EDISON

Onconova Therapeutics

Initiation of coverage

ONTIME to deliver

Pharma & biotech

If rigosertib (IV) meets its primary endpoint in the ONTIME Phase III trial in higher-risk, second-line MDS in Q114, Onconova could be in a position to file its first NDA next year. This would represent something that few recent IPO companies could aspire to, even looking several years out. Oral rigosertib, which is in Phase II trials for lower-risk MDS, could open a much larger market if positive Phase II data are confirmed in a pivotal trial. With three drug candidates in clinical trials, six active preclinical programmes and cash beyond 2014, Onconova appears to be an attractive investment. We value the company at $476m, or $22.3/share.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/11	1.5	(27.6)	(14.8)	0.0	N/A	N/A
12/12	46.2	(30.3)	(15.5)	0.0	N/A	N/A
12/13e	3.3	(68.5)	(8.86)	0.0	N/A	N/A
12/14e	50.0	(48.9)	(2.34)	0.0	N/A	N/A

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

Rigosertib (IV) ONTIME to deliver

Rigosertib is compared to best supportive care (BSC) in a 270-patient Phase III trial (ONTIME) of second-line MDS with overall survival as the primary endpoint. Rigosertib's Phase II results suggest the trial has a high probability of meeting its primary endpoint. A clear survival benefit should lead to a relatively easy approval in second-line MDS, since there are no approved drugs for this indication. This would pave the way for a successful launch in an estimated $275-325m US and $585-690m worldwide market in which there is little competition on the horizon.

A balanced pipeline and good partnerships

Besides rigosertib (IV), Onconova is developing oral rigosertib for lower-risk MDS, a market three times larger than second-line high-risk MDS, ON 013105 for refractory lymphoma (Phase I), recilisib for acute radiation syndrome (ARS) and six pre-clinical assets for various cancers. Its partnership agreements with Baxter in Europe and SymBio in Japan and Korea could lead to up to $545m in pre-launch milestone payments, non-dilutive funds that could be used to advance more drug candidates in pre-clinical and human clinical trials.

Valuation: There is still upside left

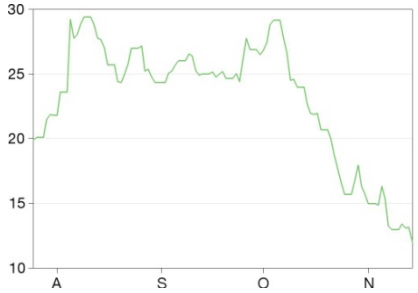
Our risk-adjusted DCF model indicates a valuation of $476m, or $22.3 per basic share, based entirely on the current status of the three clinical-stage drug candidates. A major valuation inflection point is the release of top-line results of rigosertib in the Phase III, second-line MDS trial, which if positive would add significant value to our model. Our model does not ascribe any value to the pancreatic cancer (PC) trial because of the high clinical hurdle for the interim analysis, leaving a positive outcome of this trial as a purely option call.

15 November 2013

Price	**US$12.0**
Market cap	**US$257m**

Net cash ($m) end Sept 13	116.6
Shares in issue (m)	21.4
Free float	21%
Code	ONTX
Primary exchange	NASDAQ
Secondary exchange	None

Share price performance



%	1m	3m	12m
Abs	(47)	(56.6)	N/A
Rel (local)	(49.4)	(59.2)	N/A
52-week high/low		$29.4	$12.0

Business descri7ption

Onconova Therapeutics is a clinical-stage bio-pharmaceutical company focused on discovering and developing novel small molecule drug candidates to treat cancer. Using a proprietary chemistry platform, it has created an extensive library of targeted anti-cancer agents. Its lead drug candidate, rigosertib (IV), is in Phase III trials for higher-risk MDS and pancreatic cancer, and an oral form of the drug is in Phase II for lower-risk MDS.

Next events

Rigosertib Phase III PC interim data	Q413
Rigosertib Phase III MDS top-line data	Q114
Rigosertib NDA filing	H214
Rigosertib (oral) MDS reg. path decision	2014

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Investment summary

Company description: Rigosertib ONTIME to deliver

Onconova Therapeutics is a clinical-stage biopharmaceutical company focused on discovering and developing novel small molecule drug candidates to treat cancer. Using a proprietary chemistry platform, it has created an extensive library of targeted anti-cancer agents. Its lead drug candidate, rigosertib (IV), is in Phase III trials for higher-risk MDS and pancreatic cancer, and an oral form of the drug is in Phase II for lower-risk MDS. Two other clinical state drug candidates are ON 013105 for refractory lymphoma (Phase I) and recilisib for ARS. It has six pre-clinical drug candidates targeting various cancer targets. The company went public in July 2013, raising net proceeds of $79.6m. It was founded in 1998 and is headquartered in Pennsylvania and New Jersey, US.

Exhibit 1: Onconova pipeline (clinical)

Drug	Indication	Status
Rigosertib (IV)	Higher-risk MDS after HMA	Phase III top-line results in Q114
	First-line pancreatic cancer	Phase III interim analysis Q413
Rigosertib (oral)	Lower-risk MDS	Phase II final results at ASH 2013
	Refractory head and neck cancer	Phase II single arm, 1st phase of 20 pts results 2014
ON 013105	Refractory lymphoma, solid tumour	Phase I (solid tumour) to resume in Q114; could be licensed out
Recilisib	Acute radiation syndrome (ARS)	Phase I ongoing; to be licensed out

Source: Company reports

Sensitivities: The main risk is the ONTIME trial

The main risk to our investment thesis is a negative outcome of the pivotal Phase III ONTIME trial and any subsequent decisions by the company's partners, particularly Baxter. We view the pancreatic cancer trial as less essential to the investment thesis given the high historical failure rates of drugs in development for this indication. While we believe a negative result ought not to be significant, there could be some short-term impact on the share price. Onconova is well financed with sufficient cash beyond 2014, but a negative ONTIME outcome could force the company to raise additional funds from the market in the future to support its operation beyond 2015.

Valuation: $476m based on three clinical drug candidates

We value Onconova based on a discounted cash flow method. Rigosertib (IV) and rigosertib (oral) account for 65.3% and 30% of the total pipeline value, respectively. Our model does not ascribe any value to the PC trial because of the high clinical hurdle for the interim analysis, leaving a positive outcome of this trial as a purely option call. Our intrinsic value is $476m, or $22.3 per share ($20.7/share fully diluted). This is much higher than the current market value of the company, suggesting significant upside potential if our investment thesis proves correct.

Financials: Net cash of $116.6m sufficient beyond 2014

Onconova reported a net loss of $20.5m for Q313, including G&A expenses of $5.9m and R&D costs of $15.3m. Cash burn for the quarter was $15.8m. The company ended the quarter with cash and cash equivalents of $116.6m and guided year end cash of $98m, enough to support operation in 2015, not including any milestone payments that could be received.

Outlook: It is ONTIME

The outcome of rigosertib (IV)'s ONTIME Phase III trial, which we argue is likely to be favourable in this note, will be the most important milestone in Onconova's 15-year history. ONTIME is a well-designed Phase III trial supported by encouraging Phase II trial results and historical data and, if positive, it should lead to a quick approval and launch for higher-risk, second-line myelodysplastic syndromes (MDS), a condition of clear unmet medical need.

Onconova's investment proposition goes beyond rigosertib (IV), despite the drug candidate's importance to the company's near-term success. Oral rigosertib, a drug that has shown encouraging activity in Phase II trials in lower-risk MDS, represents a bigger opportunity than rigosertib (IV) because the addressable market is approximately three times larger. The company is financially well positioned with total cash of $116.6m at end of Q313, having taken advantage of the receptive US IPO market. Its partnerships, particularly the one with Baxter, should also provide the company with non-dilutive financing, in addition to a dedicated and hungry commercial player in Europe.

