EDISON

Onconova Therapeutics

Clinical update

Down but not out

Pharma & biotech

Rigosertib did not meet its primary endpoint of overall survival (OS) in the Phase III ONTIME trial in higher-risk myelodysplastic syndromes (MDS), but showed a statistically significant OS improvement in the subgroup of patients who had progressed or failed on hypomethylating agents (HMAs). The news is a setback, but there remains a path forward for rigosertib in a substantial subpopulation of higher-risk MDS in our opinion. We have reduced our valuation to $303m or $14.1/basic share by lowering rigosertib sales estimates and the probability of success in higher-risk MDS.

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)	(8.9)	0.0	N/A	N/A
12/14e	0.0	(77.4)	(3.6)	0.0	N/A	N/A

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

ONTIME missed its primary endpoint…

The ONTIME Phase III trial compared rigosertib IV to best supportive care (BSC) in higher-risk MDS patients who had progressed, failed or relapsed after previous HMA therapy. Although there was a numerical advantage favouring rigosertib (median OS was 8.2 months vs 5.8 months for control) and a hazard ratio (HR) of 0.86, this did not achieve the p<0.05 level of statistical significance (p=0.27). Rigosertib performed as expected (the Phase III design assumed a median OS of c 35 weeks, or 8.16 months), but the BSC arm exceeded expectations (assumed median OS of 17-22 weeks, or 3.96-5.13 months).

…but showed efficacy in a post hoc subgroup

However, a post hoc analysis of efficacy in subgroups found rigosertib to be efficacious in patients who progressed or failed previous treatment with HMAs. The median OS was 8.5 vs 4.7 months, HR of 0.67 and p-value of 0.022. The subgroup was not predefined, but nevertheless represents a substantial proportion (184 of 299, or 61.5%) of patients in the study. It is also clinically distinct (all patients are HMA non-responders) and the most challenging to treat (HMA failures have the poorest prognosis), and therefore has the greatest clinical need. For these reasons, we consider rigosertib could be further developed for this patient group, pending a dialogue with the FDA in the near future.

Valuation: Reduced to $303m

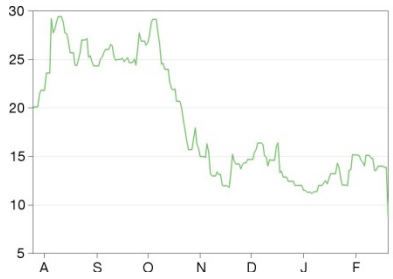
We have reduced our valuation to $303m by lowering the rigosertib sales estimates (peak sales $305m, down from previously $625m in higher-risk MDS) and the assumed probability of clinical success rate to 50% (from 65%). Given the share price reaction to the news, this suggests there is still upside to the shares if development of rigosertib for higher-risk, HMA non-responder MDS patients can be continued.

21 February 2014

Price	**US$8.8**
Market cap	**US$188m**

Net cash ($m) at Dec 2013	99
Shares in issue	21.4m
Free float	21%
Code	ONTX
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(33.3)	(42.2)	N/A
Rel (local)	(33.3)	(44.0)	N/A
52-week high/low	US$29.4	US$8.8	

Business description

Onconova Therapeutics is a clinical-stage bio-pharmaceutical company focused on developing novel small molecule drug candidates to treat cancer. Its lead drug candidate, rigosertib, is partnered with Baxter (Europe) and SymBio (Japan/Korea) and is in a Phase III trial for higher-risk MDS (IV form), and in Phase II for lower-risk MDS (oral form).

Next events

Rigosertib ONTIME data presentation	H114
Rigosertib higher risk MDS regulatory update	2014
Ribosertib (oral) MDS reg. path decision	2014

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Onconova datasheet

Exhibit 1: Onconova pipeline summary

Drug	Indication	Status	Notes
Rigosertib	Higher-risk MDS after HMA (IV)	Top-line results announced: missed primary endpoint; post hoc analysis suggests OS benefit in HMA non-responders.	Licensed to **Baxter** (total earnable payments of $600m) for Europe, and **SymBio** (total earnable payments of $50m) for Japan/Korea. Onconova retains all rights elsewhere (including in the US). Temple Univ. is entitled to 25% of sub-licence fees from Baxter and SymBio and a low single-digit royalty on net sales.
	Lower-risk MDS (oral)	Phase II final results at ASH	
	Refra. head and neck cancer (oral)	Phase II single arm, first results: 2014	
ON 013105	Refractory lymphoma, solid tumours	Phase I (solid tumour)	Cyclin D1 targeting agent. Studies could resume in Q114.
Recilisib	Acute radiation syndrome	Phase I ongoing	Collaboration with the US Department of Defence for radiation-induced cytopenia. Expected to be licensed out early.

