EDISON

Sierra Oncology

Initiation of coverage

Expanding on a proven class of anti-cancer drugs

Pharma & biotech

We are initiating coverage on Sierra Oncology, a drug developer targeting the DNA damage response (DDR) network to treat cancer. The company has two Phase I trials with SRA737 targeting checkpoint kinase 1 (Chk1) in patients with genetic tumor types expected to respond to the drug. Inhibition of Chk1 is lethal in cells with defective p53 (among others), one of the most common cancer mutations, and also enhances the response to chemotherapy. Sierra also has the cell division cycle 7 (Cdc7) inhibitor SRA141 in preclinical testing. Our initial valuation is $206m or $3.95/share.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/15	0.0	(32.6)	(2.26)	0.0	N/A	N/A
12/16	0.0	(41.4)	(1.37)	0.0	N/A	N/A
12/17e	0.0	(38.1)	(0.76)	0.0	N/A	N/A
12/18e	0.0	(42.8)	(0.77)	0.0	N/A	N/A

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

DDR: A network with validated anti-tumor targets

The potential of therapies attacking the DDR network has recently been validated, with the approval of poly-ADP-ribose polymerase (PARP) inhibitors. For instance, Lynparza (olaparib, AstraZeneca), approved in 2014 for ovarian cancer, had $218m sales in 2016, but these are expected to increase substantially with approval for breast cancer. SRA737 and SRA141 both target other proteins in the DDR network.

SRA737: A new type of Phase I clinical trial

Sierra amended its Phase I dose-ranging clinical trial protocol to preselect patients with genetic markers with the highest chance to respond to Chk1. Defects in the DDR pathway are common in an array of cancers. Because of this, Chk1 inhibitors are expected to have broad applicability across tumor types, although stronger responses are expected in tumors with specific defects in cell checkpoints and replication stress. The two trials will prospectively enroll patients across four such genetic classes in seven indications, with initial data in early 2018.

SRA141: After the untapped DDR target Cdc7

Cdc7 is a protein important for the unwinding of DNA prior to replication that has been implicated in helping the cell respond to DNA replication stress. The protein is known to be over-expressed in cancers and protects these cells from DNA damage, and its inhibition is known to induce tumor death, but few drugs have been developed targeting it. Sierra plans to file an IND for SRA141 by late 2017.

Valuation: $206m or $3.95 per share

We arrive at an initial valuation of Sierra Oncology of $206m or $3.95 per share based on a risk-adjusted NPV. We value SRA737 at $119.4m based on a 15% probability of success, and we do not value SRA141 at this time. The company ended Q217 with $117m in cash, enough to provide a runway to 2019. We expect that the company will need an additional $170m to reach profitability in 2024.

18 September 2017

Price	**$1.56**
Market cap	**$82m**
Net cash ($m) at 30 June 2017	117
Shares in issue	52.3m
Free float	59%
Code	SRRA
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(2.5)	31.6	(16.8)
Rel (local)	(3.7)	28.6	(29.1)
52-week high/low		$1.91	$1.12

Business description

Sierra Oncology is developing new therapies targeting the DNA damage response to treat cancer. It is in Phase I clinical trials of SRA737, an inhibitor of Chk1, both as a monotherapy and in combination with chemotherapy. It is also in IND enabling studies of SRA141, a Cdc7 inhibitor with an IND expected in late 2017.

Next events

SRA141 IND	H217
SRA737 interim results	Early 2018

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Sierra Oncology is a research client of Edison Investment Research Limited

Investment summary

Company description: Novel targets in DNA damage response

Sierra Oncology is a pharmaceutical company headquartered in Vancouver, British Columbia, developing small molecule drugs targeting the DNA damage response network for the treatment of cancer. The company's lead product SRA737 is a checkpoint kinase 1 (Chk1) inhibitor and is in two Phase I clinical trials for seven different solid tumor indications. Drugs attacking this target are synthetically lethal with certain common cancer mutations and efficacy may be further enhanced by the replication stress induced by chemotherapy/radiotherapy or through increased neoantigen expression in combination with checkpoint inhibitors. In an innovative step, Sierra is leveraging the preclinical and clinical data on synthetic lethality in the ongoing clinical trials to include genetic pre-screening for patients with mutations that are expected to confer sensitivity to Chk1 inhibitors. The company is also developing a cell division cycle 7 (Cdc7) inhibitor, SRA141. Cdc7 is also involved in DNA replication and the response to DNA damage, but has a different activity profile to Chk1 inhibition. SRA141 is currently in preclinical testing and expected to have an IND filed by year end 2017.

Valuation: $206m or $3.95 per share per share

We arrive at an initial valuation of Sierra Oncology of $206m or $3.95 per share based on a risk-adjusted NPV analysis. We assign a 15% probability of success to the SRA737 program, which is a typical risk for programs of this stage, based on limited data on this class of drugs in humans, but a solid preclinical profile. We only value SRA737 at this time but expect to add SRA141 to our valuation if it enters the clinic with more insight into its potential market. We also expect to update our valuation with the release of data from the ongoing Phase I trials, expected in early 2018.

Financials: Cash through to 2019

Sierra reported a loss of $10.3m for Q217, primarily attributable to R&D at $7.2m. We forecast a net loss of $44.3m for 2017 with $32.0m in R&D spending largely attributable to the Phase I clinical program, and expect a steady increase in these expenses as the clinical programs advance. The company completed a financing in February 2017 (21.8m shares at $1.35) for $27.4m net, and ended Q217 with $117m in cash. The company stated that this should provide a runway into approximately mid-2019. We expect that Sierra will need $170m in additional financing before forecast approval in 2023 ($95m in 2019 and $75m in 2022).

Sensitivities: Clinical risk dominates

The main risks to the company's success are clinical in nature. First generation Chk1 programs have been initiated at a number of companies, but most have been abandoned due to a poor pharmacokinetic profile or off-target interactions. However, the new generation of Chk1 inhibitors (including SRA737) appear to have fewer issues on both of these fronts. This said, there is little in human data for the class as a whole. Sierra has a clinical trial design that has not been attempted for Chk1 inhibitors and pre-selects patients that are the most likely to respond to treatment. We expect the data from this trial to be rich, but highly granular given they encompass two treatment regimens, seven indications, and four classes of mutation. There is less data on Cdc7 as a target for treating cancer, and the company has not provided a detailed breakdown of SRA141's profile or potential indications. It is therefore difficult to speculate on its potential. The company had a loss of $10.3m for Q217 and will need to raise additional capital to finance its development programs. Outside of clinical risk, the company may face competition from larger pharmaceutical companies, as there are currently trials of Chk1 inhibitors sponsored by Eli Lilly (Phase II) and Roche (Phase I) and Cdc7 clinical trials sponsored by Cancer Research UK/Eli Lilly (Phase I) and Takeda (Phase I).

Company description: Leveraging cancer's weaknesses

Sierra Oncology listed in 2015 with net proceeds of $143.6m as ProNAi Therapeutics. The company's lead asset PNT2258 was a DNA interference (DNAi) based drug that was discontinued in June 2016 following Phase II results, and the company redirected its efforts toward the development and licensing of other assets. These included the Cdc7 inhibitor SRA141 (licensed in May 2016) and the Chk1 inhibitor SRA737 (licensed in September 2016), both of which target aspects of the DNA damage response (DDR) network. It officially changed its name to Sierra Oncology in January 2017 and announced that DDR would be the focus of the company. This shift in development to small molecules is not outside the company's area of expertise as management collectively has wide development experience from prior stints at YM Biosciences, Onyx Pharmaceuticals, and Aragon, among others.