Rigosertib: Unique mechanism of action (MOA)

Onconova's most advanced drug candidate, rigosertib, is a multi-kinase pathway inhibitor. Originally[1] it was thought to inhibit polo-like kinase1 (PLK1), a kinase with elevated expression in many human tumours. Further studies[2] could not confirm the direct binding of the compound to PLK1, but demonstrated that rigosertib may disrupt the interaction of PLK1 with the Raf family of kinases, a family of kinases that are often abnormally expressed or mutated in cancer cells. In addition[3], rigosertib was found to inhibit the phosphatidylinositol-3 kinase (PI3K) pathway, a pathway that is altered in, and often the driving force in the development of, cancer cells.

Rigosertib appears to be a weak and pan-subtype inhibitor of PI3K, as compared with some of the more specific subtype inhibitors of PI3K, such as idelalisib (PI3K δ, Gilead) and IPI-145 (PI3K δ and γ, Infinity), with IC_{50} in the micro-molar (μM) range (most other PI3K inhibitors have stronger binding affinity to the enzyme with IC_{50} in the nano- to pico-molar range, or nM to pM). At the cellular level, rigosertib causes profound abnormal cell division in cancer cells, including irregular chromosomal segregation (a hallmark of PLK inhibition) and cell cycle arrest at the G_2 to M check point, leading to mitotic catastrophe cell death. Rigosertib's effect on cell cycle arrest in cancer cells was correlated with rapid decrease of cyclin D1, a protein involved in cell cycle regulation. The exact mechanism of action of rigosertib on cyclin D1 and cell cycle regulation has not been fully elucidated, but some evidence suggests it is due to the drug's impact on some of the enzymes mentioned above. Discovered by scientists at Onconova with original technologies developed at Temple University, the drug has a composition of matter (COM) patent that runs till 2026 in the US.

Rigosertib's lead indication is MDS, with a Phase III trial in higher-risk, second-line MDS expected to report top-line data in Q114 and two Phase II trials in low-risk MDS ongoing. The decision to go to MDS was based on strong pre-clinical and encouraging Phase I/II data. Cyclin D1, the cycle protein that rigosertib was found to reduce, was over-expressed in MDS patients. When bone marrow mononuclear cells (BMMNCs; the expansion of this type of cell is a hallmark of MDS) of MDS patients were treated with rigosertib *in vitro*, they die quickly. However, BMMNCs from healthy subjects are not affected by rigosertib, demonstrating the drug's tumour cell selectivity. Several Phase I and II clinical trials in MDS demonstrated encouraging activity (detailed results are in later sections), which led to the ultimate decision by Onconova to pursue this indication for the drug.

1 K. Gumireddy et al., Cancer Cell, 2005, 7:275-286.
2 M. Steegmaier et al., Current Biology, 2007, 17:316-322.
3 A. Prasad et al., Oncogene 2009, 28:1518-1528.

MDS primer and treatment landscape

Myelodysplastic syndromes are a group of bone marrow diseases characterised by cytopenias (low blood counts) due to ineffective haematopoiesis (the formation and development of blood cells) caused by progressive bone marrow failure. The most common symptom is anaemia, which if severe would require blood transfusion. Other symptoms are also haematopoiesis related, including neutropenia (low neutrophil count), thrombocytopenia (low platelet count) and the consequential symptoms of infection or bleeding. Patients with MDS also carry high risk of progression to acute myelogenous leukaemia (AML), which is often refractory to standard treatment.

The International Prognostic Scoring System (IPSS) of MDS divides it into four groups, including low, Intermediate-1 (Int-1), Int-2 and high risk, based on three main criteria: bone marrow cytogenetics, marrow blast percentage and cytopenias. The system[4], first published in 1997, has replaced two other classification methods, the World Health Organization (WHO) and the French-American-British (FAB) classifications, because IPSS provides more meaningful differences for patients' clinical outcomes. The IPSS working group estimated that the low-risk subgroup accounts for 37%, Int-1 40%, Int-2 16% and high-risk 7% of all MDS, with median survival of 7, 3.6, 1.5 and 0.9 years respectively (Exhibit 2).

Several population-based studies[5] estimated the incidence rate of MDS to be 3.3 to 4.9 per 100,000 people/year, translating to 9,900 to 14,700 annually in the US. Among the age group that is mainly affected, people older than 70 years, the incidence could be as high as 25 to 75 cases per 100,000 people/year. The actual new incidences in 2013 and beyond could be higher because there was a trend of increasing incidences (at about 3% a year) among these studies as compared to previously reported studies. Based on these statistics, we estimate that the new incidences of MDS in US in 2014 could be 15,500, with 23% in the higher-risk group (Int-2 and high), and 77% in the lower risk group (low and Int-1). We estimate the incidence in the major developed countries of North America, Europe and Japan are about 2.5 times of the US or about 38,750 annually.

Treatment of MDS depends on a patient's performance status and IPSS status. For lower-risk patients, treatment objectives are to improve blood cytopenia and improve quality of life. In higher-risk patients, treatment aims to delay disease progression and prolong survival. Lower-risk patients with symptomatic anaemia are typically treated with erythropoetin (Epo) or blood transfusion, or in some cases immunosuppression drugs. Celgene's Revlimid is approved for lower-risk patients with 5q deletion (Del 5q-, about 10-15%[6] of MDS patients) based on achievement of transfusion independence (TI) in 65% transfusion-dependent patients in a Phase II, single arm study (TI was 69% in low/Int-1 patients). In a Phase III trial in Del 5q- patients, the TI rate was 43% and 56% for 5mg and 10mg of Revlimid vs only 6% for placebo.

Currently, lower-risk patients with thrombocytopenia or neutropenia have no standard of care and are often referred to clinical trials or hypomethylating agents (Vidaza and Dacogen). Vidaza (US and worldwide approval based on survival) and Dacogen (approved in the US based on response rate) or transplantation (if age eligible) are in fact the standard of care for higher-risk patients with good performance status. However, higher-risk patients with poor performance status are usually given supportive care or referred to clinical trials. In one Vidaza Phase III trial[7], the drug was associated with an overall response of 23% (7% complete and 16% partial response) and 37% of haematological improvements (HI). Similarly in Dacogen's Phase III trial[8], there was an overall response of 17% (9% complete and 8% partial) and stable disease of 13%. However, the majority of patients who responded to both drugs ultimately relapse, and currently these patients have no approved treatment options.

4 P. Greenberg et al., Blood 2012, 120:2454-2465.
5 D.E. Rollison et al., Blood. 2008;112:45-52 and J. Neukirchen et al., Leuk Res. 2011, 35:1591-1596.
6 A. N. Aristoteles et al., Clin Cancer Res, 2006 12:5-10.
7 L. R. Silverman et al., J Clin Oncol. 2002,20:2429-2440.
8 H. Kantarjian et al., Cancer. 2006, 106:1794-1803.

Exhibit 2: MDS classification and treatment

IPSS	No. of pts	%	Median survival (years)	Treatments
Low	2,625	37	7	EPO (<500 U serum EPO and/or transfusion requirement is less than two units/month), Revlimid for Del 5q-, or blood transfusion.
Int-1	2,778	40	3.6	
Int-2	1,126	16	1.5	Vidaza (preferred) or Dacogen for pts with good performance status (PS); stem cell transplantation for eligible pts; clinical trials or supportive care for poor PS pts.
High	479	7	0.9	

Source: MDS IPSS Working Group. Note: No. of patients refers to patients in a survey.

