EDISON

Angle

Development update

Positive evaluations in multiple cancer types

Pharma & biotech

Angle's proprietary cell separation system, Parsortix, can be used to capture and harvest circulating tumour cells from blood, enabling a liquid biopsy. In the near term, Parsortix is being evaluated for use in the pre-surgery triaging of ovarian masses, with a clinical study expected to commence in Q415. H215 has seen positive evaluations of Parsortix in lung, prostate and breast cancer, supporting its potential utility in the multi-billion dollar cancer care market. We value Angle at £96m.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
04/14	0.0	(2.0)	(2.4)	0.0	N/A	N/A
04/15	0.0	(3.6)	(7.5)	0.0	N/A	N/A
04/16e	0.3	(5.1)	(8.4)	0.0	N/A	N/A
04/17e	2.2	(3.3)	(5.1)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items

100% sensitivity in lung cancer study

Cancer Research UK (CRUK) has published findings from its work in lung cancer comparing Parsortix to CellSearch, the FDA-approved antibody-based isolation system. The study found 100% sensitivity for Parsortix for small cell lung cancer at a ≥20 CTC threshold, compared to 83% for CellSearch at a ≥1 CTC threshold (and only 58% at a ≥5 CTC threshold). This demonstrates that Parsortix is able to harvest CTCs of a non-epithelial phenotype, which may otherwise be missed by antibody-based systems such as CellSearch.

Parsortix: Pure and simple in prostate cancer study

The Barts Cancer Institute (BCI) published the findings of its work in prostate cancer patients using Parsortix compared with two other antibody-based isolation systems. In patient samples, cell capture with Parsortix was comparable to IsoFlux but with a higher purity, and was significantly higher than CellSearch. Its ease and speed of use was highlighted as a particular advantage. Importantly, unlike many antibody-based systems which are limited to epithelial cells, Parsortix captured a range of cells including mesenchymal cells and cell clusters.

Promising initial findings in metastatic breast cancer

The University of Southern California is comparing molecular profiles of CTCs captured with Parsortix with solid biopsies in metastatic breast cancer patients. Initial findings suggest CTCs may provide more clinically-relevant information than the solid biopsies. This suggests a potential for liquid biopsies to replace metastatic biopsies and may enable more informed treatment decisions for these patients.

Valuation: DCF valuation of £96m or 162p/share

Our three-phase DCF valuation of Angle has increased to £96m or 162p/share (vs £93m or 157p/share), due to rolling the model forward in time. Our valuation is based on sales of Parsortix for use in research and clinical sales for the pre-surgery triaging of ovarian masses, with no contribution from other potential applications or the technology platform; our underlying assumptions are unchanged.

18 November 2015

Price	**77.50p**
Market cap	**£46m**
Net cash (£m) at 30 April 2015	8.4
Shares in issue	59.0m
Free float	89%
Code	AGL
Primary exchange	AIM
Secondary exchange	OTC QX

Share price performance

%	1m	3m	12m
Abs	(5.5)	(12.9)	12.3
Rel (local)	(4.3)	(9.3)	16.3
52-week high/low	104.00p		54.75p

Business description

Angle is a pure-play specialist diagnostics company. The proprietary Parsortix cell separation platform can be used for the detection and harvesting of very rare cells from a blood sample, including circulating tumour cells (CTCs). The resulting liquid biopsy enables the analysis of these cells for precision cancer care.

Next events

Start of ovarian cancer clinical study with the Medical University of Vienna	Q415
Results from KOL studies in other cancer indications	Q415/ H116
Further data from breast and prostate cancer studies	H116
H116 results	Jan 2016

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Edison profile page

Development update

The Parsortix cell separation system is able to capture circulating tumour cells (CTCs) from a blood test, constituting a liquid biopsy. Endorsement of its medical utility by key opinion leaders will be crucial to securing its widespread use in the diagnosis and treatment of cancer. H215 saw positive evaluations in multiple cancer types, adding to the H115 positive evaluation in ovarian cancer.