The company had accumulated losses of approximately $155m (an accumulated deficit of $582m less $428m in non-cash adjustments associated with convertible preferred stock) at the end of 2016, predominantly associated with these prior development programs. The company has two ongoing Phase I dose-ranging clinical trials of SRA737 (one with chemotherapy and one as a monotherapy) in an array of solid tumor indications, with patients who have been preselected for genotypes expected to respond to Chk1 inhibition.

Exhibit 1: Sierra Oncology development programs

Product	Target	Stage	Notes
SRA737	Chk1	Phase I	Licensed from Cancer Research Technology Pioneer Fund
SRA141	Cdc7	Preclinical	Licensed from Carna Biosciences

Source: Sierra Oncology

DNA damage and cancer

The interplay between DNA damage and oncogenesis is highly complex. At its most basic level, cancer is a disease caused by the accumulation of DNA damage leading to mutations that enable uncontrolled proliferation. This is why DNA damaging agents such as ionizing radiation and carcinogenic chemicals can induce the formation of cancer. The cell's natural DNA homeostasis is frequently disrupted in cancer cells, because genomic instability can allow cancer cells to acquire an increased number of mutations, including those mutations necessary for transformation and adaptation of the disease. For instance, the BRCA1 and BRCA2 genes that are commonly associated with congenital forms of breast and ovarian cancer encode enzymes involved in repairing double-strand breaks in DNA, and people with impaired BRCA1 and BRCA2 are at a higher risk for cancer because they are more likely to accumulate further mutations. These defects can either be congenital or acquired due to the presence of other mutations in the DNA repair system. Similarly, proteins involved in sensing and responding to DNA damage are also frequently implicated in oncogenesis. The protein p53 (also known as transformation-related protein 53, Trp53 or TP53) is activated in response to DNA damage, and will trigger apoptosis in the event that the damage is irreparable. Cancers that have mutated copies of p53 are therefore able to replicate and acquire additional adaptive mutations without triggering apoptosis. This mechanism drives a wide array of cancers and is very common in solid tumors. The Catalogue of Somatic Mutations in Cancer (COSMIC) database, which aggregates mutation prevalence from a range of sources, records p53 mutations in 34% of lung cancers, 42% of colorectal cancers, and 45.5% of ovarian cancers. The recent MSK-IMPACT genetic survey performed by Memorial Sloan Kettering examining only advanced cancer patients found significantly higher rates: 55% of non-small cell

lung cancers, 72% of colorectal cancers, and 71% of ovarian cancers (rising to 98% in high-grade serious ovarian cancer).[1]

This raises the question therefore of how the same environmental factors that cause cancer such as radiation and DNA damaging chemicals can simultaneously be used to treat it. Although the origin of cancer is rooted in DNA damage, as it progresses, it becomes increasingly incapable of responding to damage as the repair machinery becomes compromised. DNA damaging agents can therefore be used to damage cancer cells beyond the point of recovery while being less toxic in normal cells (albeit not without side effects). The majority of chemotherapies fall into this category and either directly modify DNA molecules, prevent their synthesis, or induce breaks in the DNA strand.

A relatively new approach to attacking cancers cells is targeting DNA repair machinery itself instead of damaging DNA. As the primary DNA repair machinery becomes compromised in cancer cells, they increasingly rely on alternative repair pathways. The notion that these agents can spare normal cells is called “synthetic lethality.” Synthetic lethality in a general sense is when the simultaneous impairment of two pathways (either by mutation or pharmacology) can lead to cell death, whereas the cell survives if just one of the pathways is inhibited and the other compensates. Synthetic lethality can be used to kill only those cancer cells where DNA repair is impaired and spare normal cells where the pathway is intact. Moreover, DNA damaging chemotherapies can potentially have synergies with these agents by increasing replication stress and the pressure on the repair machinery. The most successful programs with this strategy have been the development of poly-ADP-ribose polymerase (PARP) inhibitors. PARP is an enzyme implicated in the repair of single-strand breaks in DNA that becomes an important pathway in BRCA mutated cancers. Lynparza (olaparib) was the first PARP inhibitor approved in 2014 by AstraZeneca for BRCA mutated refractory ovarian cancer, and had sales of $218m in 2016. The drug has also recently (February 2017) shown positive results for BRCA mutated breast cancer. PARP inhibitors have also been developed by Clovis (approved December 2016), TESARO (approved March 2017), AbbVie (Phase III) and Pfizer (Phase III). The PARP in development at Pfizer was initially developed (into Phase III) by BioMarin, which sold the program to Medivation in 2015 for $410m upfront and $160m in milestones. Medivation was later bought by Pfizer for $14.3bn in 2016 (although this deal also included a profit split with Astellas from the approved drug Xtandi).

Checkpoints, Chk1, and cancer

The cell division cycle is divided into four phases: gap 1 (G1) when the cell grows, synthesis (S) when the cell duplicates its DNA, gap 2 (G2) when the cell grows again, and mitosis (M) when the cell divides. As the cell transitions from one phase to another, it reaches a so-called checkpoint where it assesses its level of DNA damage to determine if it is fit to continue its progress toward division. The protein p53 that is so often mutated in tumors is an important checkpoint mediator that is involved in the transition from the G1 to S phases of the cell cycle.

An interesting study was performed in 1982 that illuminated a novel method of leveraging cell cycle checkpoints to attack cancer. When a kidney cell line was treated with a nitrogen mustard chemotherapy, the cells became arrested in G2 phase. Treating these cells with caffeine would cause them to progress through the cell, but due to the accumulation of DNA damage from the mustard agent, the cell division would fail and the cell would die.[2] Later it was found that caffeine

[1] Zehir A, et al. (2017) Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nature Med.* 23, 703-713.

[2] Lau CC and Pardee, AB (1982) Mechanism by which caffeine potentiates lethality of nitrogen mustard. *Proc. Natl. Acad. Sci. U.S. A.* 79, 2942–2946.

only induced cell death in cells that were deficient in p53.[3] The reason why caffeine caused these cells to die was because it inhibited the phosphorylation of the checkpoint protein checkpoint kinase 1 (Chk1), and when combined with lack of p53, the cell effectively did not have any way to halt cell cycle progression. Chk1 has been identified as important for preventing the progression of the cell cycle into S phase and into G2 phase in response to DNA damage.[4] It both triggers the arrest in cell cycle progression and recruits the machinery to address the DNA damage. The synthetic lethality seen with p53 makes Chk1 an exceptionally attractive target for anti-cancer therapies because of the exceptionally high rate of p53 mutations across cancer types. Moreover, Chk1 inhibition should show synthetic lethality with any other proteins like p53 that are involved in regulating the G1 to S checkpoint and are mutated in cancers.

Outside of checkpoint inhibition, synthetic lethality has also been observed with Chk1 and a number of other common cancer cell genotypes associated with DNA damage repair. For instance, BRCA2 mutated pancreatic cancer cells can be selectively targeted by Chk1 inhibition,[5] as can cells with mutations in the Fanconi anemia (FA) DNA repair pathway.[6]

An interaction has also been found between oncogenic drivers such as Myc mutations and Chk1. Tumors driven by mutations in Myc have increased levels of Chk1 activity.[7] Myc is a transcription factor involved in growth regulation that is frequently mutated in quickly growing cancer cells. Additionally, Myc is implicated in the initiation of DNA synthesis at origins of replication, sharing some biology with Chk1. The theory behind its synthetic lethality with Chk1 is that Myc activation increases pressure on the DNA replication apparatus, so-called DNA replication stress, and that this stress leads to a higher rate of errors and failures such as stalled replication that necessitate Chk1 activation for recovery.

