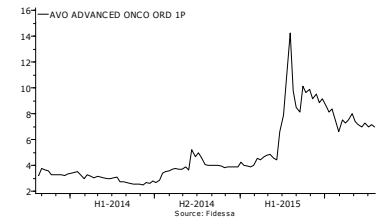
hardman&co

Healthcare Equipment & Services



Source: Fidessa

Market data	
EPIC	AVO
Price (p)	6.75
12m High (p)	16.9
12 Low (p)	3.5
Shares (m)	1418.3
Mkt Cap (£m)	95.7
EV (£m)	92.7
Free Float* (%)	82
Market	AIM

**As defined by AIM Rule 26*

Description

Developing next generation proton therapy systems for the use in radiation therapy of cancers. The first system is expected to be installed in Harley Street, London in 2016-17 and treating patients in 4Q 2017; to be operated through a joint venture company with CircleHealth.

Company information

4-7 Manchester Street
London
W1U 3AE

www.advancedoncotherapy.com
+44 (0)203 617 8728

Next Event

Finals	June 2016

Analysts

Mark Brewer 020 7148 1434
mb@hardmanandco.com
Martin Hall 020 7148 1433
mh@hardmanandco.com

Advanced Oncotherapy

Disruptive technology in high growth market

Focused on delivering a more affordable, novel proton-based radiotherapy system, based on a technology originally developed and tested at the world renowned CERN facility in Switzerland. Its uniqueness lies in the fact that the accelerator is a linear one which confers substantial benefits and flexibility to the operator, payor and patient. With its first purchase order in March 2015 ($40m) as well as the recent agreement with CircleHealth, to have the first installation of a LIGHT system in 2016-2017 in London, the Company is entering a c.$680m market on the cusp of a steepening adoption curve with a disruptive technology.

- **Strategy:** To develop a proton therapy (PT) system addressing the needs of the patient, operator and payor (private, insurance or national health system), at an affordable price for the payor, which is financially attractive to the operator and, most importantly, generates superior clinical outcomes for the patient.
- **Addressable market:** Entering a PT market that is currently valued at c.$680m but forecast to grow to c.$10bn in 2025, +27% pa; driven by rising cancer incidence, increased use of radiotherapy ("RT"), particularly in emerging markets, clinical validation of PT, technological advances and market adoption.
- **Valuation:** With one system sale completed ($40m), a potential order book of 9 systems ($360m+), and the capacity to produce up to 30 systems p.a. there is still insufficient visibility to produce meaningful long term forecasts. Suffice to say, additional orders should translate into further significant share price gains.
- **Risks:** Delays to completing LIGHT installation in Harley Street in 2017 and first patient treatment in 4Q 2017 – both mitigated by partnership supplier network, and the small size relative to its principal competitors which impacts potentially on vendor financing capability as well as external perceptions.
- **Investment summary:** AVO is entering a market on the cusp of a steepening adoption curve with a PT solution that is unique with respect to its competitors and addresses the needs of all key stakeholders (patient, payor and operator). The company has sufficient cash to achieve its near term goal of first patient treatment in 2017 beyond which additional capital may be required.

Financial summary and valuation

Year end Dec (£,000s)	2013	2014	2015E	2016E	2017E	2018E
Sales	69	106	1,370	35,484	80,645	137,097
Underlying EBITDA	-2,041	-5,063	-7,517	-4,522	3,547	19,871
Underlying PTP	-2,382	-5,059	-7,754	-4,933	2,362	18,083
Statutory PTP	-3,970	-7,563	-8,491	-4,933	1,863	18,363
Underlying EPS (p)	-0.59	-0.60	-0.60	-0.38	0.18	1.27
Statutory EPS (p)	-0.99	-0.89	-0.66	-0.38	0.14	1.29
Net (debt)/cash	-3,042	477	3,038	-16,740	-37,752	-46,785
Shares issued	2,437	10,158	20,127	0	0	0
P/E (x)	-11.4	-11.3	-11.2	-17.7	37.2	5.3
EV/sales (x)	1,433	895.5	67.6	3.2	1.7	1.0
EV/EBITDA (x)	-48.4	-18.8	-12.3	-24.9	37.6	7.2

Source: Hardman & Co Life Sciences Research

Table of Contents

Executive summary – Investment thesis **3**
Scientific background **7**
External beam radiation market **9**
Drivers of growth 9
Proton Therapy Market 11
LIGHT System **20**
Competition **25**
Commercial outlook **27**
Financials & Investment case **29**
History 29
Capital increases 29
Share price performance 29
Share capital 30
Financial statements 31
Valuation 36
Company matters **37**
Risks **41**
Glossary **42**
Disclaimer **43**
Hardman Team **44**

Executive summary – Investment thesis

History and overview

Company with a clear strategic focus….

Advanced Oncotherapy was established in 2012, changing its name from CareCapital plc, to focus specifically on opportunities within the field of cancer diagnosis and treatment, having announced its decision to divest its healthcare property portfolio. In 2013, Advanced Oncotherapy streamlined further its investment case by acquiring the entire share capital of ADAM SA, via a vendor placing. ADAM is a CERN spin-off company based in Geneva. Its technology included the Company's core proton therapy platform as well as the exclusive rights to various IP developed by TERA, an Italian foundation for hadron therapy, which is advancing new particle physics-based technology for therapeutic use, including carbon-ion particle therapy. The Company is focused on one singular goal: the development and commercialisation of its potentially game-changing proton therapy system.

Strong pedigree

Tested at AVO's R&D arm, ADAM, at CERN

A prototype system, called LIBO, was developed and tested in 2000 using the same linear acceleration technology being used in the current product. Around €14m (£11m) had been invested by ADAM into the LIGHT project, prior to ADAM's acquisition by Advanced Oncotherapy.

LIGHT system

Differentiated from cyclotrons and synchrotrons (circular accelerators)

LIGHT (Linac Image-Guided Hadron Technology) is the first proton LINAC (linear particle accelerator, similar to systems that generate X-rays), developed exclusively by Advanced Oncotherapy to treat cancer and designed to accelerate protons to energy levels sufficient to treat tumours to a depth of 32 cm. It is unique in that it uses a high frequency, low energy injection energy system, enabling it to be compact and modular in design, uses considerably less energy to power it and requires less radiation shielding during construction than cyclotrons, thereby providing the operator with greater flexibility when considering operating costs, choice of location and installation.

LIGHT – comparison with other PT systems

	Large PT centres	Compact systems	LIGHT
Accelerator	Cyclotron/Synchrotron	Cyclotron/Synchrotron	LINAC
Capital cost	High	Lower	Lower
Annual maintenance cost	High (8-10% of system cost)	High (8-10% of system cost)	Lower/fixed ($1.5m)
Operating costs	High	Medium	Lower
Modular	No	No	Yes
Multi- treatment rooms	Yes	No	Yes

Source: Hardman & Co Life Sciences Research

Medical need for proton therapy

Unquestionable medical need for proton therapy

Proton therapy, employed since the 1950s, is currently used in around 1% of all radiotherapy procedures and is specifically recommended for the treatment of most paediatric cancers, brain cancers and, generally speaking, many hard-to-treat radio-sensitive cancers, whilst PT is also routinely used in some high volume cancers such as prostate cancer.

LIGHT – Stakeholders' Benefits		
Patient	**Operator**	**Payor**
Personalised radiotherapy	Lower capital investment	Demonstrable clinical utility
Non-invasive and painless. Patients maintain a good quality of life during the treatment	Lower building costs: possible installation in existing buildings and lower shielding requirements	Clinical validation provided by the LIBO prototype
Fewer visits required in the case of hypo-fractionation	Lower maintenance costs and less downtime for maintenance	Reimbursable at a price that is potentially similar to IMRT
Facilities available in metropolitan cities	Lower operating costs - lower energy requirements and lower staffing costs	Similar or better clinical outcomes to radiotherapy, at a price that is potentially similar to IMRT
Less collateral damage to healthy tissues and reduced long term risk of secondary cancers	Provides workflow flexibility	Expected to be reimbursed
More cancer cases being referred for PT	Generates an acceptable ROI whilst meeting the needs of the payor	

Source: Hardman & Co Life Sciences Research

Addressing the needs of the patient, operator and payor…

Meeting the needs of Patient, Operator and Payor

Advanced Oncotherapy is specifically developing an integrated turn-key system with accompanying imaging modalities, patient workflow and software solutions to address the needs of the patient, operator (private or publicly funded) and payor (self-pay, insurance or national). The strategic objective is to provide personalised radiotherapy solutions (arguably similar to personalised cancer treatment) at an affordable price for the payor, which is financially attractive to the operator and, most importantly generates superior clinical outcomes for the patient whilst also addressing the issue of wider access and greater convenience. As cancer patients live longer through better treatment paradigms, the long term risk to vital organs and increased risk of secondary cancers, resulting from the use of traditional radiotherapy, becomes an issue to both patient and the healthcare system.

Addressable market of c.$680m on the cusp, potentially, of a steepening adoption curve

Addressable market

The market for proton therapy facilities is currently estimated to be worth around $680m, having grown at 14% in 2014. It is dominated by the Belgian company IBA, which has a c.50% share of the installed proton therapy facilities and treatment rooms. The adoption of proton therapy is expected to accelerate over the next 10 years so that the sale of PT facilities could represent around $10bn per annum (+27% pa), driven by lower capital costs ($25-40m per centre compared with current large proton centres which typically cost $100-200m), increased clinical validation and demonstrable healthcare economic outcomes.

Proton Therapy – Drivers and Obstacles	
Drivers	**Obstacles**
Growing cancer prevalence	Installation costs
Growing use of radiation therapy	Competitive technologies
Emerging markets under penetrated	Clinical benefit yet to be fully elucidated
Technological innovation (imaging solutions, dose delivery, robotic positioning systems)	Reimbursement rates

Source: Hardman & Co Life Sciences Research

First installation in Central London and patient treatment in 2017…

Strategy

Management is focused on building and installing the first LIGHT system in Harley Street, London, in 2017, with the first patient treated in 4Q 2017; to be operated through a joint venture agreement established with CircleHealth in October 2015. Whilst its business model remains one of manufacturing and selling LIGHT systems, the Company deemed it sufficiently important to have a vested interest in the operational

success of its Harley Street facility, given the fact that LIGHT system is not yet on the market but also because of the associated cachet of being associated with a proton therapy centre in one of the world's most pre-eminent medical addresses.

Significantly, AVO is selling a fully integrated turn-key system unlike many of its competitors which supply the accelerator only, leaving the operator to source and integrate the other systems required (eg. treatment planning system, oncology information system, etc.), some of which are not designed to work together. This has 3 major implications:

- Limits the risk of installation delays;
- Reduces the overall cost for operators;
- Reduces the risk of treatment mis-planning.

Execution risk mitigated by adopting partnership model with leading supplier network and leading edge technologies

Partnership model

AVO has pursued a partnership model with key industry suppliers with a view to deliver the project on time and within budget. Established suppliers such as Toshiba, Scandinova, Pyramid, ICT and P-Cure have the relevant experience and certifications within the PT field which allows the Company to accelerate its plan and reduce risk.

First purchase order ($40m)

Revenue model

The revenue model is a composite one, comprising one-off sales of hardware (c.$40m unit cost with mature 20% EBITDA margins) and annual service contract revenues (c.$1.5m per annum with mature 65% EBITDA margins). The Company is building a pipeline of orders, having announced its first purchase order ($40m) to Sinophi Healthcare for use in China in March 2015.

The following table provides key comparator financial information for AVO's principal competitors in the radiotherapy segment. Whilst AVO is a pure play on the proton therapy segment the closest comparator is IBA, in which proton therapy represented c.57% of 1H 2015 revenues and 62% of EBITDA. IBA trades on prospective 2016 EV/Sales and EV/EBITDA multiples of 3.1x and 23.7x, respectively.

Comparative valuations for radiotherapy companies

Company			Share price	Shares (m)	Mkt. Cap. (lc.m)	Net Cash (m)	EV (lc. m)	Mkt. Cap. (£m)	EV (£m)
IBA	IBAB.BR	EURO	28.92	28	819	(13)	832	602	611
Varian Medical Systems	VAR	USD	77.08	100	7,696	524	7,171	4,985	4,645
Elekta *	EKTA-B.ST	SEK	64.15	381	24,458	(2,437)	26,896	1,914	2,105
Accuray *	ARAY	USD	5.52	79	438	(39)	477	284	309
Advanced Oncotherapy	AVO.L	p	6.75	1,418	96	15	81	96	81

		PER			EV/Sales			EV/EBITDA		
Company		2014	2015E	2016E	2014	2015E	2016E	2014	2015E	2016E
IBA	IBAB.BR	39.6	734.5	608.3	3.8	2.7	3.1	29.4	25.4	23.7
Varian Medical Systems	VAR	18.6	17.6	17.0	2.4	2.3	2.2	10.8	11.0	10.4
Elekta *	EKTA-B.ST	51.5	34.1	27.4	2.5	2.3	2.2	15.5	14.7	12.2
Accuray *	ARAY	-11.3	-14.3	-47.8	1.3	1.2	1.1	348.3	58.2	19.6
Advanced Oncotherapy	AVO.L	-11.3	-11.2	-17.7	762.3	59.2	2.3	-16.0	-10.8	-17.9

* Valuation ratios adjusted for calendar year end
Prices as at 16 October 2015

Source: Hardman & Co Life Sciences Research

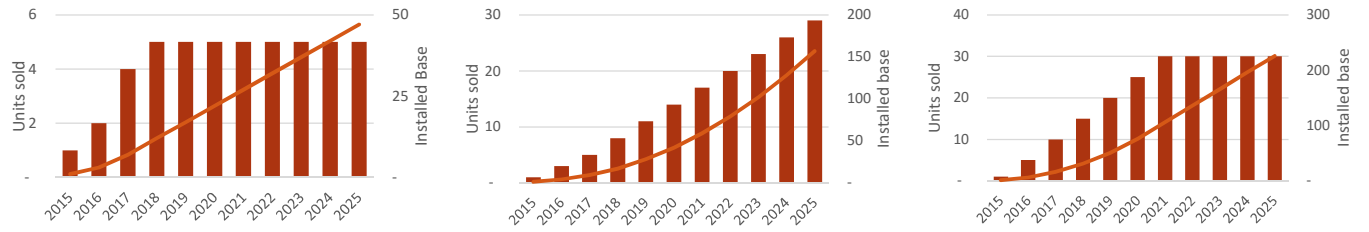
Investment conclusion

AVO is addressing the proton therapy market on the cusp of a steepening adoption curve with a solution that could be very disruptive to current incumbents. It is almost impossible to gauge the ramp of LIGHT's penetration of the proton therapy market. Suffice it to say it has sold one system to date and currently has a potential order book of a further 9 systems (worth more than $360m), which if converted to purchase orders, would be expected to be reflected in further significant share price gains. There is simply insufficient visibility to generate meaningful long term P&L and cashflow forecasts. However, the sales and EBITDA trends below provide the investor with a reference as to the impact that varying annual orders would have. Given that the company has the capacity to produce up to 30 systems per annum, the following table outlines three potential scenarios:

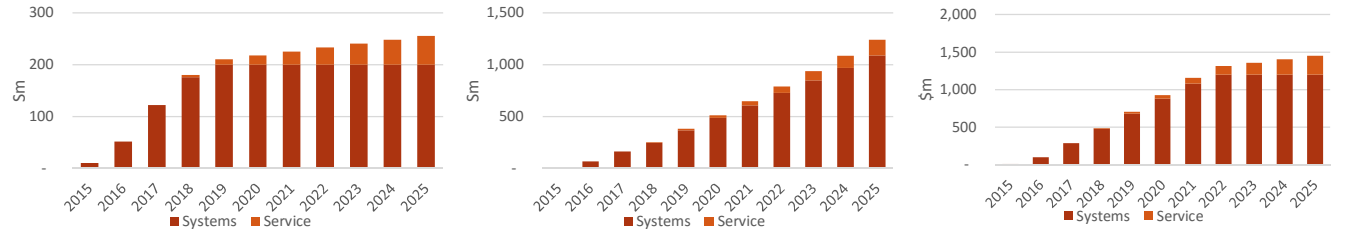
- **Low case:** Unit sales rise from 1 in 2015 to 5 in 2018 and remain as such through until 2025. This implies an installed base of 47 systems by 2025, servicing perhaps 100 treatment rooms. This would represent c.2-4% of the anticipated global capacity in 2025, which we estimate could be in the range of c.2,500-4,600 treatment rooms.
- **Medium case:** Unit sales rise steadily from 1 to 29 units pa in 2025. This implies an installed base of 157 systems by 2025, servicing perhaps 320 treatment rooms or c.7-13% of the anticipated global capacity in 2025.
- **High case**: Unit sales rise from 1 in 2015 to 30 in 2021 and remain so through 2025, implying an installed base of 226 systems by 2025, servicing perhaps 450 treatment rooms (c.10-18% of the anticipated treatment room capacity).

