EDISON

e-Therapeutics

A matter of time until prime time

Full-year results

Pharma & biotech

With the refocusing of the business and the new CEO's strategic review now implemented, e-Therapeutics (ETX) finds itself with the NDD platform and at least two lead preclinical small molecule immuno-oncology (I/O) assets at a time when big pharma partners are clamouring for those assets. This is because Merck and BMS's marketed anti-PD-1 antibodies need synergistic mechanisms to broaden and extend the number and duration of their responses. ETX's first partnership announcement will be a value inflection point.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
01/17	0	(14.1)	(4.1)	0.0	N/A	N/A
01/18	0	(6.7)	(2.0)	0.0	N/A	N/A
01/19e	0	(6.0)	(1.7)	0.0	N/A	N/A
01/20e	0	(4.0)	(1.2)	0.0	N/A	N/A

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

FY18 results demonstrate prudent stewardship

Last year's focus on ETX's costs demonstrated the company's commitment to containing costs. The operating loss in H218 was 16% below the first half's £3.7m. As impressive was the 58% reduction (to £6.8m) in the full-year operating loss over FY17 while at the same time preparing two network-driven drug discovery (NDD) assets for licensing. Cash at the year-end to 31 January 2018 was £9.6m and, outside of business development activities, options are available to extend the cash runway into 2020. Our model now includes slight changes to correct our previous estimates of R&D expense and share-based transactions to the reported values.

It's surge-pricing for immune-oncology assets

The establishment of programmed cell death protein 1 (PD-1) inhibitors as potent agents by big pharmaceutical companies to treat metastatic melanoma, kidney cancer and most commercially important, non-small cell lung cancer (NSCLC), has brought about a sea change in the treatment of solid tumours. But the successes and the responses have highlighted the need for combination therapies that broaden and enhance anti-PD-1 activity. As with the treatment of HIV and HCV, combinations of synergistic agents will be required to achieve prolonged responses. ETX's NDD platform that generated its small molecule tryptophan catabolism and immune checkpoint modulators, drop straight into this sweet spot.

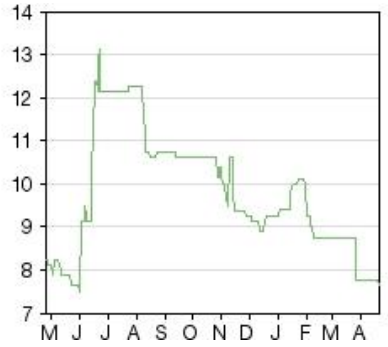
Valuation: Recent deals have led us to upgrade

We have updated our model for the FY18 results. With ETX's active business development efforts now ratcheting-up, we have reviewed the recent early-stage I/O deals like Nektar's and Viralytics's Phase I transactions with Bristol Myers Squibb (BMS) and Merck & Co, respectively, We have also reviewed ten preclinical I/O licensing transactions. Adding one median preclinical I/O transaction to ETX's market capitalisation increases our valuation from $42m to £60m.

23 April 2018

Price	**7.63p**
Market cap	**£21m**
Net cash (£m) at 31 January 2018	£9.6m
Shares in issue	268.5m
Free float	44.6%
Code	ETX
Primary exchange	LSE (AIM)
Secondary exchange	NA

Share price performance



%	1m	3m	12m
Abs	(12.9)	(23.8)	(7.6)
Rel (local)	(16.2)	(20.4)	(10.9)
52-week high/low		13.1p	7.5p

Business description

e-Therapeutics is a UK-based drug discovery company that has developed an in silico network-driven drug discovery platform. Following a strategic review by the new CEO, the focus is now on commercialisation: securing partners for its platform, discovery and development projects.

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FY18 financials

While the strategic direction of ETX now moves towards partnering and marketing and maintaining the assets and platform, the continuing stewardship of its resources figured highly in the FY18 results.

