EDISON

Sierra Oncology

Clinical update

Progress with ongoing trials and future plans

Pharma & biotech

Sierra Oncology held an investor meeting on 27 February 2018, which provided a comprehensive update on its programs. The most immediately impactful data was a favourable safety profile reported from the ongoing Phase I/II clinical trials (monotherapy and gemcitabine combination). It was announced that the monotherapy trial had entered the Phase II dose-expansion portion of the trial and that the combination study will enter this phase in Q218. Preliminary results for this trial are expected in Q418.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/16	0.0	(41.4)	(1.37)	0.0	N/A	N/A
12/17	0.0	(36.0)	(0.72)	0.0	N/A	N/A
12/18e	0.0	(45.9)	(0.65)	0.0	N/A	N/A
12/19e	0.0	(50.5)	(0.68)	0.0	N/A	N/A

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

SRA737 safety largely in line with expectations

The safety data for the two ongoing SRA737 trials largely showed an adverse events (AEs) profile similar to other drugs of its class (including gastrointestinal and hematological), albeit less severe (predominantly Grade 1 and 2). The monotherapy trial had one heart failure serious AE that could not be ruled out as drug related, but we do not consider this concerning in isolation. The current safety profile is attractive compared to other Chk1 inhibitors in development, and we will monitor whether it can be maintained through the expansion cohorts.

Both SRA737 clinical trials expanded

The company announced that it has amended the clinical trial protocol for both the monotherapy and combination trials to expand the number of indications under investigation, and the number of patients in each cohort to 20 (from eight). The new indications will be CCNE1-driven, high-grade serous ovarian cancer in the monotherapy trial, and small cell lung cancer, sarcoma and cervical/anogenital cancer in the combination trial (pancreatic cancer has been removed).

PARP inhibitor combination study on deck

The company also provided preclinical data to support the recently announced combination study with SRA737 and Zejula (niraparib, Janssen/Tesaro) in metastatic castration-resistant prostate cancer. The hope is that dual inhibition of two DNA damage-response mechanisms will synergistically enhance the activity of these drugs and provide broader efficacy. The trial is slated to start in Q418.

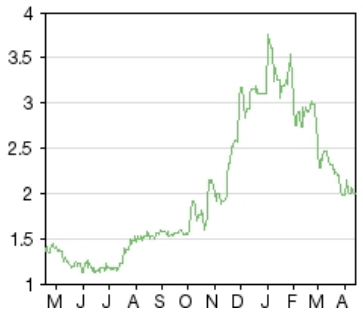
Valuation: Increased to $330m or $4.44 per share

We have increased our valuation of Sierra to $330m or $4.44 per basic share from $206m or $3.95 per basic share. This is mainly driven by an increase in the probability of success for SRA737 to 25% from 15% based on the new safety data and new cash from the March 2018 offering (19m shares at $2.25). The increase is partially offset by increased R&D costs and higher share count.

16 April 2018

Price	**US$1.99**
Market cap	**US$148m**
Net cash ($m) at end FY17 + offering + greenshoe	146.2
Shares in issue (incl. greenshoe)	74.3m
Free float	62%
Code	SRRA
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(16.4)	(38.8)	41.1
Rel (local)	(13.0)	(35.8)	23.7
52-week high/low	US$3.8	US$1.1	

Business description

Sierra Oncology is developing new therapies targeting the DNA damage response to treat cancer. It is in Phase I/II clinical trials with SRA737, an inhibitor of Chk1, both as a monotherapy and in combination with low-dose gemcitabine, and there is a planned Phase Ib/II in combination with the PARPi niraparib in Q418. It is also is in preclinical development of SRA141, a Cdc7 inhibitor with a different DNA damage response mechanism.