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3 Powell, S.N. et al. (1995) Differential sensitivity of p53(-) and p53(+) cells to caffeine-induced radiosensitization and override of G2 delay. *Cancer Res.* 55, 1643–1648.

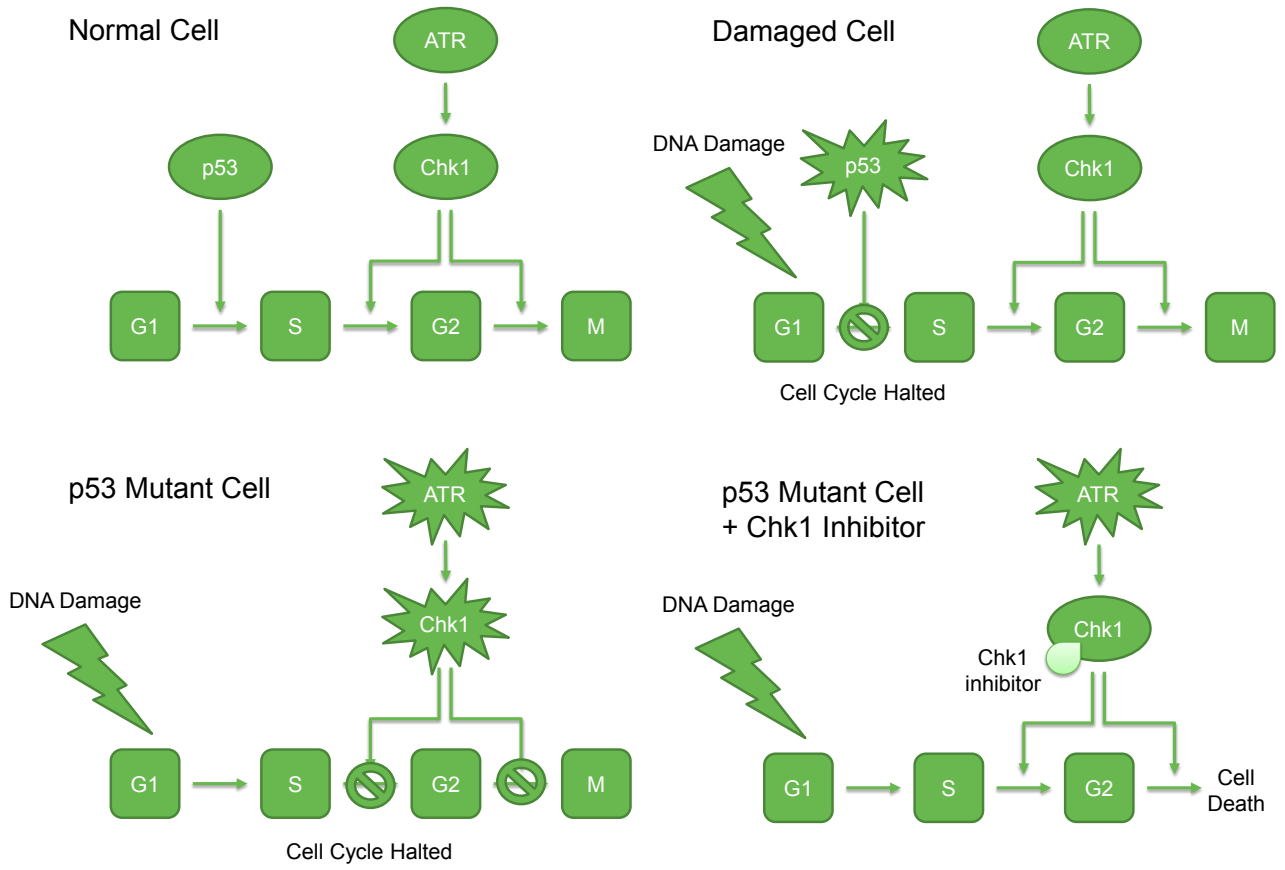
4 Liu Q, et al. (2000) Chk1 is an essential kinase that is regulated by Atr and required for the G2/M DNA damage checkpoint. *Genes & Dev.* 14, 1448-1459.

5 Hattori H, et al. (2011) Context Dependence of Checkpoint Kinase 1 as a Therapeutic Target for Pancreatic Cancers Deficient in the BRCA2 Tumor Suppressor. *Mol. Can. Ther.* 10, 670-678.

6 Chen CC, et al. (2009) CHK1 inhibition as a strategy for targeting Fanconi anemia (FA) DNA repair pathway deficient tumors. *Mol. Can.* 8, 24.

7 Höglund A, et al. (2011) Therapeutic Implications for the Induced Levels of Chk1 in Myc-Expressing Cancer Cells. *Clin. Can. Res.* 17, 7067-7079.

Exhibit 2: Chk1 synergizes with p53 mutations and DNA damage



Source: Various. Note: p53 or the ATR/Chk1 axis will halt cell cycle progression (G1, S, G2, and M phases) in response to DNA damage to give the cell time to heal. When these two systems are disabled, the cell progresses to mitotic failure and death.

Chk1 inhibition has an exceptionally high potential to address multiple cancers of different lineages due to the ubiquity of the mutations it has demonstrated synthetic lethality with. It is no wonder therefore that significant investment has been made into the development of inhibitors of Chk1. A driving force behind this interest is that these drugs should be applicable to a huge array of cancers given their expected synergy with chemotherapy and cancers with mutated G1/S checkpoint proteins. Major pharmaceutical companies, including Pfizer, Merck, Merck Serono, and Eli Lilly, have developed Chk1 inhibitors. However, the first generation of these drugs has seen a number of failures, and at least seven Chk1 programs have been terminated. This is not unusual for small molecule development in areas such as DDR that are of intense interest to large pharmaceutical companies, and by our estimation, there have been at least as many abandoned PARP development programs. However, it is useful to understand the progress of drug design for the class. The major limiting factors with this class of drug center on its broader pharmacologic profile as opposed to efficacy, and there have been a series of issues with both the pharmacokinetics as well as off target activity leading to severe side effects. These drugs had a high degree of cross reactivity with other kinases in the cell, including cell cycle regulating proteins such as cyclin dependent kinase 1 and 2 (CDK1 and CDK2). Inhibition of CDK1 and CDK2 is counterproductive as these proteins are essential for cell cycle progression and inhibiting them could mask the activity of Chk1 inhibitors. Additionally, many Chk1 inhibitors also inhibit Chk2, including prexasertib, which is the most advanced drug in the class. There has been some uncertainty as to the role of Chk2 activity in the clinical profile of these drugs because Chk2 also regulates cell cycle progression in response to DNA damage and replicates some of the function of Chk1. However, studies have

shown that Chk2 knockdown does not synergize with Chk1[8] and Chk2 may in fact protect cells from becoming cancerous, and its inhibition should be avoided.[9] In addition to these proteins, there have been a large number of interactions with other classes of kinase, highlighting the difficulty in designing specific inhibitors. Finally, the development of AZD7762 and MK-8776 were both terminated after identifying cardiac dose-limiting toxicities (although different in the two compounds), presumably due to off-target effects. Across the board, the Chk1 inhibitors whose development has been abandoned generally had extensive off target effects.