Cancer Research UK Manchester Institute and lung cancer

CRUK Manchester Institute published the results of a study comparing Parsortix to CellSearch for CTC isolation in small cell lung cancer (SCLC). CellSearch is the only FDA-approved CTC device (approved for enumeration of CTCs for prognostic purposes in metastatic breast, colorectal and prostate cancer); it isolates CTCs using magnetic particles coated with anti-epithelial cell adhesion molecule (EpCAM) antibodies. Once extracted, CTCs are enumerated on the basis of their morphology, expression of cytokeratins and a lack of the CD45 leucocyte marker. However, CTCs are heterogeneous, and CTCs can change phenotype in a process called epithelial-to-mesenchymal transition (EMT) that results in reduced expression of the target markers. Therefore, antibody-based systems limited to epithelial phenotypes could result in false negatives. In addition, mesenchymal CTCs have been implicated in the process of cancer metastasis,[1] and so have significant clinical implications. Parsortix uses a patented step-based microfluidic technology to capture CTCs on the basis of their size and compressibility, and therefore is not limited by cell marker bias. The main study findings were as follows:

- **Comparable EpCAM-positive CTC capture using spiked samples.** Using a highly EpCAM positive cancer cell line, the average percentage of spiked cells captured using Parsortix (79% +/-11%) was not significantly different to that of CellSearch (83% +/-6%).
- **Superior recovery of EpCAM negative or low expressing cells in spiked samples.** Using a cancer cell line with low EpCAM expression, the average capture was significantly superior using Parsortix: 41% +/-1% vs 0.35% +/-0.05% (p=0.02).
- **100% sensitivity using Parsortix in SCLC patient samples.** Using paired samples, CTCs were detected in 12 out of 12 samples using Parsortix (with a range of 20-1474). Using CellSearch, CTCs were detected in only 10 out of 12 samples (range of 1-3780), with three of the samples containing fewer than five CTCs. This indicates that Parsortix is enriching for EpCAM negative SCLC CTCs, and is able to encompass CTC heterogeneity, which has important clinical implications.
- **Parsortix can be used in tandem with cfDNA analysis.** 11 of the 12 patient samples were of sufficient volume to enable isolation of blood plasma prior to CTC enrichment using Parsortix. The investigators were then able to obtain cfDNA from all 11 samples, which could then be analysed by qPCR.

Lung cancer is the leading cause of cancer death globally (cancerresearch.org); its location makes initial biopsy difficult, and repeat biopsies even more so. SCLC accounts for 15% of all lung cancers. In advanced SCLC large numbers of EpCAM expressing CTCs are seen, but the CTC heterogeneity demonstrated in the study underlines that one cannot solely rely on marker-dependent CTC isolation methods.

Further, as Parsortix enables the harvesting of the CTCs for analysis, it can be used to provide additional information for treatment stratification, particularly as many cancer therapies are now targeted to specific mutations of the cancer. In addition, biomarkers are increasingly used to guide therapy. The recent FDA approval of the immunotherapy Keytruda (Merck) was limited to PD-L1

[1] Krebs MG, et al. (2014) Molecular analysis of circulating tumour cells – biology and biomarkers. Nat. Rev. Clin. Oncol. 11:129-144.

positive non-small cell lung cancer, as high tumour expression of PD-L1 appears to predict those most likely to benefit. This highlights the significant value-add that Parsortix could provide to cancer care, across multiple cancer types.

Compatibility with cfDNA analysis

cfDNA consists of small DNA fragments from the dead cells. In cancer patients, a proportion of the cfDNA will be circulating tumour ctDNA (ctDNA), which is released as fragments from necrotic and apoptotic tumour cells. The potential of liquid biopsies utilising ctNDA has recently been highlighted in a case study that followed a single patient with metastatic breast cancer over three years, extensively comparing biopsy and plasma samples. The study found that mutation levels in the plasma reflected those inferred from sequencing tumour biopsies and tracked different treatment responses across metastases. While these results would need to be confirmed in a larger cohort of patients, the findings lend further support to the potential utility of liquid biopsies in precision cancer medicine.