Next events

SRA737 gem combo Phase II expansion	Q218
SRA737 monotherapy preliminary data	Q418
SRA737 gem combo update	Q418
SRA737 + niraparib mCRPC Phase Ib/II initiation	Q418

Analysts

Nathaniel Calloway +1 646 653 7036

Maxim Jacobs +1 646 653 7027

healthcare@edisongroup.com

Edison profile page

A big day of updates for SRA737

On 27 February 2018, Sierra provided a comprehensive update on its clinical programs for the development of SRA737. SRA737 is an inhibitor of Chk1, a key protein for the regulation of the replication stress response (for a useful review of the replication stress response and cancer, see Forment & O'Connor 2018).[1]

Initial safety data were provided for both the SRA737 monotherapy and gemcitabine combination studies. The company has decided to expand both the number of indications being examined and the number of patients per cohort for both of these studies, increasing the combined enrolment in the Phase II portions to 200. It announced that the SRA737 monotherapy study has already progressed to the Phase II dose-expansion portion of the trial, which is enrolling well across the genetic subtypes being examined, and that it intends to enter the Phase II portion of the combination study in Q218.

The company also provided a rationale for a study examining SRA737 in combination with the poly ADP-ribose polymerase (PARP) inhibitor, Zejula (Janssen/Tesaro). The company concurrently announced that it had reached an agreement with Janssen to provide the drug for a Phase Ib/II study in patients with metastatic castration-resistant prostate cancer (mCRPC). The study is expected to initiate in Q418. In other news, the company provided an up-to-date timeline for the initiation of an SRA737/immuno-oncology combination study for which it expects to have clinical trial authorization in Q418. Finally, it announced that its Cdc7 inhibitor SRA141 should have a completed IND application submitted in H218.

SRA737 monotherapy dose-escalation complete

In February 2018, the company completed the dose-escalation portion of its ongoing SRA737 monotherapy trial after enrolling 11 patients and proceeded to the expansion portion of the trial (20 patients enrolled at the time of the update). The Phase I/II clinical trial was designed with two phases:

- A Phase I ascending dose portion. Patients were all comers and not preselected based on genetic criteria. Readouts are maximum tolerated dose and safety.
- A Phase II dose-expansion cohort in patients with mutations potentially conferring sensitivity to SRA737. Readouts are efficacy and safety.

The dose escalation identified 1,000mg a day as the maximum tolerated dose, following two dose-limiting toxicities (DLTs) experienced at the 1,300mg dose. Per the protocol, a DLT is defined as events preventing the patient from receiving at 75% of the planned dose, in this case triggered by two cases of GI intolerability. The company is also currently investigating 500mg twice a day as an alternative to the single daily dose.

The adverse event (AE) profile observed in the trial (from all 31 patients to date) is described in Exhibit 1. The most common AEs were fatigue and GI related (over 20% of events combined), and a majority of events were Grade 1 or 2. Neutropenia and other hematologic toxicities were also observed in the trial and, although most cases were Grade 1 or 2, there were two Grade 3 reports at high doses, one of which was a serious adverse event (SAE).

[1] Forment JV and O'Connor MJ (2018) Targeting the replication stress response in cancer. *Pharmacol & Thereapuetcs,* online 24 March 2018.

Exhibit 1: SRA737 adverse event profile

Adverse events	Notes
Hematologic	Grade 3 neutropenia in two patients (7%) at 1,300mg and 1,000mg
	One grade 3 was an SAE
	<20% with grade 1, 2
GI	Two GI related DLTs (inability to receive 75% of planned dose) at 1300mg QD
	Grade 3 nausea in two patients (7%)
	Remaining cases primarily Grade 1
Cardiac	One Grade 3 heart failure/cardiomyopathy (SAE)

Source: Sierra Oncology

Both GI and hematologic AEs are consistent with the mechanism of action of the drug, and are common for this class. Previous reports of AEs for the Chk1 inhibitor prexasertib (Eli Lilly) also showed these events. Although the results are not strictly comparable due to different trial structures, in one recent study prexasertib showed significantly more AE of these types in Phase II: 64% of patients (out of 28) experienced Grade 1 nausea and 93% of patients experienced neutropenia, 79% at Grade 4.[2] The AE profile of Genentech's second-generation Chk1 also shows more common events: 80% neutropenia and 46% nausea as the most common of these two classes (all grades).[3]

There was one other SAE: a Grade 3 heart failure in a patient in the 1000mg cohort. The company (as well as invited speakers) noted that this patient had rapidly progressing disease, which could contribute to cardiac events, although it cannot be ruled out as a drug effect. Dose-limiting heart failure (as well as a dose-limiting troponin increase) was seen in clinical trials of the first-generation Chk1 inhibitor AZD7762 (AstraZeneca) However, these AEs were considered off target effects and heart failure is not a feature of this class of drug (although MK-8776 from Merck did show dose-limiting QT prolongation). Due to its isolated nature, we do not consider this event to be of particular concern at this point.