Despite the limitations of first-generation Chk1 inhibitors, these drugs have consistently demonstrated clinical activity, albeit in limited pilot studies, providing support that this mechanism of targeting cancer is viable. Responses have been seen across an array of cancer types including sarcoma and lung cancers, and prexasertib had a response rate of 38% in an interim report from a Phase II ovarian cancer study.

These early compounds have subsequently been followed by a second generation of Chk1 inhibitors that integrate the knowledge gathered from early development as well as the increased understanding regarding checkpoint inhibition and the development of similar drugs (such as the PARP inhibitors). These include LY2880070, GDC-575, and Sierra's compound SRA737. Although these drugs are in early stages, from the limited information available, it appears that the profiles of these drugs are improved.

Exhibit 3: Chk1 development programs

Product	Company	Stage	Known cross-reactivity	Notes
Generation 1				
Prexasertib	Eli Lilly, Array	Phase II	Chk2, RSK kinase family	38% response in ovarian cancer, grade 4 neutropenia as a monotherapy in >70% of patients, biweekly injection
LY2603618	Eli Lilly, Array	Abandoned		Variable PK profile, no benefit with gem in pancreatic cancer
MK-8776	Merck & Co	Abandoned	Pim1, CDK2	7% response in solid tumors, cardiac dose limiting toxicities
UCN-01	Keryx	Abandoned	CDK1, CDK2, PKC	First developed Chk1 inhibitor, bad PK and off target effects
RG7602	Array, Roche	Abandoned		Low tolerability and enhanced bone marrow toxicity
AZD7762	AstraZeneca	Abandoned	Chk2, CDK1, CAMK, Src kinase family	Cardiac dose limiting toxicities
PF-477736	Pfizer	Abandoned	Chk2, VEGFR2, Fms, Yes. Flt3, Ret	Response in mesothelioma, lung cancer, squamous cell carcinoma
XL855	Exelixis	Abandoned	Chk2	
Generation 2				
LY2880070	Eli Lilly, Esperas	Phase Ib/IIa		
GDC-0575	Array, Roche	Phase I		Response in soft tissue sarcoma with low dose gemcitabine
SRA737	Sierra Oncology	Phase I		No grade 2 or higher drug related AE, no DLT observed

Source: Evaluate Pharma, various. Notes: AE=adverse event, DLT=dose limiting toxicity.

SRA737

Sierra Oncology is developing the Chk1 inhibitor SRA737 (formerly known as CCT245737) and it is currently in Phase I clinical trials. The rights to the product were licensed in September 2016 from the Cancer Research Technology Pioneer Fund (CPF), a joint venture between Cancer Research Technology (CRT) and the European Investment Fund (EIF). CRT is a subsidiary of Cancer Research UK (CRUK), which is the largest not-for-profit cancer research and development charity in the world. The organization has brought approximately 120 drugs to the clinic including the subsequently approved Alimta (pemetrexed, Eli Lilly $2.8bn peak sales in 2014), Zytiga (abiraterone, Janssen, $2.3bn in 2016), and Temodar (temozolomide, Merck, $1.1bn peak sales in 2009). SRA737 was initially discovered through a collaboration between Sareum Holdings plc and the Institute of Cancer Research (IRC), and two Phase I studies were initiated by CRUK, which were transferred to Sierra in January 2017. Sierra paid $7m upfront and $2m upon the transfer of

[8] Carrassa L, et al. (2004) Chk1, but not Chk2, is involved in the cellular response to DNA damaging agents: differential activity in cells expressing or not p53. *Cell Cycle* 3, 1177–1181

[9] Manic G, et al. (2015) Trial Watch: Targeting ATM–CHK2 and ATR–CHK1 pathways for anticancer therapy. *Mol. Cell. Oncol.* 2, e1012976.

the clinical trials, and may owe CPF up to $319.5m in potential milestones as well as a high single-digit to low double-digit royalty on sales. The expected term of patent protection for the product is to 2033, before any extensions.

SRA737 has several properties that position it attractively among its peers. It is one of the most selective Chk1 inhibitors developed to date (Exhibit 4).[10] It is a thousand times or more selective for Chk1 compared to Chk2, CDK1, and CDK2. No cross-reactivity was found for any other kinases at concentrations less than 93x that of Chk1. By comparison, prexasertib selectivity over Chk2 and RSK family kinases is less than 10x. Although it is not a guarantee of safety, SRA737's selectivity profile eliminates a significant limiting factor that hampered the development of these drugs.

Exhibit 4: SRA737 kinase selectivity

Kinase	IC50 (nM)	Fold selectivity
CHK1	1.4	
ERK8	130	93x
PKD1	298	213x
RSK2	361	258x
RSK1	362	259x
FLT3	582	416x
MARK3	698	499x
NUAK1	711	508x
CLK2	1,370	979x
BRSK1	1,660	1,186x
CHK2	**1,850**	**1,321x**
VEGFR2	2,110	1,507x
AMPK	2,970	2,121x
PHKG1	3,470	2,479x
CDK2	**3,850**	**2,750x**
CDK1	**9,030**	**6,450x**

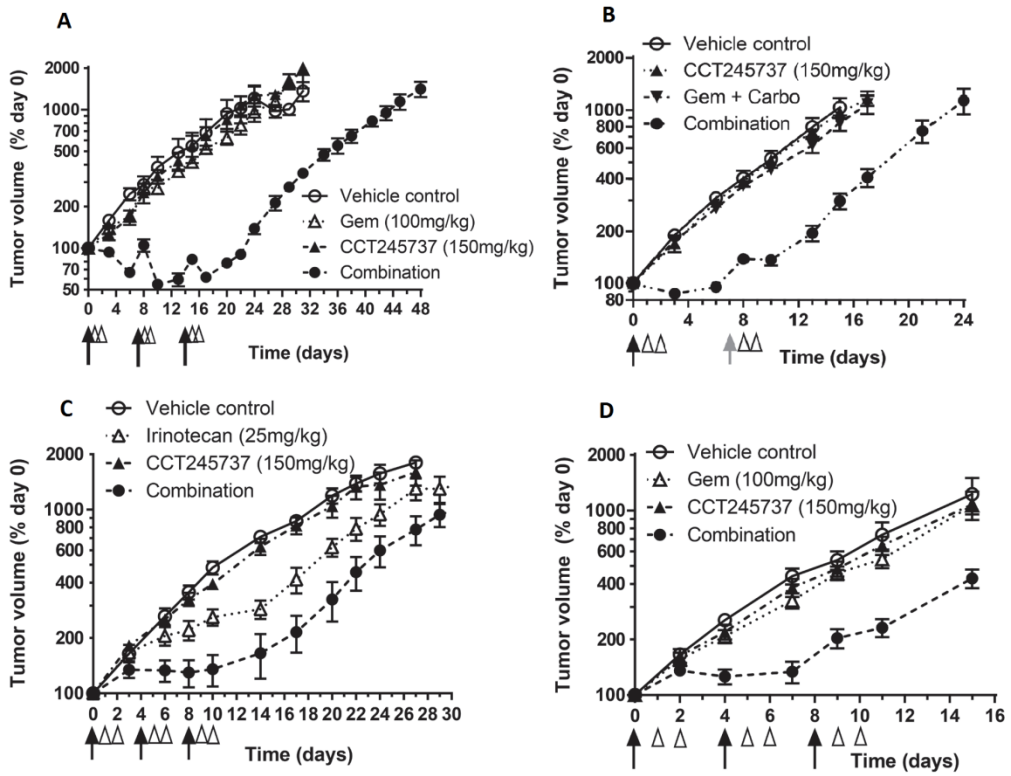
Source: Walton et al[10]

Additionally, SRA737 has an attractive pharmacokinetic profile compared to many other Chk1 inhibitors. The drug shows 100% oral bioavailability in mouse xenograft models,[10] and early data from the ongoing clinical studies show a pharmacokinetic profile consistent with a once-a-day dosing in humans. The most advanced Chk1 inhibitor prexasertib needs to be administered intravenously on a biweekly basis.