Careful with the cash

Cash and deposits were reported at £9.6m at 31 January 2018, down from £14m at the end of FY17, but were helped by the addition of £3.0m in R&D tax credits during the year. The cost-base has been significantly trimmed since the restructuring and a positive take-home message from the results announcement was that cautious financial stewardship will be a continuing effort. The 16% lower operating loss in H218 (to £3.1m; £6.8m for the FY) was testament to the longevity and the cadence of ETX's focus on costs. Since the JP Morgan Healthcare Conference in January, ETX's business development activities have ratcheted-up and these will take time to result in a licensing transaction. We are aware from projects in Edison's life science consulting business that typically, first meetings conducted at JPM in January are only now moving to full diligence in April. Between now and when these business development efforts come to fruition, R&D tax credits are expected to contribute £1.4m in FY19 – a function of the reduced R&D spend (FY18 tax credits were £3.1m) – and subject to more draconian management of the cost base, the cash runway could be extended into 2020. We have updated our model which results in very minor changes from our estimates to the reported values of R&D and administration expenses, and share-based transactions.

Focus, focus, focus

The last year has seen CEO Ray Barlow's systematic review focus ETX's most advanced assets on the NDD platform and the two NDD-derived immuno-oncology programmes. This has meant some difficult but necessary decisions in non-oncology areas and even in the non-immuno-oncology therapeutic area with ETX's hedgehog signalling modulator. ETX has developed and is now marketing both the NDD platform and its two I/O assets as proof that the platform works. This is at a time where there is an intense demand for any I/O assets that have the potential to be synergistic with the CPIs already on the market.

Externalisation

The full-year results stated that the detailed systemic externalisation of ETX's NDD platform which generated the two lead assets started in March 2018 and that those discussions are at a late-stage with a number of parties. In the past, these discussions would take the form of a prolonged dialogue between a biotechnology company and the potential pharmaceutical licensor with requests for incremental data on the assets as and when they become available. Our discussions with ETX's management suggest that the urgency and interest in complementary I/O assets make partnering much less of an iterative process.

Business development in the right space

ETX has refined its platform and pipeline for out-licensing and is in late-stage discussions with a number of parties that should change the complexion of the company. One possible transaction could be based upon the NDD platform and discovery deals with partners either to use ETX's technology in their drug discovery programmes, or to incorporate enhanced technologies into ETX's NDD product offering.

The licensing and enhancing of the NDD platform is what investors should expect in the near term and this should give ETX its first commercial validation. Subsequent commercial validation would come first from the licensing of either of ETX's I/O assets. This, at a time when there is intense demand for that type of asset and the platform to generate them. There are over 50 ongoing clinical studies in NSCLC alone that combine checkpoint inhibitors (CPIs) with another agent. The CPIs of Merck & Co, Bristol Myers Squibb, Pfizer, Roche and AstraZeneca act to make the patient's immune system recognise tumours. For patients whose tumours have high level expression of PD-1/PD-L1, even what is termed a complete response will not be the end of the patient's journey with the disease. Many patients' solid tumours have heterogeneous expression of PD-1/PD-L1 at the start of treatment, which declines as only those particular cells in the tumour are killed. What remains, and results in tumour progression, are cells within the tumour that either do not express PD-1/PD-L1, or express a mutated form, or express at a lower level. Thus the need has now become apparent to all those pharmaceutical companies that are marketing CPIs to in-license early-stage molecules which act in different parts of the cancer immunity cycle. These new molecules are required to be used in combination with the CPIs to achieve better responses and outcomes than with the CPIs alone. ETX's lead two molecules have been selected from network interactions to overcome the tumour-induced T-cell exhaustion (a hot target in I/O), rather than inhibiting a single molecular target, and we believe are likely to act synergistically with CPIs to restore the patient's immune system's ability to kill tumour cells.

The field of I/O is a high risk/high reward environment with Merck's Keytruda (pembrolizumab) and BMS's Opdivo (nivolumab) recording sales of $3.8bn and $5.0bn respectively, in 2017. It is into this environment that ETX is now offering its NDD platform and subsequently the tryptophan catabolism inhibitors and checkpoint (CP) signalling modulation inhibitors for partnering. It should be taken as partial validation that ETX is continuing to generate data on the two lead assets to aid partnering discussions. We believe that this is the result of a dialogue with partners that need more data in order to get them to the finish line.

Recent I/O transactions

The history of IO licensing transactions can be traced back to at least BMS's licensing of the anti-CLA4 monoclonal antibody ipilimumab (Yervoy) from Medarex in a collaboration that started in 2007 and led to Medarex's acquisition by BMS in 2009 for $2.4bn. That transaction was before IO really took-off and we believe that recent examples can be more instructive.

The indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor epacadostat was discovered by Incyte. IDO1 is an immunosuppressive enzyme that allows tumours to escape immune surveillance (in a similar way, but at a different part of, the cancer immunity cycle to PD-1/L-1). BMS's acquisition of Flexus Biosciences for $800m up-front and $450m in milestones was a visible indication of the value of an in-licensed CPI companion product. Flexus's lead asset was F001287, a preclinical small molecule IDO1 inhibitor. Incyte's epacadostat demonstrated activity when combined with Merck's anti-PD-1 monoclonal antibody Keytruda in *in vivo* solid tumour models. The collaboration agreement between Merck and Incyte dates back to 2014 when both products were combined in a single-arm Phase I study. Incyte retained global development and commercialisation rights for epacadostat,

although it also signed clinical collaborations with Merck, BMS, AstraZeneca and Roche and until 5 April 2018, had a market capitalisation of $17.8bn.

Until 5 April 2018, IDO1 inhibition as a companion to CP inhibition was the great hope for I/O combinations, but the Phase III failure of epacadostat in combination with Keytruda in melanoma has cast a cloud over IDO1 inhibition as a companion activity to CP inhibition. However, it has not diminished the demand for agents complementary with CPIs, but has raised the evidence requirement bar for new I/O agents like those from ETX to be part of potential I/O combination therapy. ETX's lead drugs are probably more attractive complements to the CPIs post IDO1 inhibition since they are selected on the basis of network activity, rather than activity against a single molecular target like IDO1.

OX40 (CD134) agonists have been in development since 2006, before the CPIs were discovered and had marginal efficacy until their combination with CPIs. Unlike PD-1/L-1inhibition, OX40 agonists in development at AstraZeneca and Pfizer are directed at activating T-cells as part of an anti-tumour response. While the OX40 inhibitors in clinical development by pharmaceutical companies were internally developed rather than being in-licensed, they also illustrate the focus of the sector in enhancing CP inhibition. The examples of IDO1 and OX40 inhibition differ from ETX's tryptophan catabolism and CP modulators in the respect that because NDD has been used to identify agents that are likely to have activity in combination and may be complementary to the CPIs.

The scope of agents that are currently incorporated into the clinical studies aimed at enhancing the response rate of the CPIs is very wide. If *Yervoy* can be considered one of the first such synergistic I/O agents, it is no surprise that a monoclonal antibody was the first type of agent as the targeting is very specific. However, the cost of goods of two monoclonal antibodies will be considerably higher than other combinations. Epacadostat was attractive as an orally-administered small molecule, but the OX40 agonists are monoclonal antibodies. ETX's lead two agents are orally-bioavailable small molecules.

Viralytics

The diversity of the agents that are being studied to enhance the clinical efficacy of the CPIs was illustrated earlier this year by Merck's acquisition of Viralytics. Viralytics is developing CVA21, an oncolytic Coxsackievirus that is in Phase I and II studies in combination with Merck's Keytruda. Early data presented at last year's American Association for Cancer Research meeting from the Phase Ib study of CVA21 in combination with Yervoy in the first 12 advanced melanoma patients which demonstrated a 50% overall response rate including four complete responses. In February, Merck announced the acquisition of Viralytics for £274m.

NKTR-214

At the Society for Immunotherapy of Cancer meeting in November last year Nektar presented early data from a Phase I/II study of NKTR-214 – a PEGylated recombinant interlukin-2 immune enhancer – in a total of 38 late-stage mixed cancer patients that included melanoma, renal cell carcinoma and non-small cell lung cancer. The patients were treated with a combination of NKTR-214 and Opdivo. Responses were observed in between 60% and 70% of those patients treated. In February this year, BMS licensed NKTR-214 for $1.85bn up-front plus a further $1.8bn in clinical and sales milestones.

From these latest two most recent transactions of products in the I/O space, which have different but complementary mechanisms to the CPIs, it struck us that ETX has two orally-bioavailable preclinical small molecules that were currently out for licensing (and the NDD platform that generated them) and these assets fit the profile of what is probably at the top of the pharmaceutical company business development wish lists. While it may take ETX's molecules three years to get

halfway through a Phase I study and then report the same sort of interim data that Viralytics and Nektar presented prior to their transactions, the valuation of ETX today does not appear to recognise the potential for collaboration and licensing that should be generated.