Phase II enrolling well across tumor genetics

The company has already begun enrolling patients into the Phase II expansion portion of the monotherapy trial at three pilot sites. This portion of the trial, unlike the Phase I portion, will only enrol patients with certain predefined genetic tumor backgrounds expected to respond to SRA737. A potential concern is that, given the many different combinations of mutations and tumor types, the expected prevalence of these different subgroups would not be born out in the clinic, and there would be gaps in the data set. A host of clinical factors could contribute to these issues, if for instance doctors favoured certain therapies over this clinical trial for a particular group or if the prognosis for a particular group was too poor to enable enrolment.

At the investor update, the company reported that patients are being enrolled in accordance with the underlying rates of these tumor mutations. Although only 20 patients have been enrolled, eight of the 16 highlighted subgroups have enrolled at least one patient (Exhibits 2 and 3). The company announced that it is expanding the cohort size for each cancer type to 20 patients (from eight), and we believe that with these encouraging early data, it should provide sufficient coverage of the expected genotypes.

2 Lee JM, et al. (2018) Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in BRCA wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study. *Oncology* 19, 207-215.

3 Italioano A (2017) Phase I study of the checkpoint kinase 1 inhibitor GDC-0575 in combination with gemcitabine (gem) in patients (pts) with refractory solid tumors. *Ann Oncology.* 28, mdx367.009.

Exhibit 2: Expected prevalence of subgroups

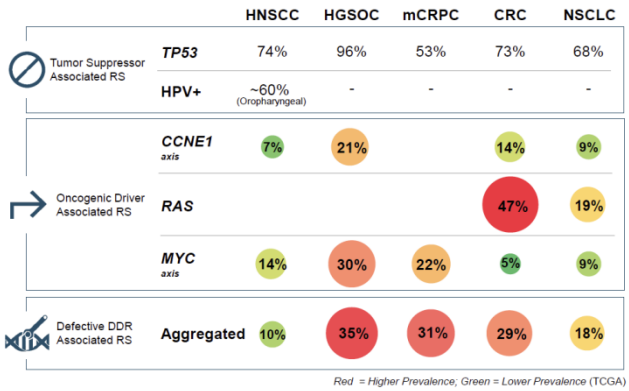
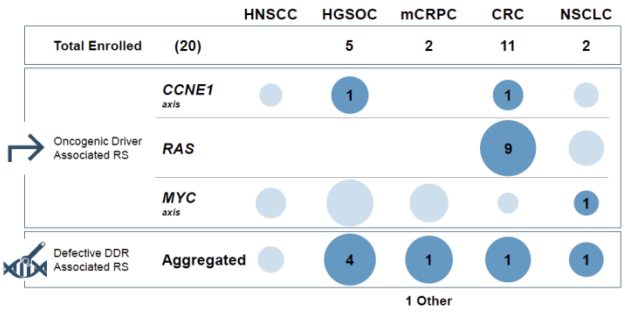


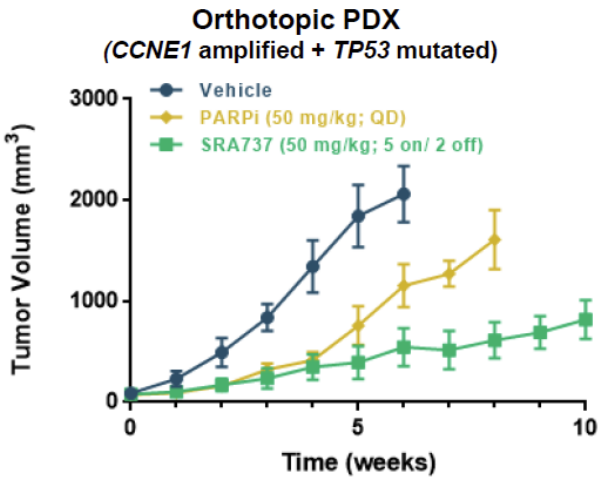
Exhibit 3: Real enrolment of subgroups



Source: Sierra Oncology. Note: HNSCC = head and neck squamous cell carcinoma. HGSOC = high-grade serous ovarian cancer. mCRPC = metastatic castration-resistant prostate cancer. CRC = colorectal cancer. NSCLC = non-small cell lung cancer.

