs Gem	2.3 (9.2 vs 6.9)	38% vs 26%	0.95
MM-398 (Merrrimack)	Phase III	Phase II	Second-line	MM-398 monotherapy	-	25%	-

Source: Edison Investment Research. Note: *Subgroup analysis of 137 patients with baseline pain.

Pancreatic cancer market opportunity – modelling aldoxorubicin peak sales of $389m

We model a 2017 launch for aldoxorubicin in second-line pancreatic cancer (locally advanced and metastatic disease) and peak sales of $389m in US and EU by 2022. This timeline assumes positive Phase II data in H113, initiation of Phase III in H114, headline data in H216 and regulatory approvals/launches in H217. We estimate that the addressable market for second-line pancreatic cancer is around 36,000 patients annually in the US and a slightly higher number in Europe. These figures are based on annual death rates (US: 37,000 in 2012; EU: c 39,000 in 2008), which we believe provide a reasonable proxy for the second-line population.[13] In both territories, we assume a 20% peak market penetration, four-month duration of use (six cycles) and similar pricing to the STS indication. Finally, we estimate that CytRx receives a 20% royalty on net sales from a potential licensing partner.

13 Globobcan 2008, SEER 2012.

Tamibarotene: Phase II lung cancer data in Q313

Summary: Novel retinoid in Phase II for first-line lung cancer

Tamibarotene (formerly INNO-507) is a novel, orally available, synthetic retinoid that is already marketed in Japan for the treatment of second-line acute promyelocytic leukaemia (APL). The drug was designed to be safer and more effective than all-trans retinoic acid (ATRA), a first-generation retinoid indicated for front-line APL. CytRx is conducting a Phase IIb study of tamibarotene in first-line NSCLC, which is based on positive Phase II results for ATRA in this indication. The company holds US and EU rights for the NSCLC indication and retains an option for other oncology settings.

Preclinical data: Potent and targeted synthetic retinoid

Retinoids suppress tumour growth by binding to intracellular retinoic acid receptors (RAR) and regulating gene expression (ie genes associated with cellular proliferation and differentiation). Tamibarotene is a specific agonist of RAR that binds with similar affinity to the RAR-alpha and RAR-beta when compared to ATRA. However, unlike ATRA, tamibarotene does not bind to RAR-gamma.[14] This specificity means that tamibarotene may exhibit fewer side effects than ATRA, particularly as RAR-gamma is the major RAR in the skin. Tamibarotene is also 10 times more potent than ATRA when tested in specific leukaemia cell lines (HL-60, NB-4).[15]

Positive Phase II lung cancer data for ATRA

The rationale for testing tamibarotene in NSCLC is based on Phase II results with ATRA in this cancer. This single-centre Mexican study evaluated chemotherapy (cisplatin and paclitaxel, PC) plus ATRA in the front-line treatment of advanced NSCLC (Stage IIIb/IV).[16] A total of 107 subjects received PC and were randomly assigned to receive ATRA or placebo one week before treatment and during two cycles of chemotherapy. Results showed that the addition of ATRA led to significantly higher overall response rates (56% vs 25%, p=0.001), longer median PFS (8.9 vs 6.0 months, p=0.008) and improved survival (24 vs 10 months, p=0.004). The key caveats, in our view, were the small study size and higher rate of CNS metastases in control patients (29% vs 15%). Aside from an increase in hypertriglyceridemia (10% vs 0%), a known manifestation of ATRA therapy, there were no significant differences in grade 3 or 4 toxicity between the treatment groups.

First-line Phase II study in advanced NSCLC

A global Phase IIb study is evaluating whether PC plus tamibarotene improves PFS and ORR in front-line patients with advanced NSCLC. Secondary end points include overall survival. The randomised, placebo-controlled trial will recruit 140 subjects with stage IIIb or IV tumours (squamous and non-squamous) at clinical sites across the US, Mexico, Europe and Asia. Results of a recent Data Safety Monitoring Committee (DSMB) identified no significant safety issues and advised continuing the trial through completion. Headline results are expected in Q413.

