EDISON

Oryzon Genomics

R&D update

Large response benefit consistent in ALICE trial

Pharma & biotech

On 11 June 2021, Oryzon presented an updated set of data from the Phase IIa ALICE trial in acute myeloid leukaemia (AML) at the virtual Congress of the European Hematology Association (EHA-2021). 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 18 evaluable patients, 15 (83%) achieved objective responses (OR). For comparison, OR rates are c 30% in AML patients treated with azacitidine monotherapy. This is now the fifth update from the ALICE trial (30 months since the start) and the maturing data are consistent with the previously released early efficacy results. Our valuation is €591m or €11.1 per share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/19	10.3	(4.6)	(0.09)	0.0	N/A	N/A
12/20	9.5	(4.8)	(0.07)	0.0	N/A	N/A
12/21e	9.9	(4.2)	(0.06)	0.0	N/A	N/A
12/22e	9.9	(4.2)	(0.05)	0.0	N/A	N/A

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

Confidence reaffirmed in iada plus aza combo in AML

OR rates were assessed by bone marrow (BM) aspirate. Of the 27 enrolled patients, 18 had at least one BM aspirate and therefore were evaluable on a per protocol basis. Of the 18 evaluable patients, 15 achieved OR (83%): 10 achieved complete response with or without incomplete haematologic recovery (CR/CRi) and five achieved partial responses (PR). These results are in line with the previously published updates from the ALICE trial. The OR rate is consistent at c 80% and is much higher than the historical response rates with classic chemotherapy (c 30%). Moreover, such rates compare well with a novel combination chemotherapy that includes BCL2 inhibitor venetoclax, a novel approved drug for front-line AML treatment (AbbVie/Genentech). Venetoclax plus azacitidine or decitabine achieved an OR rate of 68% in a late-stage trial and the consensus estimate is for sales to reach $1.4bn in AML alone by 2026 (EvaluatePharma).

Next steps

The trial aims to enrol 36 patients in total, so the data will be expanded in coming months with additional patients and longer follow-up times. Oryzon also reiterated its view that the late-stage development strategy could be focused on combination of iadademstat with other targeted therapy agents like BCL2 inhibitors or others to assess its potential in refractory or relapsed patients. We expect the next update from the ALICE trial at ASH in December 2021.

Valuation: €591m or €11.1 per share

Our valuation is slightly higher at €591m or €11.1 per share, versus €560m or €10.6 per share previously, due to rolling our model forward, which was partially offset by lower net cash. At end-Q121, the cash position was €38.5m (net cash of €23.0m). We make no changes to our product assumptions for now.

15 June 2021

Price	**€3.8**
Market cap	**€202m**
Net cash (€m) at end Q121	23.0
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	11.4	1.5	12.1
Rel (local)	9.8	(5.5)	(11.9)
52-week high/low		€4.3	€2.6

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

Next update from the ALICE trial	December 2021

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Phase IIa ALICE update

The single-arm, open-label study is enrolling newly diagnosed, elderly AML patients and investigates iadademstat in combination with standard-of-care chemotherapy drug azacitidine. At the time of writing the EHA-2021 poster (up to 24 May 2021), 27 patients had been enrolled.

Besides dose-finding data and safety/tolerability evaluation (primary endpoints), initial efficacy was evaluated using the secondary endpoints, OR, time to response (TTR) and duration of response (DOR).

As mentioned, the ORR results are in line with the previously published updates from the ALICE trial (Exhibit 1). As the data have matured, Oryzon has reported durability results. In total, 53% of the responding patients had responses lasting more than six months (durable response), while median time to response was 29 (better durability means more likelihood there will be a clinical survival benefit; as the trial is still ongoing, data are yet to reach maturity). Oryzon noted one standout patient case who had been diagnosed with M5b (monocytic) AML, a hard-to-treat form of leukaemia. This patient achieved CRi in 29 days while on iadademstat plus azacytidine therapy.

Exhibit 1: Evolution of Phase IIa ALICE trial efficacy data

	Phase IIa ALICE trial (iadademstat + azacytidine)					Venetoclax + azacitidine or decitabine	Azacitidine
Update/publication	EHA 2019	ASH 2019	EHA 2020	ASH 2020	EHA 2021	DiNardo et al, 2019	Dombret et al, 2015
Enrolment	17% (6/36)	36% (13/36)	50% (18/36)	50% (18/36)	75% (27/36)	-	-
Evaluable patients	5 patients	8 patients	13 patients	13 patients	18 patients	145 patients	241 patients
ORR(CR, CRi, PR)	**80% (4/5)**	**75% (6/8)**	**77% (10/13)**	**85% (11/13)**	**83% (15/18)**	68% (99/145)	31% (75/241)

Source: Edison Investment Research, Oryzon Genomics

Safety and tolerability

Overall, the authors of the EHA 2021 poster concluded that the combination of iadademstat and azacitidine shows a relatively good safety profile in elderly AML patients at the selected iadademstat dose level (60µg/m^2). Most patients experienced adverse reactions (ARs) that were considered related to the study drugs (azacitidine and/or iadademstat), but most of those were expected haematological AEs (neutropenia and thrombocytopenia). Only two ARs were deemed serious (reported previously). 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 fifth safety update shows the non-haematological safety profile of the combination treatment in the ALICE trial remains good.