Consistent with the notion that chemotherapy induced DNA damage should potentiate the effects of Chk1 inhibition, the drug showed significant synergy in combination with either gemcitabine or irinotecan in colon cancer xenografts and with gemcitabine or carboplatin in lung cancer xenografts (Exhibit 5). In the HT29 colon cancer xenograft model, the potency seen with the combination was higher than the maximum tolerated dose for either compound alone. This supports the notion that SRA737 is bioavailable and active in a manner consistent with other Chk1 inhibitors in the tumor tissue. These data were seen as sufficient evidence to warrant clinical testing in humans.

[10] Walton MI, et al. (2015) The clinical development candidate CCT245737 is an orally active CHK1 inhibitor with preclinical activity in RAS mutant NSCLC and Eμ-MYC driven B-cell lymphoma. *Oncotarget* 7, 2329-2342.

Exhibit 5: SRA737 potentiates chemotherapy in mouse xenografts



Source: adapted from Walton et al.[10] Note: A) HT29 colon cancer xenograft, B) CoLu6 lung cancer xenograft, C) HT29 colon cancer xenograft, D) SW620 colon cancer xenograft.

SRA737 clinical trial design

In January 2017, Sierra assumed the role of sponsor of the two ongoing Phase I clinical trials investigating SRA737 in solid tumors. One trial was designed to test the molecule for activity as a monotherapy and the other in combination with low dose gemcitabine or gemcitabine and cisplatin. These trials are dose escalation and expansion trials with the primary endpoint of determining the maximum tolerated dose.

This type of broad-based, multi-indication Phase I trials is typical compared to what other companies have done when developing Chk1 and ATR inhibitors. However, in May 2017, the company announced that it had received approval from UK regulators to amend the trial design. First, the dose escalation portion of the trial will initially enroll one patient per cohort, as opposed to the typical three patients, to ensure fast dose escalation (the trial will revert to a three patient per cohort design if or when high-grade adverse events emerge). This portion of the trial can be run in parallel to the expansion portion and patients in the expansion portion can be up-dosed following the identification of higher tolerable doses. Additionally, the company added a series of genetic requirements for enrolment in the dose expansion portion of the trials with the goal of selecting individuals with the highest likelihood to respond to Chk1 inhibition (Exhibit 6). It is somewhat unique to include these requirements at this early stage, and should provide a wide array of data combining a combination of genotypes and indications for guiding future targeting of the program.

Exhibit 6: SRA737 trial designs

Trial	Estimated enrolment*	Target completion date*	Target indications	Genetic requirements
Monotherapy Trial	90	February 2019	Metastatic Colorectal Cancer Platinum-Resistant Ovarian Cancer Advanced Non-Small Cell Lung Cancer Metastatic Castration-Resistant Prostate Cancer Head and Neck Squamous Cell Carcinoma	Tumor suppressor mutation regulating the G1/S checkpoint AND one of the following: ■ Deleterious mutation in the DNA damage response pathway ■ Deleterious mutation of Chk1 or ATR or other related genes ■ Deleterious mutation of an oncogenic driver
Combination Trial	65	April 2019	Bladder Cancer Unresectable Locally Advanced or Metastatic Pancreatic Cancer	Tumor suppressor mutation regulating the G1/S checkpoint AND one of the following: ■ Deleterious mutation in the DNA damage response pathway ■ Deleterious mutation of Chk1 or ATR or other related genes ■ Deleterious mutation of an oncogenic driver

Source: Clinicaltrails.gov. Note: Enrolment and completion dates subject to degree of dose escalation.

The trials will require all patients to have a mutation in a tumor suppressor gene involved in the G1 checkpoint. This includes proteins like p53 among others, and without such a mutation, one would not expect the synthetic lethality of Chk1 inhibition to be leveraged. Given the high rate of p53 (32% to 72% in the selected indications), without even considering other G1/S checkpoint proteins, the recruitable population should be large. However, the prescreening requirement might affect enrolment rates.

Additionally the trials will require that patients have an identified defect in one of the following systems: DNA damage response (eg BRCA1, BRCA2), oncogenic cell proliferation drivers (Myc, KRAS, etc), or the ATR/Chk1 system. Defects in any of these systems are likely to increase the stress on the DNA replication and repair machinery, which should in theory improve the efficacy of SRA737. We believe that these requirements should not dramatically decrease enrolment. Oncogenic driving mutations are common in solid tumors (although they vary by indication) and a significant fraction of enrollees could potentially fit into this category. KRAS mutations alone are present in up to 26% of all tumors, depending on the data source,[11] and at exceptionally high levels for certain advanced cancers (74% of advanced pancreatic cancer, 44% of advanced colorectal cancer).[1]

The benefit of this new trial design is that the patient population should be preselected for those people with the highest chance to respond to Chk1 inhibition. However, a downside is that the data from this trial may be more complicated to interpret. The stated primary endpoint of the trial is determination of the maximum tolerated dose, and these changes should not affect the company's ability to gather this data. But the increased granularity from having such a broad range of mutations combined with the multiple indications means there may be only one of any given type of patient. The company will be able to further adapt the trial design to target particular subgroups of patients with high responses once they are identified, and this should provide increased insight into future directions the program can take. However, the evidence of efficacy gathered in this trial will be largely anecdotal, unless a clear target indication becomes quickly apparent. Sierra has stated that preliminary data from both trials will be available in early 2018.

Additionally these data may enable other combination studies such as with PARP inhibitors and PD-1 inhibitors, which the company has stated it plans to investigate in 2018. Recent data from Memorial Sloan Kettering suggests that patients with DDR defects may respond more strongly to PD-1/PD-L1 inhibitors, supporting this program.[12] Increased mutation rates associated with DDR

[11] Cox AD, et al. (2014) Drugging the undruggable RAS: Mission Possible? *Nat. Rev. Drug Disc.* 13, 828-851.

[12] Teo, MY, et al. (2017) DNA damage repair and response (DDR) gene alterations (alt) and response to PD1/PDL1 blockade in platinum-treated metastatic urothelial carcinoma (mUC). *J. Clin. Oncol.* 35, suppl. abstr 4509.

defects result in an increase in neoantigen generation and therefore have the potential for synergy with immuno-oncology agents.

The company announced progress on the trials at the American Society of Clinical Oncology (ASCO) annual meeting in June 2017. In the dose escalation portion of the monotherapy trial, patients progressed through a 600mg daily dose without reaching the maximum tolerable dose. In fact, no grade 2 or higher adverse events associated with treatment were observed. New patients enrolled into the genetically pre-screened cohort will be initiated at the 600mg dose and may receive higher doses following the results of the dose escalation portion. The company also stated that the combination trial had concluded the portion of the study examining SRA737 with gemcitabine and cisplatin and would proceed to SRA737 and low-dose gemcitabine.

