EDISON

Oryzon Genomics

R&D update

Response rates consistently high in ALICE trial

Pharma & biotech

Oryzon presented an updated set of data from the Phase IIa ALICE trial in acute myeloid leukaemia (AML) at this year's virtual ASH conference (5–8 December). This is now the fourth update from the ALICE trial and the maturing data are consistent with the previously released positive efficacy results. The single-arm, open-label study enrolled newly diagnosed, elderly AML patients who were administered iadademstat in combination with standard of care chemotherapy drug azacitidine. Of the 13 evaluable patients, 11 (85%) achieved objective responses (OR). For comparison, OR rates are 25–32% in AML patients treated with azacitidine monotherapy. More data are due to follow. Our valuation is €560m or €10.6 per share (vs €9.9 per share previously).

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/18	6.8	(3.7)	(0.03)	0.0	N/A	N/A
12/19	10.3	(4.6)	(0.09)	0.0	N/A	N/A
12/20e	9.9	(4.7)	(0.07)	0.0	N/A	N/A
12/21e	9.9	(4.2)	(0.06)	0.0	N/A	N/A

Note: *Normalised, excluding amortisation of acquired intangibles and exceptional items.

Consistent response rate

Besides dose-finding data and safety/tolerability evaluation (primary endpoints), initial efficacy was evaluated using the secondary endpoints: objective response rates (ORR), time to response and duration of response. These secondary endpoints were measured by bone marrow aspirate. Of the 18 enrolled patients, 13 had at least one aspirate and were evaluable. Of the 13 evaluable patients, 11 (85%) achieved OR (seven complete responses or complete responses with incomplete haematologic recovery and four partial responses). As the data have matured, Oryzon has reported durability results. Eight of the 13 evaluable patients (62%) had a durable response (over six months), while time to response and duration of response were 34 and 308 days, respectively (better durability means more likelihood there will be a clinical survival benefit; as the trial is still ongoing, data are yet to reach maturity).

Excellent comparative performance so far

These results are in line with the previously published updates from the ALICE trial (Exhibit 1). The OR rate is consistently 75–85% and is higher than the historical response rates with classic chemotherapy (25–32%). Moreover, such rates compare well with a novel combination chemotherapy that includes venetoclax, an approved drug for front-line AML treatment (AbbVie/Genentech). Venetoclax plus azacitidine or decitabine achieved an OR rate of 67% in a late-stage trial and the consensus expects sales to reach $1.4bn in AML alone by 2026 (EvaluatePharma). More data will be released from the ALICE study, which will enrol up to 36 patients.

Valuation: €560m or €10.6 per share

Our valuation is slightly higher at €560m or €10.6 per share versus €527m or €9.9 per share due to rolling our model forward, which was partially offset by lower net cash. At end-Q320, Oryzon reported €44.6m in cash and €11.2m in total debt. We make no changes to our product assumptions for now.

11 December 2020

Price	**€2.68**
Market cap	**€142m**
Net cash (€m) at end Q320	33.4
Shares in issue	53.1m
Free float	80%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(7.0)	(5.8)	(13.3)
Rel (local)	(12.3)	(19.4)	(1.2)
52-week high/low		€3.70	€1.63

Business description

Oryzon Genomics is a Spanish biotech focused on epigenetics. Iadademstat (Phase IIa) is being explored for acute leukaemias and SCLC; vafidemstat, its CNS product, has completed several Phase IIa trials and a Phase IIb trial in borderline personality disorder has received an approval to start. Newer asset ORY-3001 is being developed for certain orphan indications.

Next events

Potential start of Phase IIb PORTICO trial with vafidemstat in aggression in BPD. Timeline to be confirmed after the extent of COVID-19 pandemic is known	H121
Updated data from iadademstat Phase IIa CLEPSIDRA in SCLC	H121

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Safety and tolerability

Overall, the authors of the ASH 2020 poster concluded that no new safety findings occurred since the last update and the combination of iadademstat and azacitidine shows a relatively good safety profile in elderly AML patients at the selected iadademstat's dose level of 60µg/m^2. Most patients experienced adverse events (AEs) that were considered related to the study drugs (azacitidine and/or iadademstat) and most of those were expected haematological AEs (neutropenia and thrombocytopenia). Only three non-haematological Grade 3–4 AEs were reported in two patients (asthenia and distortion of the sense of taste in one patient and weight reduction in another patient). Two serious AEs were considered to potentially relate to iadademstat, including one Grade 5 (fatal) intracranial haemorrhage, which was previously reported. LSD1 inhibitor class drugs are known to have haematological side effects at higher doses. However, these are usually predictable and manageable. The key point, in our view, is that this fourth safety update shows the non-haematological safety profile of this combination treatment remains good.

Exhibit 1: Evolution of Phase IIa ALICE trial efficacy data

Trial/ regimen	Phase IIa ALICE trial (iadademstat + azacytidine)				Venetoclax + azacitidine or decitabine	Azacitidine
Update/publication	EHA 2019	ASH 2019	EHA 2020	ASH 2020	DiNardo et al, 2019	Maurillo et al, 2012
Enrolment	17% (6/36)	36% (13/36)	50% (18/36)	50% (18/36)	-	-
Evaluable patients	5 patients	8 patients	13 patients	13 patients	145 patients	82 patients
ORR	**80% (4/5)**	**75% (6/8)**	**77% (10/13)**	**85% (11/13)**	68% (99/145)	32% (26/82)

Source: Edison Investment Research, Oryzon Genomics

Next steps

At the time of preparing the ASH 2020 poster, 18 patients had been enrolled in the trial, with a goal of recruiting up to 36 patients. Following interruptions in recruitment due to the COVID-19 pandemic, enrolment speed is now back up. Oryzon also stated that 'considering the different mechanisms of action of proapoptotic BCL2 inhibitors and the pro-differentiating agent iadademstat, we believe that combination approaches with iadademstat might increase therapeutic options for patients in first line, as well as for refractory or intolerant patients who have received BCL2 inhibitors as first line'. We view this as an indication the company has gained the confidence to investigate iadademstat combination with chemotherapy across broader setting in AML, including first line and second line.