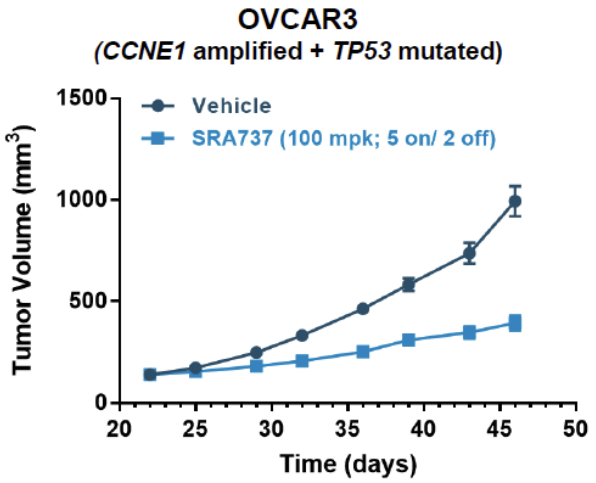
One factor that the company has highlighted in this release is the inclusion of mutations along the CCNE1 axis as a genetic subgroup it is monitoring, although only two patients have been enrolled in this set to date. CCNE1 is the gene expressing cyclin E1, a protein important for cell cycle progression (similar to Chk1) and a known tumor driver. In Q118, the company amended the trial protocol to include CCNE1-driven, high-grade serous ovarian cancer (HGSOC) as a new cohort (in addition to the previous platinum-resistant ovarian cancer cohort), bringing the expected total enrolment for the trial to 120 patients. There is increasing evidence of CCNE1 as a tumor driver that induces replication stress.[1] Recent Phase II results of prexasertib in ovarian cancer identified a higher response rate in patients with a mutation or amplification this gene.[2] The company additionally presented its own preclinical data supporting the activity of SRA737 in this subgroup (Exhibits 4 and 5). The company will be presenting additional information on the activity of SRA737 in CCNE1 driven ovarian cancer at the American Association of Cancer Research (AACR) meeting in April 2018.

Exhibit 4: Patient derived xenograft model of HGSOC



Source: Sierra Oncology

Exhibit 5: OVCAR3 cell line model of HGSOC



Source: Sierra Oncology

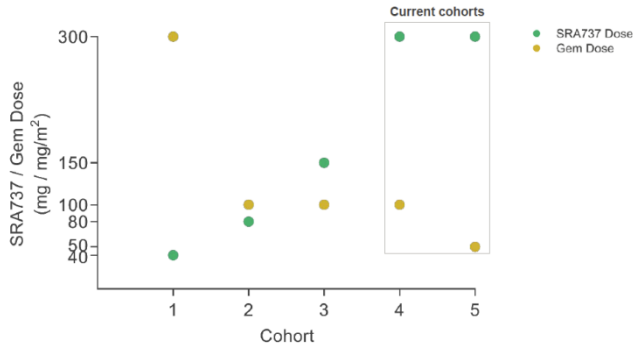
The company has guided to preliminary data being available from the trial at a medical conference in Q418.

Low-dose gemcitabine trial update

The company is still in the dose-escalation portion of its Phase I/II trial of SRA737 in combination with low-dose gemcitabine. The trial is examining a range of doses for each drug to find the optimal

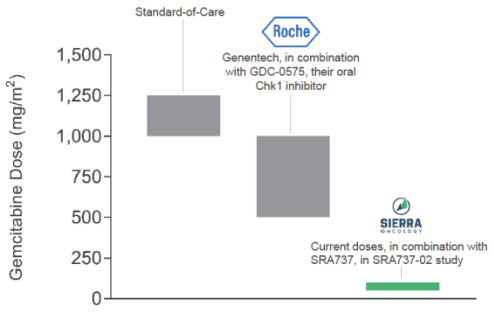
combination (Exhibit 6). Gemcitabine is an inducer of replication stress and can directly potentiate the clinical activity of SRA737, even at low concentrations. The company is therefore examining concentrations of gemcitabine that are dramatically lower than cytotoxic levels (Exhibit 7).

