We upgrade AVO to OUTPERFORM with a fair value of 155 GBp. The company has significant growth potential in the nascent Proton therapy (“PT”) industry. The dented growth trajectory from the industry leaders in PT signals the limitation of the conventional cyclotron technology in PT. We are encouraged by AVO’s technology to benefit from this bottleneck through delivery of a better and easier-to-install technology with its PT Linac. Execution on scaling up production will easily lower machine prices and therefore represents a significant opportunity to expand margins on the services business, which will remain at a higher price level. We are also encouraged by an upgraded management team, which is experienced in installations, service and sales - OUTPERFORM.

Advanced Oncotherapy - Early stage but technological advantage of AVO’s LIGHT. The PT incumbents, IBA and Varian are far ahead of its competition dominating the market with a combined market share of more than 70%. However, besides pricing, all PT players share one significant hurdle for fast adoption rate. The cyclotron technology involves lengthy and complicated building preparation. Heavy cyclotrons and large concrete bunkers make the installation a major building project, which is, regardless of pricing, often a big hurdle. AVO could carve out a significant advantage with their modular system, which could in theory allow a much faster and easier installation almost comparable with conventional Linac. AVO could tap into a new market for mid-sized hospitals, which could be a significant volume play.

Fast and easy installation of LIGHT could take PT to a faster adoption rate with a higher margin expansion opportunity vs. conventional cyclotron based PT. The advantage of AVO’s technology being faster and less complicated combined with a cheaper production process could give the company a fast head-start with a future margin expansion opportunity driven by an attractive service revenue stream.

Price of PT machines is not the biggest hurdle. While the current debate in the clinical community is about pricing and clinical evidence, we believe that the above-mentioned installation hurdles are more significant in holding back a faster adoption rate. In this update report we have compared cost of cancer treatments, which makes PT look less expensive over a longer time period compared to drug-based approaches. We feel that the pricing element will become even less of an issue once the read out of trials comparing PT vs. Radiotherapy (“RT”) in 2020 brings clinical evidence to light. Should PT machines stay at the $15m price band by 2030, margins could look significantly more attractive for the whole PT industry.

Reinforced management team changes the equity story significantly. AVOs management team has changed the equity story significantly compared to 2016. While the patents and the promising technology was already in place then, the company has added veterans of the PT industry from science, engineering, installation, application experience and compliance. We feel that the success of the industrialisation is entirely hinging on the top professionals.

The Proton therapy industry offers significant structural growth. We assume a PT conversion rate of 15% by 2030, which would make it a c.$8.0bn market ($4.5bn for 380 machines in that year sold and $3.5bn for the service of all machines installed up to 2030 (c.2,900 PT vs. c.16,500 conventional PT machines)). PT is amongst the most attractive subsectors in Medtech, which grows significantly above the sluggish Medtech sector with low single digit top line growth. Medtech as a whole has lost its steam due to lack of innovation, which was followed by price pressure from payers, who no longer pay top dollar for commoditised devices and instruments.

Valuation - We upgrade AVO from non-rated to OUTPERFORM and a price target of 155 GBp based on new funding, strengthened management and a robust strategy.
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Executive Summary

- The Proton therapy ("PT") industry offers significant structural growth in terms of volumes. The two main players Ion Beam Applications [OUTPERFORM – TP €50] and Varian Inc. [NC] dominate this fast-growing industry albeit with a dented outlook. While we believe that the strong underlying demand for particle therapy remains broadly unchanged, recent profit warnings from IBA demonstrated that cyclotron technology has reached its commercial limits. We continue to advocate a PT conversion rate of 15% by 2030. This would make PT a €8bn market (€4.5bn for 380 machines in that year sold) and €3.5bn for the service of all machines installed up to 2030 (c.2,900 PT vs c.16,500 conventional RT machines).

- Management team has been substantially reinforced by appointment of high calibre industry veterans. AVO’s management team has changed the equity story significantly compared to 2016. While the patents and the promising technology were already in place then, the company has managed to attract veterans of the PT industry from science, engineering, installation, application experience and compliance. We feel that the success of the industrialisation is entirely hinging on the top professionals like Prof Myers, Ed Lee, Dr Jonathan Farr and Dr Michel Baelen, supported by a team that has the right credentials to implement an attractive funding and execution strategy such as Dr Mike Sinclair or Nicolas Serandour.

- Advanced Oncotherapy - Early stage, but technological advantage. The PT incumbents, IBA and Varian are far above the few other players like Mevion, Hitachi, Mitsubishi. However, all these players share one significant hurdle for fast adoption rate. The technology involves lengthy and complicated preparation to install PT machines. Heavy cyclotrons and large concrete bunkers make the installation a major building project. We feel that AVO could carve out a significant advantage with their modular system and the first commercially available linear PT accelerator. AVO could open up a new market for mid-sized hospitals, which could be a big volume play.

- The industrialisation process of LIGHT is a significant value driver. With much of the Linac for Image Guided Hadron Therapy ("LIGHT") accelerator technology now developed AVO’s technology is on track to meet its production and commercial rollout goals. AVO has reached a number of important milestones and overcome some technical challenges in recent months, paving the way for future mass-production. In contrast to cyclotrons, LIGHT’s mass production will benefit from scale effects. Scale effects, the company will be able to deliver cheaper machines and maintain the service contracts price.

- Proton with a faster and easier installation could take the technology to a faster adoption rate. The advantage of AVO’s technology being faster and less complicated combined with a cheaper production process could give the company a fast head-start. While the production scale-up and sourcing is not trivial, AVO has a number of well-established industry partners for this role.

- Price of PT machines is not the biggest hurdle. While the current debate in the clinical community is about pricing and clinical evidence, we believe that the above-mentioned installation hurdles are more significant in holding back a faster adoption rate.

- Commercial execution and industrialisation of LIGHT are significantly de-risked. AVO has an interesting technological approach and established good industrial partnership to bring the product to fruition. Execution has become significantly de-risked with both recent financing injection, a new distribution partner in China and high calibre management. We highlight to investors, that while AVO could be a fast-growing new comer in the PT industry, the risk factors and low liquidity of the stock remain a modest downside to the investment case. The upside is a significant scale effect, once LIGHT enters mass production by the end of the next decade.