Source: Edison Investment Research. Notes: Only clinical-stage assets shown.

Exhibit 2: Ongoing rigosertib clinical trials

Trial name	Patients	Treatment	Details
ONTIME (04-21)	MDS, Vidaza or Dacogen failure	Rig (CI, 3-d Q2W for eight cycles or Q4W after eight cycles) plus BSC vs BSC alone	299-pt Phase III shows median OS of 8.2 vs 5.8 months, HR= 0.86, p=0.27. Post hoc analysis suggests OS benefit in HMA non-responders (median OS of 8.5 vs. 4.7 months, HR of 0.67, p=0.022).
ONTARGET (09-05)	MDS, TD, low, Int-1 or trisomy 8 Int-2	Oral, 560mg bid for two weeks Q3W	60-pt Phase II, single arm, primary endpoint: units of blood cell transfusions at week eight. Start: May 2012, results: Oct 2014.
09-08	MDS, AML and CML	Oral, various doses bid for three weeks 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 two weeks 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 two weeks 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 three days Q2W (eight cycles) or Q4W (after eight cycles)	90 pt Phase IIIB, primary endpoint: relationship btw Bone marrow response and survival. Start: Aug 2013. Results Dec 2015.

Source: Edison Investment Research, Clinicaltrials.gov

Exhibit 3: Competitive environment – approved or developmental drugs 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 (azacitidine)	Celgene	HMA	High risk MDS	Approved in all major countries	IV and SC		N/A
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	Otsuka/ 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 weeks had HI	ASH 2013 Abs# 387
Sapacitabine	Cyclacel Pharma	Nucleoside analogue	Elderly MDS ref. to HMA	Phase II randomised	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 azacitidine (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 Therapeutics	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	N/A

Source: Edison Investment Research. Note: IMiDs = immunomodulatory drugs.

Update: ONTIME miss, but efficacy in HMA subgroup

The ONTIME Phase III study of rigosertib in higher-risk myelodysplastic syndromes (MDS) failed to show a statistically significant improvement in overall survival (OS), but a post hoc analysis did show a statistically significant OS improvement in the subgroup of patients who had progressed or failed on hypomethylating agents (HMAs). The news is a setback for Onconova, but there remains a path forward for rigosertib in a substantial subpopulation of higher-risk MDS in our opinion.

The ONTIME trial compared rigosertib IV to best supportive care (BSC) in higher-risk MDS patients who had progressed, failed or relapsed after previous HMA therapy. Although there was a numerical advantage favouring rigosertib (median OS was 8.2 months vs 5.8 months for control) and a hazard ratio (HR) of 0.86, this was not sufficient to reach the $p<0.05$ level of statistical significance ($p=0.27$). Rigosertib performed as expected (the Phase III design assumed a median OS of c 35 weeks, or 8.16 months), but there was a better than expected survival in the BSC arm (assumed median OS of 17-22 weeks, or 3.96-5.13 months).

However, a post hoc analysis of efficacy by subgroups suggests rigosertib may be efficacious in patients who progressed on or failed previous treatment with HMAs. There were 184 patients in this group (61.5%, 127 in the treatment arm and 57 on BSC) and the median OS was 8.5 months vs 4.7 months, equivalent to an HR of 0.67, achieving a p-value of 0.022. The subgroup was not predefined in the statistical analysis plan, but does represent a substantial proportion of second-line, higher-risk MDS patients. It is also clinically distinct (all patients are HMA non-responders) and is the most challenging to treat (HMA failures have the poorest prognosis), and therefore has the greatest clinical need. For these reasons, we believe that rigosertib could be further developed for this subtype, pending a dialogue with the FDA in the near future.

The other subset, comprising patients who had relapsed after responding to previous treatment with HMAs (115 of 299 enrolled), did not show a survival benefit. Additional analysis is underway to identify potential survival benefit in other subsets of patients.

Preliminary safety analysis indicates that rigosertib was generally well tolerated in the study. Severe adverse events were uncommon, with a similar profile of serious adverse events in both study arms. Grade 3/4 treatment-related hematologic and non-hematologic adverse events were reported in less than 7% and 3% of patients, respectively. Incidence of all grades of treatment-related nausea, diarrhoea, fatigue and constipation were 22%, 17%, 17% and 15%, respectively. All other treatment-related adverse events were reported in less than 10% of patients.

Onconova intends to present additional details, including secondary endpoints, at the 2014 ASCO Annual Meeting.