CTCs offer advantages over ctDNA as the information provided is not limited to DNA only, so also allowing for analysis at the RNA and protein levels. Further, having come from dead cancer cells, information from ctDNA may not be as clinically relevant. Previously, one of the great appeals of ctDNA is the ease with which it can be isolated from blood plasma, with CTCs being comparatively more difficult to capture. Now, Parsortix offers the capability to capture CTCs. When designing Parsortix, Angle recognised the utility of ctDNA and designed the machine so that the same blood sample can be used to harvest both CTCs and ctDNA, as demonstrated by the CRUK study. This provides flexibility to those using the machine and also enables the direct comparison of molecular readouts from both cfDNA and CTCs.

Barts Cancer Institute and prostate cancer

The BCI published the results of a study in which it evaluated the Parsortix system for CTC harvest in prostate cancer. The study compared Parsortix to CellSearch and to IsoFlux, another antibody-coated magnetic bead-based CTC isolation system that relies on cell surface markers to select CTCs. The findings were as follows:

- The investigators highlighted the **ease and speed of use** of the Parsortix system.
- **Higher purity and comparable capture in matched patient samples.** In spiked samples, capture and harvest rates by Parsortix were comparable to reported recovery rates by CellSearch, but lower than those of IsoFlux. However, in matched patient samples, the Parsortix system not only harvested comparable numbers of CTCs to IsoFlux, and significantly more than CellSearch, the purity of the CTC harvest was significantly higher using Parsortix than IsoFlux. White blood cell contamination can make downstream CTC analysis very difficult.
- **Parsortix harvested a range of CTC phenotypes, including mesenchymal cells and cell clusters.** Like mesenchymal CTCs, CTC clusters are reported to have increased metastatic potential, and to be more resistant to apoptosis and correlated with poorer prognosis.[2]
- **Parsortix-captured CTCs were found to be undamaged and viable**. Capture of viable cells not only allows for detailed analysis, but could also enable the culture of the cancer cells. In contrast, the use of magnetic beads for capture can lead to damage to, or death of the cell, which can limit detailed analysis and impede culture. In the future, culturing a patient's cancer could eventually allow for the testing of proposed treatments prior to patient administration.

The study concluded that, if the clinical value of Parsortix-captured CTCs can be confirmed, Parsortix will make CTC analysis much easier for clinical diagnostic application owing to its simple

[2] Xu L, et al. (2015). Optimisation and evaluation of a novel size-based circulating tumour cell isolation system. PLoS One. 10(9):e0138032.

approach, ability to capture varying phenotypes of CTCs, with shorter isolation time, higher purity and lack of contaminating beads. Incidentally, the study used an earlier version of software with Parsortix, with the newer software enabling it to process larger blood volumes, at greater speed, while maintaining optimal capture.

Other than skin cancer, prostate cancer is the most common cancer in American and European men, and the second most frequent cause of cancer-related death.[2,3] As CTCs hold valuable information about the tumour, including the genetic mutations that drive the tumour's growth and resistance mechanisms, liquid biopsies could provide an alternative diagnostic and monitoring tool for real-time personalised treatment of prostate cancer. Further work is being done in the study, with further announcements expected in H116.

University of Southern California and breast cancer

In September, the University of Southern California Norris Comprehensive Cancer Centre presented the results from the first phase of its work with the Parsortix system in breast cancer. The work compared RNA molecular analysis of a Parsortix liquid biopsy with that of conventional solid biopsies of metastatic sites in metastatic breast cancer patients. Parsortix provided highly enriched CTCs from all of the patients initially tested (n=4); the CTCs were suitable for rare cell amplification and RNA sequence analysis to detect biomarkers. Comparable gene expression between the CTCs and traditional solid biopsies was found, suggesting that a simple blood test may provide the same information as that provided by a solid biopsy on a repeatable and 'real-time' basis. Biopsies of metastases are often difficult due to the common locations of metastases so require invasive surgery that carries risks, are not easily repeatable and are costly and time-consuming.