- Valuation – We upgrade Advanced Oncotherapy ("AVO") to an OUTPERFORM recommendation, and set a new target price of 155 GBP and a total equity value of £230m. This represents a 385% upside from current trading levels. Our DCF results in £230m equity value for AVO’s business on these assumptions. This would result in an equity value of £230m.
Valuation Summary

Valuation framework – We have chosen to value the company on a DCF basis and on a comparable multiple approach based on mid- to long-term multiples since the company is not profitable yet. We advocate applying a DCF valuation for a number of reasons. Firstly, AVO is still a relatively new company in terms of its commercialisation stage of PT. While the technology is older than sixty years, PT has only been recently enjoying a significant uptake in clinical adoption and AVO’s approach is new and yet commercially untested. The potential of AVO to build a strong market share in the dominant radiation therapy technology of the future could be significant.

The chart illustrates a blend of two valuation methods – we have modelled AVO with a DCF and undertook an extensive scenario analysis, which we have laid out in a later section of the note in detail. We arrived at a blended value of £230m (€230m DCF, €200m from mid to long term EV/sales/EBITDA).

Below we show a comparable company table, where we have chosen a number of medtech peers with representative parameters, for which we felt they are relevant for AVO’s future. Since AVO has neither profits nor sales at present, we applied long term EV/sales multiples from the industry group as illustrated below. The average of mid and longer-term multiples for AVO’s projected sales resulted in £200m for its EV.

We applied mid to long term trading multiples from comparable companies to assess AVO’s value. Sales multiples the earliest from 2023E and EBITDA from 2025E are fair. In those years AVO would reach a meaningful level of sales and profitability.

<table>
<thead>
<tr>
<th>Company</th>
<th>comp rational</th>
<th>2019e</th>
<th>2021e</th>
<th>2023e</th>
<th>2025e</th>
<th>Sales CAGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBA</td>
<td>Protontherapy</td>
<td>1.3x</td>
<td>1.4x</td>
<td>1.3x</td>
<td>1.2x</td>
<td>3%</td>
</tr>
<tr>
<td>Varian</td>
<td>Radio oncology</td>
<td>3.4x</td>
<td>2.9x</td>
<td>2.5x</td>
<td>2.1x</td>
<td>8%</td>
</tr>
<tr>
<td>Elekta</td>
<td>Radio oncology</td>
<td>2.5x</td>
<td>2.1x</td>
<td>1.8x</td>
<td>1.5x</td>
<td>8%</td>
</tr>
<tr>
<td>Ambu</td>
<td>Fast growing Med</td>
<td>10.5x</td>
<td>7.3x</td>
<td>5.3x</td>
<td>3.8x</td>
<td>15%</td>
</tr>
<tr>
<td>Boston</td>
<td>Established Med</td>
<td>4.1x</td>
<td>3.4x</td>
<td>2.8x</td>
<td>2.3x</td>
<td>9%</td>
</tr>
<tr>
<td>Raysearch</td>
<td>Disruptor</td>
<td>5.1x</td>
<td>3.2x</td>
<td>2.1x</td>
<td>1.3x</td>
<td>20%</td>
</tr>
<tr>
<td>ViewRay</td>
<td>MRI Imaging</td>
<td>2.8x</td>
<td>1.5x</td>
<td>0.7x</td>
<td>0.4x</td>
<td>30%</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>4.2x</td>
<td>3.1x</td>
<td>2.3x</td>
<td>1.8x</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Company</th>
<th>comp rational</th>
<th>2019e</th>
<th>2021e</th>
<th>2023e</th>
<th>2025e</th>
<th>EBITDA CAGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBA</td>
<td>Protontherapy</td>
<td>13.9x</td>
<td>15.2x</td>
<td>11.7x</td>
<td>9.0x</td>
<td>12%</td>
</tr>
<tr>
<td>Varian</td>
<td>Radio oncology</td>
<td>16.7x</td>
<td>15.1x</td>
<td>13.4x</td>
<td>12.0x</td>
<td>6%</td>
</tr>
<tr>
<td>Elekta</td>
<td>Radio oncology</td>
<td>11.3x</td>
<td>8.8x</td>
<td>6.9x</td>
<td>5.4x</td>
<td>12%</td>
</tr>
<tr>
<td>Ambu</td>
<td>Fast growing Med</td>
<td>36.6x</td>
<td>21.0x</td>
<td>12.5x</td>
<td>7.4x</td>
<td>23%</td>
</tr>
<tr>
<td>Boston</td>
<td>Established Med</td>
<td>13.8x</td>
<td>10.7x</td>
<td>8.4x</td>
<td>6.6x</td>
<td>11%</td>
</tr>
<tr>
<td>Raysearch</td>
<td>Disruptor</td>
<td>11.1x</td>
<td>6.2x</td>
<td>3.4x</td>
<td>1.9x</td>
<td>26%</td>
</tr>
<tr>
<td>ViewRay</td>
<td>MRI Imaging</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>17.2x</td>
<td>12.8x</td>
<td>9.4x</td>
<td>7.0x</td>
<td></td>
</tr>
</tbody>
</table>

Source: goetzpartners Research estimates, Factset.
Recent milestones and upcoming catalysts

Recent accomplishments fuel confidence
With much of the LIGHT accelerator technology now developed and tested, and with multiple manufacturing agreements in place, AVO’s technology is on track to meet its production and commercial rollout goals. AVO has reached a number of important milestones and overcome some technical challenges in recent months, paving the way for future mass-production.

Development of the first LIGHT system at Harley Street on schedule
AVO recently announced that the progress at the Harley Street site remains on-track and that the technological development of the accelerator is progressing well. Harley Street is home to a large number of private specialists in medicine and surgery, representing an ideal location to showcase the first installation of LIGHT, and to illustrate its technical advantages and modular flexibility: the fact that the system can be installed in a location in central London highlights its suitability for urban environments, thus bringing the technology closer to the patient and making it more accessible. Demolition and piling works have now been completed by Deconstruct, the principal contractor company; next steps include further excavation works. Construction is expected to total 18 months from start in Q1/2017, and with regulatory approval and certification being done in parallel, Harley Street is on track to receiving its first patient in H2/2020E.