Sensitivities

The near-term investment case now rests on rigosertib's fate in higher-risk MDS, following the ONTIME trial result. A positive outcome from a pending meeting with the FDA, which may open the way for further development in HMA non-responders, would be positive and serve as a major catalyst for the stock. The longer-term investment case now rests on the ability to develop oral rigosertib for lower-risk MDS, with a decision on the Phase III pivotal programme possible in 2014. Given the disappointment of ONTIME, continuing support from partners Baxter and SymBio, which we expect to be the case, will be crucial. Onconova is currently well financed with sufficient cash to last into 2015, but may need to raise additional funds to support operations beyond 2015, particularly if new trials in higher-risk MDS patients are to be started.

Valuation

We have updated our valuation of Onconova in the light of the ONTIME study. The valuation remains based on a DCF model that examines revenues, possible milestone payments and royalties over rigosertib's lifecycle (from approval to patent expiry in 2026-27) based on forecast sales in second-line, higher-risk HMA non-responders (previously all high-risk, second-line MDS) and first-line, lower-risk MDS, with assumed probabilities of 50% (previously 65%) and 35% applied to these indications. Peak sales for rigorsertib IV for second-line, high-risk MDS has been reduced to $305m, based on HMA failures only, compared to a previous forecast of $625m, which had assumed all patient subtypes. This approach yields an intrinsic value of $272m for the pipeline. Adding forecast year-end 2014 cash of $30.5m yields a total value is $303m, equivalent to $14.1 per basic share ($13.5 per diluted share). Previously, we had valued Onconova at $476m, or $22.3 per basic share ($20.7 per diluted share).

Exhibit 4: 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, HMA non-responder	Phase III	50%	2016	$305	2026	Fully own in US; low teens to high 20s for EU	$115m
Rigosertib (oral)	MDS, lower risk, non-5q-	Phase II	35%	2017	$1,036	2026		$136m
ON 013105	Head & neck	Phase I	25%	2019	$149	>2026	Fully own	$11m
Recilisib	Acute Radiation Syndrome	Phase I		N/A	Expected to be licensed out			$10m
Total								$272m
Cash and cash equivalents (year end 2014)								$30.5m
Total firm value								$303m
Total basic shares (m)								21.4
Value per basic share								$14.1
Stock options (2014, m)								2.8
Weighted average exercise price								$8.5
Cash on exercise								$23.8m
Total firm value								$326m
Total number of shares (m)								24.2
Diluted value per share								$13.5

Source: Edison Investment Research

Financials

We have updated our financial model to eliminate a $50m milestone payment ($100m expected, but 50% risk-adjusted) in 2014 that would have been receivable from partners on a positive ONTIME result. Onconova has guided to ending 2013 with of $98m of cash (our model suggests $99m) and as we continue to estimate cash utilisation of c $68m in 2014, we expect Onconova to end the year with cash of c $31m. We expect the company to provide new financial guidance at its 2013 year-end financial conference call and will update our model accordingly.

Exhibit 5: Financial summary

$m	2011	2012	2013e	2014e
	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	1.5	46.2	3.3	0.0
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	1.5	46.2	3.3	0.0
EBITDA	(27.9)	(44.7)	(77.8)	(87.0)
Operating Profit (before amort. and except.)	(27.6)	(22.3)	(69.0)	(78.6)
Intangible Amortisation	0.0	0.0	0.0	0.0
Exceptionals	1.3	0.4	(0.1)	(0.1)
Other	0.0	0.6	0.5	1.2
Operating Profit	(26.3)	(21.3)	(68.5)	(77.5)
Net Interest	(0.0)	(8.6)	0.0	0.0
Profit Before Tax (norm)	(27.6)	(30.3)	(68.5)	(77.4)
Profit Before Tax (FRS 3)	(26.3)	(29.9)	(68.5)	(77.5)
Tax	0.0	0.0	0.4	0.0
Profit After Tax (norm)	(27.6)	(30.3)	(68.1)	(77.4)
Profit After Tax (FRS 3)	(26.3)	(29.9)	(68.1)	(77.5)
Average Number of Shares Outstanding (m)	2.14	2.21	7.97	22.00
EPS - normalised ($)	(14.79)	(15.51)	(8.86)	(3.64)
EPS - normalised and fully diluted ($)	(14.79)	(15.51)	(8.86)	(3.64)
EPS - (IFRS) ($)	(12.30)	(13.55)	(8.54)	(3.52)
Dividend per share (p)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	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	30.5
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	30.5
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	(3.5)
CASH FLOW				
Operating Cash Flow	(14.2)	1.6	(62.5)	(67.7)
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	(67.5)
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	1.0	(1.0)
Closing net debt/(cash)	(2.7)	(81.5)	(99.0)	(30.5)

Source: Company accounts, Edison Investment Research

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