Scenario – Low	Scenario – Medium	Scenario – High

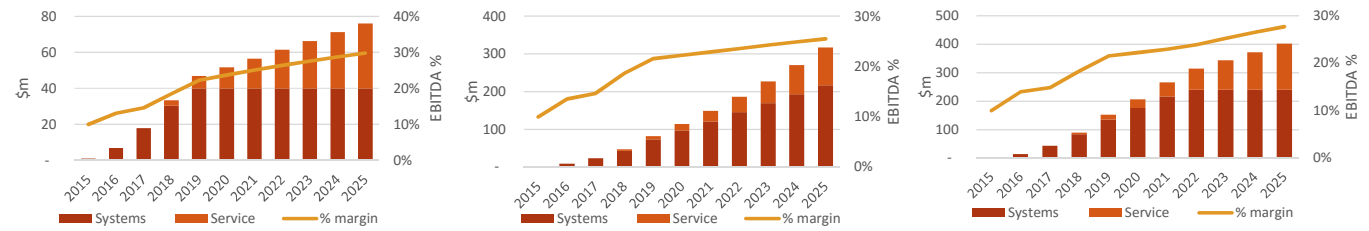
LIGHT systems – Units sold and installed instrument base



Revenues – Systems and service ($m)



EBITDA & EBITDA margin (%)



Source: Hardman & Co Life Sciences Research

Scientific background

Introduction

External beam radiotherapy to treat cancer

External beam radiotherapy, historically delivered in the form of X-rays, is designed to kill cancer cells with a radiation beam made of ionising particles which cause damage to the DNA within cells, thereby resulting in their death or inability to replicate. Cancer cells are particularly susceptible to radiation damage due to the abnormally high rate of cell division, which also makes them less able to repair the ionisation damage to the DNA.

X-ray radiotherapy works...

... but collateral damage to healthy tissues and long term risks

X-ray therapy (using photons) and proton therapy (using protons) are both radiation therapy techniques. However, the photon radiation beam also irradiates healthy tissues on the way to the cancer/target, which can induce fatigue, skin irritation or specific side effects related to the irradiated organs, eg, heart, lungs and other critical organs/structures. In the long term, there is an increased risk of developing secondary cancers. In order to reduce these side effects and give normal cells time to recover, radiation treatments are typically given in small daily doses, five days a week for up to 7 weeks. Each daily dose is referred to as a fraction. However, collateral damage still occurs to healthy tissues.

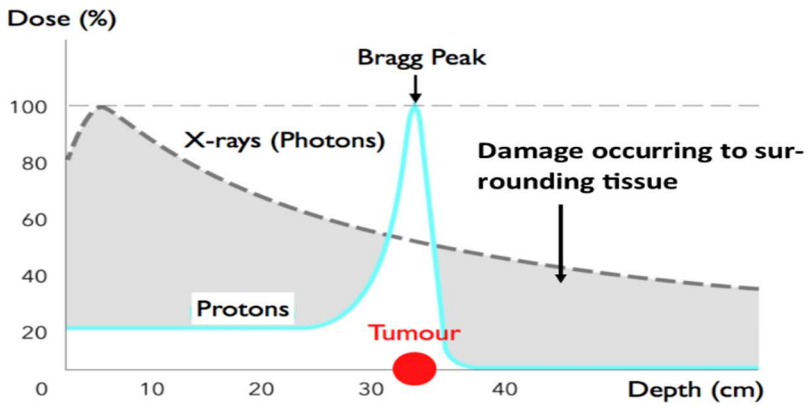
Protons have different physical properties ...

Unlike photons which have no mass and no charge, protons are considered as "heavy" particles and are positively charged. This confers different properties when interacting with human living cells.

... which generate considerably less collateral damage and reduced risk of longer term secondary cancers

Photons are highly penetrating and deliver their dose throughout any volume of tissue irradiated. However, most of the radiation energy is delivered 1-3cm from the patient's surface with a gradual reduction in energy deposition along its beam path as photons pass through the target and then through an exit point from the body (exit dose). By contrast, the absorbed dose of a proton beam increases very gradually with depth, depositing relatively less radiation energy upon entering the body compared with a photon beam. The radiation energy increases very suddenly over a narrow range of tissue at a pre-determined depth (depending on initial energy used), rising to a peak, termed the "Bragg Peak", where it releases all its energy. Beyond the Bragg Peak there is a rapid fall off in radiation energy, resulting in the absence of any significant exit dose in normal tissue beyond the target.

Bragg Peak – the energy delivered by protons peaks at the tumour site unlike photons



Source: Advanced Oncotherapy

Proton beam targets the tumour only, with less collateral damage to healthy tissues

The proton beam can be directed by varying the input energy so that the Bragg Peak occurs precisely within the tumour volume, which can never be achieved with X-rays (photons) that deposit their peak energy near the surface. Consequently, a highly conformed dose distribution to the target volume can be obtained by using the Spread-Out Bragg Peak (sum of several individual Bragg Peaks at staggered depths). It is therefore possible to obtain a lower dose both to healthy tissue surrounding the target and to non-target tissues in general.

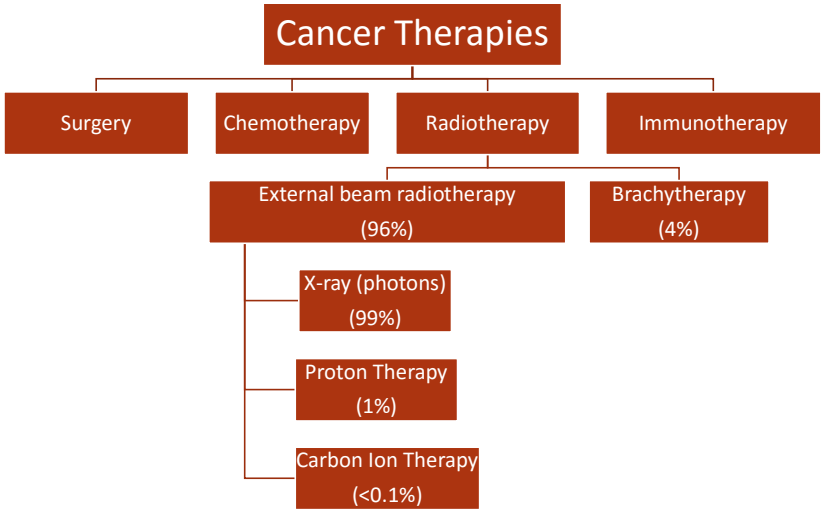
The key take-away messages of proton therapy can be summarised as:

- Protons have been used in radiotherapy since the 1950s;
- Protons cause ionisation damage to DNA, similar to conventional X-rays;
- Unlike photons, protons have a mass that confers different physical properties;
- As protons traverse matter, their maximum energy is not distributed at first interaction, causing them to scatter in a different direction, unlike X-rays which cause collateral tissue damage and leaves a void down range;
- Protons stay on relatively straight paths. Interactions along that path simply slow down the proton and shorten its distance;
- Maximum energy is delivered at the end of the proton beam's path (at the Bragg Peak) with significantly decreased dose to normal tissues (fewer side effects and complications);
- Enables treatment of tumours close to critical organs like the spinal cord or heart
- Because of its reduced toxicity, proton therapy offers the possibility to improve local tumour control by increasing the dose compared with photons, which may result in fewer visits and improved cancer-specific and overall survival.

Where Proton Therapy fits into cancer treatment

Between 20% and 63% (in the US) of patients treated for cancer have some form of radiotherapy, used alone or in combination with other treatment modalities, delivered either as an external beam or as brachytherapy (internally placed source of radiation). Proton therapy is a form of external beam radiotherapy.

Cancer treatment paradigms



Source: Hardman & Co Life Sciences Research

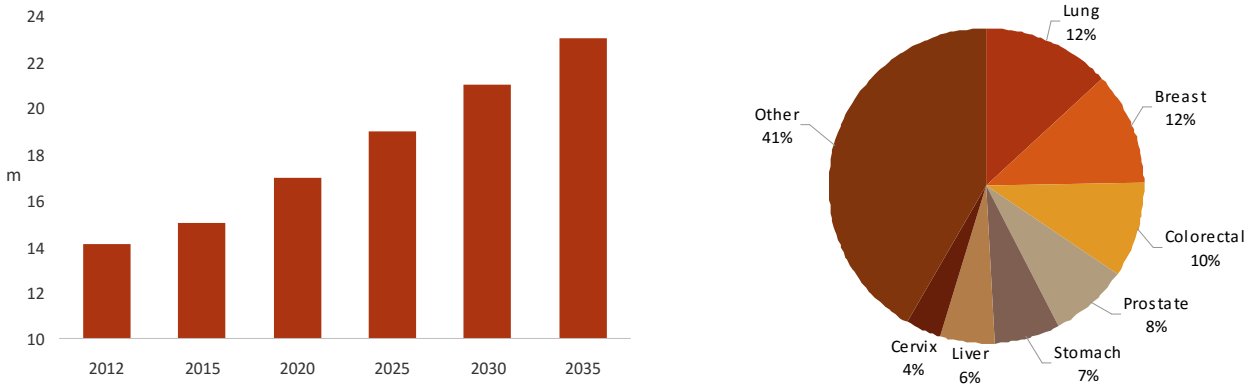
External beam radiation market

Drivers of growth

The following macro trends are forecast to grow the broader external beam radiation market, namely:

- Rising incidence of cancer, driven in part by population and diagnosis;
- Increasing utilisation of radiation therapy in treatment of cancer;
- Growth in emerging markets with rising per capita healthcare expenditure.

Increasing incidence of cancer (14.1m cases in 2012) and breakdown by cancer type

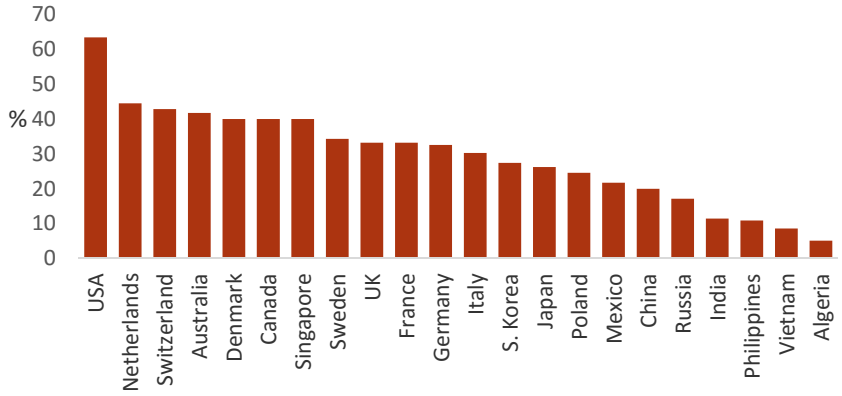


Source: GLOBOCAN 2012

WHO forecasts global cancer incidence to rise at around 2% per annum from 14.1m cases in 2012 to c.19m in 2025 and c.23m in 2035, with the predominant cancer types remaining lung, breast, colorectal and prostate.

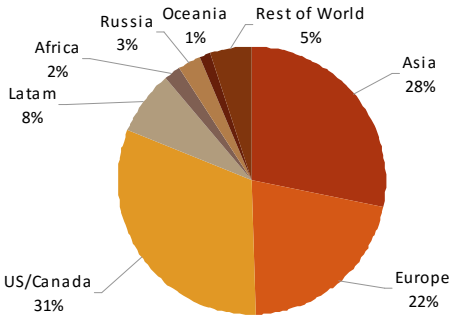
Around 30-40% of all cancers are treated with some form of radiation, according to Elekta, with rates of use greater than 60% in the USA, c.30-40% in Europe and 10-20% in the larger emerging markets such as India and China.

Share of cancer patients treated with radiotherapy (inc. re-treatment)



Source: Elekta Capital Markets Day June 2014

Radiotherapy accelerators by region and LINACs per million vs. healthcare spending



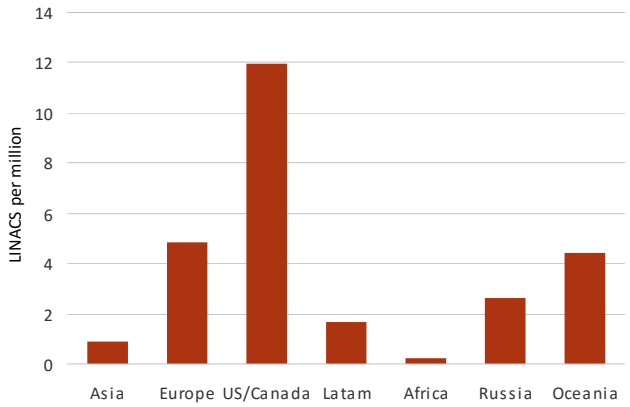
Source: IAEA, Elekta Capital Markets Day June 2014

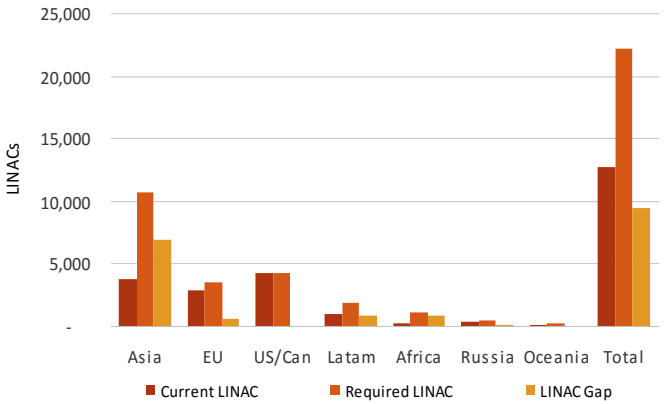
Expectations are that utilisation rates for radiotherapy will increase further both in the emerging markets as well as in some of the developed European markets. According to the IAEA, globally there are currently around 13,400 radiotherapy accelerators providing both curative and palliative treatments to cancer patients with the largest concentration being in North America (4,242 systems, including Cobalt-60 systems). Elekta presented a chart that plots access to radiotherapy (LINACs per million inhabitants) against per capita healthcare expenditure with a clear linear relationship between the two variables.

Taking IAEA's number of radiotherapy accelerators and population statistics from the UN, it is clear that there is significant variation across geographies when comparing the number of accelerators per million inhabitants; ranging from 11.9 per million in the US/Canada to 4.8 in Europe, to 0.9 in Asia and 0.3 in Africa. Elekta estimated that the global LINAC under-capacity is currently around 10,000 units, of which 7-8,000 are required in the emerging markets and a further 2,000 in established markets.

By targeting 2.5 LINACs per million of population in Asia, for example, would necessitate a further 7,000 units. If one takes into account global population growth, which is expected to grow to 8.1bn in 2025 (currently 7.2bn), the implied number of LINACs required is nearer 26,000, of which 51 are currently proton therapy facilities.

LINACs per million inhabitants by region and potential need for additional accelerators





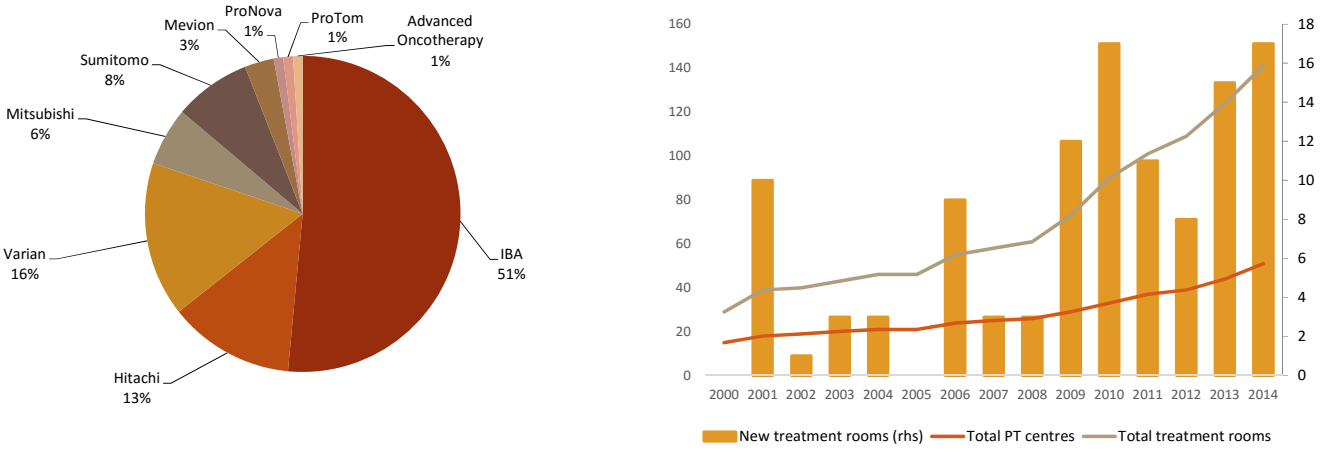
Source: UN, IAEA, Hardman & Co Life Sciences Research

Proton Therapy Market

Introduction

The global proton therapy market is currently dominated by IBA with a further 8 companies having sold instruments into this market. Of these, Mitsubishi and Sumitomo have only sold into Japan.

Proton Therapy market – Market share (installed base) and market growth



Source: PTCOG, IBA, MEDraysintell, industry sources

The first patient treated with proton therapy was in 1954 at the Lawrence Berkeley National Laboratories in California, since when over 120,000 patients have been treated globally.

51 PT centres globally with 141 treatment rooms

According to the Particle Therapy Co-operative Group (PTCOG) and IBA, there were 51 operational facilities globally with 141 treatment rooms at the end of 2014, an increase of 14% on treatment rooms in 2013. This is the equivalent of 0.02 PT treatment rooms per million inhabitants.

c.15,000 patients treated annually

It is estimated that around 14-15,000 patients were treated in 2014, implying c.100 patients treated per treatment room. This low utilisation rate has been one of the key impediments to greater take up. Most of the earlier systems were laboratory based systems, designed to demonstrate the benefits of PT and create awareness, rather than to optimise patient throughput at an affordable cost.

Acceleration in PT facilities under construction and in planning

The PTCOG database indicates further acceleration in the confirmed number of treatment rooms coming on stream over the next few years. There are an additional 34 centres with 87 treatment rooms under construction and 16 facilities (with 26 treatment rooms) in the planning phases, all due to come on stream by 2018/2019.

This implies that there will be around 100 proton therapy facilities with c.250 treatment rooms in operation by 2018/19. To put into perspective this represents less than 2% of the forecast number of radiotherapy systems expected to be in the market by 2018/2019.

Current applications of proton therapy

Current applications of proton therapy are shown in the following table.

Current applications of proton therapy

Area of focus	Tumour types
Central Nervous System	Adult low and high grade gliomas; paediatric gliomas; Acoustic Neuromas; Meningiomas; Craniopharyngiomas; Chondromas and low grade Chondrosarcomas; Medulloblastomas; Pituitary Adenomas; Posterior Fossa Tumours
Eye and orbit	Uveal Melanomas; Macular degeneration; Choroidal Melanomas; Orbital Rhabdomyosarcomas; Choroidal Hemangiomas; Optic Gliomas
Head & Neck	Paranasal sinus; Salivary glands carcinomas; Nasopharynx – primary and recurrent; Esophageal carcinomas,; Recurrent carcinomas
Thorax	Non Small Cell Lung; Breast; Early stage inoperable paraspinal tumours; Soft tissue sarcomas; Lymphomas
Gastrointestinal	Oesophageal carcinomas; Recurrent rectal cancer; Pancreatic cancer; Hepatocellular carcinoma
Pelvis	Early stage prostate carcinoma; Locally advanced prostate carcinoma; Pelvic sarcoma; Paediatric malignancies; Ewing's Sarcomas; Retroperitoneal Sarcomas; Gynaecologic carcinomas

Source: IBA

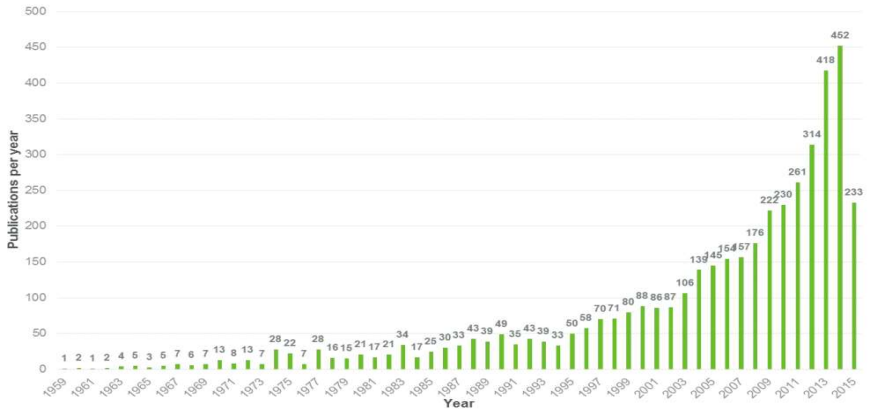
Drivers of adoption of proton therapy

Factors that will drive the increased adoption of proton therapy from 1% of RT to c.10-20% are considered to include:

- **Affordability** – lower capital, maintenance, and running costs, together with greater flexibility. Traditional multi-room proton therapy centres typically cost $100-200m to build and equip; are out of town facilities due to the sheer size of the site (size of a football pitch) and, therefore, do not address the issue of patient convenience either (considering that a patient would have to make 18-36 trips to receive PT, i.e. over 4 to 8 weeks). For example, AVO is selling a fully integrated proton therapy system for c.$40m;
- **Market awareness** – cancer patients are increasingly aware of proton therapy and the relative merits compared with X-rays. Self-referral is common in the US given consumer advertising;
- **Replacement cycle** – LINACs have a working life of c.10 years. The global installed base is around 13,400 systems, of which c.4,200 are in the US. As these come up for replacement, we expect some to be replaced with PT systems;
- **Advances in technology** – the adoption of PT is dependent to a large extent on the ability to map and image the tumour in real-time, linking beam delivery with organ motion so that the true benefits of PT (delivery of higher doses over shorter periods of time – hypo-fractionation) can be harnessed. The P-Cure treatment room solution, used by AVO for example, is compact and requires only 40 m^2 to fit all treatment room equipment with the target to generate annual patient throughput of around 500 patients;
- **Clinical validation** – to demonstrate reduced side effects, superior tumour control, reduction in secondary cancer and the benefit compared with IMRT, all of which are likely to require long term (5 years plus) studies. The relevance of proton therapy can best be demonstrated by the rising number of publications

and clinical trials. Since 2000 annual publications have risen approximately fivefold to near 500 per annum. According to the ClinicalTrials.gov website there are currently 122 clinical trials assessing the safety and, increasingly, the benefit of proton beam radiotherapy compared with IMRT; a 110% increase in the number of studies in 2009, according to IBA. The majority of these studies are being conducted at leading cancer institutes in the USA and Europe. As evidence for PT builds across a broad range of cancers, not only should the long term reduction of risk of developing secondary cancers when compared to photon therapy[1] be fully elucidated, but the full potential of reduced side effects and the enhanced quality of life of patients both during and after treatment should be demonstrated. For many, the jury is still out on the relevance and economic benefits of PT in all but a few cancers types.

Proton therapy publications



Source: IBA 2Q 2015 presentation

Proton beam therapy significantly improved disease-free survival (DFS) and tumour control (TC) when compared to IMRT in head and neck cancer[2]. Researchers found DFS to be significantly higher at five years for patients receiving proton therapy than for patients receiving IMRT (72% vs. 50%). Whilst TC did not differ between treatment groups at five years, however, it was higher for patients receiving proton therapy than for IMRT at the longest follow-up (81% vs. 64%);

- **Reimbursement** – affordability to the payor, whether insurance company or national healthcare system;
- Demonstrable healthcare economic outcomes both in the short term (comparable to LINACs) as well as long term (overall costs to the healthcare system of addressing secondary cancers).

Reimbursement

Proton therapy is broadly reimbursed by national health systems and private insurance companies, particularly for those cancer cases where there is a clear medical need (paediatric cancers, brain cancers and cancers near vital organs) and a desire to ensure reduced long term risk to tissues (eg. heart) and secondary cancers.

[1] Chung CS, Keating N, Yock T et al. Int J Radiat Oncol Biol Phys 2008; 72: S8

[2] Lancet Oncology 2014

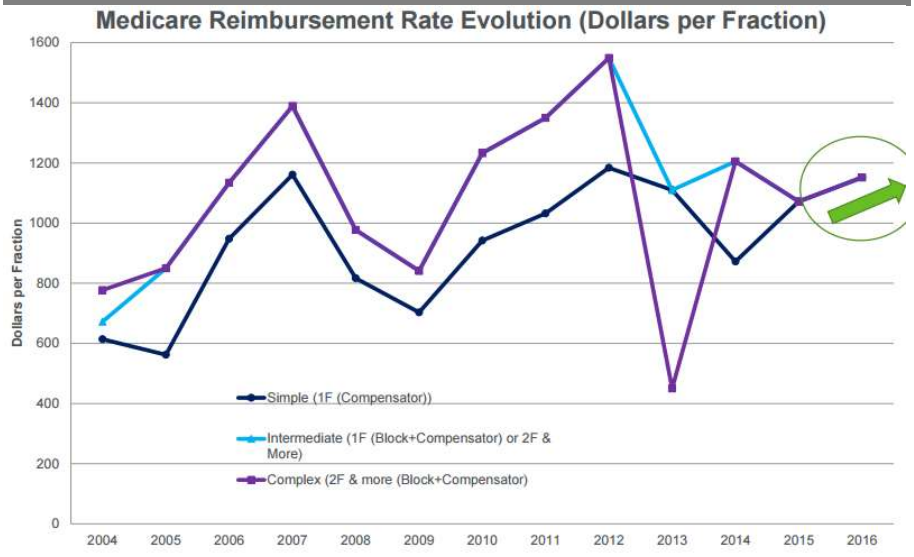
Nevertheless there remains a division of opinion as to the suitability of proton therapy use and consequent value for money. Those for proton therapy argue that it is safer, with lower complication rates and less damage to healthy tissue, whilst opponents argue that there is a lack of supporting evidence (ie clinical trials) to justify the higher prices. Gerald Chodak, MD, director of the Midwest Prostate and Urology Health Center in Michiana Shores, Indiana, for example, said in 2014:

> *"proton therapy is a technology that is at least 30% more costly than IMRT, with no clear evidence that it does reduce long-term side effects and absolutely no data to show that it provides better outcomes"*

Despite this there has been substantial growth in the number of prostate procedures in the US according to the American Cancer Society, despite the median Medicare reimbursement for proton therapy being $32,428 versus $18,575 for IMRT.

Medicare reimbursement rates for complex cases are broadly stable at around $1,050 per fraction.

Medicare reimbursement rates



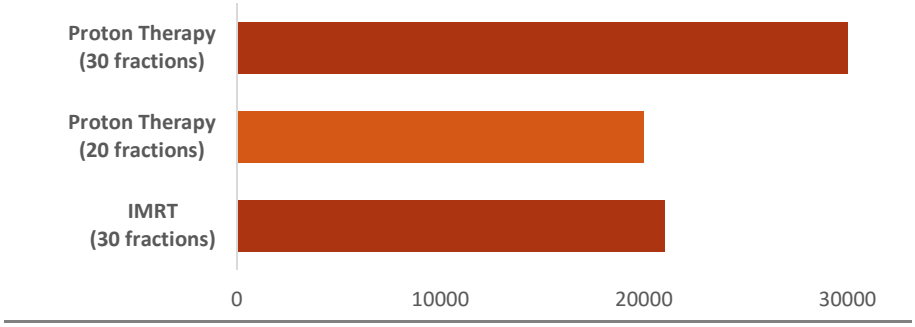
Source: IBA 2Q 2015 presentation

Whilst Medicare continues to reimburse PT for prostate cancer, a number of US insurance companies have stopped doing so (Aetna, Blue Shield of California), which drives at the heart of the issue: how to bring the cost of PT down to the level of IMRT, such that it can be more widely used, is the goal of the PT industry.

The aim of LIGHT is to bring treatment costs into line with IMRT

IBA made the comment in its Q2 2015 conference call that much of the acceleration of growth in its proton therapy business could be attributed to the price positioning of its single room compact accelerator against traditional LINACs. The same should, in our view, be true for LIGHT but with the added benefits that the LIGHT system offers; namely, the ability to add more treatment rooms at a marginal cost increase, modularity, lower radiation shielding, rapid energy switching and the potential to hypo-fractionate tumours, delivering the same overall dose of radiation but in fewer treatments. For example, IMRT and proton therapy, if delivered over 30 fractions, costs are reimbursed at around $20,000 and $32,000 respectively, assuming a reimbursement rate per fraction of $680 and $1,000. Should proton therapy be delivered over 20 fractions, for example, the cost would be similar to IMRT, but with the benefits that PT offers (lower collateral damage and reduced long term secondary cancer risk).

Proton therapy – Cost vs. IMRT and potential hypo-fractionation



Source: IBA 2Q 2015 presentation

Economics – financial return to operator

The cost to equip and construct a proton facility can range from $40m (single room compact accelerator) to $250m (e.g. UK government funding two fully integrated cancer centres each with three PT treatment rooms at UCLH, London and The Christie Hospital, Manchester, the cost of which is expected to be £250m – of which £80m represents the cost of the two accelerators[3] – an estimated annual patient throughput of 1,500 patients, annual running costs of around £26m and not opening until 2018). Comparing the economics and financial returns of compact PT systems with multi-room systems is not always clear-cut, the selection of either system dependent to a large extent on patient loading or financing. Historically the ROI for a multi-room facility, given higher throughput, economies of scale and longer depreciation, has been higher than for a single room.

AVO's solution is to improve operators' ROI

AVO's solution, however, aims to redress this cost imbalance. LIGHT comes with the flexibility to offer multi-room facilities, the modularity to enable installation within existing facilities and/or hospitals with minimal disruption and lower operating costs than cyclotron-based systems. This should materially change the ROI characteristics for the PT operators.

LIGHT system- considerations for ROI

	Large PT centres	Compact systems	LIGHT
Capital cost	High	Lower	Lower
Annual maintenance cost	High (8-10% of system cost)	Medium (8-10% of system cost)	Lower/fixed ($1.5m for integrated system)
Operating costs	High	Medium	Lower
Modular	No	No	Yes

Source: Hardman & Co Life Sciences Research

Addressable Market

There are currently 141 treatment rooms globally that offered proton therapy to c.14,500 patients in 2014. We look at the potential addressable market for PT, both in terms of the number of potential treatable patients and, consequently, the number of treatment rooms likely to be needed to satisfy such demand.

External Beam Radiotherapy

According to WHO/GLOBOCAN, there were 14.1m cancer patients in 2012, of which 43% were in the developed markets.

[3] Varian Medical Systems, July 27 2015 press release

If one assumes that c.60% of those patients in the developed markets are suitable for radiotherapy (currently c.63% of cancer patients in USA are given RT) and c.30% in the less developed markets, it implies that c.6m patients should potentially receive some form of radiotherapy. This rises to c.8.5m patients if one assumes c.60% suitability in the less developed markets.

Proton therapy

PT standard of therapy in 1% of radiotherapy

Proton therapy is the standard of therapy for c.1% of cancer patients (intraocular tumours, chordomas/chondrosarcomas and most paediatric cancers), according to the Health Council of the Netherlands and Cancer Research UK, amongst other bodies. There is very little external published information pointing to the suitability of proton therapy. However, in a report published in December 2009,[4] the National Health Council estimated that based on 2005 cancer registry data 7,098 Dutch cancer patients, or c.18% percent of all cancer patients in the country, could benefit from proton therapy, which would rise to c.9,400 patients by 2015.

The report concluded the suitability of proton therapy could be attributed to three additional factors, beyond standard current treatment which included better tumour control in intracranial, urologic (prostate and bladder) and lung (NSCLC) cancers among others, reduced side effects (in the above cancers as well as breast, gynaecological, and GI cancers as well as lymphomas and sarcomas) and the reduction in secondary tumours.

But indications that could be used in c.18% of radiotherapy cases

Potential for proton therapy (as percentage of total radiotherapy)

Indication	Percent of RT market
Standard indications	0.6%
Potential indications (improved tumour control)	3.0%
Reduction/prevention of side effects	12.1%
Reduction of secondary cancer	2.0%
	17.7%

Source: Health Council of Netherlands

Based on the Netherland's Health Council findings, we have outlined the potential number of patients suitable for PT based on a 10-20% penetration of the RT market. This suggests that there could be 0.8-1.7m suitable PT patients (assuming no improvement in access to RT in emerging markets) which rises to c.2.3m patients, if one assumes that emerging markets had similar access to RT as in the developed markets. Whilst this is considered a less likely scenario it nevertheless is appropriate to consider as many emerging healthcare systems (e.g. China) are looking to leapfrog technology by bypassing older LINAC based RT systems and installing state-of-the-art PT systems.

Taking these potential patients and assuming that the annual patient throughput per treatment room rises from c.110 patients per annum to 500 (targets mentioned by operators and suppliers of PT systems; e.g. IBA, Mevion and P-Cure, although Proton Partners International state that target annual patients at their 3 facilities, opening in the UK in 2017, will each ramp up to 1,000 patients per annum), there would be a need for c.1,700 treatment rooms assuming 10% of all radiotherapy patients are given PT. This rises to c.3,300 if PT penetration was 20% or c.4,600 if access to RT in emerging market improved.

[4] www.gezondheidsraad.nl/sites/default/files/proton_radiotherapy200917E_0.pdf

Addressable market for Proton Therapy – Treatment rooms required

		Sensitivity to emerging market and PT penetration				
	2012	**2025**	**2025**	**2025**	**2025**	**Comment**
Cancer patients	14,100,000	19,300,000	19,300,000	19,300,000	19,300,000	GLOBOCAN 2012
Developed world	6,063,000	8,299,000	8,299,000	8,299,000	8,299,000	43% in developed world (GLOBOCAN 2012)
Less developed world	8,037,000	11,001,000	11,001,000	11,001,000	11,001,000	
Suitable for radiotherapy (RT)						
Developed world (m)	3,637,800	4,979,400	4,979,400	4,979,400	4,979,400	
% suitable for RT	60%	60%	60%	60%	60%	c.63% of US cancer patients receive RT
Less developed world (m)	2,411,100	3,300,300	4,400,400	5,500,500	6,600,600	
% suitable for RT	30%	30%	40%	50%	60%	
Total suitable for RT (m)	**6,048,900**	**8,279,700**	**9,379,800**	**10,479,900**	**11,580,000**	
% of global cancer incidence	43%	43%	49%	54%	60%	
Potential patients suitable for Proton Therapy (PT)						
% of RT suitable for PT	1%	5%	10%	15%	20%	Based on Netherlands Health Council
No growth in emerging markets	**36,293**	**413,985**	**827,970**	**1,241,955**	**1,655,940**	
With growth in emerging markets		**413,985**	**937,980**	**1,571,985**	**2,316,000**	
Potential treatment rooms required						
Patients per year per room	100	500	500	500	500	Current usage is c.110 per annum.
No growth in emerging markets	**363**	**828**	**1,656**	**2,484**	**3,312**	
With growth in emerging markets		**828**	**1,876**	**3,144**	**4,632**	

Source: Hardman & Co Life Sciences Research

What is clear from this top down assessment is that the market is set to expand exponentially over the next decade.

Even at the bottom end of expectations, there should be a 12-fold increase in the number of treatment rooms, representing a CAGR of 35% or an annual increase in treatment room capacity of c.250 pa. At first sight this seems a tall order given that the current base is 141 and it has taken 30 years to install this capacity.

As well as a base case model, we have looked at what the market evolution might look like on a more pessimistic and optimistic scenarios. In these scenarios, the potential number of treatment rooms is derived from the above model.

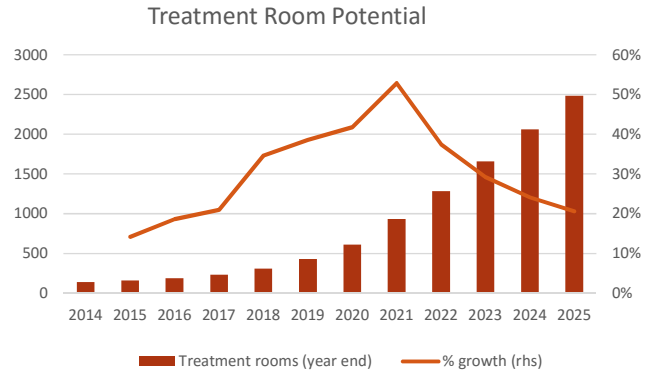
Base case

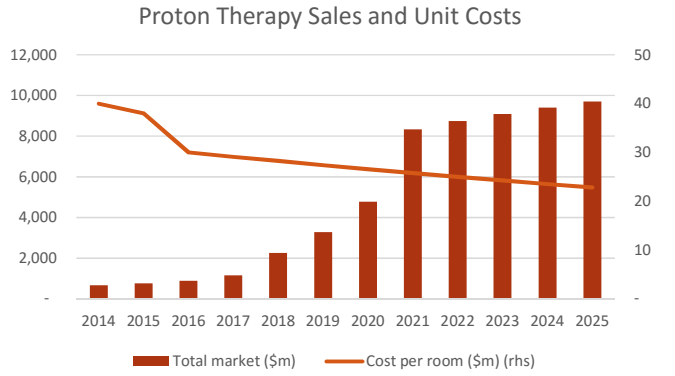
Proton therapy used in 15% of radiotherapy procedures ....

... requiring 2,484 treatment rooms

In our base case assessment of the potential proton therapy market, the number of treatment rooms needed for proton therapy is expected to rise from 141 in 2014 to c.2,484 in 2025, implying annual growth of 30% CAGR and assuming an increase in additional treatment rooms from 80 in 2018 to 425 new treatment rooms in 2025.

Base Case: Proton Therapy market –treatment room, market and unit cost per treatment room





Source: Hardman & Co Life Sciences Research

It assumes that 15% of all RT patients are suitable for PT. The market, as a consequence is expected to grow from c.$680m in 2014 to c.$10bn, a 27% CAGR. This is a slower rate than the growth in treatment rooms as we assume a gradual reduction in the cost per treatment room falling from c.$40m in 2014 to around $23m as economies of scale, technological advances and competition are considered. This scenario assumes that PT treatment room capacity would represent c.10% of the overall RT capacity (c.26,000 treatment rooms) expected to exist at the end of the next decade

Low

Proton therapy used in 5% of radiotherapy procedures ....

... requiring 828 treatment rooms

This scenario paints a rather pessimistic outlook, despite the outlook for PT, particularly from a patient's perspective. However, it still equates to a 17% CAGR in treatment rooms to 828. The key assumption is that c.5% of patients suitable for RT receives PT in 2025. This compares with the current 1% of RT patients receiving PT. It assumes a broadly linear increase in additional treatment rooms from 40 in 2018 to 115 new treatment rooms in 2025 (cf. 40 rooms set to open in 2017 – PTCOG). Under this scenario the market would grow to around $2.9bn or 14% CAGR, with the unit cost falling to around $25m per treatment room. In this scenario the PT treatment room capacity would represent c.3% of the overall RT capacity anticipated to be in existence then.

High

Proton therapy used in 20% of radiotherapy procedures, including emerging market growth.

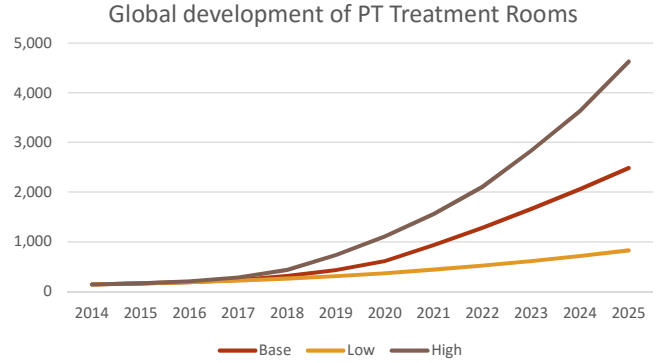
... requiring 4,632 treatment rooms in 2025

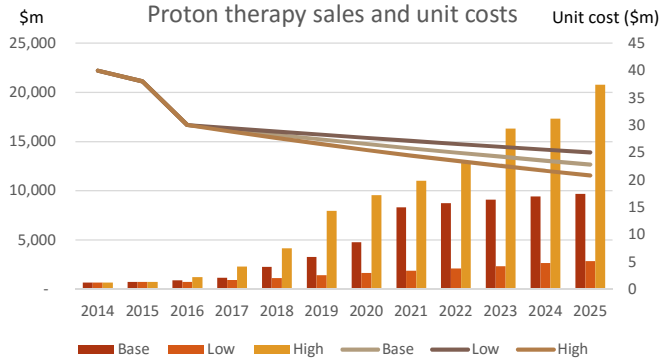
This is not an unrealistic scenario but one that is less easy to envisage given where we are today. It would require a number of things to fall into place, not least the ability of the systems' suppliers to build additional production capacity but also for the payors to be able to justify and fund the higher cost of treatment compared with radiotherapy. Reimbursement rates for operators would likely fall in this scenario.

In this scenario we have modelled a growth in treatment rooms to around 4,632 over the next decade, assuming an increase in additional treatment rooms from 340 in 2018 to 1,000 new treatment rooms in 2025 and assuming that 20% of patients who are suitable for RT receive PT.

This represents a CAGR of 37% with the value of the market rising to c.$21bn (+35% pa) with the unit cost falling to around $21m. In this scenario the PT treatment room capacity would represent c. 18% of the overall anticipated RT capacity.

Base Case: Proton Therapy market –treatment room, market and unit cost per treatment room





Source: Hardman & Co Life Sciences Research

Assuming that Advanced Oncotherapy is able to deliver successfully its first LIGHT system in 2017, the issue then is what share of the market should or could it win? Given the advantages that LIGHT offers a 10-20% share of the market is not an inconceivable thought.

Under the three market scenarios previously described and assuming that, on average, there are 2 treatment rooms per proton therapy system it would imply that by 2025 Advanced Oncotherapy would be supplying the following number of systems per annum by 2025 if it was to achieve a 10-20% share of the market:

- Low case – 5-10 systems;
- Base case – 20-40 systems;
- High case – 50-100 systems.

If one looks at the base case in which there are an estimated 2,484 treatment rooms in 2025, there would be an increased requirement in 2025 for c.425 treatment rooms. Assuming that each proton therapy system would support two treatment rooms, it implies that c.200 proton therapy systems would have to be sold/installed to fulfil this need. A 10% share of that output implies that Advanced Oncotherapy would be producing 20 system a year with a value of c.$800m.

Market share implications for Advanced Oncotherapy LIGHT production

	Treatment rooms in 2025		Implied Annual Proton Systems	Annual LIGHT production under market share assumptions	
	Global	Annual Inc		10%	20%
Low case	828	115	50	5	10
Base case	2,484	425	200	20	40
High case	4,632	1,000	500	50	100

Source: Hardman & Co Life Sciences Research

Advanced Oncotherapy currently has the capacity, through its supplier network, to produce up to 30 LIGHT systems per annum, which is sufficient to meet the anticipated needs of the market in all but the high case where proton therapy would have to be routinely used in c.20% of radiotherapy procedures.

LIGHT System

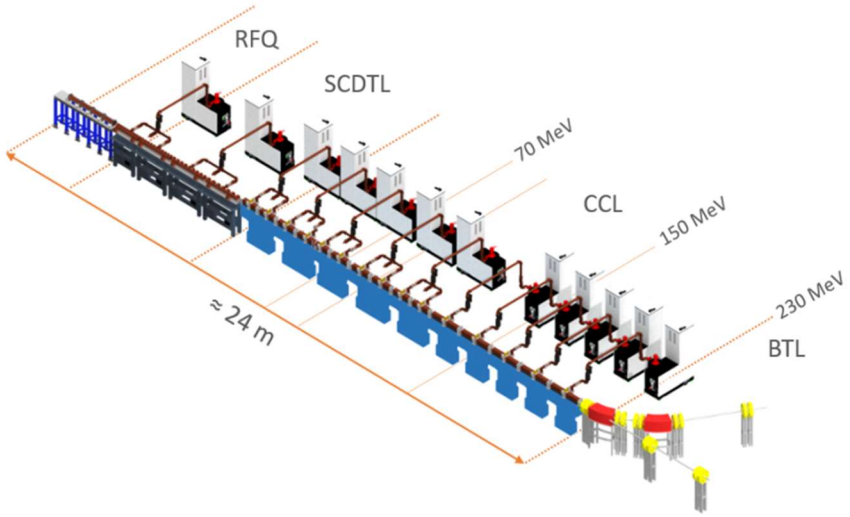
Introduction

Advanced Oncotherapy has set out to develop a system with accompanying imaging modalities, patient workflow and software solutions to address the needs of patient, operator and payor. As an investor, one needs to ask whether or not LIGHT's attributes and execution thereof, are sufficient solutions to address these multiple needs. It is clear that the market is going to expand rapidly. The question is how well positioned is Advanced Oncotherapy to capture a significant portion of this growth.

The only linear proton accelerator

LIGHT (Linac Image-Guided Hadron Technology) is a linear proton accelerator, developed exclusively by Advanced Oncotherapy to treat cancer using external beam proton radiation, and designed to accelerate protons up to 230 MeV, which is sufficient to treat tumours to a depth of 32cm. The following diagram provides a schematic overview of the accelerator structures involved.

LIGHT – schematic of key components of the LIGHT accelerator



Source: Advanced Oncotherapy

Key attributes of LIGHT

Uses radiofrequency to energise the protons rather than super-conducting magnets

What is unique about LIGHT is the fact that it is uses innovative linear accelerators, with the beam energy being generated by electrical radiofrequency rather than powerful super-conducting magnets as used in the current generation of circular accelerators - cyclotrons, synchrotrons and cyclosynchrotrons. Not only does this obviate the need for massive infrastructure and extensive radiation shielding but it confers several other key advantages over the circular accelerators, namely:

- **Compact dimensions:** It competes with the compact systems offered by IBA (ProteusOne) and Mevion (S250). Whereas these systems can offer only a single treatment room, LIGHT has the flexibility for 3 or more rooms whilst still being only 25-33% the size of larger proton therapy centres with 3-5 treatment rooms;
- **Modular design:** Offers radiation therapy centres the flexibility to customise their systems, depending on the treatment energies required. For example, small hospitals might initially choose a 70 MeV accelerator for eyes, head and neck treatment (where depth of beam penetration remains shallow), without precluding the potential to move up to higher energies (230 MeV) which would

be achieved by installing additional accelerator units (CCLs) but, importantly, without the need to dismantle and then re-install a completely new system (as is the case with cyclotrons and synchrotrons);

Rapid energy switching of LIGHT should provide more effective, time-efficient scanning of the tumour

- **Precision:** Beam energy delivery can be varied electronically. Moreover the beam can be moved very rapidly during therapy at 200 times per second (active longitudinal modulation along the beam propagation axis). This compares favourably with cyclotrons which use a passive modulation system (fixed initial energy which is degraded by using energy absorbers between the accelerator and the patient, which can cause a quality loss of the beam). Additionally, the LIGHT system has a dynamic transverse modulation that allows a precise 3D treatment of the tumours (spot scanning) with every spot (voxel) painted up to ten times during a treatment. Many experts in the proton therapy field believe that it will obviate the need for a gantry;
- **High frequency:** The very short pulse (a few microseconds) and the high repetition frequency (up to 200 Hz) compare favourably with the longer cycles (typically up to 1 sec) of the synchrotrons. This provides the radiation oncologist with greater flexibility to perform a highly conformational therapy based on a fast 3D spot scanning of the tumour using various scanning techniques. The LIGHT accelerator operates at very high frequency (3GHz) similar to X-ray LINACs and unlike circular systems. This generates the required energies in a relatively short distance (+15 MeV per metre) without the need for large accelerating magnets that are used in cyclotrons;
- **Lower shielding requirements:** The fact that the energy is RF-driven, rather than using superconducting magnets, means that LIGHT requires substantially less shielding (to protect from secondary radiation, neutrons) than cyclotrons and synchrotrons which, in turn, reduces construction costs;
- **Lower maintenance costs:** Its modularity, compactness and use of "off the shelf" sub-units should allow for lower cost maintenance as well as shorter downtime periods for maintenance.

Modularity and novel accelerator type provide meaningful benefits....

The smaller size, modularity and lower shield requirements are meaningful differences in themselves. It should enable the PT operator or hospital to incorporate the LIGHT system into its existing facilities (unlike the purpose built or add-on units that the cyclotrons require), in central metropolitan areas where the large proportion of cancer patients reside rather than in out of town centres (for example the Harley Street installation in the middle of London). This is not a trivial issue either, as it addresses the needs of the patient/family/carer who otherwise have to organise multiple (up to 36 treatments) trips to the treatment centre.

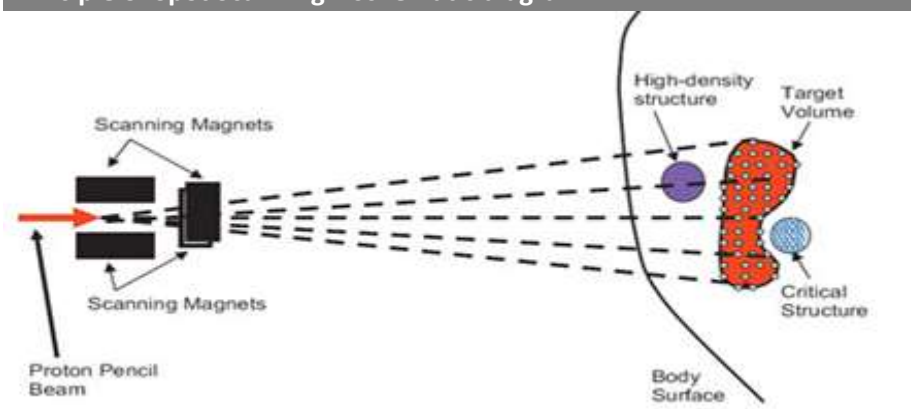
Dynamic Spot scanning technique for LIGHT

Over the years the delivery of the proton beam to the target has evolved and continues to do so. It remains an important consideration from the radiologist's perspective. The two main forms of beam delivery are:

- passive spreading, which includes single and dual scattering using a combination of custom-made collimators and compensators which conform the dose to the target volume. However, it is time consuming and expensive as it has to be tailored to each patient;
- active spreading or pencil beam scanning (PBS), in which magnets deflect and steer the proton beam under computer control. Clinicians have more flexibility to shape the beam; but with this sophisticated capability comes increased complexity in planning, computation and equipment, at least with the first generation of PBS.

One of the main advantages of the LIGHT accelerator over all of its competitors will be the possibility of implementing effectively the *Multi-painting Spot Scanning* technique, due to the ability to rapidly move the beam and the very short energy pulse time. Essentially a second generation PBS, this technique consists in depositing the dose in the whole tumour volume not in one go, but, by using a focused proton pencil beam, in successive dose applications to small elements called *voxels*. This technique allows delivering the maximum dose to the tumour and reducing the dose received by the surrounding healthy tissues. The beam is moved by active methods in all three dimensions; in the transverse plane by bending magnets, while the longitudinal coordinate is changed by continuously and rapidly varying electronically the energy of the beam. This is unlike existing systems where the beam is turned off as the scanning magnet is changed for the next spot and after each layer is painted at one beam energy, after which the beam energy is reduced layer by layer.

Principle of Spot Scanning – schematic diagram



Source: Advanced Oncotherapy

This should certainly be more cost effective than passive beam systems (which includes single and dual scattering using a combination of custom-made collimators and compensators which conform the dose to the target volume) or first generation active scanning beam systems, for example Pencil Beam Scanning which the majority of its competitors (IBA, Varian, Hitachi) offer. Advanced Oncotherapy's key competitive advantage is the repetition rate (speed) with which it can "paint" the tumour, thereby potentially increasing throughput.

Dynamic spot scanning should allow for greater hypo-fractionation of tumours. Typically radiation therapy is spread out over time, referred to as fractionation. This is done to allow:

- normal healthy cells that have been exposed to radiation time to recover, while tumour cells are generally less efficient in repairing themselves between fractions;
- tumour cells that were in a relatively radio-resistant phase of the cell cycle during one treatment to cycle into a sensitive phase of the cycle before the next fraction is given;
- tumour cells that were chronically or acutely hypoxic (radio-resistant) to potentially re-oxygenate between fractions, thus improving the tumour cell kill.

The following table outlines the key technologies, accelerator components and supporting systems required together with key milestones that are targeted by the company to ensure that it meets its stated objective of having an installed system in Harley Street ready for testing in early 2017 and treating its first patient in 4Q 2017.

LIGHT system – Key Components

Unit/technology	Supplier/Partner	Description	Milestone
Supporting Power Systems			
Proton Source	TBA	A commercial device composed of several elements. It can produce any ion coming from hydrogen gas source. System will end with Einzel lens and a water-cooled collimator to fix the maximum beam intensity entering the system.	Delivery by March 2016
RF Power (modulator)	ScandiNova	Supplies power to the klystron (12 modulator/klystron units for CCL and SCDTL, and by 4 IOTs for the RFQ. RF power unit. First two RF power units were delivered in May 2015. ScandiNova's patented pulsed power technology creates a proton beam with higher accuracy than traditional techniques, thus allowing better precision and more successful treatments of cancer patients.	
RF Power (klystron)	Toshiba	Provides the required frequency wave accelerator. First two RF power units delivered in May 2015	
LIGHT System - Acclererator			
RFQ (Radio Frequency Quadrupole)	CERN/TBD	First part of the LIGHT system that accelerates protons up to 5MeV.The 750MHz RFQ is currently being built at CERN for ADAM. It is 2 meters long and composed of 4 parts.	Delivery by March 2016
SCDTL (Side Coupled Drift Tube Linac)	VDL/TSC Srl	There are 4 SCDTL modules, each with its own power unit. These accelerate protons from 5 MeV to 37.5 MeV. The first testing of SCDTL module was announced on 2 July 2015 at TSC's facilities in Rome	Testing in August 2015. Ready for high power testing in March 2016
CCL (Cell Coupled Linac)	VDL Enabling Technologies Group	The CCL accelerating structures are an essential part of the LIGHT proton therapy system. They consist of a series of cells which accelerate the protons from energies of 37.5 Mega-electron Volts ("MeV") to 230 MeV (energies required to treat radiosensitive tumours in a clinical setting). Successful testing of the first two units completed in mid-August. Complete LIGHT system will incorporate 10 CCL units. Second CCL was delivered 28 July 2015.	High power testing in August 2015
BTL (Beam Transport Line)	TBA		
Other Systems			
Treatment room	P-Cure	Next generation patient positioning and imaging systems utilised by others	
Software	ICT Automatisering	Software integration	
Dose delivery system	Pyramid	Provides PBS systems to many of the leading PT companies and centres	
Control system		Software to control accelerator hardware	
Cooling system		Already installed. Low conductivity water systems to keep electrical components at operating temperatures.	
Vacuum system		Already installed. Maintaining vacuum in Linac transport lines, drift tube and CCLs allows the beam to tracel through the machine without interference from gas molecules. Vacuum also acts as an electrical insulator.	
Support system		Already installed	
RF network		The RF power delivered by the RF power system is brought to the accelerator via the RF network system.	

Source: Hardman & Co Life Sciences Research

Scope to use hypo-fractionation

Fractionation regimens in IMRT are typically given as 2Gy per day, five days a week for up to 6 weeks. Hypo-fractionation is increasingly being used in which the total radiation treatment is divided into larger doses; from 2Gy up to 20Gy/fraction. Short course hypo-fractionated treatments over 3–4 weeks, for example 40Gy in 15 fractions in early breast cancer (compared with normal 50Gy in 25 fractions), have been shown to be as effective as more protracted treatments[5]. The LIGHT system should provide for greater use of hypo-fractionated treatment courses and, by doing so, should reduce the number of treatment visits per patient, increase patient throughput as well as improve financial metrics for PT operator.

LIGHT will use P-cure's P-ART Adaptive Proton Therapy package to precisely deliver the beam directly to the changing size and position of the tumour site without damaging healthy tissues and critical organs. P-ART has been designed specifically to provide real-time plan adaptation to ensure constant focusing of the beam on the tumour.

It is expected that the treatment rooms will be equipped with:

[5] Lancet 2008 Mar 29;371:1098-107

- Sliding CT (parked on the ceiling) for seated and horizontally positioned patient.
- Sliding Pencil Beam Scanning (PBS) Ion Nozzle.
- Gating system that provides clean images for planning so that clinicians can more clearly visualise the target with fewer of the image artefacts associated with respiratory motion.
- Patient positioning robotic systems for:
    - Seated immobilisation of adults
    - Horizontal immobilisation of adult
    - Paediatric immobilisation
- Additional imaging modules such as:
    - Orthogonal X-ray Imaging – maps 3D tumour motion.
    - NDI Medical's optical cameras that track the 3D position and orientation of active or passive markers attached to surgical tools.
    - Vision RT's stereo-optical cameras to make sure that the patient is positioned in the same way during radiation treatment as they were during simulation/pre-planning.

P-Cure treatment room – examples for seated patient and horizontal patient

Source: Advanced Oncotherapy

Competition

Nine potential PT suppliers...

The following table outlines the key players within the proton therapy field. Advanced Oncotherapy stands apart from this group in that it will sell a fully integrated turn-key system unlike its competitors such as the treatment planning and oncology information systems, leaving the operator to source and integrate other systems required. This has 3 major implications:

.... but only AVO offers a fully integrated turn-key PT system

- Limits the risk of installation delays and thereby potentially lowers the cost;
- Reduces the overall cost for operator, both in terms of capital investment as well as maintenance costs;
- Reduces the risk of treatment mis-planning.

AVO stands apart from the current incumbents (IBA, Varian, Sumitomo, Hitachi) and the more recent entrants offering a compact system (Mevion, ProTom, ProNova) due to its fundamental technology; the unique difference being the use of a LINAC as its accelerator with rapid energy switching capabilities.

AVO uniquely positioned to exploit PBS or scanning of tumour

This, together with its dynamic spot scanning technology, should provide the radiation oncologist with greater precision and the consequent ability to use higher doses (without the concern of increased side radiation toxicity to healthy tissues) which allows for hypo-fractionation. From an operator's perspective this should lead to faster treatment times, higher daily patient throughput and consequently better financial returns.

Price competitive

Not only will the LIGHT system be price-competitive with other compact accelerators, but being a less complex system it is expected to have less operational downtime, lower maintenance costs as well as lower running costs due to the system's lower energy consumption. Suffice it to say, without an integrated patient planning and imaging system, patient workflow planning system and accompanying software capabilities these instrument advantages are unlikely to maximise the commercial attraction but it seems that with the assistance of its eminent medical advisory board that the Company is bringing together a complete solution designed for proton therapy.

Competition

Company	System	Approx. Cost	Treatment Rooms	Gantry	FDA	Accelerator type	Beam	Energy (MeV)
Advanced Oncotherapy	LIGHT	$40m	1-3	Optional	No	LINAC	Dynamic Spot Scanning	70-230
Mevion Medical Systems	MEVION S250	$25-35m	1	Yes	Yes	Synchrocylotron	Direct dose beam	70-250
ProTom International	Radiance 330	$50m	1	Yes	Yes	Synchrotron	PBS, passive or fixed	70-250
IBA	ProteusPLUS	$100-200m	1-3	Yes	Yes	Cyclotron	PBS, passive or fixed	70-230
	ProteusONE	$35-40m	1	Yes	Yes	Synchrocyclotron	PBS, passive or fixed	70-230
Varian Medical Systems	ProBeam	$100-200m	1-5	Yes	Yes	Cyclotron	PBS exclusively	70-230
	ProBeam Compact		1	Yes	Yes	Super-conducting Cyclotron	Dynamic beam scanning	70-230
Hitachi	Hitachi		1-4	Yes	Yes	Synchroton	PBS, passive or fixed	70-250
ProNova	SC360	$100m	1-3	Yes	Yes	Cyclotron	PBS, passive or fixed	70-230
Mitsubishi			1-6	Yes	No (only Japan)	Synchrotron	Passive or fixed	70-250
Sumitomo			1-5	Yes		Cyclotron	PBS, passive or fixed	70-230

Source: Hardman & Co Life Sciences Research

Technologies in development

Proton particle accelerators

Other proton projects at prototype stage

In addition to the current operating proton therapy facilities which are using cyclotrons or synchrotrons, the following PT projects are being developed:

- Dielectric wall accelerator (DWA), being developed by CPAC in the USA. This involves a linear accelerator equipped with a high gradient dielectric wall accelerator. This concept was developed by Lawrence Livermore National Laboratory in the US and is still in the 'proof of concept' phase without any prototype. The company has lacked funding and little/nothing has been reported since it received a Letter of Intent from Southwest Oncology Centres in the US in 2012 to deliver a PT system.
- Laser-based accelerator being developed by HIL Applied Medical in Israel. A development stage project with limited funding (crowdfunding) utilising nano-technology, ultra-high intensity lasers and ultra-fast magnets to generate proton acceleration.

Carbon-ion particle accelerators

But what of carbon-ion particle therapy?

Carbon-ion therapy is another form of particle therapy; in this case using carbon ions which have greater mass than protons and are accelerated to 400 MeV. As a consequence the capital costs, annual maintenance costs and operating costs (greater energy consumption) are considerably higher than for the current PT systems which AVO's LIGHT system is expected to reduce further.

Currently used to treat radio-resistant tumours

Carbon-ion therapy is currently less developed than proton therapy; it is indicated for treatment for radio-resistant tumours, which represent around 10% of radiotherapy cases. There are currently eight operational centres[6] globally, with four under construction (two of which will offer both carbon-ion and proton therapy).

... but AVO has proprietary LINAC technology to have a place at the top table

Although not the main focus of Advanced Oncotherapy, the Company, through its wholly owned subsidiary TERA IP, also has a foothold in this area, having entered into a Memorandum of Understanding with TECHNA Research Institute of the University Health Network in Canada. This provides a framework to explore the advancement of TERA's Carbon Booster for Therapy in Oncology ('CABOTO') technology and to evaluate the feasibility of integration of complementary therapeutic tools. Early development work on a compact accelerator for dual carbon-ion and proton beam therapy is being pursued.

Whilst all the major players have development programmes in carbon-ion therapy, alone or in combination with proton therapy, we do not consider carbon-ion therapy as a mainstream threat to Advanced Oncotherapy's current activities and, consequently, valuation. It may well become an additional and important radiation modality in the future, but the substantially higher costs (capital and operational), lack of compelling clinical comparator data with proton therapy and lack of facilities are expected to limit its use to radio-resistant tumours and some paediatric tumours.

[6] Particle Therapy Co-Operative Group http://www.ptcog.ch

Commercial outlook

First product sale for $40m in March 2015 with momentum building...

From a commercial standpoint Advanced Oncotherapy has seen a positive change in momentum during 2015 with its first commercial sale ($40m) to Sinophi Healthcare in March.

The Company announced also on 12th October that it had signed a joint venture agreement with CircleHealth, owned by Circle Holdings plc, to operate the Company's proton therapy centre in Harley Street, Central London, having already signed a 50 year lease with Howard de Walden Estates Limited in January 2015 to convert 8,000 sq ft of 141 and part of 143 Harley St for use as a proton therapy centre. The cost of re-development estimated at £6-7m will be undertaken by Howard de Walden Estates. The scale of re-development has been enlarged to c.11,000 square feet, enabling the joint venture to provide a broader range of services around proton therapy which will be offered out to other hospitals, including the NHS, that want access to the system.

Under the terms of the agreement, AVO and Circle plan to own jointly, on a 49.9%/50.1% basis, a newly formed company into which £6m of equity funding with be provided in equal portions which will cover, among other things, pre-opening costs and working capital. Vendor financing proposals from a number of international financial institutions for the purchase of the LIGHT system are being assessed.

Circle will take responsibility for operational and clinical matters as well as the procurement, fit-out and testing requirements whilst Advanced Oncotherapy will be responsible for technical matters.

Commercial pipeline

Location	Name	Date	Status	Sites	Rooms	Comment
Birmingham, UK	Circle Holdings	Oct-15	Letter of Intent	1	3	Intention to operate a similar facility to that being developed in Harley Street, London
Changchun, China	Jilin University	Aug-15	Framework Agreement	TBD	TBD	Framework Agreement signed between Sinophi and China-Japan Union Hospital of Jilin University. It could lead to a purchase order
Huai'an, China	Sinophi Healthcare	Mar-15	Commercial Sale	1	3	First sale of LIGHT system for c. US$40m and 15 year distribution agreement in China and a select number of other countries in SE Asia. Payment will be satisfied through milestone payments, to support working capital requirements and linked in part to the installation of LIGHT in Harley Street
London, UK	London Harley Street Proton Centre	Jan-15 and Oct-15	Lease to install	1	2	Agreement with Howard de Walden Estates Ltd, granting a 50 year lease for 141 and 143 Harley Street to the Company, comprising c.11,000 sq ft, to be converted for use as a Proton Therapy Centre. Housing the first LIGHT machine to be constructed and operated by joint venture with CircleHealth. HdW is paying £6-7m of construction costs. Vendor financing being assessed for purchase of LIGHT system
Syracuse, USA	SUNY Upstate Medical University Hospital	Dec-14		1	3	Agreement to exclusively work with AVO to install the first LIGHT system in Syracuse, Central New York State. Extends the collaboration previously announced on 20 May 2014 (Letter of Intent)
UK, various	Spire Healthcare	Aug-13	Letter of Intent	3	TBD	Provision of three LIGHT systems. Spire operates 39 hospitals and 11 clinics in the UK
UK, various	BMI Healthcare	Jun-13	Letter of Intent	3	9	Focused on developing three sites, each with three treatment rooms, in Birmingham, Manchester and Glasgow. BMI is UK's largest independent hospital provider with 70 hospitals and healthcare facilities

Source: Hardman & Co Life Sciences Research

In addition, the Company has a pipeline of interest amounting to at least 9 systems with at a minimum of 17 treatment rooms, with Circle having also announced that it is looking to operate a similar proton therapy centre alongside its proposed new-build hospital in Birmingham for which planning permission has recently been granted. The likelihood, in our view, is that these will convert to purchase orders as the Company installs, tests and treats the first patients with the LIGHT system in Harley Street during 2017.

In August 2015 the company announced also that its Chinese partner, Sinophi Healthcare, has signed a framework agreement with China-Japan Union Hospital of Jilin University in relation to a proton therapy centre. Although it does not constitute a purchase order, there is a good chance that it will become one.

Financials & Investment case

History

Advanced Oncotherapy was established in 2012, changing its name from CareCapital plc, to focus specifically on opportunities within the field of cancer diagnosis and treatment, having announced its decision to divest its healthcare property portfolio. In 2013, Advanced Oncotherapy streamlined further its investment case by acquiring the entire share capital of ADAM SA, via a vendor placing. ADAM is a particle physics CERN spin-off company based in Geneva.

Prior to 2012, CareCapital was established in 2006 as a healthcare property developer which underwent an IPO in 2009. Today, Advanced Oncotherapy is solely focused on the development of LIGHT having taken the strategic decision to divest itself of all non-LIGHT operations.

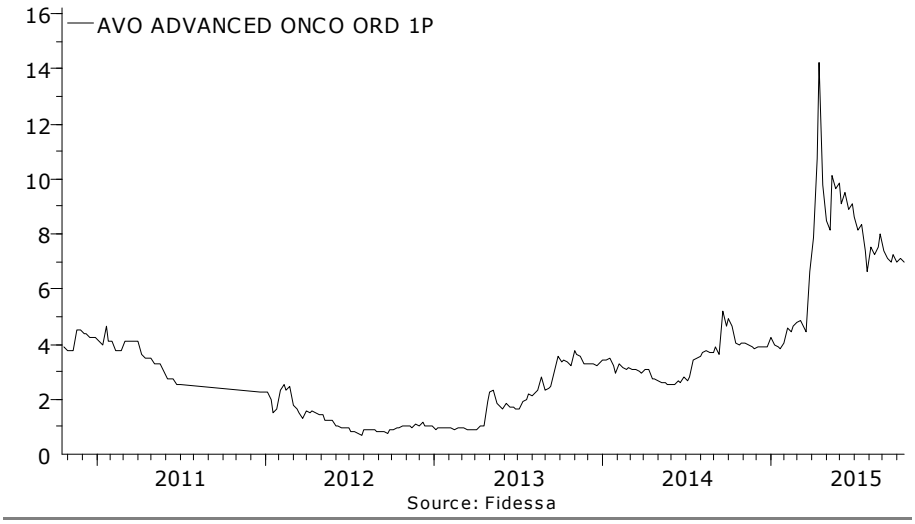
Capital increases

Prior to the acquisition of ADAM in September 2013 c.€14m had been invested into the development of the LIGHT system over a 10-year period. Since 2012 the Company has raised c.£34m, £21m (gross) of which was raised in a Placing in May 2015. With a cash position of £15.6m at 30th June 2015, it implies that a total of c.£32m has been invested to date in LIGHT.

Share price performance

Advanced Oncotherapy has had an eventful year, with the shares rising significantly in March 2015 on the announcement that it had secured the first commercial sale of a LIGHT system to Sinophi Healthcare for $40m.

Share price performance



Source: Fidessa

The enterprise value rose by almost £100m following this announcement, similar to the €130m increase in IBA's enterprise value when it announced the first sale of a proton therapy system (€80m value to IBA for sale of accelerator and long term service contract) to China in January 2015.

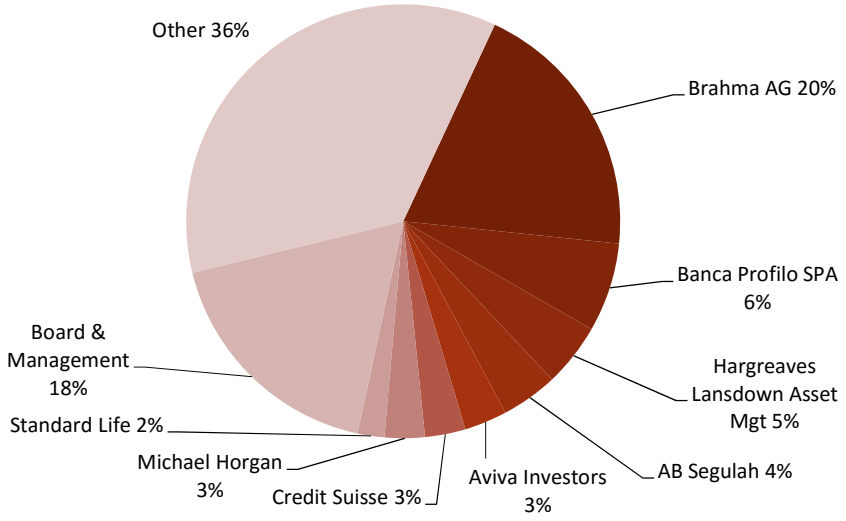
This was the trigger that the market had being looking for; verification that an operator was willing to commit to purchasing a system despite the fact that the Company already had a potential order book of more than £200m with operators in the UK and USA. On the back of this announcement, the Company sought to raise £21m (gross) which was completed in May 2015 at 8p per share.

Since then the shares have drifted lower, partly on the back of a declining broader market but also as the market awaits further commercial milestones/newsflow. Advanced Oncotherapy continues to meet the milestones set in November 2014 for the installation of its first operational LIGHT system, since determined to be in Harley Street, in 2016-2017 and the first patient treated in 4Q 2017.

Share capital

There are 1,411.16m ordinary shares in the company in issue, with Brahma AG being the largest shareholder.

Share capital – September 2015



Source: Advanced Oncotherapy

Financial statements

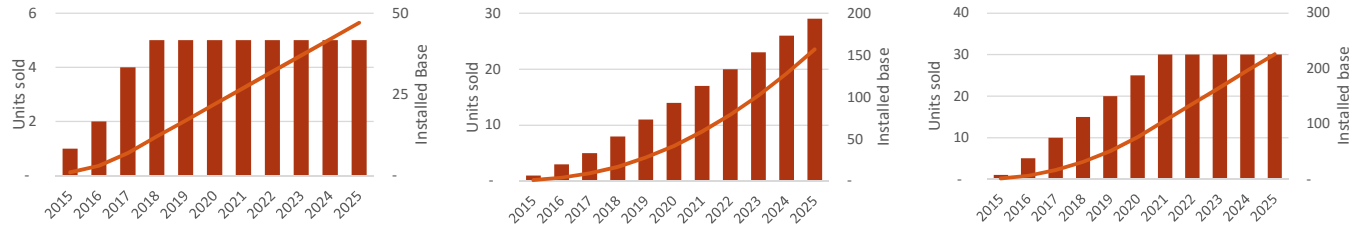
Scenario analysis

There is simply insufficient visibility to generate meaningful long term P&L and cashflow forecasts. However, the sales and EBITDA trends below provide the investor with a reference as to the impact that varying annual orders would have. Given that the company has the capacity to produce up to 30 systems per annum, the following table outlines three potential scenarios:

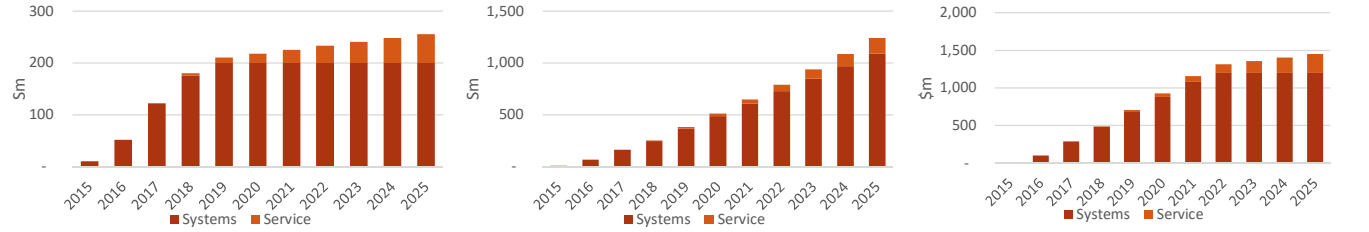
- **Low case:** Unit sales rise from 1 in 2015 to 5 in 2018 and remain as such through until 2025. This implies an installed base of 47 systems by 2025, servicing perhaps 100 treatment rooms. This would represent c.2-4% of the anticipated global capacity in 2025, which we estimate could be in the range of c.2,500-4,600 treatment rooms.
- **Medium case:** Unit sales rise steadily from 1 to 29 units pa in 2025. This implies an installed base of 157 systems by 2025, servicing perhaps 320 treatment rooms or c.7-13% of the anticipated global capacity in 2025.
- **High case**: Unit sales rise from 1 in 2015 to 30 in 2021 and remain so through 2025, implying an installed base of 226 systems by 2025, servicing perhaps 450 treatment rooms (c.10-18% of the anticipated treatment room capacity).