Rigosertib monotherapy studies in high-risk, second-line MDS

Rigosertib was given as 24-hour continuous infusion (CI) for three days in a 21-day cycle (investigators have tested various other schedules before settling into this one). The drug has been tested in four (04-15, 04-05, 04-17 and 07-H-0225, Exhibit 9) Phase I or II trials in mostly higher-risk MDS, with some patients relapsed after receiving HMA treatments. Various responses, including bone marrow complete response (bmCR, defined as having <5% of bone marrow blast), bmPR (bmPR, >50% of bone marrow blast reduction compared to baseline), or stable disease (SD, less than 50% of bone marrow blast reduction compared to baseline), were observed in these patients. In one trial, rigosertib efficacy was related to reduction of cyclin D1 level in tumour cells because cyclin D1 level was reduced in three HI patients, but not in any non-HI patients, supporting the hypothesis that inhibition of cyclin D1 is part of the drug's MOA.

Raza *et al.* conducted a cross-trial analysis of MDS patients enrolled in these four independent rigosertib trials, focusing particularly on bone marrow responses and their relationship to overall survival. Among 51 RAEB-1, -2, -t (corresponding to IPSS Int-1, -2 and high-risk) MDS patients, 16/51 (31%) achieved bmPR or better and 20/51 (39%) achieved bmSD. In 39 patients (Exhibit 4) who were previously treated with Vidaza or Dacogen, 12/30 (33%) had bmPR or better, including five with bmCR, and 15/30 (50%) had stable disease. OS of these patients was 35 weeks (8.2 months). Despite the general view that CR or PR are prerequisites of prolonged survival in diseases such as AML and MDS, prolonged survival was related to bone marrow responses among rigosertib-treated patients, with OS of 40 weeks for patients with stable disease or better, vs only 10 weeks for patients with progressive disease or those without bone marrow biopsy (Exhibit 3).

A response-survival analysis[9] of the Phase III trial AZA-001 (Vidaza was demonstrated to have survival benefit over best supportive care [BSC] in this trial) showed that patients who achieved stable diseases (haematological improvement without PR or CR) had the similar risk reduction as those with PR or CR, highlighting the importance of SD (HI) to longer survival in MDS patients. We therefore believe the response-survival relationship in rigosertib-treated MDS patients, despite being derived from a small sample size analysis, is authentic, and these responses (about 50% in rigosertib-treated second-line MDS) should lead to survival benefit in the Phase III trial.

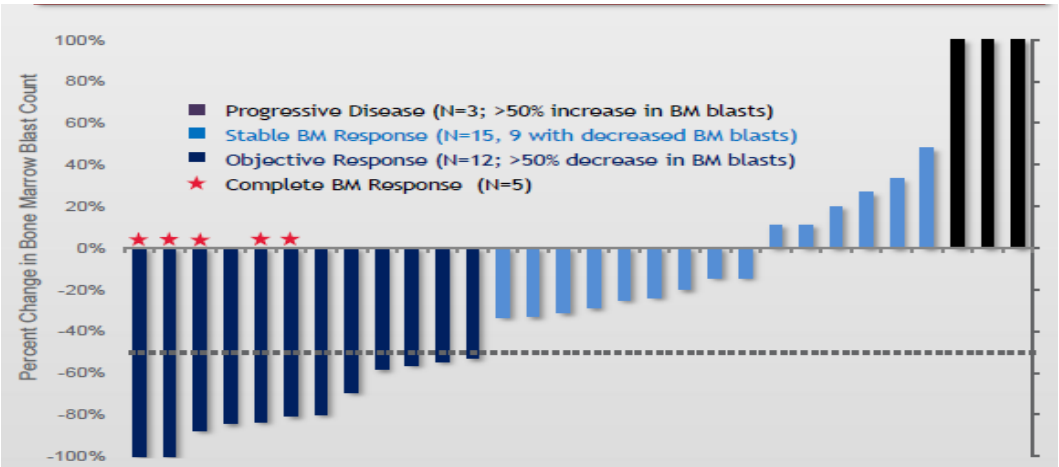
Exhibit 3: Relation between BM response and survival

Bm blast response	No biopsy	Progressive disease	Stable BM response	>50% blast decrease (bmPR or better)
In 51 IPSS INT-1, -2 and high-risk patients:				
Number of patients	10	5	20	16
Median survival (weeks)	11	15	37	48
In 39 patients previously treated with a HMA:				
Number of patients	9	3	15	12
Median survival (weeks)	11	10	40	40

Source: Onconova Therapeutics; ASH 2011 Abs# 3822

9 S.D. Gore et al., Haematological 2013; 98:1067-1072

Exhibit 4: BM blast response in second-line higher-risk MDS patients treated with rigosertib



Source: Onconova Therapeutics; ASH 2011 Abs# 3822

Phase III design and its rationale

Based on the Phase I/II data in patients who have failed HMAs, Onconova decided to start a Phase III trial (ONTIME) in this patient population comparing rigosertib to supportive care. The trial, for which the company obtained a special protocol agreement (SPA) from the FDA, has recruited 270+ patients with MDS who have failed either Vidaza or Dacogen in July 2013. Patients were randomised 2:1 to rigosertib (1,800mg/24hr x three days Q2W) plus best supportive care (BSC) vs BSC. Based on a median survival difference of 13-18 weeks between the treatment arm (35 weeks in the treatment and 17-22 weeks in the control arm, more discussion later), the trial has a 90% statistical power to detect a difference of survival.

Designing a Phase III trial without randomised Phase II results carries considerable risk because the size and statistical assumptions are all hypothetical. In the case of ONTIME, the median survival for the treated groups is based on the combined analysis of 39 patients in four Phase I and II trials, whereas the survival of the control patients is based on historical observation. Although historical observation tends to underestimate actual survival time in many cancer trials, we believe what was used in the ONTIME analysis is very close to reality. Two recent publications (Exhibit 5), one focusing on Dacogen failures and the other on Vidaza failures, have placed median overall survival at 4.3 months (18 weeks) and 5.6 months (24 weeks), respectively. Furthermore, one analysis (Vidaza failure) has shown that patients treated with BSC had only median survival of 4.1 months (17.6 weeks), at the lower end of the range assumed in the ONTIME trial.

Despite being adequately sized based on reasonable assumptions of rigosertib efficacy vs control, there are other factors that could render the ONTIME trial a failure. One uncontrollable variable is the post-study treatment choices in the trial. In ONTIME, cross-over of BSC patients to rigosertib after progression is not allowed, which helps preserve the drug's survival advantage in the treatment arm. However, patients in the control arm are allowed, as medically justified, access to low-dose cytarabine 20mg/m^2 sc once daily for the first consecutive 14 days of each 28-day cycle, up to four cycles, until progression or unacceptable toxicity.

As shown in the Vidaza failure analysis (Exhibit 5), patients received low-dose chemo (including low-dose cytarabine) had median survival of 7.3 months (31.2 weeks), which is very close to rigosertib's assumed median OS of 35 weeks. It is also likely that some patients in the control arm could go on to receive investigational agents, and could have even longer survival as shown in the Vidaza failure analysis (13.2 months). Ultimately, if post-study treatments of both the rigosertib and the control arms are balanced, as it is likely to be the case, a rigosertib survival benefit will likely be demonstrated in the ONTIME trial.