Valuation and financials

Our valuation is slightly higher at €560m or €10.6 per share versus €527m or €9.9 per share due to rolling our model forward, which was partially offset by lower net cash. Oryzon's total operational spending for the first nine months (9m) of 2020 was €10.5m, flat compared to 9m19. Oryzon booked €7.3m as other income, which represents capitalised R&D costs (Oryzon follows local GAAP). The reported Q319 cash position was €44.6m (net cash €33.4m). Our model suggests the current cash position should be sufficient until 2023.

Exhibit 2: Oryzon NPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability of success (%)	rNPV (€m)	NPV/share (€/share)
Iadademstat (ORY-1001)	AML	2023	927	313.0	15%	62.0	1.2
Iadademstat (ORY-1001)	SCLC	2026	571	163.7	8%	40.5	0.8
Vafidemstat (ORY-2001)	AD	2026	4,510	1,199.3	15%	203.2	3.8
Vafidemstat (ORY-2001)	MS	2027	1,940	502.5	20%	133.2	2.5
Vafidemstat (ORY-2001)	BPD	2027	1,340	335.7	20%	87.9	1.7
Net cash (end-Q320)				33.4	100%	33.4	0.6
Valuation				**2,547.5**		**560.2**	**10.6**

Source: Edison Investment Research. Note: AML: acute myeloid leukaemia; SCLC: small cell lung cancer; AD: Alzheimer's disease; MS: multiple sclerosis; BPD: borderline personality disorder.

Exhibit 3: Financial summary

€000s	2017	2018	2019	2020e	2021e
December	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS					
Revenue	4,317	6,781	10,278	9,857	9,857
Cost of Sales	0	0	0	0	0
Gross Profit	4,317	6,781	10,278	9,857	9,857
Research and development	(5,306)	(7,412)	(11,322)	(11,060)	(11,060)
EBITDA	(3,498)	(2,766)	(3,679)	(4,091)	(4,095)
Operating Profit (before amort. and except.)	(3,660)	(2,905)	(3,820)	(4,225)	(4,225)
Intangible Amortisation	(664)	(7)	(9)	0	0
Exceptionals	0	(4)	(11)	0	0
Other	0	0	0	0	0
Operating Profit	(4,324)	(2,916)	(3,839)	(4,225)	(4,225)
Exceptionals	0	0	0	0	0
Net Interest	(928)	(796)	(737)	(471)	0
Profit Before Tax (norm)	(4,588)	(3,701)	(4,557)	(4,696)	(4,225)
Profit Before Tax (reported)	(5,252)	(3,712)	(4,576)	(4,696)	(4,225)
Tax	55	2,535	892	1,713	1,302
Profit After Tax (norm)	(4,533)	(1,166)	(3,666)	(2,983)	(2,922)
Profit After Tax (reported)	(5,197)	(1,177)	(3,685)	(2,983)	(2,922)
Average Number of Shares Outstanding (m)	31.7	34.6	41.6	45.8	45.8
EPS - normalised (€)	(0.14)	(0.03)	(0.09)	(0.07)	(0.06)
EPS - reported (€)	(0.16)	(0.03)	(0.09)	(0.07)	(0.06)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	24,914	31,786	42,357	52,196	62,039
Intangible Assets	22,458	29,330	39,938	49,795	59,653
Tangible Assets	638	665	631	613	598
Investments	1,818	1,791	1,788	1,788	1,788
Current Assets	36,130	35,664	37,738	43,012	29,445
Stocks	7	135	289	289	289
Debtors	857	971	2,071	1,521	1,796
Cash	34,950	34,320	35,111	40,935	27,093
Other	316	239	267	267	267
Current Liabilities	(8,696)	(10,441)	(10,546)	(9,642)	(8,840)
Creditors	(1,343)	(2,192)	(4,000)	(3,096)	(2,293)
Short term borrowings	(7,354)	(8,249)	(6,547)	(6,547)	(6,547)
Long Term Liabilities	(17,915)	(11,884)	(8,420)	(8,420)	(8,420)
Long term borrowings	(16,041)	(9,977)	(6,699)	(6,699)	(6,699)
Other long term liabilities	(1,874)	(1,907)	(1,721)	(1,721)	(1,721)
Net Assets	34,432	45,125	61,129	77,146	74,223
CASH FLOW					
Operating Cash Flow	(4,281)	(2,799)	(3,610)	(4,916)	(5,172)
Net Interest	(426)	2,133	(324)	0	0
Tax	0	0	0	1,713	1,302
Capex	(105)	(170)	(115)	(115)	(115)
Acquisitions/disposals	0	0	0	0	0
Financing	16,887	11,949	18,374	19,000	0
Other*	653	(6,576)	(9,916)	(9,858)	(9,590)
Dividends	0	0	0	0	0
Net Cash Flow	12,728	4,538	4,409	5,824	(13,575)
Opening net debt/(cash)	1,172	(11,555)	(16,093)	(21,866)	(27,689)
HP finance leases initiated	0	0	0	0	0
Other	0	0	1,364	0	0
Closing net debt/(cash)	(11,555)	(16,093)	(21,866)	(27,689)	(14,114)

Source: Oryzon Genomics, Edison Investment Research. Note: Oryzon reports in Spanish GAAP. *Includes cash outflows related to development costs that were capitalised.

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