NSCLC market opportunity – modelling tamibarotene peak sales of $650m

An estimated 230,000 new lung cancer diagnoses (non-small cell and small cell combined) will be diagnosed in the US in 2013, accompanied by more than 160,000 disease-related deaths.[17] This makes lung cancer the leading cause of cancer-related mortality in the US. Across Europe, there are an estimated 400,000 new diagnoses and 360,000 deaths annually. Globally, there are over 1.6m annual diagnoses and approximately 1.4m cancer-related deaths. NSCLC accounts for around 90% of

14 Naina et al, J Clin Oncol 2011;29(18):534-536.
15 Di Veroli et al, J Haematol 2010;151(1):99-101.
16 Arrieta et al, J Clin Oncol 2010;28(21):3463-3471.
17 Cancer.gov.

all lung cancers and around 60% are advanced (Stage IIIb or IV) at diagnosis. Treatment options for advanced NSCLC include cytotoxic chemotherapy and targeted agents. First-line options include doublet chemotherapy with platinum (ie cisplatin) and other agents (ie paclitaxel, pemetrexed), targeted therapies (bevacizumab, cetuximab, erlotinib, crizotinib) and, potentially, maintenance therapy (ie erlotinib). In fit patients, platinum/new agent combos have shown a plateau in ORR (25-35%), PFS (4-6 months), median OS (8-10 months) and one-year survival rate (30-40%).

We estimate that the addressable market for front-line NSCLC includes approximately 100,000 patients in the US (excluding EGFR and ALK+ patients) and around 180,000 in Europe. Provided Phase IIb data are positive and CytRx secures a partnership, we assume that tamibarotene could have a NSCLC indication by 2018 in both territories. To arrive at peak sales of $650M in 2024, we assume a 20% market penetration, four-month duration of use and monthly pricing of $3,000. We estimate that CytRx could receive a net 12.5% royalty on in-market sales, equating to peak revenues of $81m.

Bafetinib: Phase II completed, licensing potential

Bafetinib (formerly INNO-406) is an orally available, potent and targeted second-generation tyrosine kinase inhibitor (TKI). It works by blocking the Bcr-Abl, Fyn and Lyn kinases, which are implicated in a range of solid and haematological cancers. The drug's potent inhibition of Fyn and Lyn are key differentiators versus existing TKIs. Originally discovered by Nippon Shinyaku, CytRx gained global rights (ex-Japan) to bafetinib following the Innovive acquisition. The drug has completed a Phase I study in Philadelphia (Ph) chromosome-positive leukaemias (CML, ALL) and a Phase II study in B-CLL, both of which showed clinical activity and acceptable safety. CytRx is now seeking to partner bafetinib for ongoing development and commercialisation. We currently assign no value to the product, which means a licensing deal would represent pure upside to our valuation and forecasts.

Valuation

We value CytRx at $120m, or $4.00 per share, based on a risk-adjusted NPV analysis. The breakdown of our rNPV valuation, which uses a 12.5% discount rate, is shown in Exhibit 11. We model cash flows for aldoxorubicin and tamibarotene from product launch through to expiration of market exclusivity (ie patent expiry, loss of orphan status). We assume both products are out-licensed, with net royalty rates (including 5% royalty pay away) of 20% for aldoxorubicin and 12.5% for tamibarotene. However, we do not model potential upfront payments or milestones from partnerships. Finally, our rNPV includes projected end-2013 cash of $15.7m. The company could raise an additional $28.7m from exercise of 6.4m warrants from a 2011 financing. However, with the exercise price ($4.48) well above the current share price and our valuation, we believe it is prudent to exclude these from our financial model.

Exhibit 11: Breakdown of rNPV valuation

Product	Indication	rNPV ($m)	rNPV/share ($)	Prob. of success	Launch	Peak sales ($m)	Net royalty estimate	Patent expiry
Aldoxorubicin	Second-line STS	70.1	2.5	40%	2016	425	20%	2021
Aldoxorubicin	Second-line Pancreatic Cancer	34.0	1.1	25%	2017	389	20%	2021
Tamibarotene	First-line NSCLC	43.7	1.4	40%	2018	650	15%	2027
R&D		(28.9)	(1.0)					
SG&A		(13.9)	(0.5)					
Capex		(0.3)	(0.0)					
Net cash		15.7	0.5					
Total		**120.2**	**4.0**					

Source: Edison Investment Research

For aldoxorubicin in second-line STS, we apply a conservative 40% probability of success pending an SPA grant (rises to 50%) and Phase II data in front-line STS (rises to 60%). We currently assign no value to aldoxorubicin in the front-line STS indication, although positive data would increase our confidence in the second-line opportunity and unwind our risk adjustment. Together, an SPA agreement and positive front-line data would increase our rNPV by c 30% to $5.10 per share. As aldoxorubicin represents the largest part of our valuation, we conducted a scenario analysis to assess the impact of different price, market share and risk adjustments on our rNPV (see Exhibits 12 and 13).