Not only was the information gleaned from the CTCs comparable to that from the solid biopsies, the study found evidence of heterogeneity in the CTCs captured with Parsortix. This is particularly significant as Parsortix-harvested CTCs may provide a more complete genomic landscape of the tumour than that provided by a single-site biopsy. This is highly relevant for breast cancer, where HER2 status guides therapy and overt distant metastases and CTCs have been found to have discordant HER2 statuses compared with the primary tumour in up to 30% of cases.[4] The second phase of the work will include analysis of the remaining patient cohort and the profiling of CTCs sequentially over time to support treatment decisions. Similar findings in a larger patient sample would help substantiate these initial findings.

Updated ovarian cancer data

In H115, the Medical University of Vienna reported the "unprecedented sensitivity and specificity" of an approach using Parsortix alongside their RNA markers in the diagnosis of ovarian cancer, with 100% sensitivity and specificity with analysis of 30 RNA markers.

At the European Cancer Congress European Society for Medical Oncology 2015, the university reported further data from its work with Parsortix in the detection of ovarian cancer. The new data relate to further work comparing the use of Parsortix and qPCR (quantitative polymerase chain reaction), with conventional immune-fluorescent (IF) staining for the molecular analysis of CTCs in patients with gynaecological cancers. Compared to conventional IF, qPCR-based analysis resulted in a significantly higher CTC detection rate in blood samples taken from patients with gynaecological malignancies, across all cancer types the mean detection rate was 70% vs 26%. Using the 30 gene markers (threshold set for 100% specificity) 100% sensitivity was achieved in ovarian cancer patients (both primary and relapse; n=7) and all cancer patients were correctly classified by the Parsortix/qPCR-based analysis, whereas just one of the sample was IF-positive.

[3] Cancer.Org. 2015. What are the key statistics about prostate cancer? Available at: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics.

[4] Alix-Panabières et al. (2014) Challenges in circulating tumour cell research. Nat. Rev. Cancer. 14(9):623-631.

This provides further support for an approach combining qPCR and the Parsortix system for the diagnosis of ovarian cancer and other gynaecological malignancies. A clinical trial evaluating this approach for the pre-surgery triaging of ovarian cancer is due to commence in Q415. Success of the study could provide validation for the Parsortix system and lead to clinical sales for use in this indication in Europe as early as H2 FY17.

Valuation

We value Angle at £96m or 162p/share, based on a three-phase DCF model, assuming a discount rate of 10%, terminal growth of 2% and a long-term tax rate of 20% (reflecting the expected benefit of the Patent Box incentives). The breakdown of our valuation is shown in Exhibit 1. We have not changed the assumptions on our modelling, and continue to include only the sales of Parsortix for use in research and clinical sales in ovarian mass triaging, with no value assigned to its use in other indications, or the inherent value of the technology platform. The potential application in multiple cancer types, as suggested by the latest studies, offers significant upside to our valuation.

Exhibit 1: Assumptions for base case DCF valuation

Key assumptions	NPV (£m)
Free cash flow model FY16-25e	17.3
Tapering growth free cash flows FY26-35e	35.6
Terminal value (2% growth rate assumed)	34.3
Total NPV	87.2
Net cash (FY15)	8.4
Valuation (£m)	**95.6**
Valuation/share (p)	**162.1**
Discount rate	10%
Tax rate	20%

Source: Edison Investment Research

Our valuation is based on the following assumptions:

- **Parsortix use for research in clinical trials** – we forecast peak sales of c £9.5m in 2021, based on only 5% of Phase II and Phase III cancer drug trials using Parsortix by 2021.
- **Parsortix use for the pre-surgery triaging of patients with ovarian masses** – we forecast peak sales of c £16.5m in 2030. This is based on the Vienna study completing in Q416, with launch in Europe in 2017 where a CE mark is already granted, and in 2019 in the US given the pending FDA approval. Our sales forecasts are based on the assumption that initial uptake will be conservative, taking nine years to reach peak penetration (20%) in Europe and the US.
- **Costs** – we forecast c £9m in R&D spend over the next three to four years in order to secure EU and US approval for clinical sales and to fund clinical trials in other applications. We assume that Angle will bear the full cost of the ovarian clinical study, leaving room for upside should funding be available under various European research programmes. Our valuation assumes that Angle will market Parsortix directly, and that manufacturing costs remain as projected, driving an effective product margin of 80%.