Exhibit 5: Survival analysis of MDS patients who failed Vidaza or Dacogen

	N	%	Median survival (mos)	Estimated 12-month survival
Dacogen failures:				
Overall	67		4.3	28%
IPSS N/A at Dacogen failure	18	27%		36%
IPSS at Dacogen failure	49	73%		
High	13	26%	N/A	27%
Int-2	23	48%	N/A	33%
Int-1	13	26%	N/A	33%
Dacogen refractory	37	43%	N/A	N/A
Dacogen relapsed	50	57%	N/A	N/A
Vidaza failures*:				
Overall	435		5.6	28.9%
IPSS at baseline				
High	223	49%	4.6	
Int-2	212	51%	7.3	
Vidaza non-responders	55%	4.6		
Vidaza responders	36%	7.4		
Intolerant	9%	N/A		
Post Vidaza treatment:				
Unknown	265	61%	3.6	
BSC	122	45%	4.1	
Low dose chemo	32	12%	7.3	
Intensive AML-like chemo	35	16%	8.9	
Investigational therapies	44	14%	13.2	
Allogeneic transplantation	37	14%	19.5	

Source: Cancer 2010,116:3830–3834 and J. Clin. Oncol., 2011, 29:3322-3327. Note: *MDS and AML patients.

Exhibit 6: Rigosertib ONTIME trial status

Date of DSMC	Patients analysed	Patients accrued	Decision
Feb. 2012	63	73	Continue w/o change
Aug. 2012	142	153	Continue w/o change
Mar. 2013	228	244	Continue w/o change
Possibly Q1 14	270+	270+	Final analysis

Source: Onconova Therapeutics. Note: DSMC = Data Safety Monitoring Committee.

So far, three interim analyses (Exhibit 6) of ONTIME have led to the decision to continue without modification of the protocol, suggesting the original assumption of the trial is still correct after 228 patients (~84% of total accrued) are analysed. A final analysis should be done and top-line results released in Q114.

Oral rigosertib: Lower-risk MDS

While the continuous infusion (CI) schedule is acceptable in the higher-risk MDS population, such a schedule would not be favoured in less advanced disease settings such as lower-risk MDS and most solid tumours. For this reason, Onconova has also developed an oral formulation of rigosertib. In a Phase I trial[10], 37 MDS patients (seven low, 16 Int-1, 10 Int-2 and four high risk; 73% previously treated with HMA) were treated with oral rigosertib and two out of eight (25%) had bmCR. In 16 patients treated with the recommended Phase II dose (560mg BID), only two had bone marrow blast increase, and the rest were considered to have bone marrow SD. Among 12 evaluable patients who were transfusion dependent at study entry, four (33%) achieved transfusion independence (TI). Given that the majority of these patients were previously treated with a HMA, this rate of TI is rather impressive. Rate of TI in lower-risk MDS is a very important response criterion because FDA has used it as the basis for Revlimid's approval. The main safety concern was urinary symptoms (grade 3) seen in three patients. Similar to the IV form, oral rigosertib was remarkably non-myelosuppressive, a key advantage as compared to Revlimid, the only approved drug for low-risk, 5q- MDS.

10 B. M. Komrokji et al., Br J Haematol. 2013;162:517-524

A Phase II trial (ONTARGET) tested the drug in 43 MDS patients (25 Int-1 and four low) and determined the best schedule of the drug is day 1-14 in a 21-day cycle because frequency of urinary side effects was much lower than other schedules. Thirteen out of 26 (50%) evaluable patients treated with this schedule had TI, a TI rate close to Revlimid's in Del 5q- patients. What is also impressive is that 11 of 13 responders were refractory to prior treatment of Epo and eight received prior Revlimid or Vidaza treatment, suggesting that rigosertib may be able to overcome erythropoietin-stimulating agent (ESA) resistance.

Full Phase II data (n=60) will be presented at the upcoming ASH meeting. Preliminary abstract (ASH 2013 Abs# 2745) showed that a correlation between a genomic methylation profile and response, which could help the company design future trials in a more targeted patient population. To put this Phase II efficacy data in the right context, it is worth noting that Revlimid at 5mg or 10mg achieved 43% or 56% TI in low-risk, 5q- MDS patients in a Phase III randomised trial.[11] Although the drug was very efficacious, its side-effect profile was not ideal, with 75% of treated patients developed grade 3 or 4 neutropenia and 5.8% developed grade 3 or 4 deep vein thrombosis (DVT).

Another Phase II study of oral rigosertib in up to 40 transfusion-dependent, documented ESA refractory, low or Int-1 or Trisomy 8 Int-2 MDS patients is on-going and could be completed by the end of 2014. The trial's primary endpoint is TI rate. These two Phase II trials could yield very meaningful data to guide Onconova's development strategy for oral rigosertib in non-5q-, lower-risk MDS patients.

MDS market analysis

As discussed above, we estimate the US incidence of MDS at about 15,500 people. US prevalence of the disease is estimated to be more than 55,000[12] and we estimate that the split between lower-risk (low and Int-1) and higher risk (Int-2 and high risk) is 77:23 (see p.4). Treatment of high risk MDS is dominated by Vidaza and Dacogen. Sales of the two drugs in the US in 2012 were $327m and $226m respectively, according to Celgene and Eisai. Worldwide sales in 2012 were $823m and c $283m, respectively. Although mainly used for MDS, both drugs, in particular Dacogen, are also used for AML in the US. Although precise numbers are hard to get, we estimate combined MDS sales in the US to be $450-500m.

Vidaza and Dacogen demonstrated objective responses (CR and PR) in about 23% and 17% of patients in their respective Phase III trials. Even if SD is included, the total response rate is about 50-60%, leaving about 40-50% as HMA non-responsive. Initially responding patients eventually relapse, leaving an estimated 5,000 (based on prevalence of 55,000 x 23% x 40%) of higher-risk MDS as second-line patients. These will be the initial patient size in the US for rigosertib if ONTIME is positive and the drug is approved in 2015. Assuming that rigosertib will be priced at the Vidaza and Dacogen price range, or $55,000-65,000 per course of treatment, the total market for the drug in the US would be c $275-325m. Worldwide, the market size is about $585-690m, assuming the patient numbers in the major developed countries (North America, Europe and Japan) are 2.5 times of that in the US and the average price outside of US is 75% of that in the US. Because we see no major competition in the first few years after rigosertib's launch, we believe the drug could reach $436m in about five years after its launch. We estimate peak sales of the drug to be c $625m worldwide.

The lower-risk, non-5q- MDS market for oral rigosertib is substantially larger than the high-risk, second-line MDS because 1) the treatable patient numbers are larger, estimated to be 10,000 in the US and 2) the treatment duration is much longer. Assuming oral rigosertib is approved (timeline uncertain because the development strategy at this point is still unclear to us) and a price range similar to that of Revlimid ($70,000-80,000 per course of treatment), the total US market size is

11 P. Fenaux et al., Blood, 2011, 118: 3765-3776.
12 CR Cogle et al., Blood. 2011;117(26):7121-7125

estimated to be c$700-800m and worldwide market c $1.5-1.7bn. We estimate peak worldwide sales of the drug to be c $1bn, assuming one or two major competitors in this segment of the market.

Competitive landscape of MDS

We have identified four new agents in development for high-risk MDS (Exhibit 8), including SGI-110 from Ostuka/Astex, sapacitabine from Cyclacel, pracinostat from MEI Pharma and mocetinostat from Mirati Therapeutics. SGI-110, a HMA, has been tested in Phase II trials for newly diagnosed and refractory AML and MDS. In 19 high-risk MDS patients who were previously treated with HMA, treatment with the drug led to 2 BmCR 3 HI-E (haematological improvement of erythrocytes). While it is impressive to see response in MDS patients previously treated with HMA, the drug's efficacy in the previously treated MDS patients is modest. SGI-110 would be developed as a drug to replace Dacogen, such as in newly diagnosed elderly AML patients in whom Dacogen has shown good activity, but its utility in HMA-treated, second-line MDS patients is probably very limited.