Exhibit 6: Doses of SRA737 and gemcitabine in dosing cohorts



Source: Sierra Oncology

Exhibit 7: Gemcitabine dose ranges



Source: Sierra Oncology

The company provided some preliminary safety data from the combination study, which were also in line with expectations. GI and hematological AEs dominated, but were mostly Grade 1 and 2. One Grade 3 neutropenia was seen with the highest dose of gemcitabine (40mg SRA737, 300mg gemcitabine). Two SAEs were observed: a Grade 1 fever and a Grade 2 deep vein thrombosis, which we do not consider to be of particular concern.

Similar to the monotherapy trial, the company is expanding the number of indications and the number of patients it is enrolling in each cohort for this study. The upcoming Phase II portion of the trial will enrol patients with small cell lung cancer, sarcoma and cervical/anogenital cancer in addition to the previous indication of bladder cancer. Pancreatic cancer has been removed from the protocol as a target indication. Additionally, each of these cohorts will now enrol a target of 20 patients. The Phase II cohort expansion potion of the trial is expected to start in Q218, and the company has stated that it anticipates providing an update in Q418.

Janssen to provide Zejula for PARP inhibitor combo study

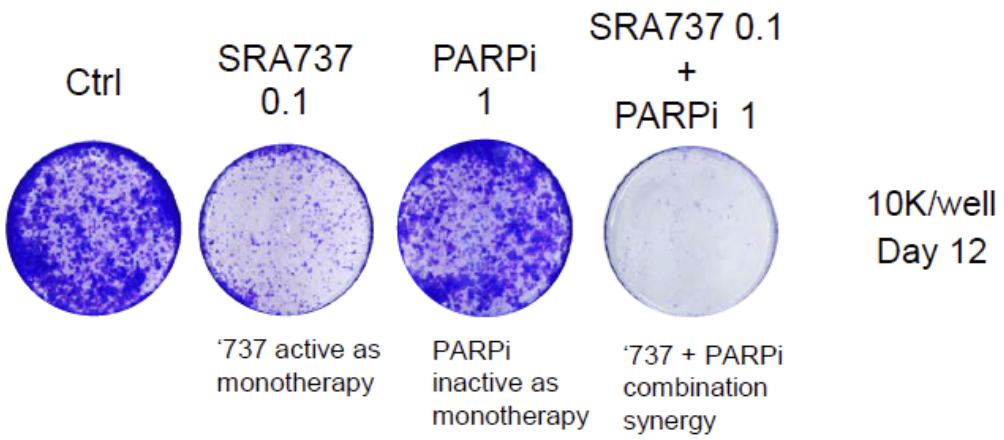
The company has long stated its intent to examine the potential synergies of SRA737 with PARP inhibitors. PARP is a protein important for the DNA damage response (DDR), similar to Chk1 targeting by SRA737, although along a different axis. Therefore, the company has been interested in learning whether a combination strategy of inhibiting multiple DDR axes can improve clinical responses or expand the array of indications these drugs can effectively treat. There are currently three approved PARP inhibitors: Lynparza (olaparib, AstraZeneca), Rubraca (rucaparib, Clovis), and Zejula (niraparib, Tesaro/Janssen), all of which are approved to treat BRCA1/2 mutated cancers (ovarian and related cancers, Lynparza also approved for HER2-negative metastatic breast cancer).

The protein PARP is important for repairing DNA single-strand breaks and, when this pathway is inhibited, these single-strand breaks can become further damaged to double-strand breaks, which are repaired via the cell's homologous recombination (HR) pathway. Cancer cells that are deficient in HR are particularly sensitive to PARP inhibition, which can occur with mutations to the BRCA1 and BRCA2 proteins (among others). The logic behind combining SRA737 with a PARPi is that Chk1 is also a key regulator of HR, and perhaps its inhibition can replicate the synthetic lethality seen in BRCA1/2 mutants.