Scenario – Low	Scenario – Medium	Scenario – High

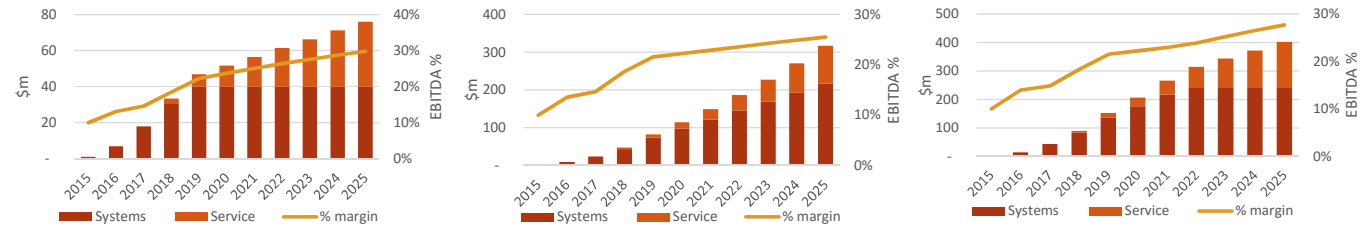
LIGHT systems – Units sold and installed instrument base



Revenues – Systems and service ($m)



EBITDA & EBITDA margin (%)



Source: Hardman & Co Life Sciences Research

Profit & Loss

Profit & Loss account

Year end Dec (£,000s)	2013	2014	2015E	2016E	2017E	2018E
LIGHT Systems sold	**0**	**0**	**1**	**3**	**5**	**8**
Sales	**69**	**106**	**1,370**	**35,484**	**80,645**	**137,097**
Cost of goods	-156	-203	-1,257	-31,935	-68,548	-108,226
Gross Profit	**0**	**-48**	**125**	**2,387**	**3,548**	**12,097**
Administrative expenses	-2,037	-5,085	-7,800	-8,250	-8,750	-9,250
Selling and marketing costs	0	0	0	0	0	0
R&D	0	0	0	0	0	0
Underlying EBITDA	**-2,041**	**-5,063**	**-7,517**	**-4,522**	**3,547**	**19,871**
Depreciation	-82	-118	-170	-180	-200	-250
Amortisation	0	0	0	0	0	0
Underlying EBIT	**-2,124**	**-5,181**	**-7,687**	**-4,702**	**3,347**	**19,621**
Share of JV profit/(loss)	0	0	0	0	-499	279
Share based costs	0	-469	0	0	0	0
Exceptional items	-1,049	-803	-737	0	0	0
Statutory Operating profit	-3,173	-6,453	-8,424	-4,702	2,848	19,900
Net financial income	-258	122	-67	-232	-985	-1,537
Underlying Pre-tax profit	**-2,382**	**-5,059**	**-7,754**	**-4,933**	**2,362**	**18,083**
Exceptional items	-539	-1,232	0	0	0	0
Reported pre-tax	-3,970	-7,563	-8,491	-4,933	1,863	18,363
Reported taxation	0	0	0	0	0	0
Underlying net income	**-2,382**	**-5,059**	**-7,754**	**-4,933**	**2,362**	**18,083**
Statutory net income	-3,970	-7,563	-8,491	-4,933	1,863	18,363
Period-end shares (m)	604.4	1,028.4	1,418.3	1,418.3	1,418.3	1,418.3
Weighted average shares (m)	401.6	848.4	1,290.5	1,290.5	1,301.2	1,418.3
Fully diluted shares (m)	463.1	1,201.6	1,560.3	1,560.3	1,571.0	1,688.1
Underlying Basic EPS (p)	**-0.59**	**-0.60**	**-0.60**	**-0.38**	**0.18**	**1.27**
U/l fully-diluted EPS (p)	-0.51	-0.60	-0.60	-0.38	0.15	1.07
Statutory basic EPS (p)	-0.99	-0.89	-0.66	-0.38	0.14	1.29
Stat. fully-diluted EPS (p)	-0.86	-0.89	-0.66	-0.38	0.12	1.09
DPS (p)	0.00	0.00	0.00	0.00	0.00	0.00

Source: Company reports; Hardman & Co Life Sciences Research

Key metrics

Year end Dec (£,000s)	2013	2014	2015E	2016E	2017E	2018E
Growth						
Sales			1188%	2489%	127%	70%
Operating profit			48%	-39%	-171%	486%
EPS			-100%	-100%	-147%	602%
DPS			n/a	n/a	n/a	n/a
Operating ratios						
Cost of goods	226.3%	190.5%	91.8%	90.0%	85.0%	78.9%
Gross margin	126.3%	-90.5%	8.2%	10.0%	15.0%	21.1%
Admin	nm	nm	569.2%	23.3%	10.9%	6.7%
Sales & Marketing	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
EBITDA	0.0%	nm	-548.6%	-12.7%	4.4%	14.5%
Operating profit	nm	nm	-561.0%	-13.3%	4.2%	14.3%
Reported tax rate	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Source: Company reports; Hardman & Co Life Sciences Research

Key points to note:

- With one LIGHT system sold to Sinophi Healthcare in 2015, the first payment for which was received in September, the forecasts are based on achieving 2, 3 and 5 system sales in 2016, 2017 and 2018, respectively;
- Payments from Sinophi are expected to be received over 3 years (2015-2018), partly linked to the installation progress of the first LIGHT system in Harley Street, with the final payment likely to be made in 2018 on successful first patient treatment in China;
- Vendor financing proposals are currently being assessed for the purchase of a LIGHT system by the joint venture company, due to be set up with CircleHealth, to operate the Harley Street Proton Centre. This funding is expected to be deployed during 2016 and 2017;
- LIGHT system revenues are based on a unit cost of c.$40m+/- depending on configuration. Typical payments are expected to be received over 18-24 months;
- Service contract revenues are c.$1.5m per treatment facility per annum (LIGHT accelerator and ancillary systems) which is unlike its competitors where annual service contracts are typically priced as a percent of all capital hardware (not just the accelerator but all accompanying third party systems, estimated to be c.$2-6m per facility;
- At maturity, EBITDA margins for systems and service contracts are estimated by the Company to be 20% and 65%, respectively.

Balance sheet

Key points to note:

- As purchase orders are won, so too is working capital requirement forecast to rise, with substantial investment in inventory;
- Working capital financed in the model through bank debt but it could be a mixture of debt, vendor financing and/or equity;
- Forecast funding requirement (for working capital) over the period to 2018 is estimated to be c.£50m;
- As a point of note, prior to withdrawing its NASDAQ IPO ($69m) in July Mevion announced that it had secured up to $200m of financing from a Chinese-led consortium of investors.

Balance sheet						
at 31st Decemer (£,000)	**2013**	**2014**	**2015E**	**2016E**	**2017E**	**2018E**
Shareholders funds	6,908	11,132	22,048	17,115	18,978	37,341
Cumulated goodwill	0	0	0	0	0	0
Total equity	6,908	11,132	22,048	17,115	18,978	37,341
Share capital	6,044	10,284	13,479	13,479	13,479	13,479
Reserves	864	847	8,569	3,635	5,499	23,862
Working capital facility	0	0	0	20,000	40,000	50,000
Bank overdrafts	3,190	988	997	997	997	997
less: Cash	149	1,465	4,035	4,257	3,245	4,212
Invested capital	**9,950**	**10,655**	**19,010**	**33,855**	**56,730**	**84,126**
Fixed assets	673	882	812	832	932	1,032
Intangible assets	8,233	9,218	10,072	11,072	12,072	13,072
Investments	2,006	1,197	997	997	997	997
Goodwill	0	0	0	0	0	0
Stocks	37	1,112	2,515	19,161	41,129	64,935
Trade debtors	29	74	2,741	8,871	20,161	34,274
Other debtors	1,168	518	606	606	606	606
Trade creditors	-723	-1,143	-629	-9,581	-20,565	-32,468
Tax liability	-76	-225	0	0	0	0
Other creditors	-1,398	-978	-1,103	-1,103	-1,103	-1,103
Debtors less creditors	-1,000	-1,754	1,615	-1,207	-901	1,309
Invested capital	**9,950**	**10,655**	**19,010**	**33,855**	**56,730**	**84,126**
Net cash/(debt)	-3,042	477	3,038	-16,740	-37,752	-46,785
Net debt/equity (%)	-44.0%	4.3%	13.8%	-97.8%	-198.9%	-125.3%
After-tax ROIC	-21%	-44%	-40%	-14%	6%	23%
Interest cover (x)	n/a	n/a	n/a	n/a	n/a	n/a
Dividend cover (x)	n/a	n/a	n/a	n/a	n/a	n/a
Cap-ex/depreciation (x)	659.3%	277.9%	58.8%	111.1%	150.0%	140.0%
Cap-ex/sales (%)	789.0%	307.3%	7.3%	0.6%	0.4%	0.3%
Net asset value/share (p)	1.7	1.3	1.7	1.3	1.5	2.6
Stock days	44	1035	526	124	161	179
Debtor days	-76	175	375	60	66	72
Creditor days	-846	1680	257	58	80	89

Source: Company reports; Hardman & Co Life Sciences Research

Cashflow

Cashflow						
Year end Dec (£,000s)	**2013**	**2014**	**2015E**	**2016E**	**2017E**	**2018E**
Operating profit	-2,124	-5,181	-7,687	-4,702	3,347	19,621
Depreciation	82	118	170	180	200	250
Amortisation	0	0	0	0	0	0
Stocks	-37	-1,075	-1,403	-16,647	-21,968	-23,806
Trade & other receivables	-83	605	-2,667	-6,130	-11,290	-14,113
Trade & other payables	43	312	-514	8,952	10,984	11,903
Exceptionals/provisions	0	-803	-737	0	0	0
Other	-413	-355	0	0	0	0
Net cash used in operations	**-2,531**	**-6,380**	**-12,838**	**-18,347**	**-18,727**	**-6,145**
Net interest	-331	-178	-67	-232	-985	-1,537
Tax	0	0	0	0	0	0
Operational cashflow	**-2,862**	**-6,558**	**-12,905**	**-18,578**	**-19,712**	**-7,683**
Capital Expenditure	-544	-327	-100	-200	-300	-350
Capitalised intangibles	-188	-985	-854	-1,000	-1,000	-1,000
Sale of fixed assets	0	0	0	0	0	0
Free cashflow	**-3,594**	**-7,870**	**-13,859**	**-19,778**	**-21,012**	**-9,033**
Dividends	0	0	0	0	0	0
Acquisitions	0	0	0	0	0	0
Disposals	1,273	6	290	0	0	0
Other investments	0	0	-3,000	0	0	0
Cashflow after investments	**-2,321**	**-7,864**	**-16,569**	**-19,778**	**-21,012**	**-9,033**
Share repurchases	0	0	0	0	0	0
Share issues	2,437	10,158	20,127	0	0	0
Currency effect	0	0	0	0	0	0
Other	42	1,225	0	0	0	0
Change in net debt	**158**	**3,519**	**3,558**	**-19,778**	**-21,012**	**-9,033**
Opening net cash	-3,200	-3,042	477	4,035	-15,743	-36,755
Closing net cash	**-3,042**	**477**	**4,035**	**-15,743**	**-36,755**	**-45,788**
Hardman cashflow/share (p)	**-0.7**	**-0.8**	**-1.0**	**-1.4**	**-1.5**	**-0.5**

Source: Company reports; Hardman & Co Life Sciences Research

Key points to note:

- Net debt is forecast to be driven largely by working capital requirements, particularly in 2016 and 2017 with operating cash outflow of £18-19m per annum;
- A £3m investment into the joint venture company, established to operate the Harley Street proton centre, is included in 2015;
- An equity investment in March 2015 (£21m gross) positioned the Company to develop and finalise the installation of its first LIGHT system into its Harley Street proton centre.

Valuation

The following table provides key comparator financial information for AVO's principal competitors in the radiotherapy segment. Advanced Oncotherapy is a pure play on proton therapy. The nearest direct competitor in terms of proton therapy is the Belgian company, Ion Beam Applications or IBA, in which proton therapy represented c.57% of 1H 2015 revenues and 62% of EBITDA. Varian Medical Systems and Elekta are the leading providers of radiotherapy systems whilst Accuray sells the only robotic radiosurgery system, CyberKnife. Of these quoted competitors, only Varian sells a proton therapy system. Neither Elekta nor Accuray are developing proton therapy solutions.

Comparative valuations for radiotherapy companies

Company			Share price	Shares (m)	Mkt. Cap. (lc.m)	Net Cash (m)	EV (lc. m)	Mkt. Cap. (£m)	EV (£m)
IBA	IBAB.BR	EURO	28.92	28	819	(13)	832	602	611
Varian Medical Systems	VAR	USD	77.08	100	7,696	524	7,171	4,985	4,645
Elekta *	EKTA-B.ST	SEK	64.15	381	24,458	(2,437)	26,896	1,914	2,105
Accuray *	ARAY	USD	5.52	79	438	(39)	477	284	309
Advanced Oncotherapy	AVO.L	p	6.75	1,418	96	15	81	96	81

		PER			EV/Sales			EV/EBITDA		
Company		2014	2015E	2016E	2014	2015E	2016E	2014	2015E	2016E
IBA	IBAB.BR	39.6	734.5	608.3	3.8	2.7	3.1	29.4	25.4	23.7
Varian Medical Systems	VAR	18.6	17.6	17.0	2.4	2.3	2.2	10.8	11.0	10.4
Elekta *	EKTA-B.ST	51.5	34.1	27.4	2.5	2.3	2.2	15.5	14.7	12.2
Accuray *	ARAY	-11.3	-14.3	-47.8	1.3	1.2	1.1	348.3	58.2	19.6
Advanced Oncotherapy	AVO.L	-11.3	-11.2	-17.7	762.3	59.2	2.3	-16.0	-10.8	-17.9

* Valuation ratios adjusted for calendar year end
Prices as at 16 October 2015

Source: Hardman & Co Life Sciences Research

Company matters

Registration

Incorporated in the UK with company registration number: 05564418

Corporate Address

Third Floor, Clearwater House, 4-7 Manchester Street, London W1U 3AE

www.avoplc.com

Board of Directors

Board of Directors			
Position	**Name**	**Remuneration**	**Audit**
Chairman	Dr Michael Sinclair	M	M
Deputy Chairman	Lord David Evans	M	M
Non-executive Director	Michael Bradfield	M	
Non-executive Director	Tim Lebus	M	M
Non-executive Director	Prof. Chris Nutting		
Non-executive Director	Dr Euan Thomson		
Non-executive Director	Dr Enrico Vanni		
Non-executive Director	Dr Sanjeev Kanoria		
Chief Executive Officer	Dr Sanjeev Pandya		
Chief Financial Officer	Nicolas Serandour		

M = member
Source: Company reports

Dr Michael Sinclair – Executive Chairman

Dr Sinclair qualified in medicine from the Middlesex Hospital, London in 1967 and held a number of appointments at teaching hospitals in London. He became a Registrar in Psychiatry at the Maudsley Hospital and Institute of Psychiatry of London University before entering business in 1971. He held senior board positions with Allied Investments Limited (1971-1977). In 1979, he founded Sinclair Montrose Trust Limited as a private investment vehicle for him and his family. He currently serves on the Board of Overseers (emeritus) of the Tufts University School of Medicine. He was Chairman and founder of Lifetime Corporation Inc, a NYSE-listed healthcare company as well as the Chairman and founder of US based Atlantic Medical Management LLP, which managed the New York based healthcare venture fund, Atlantic Medical Capital LP. Between his experience at Allied Medical and Lifetime Dr Sinclair was President (International) of Hospital Affiliates (the largest hospital company in the world at that time) and Founder Chairman of Hospital Capital Corporation Plc.

Lord David Evans – Deputy Chairman

Lord David Evans is Chairman of Newsdesk Media Ltd, a publishing company producing books for government and organisations, promoting foreign trade and investment. He is also currently Chairman of Senate Consulting Ltd, Evans Mitchell Books, Forum Print Management Ltd, TU Ink Ltd, and Kennedy Scott Ltd. He is Chairman of the Institute of Collaborative Working and a Fellow of the Chartered Institute of Marketing and the City and Guilds Institute. He is president of the 'Pioneers' for Prostate Cancer UK and a strong supporter of Cancer Research UK.

Dr Sanjeev Pandya – Chief Executive Officer

Sanjeev Pandya joined the Company in October 2013 as a consultant for special projects before being promoted to COO in October 2013. He has a broad and diverse background in healthcare, having trained and worked as an orthopaedic surgeon in the NHS and the various Third World countries before joining McKinsey and Company as a strategy consultant. He was an investment banker in healthcare M&A at Lehman Brothers, prior to which he worked at Pfizer Global Pharmaceuticals and Reckitt Benckiser. He has a medical degree from Trinity College, Cambridge and an MBA from INSEAD.