Valuation and financials

Our valuation is slightly higher at €591m or €11.1 per share, versus €560m or €10.6 per share previously, due to rolling our model forward, which was partially offset by lower net cash. Oryzon's total operational spending in Q121 was €4.8m, similar to that of a year ago. Oryzon booked €3.0m as other income, which represents capitalised R&D costs (Oryzon follows local GAAP). The reported Q121 cash position was €38.5m (net cash: €23.0m). We are introducing 2022 estimates, which indicate a similar trend of spending to 2021. As a result, our model suggests the current cash position should be sufficient until early 2023, which is in line with the company's guidance.

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	332.7	15%	65.9	1.2
Iadademstat (ORY-1001)	SCLC	2026	571	171.5	8%	37.7	0.7
Vafidemstat (ORY-2001)	AD	2026	4,510	1,281.8	15%	223.0	4.2
Vafidemstat (ORY-2001)	MS	2027	1,940	539.7	20%	144.1	2.7
Vafidemstat (ORY-2001)	BPD	2027	1,340	360.8	20%	97.5	1.8
Net cash (last reported)				23.0	100%	23.0	0.4
Valuation				**2,709.5**		**591.0**	**11.1**

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	2018	2019	2020	2021e	2022e
Year end 31 December	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS					
Revenue	6,781	10,278	9,521	9,857	9,857
Cost of Sales	0	0	0	0	0
Gross Profit	6,781	10,278	9,521	9,857	9,857
Research and development	(7,412)	(11,322)	(11,075)	(11,060)	(11,060)
EBITDA	(2,766)	(3,679)	(4,148)	(4,077)	(4,076)
Operating Profit (before amort. and except.)	(2,905)	(3,820)	(4,293)	(4,225)	(4,225)
Intangible Amortisation	(7)	(9)	0	0	0
Exceptionals	(4)	(11)	0	0	0
Other	0	0	0	0	0
Operating Profit	(2,916)	(3,839)	(4,293)	(4,225)	(4,225)
Exceptionals	0	0	0	0	0
Net Interest	(796)	(737)	(471)	0	0
Profit Before Tax (norm)	(3,701)	(4,557)	(4,765)	(4,225)	(4,225)
Profit Before Tax (reported)	(3,712)	(4,576)	(4,765)	(4,225)	(4,225)
Tax	2,535	892	1,379	1,302	1,508
Profit After Tax (norm)	(1,166)	(3,666)	(3,386)	(2,922)	(2,717)
Profit After Tax (reported)	(1,177)	(3,685)	(3,386)	(2,922)	(2,717)
Average Number of Shares Outstanding (m)	34.6	41.6	49.2	53.1	53.1
EPS - normalised (€)	(0.03)	(0.09)	(0.07)	(0.06)	(0.05)
EPS - reported (€)	(0.03)	(0.09)	(0.07)	(0.06)	(0.05)
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	31,786	42,357	51,729	61,592	71,453
Intangible Assets	29,330	39,938	49,216	59,074	68,931
Tangible Assets	665	631	644	649	652
Investments	1,791	1,788	1,869	1,869	1,869
Current Assets	35,664	37,738	42,377	29,045	16,467
Stocks	135	289	317	317	317
Debtors	971	2,071	2,351	2,211	2,281
Cash	34,320	35,111	39,605	26,412	13,764
Other	239	267	105	105	105
Current Liabilities	(10,441)	(10,546)	(7,693)	(7,145)	(7,144)
Creditors	(2,192)	(4,000)	(2,839)	(2,291)	(2,290)
Short term borrowings	(8,249)	(6,547)	(4,854)	(4,854)	(4,854)
Long Term Liabilities	(11,884)	(8,420)	(10,483)	(10,483)	(10,483)
Long term borrowings	(9,977)	(6,699)	(8,680)	(8,680)	(8,680)
Other long term liabilities	(1,907)	(1,721)	(1,803)	(1,803)	(1,803)
Net Assets	45,125	61,129	75,931	73,009	70,292
CASH FLOW					
Operating Cash Flow	(2,799)	(3,610)	(5,432)	(4,485)	(4,146)
Net Interest	2,133	(324)	(247)	0	0
Tax	0	0	862	1,302	1,508
Capex	(170)	(115)	(153)	(153)	(153)
Acquisitions/disposals	0	0	0	0	0
Financing	11,949	18,374	18,181	0	0
Other*	(6,576)	(9,916)	(9,007)	(9,753)	(9,857)
Dividends	0	0	0	0	0
Net Cash Flow	4,538	4,409	4,205	(13,088)	(12,648)
Opening net debt/(cash)	(11,555)	(16,093)	(21,866)	(26,071)	(12,878)
HP finance leases initiated	0	0	0	0	0
Other	0	1,364	0	0	0
Closing net debt/(cash)	(16,093)	(21,866)	(26,071)	(12,983)	(230)

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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