A common resistance mechanism to PARP inhibitors is reversion of mutated BRCA1/2 to a functional form, restoring homologous recombination. SRA737 could potentially overcome BRCA1/2 reversion to restore activity following PARPi resistance because it inhibits HR through a

different mechanism. The company has provided some preliminary *in vitro* evidence that SRA737 has a synergistic anti-cancer activity with PARP inhibition in PARP-resistant tissue cultures (Exhibit 8). The company will be presenting additional data on the activity of SRA737 in PARP resistant ovarian cancer at the AACR meeting in April 2018.

Exhibit 8: Synergistic activity of SRA737 and PARP inhibition *in vitro*



Source: Sierra Oncology. Note: Shows stained PEO1-PR cells, from HGSOC, which developed PARP inhibitor resistance, units in μM.

The company announced that it has entered into an agreement with Janssen to provide Zejula for an upcoming Phase Ib/II combination study with SRA737 in patients with mCRPC. We expect the trial to be of a similar dose ranging/expansion format to the current ongoing Phase I/II trials and to examine an array of tumor mutations. It is expected to initiate in Q418.

Valuation

We have increased our valuation of Sierra to $330m or $4.44 per basic share from $206m or $3.95 per basic share. This upgrade is driven largely by an increase in our probability of success for the SRA737 to 25% from 15% based on the release of safety data from the Phase I portions of the ongoing clinical trials. We are encouraged by the data and believe that it will favorably position SRA737 among competitors if it can be maintained in the dose-expansion cohorts. This could be stymied if there are additional reports of cardiac AEs but, given the isolated nature of the currently reported event, we are remaining optimistic. Additionally, we have increased our valuation from advancing our NPVs and to reflect the increased cash following the March 2018 offering ($146m total, after including net proceeds from the offering and greenshoe). The upward adjustments are partially mitigated by an increase in our negative NPV (to year-end 2017) for development costs (increased probability of success and increased clinical trial costs associated with the trial expansions), and a higher share count.

There are multiple potential upcoming events in which we expect to update our valuation. First, if the complete safety data from the Phase I portion of the gemcitabine combination study remain in line with the current safety data, in particular if no cardiac events are observed, it will increase our confidence. As a reminder, because the company has not currently selected a target indication, our projected sales for the product are a proxy composed of multiple announced indications. As more data on the efficacy in the subgroups become available, we expect to hone this estimate and, if activity is seen across multiple indications, we may adjust our projected sales. Moreover, we may adjust our estimates with the inclusion of additional avenues of treatment such as SRA737 in combination with PARP inhibition or immuno-oncology agents. Finally, we expect to add SRA141 to our model once it has entered the clinic.

Exhibit 9: Valuation of Sierra Oncology

Development program	Region	Prob. of success	Launch year	Peak sales ($m)	Margin	rNPV ($m)
SRA737	US	25%	2023	562	55%	135.9
SRA737	Europe	25%	2023	471	53%	111.0
SRA737		Development costs				(34.4)
Unallocated costs						(29.1)
Total						$183.4
Net cash and equivalents (YE17 + offering + greenshoe) ($m)						$146.2
Total firm value ($m)						$329.7
Total shares (m)						74.3
Value per share ($)						$4.44
Options (m)						4.00
Total diluted shares						78.3
Value per diluted share ($)						$4.37

Source: Sierra reports, Edison Investment Research

Financials

The company reported its 2017 financial results on 27 February 2018. It reported an operating loss of $42.6m for the year, driven by R&D expenses of $30.2m. We expect R&D spending to increase in 2018 to $39.7m due to the advancement of the clinical trials. We have increased this estimate since our last report (from $36.3m) due to the expanded ongoing clinical programs. The company ended the year with $100.3m in cash, but in March 2018 supplemented this by completing an offering of 19m shares at $2.25 ($42.75m gross, estimated $39.9m net, 2.85m shares/$6.0m net in greenshoe), which we expect to provide a runway into 2020. Our new expected financing schedule is $50m in 2020 and $80m in 2022 before approval of SRA737 in 2023, from $170m total previously.