Financials

Following the £8.2m net equity raise in February and March 2015, Angle finished FY15 with £8.4m cash; Angle has no debt. Our model continues to suggest that this should be sufficient to fund operations through to 2017. We forecast £1.3m of illustrative financing included nominally as long-term debt on the balance sheet in 2018 (as per our policy). We anticipate profitability in 2019. The

increase in net loss to £3.9m in 2015 from £2.2m in 2014 reflects the planned increase in operating expenditure on the Parsortix system.

Exhibit 2: Financial summary

£000s	2013	2014	2015	2016e	2017e
Year-end April	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	969	0	0	341	2,186
Cost of Sales	0	0	0	(102)	(648)
Gross Profit	969	0	0	238	1,537
Research and development	(300)	(900)	(1,600)	(3,080)	(2,458)
EBITDA	(674)	(1,994)	(3,452)	(5,007)	(3,081)
Operating Profit (before amort. and except.)	(693)	(2,051)	(3,563)	(5,170)	(3,267)
Intangible Amortisation	(308)	(99)	(204)	(342)	(366)
Share-based payments	(71)	(61)	(111)	(450)	(480)
Other	0	0	0	0	0
Operating Profit	(1,072)	(2,211)	(3,878)	(5,963)	(4,112)
Net Interest	42	13	9	33	15
Profit Before Tax (norm)	(652)	(2,038)	(3,554)	(5,137)	(3,252)
Profit Before Tax (FRS 3)	(1,031)	(2,198)	(3,869)	(5,929)	(4,097)
Tax	0	0	0	200	200
Discontinued operations		960	(18)		
Net Income (norm)	(652)	(1,078)	(3,572)	(4,937)	(3,052)
Net Income (FRS 3)	(1,031)	(1,238)	(3,887)	(5,729)	(3,897)
Average Number of Shares Outstanding (m)	40.6	45.1	47.6	59.1	59.3
EPS - normalised (p)	(1.61)	(2.39)	(7.50)	(8.35)	(5.14)
EPS - normalised and fully diluted (p)	(1.61)	(2.39)	(7.50)	(8.35)	(5.14)
EPS - (IFRS) (p)	(2.54)	(2.74)	(8.16)	(9.69)	(6.57)
Dividend per share (p)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	70.0	70.3
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	3,579	1,882	1,572	1,239	944
Intangible Assets	1,080	1,142	1,149	911	649
Tangible Assets	138	139	423	328	295
Investments	2,361	601	0	0	0
Current Assets	3,812	4,278	9,648	4,457	1,655
Stocks	62	52	197	200	250
Debtors	454	328	1,008	407	599
Cash	1,828	3,898	8,443	3,850	806
Other	1,468	0	0	0	0
Current Liabilities	(604)	(645)	(1,131)	(886)	(1,207)
Creditors	(604)	(645)	(1,131)	(886)	(1,207)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	0	0	0	0	0
Long term borrowings	0	0	0	0	0
Other long term liabilities	0	0	0	0	0
Net Assets	6,787	5,515	10,089	4,810	1,393
CASH FLOW					
Operating Cash Flow	(1,351)	(1,899)	(3,413)	(4,604)	(3,002)
Net Interest	110	(4)	5	33	15
Tax	0	0	0	150	200
Capex	(139)	(83)	(325)	(68)	(153)
Acquisitions/disposals	154	4,326	126	0	0
Financing	2,065	(270)	8,152	0	0
Dividends	0	0	0	0	0
Net Cash Flow	839	2,070	4,545	(4,489)	(2,940)
Opening net debt/(cash)	(989)	(1,828)	(3,898)	(8,443)	(3,850)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	(104)	(104)
Closing net debt/(cash)	(1,828)	(3,898)	(8,443)	(3,850)	(806)

Source: Company accounts, Edison Investment Research. Note: Historic reported revenues relate to the legacy business, which has now been divested. FY14 has been restated to exclude discontinued operations.

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