Nicolas Serandour – Chief Financial Officer

Mr Serandour joined the Company in September 2014 as Chief Financial Officer. He has over 15 years of experience in the investment banking industry, having worked at JP Morgan, Lehman Brothers and Lazard, where he was responsible for coordinating the European Healthcare sector coverage. He has extensive experience providing strategic and financial advice to senior executives and boards of directors at leading healthcare companies internationally. He has broad experience in both private and public strategic transactions, including acquisitions, divestitures, complex alliances and funding of growth companies. Mr Serandour graduated from ESSEC with a background in finance and accounting. He received a post-degree master in risk management at Universite Paris Dauphine.

Michael Bradfield – Non-Executive Director

Michael Bradfield has over 30 years' experience of direct marketing and the insurance industry as founder and CEO of Hospital Plan Insurance Services (HPIS), a direct seller of low cost health, accident and life insurance which was sold to AIG in 2000. He has a law degree from LSE, is a full Member of Lloyds of London and a computer application programmer since the late 1960's, specialising in insurance based administration and correspondence systems and database marketing. Since 2004 he has been an active investment manager, especially in technology based companies and sustainable industries.

Tim Lebus – Non-Executive Director

Tim Lebus has spent over 30 years in private equity and banking and is currently Senior Adviser to Duke Street, a private equity group, having previously been a Partner from 2001 to 2012. Prior to this he was an investment banker, most recently as a Managing Director in the Financial Sponsor group at Deutsche Bank. He also works with Octopus Ventures, the venture capital arm of Octopus Investments where he is an observer to a number of its investee companies as well as a director of Octopus Titan VCT 3 plc. In addition, he is a director of Bibby Line Group Limited. He qualified as a lawyer and practised as a barrister in London and subsequently as a corporate lawyer in New York.

Professor Chris Nutting – Non-Executive Director

Professor Nutting is Consultant Clinical Oncologist and Chair in Radiation Oncology at the Royal Marsden Hospital, and The Institute of Cancer Research London. He is the Past President of the British Oncological Association. He is a world leading oncologist specialising in the management of cancer of the head and neck, thyroid, thorax and other forms. He is an expert in solid cancer treatment with state of the art radiotherapy techniques designed to reduce complications of treatment and improve cure rates.

Dr Euan Thomson – Non-Executive Director

Dr Thomson has nearly 20 years of experience in research, clinical practice, consulting and corporate management in the field of radiation therapy. He is currently an operating Partner at Khosla Ventures. Having been a consultant for other medical device companies, including Varian Oncology Systems and Radionics as well as other European and US companies, he served as the CEO of Accuray Inc. (CyberKnife radiotherapy) from 2002-2012 (sales rose $10m to $400m), taking the Company through its IPO in 2007. He has served as a scientific and management consultant to many hospitals, specialising in precision radiotherapy techniques. He holds a BSc in physics with medical applications, an MSc in radiation physics and a PhD in physics from the University of London. He also has authored numerous scientific papers and holds six U.S. patents. He served as the head of the Radiotherapy Department at the Norfolk and Norwich Hospital in the UK.

Dr Enrico Vanni – Non-Executive Director

Dr Vanni is currently a Vice Chairman of the Novartis Board of Directors and an independent consultant. He is also a member of several boards of directors, in industries from healthcare to private banking, for non-listed Swiss companies including Eclosion2, Denzler & Partners SA, Lombard Odier SA and Banque Privée BCP (Suisse) SA. Having started his career as a research engineer for IBM, he joined McKinsey in 1980 where he managed its Geneva office from 1988-2004 and led its European pharmaceutical practice, serving also as a member of the partner review committee, prior to his retirement in 2007.He holds an engineering degree in chemistry from the Federal Polytechnic School of Lausanne, a Ph.D. in chemistry from the University of Lausanne, as well as a MBA from INSEAD, France.

Dr Sanjeev Kanoria – Non-Executive Director

Dr Kanoria is a qualified surgeon, with over 15 years' experience in liver transplant and hepato-pancreato-biliary surgery. He is a Fellow of the Royal College of Surgeons as well as being included on the General Medical Council Specialist Register. Dr Kanoria received an MBA from London business school in 1997, before joining McKinsey & Co as a senior consultant in strategy & finance. In 1999, Sanjeev left McKinsey to start his own company, Advinia Health Care, building a chain of nursing homes across the UK, which now employs close to 1,000 people. In 2013, he acquired 100% of the shares of Hypo Alpe-Adria-Bank AG, renamed Austrian Anadi Bank AG and has been appointed as the Vice Chairman of the Supervisory Board following FMA approval. He is currently setting up a $200m multi-specialty hospital in Mumbai for cancer and trauma surgery.

Senior Management & Medical Advisory Board

Senior Management	
Position	
Executive Chairman	Dr Michael Sinclair
Chief Executive Officer	Dr Sanjeev Pandya
Chief Financial Officer	Nicolas Serandour
Global Head of QMS & Product Realisation	Michael Graham
Head of Product Integration	Bob Rose
US Operations Director	Jay Sinclair
Head of Physics	Marina Giunta
ADAM Managing Director	Donatella Ungaro

Source: Advanced Oncotherapy

Medical Advisory Board

	Experience
Prof Ugo Amaldi	Working at CERN since the 1970s. Founded and directed the DELPHI Collaboration at CERN's LEP Accelerator. Professor of Medical Physics (1990-2006) in Milan. Established TERA in 1992 (Italian Foundation for Hadron therapy). He led the design effort of the Italian National Centre of Oncological Hadron therapy which has been treating patients with protons and carbon ions since 2011.
Dr Hanne Kooy	Associate Professor at Harvard Medical School (radiation oncology). Key interest is in the effective deployment of the appropriate, advanced and integrated technologies to support proton radiation therapy.
Jay Loeffler	Professor of Radiation Oncology at Harvard Medical School and Chair of the Department of Radiation Oncology at the Massachusetts General Hospital.
Dr Nick Plowman	Chairman of Medical Advisory Board. Head of Clinical Oncology at St Bartholomew's Hospital and Senior Clinical Oncologist to the Hospital for Sick Children at Great Ormond Street in London. Director of The CyberKnife Centre in Harley Street, London.
Dr Margaret Spittle	Clinical oncologist at University College London Hospital and consultant adviser in radiation medicine to the Royal Navy. Member of the Nuclear Safety Committer and medical adviser to UK All Party Committee on Breast Cancer.

Source: Advanced Oncotherapy

Risks

Background

Investments in small early stage companies carry a significant risk and investors must be aware of this fact. In our opinion, the following risks are particularly relevant. Each of them could have an impact on time to reach market, cash flow breakeven and profitability.

Dilution risk

The company has sufficient cash to fund the ongoing development programme for LIGHT and to ensure the delivery of its first LIGHT system to Harley Street, Central London. Thereafter, it will most probably need additional capital to fund the working capital requirements of production scale-up.

Commercialisation

Management currently intends to sell the LIGHT system globally which, for a small company, presents many challenges.

Manufacturing and suppliers

The current strategy of management is to have all product supply out-sourced, through an integrated supply chain. These processes inherently carry risks of failure over which the Company has a lower degree of control. Problems at contractors' facilities may also lead to delay. The Company has mitigated against this by using large and reputable manufacturers with existing experience in the PT field.

Patent robustness

As with all IP-rich companies, there is risk that the intellectual property is insufficiently covered by the global patents, allowing a competitor to gain market access. Any litigation could involve significant costs and uncertainties.

Regulatory

It is important for companies to liaise with regulators on a regular basis throughout the development programme. Any inadequacies could lead to regulatory action such as cessation of product development and loss of manufacturing or product licences.

Share liquidity

As with many small cap companies listed on AIM, there can be difficulty in buying and selling shares in volume. Market makers only guarantee prices in a very small number of shares.

Competition

The Company operates in a market dominated by larger competitors, many of which have greater financial resources to fund development programmes, provide add-on solutions, evolve imaging modalities etc. Additionally, they have ability to provide substantive vendor financing solutions to potential operators given the strength of balance sheets.

Glossary

Bragg Peak	The point at which protons deposit most of their energy. This point occurs at the ends of the protons' paths. By varying the beam's energy, radiation oncologists can vary the depth into the patient at which the Bragg Peak is reached and can spread this peak to match the contours of tumours.
Cyclotron	One of earliest particle accelerators in which particles are accelerated in a circular spiral fashion (from the centre to the outer edge of the structure) using a magnetic field at a constant radiofrequency (RF). Cyclotrons were replaced by synchrotrons. Variants of the cyclotron include the Synchrocyclotron in which RF frequency is varied and the Isochronous cyclotron in which the magnetic field increases with radius.
Gantry	A rotating steel structure that moves around the patient to guide the proton beam from the beam transport line to the beam delivery nozzle, thereby treating the tumour from different angles. In most cases gantries are 30m in diameter and can weigh up to 630 tons.
HF-RFQ	High Frequency Radio Frequency Quadrupole is a linear accelerator which focuses, bunches and accelerates a continuous beam of charged particles with high efficiency whilst preserving the emittance up to 5 MeV. It is the only accelerator unit that can accept a low energy continuous beam of particles.
IMPT	Intensity Modulated Proton Therapy. IMPT allows for the radiation dose to conform more precisely to the three-dimensional (3D) shape of the tumour by modulating—or controlling—the intensity of the proton beam in multiple small volumes.
IMRT	Intensity Modulated Radiotherapy. A format for delivering high-dose radiotherapy whereby a broad radiation field is divided into multiple small beams of radiation, the intensity of which is determined by computer optimisation.
Klystron	A high-power pulsed RF amplifier, in a linear beam vacuum tube, used to generate and drive the power for particle accelerators. This can be bought off the shelf from Toshiba.
LINAC	Linear particle accelerator in which particles are accelerated in a straight line with a target of interest at one end. They are often used to provide an initial low-energy start to particles before they are injected into circular accelerators. Medical grade LINACs accelerate electrons using a klystron and a complex bending magnet arrangement which produces a beam of 6-30 MeV of energy.
MeV	1 million electron volts. An electron volt is a unit of energy. For clinical applications particles are accelerated to between 70 and 250 MeV (protons) and up to 400 MeV in the case of carbon ions.
Modulator	A pulse generator that supplies high-voltage pulses and other AC and DC voltages and currents required for the operation of high-power pulsed RF amplifiers (also called klystrons). The pulses are delivered to the cathode of the klystron.
PBS	Pencil Beam Scanning, also referred to as spot scanning. PBS delivers a single, narrow proton beam that is magnetically swept across the tumour, depositing the radiation dose like a painter's brush strokes, without the need to construct beam shaping devices, allowing for a higher degree of precision, minimising overall exposure of healthy tissue to radiation and allowing for treatment of more complex tumour shapes and morphology. PBS is only as good as the complex and intricate treatment planning systems used to direct the beam's motion, depth and strength which are evolving all the time. Traditional proton therapy use a passive beam, which is delivered through the use of custom-made compensators and apertures that must be designed for each patient and changed throughout the course of therapy as tumours change shape or position.
Photon	An energy packet of electromagnetic radiation; the elementary particle of photon radiation therapy (RT). X-rays and gamma rays are photon radiation.
Proton	A positively charged particle of an atom. The charge and relatively large mass (1,800 times that of an electron) of protons account for the Bragg Peak effect.
Synchrocyclotron	Particle accelerators in which the frequency of the RF field is varied unlike the cyclotron, where this frequency is constant and in which super-conducting magnetic field enables the construction of a more compact system than the cyclotron or synchrotron.
Synchrotron	Particle accelerator, descended from the cyclotron in which particles are bent into a closed orbit, using a magnetic field which is synchronised to a particle beam of increasing kinetic energy, thereby keeping the orbit radius constant (unlike a cyclotron).
Voxel	Basic unit of computed tomography reconstruction – used in 3D modelling; smallest distinguishable box shaped part of a 3D space, represented as a pixel in a CT image display.

Disclaimer

Hardman & Co provides professional independent research services. Whilst every reasonable effort has been made to ensure that the information in the research is correct, this cannot be guaranteed.

The research reflects the objective views of the analysts named on the front page. However, the companies or funds covered in this research may pay us a fee, commission or other remuneration in order for this research to be made available. A full list of companies or funds that have paid us for coverage within the past 12 months can be viewed at http://www.hardmanandco.com/

Hardman & Co has a personal dealing policy which debars staff and consultants from dealing in shares, bonds or other related instruments of companies which pay Hardman for any services, including research. They may be allowed to hold such securities if they were owned prior to joining Hardman or if they were held before the company appointed Hardman. In such cases sales will only be allowed in limited circumstances, generally in the two weeks following publication of figures.

Hardman & Co does not buy or sell shares, either for its own account or for other parties and neither does it undertake investment business. We may provide investment banking services to corporate clients.

Hardman & Co does not make recommendations. Accordingly we do not publish records of our past recommendations. Where a Fair Value price is given in a research note this is the theoretical result of a study of a range of possible outcomes, and not a forecast of a likely share price. Hardman & Co may publish further notes on these securities/companies but has no scheduled commitment and may cease to follow these securities/companies without notice.

Nothing in this report should be construed as an offer, or the solicitation of an offer, to buy or sell securities by us.

This information is not tailored to your individual situation and the investment(s) covered may not be suitable for you. You should not make any investment decision without consulting a fully qualified financial adviser.

Hardman Research Ltd, trading as Hardman & Co, is an appointed representative of Capital Markets Strategy Ltd and is authorised and regulated by the Financial Conduct Authority (FCA) under registration number 600843. Hardman Research Ltd is registered at Companies House with number 8256259. However, the information in this research report is not FCA regulated because it does not constitute investment advice (as defined in the Financial Services and Markets Act 2000) and is provided for general information only.

Hardman & Co Research Limited (trading as Hardman & Co)
11/12 Tokenhouse Yard
London
EC2R 7AS
T +44 (0) 207 929 3399

Follow us on Twitter @HardmanandCo

Version 2 - August 2015

Hardman Team

Marketing / Investor Engagement

+44 (0)20 7929 3399

Richard Angus	ra@hardmanandco.com	+44 (0)207 148 0548
Max Davey	md@hardmanandco.com	+44 (0)207 148 0540
Keith Hiscock	kh@hardmanandco.com	+44 (0)207 148 0544
Felicity Reid	fr@hardmanandco.com	+44 (0)207 148 0546

Analysts +44 (0)20 7929 3399

Agriculture		**Bonds**	
Doug Hawkins	dh@hardmanandco.com	Brian Moretta	bm@hardmanandco.com
Yingheng Chen	yc@hardmanandco.com		
Meghan Sapp	ms@hardmanandco.com		
Building & Construction		**Consumer & Leisure**	
Tony Williams	tw@hardmanandco.com	Mike Foster	mf@hardmanandco.com
Mike Foster	mf@hardmanandco.com	Steve Clapham	sc@hardmanandco.com
Financials		**Life Sciences**	
Brian Moretta	bm@hardmanandco.com	Mark Brewer	mb@hardmanandco.com
		Martin Hall	mh@hardmanandco.com
Media		**Mining**	
Derek Terrington	dt@hardmanandco.com	Ian Falconer	if@hardmanandco.com
		Stephen Thomas	st@hardmanandco.com
Oil & Gas		**Property**	
Stephen Thomas	st@hardmanandco.com	Mike Foster	mf@hardmanandco.com
Mark Parfitt	mp@hardmanandco.com		
Services		**Social Impact**	
Mike Foster	mf@hardmanandco.com	Mike Foster	mf@hardmanandco.com
Special Situations		**Technology**	
Steve Clapham	sc@hardmanandco.com	Michael Kovacocy	mk@hardmanandco.com
		Mike Foster	mf@hardmanandco.com

Hardman & Co

11/12 Tokenhouse Yard
London
EC2R 7AS
United Kingdom

Tel: +44(0)20 7929 3399
Fax: +44(0)20 7929 3377

www.hardmanandco.com