Exhibit 10: Financial summary

$000s	2015	2016	2017	2018e	2019e
31-December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
INCOME STATEMENT					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
Gross Profit	0	0	0	0	0
R&D	(26,356)	(33,895)	(30,157)	(39,661)	(44,008)
SG&A	(9,472)	(14,180)	(12,462)	(12,522)	(12,772)
EBITDA	(32,531)	(41,557)	(36,456)	(46,278)	(50,875)
Operating profit (before amort. and except).	(32,642)	(41,754)	(36,714)	(46,278)	(50,875)
Amortisation of acquired intangibles	0	0	0	0	0
Exceptionals	0	(811)	0	0	0
Share-based payments	(3,186)	(5,510)	(5,905)	(5,905)	(5,905)
Reported operating profit	(35,828)	(48,075)	(42,619)	(52,183)	(56,780)
Net Interest	66	351	760	344	329
Joint ventures & associates (post tax)	0	0	0	0	0
Exceptionals and Other	(17,443)	0	0	0	0
Profit Before Tax (norm)	(32,576)	(41,403)	(35,954)	(45,934)	(50,546)
Profit Before Tax (reported)	(53,205)	(47,724)	(41,859)	(51,839)	(56,451)
Reported tax	(55)	(143)	(156)	(159)	(174)
Profit After Tax (norm)	(32,576)	(41,403)	(36,065)	(46,076)	(50,702)
Profit After Tax (reported)	(53,260)	(47,867)	(42,015)	(51,999)	(56,625)
Non-cash adjustments	(399,924)	0	0	0	0
Net income (normalised)	(32,576)	(41,403)	(36,065)	(46,076)	(50,702)
Net income (reported)	(453,184)	(47,867)	(42,015)	(51,999)	(56,625)
Basic average number of shares outstanding (m)	14	30	50	71	74
EPS - normalised (c)	(226.2)	(136.9)	(72.3)	(65.2)	(68.2)
EPS - normalised fully diluted (c)	(226.2)	(136.9)	(72.3)	(65.2)	(68.2)
Dividend per share (c)	0.00	0.00	0.00	0.00	0.00
BALANCE SHEET					
Fixed Assets	915	623	473	473	473
Intangible Assets	0	0	0	0	0
Tangible Assets	566	400	154	154	154
Investments & other	0	0	0	0	0
Other	349	223	319	319	319
Current Assets	151,853	110,350	101,725	101,470	50,879
Stocks	0	0	0	0	0
Debtors	0	0	0	0	0
Cash & cash equivalents	150,180	109,007	100,348	100,093	49,502
Other	1,673	1,343	1,377	1,377	1,377
Current Liabilities	(7,397)	(7,725)	(7,472)	(7,426)	(7,554)
Creditors	(358)	(2,604)	(1,339)	(1,293)	(1,421)
Tax and social security	0	0	0	0	0
Short term borrowings	0	0	0	0	0
Other	(7,039)	(5,121)	(6,133)	(6,133)	(6,133)
Long Term Liabilities	0	0	0	0	0
Long term borrowings	0	0	0	0	0
Other long term liabilities	0	0	0	0	0
Net Assets	145,371	103,248	94,726	94,517	43,797
Minority interests	0	0	0	0	0
Shareholders' equity	145,371	103,248	94,726	94,517	43,797
CASH FLOW					
Op Cash Flow before WC and tax	(32,531)	(41,557)	(36,456)	(46,278)	(50,875)
Working capital	4,221	171	(342)	(46)	128
Exceptional & other	45	223	635	0	0
Tax	0	0	0	0	0
Net operating cash flow	(28,265)	(41,163)	(36,163)	(46,324)	(50,747)
Capex	(414)	(171)	(93)	0	0
Acquisitions/disposals	10,010	0	0	0	0
Net interest	0	0	0	0	0
Equity financing	145,419	196	27,588	45,885	0
Dividends	0	0	0	0	0
Other	(5,693)	25	13	0	0
Net Cash Flow	121,057	(41,113)	(8,655)	(439)	(50,747)
Opening net debt/(cash)	(29,154)	(150,180)	(109,007)	(100,348)	(99,909)
FX	(31)	(60)	(4)	0	0
Other non-cash movements	0	0	0	0	0
Closing net debt/(cash)	(150,180)	(109,007)	(100,348)	(99,909)	(49,162)

Source: Sierra reports, Edison Investment Research

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Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
295 Madison Avenue, 18th Floor
10017, New York
US

Sydney +61 (0)2 8249 8342
Level 12, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia