EDISON

Onconova Therapeutics

Regulatory/clinical update

The path forward for rigosertib (IV)

Pharma & biotech

Onconova recently updated the scientific and investment communities on its development plans for rigosertib (IV) in myelodysplastic syndrome (MDS). While another Phase III trial will be necessary to gain FDA approval, European Medicines Agency (EMA) draft guidelines regarding subgroup analyses of clinical studies suggest a filing in Europe with the existing data may be possible. We expect clarity on the Phase III protocol necessary for US approval and the EU regulatory path in Q115. We have adjusted our valuation slightly to $254m or $11.70 per share.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/13	4.8	(62.2)	(6.05)	0.0	N/A	N/A
12/14e	0.8	(65.2)	(2.99)	0.0	N/A	N/A
12/15e	4.0	(64.0)	(2.87)	0.0	N/A	N/A
12/16e	4.0	(66.1)	(2.90)	0.0	N/A	N/A

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

Healthier data in sicker patients

While the ONTIME trial failed on an intent-to-treat (ITT) basis, subgroup analyses presented at the American Society of Hematology (ASH) illuminate the path forward for the programme. In a pre-defined subgroup of patients who progressed on or failed to respond to previous treatment with hypomethylating agents(HMAs), rigosertib demonstrated a 4.1-month survival benefit with a hazard ratio(HR) of 0.63 and a p-value of 0.01. The data also showed encouraging trends or statistically significant benefits in a number of cytogenetic abnormalities, and in patients deemed ‘very high risk’, according to a revised international prognostic scoring system (IPSS-R).

Early filing in Europe possible

Recent EMA draft guidelines on the use of subgroup analyses indicate that a filing in the EU, with the data already in hand, could be possible. This would trigger a $50mmilestone from EU partner Baxter upon Baxter’s decision to file with the EMA, and another $25mupon the actual filing. This scenario would lead to meaningful upside for shares as the milestones equate to $3.50 a share and would eliminate the need for a dilutive financing in 2015, the possibility of which is currently overhanging shares.

Valuation: Adjusted to $254m, or $11.60 per share

We have lowered our valuation slightly to $254m, or $11.70 per basic share, from $262m, or $12.1 per basic share, previously, due to a number of factors. Most notably we have lowered our rNPV for rigosertib IV. This is as a result of increased R&D expenses and lower profitability for the product post-launch, partially offset by increasing the chance of success from 50% to 60%, due to increased clarity on the data set. Our valuation suggests upside potential in the stock, which could start to be realised upon FDA and EMA clarity on the clinical and regulatory path for rigosertib (IV).

9 January 2015

Price	**$4.41**
Market cap	**$96m**

Net cash ($m)at end September 2014	57.3
Shares in issue	21.7
Free float	55.5%
Code	ONTX
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	8.9	7.6	(60.8)
Rel (local)	8.8	2.7	(65.0)

52-week high/low	US$15.2	US$3.3

Business description

Onconova Therapeutics is a clinical-stage biopharmaceutical 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).

Next events

Decision on US pivotal trial design	Q115
Clarity on EMA path to approval	Q115
Start oral rigosertib Phase III study in lower-risk MDS	H215

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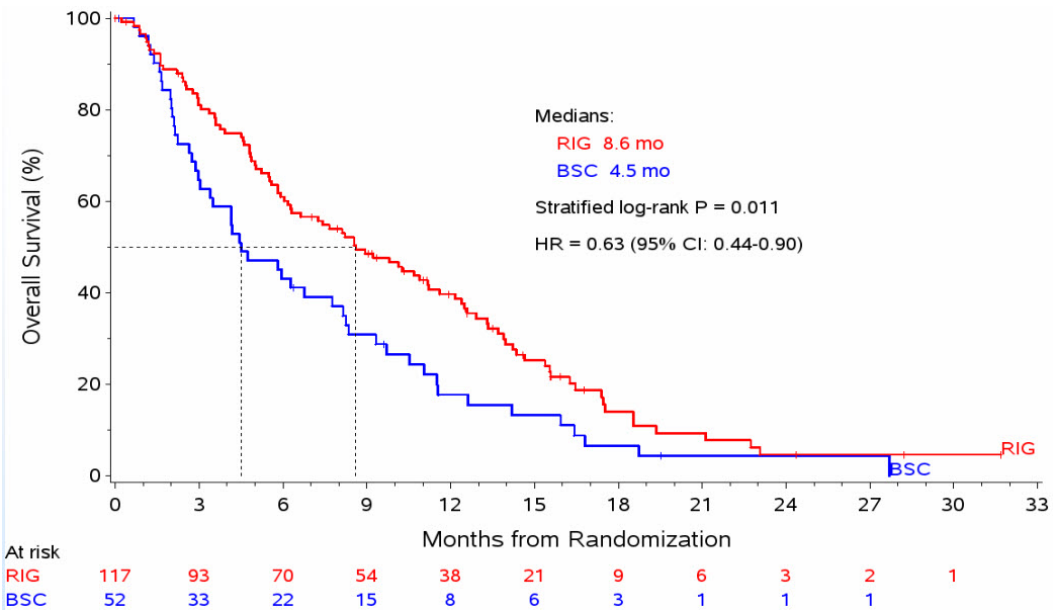
The path forward for rigosertib (IV) in higher risk MDS

At ASH, as well as at an analyst and investor event in New York, Onconova presented the potential path forward for rigosertib IV thanks to very compelling data in predefined or cytogenetic subgroups, which generally represented the sickest patients. The largest subgroup were primary HMA failures (those who had no response to HMA therapy, representing 64% of the trial population) where there was a significant benefit for patients in the treatment arm versus those receiving best supportive care. There was a 4.1-month median survival benefit (Exhibit 1), with an HR of 0.63 (p=0.011).

Exhibit 1: Kaplan-Meier Curve in the primary HMA failure subgroup in the ONTIME trial



Source: Onconova Therapeutics; ASH 2014

There was also a benefit observed across several cytogenetic abnormalities (Exhibit 2), with significant benefits in Monosomy 7 patients (~10% of the total) and Trisomy 8 patients (~10% of the total) and a strong trend in Del 7q patients (~7% of the total).There was also a significant benefit among those labelled 'very high risk' according to IPSS-R (~45% of the total).

Exhibit 2: Cytogenetic and IPSS-R subgroup data in the ONTIME trial

	Rigosertib		BSC			
Subgroup	N	Median (mos)	N	Median (mos)	HR (95% CI)	p-value
Monosomy 7	16	5.6	13	2.8	0.24 (0.09-0.66)	0.003
Trisomy 8	22	9.5	8	4.5	0.34 (0.12-0.95)	0.035
Del 7q	17	5.0	3	2.7	0.38 (0.10-1.48)	0.14
Very high risk per IPSS-R	93	7.6	41	3.2	0.56 (0.37-0.84)	0.005

Source: Onconova Therapeutics; ASH 2014

In order to gain FDA approval for rigosertib IV, Onconova plans to amend the protocol in its ongoing 04-24 study, a single-arm trial in HMA failures, and potentially use it for registration purposes. The company has said that the FDA is open to the use of a single-arm trial for this purpose, which would be easier to enrol as patients would not have to risk receiving no active therapy (while no therapy is

approved for HMA failures, patients may opt to go on other clinical trials) and would probably only require100-150 patients (~50 patients are already enrolled in the trial). The endpoint could be based on IWG response criteria and not survival. Under this scenario, the timing of the confirmatory trial would be much quicker than currently expected and the associated expenses lower. We should receive clarity on the US registration trial design in Q115.

Potential filing in Europe

In Europe, there is a chance that Onconova and its EU partner Baxter could file for approval based on the data they already have. Earlier in 2014, the EMA published draft guidelines titled “Guidelines on the investigation of subgroups in confirmatory clinical trials” where it indicates that approval based on subgroup analysis from one trial is possible. The company mentioned eight key criteria from these guidelines (summarised below):

1. Life-threatening condition and high unmet medical need.
2. Data from at least one additional trial to replicate the subgroup effect. Data from other trials may be relevant. In the case of a single pivotal study, the biological plausibility and clinical trial data would have to be exceptionally strong.
3. Clear rationale why the trial failed despite the drug being efficacious.
4. A well-defined and clinically relevant subgroup.
5. Pharmacological or mechanistic explanation why there is a different efficacy in a subgroup versus the rest of the population.
6. A larger treatment effect in the subgroup in absolute terms versus the intent-to-treat population.
7. Strong statistical evidence that the treatment effect is not random.
8. Careful assessment of the overall evidence and demonstration of credibility.

The company seems to meet at least seven of the eight criteria, with the big unknown being number two. The company has not disclosed whether it saw efficacy in the same subgroups in the earlier Phase I and Phase II studies as it did in the ONTIME trial, but if it did, that would buttress its argument for filing with the EMA early, with a confirmatory trial coming post-approval. If it were to file early, it would receive $50mfrom EU partner Baxter upon the decision to file, and an additional $25mupon the filing itself, amounting to $3.50/share in cash. That said, this scenario would depend on the outcome of ongoing discussions with the EMA as well as the agreement of Baxter, neither of which can be predicted with any certainty at this time.

If an early filing is not possible, the company would seek to repurpose the 04-24 study to meet registration requirements in the EU. However, while the FDA is amenable to using response criteria, the EMA would want an overall survival endpoint, which means that it would take longer to get a readout for the EMA than for the FDA. Our base scenario continues to be a launch in the US and EU in 2017 for rigosertib IV.

Optimising the oral programme in lower-risk MDS

In our view, the oral programme in lower-risk MDS patients represents the bulk of the value and ultimate potential of Onconova as it would be targeting a larger market (frontline patients) and, assuming IV is approved, be extremely profitable for the company (as it would be sold through an existing sales and marketing infrastructure). Timing of the initiation of the pivotal clinical trial is to be determined and will depend upon funding, results and approvals. The company still needs to optimise the dose and is still developing a prognostic genomic test, which would help it enrich the patient pool of the trial to its benefit (making sure those patients with mutations that have historically responded to rigosertib are enrolled in the trial).

Front-line potential in MDS/AML through combination use

Onconova is testing the use of oral rigosertib as a front-line therapy in MDS/AML patients in combination with azacitidine. Preclinical data showed a distinct synergistic effect when rigosertib is used in combination with azacitidine in leukemic cells (See Exhibit 3).

Exhibit 3: Synergy data of rigosertib+azacitidine

Combination index (CI) values from median-effect analysis†

Drug Combination				
Rigosertib (nM)	Azacitidine (nM)	Ratio	C.I.‡	Comment
125	2000	1:63	0.44	synergism
125	4000	1:31	0.30	strong synergism
250	2000	1:125	0.68	synergism
250	4000	1:63	0.57	synergism
500	2000	1:250	0.63	synergism
500	4000	1:125	0.75	moderate synergism

†HL-60 cells (1×10^6/mL) were first exposed to (E)-2-(5-((2,4,6-trimethoxystyrylsulfonyl) methyl)-2-methoxyphenylamino)acetic acid sodium salt ("Compound A") (125, 250, or 500 nM). After 24 h, azacitidine (2000 or 4000 μM) was added. The cytotoxic effect of the drug combination was evaluated at 72 h.
‡C.I. < 1 indicates synergism.

Source: Onconova Therapeutics; US Patent 8,664,272

We saw some hints of that in the data from a Phase I trial of oral rigosertib and azacitidine, which was also presented at ASH. Out of 18 patients, five had marrow complete remissions and an additional four had a complete remission with incomplete recovery of blood counts. Importantly, the addition of oral rigosertib to azacitidine did not worsen the adverse event profile compared to that of azacitidine alone. If this and the efficacy hold up, this would make the addition of oral rigosertib to front-line azacitidine therapy much more compelling from a medical point of view. The Phase II portion of this combination trial is currently open in the US and EU and we look forward to seeing additional data from this exciting programme. We continue to expect approval for rigosertib oral as a single agent in the US and EU in 2018.

Valuation

We have updated our valuation of Onconova after the Q314 results as well as the recent data presentations. We have lowered our rNPV for rigosertib IV in second-line, higher-risk MDS to $69m from $101m previously. This is as a result of increased R&D expenses and lower profitability for the product post-launch, partially offset by increasing the chance of success from 50% to 60%, as there seems to be compelling data that the drug is efficacious in various defined subsets of patients. We have also increased our rNPV for rigosertib oral in lower-risk MDS to $122m from $113m previously to reflect greater profitability post-launch, due to the advantages of using an already existing sales and marketing infrastructure. This approach yields an intrinsic value of $209m for the pipeline. Adding forecast year-end 2014 cash of $45.3 yields a total value of $254m, equivalent to $11.70 per basic share ($11.60 per diluted share, after options). Previously, we had valued Onconova at $262m, or $12.10 per basic share ($11.50 per diluted share).

Exhibit 4:Onconova valuation model

Product	Main Indication	Status	Prob. of success	Launch year	Peak sales ($m)	Patent protection	Royalty	rNPV ($m)
Rigosertib (IV)	2nd-line MDS, higher risk	Phase III	60%	2017	366	2026	Fully own in US; low teens to high 20s for EU	69
Rigosertib (oral)	MDS, lower-risk, non-5q-	Phase II	35%	2018	942	2026		122
ON 013105	Head & neck	Phase I	25%	2019	149	>2026	Fully own	9
Recilisib	Acute radiation syndrome	Phase I		N/A			To be licensed out	10
Total								209
Cash and cash equivalents (YE14e) ($m)								44.9
Total firm value ($m)								254.0
Total basic shares (m)								21.8
Value per basic share ($)								11.6
Stock options (3/2014, m)								4.1
Weighted average exercise price ($)								11.1
Cash on exercise ($m)								45.8
Total firm value ($m)								299
Total number of shares								25.9
Diluted value per share ($)								11.6

Source: Edison Investment Research

Financials

Onconova reported a net loss of $14.8m for Q314, including G&A expenses of $3.1m and R&D costs of $11.9m. The company ended the quarter with cash and cash equivalents of $57.3m. We have changed our 2014 forecast slightly based on actual Q314 results and we now estimate Onconova will end the year with cash of $45m. We estimate that Onconova would need additional financing of c $47m in 2015 to support its operation if the current burn rate continues and no milestone payment is to be received from its partners.

Exhibit 5: Financial summary

$m	2011	2012	2013	2014e	2015e	2016e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	1.5	46.2	4.8	0.8	4.0	4.0
Cost of Sales	0.0	0.0	0.0	0.0	0.0	0.0
Gross Profit	1.5	46.2	4.8	0.8	4.0	4.0
EBITDA	(27.9)	(44.7)	(70.7)	(71.9)	(66.5)	(68.6)
Operating Profit (before amort. and except.)	(27.6)	(22.3)	(62.2)	(65.2)	(64.0)	(66.1)
Intangible Amortisation	0.0	0.0	0.0	0.0	0.0	0.0
Exceptionals	1.3	0.4	0.0	0.0	0.0	0.0
Other	0.0	0.6	0.1	0.0	0.0	0.0
Operating Profit	(26.3)	(21.3)	(62.1)	(65.2)	(64.0)	(66.1)
Net Interest	(0.0)	(8.6)	(0.0)	(0.0)	(0.0)	(0.0)
Profit Before Tax (norm)	(27.6)	(30.3)	(62.2)	(65.2)	(64.0)	(66.1)
Profit Before Tax (FRS 3)	(26.3)	(29.9)	(62.1)	(65.2)	(64.0)	(66.1)
Tax	0.0	0.0	0.4	0.0	0.0	0.0
Profit After Tax (norm)	(27.6)	(30.3)	(61.7)	(65.2)	(64.0)	(66.1)
Profit After Tax (FRS 3)	(26.3)	(29.9)	(61.7)	(65.2)	(64.0)	(66.1)
Average Number of Shares Outstanding (m)	2.14	2.21	10.59	21.80	22.30	22.80
EPS - normalised ($)	(14.79)	(15.51)	(6.05)	(2.99)	(2.87)	(2.90)
EPS - normalised and fully diluted ($)	(14.79)	(15.51)	(6.05)	(2.99)	(2.87)	(2.90)
EPS - (IFRS) ($)	(12.30)	(13.55)	(5.82)	(2.99)	(2.87)	(2.90)
Dividend per share ($)	0.0	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET						
Fixed Assets	0.6	0.6	0.8	0.6	0.9	1.2
Intangible Assets	0.0	0.0	0.0	0.0	0.0	0.0
Tangible Assets	0.6	0.6	0.8	0.6	0.9	1.2
Investments	0.0	0.0	0.0	0.0	0.0	0.0
Current Assets	3.8	83.3	104.4	44.9	26.4	18.9
Inventory	0.0	0.0	0.0	0.0	0.0	0.0
Accounts receivable, net	0.0	0.0	0.0	0.0	0.0	0.0
Cash and cash equivalents	2.7	81.5	100.0	44.9	26.4	18.9
Other	1.1	1.7	4.4	0.0	0.0	0.0
Current Liabilities	(12.1)	(25.4)	(10.3)	(12.6)	(12.4)	(12.2)
Creditors	(5.6)	(5.5)	(3.7)	(5.8)	(5.3)	(4.8)
Short term borrowings	0.0	0.0	0.0	0.0	0.0	0.0
Accrued expenses/other	(6.5)	(19.9)	(6.6)	(6.8)	(7.1)	(7.4)
Long Term Liabilities	(10.8)	(15.5)	(13.9)	(13.1)	(56.1)	(112.1)
Deferred revenue, long term	(10.7)	(15.4)	(13.9)	(13.1)	(9.1)	(5.1)
Long-term borrowings	(0.1)	(0.0)	(0.0)	(0.0)	(47.0)	(107.0)
Net Assets	(18.4)	43.0	80.9	19.9	(41.1)	(104.3)
CASH FLOW						
Operating Cash Flow	(14.2)	1.6	(61.4)	(55.3)	(65.7)	(67.8)
Net Interest	(0.0)	0.0	(0.0)	(0.0)	(0.0)	(0.0)
Tax	0.0	0.0	0.0	0.0	0.0	0.0
Capex	(0.2)	(0.3)	(0.6)	(0.2)	(0.3)	(0.3)
Acquisitions/disposals	0.0	0.0	0.0	0.0	0.0	0.0
Financing	9.8	77.5	79.8	0.5	0.5	0.5
Net Cash Flow	(4.6)	78.8	17.8	(55.1)	(65.5)	(67.6)
Opening net debt/(cash)	(7.3)	(2.7)	(81.5)	(100.0)	(44.9)	20.6
HP finance leases initiated	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.7	0.0	0.0	0.0
Closing net debt/(cash)	(2.7)	(81.5)	(100.0)	(44.9)	20.6	88.1

Source: Onconova Therapeutics accounts, Edison Investment Research. Note: The long-term borrowings of $47m in FY15 are indicative of the company's funding requirement during this year.

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