EDISON

Oryzon Genomics

R&D results

Third positive update from Phase II ALICE trial

Pharma & biotech

Last Friday, Oryzon presented an updated set of data from the Phase IIa ALICE trial in acute myeloid leukaemia (AML) at the virtual 25th Congress of the European Hematology Association (EHA-2020). This is now the third update from the ALICE trial and the maturing data are consistent with the previously released positive early 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, 10 (77%) 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 €496m or €10.8 per share.

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.

Growing confidence in iada plus aza combo in AML

OR rates were assessed by bone marrow (BM) aspirate. Of the 18 enrolled patients, 13 had at least one BM aspirate and therefore were evaluable. Of the 13 evaluable patients, 10 (77%) achieved ORs: four complete responses (CRs), two CRs with incomplete haematologic recovery (CRi) and four partial responses (PR). These results are in line with the previously published updates from the ALICE trial. The OR rate is consistently 75–80% and is much higher than the historical response rates with classic chemotherapy (25–32%). Moreover, such rates compare well with a novel combination chemotherapy that includes venetoclax, a recently 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.

No major disruption from COVID-19

As per its last update (17 April 2019) on the expected impact of the COVID-19 pandemic, Oryzon stated that despite all the precautionary measures none of the ongoing trials were cancelled and patient recruitment was not postponed. Hospital visits, when possible, were replaced by remote monitoring. Oryzon had planned to initiate a new Phase IIb trial in agitation-aggression in patients with borderline-personality disorder (PORTICO trial). This has now been postponed by 'a few months', which we believe is a manageable delay given the circumstances.

Valuation: €496m or €10.8 per share

Our valuation is slightly higher at €496m or €10.8 per share due to rolling our model forward, which is offset by lower net cash. As of end-Q120, Oryzon reported €29.3m in cash and €11.0m in total debt. We make no changes to our rNPV for the time being. A detailed review of all of the company's ongoing programmes including upcoming catalysts can be found in our recent outlook report.

15 June 2020

Price	**€3.39**
Market cap	**€155m**
Net cash (€m) at end Q120	18.4
Shares in issue	45.8m
Free float	70%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(5.8)	108.0	(5.4)
Rel (local)	(12.7)	82.3	19.8
52-week high/low		€4.05	€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, is in Phase IIa trials in MS, AD and aggression. 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	2020
Updated data from iadademstat Phase IIa CLEPSIDRA in SCLC	2020
Updated data from iadademstat Phase IIa ALICE in AML 2020	2020

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Edison profile page

Phase IIa ALICE update

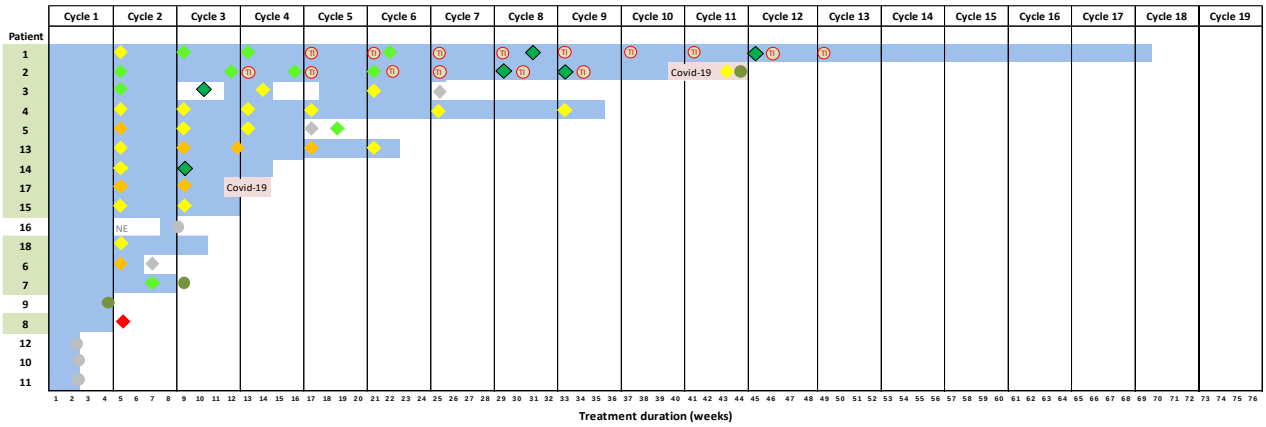
The single-arm, open-label study is enrolling newly diagnosed, elderly AML patients and investigates iadademstat in combination with standard-of-care chemotherapy drug azacitidine. At the time of writing the EHA-2020 poster, 18 patients have been enrolled.

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). These secondary endpoints were measured by BM aspirate.

Of the 18 enrolled patients, 13 had at least one BM aspirate and therefore were evaluable (the last trial update released in December 2019 included data from eight evaluable patients). New data include:

- 10 of the 13 evaluable patients (77%) achieved ORs: four CRs, two CRis and four PRs.
- TTR and DOR were 37 days and 20 weeks, respectively.

Exhibit 1: Patients enrolled in the Phase IIa ALICE trial



Source: Oryzon

Safety/tolerability

Overall, the authors of the EHA-2020 poster concluded that 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 AEs were neutropenia and thrombocytopenia. Only three non-haematological AEs (asthenia and distortion of the sense of taste in one patient and weight reduction in another patient) were observed. 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, from this third safety data update is that the non-haematological safety profile of this combination treatment remains good.

Iadademstat/azacitidine combo efficacy results in perspective

OR rates in AML patients treated with azacitidine monotherapy are 25–32% depending on age (Maurillo et al, 2012). A recently published article (DiNardo et al, 2019) described a clinical trial (n=145) where AML patients received venetoclax plus azacitidine or decitabine (both chemical analogues of cytidine) and the OR rate was 67%. Venetoclax (Venclexta, AbbVie/Genentech) is a novel anticancer drug approved (accelerated approval) by the FDA for frontline treatment of AML in combination with azacitidine or decitabine or low-dose cytarabine.

In the first set of data from the ALICE trial published in June 2019, the OR rate was 80% in five evaluable patients. In the second data update released in December 2019, the OR rate was 75% in eight evaluable patients. The current update, now from 13 evaluable patients, shows an OR rate of 77%, so even though the patient number is still relatively small, the results clearly track the 75–80% range. This is much higher than the historical response rates with classic chemotherapy and compares well with venetoclax's OR of 67%. Consensus expects venetoclax to reach $1.4bn in sales in AML alone by 2026 (EvaluatePharma).

Next steps

The second part of the ALICE study is still enrolling patients, so these results will be expanded in the coming months with additional patients and longer follow-up times. Oryzon also indicated that if these results are maintained, then 'further trials with this combination therapy in a confirmatory study setting' will be warranted.

Exhibit 2: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability of success (%)	rNPV (€m)	NPV/share (€/share)
Iadademstat (ORY-1001)	AML	2023	927	311.3	15%	53.2	1.2
Iadademstat (ORY-1001)	SCLC	2026	571	160.2	8%	29.4	0.6
Vafidemstat (ORY-2001)	AD	2026	4,510	1,192.5	15%	192.0	4.2
Vafidemstat (ORY-2001)	MS	2027	1,940	523.7	20%	126.2	2.8
Vafidemstat (ORY-2001)	BPD	2027	1,290	322.4	20%	76.5	1.7
Net cash (end-2019)				18.4	100%	18.4	0.4
Valuation				**2,528.5**		**495.7**	**10.8**

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	2020e	2021e
Year end 31 December	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS				
Revenue	6,781	10,278	9,857	9,857
Cost of Sales	0	0	0	0
Gross Profit	6,781	10,278	9,857	9,857
Research and development	(7,412)	(11,322)	(11,060)	(11,060)
EBITDA	(2,766)	(3,679)	(4,091)	(4,095)
Operating Profit (before amort. and except.)	(3,660)	(2,905)	(2,905)	(3,820)
Intangible Amortisation	(7)	(9)	0	0
Exceptionals	(4)	(11)	0	0
Other	0	0	0	0
Operating Profit	(2,916)	(3,839)	(4,225)	(4,225)
Exceptionals	0	0	0	0
Net Interest	(796)	(737)	(471)	0
Profit Before Tax (norm)	(3,701)	(4,557)	(4,696)	(4,225)
Profit Before Tax (reported)	(3,712)	(4,576)	(4,696)	(4,225)
Tax	2,535	892	1,713	1,302
Profit After Tax (norm)	(1,166)	(3,666)	(2,983)	(2,922)
Profit After Tax (reported)	(1,177)	(3,685)	(2,983)	(2,922)
Average Number of Shares Outstanding (m)	31.7	34.6	41.6	45.8
EPS - normalised (€)	(0.03)	(0.09)	(0.07)	(0.06)
EPS - reported (€)	(0.03)	(0.09)	(0.07)	(0.06)
Dividend per share (€)	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	31,786	42,357	52,196	62,039
Intangible Assets	29,330	39,938	49,795	59,653
Tangible Assets	665	631	613	598
Investments	1,791	1,788	1,788	1,788
Current Assets	35,664	37,738	24,012	10,445
Stocks	135	289	289	289
Debtors	971	2,071	1,521	1,796
Cash	34,320	35,111	21,935	8,093
Other	239	267	267	267
Current Liabilities	(10,441)	(10,546)	(9,642)	(8,840)
Creditors	(2,192)	(4,000)	(3,096)	(2,293)
Short term borrowings	(8,249)	(6,547)	(6,547)	(6,547)
Long Term Liabilities	(11,884)	(8,420)	(8,420)	(8,420)
Long term borrowings	(9,977)	(6,699)	(6,699)	(6,699)
Other long term liabilities	(1,907)	(1,721)	(1,721)	(1,721)
Net Assets	45,125	61,129	58,146	55,223
CASH FLOW				
Operating Cash Flow	(2,799)	(3,610)	(4,916)	(5,172)
Net Interest	2,133	(324)	0	0
Tax	0	0	1,713	1,302
Capex	(170)	(115)	(115)	(115)
Acquisitions/disposals	0	0	0	0
Financing	11,949	18,374	0	0
Other*	(6,576)	(9,916)	(9,858)	(9,590)
Dividends	0	0	0	0
Net Cash Flow	4,538	4,409	(13,176)	(13,575)
Opening net debt/(cash)	(11,555)	(16,093)	(21,866)	(8,689)
HP finance leases initiated	0	0	0	0
Other	0	1,364	0	0
Closing net debt/(cash)	(16,093)	(21,866)	(8,689)	4,886

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

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