Partnerships paving the way to industrialisation and manufacturing
While LIGHT’s modular design has far-reaching logistical advantages when it comes to system installation, other benefits include the possibility to outsource the production of separate complex components to different specialists. This streamlines manufacturing and allows for a degree of flexibility that distinguishes AVO from its competitors, while at the same time preserving a very high level of quality. Through this approach, LIGHT lends itself to mass-production, which is not possible with currently available systems, giving AVO an additional competitive edge. Furthermore, the implementation of “best practice” manufacturing procedures by AVO’s partners place the company in a good position to fast-track the regulatory process and CE mark approval by being able to maintain a high qualitative manufacturing standard despite production being ramped up. As such, these strategic partnerships are an important requirement for the commercial rollout of the LIGHT system and AVO’s future commercial success.
Upcoming catalysts

CHART 5: Timeline and catalysts for the next 24 months

<table>
<thead>
<tr>
<th>Event</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery of all CCL Units</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beam trough RFQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beam through 1st SCDTL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of the PPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beam through the first CCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nozzle ready for installation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beam capable to treat superficial tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testing and assembly - Building ready to receive components</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harley Street ready to receive components</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LINAC components installation and testing at 230 Mev</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfer components in HS / Install and commission BTL in HS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulatory &amp; clinical commissioning test / Customer acceptance test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Patient treatment start</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Company data
Cancer Epidemiology

Cancer is a major public health issue. In 2012 more than 14.1m cases of cancer were recorded and WHO expects this number to reach 23.6m cases by 2030. The growing global socio-economic burden of cancer is expected to balloon in coming decades. Worldwide, almost 32.5m people diagnosed with cancer within the previous five years were alive at the end of 2012 and an estimated 169.3m years of healthy life were lost globally because of cancer in 2008.

Approximately 44% of cancer cases and 53% of cancer deaths occur in countries with a low or medium level of the Human Development Index ("HDI"). As low HDI countries become more developed through rapid social and economic changes, they are likely to become "westernised".

If recent epidemiological trends seen in major cancers continue into the future, the burden of cancer will increase to 23.6m new cases each year by 2030. This represents an increase of 68% compared with 2012.
Cancer Treatment Modalities

The preferred treatment modality for any given type of cancer largely depends on the type, size and location of the tumour. Other factors include patients’ age, presence of comorbid conditions and debilitation due to cancer.

In practice, modalities are often combined to create a treatment program that is appropriate for each patient and is based on tumour characteristics as well as patient preference. CHART 10 outlines the most common types of cancer treatment currently used.

Cancer treatments - a cost comparison

The cost of cancer drugs has been a sensitive debate since innovative drug companies have launched their first “modern” drugs targeting checkpoints of molecular pathways like the first receptor tyrosine kinases such as Avastin and others. In some cases, annual drug expenditure has exceeded $250,000 per patient per year with those types of treatment. Another example of high drug cost is Optivo, the new melanoma treatment from Bristol-Myers Squibb (NC), which will cost $141,000 for the first 12 weeks of treatment and $256,000 for a full year of treatment.
Each year, cancer costs the world more money than any other disease, totalling c.$900bn annually according to the American Institute of Cancer Research (“AICR”). Cardiovascular diseases amount to c.$750bn followed by Diabetes with $200bn. According to the AICR, the price for one year of life increased to $139,100 in 2005 and $207,000 in 2013.

A study by the Lancet from 2014 calculated that cancer cost the EU €126bn in 2009, with direct health care spend accounting for €51.0bn (40%). Across the EU, the health-care costs of cancer were equivalent to €102 per citizen, but varied substantially across Europe, from €16 per capita (Bulgaria) to €184 per capita (Luxembourg). Productivity losses because of early death cost €42.6bn and lost working days €9.43bn. Informal care cost €23.2bn.

The breakdown of spend on cancer in the US (c.$125bn) according to the Agency for Healthcare Research and Quality (“AHRQ”) was 50% from hospital outpatient or doctor office visits, 35% from inpatient hospital stays and 11% from prescription drugs. The National Bureau of Economic Research stated that launch prices for cancer drugs increased by 10% ever year between 1995 and 2013, equating to a c.$8,500 annual increase after adjusting for inflation and survival benefits.

CHART 11 and CHART 12 below show the progression of monthly treatment costs of cancer drugs at the time of FDA approval. Annualised average treatment costs are already at $120,000. While the approved cancer drugs have shown good results in overall survival benefits, most of them have heavy systemic toxicity causing serious quality of life issues.
The chart below shows a plot of drug price over life years gained. There is a 95% confidence interval for each additional life year. In financial terms, the effect is $75,000 per year gained. The additional component is "the willingness-to-pay-for a quality-adjusted life-year" which is often difficult to satisfy given low life expectancy and harsh side effects.

Drug therapy costs are exceeding PT costs by far (up to 5.0x on a 3-year investment horizon)

The above-illustrated overview of price trends relativises the price discussion on PT technology, in our view. Investors focus on expected price decreases for proton machines, but we feel that clinical evidence and a constant improving beam delivery could render the cost debate obsolete. As a result, a capitated PT treatment could approximate cost of drug treatment.

Price trends of drugs are putting PT costs in perspective

The steady introduction of expensive cancer treatments has prompted policy makers to explore alternative payment approaches that might rein in costs. We believe there will be more frameworks for "episode-based" payments during cancer treatment, which would cover the costs of drugs, radiotherapy in whatever form, and the administration for a predefined period of treatment. This approach would have the potential to reduce costs and improve patient outcomes. If bundling or episode-based treatment is successful, the concept could be expanded to encompass longer periods in most cancer diagnoses for all oncology care components.