Sapacitabine, an oral nucleoside analogue, showed some efficacy in 63 MDS patients refractory to HMA, including 2CR, 9CRp and 5 major HI, for an ORR of 14%. Although the median OS of 8.3 months is impressive, the response rate for this drug is rather low. Another intriguing drug is pracinostat, an HDAC (histone deacetylase) inhibitor. In a pilot, one-centre trial in combination with Vidaza, the combination produced an ORR of 78% (7/9) in newly diagnosed MDS patients. Data from more patients in multi-centre trials are needed to prove this impressive efficacy before we could assign credibility to this early data. At the moment, we do not think the drug would be a competitor to rigosertib (IV) because paracinostat is being developed for first-line MDS in combination with Vidaza. Another HDAC inhibitor in development is mocetinostat, with efficacy shown in newly diagnosed and previously treated MDS with Vidaza.

Three drugs (Exhibit 8) are in development for lower-risk MDS, including ARRY-614 from Array Pharma, Telintra from Telik and oral azaciditine (CC-486) from Celgene. Among the three, Telik's Telintra has seen very little activity in clinical development because of the company's financial weakness. CC-486, on the other hand, has been developed as a maintenance therapy in AML patients who achieved CR, and therefore is not a direct threat to oral rigosertib. ARRY-614, a dual p38 MAPK and Tie2 inhibitor, produced TI in 4/12 (33%) of low/Int-1 MDS patients. Currently in Phase I development, more data are needed to assess the drug's activity in low/Int-1 MDS.

Exhibit 7: Ongoing rigosertib clinical trials

Trial name	Patients	Treatment	Details
ONTRAC (04-22)	Pancreatic cancer	Rig (CI) plus gemcitabine vs gem alone	650 pt Phase III, primary endpoint: OS. Interim (n=150) results: possibly Q413.
ONTIME (04-21)	MDS, Vidaza or Dacogen failure	Rig (CI, 3-d Q2W for 8 cycles or Q4W after 8 cycles) plus BSC vs BSC alone	290 pt Phase III, primary endpoint: OS. Start: Nov. 2010; results: Q114
ONTARGET (09-05)	MDS, TD, low, Int-1 or trisomy 8 Int-2	Oral, 560mg BID for 2 wks Q3W	60 pt Phase II, single arm, Primary endpoint: Units of blood cell transfusions at wk 8. Start: May 2012, results: Oct. 2014.
09-08	MDS, AML and CML	Oral, various doses BID for 3 wks Q4W; plus Vidaza	40 pt Phase I/II, primary endpoints: safety. Trial start: Aug. 2013. Results: Aug. 2015
09-09	Squamous cell carcinoma, refractory	Oral, 560mg BID for 2 wks Q3W	80 pt Phase II, primary endpoint: ORR; trial start: March 2013. Results: Sept. 2015
09-07	MDS, transfusion dependent, low, Int-1	Oral, 560mg BID for 2 wks Q3W	40 pt Phase II, primary endpoints: HI. Trial start: July 2013. Results: June 2015
04-24 (ONTIME)	MDS, failure after Vidaza or Dacogen, excess blasts	CI, 1,800mg/m^2 for 3 days Q2W (8 cycles) or Q4W (after 8 cycles)	90 pt Phase IIIB, primary endpoint: relationship btw Bm response and survival. Start: Aug. 2013. Results Dec. 2015

Source: Clinicaltrials.gov

Exhibit 8: Drugs approved or in development for lower and higher-risk MDS

Drug	Company	MOA	Main indication	Status	Route of admin.	Selected relevant data in higher and lower-risk MDS	Reference
Vidaza (azaciditine)	Celgene	HMA	High risk MDS	Approved in all maj. countries	IV and SC		
Dacogen (decitabine)	Eisai/ Astex	HMA	High risk MDS; elderly AML	Approved in US for MDS, EU for elderly AML	IV	Phase I, n=36 Int-2/high MDS failed Vidaza, 7/36 (19.4%) ORR, incl. 3mCR and 2SD, med. OS 7.3 months	ASH 2013 Abs#2796
Revlimid	Celgene	IMiDs	Low risk, 5q-; MM	Approved worldwide	Oral	Phase II plus pred., n=25 low/Int-1, non-5q- MDS, 5/23 (22%) RBC TI	ASH 2013 Abs# 1506
SGI-110	Ostuka/ Astex	HMA	New or ref. MDS, AML	Phase II	SC	n=93, 74 AML, 19 MDS, 2 CR, 1CRp and 2CRi in AML; 2mCR, 3 HI-E, 1 HI-N and 1 HI-P in MDS (prior HMA)	ASH 2013 Abs# 1548
ARRY-614	Array Biopharma	p38 MAPK and Tie2 inhibitor	Low/Int-1 MDS	Phase I	Oral, QD or BID	n=62, 12/54 evaluable and 9/31 on drug >16 wks had HI	ASH 2013 Abs# 387
Sapacitabine	Cyclacel Pharma	Nucleoside analogue	Elderly MDS ref. to HMA	Phase II randomized	Oral, QD or BID	n=63; 2 CR, 2 CRp, and 5 major HI; med. OS 8.6-9.7 months	ASH 2013 Abs# 2752
Clolar/ clofarabine	Sanofi/ Genzyme	second-gen nucleoside analogue	rr ALL, AML etc	Approved for rr ALL	IV daily x5	Phase II w/ cytarabine, n=29, 8/24 (33%) CR/CRp/mCR, 4/24 (17%) had SD, med. OS 4.8 months	ASH 2013 Abs# 1525
Pracinostat (SB939)	MEI Pharma	HDAC inhibitor	New AML and MDS	Phase II	Oral, thrice weekly (TIW)	In pilot Phase II, MDS, w/aza, 7/9 (CR+CRi+PR) incl 7 CR	ASH 2012 ABS# 3821
TELINTRA (TLK199)	Telik	Glutathione S-transferase Inh.	Lower risk MDS	Phase II	Oral	n=38 low/Int-1 MDS, 11 of 38 (29%) had HI-E; 3 of 11 (27%) had TI	Cancer. 2012, 118:2138-2147
Oral azaciditine (CC-486)	Celgene	HMA	Maintenance Rx in AMLw/ CR	Phase III	Oral	n=53 low/Int-1 MDS; 18/53 (34%) ORR, 13/53 (24.5%) HI, 12/30 (40%) TI>56 d, 7/30 (23.3%) TI>84 d	ASH 2012 Abs# 424
Mocetinostat	Mirati Therap.	HDAC inhibitor	Int-2/high MDS	Phase I/II	Oral	n=66 AML and MDS, w/aza., 22 MDS (13/22 (59%, CR+CRi), 6/17 (35%) TI	ASH 2013 Abs# 1550
Vosaroxin	Sunesis Pharm.	Nucleoside analogue	AML or MDS	Phase I/II	IV	Data in MDS pending	Company press release
Rigosertib (IV)	Onconova	PI3K and PLK1 path. inhibitor	High risk, second-line MDS	Phase III	CI 3d Q3W	n=30, 5/30 (17%) BmCR, 12/30 (40%) ORR, med. OS 8.2 months	ASH 2012 Abs
Rigosertib (Oral)	Onconova	PI3K and PLK1 path. inhibitor	Low/Int-1 MDS	Phase II	Oral	n=60, 17/48 (35%, ITT) and 15/33 (45%, intermittent dose,) TI>56 d	ASH 2013 Abs# 2745

Source: Company reports and Edison Investment Research. Note: IMiDs = immunomodulatory drugs.

