Healthcare Equipment & Services

Source: Refinitiv

Market data

EPIC/TKR	**AVO**
Price (p)	**38.0**
12m High (p)	52.0
12m Low (p)	32.5
Shares (m)	243.8
Mkt Cap (£m)	92.7
EV (£m)	106.6
Free Float*	72%
Market	AIM

**As defined by AIM Rule 26*

Description

AVO is developing next-generation PBT for use in cancer radiotherapy. The first system is expected to undergo CE marking during 2020. Standard radiation procedures have evolved over many years. PBT delivers radiation via a beam of proton particles rather than a beam of photons used in conventional radiotherapy (X-rays).

Company information

Exec. Chairman	Michael Sinclair
CEO	Nicolas Serandour
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	www.avoplc.com

Key shareholders

Liquid Harmony (Board)	18.5%
Other Board	9.6%
P. Glatz	6.4%
DNCA Investments	4.9%
Brahma AG	3.2%
Barrymore Inv.	3.2%
Lombard Odier	3.1%

Diary

4Q'19	All modules delivered
4Q'19	Patient positioning delivered

Analysts

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ADVANCED ONCOTHERAPY

Proving the accuracy and superiority of minibeams

The goal of Advanced Oncotherapy (AVO) is to deliver an affordable and more effective proton beam therapy (PBT) system, based on state-of-the-art technology developed originally at the world-renowned CERN. In the past 18 months, the project has been de-risked through important technical milestones. AVO is now working on the verification and validation phase, prior to CE marking and LIGHT being used on the first patients. Meanwhile, AVO has entered into a research collaboration with the Cleveland Clinic aimed at proving the accuracy of targeting cancerous tissue, and sparing normal tissue, with proton minibeams in comparison with other methodologies.

- **Strategy:** AVO is developing a compact and modular PBT system, which is affordable for the payor, financially attractive to the operator, and generating superior patient outcomes. AVO benefits from technology know-how developed by ADAM (CERN spin-off) and relies on a world-class supplier base.

- **Collaboration:** The renowned Cleveland Clinic will undertake a two-year study to evaluate the target conformality of proton minibeams in comparison with stereotactic X-ray radiotherapy currently used for several types of cancer, particularly those located in the brain.

- **Goals:** Industry and oncologists are focused on overcoming the key challenge of ensuring that radiotherapy is targeted only at cancerous tissue, and avoiding healthy tissue. LIGHT has been designed for accuracy and improved patient outcomes. It is also being positioned to highlight its commercial advantages.

- **Risks:** Since 2018, the more complex technical challenges have been overcome, and progress towards a fully-functional accelerator is under way in readiness for CE marking. Execution risk remains, but management's ability to raise funding and meet its milestones for the past 30 months has lowered this risk.

- **Investment summary:** AVO's market capitalisation of £93m equates only to the amount invested into LIGHT to date, which does not reflect either the enormous technical challenges that have been overcome or the market potential. A DCF analysis of the LIGHT prospects generates an NPV of at least 224p per share (fully-diluted). The disconnect between fundamental and market valuations offers an interesting investment opportunity, in our opinion.

Financial summary and valuation

Year-end Dec (£m)	2017	2018	2019E	2020E	2021E	2022E
Sales	0.0	0.0	0.0	21.5	65.5	111.5
Gross profit	0.0	-1.9	0.0	1.9	11.4	27.6
Administration costs	-12.9	-15.7	-15.0	-15.4	-15.8	-16.2
EBITDA	-14.1	-21.4	-18.9	-16.6	-10.5	1.6
Underlying EBIT	-14.5	-21.8	-20.6	-20.6	-14.6	-2.4
Statutory EBIT	-14.5	-21.8	-20.6	-21.2	-13.9	-0.7
Underlying PTP	-16.5	-21.9	-21.7	-22.3	-16.7	-4.6
Statutory PTP	-16.5	-21.9	-21.7	-22.9	-16.0	-2.9
Underlying EPS (p)	-17.6	-14.0	-8.9	-8.3	-6.1	-1.3
Statutory EPS (p)	-18.9	-13.4	-8.9	-8.5	-5.9	-0.7
Net (debt)/cash	-9.2	-2.0	-13.9	-21.5	-31.0	-34.7
EV/EBITDA (x)	-	-	-	-	-	61.9

Source: Hardman & Co Life Sciences Research

Radiotherapy research collaboration

Two-year collaboration

AVO has signed a two-year research collaboration with the Cleveland Clinic, a leading academic medical centre, based in Cleveland, Ohio. This centre provides clinical and hospital care, and is a leader in research, education and health information. The aim of the collaboration is to evaluate the target conformality[2] of proton minibeams in comparison with X-ray stereotactic radiosurgery (SRS)[1].

$$\text{Target conformality (TC)} = \frac{\text{Volume of tissue receiving the prescription dose of radiation (PIV)}}{\text{Target volume (TV)}}$$

As highlighted in our recent report[3], innovation in radiotherapy (RT) is focused on increasing the efficacy of treatment and improving quality of life for patients through a reduction of side effects or an increase in long-term survival rates. The most challenging goal for both the industry and the treating physicians is ensuring that RT is targeted only at cancerous tissue, and avoiding the irradiation of healthy tissue.

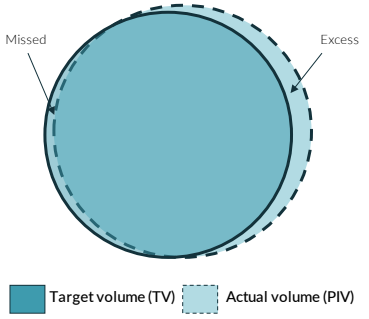
The use of a smaller proton beam (minibeams) means greater accuracy in targeting the desired tissue, which is essential when treating tumours that are near critical organs, particularly those close to the edge of the tumours. PBT is focused on initiatives to generate pencil-thin and more accurate beams. Indeed, AVO's LIGHT system has been designed to generate an industry-leading minibeam (see below) compared with anything possible using current proton therapy technology.

Proton minibeam radiation therapy

A new approach in RT that allies the inherent physical advantages of protons with the normal tissue preservation observed when irradiated with sub-millimetric spatially fractionated beams (i.e. below the current standard size of proton beams) has been termed proton minibeam radiation therapy (pMBRT). A recent study[4] described a dosimetry evaluation of pMBRT that was aimed at demonstrating the feasibility of the technical implementation of this technology. The study concluded that pMBRT was a novel strategy that could be used to reduce the side effects of RT. It provided the experimental proof-of-concept for pMBRT: clinical proton beams could be deposited in a (high) uniform dose in a brain tumour located in the centre of the brain (7.5 cm depth – the worst scenario), while a spatial fractionation of the dose could be retained in the normal tissues in the beam path, potentially leading to a gain in tissue sparing.

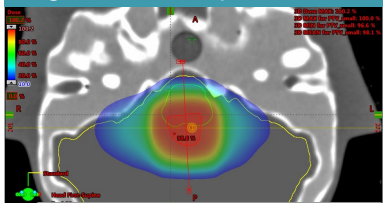
AVO's LIGHT system is designed to provide pMBRT using the latest scanning technology. A figure of merit is shown comparing conventional PBT with pMBRT for a challenging tumour location in the base of the skull, encroaching on the brainstem (sensitive normal tissue). The colour wash in the figure on the left indicates the relative amount of radiation dose that the patient would receive from PBT and pMBRT. The pMBRT treatment plan is more sparing of the brainstem. The relative sparing

Target conformality

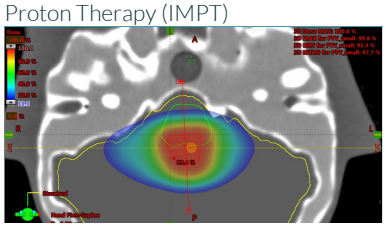


Source: Adapted from Ohtakara et al[1]

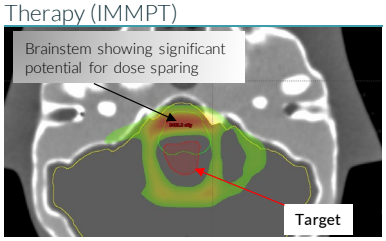
Target conformality



Conventional Intensity Modulated Proton Therapy (IMPT)



Intensity Modulated Minibeam Proton Therapy (IMMPT)



Dose difference IMPT minus IMMPT

Source: Advanced Oncotherapy

Proton beam sizes

Source: Hardman and Co Life Sciences

[1] Ohtakara, K., Hayashi, S. and Hoshi, H. The relation between conformality indices and the influence of the target coverage difference in prescription isodose surface on these vales in intracranial stereotactic radiosurgery. *Br.J.Radiology*. 2012, 85: 223-228.

[2] Conformality represents the ability of LIGHT to deliver a proton beam in such a way that the deposited radiation perfectly matches the irregular shapes of the tumour.

[3] Hardman & Co. Advanced Oncotherapy: Flash benefits from new US reimbursement. 11 November 2019, https://www.hardmanandco.com/wp-content/uploads/2019/11/AVO-technical-update-11-Nov-2019-2.pdf

[4] Peucelle, C., Nauraye, C., Patriarca, A., Hierso, E., Fournier-Bidoz, N., Martínez-Rovira, I and Prezado, Y. Proton minibeam radiation therapy: Experimental dosimetry evaluation. *Med Phys*. 2015, 42(12): 7108-13.

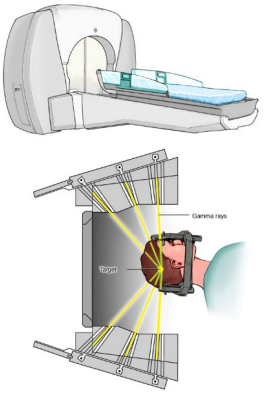
difference between PBT and pMBRT is observed in the lower tile of the figure, which highlights the advantages of using minibeams and sparing healthy tissues.

X-ray stereotactic radiosurgery

SRS is a non-surgical radiation therapy used to treat functional abnormalities and small tumours of the brain. It can deliver precisely-targeted radiation in fewer high-dose treatments than conventional therapy. When SRS is used to treat body tumours, it is called stereotactic body radiotherapy (SBRT).

As with most aims of the technologies/procedures described, the goal with SRS is to deliver a prescribed dose of radiation to the target geometry in as conformal a manner as possible, while spilling as little as possible into the surrounding normal tissue.

Stereotactic radiosurgery



Source: Mayo Clinic

SRS uses many small, precisely-focused, radiation beams to treat tumours in the brain, neck, lungs, liver, spine and other parts of the body. Each beam has very little effect on the tissue it passes through, but a targeted dose of radiation is delivered to the site where all the beams intersect (see example graphic on left from Mayo Clinic). SRS is not surgery in the traditional sense, because no incisions are made; instead, it uses 3D imaging to target high doses of radiation to the affected area, with minimal impact on the surrounding healthy tissue.

Like other forms of radiation, SRS works by damaging the DNA of the targeted cells. The affected cells then lose the ability to reproduce, which causes tumours to shrink and blood vessels to close off over time following treatment, robbing the tumour of its blood supply. SRS of the brain and spine is typically completed in a single session, whereas body radiosurgery is used to treat lung, liver, adrenal and other soft tissue tumours, and treatment typically involves multiple sessions.

A further scientific endorsement

AVO has been able to form a very strong management team and attract key talent in the industry (the latest appointment being that of the previous head of Proton Therapy head of Varian as Chief Commercial Officer and President of North America). In addition, AVO has built a large network of suppliers with great track records. Today's announcement is a further external endorsement that bodes well for the scientific reputation of the company. The following is a brief overview of the Cleveland Clinic:

- American academic medical centre based in Cleveland, Ohio.
- Owned and operated by the Cleveland Clinic, an Ohio non-profit corporation established in 1921.
- Runs a 170-acre campus in Cleveland, as well as 11 regional hospitals and 19 family health centres in northeast Ohio. Also manages hospitals in Florida and Nevada.
- Also operates outside of the US, with the Cleveland Clinic Abu Dhabi hospital, a sports medicine clinic in Toronto. In addition, it expects to have a hospital campus in London in 2021.
- Consistently ranked as one of the best hospitals in the US. In 2018-19, the U.S. News & World Report ranked the Cleveland Clinic as the number two hospital in the Best Hospitals Honor Roll, and it was nationally ranked in 14 adult and 10 paediatric specialties.
- It counted 7.6 million patient visits and 229,132 admissions in 2017.
- It has more than 60,000 employees, a figure that includes over 11,800 nurses, and over 3,953 physicians and scientists in 140 specialties.
- It is the first healthcare provider in the US to become a signatory to the United Nations Global Compact, and the second in the world.

Conclusion

Much of the research being undertaken in the field of PBT, together with clinical investigations, is aimed at focusing the RT onto the cancerous tissue while sparing normal tissue. The collaboration reported here and the previously reported use of ultra-efficient hypofractionation (FLASH technology) are both attempting to satisfy these goals.

The results of the collaboration with the Cleveland Clinic are not needed for the certification of LIGHT, but the quality and track record of the medical centre, together with the design of LIGHT that allows a much smaller proton beam to be generated, provide a further strong foundation of the superiority of LIGHT.

The LIGHT system being developed by AVO is particularly well positioned with respect to all these new initiatives and technologies:

- It generates high energy proton beams, but only up to the required level, avoiding the need for diffusers and associated high levels of shielding.
- It allows an ultra-fast (up to 200 times per second vs. 1-2 times per second for competitive systems) change of energy and deposition of radiation onto the tumour – hence optimising the effect of radiation on moving organs/tumours.
- It is suitable for hypofractionation procedures.
- It is suitable for FLASH technology.
- It is well positioned to reduce the number of hospital/clinic treatment visits to minimal levels and for the new US reimbursement model (assuming implementation in early 2020). It is well positioned for new US reimbursement model (assuming implementation in early 2020).

The collaboration with the Cleveland Clinic is designed to show that the accuracy of hypofractionated proton minibeams is at least as good as complex stereotactic radiotherapy with respect to target conformality.

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