Episode-based models or capitation models could trigger a higher adoption rate of PT in a more holistic approach to treat cancer

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Radiotherapy treatment – reimbursement trends

The incentives for bundled payment metrics to encourage cost reduction may be too large. The differences between potential payment levels and care costs are so great in some cases that they may encourage physicians to make decisions overly influenced by financial considerations and inadequately informed by individual patients’ needs. Capitation models could encourage a higher adoption of proton therapy, which would make financial sense by lowering overall costs to treat cancer patients. We saw similar effects in drug use rationalisation for dialysis in the US, when the government bundled drugs in treatment costs into overall treatment reimbursement and epo was reduced by 30% - 40%.

We looked up prostate cancer treatment procedures and their costs in the US as an example to put PT costs in context. The table below gives an overview of the costs for the clinical treatment course.

CHART 14: Medicare reimbursement Rate Evolution (dollars per fraction)

Source: goetzpartners Research.

Drug industry loses lobbying power after capitation models and bundling

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The average annualised drug cost of $120,000 equates to $30m for 250 patients per year. At present, a proton room costs between $18m and $30m (declining) and can treat about 250 patients/year (6,250 radiations / a equals 25 fractions per patient). If we assume an investment horizon of 10 years (depreciation period), the average economical cost per year is $8,000/patient per year based on a PT room that cost $20m. This would be comparable to current US reimbursement rate of $1,200 per fraction with 25 fractions per patient, which results in $30,000/patient/year. 6,250 fractions/machine per year would equal the annual reimbursement income of $7.5m per year.

Including the service charges of 7% of $20m ($4.2m in three years), the purchase of a PT would almost break even after year three. Below we have illustrated a comparison of cancer treatment costs.

---

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>Mean Cost estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete removal of the prostate gland is performed with the use of one of three surgical approaches: radical retropubic prostatectomy, laparoscopic radical prostatectomy, or robot-assisted prostatectomy; the latter two are less invasive</td>
<td>16,762</td>
</tr>
<tr>
<td>Brachytherapy with the use of low-dose-rate isotopes involves permanent implantation of seeds that emit a low dose of radiation over a period of several months. Some patients also receive a boost of external-beam radiation therapy or androgen-deprivation therapy.</td>
<td>17,076</td>
</tr>
<tr>
<td>This advanced form of three-dimensional radiation therapy involves the use of a computer-driven machine that revolves around the patient as it delivers radiation. Radiation beams are aimed at the prostate from multiple angles. Intensity can be adjusted to maximize the dose targeted at the cancerous tissue and minimize the dose to surrounding healthy tissue</td>
<td>31,574</td>
</tr>
<tr>
<td>This hormone treatment reduces the effects of testosterone, thereby slowing the growth of prostate cancer. Medications are administered orally or injected to reduce or block circulating androgens</td>
<td>2,112</td>
</tr>
<tr>
<td>This active plan to postpone intervention typically involves monitoring with office visits every 6 months, prostate-specific antigen testing, digital rectal examination, and prostate biopsy</td>
<td>4,228</td>
</tr>
<tr>
<td>Liquid nitrogen or liquid carbon dioxide is used to freeze tissue in order to destroy abnormal cells.</td>
<td></td>
</tr>
<tr>
<td>This type of external-beam radiation therapy involves the use of special equipment to position a patient and precisely deliver radiation to tumors in the body (except the brain). The total dose of radiation is divided into smaller doses given over a period of several days. This type of radiation therapy helps spare normal tissue.</td>
<td></td>
</tr>
<tr>
<td>Also called three-dimensional radiation therapy and three-dimensional conformal radiation therapy, this procedure uses a computer to create a three-dimensional picture of the tumor, allowing doctors to give the highest possible dose of radiation to the tumor, while sparing as much of the normal tissue as possible.</td>
<td>20,588</td>
</tr>
</tbody>
</table>

Source: NEJM, 2015 Note: The mean cost for each treatment is provided in 2005 dollars. Reliable cost-estimate data are not available for cryosurgery and stereotactic body radiation therapy because these procedures are much less common than the other procedures listed.
Chemotherapy has, for example, fosfomycin, as well as technological improvements in cancer diagnosis.

Modern therapy

<table>
<thead>
<tr>
<th>Cost</th>
<th>Modern therapy</th>
<th>Standard therapy</th>
<th>Modern therapy</th>
<th>Standard therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material cost</td>
<td>90,000</td>
<td>1,200</td>
<td>8,000</td>
<td>2,800</td>
</tr>
<tr>
<td>Service Cost</td>
<td>2,800</td>
<td>-</td>
<td>5,600</td>
<td>980</td>
</tr>
<tr>
<td>Treatment</td>
<td>2,800</td>
<td>-</td>
<td>2,800</td>
<td>2,800</td>
</tr>
<tr>
<td>Hospital stay/lodging</td>
<td>10,000</td>
<td>10,000</td>
<td>7,500</td>
<td>7,500</td>
</tr>
</tbody>
</table>

Total Cost | 102,800 | 14,000 | 23,900 | 14,080 |

Reimbursement | 113,080 | 15,400 | 40,000 | 35,761 |

The average costs of cancer surgery in the US ranges from $14,161 for a prostatectomy to $56,587 for a pancreatocutaneous. The average costs of a chemotherapy (includes both modern combined with standard chemo in most cases) is c.$102,395/year.

Following on from the table above, the more important and crucial question is how much particle therapy (proton, carbon, helium etc.) can penetrate the radiotherapy market and how its need and potential market can be determined.

Biggest efficiency gaps in treating cancer today

As continuous technological improvements in cancer diagnosis increase precision and reliability, the point of diagnosis progressively shifts to an earlier stage through successful identification of smaller tumours. While current treatments are relatively effective in reducing or eliminating the spread of cancerous tissue, their side effect profiles leave substantial room for improvement. Together, this increases pressure on the development of new treatment options that effectively target the tumour site, while presenting minimal adverse effects on a systemic level.