Mono or combo studies in solid tumour

Rigosertib has been tested in various Phase I/II trials as monotherapy or in combination with chemotherapy (gemcitabine or oxaliplatin) in various solid tumours (Exhibit 9). The drug has shown modest activity in solid tumours as a monotherapy or in combination with chemotherapy, with partial responses (low percentage) seen in chemotherapy refractory ovarian cancer, metastatic breast (mBC) and pancreatic cancer. In 18 advanced pancreatic cancer (PC) patients, the drug in combination with gemcitabine achieved one confirmed PR in a gemcitabine-pre-treated patient, and CA 19-9 decrease (decrease of 19-9 is correlated with prolonged survival in PC) in eight of 13 evaluable patients. In 16 metastatic PC patients with 11 of whom were previously treated with gemcitabine, the median OS was 48 weeks. This result led to the initiation of a Phase III trial in PC.

In 48 patients with refractory metastatic head and neck cancer and advanced solid tumours, oral rigosertib was given at doses from 70mg to 700mg BID. Two metastatic head and neck squamous cell carcinoma patients who are refractory to platinum-based therapy had a confirmed CR and a PR, respectively, and two patients with ovarian cancer, one each with pancreatic, carcinoid, nasopharyngeal and renal cell tumour had stable disease. Onconova is conducting a single arm Phase II trial of rigosertib in squamous cell carcinoma (SCC) that no longer responds to standard therapy. This study will enrol 80 patients with various types of SCC, including head & neck (H&N), lung, anal and oesophageal. The trial tests oral rigosertib at 560mg BID for two weeks every three weeks (14d Q3W), and has ORR as the primary endpoint. The company expects to complete enrolment in H214 and obtain top-line results in September 2015.

Exhibit 9: Rigosertib clinical data

Study number	Phase	Schedule	Patient type	N	Efficacy	Reference
04-15	I/II	Rig mono; two- to three-day CI Q2W	MDS and AML	36, 13 prior HMA failures	1/13 BmPR and 4/13 SD	A Raza et al., ASH 2009 Abs# 3815
04-05	I/II	Rig mono; three- to six-day CI Q2W; three-day CI at 1,375 mg/m² for Phase II	MDS and AML ref. to hypomethylating agents (HMAs)	21; 2 IntT-2 and 5 high-risk MDS, 1 CMMOL and 13 AML	4 BmCR, 2 BmPR, 2 HI, 3 SD	SC Navada et al., 12th (2013) International Symposium on MDS Abs# 0367
04-17	I/II	Rig mono; two-day CI Q2W	MDS unresponsive to HMA	26; 13 Trisomy 8 and 13 Int-2/high-risk MDS	1PR, 1 SD; 4 BmCR and 8 SD	M Seetharam et al., Leukaemia Research 36 (2012):98–103
07-H-0225	I	Rig mono; three- or five-day CI Q2W	MDS, high risk and AML with Trisomy 8	14 (12 MDS and 2 AML)	3 BmPR and 3 HI	Olnes et al., Leukaemia Research 36 (2012):982–989
09-05	II	Rig mono; oral, 560 mg BID	MDS	43, 7/34/2 low/Int-1/Int-2	13 (50%) of 26 eval. had TI; 10 were ESA ref. and 8 had prior Rev or Vidaza Rx	A Raza et al., ASCO 2013 Abs# 7031
09-01	I	Rig mono; oral, BID for 14 days of a 21-day cycle	Advanced MDS, low, Int-1, Int-2 or high-risk	37; 7 low, 16 Int-1, 10 Int-2 and 4 high; 73% prev. treated with HMAs	2/8 with BMCR, 4 TI and 4 HI	RS Lomrokji et al., Br J Haematol. 2013 Aug;162(4):517-24
N/A	I	Rig mono; oral BID	Advanced tumour refractory standard care	40	1 CR and 1 PR in platinum refractory H&N, 2SD in ovarian, 1SD each in pancreatic, carcinoid, nasopharyngeal and renal cell	A Jimeno et al., ASCO 2013 Abs# LB-198
09-H_0094	I	Rig mono; two- to three-day CIV	Relapsed CLL, MCL, MM and HL	16	7/16 had SD	M. Roschewski et al., Leukemia. 2013 Sep;27(9):1920-3
	I	Rig mono; three- to five-day CIV	r/r acute leukaemia or MPN	30; 17 Phase I, 13 Phase II	7 (23%) had SD	ASH 2012 Abs # 3606
04-01	I	Rig mono; two-hour IV on days one, four, eight, 11, 15, and 18 in 28-day cycles	Advanced solid tumour	20	One OR in a refractory ovarian cancer	A. Jimeno et al., J Clin Oncol. 2008 Dec 1;26(34):5504-5510.
04-02	I	Rig mono; three-day continuous infusion (CI) every two weeks (Q2W)	Advanced solid tumour	29	9 (41%) had SD	T Ohnuma et al., Am J Cancer Res 2013;3(3):323-338
04-09	I	Rig combo; rig: two-hour IV on days one, four, eight, 11, 15, and 18 in 4W cycles; plus gemcitabine (G)	Advanced solid tumour:	36	1 PR in G-pret. HL, 2 PR (CA125 50% red.) in ovarian, 1 SD in NSCLC, and 1PR in thymic cancer. For pancreatic: 1 PR in 13 eval. and 8/13 with CA 19-9 decrease.	W Ma et al., Clin Cancer Res. 2012 Apr 1;18(7):2048-2055; ASCO 2011 Abs #3101
04-06	I	Rig combo; 24-hour CI, weekly; oxaliplatin	Advanced solid tumours	13	1 PR in chemo-ref ovarian cancer, 1 SD in colon cancer and ovarian cancer	I Chaudhary et al, ASCO 2010, Abs# e13133
04-08	I	Rig combo; 24-hour CI, weekly; oxaliplatin	Advanced solid tumours	30	1PR in ref. ovarian, 1 PR in mBC, 2 SD in colon, 1 SD in ovarian and 1 SD in renal cancer.	T Ohnuma et al., ASCO 2011 Abs# e13584

Source: See references column. Note: CLL: Chronic lymphocytic leukaemia; MCL: Mantle cell lymphoma; MM: Multiple myeloma; HL: Hodgkin's lymphoma; MPN: myeloproliferative neoplasm

Rigosertib (IV) in pancreatic cancer

Data from the Phase I study in pancreatic cancer suggested the combination of rigosertib with gemcitabine was active in pancreatic cancer patients. Furthermore, gene expression analysis in pancreatic tumours treated with gemcitabine identified PLK1 gene as related to gemcitabine resistance. Based on these two lines of evidence, Onconova initiated a Phase III trial in first-line pancreatic cancer patients in which the combination of the two drugs was compared to gemcitabine alone. This adaptive Phase III trial has built in an interim analysis among 150 patients, which according to the company, could take place in December this year. The interim analysis will decide 1) whether the trial will fail to demonstrate survival benefit for the combination and therefore will stop for futility; 2) whether to continue with or without size modification; or 3) whether it should be stopped early if significant efficacy is demonstrated with the combination.