Cdc7: An untapped DNA repair target

The core functionality of Cdc7 is in the regulation of initiating DNA replication. During the G1 phase of the cell cycle, as the cell is preparing to replicate its DNA, the proteins of the minichromosome maintenance (MCM) protein complex form a ring-like structure and bind to origins of replication in the cell's genome. This process is essential for DNA replication. Cdc7 (along with CDK2) binds to and phosphorylates proteins in the complex, which allows for the binding of the protein machinery needed for replication. This event marks the transition of the cell from the G1 phase to S. Therefore, the activity of Cdc7 is required for the progress of the cell cycle, the opposite of the activity of Chk1.

Cdc7 is also implicated in DNA damage response. Independent of its activity on the MCM complex, it binds to and phosphorylates claspin in response to DNA replication stress. Claspin then transmits this information to Chk1, which prevents cell cycle progression to provide sufficient time to repair DNA errors. In this way, Cdc7 is an upstream effector of Chk1.

Cdc7 is commonly overexpressed in tumors, including breast cancer,[13] diffuse large B-cell lymphoma,[14] melanoma,[15] pancreatic cancer,[16] and the vast majority of ovarian cancers.[17] Half of all tumor cell lines show Cdc7 overexpression suggesting that the protein confers some benefit to these cells or is important for transformation.[18] Moreover, the overexpression appears to be a response to loss of functional p53, suggesting that Cdc7 may be compensatory in these cells. Additionally, depletion of Cdc7 from these cells can induce apoptosis,[16,19] which opens up the possibility of targeting Cdc7 pharmacologically. However, despite all that is understood about this molecule, the precise mechanism by which it supports cancer growth is not entirely understood.

Efforts to drug Cdc7 are still in relatively early stages, and only a small number of molecules have been developed. The first published Cdc7 inhibitor, PHA-767491, was developed in 2008 by

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13 Choschzick M, et al. (2010) Overexpression of cell division cycle 7 homolog is associated with gene amplification frequency in breast cancer. *Hum Pathol* 41, 358–65.

14 Krawczyk J, et al.(2009) Increased activity of the S phase kinase Cdc7 is associated with poor outcome in diffuse large B cell lymphoma (DLBCL) *Blood* (ASH Annual Meeting Abstracts 114, Abstract nr 1914.

15 Clarke LE, et al. (2009) Cdc7 expression in melanomas, spitz tumors and melanocytic nevi. *J. Cutan. Pathol.* 36, 433–8.

16 Huggett M, et al. (2016) Cdc7 is a potent anti-cancer target in pancreatic cancer due to abrogation of the DNA origin activation checkpoint. *Oncotarget* 7 18495-18507.

17 Kulkarni AA, et al. (2009) Cdc7 kinase is a predictor of survival and a novel therapeutic target in epithelial ovarian carcinoma. *Clin. Cancer Res.* 15, 2417–25.

18 Bonte S, et al. (2008) Cdc7-Dbf4 Kinase Overexpression in Multiple Cancers and Tumor Cell Lines Is Correlated with p53 Inactivation. *Neoplasia* 10, 920-931.

19 Ito S, et al (2012) Mechanism of Cancer Cell Death Induced by Depletion of an Essential Replication Regulator. *PLoS One*, 7, e36372.

Nerviano Medical Sciences and showed anti-tumor activity in acute myeloid leukemia, colon, and breast xenograft models.[20] Nerviano subsequently shifted to development of other Cdc7 inhibitors, including RXDX-103, which was out-licensed to Ignyta, although subsequently discontinued. Cdc7 inhibitors have been internally developed at a Novartis, Pfizer, Roche, and Sanofi,[21] although none of these have progressed to the clinic. Bristol-Myers Squibb advanced BMS-863233 (developed in collaboration with Exelixis) to Phase I in 2009, although the trial was terminated due to an "unfavourable pharmacological profile." Takeda and Eli Lilly/CRUK currently have compounds in Phase I.

Exhibit 7: Cdc7 programs

Product	Company	Stage
TAK-931	Takeda	Phase I
LY3143921	Eli Lilly, CRUK	Phase I
SRA141	Sierra Oncology	Preclinical
LBS-007	Lin BioScience	Preclinical
BMS-863233	Bristol-Myers Squibb, Exelixis	Abandoned
NMS-1116354	Nerviano	Abandoned
PHA-767491	Nerviano	Abandoned
RXDX-103	Ignyta, Nerviano	Abandoned

Source: Evaluate Pharma, clinicaltrials.gov.

SRA141

Sierra is developing SRA141 as a selective, oral Cdc7 inhibitor for the treatment of solid or hematological cancers. The molecule was licensed in May 2016 from Carna Biosciences, and is currently in IND enabling studies. The company paid Carna $0.9m upfront and owes up to $270m in milestones and tiered single-digit royalties. The product is protected by intellectual property through 2032 (before any patent term extensions). At this time we do not have very much information on the drug's profile, but the company plans to submit an IND to the FDA before the end of 2017.

Sensitivities

In the near term, the primary risks faced by Sierra are clinical in nature given the early stage of its development programs. This company has prior clinical experience with its development of DNAi based therapeutics. The company accrued losses of $155m (at year-end 2016) largely associated with this program. However, it recently underwent a significant shift in focus with the in-licensing of SRA737 and SRA141. While Sierra has not previously developed DDR drugs or small molecules in general, management has significant prior experience in oncology and small molecules. There are no clinical measures of efficacy for either of its products, and it is therefore difficult to speculate about the approvability of either compound. There have been a number of development programs in the Chk1 space, and this adds credence to the mechanism of action. However, the majority of these programs have been abandoned, which may indicate broader issues. These earlier programs had significant issues with drug design such as off target interactions, but the next generation of Chk1 inhibitors including SRA737 appear better optimized in this regard from the data that we currently have. This is supported by the early dosing data from the Phase I trial showing no safety concerns when dosed up to 600mg/day.

The SRA737 trials have been designed in a unique fashion by leveraging knowledge of Chk1's interactions to select for patients with a high chance to respond to therapy. However, the inclusion of genotypic classifiers in the trial design significantly increases the complexity of drawing statistical conclusions from the results. The trials will examine seven indications with four genetic marker

[20] Montagnoli A et al. (2008) A Cdc7 kinase inhibitor restricts initiation of DNA replication and has antitumor activity. *Nat. Chem. Biol.* 4, 357–65.

[21] Swords R, et al. (2010) Cdc7 kinase – A new target for drug development. *Eur. J. Can.* 46, 33-40.

classes, over multiple doses of two different regimens. Given this granularity, it is probable that there will be only one patient of any given class in the trial. If the early signals in the trials are definitive, this may be used to guide an adaptive design toward enrichment of a particular subgroup early on.

The SRA141 program has similar risks. Cdc7 as a target is less well understood than Chk1, and there is essentially no in human data for the entire class of Cdc7 inhibitors. Moreover, we do not know at this point if the SRA141 molecule is fit for clinical trials, because it has not completed preclinical testing.

Both molecules could potentially face competition if they are approved. The most advanced programs in both Chk1 inhibitors and Cdc7 inhibitors are sponsored by large pharmaceutical companies with significantly more resources than Sierra. Moreover, barring disruptions, Sierra will not be the first to market in either case. SRA737 may have advantages over the lead Chk1 inhibitor prexasertib (from Eli Lilly, Phase II) as it is oral and can be dosed daily, although other drugs in the class (such as the Lilly follow-on LY2880070 in Phase Ib/IIa and Genentech's GDC-0575 in Phase I) are oral as well.