Surgery

Although conventional open surgery remains dominant in the treatment of most cancers, increasing early diagnosis of smaller non-metastatic cancer combined with greater choice and availability of robotic systems should see a steady increase in the use of minimally invasive surgery. However, the technical skill required for laparoscopy, for example, is very high. While this hurdle can be overcome using robot-assisted surgery, the cost of available systems and their running expenses has restricted adoption in more economically constrained health systems outside the US.

Radiotherapy

Radiotherapy has undergone a dramatic change from palliative care to curative care. The industry has been transformed with the introduction of volumetric modulated arc therapy (“VMAT”) and intensity-modulated radiotherapy (“IMRT”) and software innovation has further contributed to the adoption of radiotherapy. In the US, more than 63% of all diagnosed cancer cases include some form of radiotherapy in standard treatment plans. In contrast, Europe only involves some 35% radiotherapy for cancer treatments and other continents a lot less than that. Despite established clinical efficacy, high installation costs have slowed down adoption.

Late Stage Therapy

Current treatment of late stage cancer is still largely dominated by chemotherapy and radiotherapy. Although there has been a proliferation of potent targeted therapies that specifically target cancer cells in individual patients, these are frequently restricted to relatively small patient subpopulations and can be prone to the development of resistance. Recent progress with immune checkpoint inhibitors (“ICIs”) in a variety of solid cancers and dramatic effects of CAR-T cell therapies in some blood cancers have demonstrated the significant potential of harnessing the patient’s own immune system to successfully

Rapid innovation in particle therapy providing cost-effective curative care
treat cancer. At present, these approaches are limited to small subpopulations, require extensive treatment and come with a range of potential adverse effects.

**Future of Cancer treatment**

The last decade has brought a number of new technologies into clinical practice, which target the tumours more precisely. This is referred to as precision medicine. There is also a rapid uptake for targeted immunotherapies for cancer. We elaborate on the technology progress in cancer treatment and which role proton therapy is likely to play in the future of precision medicine. Rather than making one of the main approaches obsolete, they will play together in a much more efficient way in the future.

Some aggressive drug approaches with systemic cytostatics might be replaced some day with a sophisticated regime of immunotherapy, precision surgery and precise tumour irradiation. Immune therapies include antibodies against tumour pathways (e.g., trastuzumab against the tyrosine kinase ERBB2 [HER2]) or immune checkpoint pathways (e.g., nivolumab against PD-1) and the use of autologous T cells engineered to target specific antigens (e.g., CD19 on B-cell cancers). These immunotherapy approaches require matching known antigens or pathways with the antibodies or the engineered T cells. Hence, the principle of coupling diagnostics and therapeutics will be a major feature of immunotherapy.

However, beyond drug therapies and companion diagnostic tests, a more precise surgery and radiotherapy will also have their place in precision medicine. We feel that tumour irradiation as a segment is here to stay, but will follow a similar path like drug therapy. Conventional radiation might be largely replaced by particle therapy. Precision medicine can be split in four particular components:

- **Drug Development** – Immune Oncology: Drugs are directed to the cancer cells by employing immunological mechanisms to target solely tumour cells rather than the toxic systemic approach from alkylating agents and other agents, which cause a radical mitotic arrest.

- **Diagnostic Testing** – Blood biopsies based on free plasma DNA: Some specific drugs do not work for everybody at all stages of tumour development, but a precise genetic profiling with modern diagnostic techniques have enabled oncologists to apply drugs more effectively and economically.

- **Surgery** – Surgical robots and endoscopic devices have increased clinical precision: The launch of new instruments in surgical robotics and the fast progress in this technique has improved modern surgery and will bring many more advantages in the near term.

- **Radiotherapy** – Radiotherapy has undergone a dramatic change in past decades, from when it was only employed for palliative care to achieve curative outcomes. Particle therapy is becoming widely accepted and we assume that 15% of radiation fractions will come from proton by 2025 (<1% today).

**The Role of Radiotherapy in future cancer treatment**

The debate on cancer economics has largely focused on expensive cancer drugs. However, a less mature debate amongst EU-28 countries and the US concerns the evaluation of radiation technologies, an area that has undergone significant development over the last 5-10 years. Considering all costs across the life cycle of the resource, it is, broadly speaking, more cost effective than surgery and chemotherapy. In addition, research efforts have grown exponentially with respect to particle therapy and some recent findings open new frontiers and arguments for particle therapy.

**Bridging the gap between technological advance and clinical application**

While the technology has been around since the early 1900s, limitations in supporting technology meant a lack of clinical application until recently. Advances in medical technology such as linear accelerators, imaging technologies, diagnostic devices and sophisticated hard- and software have made radiotherapy very targeted and effective. Today, beams can be delivered with sub-millimetre precision to target tumours while altering direction, shape, size and strength of the treatment beam on a case-by-case basis.

**Better insight with new imaging techniques**

As the precision at which radiation is delivered to the tumour increases, the exposure of healthy tissue can be further minimised, thereby providing a safer and more cost-effective alternative to other
approaches including chemotherapy and surgery. In our view, improvements in imaging technology will represent some of the most exciting developments in radiotherapy technology in the coming years, allowing radiographers to identify structures they are treating in real time, thereby enabling them to target difficult tumours more accurately, e.g. a lung cancer tumour that moves as the patient breathes. In collaboration with PRaVDA, AVO is working on proton tomography, a novel method for live imaging during irradiation.

**Bright future ahead**

We estimate that better collaboration between centres, along with an increasing body of evidence for the clinical efficacy, will generate substantial momentum for the field of radiotherapy in years to come. Furthermore, technological advances will increase accuracy, thus reducing the required dose, the number and/or the duration of consecutive fractions required to achieve a successful treatment outcome.

**CHART 17: Radiotherapy growth drivers**

Taken together, recent as well as future technological advances represent strong arguments for the use of radiotherapy in terms of cost-efficiency and clinical efficacy, paving the way for accelerated adoption rates in the future. Furthermore, radiation therapy is well suited to complement other treatments and can, for example, be used pre-surgical, to shrink a tumour and to facilitate removal, or post-surgical, to treat the site for remaining cancer cells. In our view, radiotherapy will soon play a central role in the shifting treatment paradigm for cancer, especially considering increasing clinical evidence that offsets high installation costs.