Given the enormous number of trials in which experimental drugs, alone or added to gemcitabine, have failed to demonstrate a survival benefit over gemcitabine (except for FOLFIRINOX [oxaliplatin, irinotecan, fluorouracil, and leucovorin] regimen and Abraxane/gemcitabine), we believe the probability of a positive interim analysis outcome is very slim. The lack of a robust Phase II trial to compare the combination to gemcitabine alone and the modest activity seen with the combination in the Phase I trial prompts us to be very cautious about the outcome of this trial. Furthermore, as Abraxane/gemcitabine is approved and FOLFIRINOX regimen also adopted for patients with a better performance status, the treatment paradigm of first-line pancreatic cancer has shifted and the new reference regimen is the Abraxane/gemcitabine, making the rigosertib/gemcitabine data rather irrelevant even if it is just slightly better than gemcitabine. The combination would have to be compared to Abraxane/gemcitabine in a further trial to have any chance of being approved and adopted. For these reasons, we think investors should be well prepared to overlook the pancreatic cancer trial results. In our opinion, the release of the data, if negative, should remove a major overhang of the stock so that investors can focus on the outcome of ONTIME, which we think has better probability of success.

Other pipeline analysis

Onconova's second drug candidate, ON 013105, is a specific inhibitor of PLK2, one of the PLK kinases that is believed to play an important role in the survival pathway by physically stabilising the TSC1/2 complex in tumour cells under hypoxic conditions. The drug is in a Phase I trial in up to 43 patients with relapsed or refractory lymphoma, including an aggressive form of non-Hodgkin's lymphoma known as mantle cell lymphoma and acute lymphoid leukaemia. The drug is given as a weekly two-hour IV infusion. In 2011, the trial was suspended because of slow enrolment, and the clinical materials have since expired. The company plans to restart the trial's enrolment in Q114 and test the drug in solid tumour.

Onconova's other clinical-stage product candidate, recilisib (Ex-RAD), is being developed in collaboration with the US Department of Defence for acute radiation syndromes, specifically radiation-induced cytopenia. The drug's mechanism of action involves the enhancement of cellular DNA repair pathways and key elements of the DNA damage cascade in response to harmful radiation. The drug protected mice from radiation when given to the animal 24 hours before receiving a 7.5 and 8 Gy dose of radiation with survival rate of 80% to 88%, respectively. However, survival rate dropped to 38% in mice receiving only 15 minutes of treatment of the drug. Oral and sc forms were well tolerated in healthy volunteers in placebo-controlled Phase I trials. Onconova is likely to license this compound out for further development.

Exhibit 10: Preclinical (IND ready) assets

Drug	Indication	Mechanism
ON 1231320	Solid tumour	PLK2 inhibitor *
ON 24160	All tumours	Oral Anti-tubulin
ON 123300	C-Myc tumours	ARK5 inhibitor
ON 108600	Solid tumours	CK2 inhibitor *

Source: Company reports. Note: *collaboration with GVK Biosciences.

Partnership analysis

The company has entered into two major product commercialisation agreements on rigosertib, one with Baxter Healthcare and the other with SymBio Pharmaceuticals from Korea (Exhibit 11). The Baxter deal, with total earnable payments of up to $770m, gives Baxter the commercialisation rights of rigosertib (IV and oral) in Europe, whereas the SymBio deal gives SymBio the rights in Japan and Korea. As such, Onconova retains all product rights in the US, which we think is strategically important for the company as it strives for commercial development. These two deals could potentially provide Onconova with up to c $125m in 2014 in non-dilutive funding, pending positive clinical data and regulatory progress. We should also mention that Baxter, a company with deep haematology expertise and a generic franchise in oncology, is very committed to enter branded oncology business with rigosertib, a feature that Onconova considered important when the agreement was signed. Onconova owes Temple University 25% of sublicence fees it receives from Baxter and Symbio and a low single-digit royalty on net sales.

Exhibit 11: Onconova partnership agreements

Definition	Amount ($m)	Time of payment
Baxter agreement: rigosertib commercialisation rights in Europe		
Upfront payment	50	September 2012
Successful completion of Phase III of rigosertib IV in higher-risk MDS	50	Q114
Decision to move rigosertib (IV or oral) into second indication	25	2014 (est.)
Decision to move rigosertib (IV or oral) into 3rd indication	25	2014
Filing of rigosertib (IV) NDA for higher-risk MDS	25	Q414 (est.)
Filing of rigosertib (IV or oral) NDA for a second indication	25	N/A
Approval of rigosertib (IV) for high risk MDS	100	Q415 (est.)
Approval of rigosertib (oral) for low risk MDS	100	N/A
Approval of rigosertib (IV or oral) for a third indication (pancreatic cancer or H&N cancer)	100	N/A
Timely approval of rigosertib for high risk MDS in Europe	20	N/A
Achievement of pre-specified threshold of annual net sales of rigosertib	250	N/A
Royalty on sales: low teens to low twenties		Post-2016
Total earnable upfront, milestone payments	770	
SymBio agreement: rigosertib commercialisation rights in Japan and Korea		
Upfront payment	8	July 2011
First patient enrolled in rigosertib Phase III pancreatic cancer	3	Q114 (est.)
US approval for rigosertib in high risk MDS	5	Q415 (est.)
Japan approval for rigosertib in high risk MDS	3	N/A
US approval for oral rigosertib in low risk MDS	5	N/A
Japan approval for oral rigosertib in low risk MDS	5	N/A
US approval for rigosertib/gemcitabine in pancreatic cancer	5	N/A
Japan approval for rigosertib/gemcitabine in pancreatic cancer	3	N/A
US and Japan approval for rigosertib in other indications	4	N/A
Tiered sales related milestone payments	30	N/A
Royalty: mid-teens to 20% on net sales		
Total earnable upfront, milestone payments	71	
LLS agreement: research grant on rigosertib		
Grant to develop rigosertib (reduced to $8m from originally $10m)	8	
Royalty and milestone payment to LLS not to exceed $24m	(24)	Post rigosertib approval
Temple Univ. agreement: license of rigosertib and related technology		
25% of all sublicense fee payable to Temple		
Low single digit royalty of net sales to Temple		Post rigosertib approval

Source: Company reports. Note: LLS: Leukaemia and Lymphoma Society.

Sensitivities

In our view, the investment case rests on the successful execution of the clinical trials of rigosertib including the pivotal Phase III ONTIME, and the Phase II lower-risk MDS trial, together with support from the partnership with Baxter in particular, and to a lesser extent with SymBio. Onconova's value is mainly tied to the clinical outcome of rigosertib (IV) in higher-risk MDS and oral rigosertib in lower-risk MDS. We have assigned no value to the pancreatic cancer trial given the high historical failure rates of drugs in development for this indication. While we believe a negative result ought not to be significant, there could be some short-term impact on the share price. On the other hand, if the outcome of ONTIME is negative, which we believe has a low probability, the shares would suffer significantly because the result would not only render the approval of this drug in higher-risk MDS unlikely, but would also cast doubt on oral rigosertib's efficacy in lower-risk MDS. Although Onconova is well financed at this point, the company will need to raise additional funds to support its operation beyond 2014, particularly if ONTIME is negative. A positive ONTIME outcome would greatly improve the company's financial strength, because the company could receive up to $100m milestone payments from its two partners.

Valuation

We value Onconova based on a modified DCF method (see Exhibit 12 for our assumptions) that examines revenues, possible milestone payments and royalties over rigosertib's entire lifecycle (from approval to first patent expiry in 2026/27) based on forecast rigosertib sales in second-line, higher-risk and first-line, lower-risk MDS. We have applied success probabilities of 65% and 35% for these two different groups respectively. The total adjusted after tax present value (rNPV) of the three pipeline drugs, using a discount rate of 12.5%, is $417m. By adding forecast 2014 year end cash of $58.5m, we derive a valuation of $476m, or $22.3 per share ($20.7/share fully diluted). The model does not include any contribution for pancreatic cancer because of a presumed low likelihood of success. We have included risk adjusted $107.25m (after paying Temple 25%) out of a potential $841m future development and sales milestone payments in the model because the remaining amount is hard to forecast. Rigosertib (IV) accounts for 63.5%, whereas rigosertib (oral) accounts for 30% of the total pipeline value, suggesting the prominence of these two drugs among the entire pipeline.