Exhibit 12: rNPV with different aldoxorubicin price and penetration assumptions

		Aldoxorubicin price		
		$2,500	$5,000	$7,500
Market penetration	25%	2.2	2.8	3.4
	50%	2.8	4.0	5.1
	75%	3.4	5.1	6.8

Source: Edison Investment Research

Exhibit 13: rNPV with different aldoxorubicin risk-adjustment and penetration assumptions

		Aldoxorubicin prob. of success		
		40%	60%	80%
Market penetration	25%	2.8	3.4	4.0
	50%	4.0	5.1	6.3
	75%	5.1	6.8	8.6

Source: Edison Investment Research

For tamibarotene, we currently model a 40% probability of success for the drug in front-line NSCLC. Depending on the detail and strength of the Phase IIb data, our rNPV could rise by a further c 18%.

Sensitivities

CytRx is exposed to the usual biotech company development risks, the unpredictable outcomes of clinical trials, decisions by regulators, success of competitors, financing and commercial risks. In particular, investors should be aware that aldoxorubicin has been tested in a relatively limited number of patients (66 in total) in Phase I/II studies. While the results in these subjects are encouraging, the limited dataset makes it difficult to call the outcome of future clinical studies. CytRx has attempted to reduce these clinical and development risks by targeting second-line STS as the initial indication for aldoxorubicin: the doxorubicin component is already indicated for STS; aldoxorubicin showed encouraging results in heavily pretreated relapsed/refractory STS patients; second-line STS is a poorly served indication with high unmet medical need; and there is a clear path to registration, namely an SPA for the Phase III trial (expected Q213), Orphan drug designation (already granted by the FDA) and potential for FDA Fast Track designation and Priority Review.

The key near-term sensitivity is aldoxorubicin Phase II data in front-line STS, where headline data are expected in Q313. This head-to-head comparison with doxorubicin will provide the first randomised data for aldoxorubicin in STS. Results favouring aldoxorubicin could broaden the product's commercial potential and, importantly, would increase our confidence in the second-line opportunity. Thus, positive data could drive a significant re-rating in CytRx's valuation. Conversely, negative data would not only eliminate the first-line indication, but could also raise questions about aldoxorubicin's utility in the second-line setting after the pivotal Phase III study is already underway.

Financials

CytRx had cash and short-term investments of $22.5m as of 30 September 2012 and a nine-month operating cash burn of $13.5m. However, CytRx subsequently raised $21.4m from an underwritten public offering in October 2012, which was priced at a c 20% discount to the market price. We estimate that the company has, in the absence of licensing deals or warrant exercise (potentially raising $28.7m), sufficient cash to operate until late-2014.

Exhibit 14: Financial summary

$'000s	2011	2012e	2013e	2014e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	250	100	100	100
Cost of Sales	0	0	0	0
Gross Profit	250	100	100	100
R&D Expenses	15,491	13,545	14,899	16,389
SG&A Expenses	7,317	7,400	7,474	7,549
EBITDA	(21,958)	(20,445)	(21,873)	(23,438)
Operating Profit (before amort and except)	(22,006)	(20,503)	(21,933)	(23,498)
Intangible Amortisation	(48)	(58)	(60)	(60)
Exceptionals	0	0	0	0
Other	7,520	(6,319)	(300)	(300)
Operating Profit	(14,534)	(26,880)	(22,293)	(23,858)
Net Interest	207	125	133	19
Profit Before Tax (norm)	(21,799)	(20,378)	(21,800)	(23,478)
Profit Before Tax (FRS 3)	(14,327)	(26,755)	(22,160)	(23,838)
Tax	(98)	0	0	0
Profit After Tax (norm)	(13,777)	(26,297)	(21,700)	(23,378)
Profit After Tax (FRS 3)	(14,425)	(26,755)	(22,160)	(23,838)
Average Number of Shares Outstanding (m)	125.6	30.4	30.4	30.4
EPS - normalised ($)	(0.11)	(0.86)	(0.71)	(0.77)
EPS - normalised and fully diluted ($)	(0.11)	(0.71)	(0.59)	(0.63)
EPS - (IFRS) ($)	(0.11)	(0.88)	(0.73)	(0.78)
Dividend per share ($)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	573	596	696	796
Intangible Assets	184	184	184	184
Tangible Assets	266	302	402	502
Investments	123	110	110	110
Current Assets	37,282	38,893	16,994	1,415
Stocks	0	0	0	0
Debtors	176	83	83	83
Cash	36,047	37,569	15,670	91
Other	1,059	1,241	1,241	1,241
Current Liabilities	(13,600)	(20,600)	(2,584)	(2,584)
Creditors	(6,861)	(7,881)	(2,584)	(2,584)
Deferred revenue	(6,739)	(12,719)	0	0
Short term borrowings	0	0	0	0
Long Term Liabilities	0	0	0	(8,000)
Long term borrowings	0	0	0	(8,000)
Other long term liabilities	0	0	0	0
Net Assets	24,255	18,889	15,106	(8,373)
CASH FLOW				
Operating Cash Flow	(16,671)	(19,842)	(21,873)	(23,438)
Net Interest	0	125	133	19
Tax	0	0	0	0
Capex	(53)	(160)	(160)	(160)
Acquisitions/disposals	6,938	0	0	0
Financing	18,940	21,400	0	0
Dividends	0	0	0	0
Other	0	0	0	0
Net Cash Flow	9,154	1,523	(21,900)	(23,578)
Opening net debt/(cash)	(26,892)	(36,047)	(37,569)	(15,670)
HP finance leases initiated	0	0	0	0
Other	0	0	0	0
Closing net debt/(cash)	(36,046)	(37,570)	(15,669)	7,908