**CHART 18: Progressive integration of radiation therapy into interventional oncology**
Radiotherapy – the technology in a nutshell

Radiation therapy uses high-energy particles to destroy or damage cells by destabilising DNA. As cells are exposed to radiation, some atoms become ionised, causing small breaks in the DNA. Ionisation of atoms within living cells can cause one of three events: (1) the cell dies, (2) the cell repairs itself, or (3) the cell mutates and may become cancerous. One of the main risks associated with radiotherapy is that healthy tissue surrounding the tumour becomes cancerous as a result of exposure to radiation, leading to the formation of secondary tumours.

RBE – Relative biological effectiveness

Ionising radiation whether photons, neutrons, protons or heavy particles have a relative biological effectiveness (“RBE”) when colliding with organic tissue. Strictly speaking, RBE is the ratio of biological effectiveness of one type of ionising radiation relative to another, given the same amount of absorbed energy. The heavier the particles the higher the RBE and the higher the likelihood that enough DNA breaks, resulting in damage beyond repair. The RBE also depends on depth, ion charge and energy, dose level, and intrinsic tissue radio-sensitivity. Systematic experimental investigation of these dependencies is of fundamental importance to further the clinical application of ion beams.

Some cells more susceptible than others

Due to their high proliferative rates and limited capacity to repair themselves, tumour cells are more susceptible to radiation exposure than healthy cells, highlighting that risk of secondary tumours can be minimised by using systems with high spatial accuracy. There are a number of radio-resistant tumour types, meaning that cells can survive despite radiation due to efficient DNA repair mechanisms. Furthermore, cells with a low oxygen content (hypoxic), as is often the case with tumours as they outpace blood supply, may be more radio-resistant, indicating that some tumours are more suitable for radiotherapy treatment than others.
Photon – Proton – Carbon – what’s best?

We review radiotherapy and its future potential for all currently available modalities (photons, protons and heavy ions like carbon). We understand that this topic assumes some imagination for various investment cases and highlight that research efforts have exponentially grown with respect to particle therapy, opening new frontiers and arguments in terms of therapeutic applications.

New arguments for particle use are emerging in the scientific community

Radiotherapy – limitations and risks in clinical practice

The goal in radiotherapy of localised cancer is a lethal dose of radiation to tumour cells, while ensuring that the smallest possible dose is applied to surrounding tissues, such as rectum and bladder in the case of prostate cancer, and thereby avoiding side effects and toxicities for patients. Striking the balance of delivering the most effective radiation dose (measured in Gy) and minimising the side effects from radiating the surrounding healthy tissue is still the major challenge of today's clinical practice. Distributing the right dose of radiation to the targeted tissue remains the most significant clinical challenge. There are some areas and components for future development to optimise this balance.

- **Particle therapy over photon based radiotherapy** – Particle therapy has enabled a more precise radiation based on the physical properties of particles. Positively charged particles can be stopped to release energy at a depth most relevant to the tumour, without exposing tissue beneath the tumour to unnecessary irradiation. Another advantage stems from their charge, meaning they can be guided and focused magnetically.
- **Improvement of radiotherapy techniques such as ART** – New techniques to customise treatment plans based on anatomical variations and tumour progress (growth/shrinking) will make treatment with both photons and particles more efficient and precise.
- **Software improvement of modern treatment planning systems (“TPS”)** – Better software improves the planning and delivery of the beam during the course of the treatment regimen.
- **Imaging techniques** – Imaging before and especially during treatment still has significant development potential. The integration of imaging techniques with better resolution of soft tissue could help to improve the dose delivery.

The evolution of radiotherapy techniques since 1990 has changed the way radiotherapy is used for cancer patients. The latest innovation was VMAT an advanced form of IMRT that delivers a precisely sculpted 3D dose distribution with a 360-degree rotation of the gantry in a single or multi-arc treatment at much shorter time from 8-10min to less than 2min treatment time. The multi-leaf collimator (“MLC”) allows to rapidly shape the beam in a more optimised way in order to spare healthy tissue as much as possible with a photon based technique, albeit with still significant toxicity for the cancer patient.
Photons technology and its limitations

Nowadays photons are the most commonly used treatment in RT for prostate, lung and breast cancer. Photons have no mass and no charge and, therefore, travel easily through target materials. There is an initial increase of energy as they interact with the target material electrons, which enhances the radiation effect. As a result of this, their peak dose is reached within a few centimetres from the entrance surface – the so-called “dose accumulation effect.” In the deeper trajectory through the body subsequently, the radiation dose decreases until it exits the body.

3D plans initially had a significant dose deposition in the entry and exit fields. With multiple field plans, rapid arc or helical techniques, these doses tend to be significantly smaller, but often a dose bath with low-to-moderate doses over surrounding organs cannot be avoided in order to deliver a deadly dose to cancer cells. The possible side effects include gastrointestinal ("GI") and genitourinary ("GU") problems and a potentially slightly higher risk for secondary malignancies. Therefore, photon radiation therapy does not seem appropriate in terms of its physical characteristics to treat those organs located at a great depth within the body. Despite modern improvements in technologies, such as MLC (described above), IMRT, or image-guided radiotherapy ("IGRT"), photon-beam therapy will always include a certain level of entrance and exit doses, resulting in healthy tissue receiving low-to-moderate radiation doses. While these doses are most likely not associated with a prominent side effect risk, such issues necessitate a serious consideration of alternative treatment options, including particle therapy.

Particle therapy – protons and heavy ions

More than 140,000 patients worldwide have received therapy with heavy particles, with PT accounting for the majority of this (over 125,000 patients). While protons can be termed particles, they are not considered “heavy,” and from their effect they can be categorised as low-linear energy transfer ("LET") radiation – comparable to photons. Heavy particles include carbon ions, helium, oxygen as well as neutrons. Particles may be charged (protons, carbon ions) or neutral (neutrons). The term “heavy particle therapy” is generally used to distinguish it from conventional X-Ray RT, which uses massless photons. Experience with heavy carbon ions is limited to only ten operating facilities worldwide. Treatment with carbon ions can therefore be considered experimental and reliable evidence regarding efficacy and toxicity is only just beginning to emerge.
The charts above show the steep adoption of particle therapy. The underlying reason behind the strong adoption increase was the addition of better imaging and software products alongside particle therapy, allowing for improvements in beam precision, thus reducing toxicity to surrounding healthy tissues.