Exhibit 12: Onconova valuation model

Product	Main Indication	Status	Probability of success	Launch year	Peak sales ($m)	Patent protection	Royalty	rNPV
Rigosertib (IV)	2nd-line MDS, higher risk	Phase III	65%	2015	$625	2026	Fully own in US; low teens to high 20s for EU	$272m
Rigosertib (oral)	MDS, lower risk, non-5q-	Phase II	35%	2017	$1,036	2026		$125m
ON 013105	Head & neck	Phase I	25%	2019	$149	>2026	Fully own	$10m
Recilisib	Acute Radiation Syndrome	Phase I		N/A			To be licensed out	$10m
Total								$417m
Cash and cash equivalents (year end 2014)								$59m
Total firm value								$476m
Total basic shares (m)								21.4
Value per basic share								$22.3
Stock options (2014, m)								2.8
Weighted average exercise price								$8.5
Cash on exercise								$23.8m
Total firm value								$500m
Total number of shares								24.2
Diluted value per share								$20.7

Source: Edison Investment Research

Financials

Onconova reported a net loss of $20.5m for Q313, including G&A expenses of $5.9m and R&D costs of $15.3m. Cash burn for the quarter was $15.8m. The company ended the quarter with cash and cash equivalents of $116.6m and guided year end cash of $98m. We estimate the company's cash utilisation will be $39m in 2014 and end the year with cash of $59m, assuming a $50m rigosertib related milestone payment (net of $37.5m after paying Temple Univ.)

Exhibit 13: Financial summary

$m	2011	2012	2013e	2014e
	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	1.5	46.2	3.3	50.0
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	1.5	46.2	3.3	50.0
EBITDA	(27.9)	(44.7)	(77.8)	(58.5)
Operating Profit (before amort. and except.)	(27.6)	(22.3)	(69.0)	(50.1)
Intangible Amortisation	0.0	0.0	0.0	0.0
Exceptionals	1.3	0.4	(0.1)	(0.1)
Other	0.0	0.6	0.5	1.2
Operating Profit	(26.3)	(21.3)	(68.5)	(49.0)
Net Interest	(0.0)	(8.6)	0.0	0.0
Profit Before Tax (norm)	(27.6)	(30.3)	(68.5)	(48.9)
Profit Before Tax (FRS 3)	(26.3)	(29.9)	(68.5)	(49.0)
Tax	0.0	0.0	0.4	0.0
Profit After Tax (norm)	(27.6)	(30.3)	(68.1)	(48.9)
Profit After Tax (FRS 3)	(26.3)	(29.9)	(68.1)	(49.0)
Average Number of Shares Outstanding (m)	2.14	2.21	7.97	22.00
EPS - normalised ($)	(14.79)	(15.51)	(8.86)	(2.34)
EPS - normalised and fully diluted ($)	(14.79)	(15.51)	(8.86)	(2.34)
EPS - (IFRS) ($)	(12.30)	(13.55)	(8.54)	(2.23)
Dividend per share (p)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0
EBITDA Margin (%)	(1877.3)	(96.7)	(2339.8)	(117.1)
Operating Margin (before GW and except.) (%)	(1854.3)	(48.2)	(2075.9)	(100.2)
BALANCE SHEET				
Fixed Assets	0.6	0.6	(0.1)	1.3
Intangible Assets	0.0	0.0	0.0	0.0
Tangible Assets	0.6	0.6	(0.1)	1.3
Investments	0.0	0.0	0.0	0.0
Current Assets	3.8	83.3	105.9	59.0
Inventory	0.0	0.0	0.0	0.0
Accounts recievable, net	0.0	0.0	0.0	0.0
Cash and cash equivalents	2.7	81.5	99.0	59.0
Other	1.1	1.7	6.8	0.0
Current Liabilities	(12.1)	(25.4)	(17.4)	(21.2)
Creditors	(12.1)	(25.4)	(17.4)	(21.2)
Short term borrowings	0.0	0.0	0.0	0.0
Long Term Liabilities	(10.8)	(15.5)	(14.1)	(14.1)
Deferred revenue, long term	(10.7)	(15.4)	(14.0)	(14.0)
Other long term liabilities	(0.1)	(0.0)	(0.0)	(0.0)
Net Assets	(18.4)	43.0	74.3	25.0
CASH FLOW				
Operating Cash Flow	(14.2)	1.6	(62.5)	(39.3)
Net Interest	(0.0)	0.0	0.0	0.0
Tax	0.0	0.0	0.0	0.0
Capex	(0.2)	(0.3)	(0.6)	(0.3)
Acquisitions/disposals	0.0	0.0	0.0	0.0
Financing	9.8	77.5	79.7	0.5
Dividends	0.0	0.0	0.0	0.0
Net Cash Flow	(4.6)	78.8	16.5	(39.0)
Opening net debt/(cash)	(7.3)	(2.7)	(81.5)	(99.0)
HP finance leases initiated	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.5	(1.0)
Closing net debt/(cash)	(2.7)	(81.5)	(98.5)	(59.0)

Source: Onconova Therapeutics reports, Edison Investment Research

Contact details	Revenue by geography
73 Route 31 North, Suite B Pennington, NJ 08534 US +1 267-759-3680 www.onconova.com	N/A

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

Management team

President and CEO: Ramesh Kumar, PhD	President, research and development: Thomas J McKearn, MD, PhD
Co-founder of Onconova, Dr Kumar received his PhD from the University of Illinois, Chicago, and trained at the NIH. He has held positions in R&D or management at Princeton University, BMS, DNX and Kimeragen. He has published more than 50 articles and co-edited the book *Molecular Basis of Human Cancer*.	Dr McKearn has served as VP, medical affairs and then as VP, strategic clinical affairs at Agennix, Inc. Previously he held positions at BMS. He was a founder and CEO of Cytogen. He is on the boards of Advaxis and Anima Cell Metrology Ltd. Dr McKearn received his degrees from the University of Chicago.
CFO: Ajay Bansal	**SVP and chief medical officer: Francois E Wilhelm, MD, PhD**
Before joining Onconova, Mr Bansal served as CFO of Complete Genomics, Lexicon Therapeutics, Tercica, and Nektar Therapeutics. He was a partner at Mehta Partners, and held positions at Novartis and McKinsey. He received master's degrees in management and operations from Northwestern University.	Dr Wilhelm previously held positions at Roche, Fujisawa, Pfizer, Procter & Gamble, Akros Pharma, and Johnson and Johnson. Dr Wilhelm has authored more than 30 publications, and received his MD and PhD degrees from Paris University.

Principal shareholders	(%)
Michael B. Hoffman	20.43
Baxter healthcare Corp	12.16
Premkumar E Reddy	5.95
Cadila healthcare Ltd	3.04
M. A. Weatherbie & Co.	2.08
Ventureast Life III LLC	1.79
FMR LLC	1.64

Companies named in this report

Baxter (BAX-NYSE), Celgene (CELG-NASDAQ), Array Pharm. (ARRY-NASDAQ), Cyclacel Pharm. (CYCC-NASDAQ), MEI Pharm (MEIP-NASDAQ), Telik (TELK-NASDAQ), Mirati Therapeutics (MRTX-NASDAQ), Sunesis Pharm. (SNSS), Sanofi (SNY-NYSE), Eisai Co Ltd (4523:Tokyo), Ostuka Corp. (4768: Tokyo)