Valuation

ETX's market capitalisation today is about £21m. This appears to significantly discount not just the investment in the NDD platform that has generated two out-licensing-ready preclinical I/O assets, but also the potential for the assets themselves. The original deals between Incyte, Viralytics and Nektar were collaborations where the partners share the costs and the pharmaceutical company pays for the drug costs of the CPIs. While ETX may not yet be in a position to start a phase I study for either of its assets, the demand and the competition for attractive assets in the complementary I/O space suggest to us that earlier transactions for preclinical assets are likely.

VC methodology revisited

We had previously used Lerner's VC valuation method to value the ETX platform on the basis of a comparator oncology systems biology company discounted back to the stage of development of ETX. Three factors make that comparator less relevant:

- The intense interest by pharmaceutical companies in assets similar to those being developed by ETX that have therapeutic combination potential with the CPIs.
- The comparator company previously used, Merrimack Pharmaceuticals is a systems biology oncology company, but not an I/O specialist.
- The number and value of transactions for I/O agents that could be combined with a CPI in the treatment of solid tumours is now relevant to ETX's assets.

We believe that while the Lerner VC valuation methodology method is useful from a discounting perspective, it is less valid if we take into account the specific I/O transactions like the acquisition of Viralytics. In using Lerner's VC valuation we were trying to provide a sophisticated answer to a simple question that could be better answered by orientating the valuation with the value of recent preclinical I/O licensing transactions detailed in Exhibit 1 below:

Exhibit 1: Preclinical I/O transactions

Licensee	Licensor	Product	Up-front value	Milestone value	Date
Celgene	Agios	Metabolic IO inhibition	$200m	$169m	May 2016
Novo Nordisk	Innate Pharma	Anti-C5a receptor	€40m	€370m	June 2017
J&J	MacroGenecs	Bispecific DC3	$75m	$665m	May 2016
Celgene	Jounce	Anti-ICOS MAb	$261m	$2.3bn	July 2016
Amgen	Advaxis	ADXS-NEO	$65m	$475m	August 2016
Merck KGaA	F-star	LAG-3/PD-L1 inhibitor	€115m	€1.0bn	June 2017
AbbVie	Argenx	Anti-GARP MAb	$40m	$645m	April 2016
Bristol-Myers Squibb	PsiOxus	NG-348 oncolytic virus	$50m	$886m	December 2016
AstraZeneca	Heptares	Adenosine A2A RA	$10m	$500m	August 2015
Lilly	BioNTech	Functional T-cell receptor	$30m	$300m	May 2015

Source: Evaluate Pharma, company announcements

Lerner's methodology; Viralytics's transaction value

On the basis of the Phase I data in combination with Merck's CPI Keytruda, Merck proposed to acquire Viralytics for A$502m (£274m). We had assumed that one of ETX's preclinical I/O drugs is 3.5 years from the time it took Viralytics to complete and present the Phase Ib analysis and negotiate the transaction. At a discount rate of 12% our valuation would move to £185m from £42m. However, we have put this methodology on the back-burner for now because while it takes into account the time, it does not take into account the spend for ETX to reach the end of Phase I. What

this disparity between our previous valuation and the valuation of a Viralytics-type transaction does demonstrate is the sort of validation that could come from a positive Phase I study. In ETX's case, that point may only be about three years away (and require a partnership or fund-raising).

The value of an I/O out-licensing transaction

From Exhibit 1's ten preclinical I/O transactions, the average up-front payment alone is £64.5m while the median up-front payment is £40m. Adding either the median or mean preclinical I/O upfront payments to ETX's current market capitalisation of about £21m would increase its value by three or four times respectively, before the value of any milestones or royalties are taken into account.

We have not included the upfront payment of $1.85bn paid by BMS to license NKTR-214 because it is (so far) an outlier, albeit the most recent, I/O licensing transaction because like Viralytics, it was about three years ahead of where ETX's out-licensing candidates are today.

Preclinical platform valuation always challenging

Even though the valuation of preclinical platforms is inherently difficult, we have tried to coordinate our valuation of ETX using the three points in valuation space of Lerner's VC method, the transactions of Vialytics and Nektar in Phase II, and the ten recent Phase I I/O transactions. The transaction value of the Viralytics acquisition discounted back to ETX's preclinical stage today would result in a valuation of £185m. However, we have shelved this valuation for the immediate future because it would require:

- A fundraising or partnership to complete Phase I
- The completion of Phase I and data report at a medical conference
- The acquisition of ETX on similar terms to Merck's acquisition of Viralytics

The Viralytics and Nektar transactions have however demonstrated that an interim analysis of a Phase I study appears to be all that is needed to prompt a transaction for an I/O asset.