Implementation of PT is currently hindered by the cost and installation hurdles

More focused beam with less damage of healthy tissue

Some organs are highly sensitive to radiation

PT can lower the risk of treatment side effects and provide a valuable tool for dose escalation or re-irradiation. Implementation of PT is currently hindered by the cost of the technology and limited approval from healthcare payers. Per treatment, PT is more expensive than standard photon therapy. However, if one factors in the cost of treating side effects and sequential mortality, PT turns out more cost-effective for management of certain tumour types. The current cost argumentation tends to overlook the existing evidence on clinical- and cost-effectiveness data.

The main reason to employ this currently expensive technology is primarily based on the advantageous physical properties of the particle beam, which can be focused more accurately than photons, thus sparing out healthy tissue (CHART 29).

For each tumour type and location, establishing an exact dose distribution is essential. Breast tumour radiation, for example, has to consider critical heart structures. Radiating prostate cancer, on the other hand, can cause incontinence and infertility if not carefully carried out. As mentioned previously, paediatric tissue as well as brain tissues in both children and adults, is very sensitive to radiation, requiring extra care.

The reason underlying PT’s superiority is the way in which the dose is distributed in the tissue. Bragg has described the physical properties of particles and photons and illustrated his findings in the Bragg peak, which shows that there is a very small entry dose for protons, a high-energy disposal at the target and no exit beam (red). Photons, however, have both entry and exit beams and lose energy as soon as they enter the tissue, which means that tissue located before the tumour tissue is exposed to high doses (CHART 30).
Despite the high costs of proton treatment, paediatric use has always been widely accepted for the aforementioned reasons. Historically, conventional photon therapy (x-ray based) was only used for palliative care (pain relief). This has changed with the introduction of IMRT, VMAT and sophisticated TPS.

There is a wide spread discussion regarding lack of evidence for proton treatment for a wide range of potential indications. Even for the most widely accepted conditions, paediatric tumours, issues remain as to whether superiority of protons over photons has been sufficiently shown. Dutch scientific and health care governance bodies have recently issued landmark reports regarding generation of relevant evidence for new technologies in health care including proton therapy. An approach based on normal tissue complication probability ("NTCP") models has been adopted to select patients who are most likely to experience fewer (serious) adverse events achievable by state-of-the-art proton treatment.

Secondary cancer is one of the main argument to increase the use of proton technology

New approach in Holland, which is based on normal tissue complication probability models has been adopted to select patients for PT vs. RT

Despite the high costs of proton treatment, paediatric use has always been widely accepted for the aforementioned reasons. Historically, conventional photon therapy (x-ray based) was only used for palliative care (pain relief). This has changed with the introduction of IMRT, VMAT and sophisticated TPS.

There is a wide spread discussion regarding lack of evidence for proton treatment for a wide range of potential indications. Even for the most widely accepted conditions, paediatric tumours, issues remain as to whether superiority of protons over photons has been sufficiently shown. Dutch scientific and health care governance bodies have recently issued landmark reports regarding generation of relevant evidence for new technologies in health care including proton therapy. An approach based on normal tissue complication probability ("NTCP") models has been adopted to select patients who are most likely to experience fewer (serious) adverse events achievable by state-of-the-art proton treatment.

---

**CHART 29: Comparative dosimetry for proton (left) versus photon (right)**

**CHART 30: Dose distribution (photon/proton) – Bragg peak**

**CHART 31: Waterfall plot of ΔNTCP (protons minus photons) – eligibility plot for appropriate RT technologies per tissue**

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**Source:** provisionproton.com, goetzpartners Research

**Source:** PubMed, goetzpartners Research

**Source:** Joachim Widder et al. International Journal of Radiation Oncology*Biology*Physics; Volume 95, Issue 1, 1 May 2016, Pgs. 30–36; (note) RCT means radio-chemotherapy
Clinical rational when to use proton

There are a number of reviews published comparing IMRT with particle therapy. While there is still not much evidence from direct head-to-head trials, there is a number of Meta analyses published showing superiority of particle therapy.

In dosimetric studies of a small patient group Vargas et al. were able to show a reduced mean rectal (59%) and bladder (35%) dose for PT compared to IMRT. Early outcomes from single arm, prospective trials confirmed these assumptions. Nihei et al. described the incidence of late grade 2 rectal and bladder toxicity at 2 years to be 2.0% and 4.1%, respectively.

Similarly, another study found good early outcomes with image-guided proton therapy, suggesting high efficacy and minimal toxicity with 1.9% grade 3 GU symptoms and <0.5% grade 3 GI toxicities. Generally, the dose to healthy tissues in the range <50% of the target prescription was substantially lower with proton therapy.

A retrospective analysis of the Medicare database compared early toxicity in 421 men using PT with 842 matched controls treated with IMRT. A statistically significant decrease in GU toxicity at 6 months for PT was seen. Other studies have also found IMRT to be favourable over PT with regard to toxicity. An analysis from the Medicare Surveillance, Epidemiology, and End Results ("SEER") database in the USA identified 684 men treated with PT between 2002 and 2007 and compared these with a cohort treated with IMRT.

With regard to the OS (overall survival) data, a few major studies have been conducted. One of the major dose-escalation studies was carried out at The Proton Center in Boston. Zietman et al. randomised 393 patients with a PSA <5 ng/ml to a low-dose arm (50.4 Gy photon therapy + 19.8 GyE proton boost) and a high-dose arm (50.4 Gy photon + 28.8 GyE proton boost). The analysis revealed a significant difference in biochemical recurrence-free survival in favour of the high-dose arm. Subgroup analysis of low and high-risk patients (depending on the Gleason score) showed a significant advantage for the high-dose group in both cases. An impact on the OS rate was not observed. Both acute and late toxicities were not increased in either arm compared to the incidence of comparable photon studies. However, modern photon treatments allow comparable high-dose application with utmost precision and safety; thus, the latter trial might be termed mainly not as a trial comparing photons and protons, but high-dose to low-dose treatments.