Finally, Sierra faces risks regarding raising additional capital. The company reported a loss of $10.3m in Q217. We currently project a financing need of $170m before the company can reach profitability in 2024. We note however that these needs have been significantly offset by the cash balance as of 30 June 2017 of $117, which is large for a pharmaceutical company at this development stage.

Valuation

We arrive at an initial valuation of Sierra Oncology of $206m or $3.95 per share. Our valuation is derived from a risk-adjusted NPV analysis on future earnings from the SRA737 clinical program. Our earnings estimates for this program are highly provisional, as the company has not announced a target indication for the product. We have constructed a model market for this product based on the average incidence rates of the indications being studied in the Phase I clinical trial combined with the prevalence of p53 mutations in these cancers (Exhibit 8). We have selected the p53 mutated subgroup of these cancers as it is the genotype with the most data supporting efficacy as well as the most significant market. We acknowledge that the eventual indication may differ significantly from this average and expect to update our valuation. We believe that our current assessment is conservative as the drug may be active in multiple indications with multiple genotypes and we are currently modelling only a single launch until such time as we have better activity data.

We assume 15% peak penetration into this hypothetical market in both the US and Europe. We assume that the company will be granted a full Hatch-Waxman extension bringing the date of patent expiration to 2038. Our launch pricing (WAC) in the US is approximately $150,000 per course, which is based on the current price of Lynparza ($135,000) adjusted for 2% growth until the launch date in 2023. We assume 40% lower pricing in Europe, as well as discounts of 30% in both regions. We assume that the product will have COGS of 15% in the US and 18% in Europe, which includes the cost to manufacture and a 10% royalty payable to CPF. Our cost of selling is modelled with a $5m base and 10% variable costs in both regions. Our valuation includes assumed milestones payable (split evenly between regions) as $19.5m for Phase III results (2021), $100m each for approval (2023), $500m (2026) and $1bn in total sales (2037). Development costs for SRA737 are currently modelled using a cost of $100,000 per patient for both the current clinical program (with 155 patients total) and a 225-patient Phase III program for the product's lead indication. Additionally we model $8m in R&D overhead for the program.

Our probability of success for SRA737 is 15%, which is our base assumption for a drug at this stage. The Chk1 inhibitor space has had numerous failed drugs, indicating issues of drug design in this class. We believe that the preclinical profile of SRA737 addresses some of these shortcomings, such as off target interactions and pharmacokinetic profile. However, there is limit data on safety and efficacy for this drug. We believe a neutral starting assumption is therefore prudent. We expect to update our risk assessment with the release of data from the ongoing Phase I clinical trials. Given the innovative nature of the Phase I clinical program, these data should be highly illuminating. We expect to update our valuation when the company picks a lead indication following the data. We may also increase our valuation if it is clear that the company can pursue multiple indications or multiple genetic markers in later trials.

We currently do not include SRA141 in our valuation given our current lack of visibility into the path to approval. Following the filing of an IND for the compound in late 2017, the company may initiate clinical development, at which time we plan to add this program to our valuation, once we have an idea about potential target indications.

We include an NPV of negative $29.7m to account for the unallocated costs such as administrative expenses, shared costs, and R&D not attributable to publically disclosed programs. We may update this value in the future if the company exercises cost control.

Exhibit 8: Indication subgroups

Indication	Subgroup	Rate	US incidence ('000)	EU incidence ('000)
Metastatic Colorectal Cancer				
	Baseline Rate	40.1/100,000		
	Stage 4	20%		
	p53 mutation	72.3%		
	Total	5.8/100,000	18.9	29.7
Platinum-Resistant Ovarian Cancer				
	Baseline Rate	11.7/100,000		
	platinum resistance	70%		
	p53 mutation	71.0%		
	Total	5.8/100,000	19.0	29.7
Advanced Non-Small Cell Lung Cancer				
	Baseline Rate	55.8/100,000		
	Non-small cell	85%		
	Nonresectable	70%		
	p53 mutation	55.4%		
	Total	18.4/100,000	60.1	94.1
Metastatic Castration-Resistant Prostate Cancer				
	Baseline Rate	119.8/100,000		
	Metastatic and castration resistant	15%		
	p53 mutation	31.8%		
	Total	5.9/100,000	19.3	30.2
Head and Neck Squamous Cell Carcinoma				
	All HNC	11.2/100,000		
	Squamous	90%		
	Nonresectable	60%		
	p53 mutation	46.8%		
	Total	2.8/100,000	9.2	14.5
Bladder Cancer				
	Baseline Rate	19.8/100,000		
	Muscle invasive	33%		
	p53 mutation	39.7%		
	Total	2.6/100,000	8.5	13.3
Unresectable Locally Advanced or Metastatic Pancreatic Cancer				
	Baseline Rate	12.5/100,000		
	Nonresectable	87%		
	p53 mutation	57.2%		
	Total	6.2/100,000	20.3	31.8
Average		6.8/100,000	22.2	34.7

Source: Various including MSK-IMPACT genetic survey

Exhibit 9: Valuation of Sierra Oncology

Development Program	Region	Prob. of success	Launch year	Peak sales ($m)	Margin	rNPV ($m)
SRA737	US	15%	2023	562	55%	77.0
SRA737	Europe	15%	2023	471	53%	62.8
SRA737	Development costs					(20.3)
Unallocated costs						(29.7)
Total						$89.7
Net cash and equivalents (Q217) ($m)						$116.7
Total firm value ($m)						$206.4
Total shares (m)						52.3
Value per share ($)						$3.95

Source: Sierra Oncology reports, Edison Investment Research

Financials

Sierra Oncology underwent a change in focus from internally developed DNAi based therapeutics (as ProNAi), to the current model of in-licensed small molecules. Because of this, previous financials may not be predictive of future costs. The company reported losses of $10.3m for Q217. The company's primary expenditure is R&D, and it spent $7.2m during the period on current programs. We forecast total R&D spending of $32.0m in 2017 largely attributed to the Phase I trial, rising incrementally in later years with the expansion of the clinical programs. G&A spending for Q217 was $3.3m, which we currently project being relatively steady until NDA submission for SRA737 (in 2022) and subsequent marketing expenses. The company ended Q217 with $117m in cash. The most recent offering was in February 2017 with $27.4m net proceeds (21.8m shares at $1.35). It has stated this is sufficient to provide a runway into approximately mid-2019, which is consistent with our projections. We expect that the company will need $170m in additional financing to reach approval in 2023 ($95m in 2019 and $75m in 2022), which we record as illustrative debt. This financing schedule may need to be adjusted based on differences in the timing of milestone payments (which have not been disclosed) from our assumptions.