Exhibit 1 is a review of the preclinical I/O upfront payments for a single asset and despite ETX having two such assets, we are only considering one transaction. The licensing of one of the two ETX assets before the end of 2018 (no discounting) would imply an increase in valuation by at least £40m. Milestones and royalties have not been included in our analysis but we have chosen to add the median preclinical I/O value to ETX's market capitalisation, to minimise the effect of outliers and obtain our new valuation of £60m. The current £21m market capitalisation of ETX reflects investors' expectations of value generation from the platform and its £9.6m cash. We believe that while investors may have considered that a licensing transaction in the near future is possible, despite management's comments in the recent results that ETX is in late-stage discussions with a number of parties, few expect one to occur.

Exhibit 2: Financial summary

£'000s	2016	2017	2018	2019e	2020e
Year ending 31 January	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	0	0	0	0	0
R&D	(9,965)	(10,911)	(5,019)	(4,500)	(3,000)
G&A	(1,375)	(2,641)	(1,749)	(1,500)	(1,000)
EBITDA	(11,267)	(14,200)	(6,696)	(5,942)	(3,955)
Operating profit (before amort. and except.)	(11,340)	(14,256)	(6,768)	(6,000)	(4,001)
Share-based payment	(215)	(99)	(105)	(100)	(50)
Operating profit	(11,555)	(16,456)	(6,873)	(6,100)	(4,050)
Net interest	271	132	49	40	20
Profit before tax (adjusted)	(11,069)	(14,124)	(6,719)	(5,960)	(3,981)
Profit before tax (as reported FRS3)	(11,284)	(16,324)	(6,824)	(6,060)	(4,030)
Tax	2,464	3,073	1,360	1,400	760
Profit after tax (norm.)	(8,605)	(11,051)	(5,359)	(4,560)	(3,220)
Profit after tax (as reported)	(8,820)	(13,251)	(5,464)	(4,660)	(3,270)
Average number of shares outstanding (m)	264.4	267.1	268.4	268.4	268.4
EPS - adj. (p)	(3.3)	(4.1)	(2.0)	(1.7)	(1.2)
EPS - as reported (p)	(3.3)	(5.0)	(2.0)	(1.7)	(1.2)
Dividend per share (p)	0.0	0.0	0.0	0.0	0.0
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	804	207	206	219	244
Intangible assets	740	156	135	111	93
Tangible assets	64	51	71	108	151
Current assets	28,783	18,225	11,556	6,171	3,297
Stocks	0	0	0	0	1
Debtors	3,941	3,749	1,455	1,455	1,455
Cash	24,842	13,975	9,597	4,716	1,840
Other	0	501	504	0	1
Current liabilities	(1,156)	(1,951)	(1,024)	(1,024)	(1,023)
Creditors	(1,156)	(1,951)	(1,024)	(1,024)	(1,024)
Other creditors	0	0	0	0	0
Short-term borrowings	0	0	0	0	1
Long-term liabilities	0	0	0	0	0
Long-term borrowings	0	0	0	0	0
Deferred taxation	0	0	0	0	0
Other long-term liabilities	0	0	0	0	0
Net assets	28,431	16,481	10,738	5,367	2,519
CASH FLOW					
Operating cash flow	(11,204)	(12,509)	(5,753)	(6,442)	(3,954)
Net interest	329	194	86	45	30
Tax	2,027	3,073	1,360	1,088	1,120
Capex	(6)	(22)	(66)	(66)	(66)
Purchase of intangibles	(138)	(143)	(5)	(5)	(5)
Acquisitions/disposals	0	(1,473)	0	0	0
Financing	12	13	0	0	0
Dividends	0	0	0	0	0
Other	0	0	0	0	0
Net cash flow	(8,980)	(10,867)	(4,378)	(5,381)	(2,875)
Opening net debt/(cash)	(33,822)	(24,842)	(13,975)	(9,597)	(4,216)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	0	0
Closing net debt/(cash)	(24,842)	(13,975)	(9,597)	(4,216)	(1,341)

Source: e-Therapeutics accounts, Edison Investment Research

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