Source: Edison Investment Research. Note: Financial model assumes additional $8m financing (long-term debt) in late-2014, which is shown in balance sheet as a long-term liability.

Contact details	Revenue by geography
11726 San Vicente Blvd, Suite 650 Los Angeles, CA 90049 +1 310 826 5648 www.cytrx.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2010-14e	N/A	ROCE 2013e	N/A	Gearing 13e	N/A	Litigation/regulatory	●
EPS 2012-14e	N/A	Avg ROCE 2010-14e	N/A	Interest cover 13e	N/A	Pensions	○
EBITDA 2010-14e	N/A	ROE 13e	N/A	CA/CL 13e	N/A	Currency	○
EBITDA 2012-14e	N/A	Gross margin 13e	N/A	Stock days 13e	N/A	Stock overhang	◖
Sales 2010-14e	N/A	Operating margin 13e	N/A	Debtor days 13e	N/A	Interest rates	○
Sales 2012-14e	N/A	Gr mgn / Op mgn 13e	N/A	Creditor days 13e	N/A	Oil/commodity prices	○

Management team

President and CEO: Steven A. Kriegsman

Mr Kriegsman has been president and CEO since July 2002 and serves on board of directors. Also serves as a director of Galena Biopharma. He was previously director and chairman of Global Genomics (from June 2000), chairman and founder of Kriegsman Capital Group, a specialist healthcare financial advisory firm, and director at Bradley Pharma (sold to Nycomed).

EVP and Chief Medical Officer (CMO): Dr Daniel Levitt, MD, PhD

Mr Levitt has been CMO since October 2009 and has over 24 years' biopharmaceutical industry experience. He was previously CMO and head of Clinical and Regulatory Affairs at Dynavax, COO and head of R&D at Affymax, president and head of R&D at Protein Design Labs, head of Global Clinical Oncology at Sandoz and director, Clinical Oncology at Roche.

Chief Financial Officer (CFO): John Y Caloz

Mr Caloz has been CFO since January 2009, having joined in October 2007 as Chief Accounting Officer. He was previously CFO of Occulogix, CFO of IRIS International; CFO of Synarc, and SVP and CFO of Phoenix International Life Sciences (acquired by MDS).

SVP, Drug Development: Scott Wieland, PhD

Mr Wieland has been SCP, Drug Development since December 2008, having joined in 2005 as VP, Clinical and Regulatory Affairs. He was previously VP, Product Development at NeoTherapeutics and director of Regulatory Affairs at CoCensys.

Principal shareholders	(%)
Management/Insiders	17.6%
Baker Bros. Advisors	3.3%
Sabby Capital	2.3%
Barclays Global Investors	1.3%
Allianz Asset Management	1.3%

Companies named in this report

Orphazyme ApS, Celgene (CELG), GlaxoSmithKline (GSK), Threshold Pharmaceuticals (THLD), Ziopharm Oncology (ZIOP), Eisai (ESALY), Zeltia (ZEL), Johnson & Johnson (JNJ), Eli Lilly (LLY), Roche (ROG), AB Science (AB), Merrimack (MACK), Nippoon Shinyaku (NPNKF).