Exhibit 10: Financial summary

$000s	2014	2015	2016	2017e	2018e	2019e
Year end 31 December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
INCOME STATEMENT						
Revenue	0	0	0	0	0	0
Cost of Sales	0	0	0	0	0	0
Gross Profit	0	0	0	0	0	0
R&D	(19,078)	(26,356)	(33,895)	(32,032)	(36,340)	(40,681)
SG&A	(3,500)	(9,472)	(14,180)	(12,584)	(12,836)	(13,092)
EBITDA	(22,264)	(32,531)	(41,557)	(38,194)	(43,116)	(47,713)
Normalised operating profit	(22,276)	(32,642)	(41,754)	(38,556)	(43,116)	(47,713)
Amortisation of acquired intangibles	0	0	0	0	0	0
Exceptionals	0	0	(811)	0	0	0
Share-based payments	(302)	(3,186)	(5,510)	(6,060)	(6,060)	(6,060)
Reported operating profit	(22,578)	(35,828)	(48,075)	(44,616)	(49,176)	(53,773)
Net Interest	87	66	351	472	339	249
Joint ventures & associates (post tax)	0	0	0	0	0	0
Exceptionals and Other	(1,380)	(17,443)	0	0	0	0
Profit Before Tax (norm)	(22,189)	(32,576)	(41,403)	(38,084)	(42,777)	(47,464)
Profit Before Tax (reported)	(23,871)	(53,205)	(47,724)	(44,144)	(48,837)	(53,524)
Reported tax	(2)	(55)	(143)	(141)	(150)	(165)
Profit After Tax (norm)	(22,191)	(32,576)	(41,403)	(38,201)	(42,909)	(47,610)
Profit After Tax (reported)	(23,873)	(53,260)	(47,867)	(44,285)	(48,988)	(53,688)
Non-cash adjustments	(49,849)	(399,924)	0	0	0	0
Net income (normalised)	(22,191)	(32,576)	(41,403)	(38,201)	(42,909)	(47,610)
Net income (reported)	(73,722)	(453,184)	(47,867)	(44,285)	(48,988)	(53,688)
Basic average number of shares outstanding (m)	1	14	30	50	56	59
EPS - basic normalised ($)	(20.79)	(2.26)	(1.37)	(0.76)	(0.77)	(0.81)
EPS - diluted normalised ($)	(20.79)	(2.26)	(1.37)	(0.76)	(0.77)	(0.81)
EPS - basic reported ($)	(69.08)	(31.47)	(1.58)	(0.88)	(0.88)	(0.91)
Dividend ($)	0.00	0.00	0.00	0.00	0.00	0.00
BALANCE SHEET						
Fixed Assets	840	915	623	568	568	568
Intangible Assets	0	0	0	0	0	0
Tangible Assets	214	566	400	256	256	256
Investments & other	0	0	0	0	0	0
Other	626	349	223	312	312	312
Current Assets	39,725	151,853	110,350	97,969	55,179	102,679
Stocks	0	0	0	0	0	0
Debtors	0	0	0	0	0	0
Cash & cash equivalents	39,164	150,180	109,007	97,403	54,613	102,113
Other	561	1,673	1,343	566	566	566
Current Liabilities	(2,095)	(7,397)	(7,725)	(6,069)	(6,207)	(6,335)
Creditors	(622)	(358)	(2,604)	(1,067)	(1,205)	(1,333)
Tax and social security	0	0	0	0	0	0
Short term borrowings	0	0	0	0	0	0
Other	(1,473)	(7,039)	(5,121)	(5,002)	(5,002)	(5,002)
Long Term Liabilities	(1,910)	0	0	0	0	(95,000)
Long term borrowings	0	0	0	0	0	(95,000)
Other long term liabilities	(1,910)	0	0	0	0	0
Net Assets	36,560	145,371	103,248	92,468	49,540	1,912
Minority interests	0	0	0	0	0	0
Shareholders' equity	36,560	145,371	103,248	92,468	49,540	1,912
CASH FLOW						
Op Cash Flow before WC and tax	(22,264)	(32,531)	(41,557)	(38,194)	(43,116)	(47,713)
Working capital	395	4,221	171	(926)	138	128
Exceptional & other	83	45	223	348	0	0
Tax	0	0	0	0	0	0
Net operating cash flow	(21,786)	(28,265)	(41,163)	(38,772)	(42,979)	(47,585)
Capex	(187)	(414)	(171)	(293)	0	0
Acquisitions/disposals	(10)	0	0	0	0	0
Net interest	0	0	0	0	0	0
Equity financing	58,793	145,419	196	27,445	0	0
Dividends	0	0	0	0	0	0
Other	(75)	(5,693)	25	13	0	0
Net Cash Flow	36,735	111,047	(41,113)	(11,607)	(42,979)	(47,585)
Opening net debt/(cash)	0	(36,735)	(147,751)	(106,578)	(94,974)	(51,995)
FX	0	(31)	(60)	3	0	0
Other non-cash movements	0	0	0	0	0	0
Closing net debt/(cash)	(36,735)	(147,751)	(106,578)	(94,974)	(51,995)	(4,411)

Source: Sierra Oncology reports, Edison Investment Research

Contact details	Revenue by geography
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Management team

CEO: Nick Glover	CDO: Barbara Klencke
Dr Glover is an accomplished life sciences professional, with extensive strategic, financial and operational experience in the biotechnology sector, evidenced by demonstrable value creation and successful outcomes. Previously, Dr Glover served as the president and chief executive officer at YM BioSciences Inc., a publically traded oncology drug development company acquired by Gilead Sciences Inc. in February 2013. Prior to that, Dr Glover served as the president and chief executive officer of Viventia Bio Inc., a publically traded biopharmaceutical company focused on the development of monoclonal antibody technologies.	Previously, Dr Klencke served as the senior vice president, development at Onyx Pharmaceuticals, a subsidiary of Amgen Inc., from January 2011 to June 2015, and prior to that was the group medical director in product development, oncology at Genentech, Inc., having joined the company in July 2003. In this period, she led a variety of oncology programs including those for Kyprolis (carfilzomib), Kadcyla (ado-trastuzumab emtansine), Avastin (bevacizumab), and Tarceva (erlotinib). Prior to that, Dr Klencke served as the medical director at Chiron Corporation, a biotechnology company later acquired by Novartis International AG, and as an assistant professor of medicine at the University of California, San Francisco Medical Center.
Chief Business & Strategy Officer: Angie You	**CMO: Mark Kowalski**
Dr You, chief business & strategy officer and head of commercial, leads the company's strategic and transactional business and commercial efforts. Previously, Dr You served as the chief business officer of Aragon Pharmaceuticals, a private oncology drug discovery and development company, where she was responsible for finance, operations, HR and business development. Prior to Aragon, Angie served as chief business officer at a number of life science companies including Synosia Therapeutics and Ren Pharmaceuticals. She also previously served as vice president at Venrock, a venture capital firm, and as a consultant at McKinsey Consulting.	Dr Kowalski was most recently the chief medical officer and senior vice president at Arbutus Biopharma, a biotechnology company devoted to discovering and developing a cure for chronic hepatitis B. Prior to that, he held the same position at Tekmira, a biopharmaceutical company focused on developing therapeutics based on RNA interference utilizing lipid nanoparticle delivery technology in oncology, infectious disease, metabolic and other clinical indications. Prior to joining Tekmira, Dr Kowalski worked in the oncology and inflammation therapeutic area at Gilead Sciences, Inc. following Gilead's $510m acquisition of YM BioSciences Inc., at which Dr Kowalski had been CMO and vice president of regulatory affairs. Dr Kowalski's experience also encompasses being the CMO and vice president of medical/regulatory affairs at Viventia Biotechnologies Inc. and the senior director of Medical Affairs at AAIPharma Inc.

Principal shareholders	(%)
Frazier Management	15.5
Deerfield Management	9.5
OrbiMed Advisors	7.1
Perceptive Advisors	7.1
New Leaf Venture Partners	5.0
Vivo Capital	4.7
Sabby Management	3.3

Companies named in this report

Array BioPharma (ARRY), AstraZeneca (AZN), Bristol-Myers Squibb (BMY), Eli Lilly (LLY), Exelixis (EXEL) Keryx Biopharmaceuticals (KERX), Merck & Co. (MRK), Merck Serono (MRK.DE), Pfizer (PFE), Roche (RHHBY)

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