Finally, the American Society for Radiation Oncology ("ASTRO") released a list recommending the use of PT after an evidence-based review for certain tumours, including central nervous system and paediatric malignancies. For others, among them prostate cancer, it recommends treatment only within the setting of clinical trials, as there was evidence for the efficacy of PT, but no suggestion that it is superior to photon-based approaches.

A high publication rate confirms continued high interest in PT and its characteristics. Reading such publications, one gets the impression that the authors often take a similar stance to ASTRO, who finished the abstract of their evidence-based review with the words: “More robust prospective clinical trials are needed to determine the appropriate clinical setting for PT”. There is much discussion and disagreement concerning toxicities, cost–effectiveness, and the potential for better outcomes. However, PT is certainly cost-intensive and yet has great potential with regard to basic physics and biological principles. Nevertheless, the advantages so far seem to remain theoretical and are brought about by a better dose distribution. Several trials are underway, among them a multi-institutional randomised phase III National Cancer Institute study (A Phase III Randomised Clinical Trial of Proton Therapy Versus IMRT for low or intermediate risk PC; clinicaltrials.gov ID NCT01617161) comparing PT to IMRT. It is now in its third year and, together with others, will hopefully shed some more light onto the discussion of PT and RT with photons and particles, which in the end will lead to individualised radiotherapy ("iRT") concepts.
Particle technologies – costing and technology comparison

The clinical benefits of IMPT vs. IMRT are obvious in principle as explained in the previous chapter. However, there is still limited clinical evidence for the prevention of secondary tumours due to the lack of long term head to head studies. There is some evidence from retrospective, observational studies, and some meta analyses. However, history bias and selection bias are strong in these studies, which makes it difficult to draw strong conclusion from those results. However, short-term benefits by avoiding adverse events provide much more robust arguments. We have looked into recent publications, which compare adverse events in head and neck cancer ("HNC") and health / economic benefits as a result when comparing IMRT with IMPT treatment.

The sparing of surrounding tissue and decreasing toxicity has been quantified by some studies, which served as data sources for our economic model. There was non-comparative study characterising and quantifying grading and occurrence with IMRT alone. M Bansal et al. published a detailed analysis on occurring toxicities in IMRT based irradiation treatment. We have grouped patients three groups i) no toxicity, ii) grade II toxicity, iii) grade III toxicity. Grade IV toxicity did not occur in this study, which was consistent with other studies in the literature.

<table>
<thead>
<tr>
<th>Site</th>
<th>Toxicity levels</th>
<th>Acute Morbidities</th>
<th>Late Morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre RT N = 45</td>
<td>During RT N = 45</td>
</tr>
<tr>
<td>Skin</td>
<td>Grade 0</td>
<td>45 (100)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>–</td>
<td>37 (82)</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>–</td>
<td>7 (15.5)</td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>–</td>
<td>7 (15.5)</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>Grade 0</td>
<td>45 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>–</td>
<td>6 (13)</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>–</td>
<td>29 (64.4)</td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>–</td>
<td>30 (66.6)</td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>Grade 0</td>
<td>45 (100)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>–</td>
<td>7 (15.5)</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>–</td>
<td>38 (84)</td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Larynx</td>
<td>Grade 0</td>
<td>45 (100)</td>
<td>18 (40)</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>–</td>
<td>22 (48.8)</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>–</td>
<td>4 (8.8)</td>
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<td></td>
<td>Grade III</td>
<td>–</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Grade 0</td>
<td>45 (100)</td>
<td>9 (20)</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>–</td>
<td>11 (24)</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>–</td>
<td>24 (53)</td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>–</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Source: M. Bansal.

Romesser has shown detailed result on toxicity occurrence in a comparative study investigating IMRT vs. IMPT. The table below, which shows consistent data for IMRT to Bansal’s study.

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In the table below, we have applied the clinical data from the findings of P. Romesser, et al. to illustrate the cost associated with the various grades of adverse events associated with IMRT in comparison with IMPT. The costs to treat the adverse events, its respective severity grade and duration, we have found from the literature.

<table>
<thead>
<tr>
<th>Site</th>
<th>Toxicity</th>
<th>IMRT N = 23</th>
<th>PBRT N = 18</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis</td>
<td>Grade 0</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>6 (26.1%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>9 (39.1%)</td>
<td>13 (72.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>8 (34.8%)</td>
<td>5 (27.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>Grade 0</td>
<td>3 (13.0%)</td>
<td>12 (66.7%)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>8 (34.8%)</td>
<td>3 (16.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>10 (43.5%)</td>
<td>3 (16.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>2 (8.7%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Grade 0</td>
<td>7 (30.4%)</td>
<td>15 (83.3%)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>3 (13.0%)</td>
<td>1 (5.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>13 (56.5%)</td>
<td>2 (11.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>Grade 0</td>
<td>4 (17.4%)</td>
<td>14 (77.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>4 (17.4%)</td>
<td>3 (16.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>15 (65.2%)</td>
<td>1 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Grade 0</td>
<td>12 (52.2%)</td>
<td>15 (83.3%)</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>5 (20.1%)</td>
<td>2 (11.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>2 (8.7%)</td>
<td>1 (5.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 0</td>
<td>2 (8.7%)</td>
<td>11 (61.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>19 (82.6%)</td>
<td>6 (33.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>2 (8.7%)</td>
<td>1 (5.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade III</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Romesser et al., 2016
Economic Evidence of IMPT vs IMRT

Recent publications of systematic reviews regarding cost effectiveness of IMPT and IMRT revealed that solid data remain very scarce. Only five studies were found to indicate some form of cost effectiveness analysis comparing IMRT with IMPT. However, these studies are poorly done and could be described as simple costing studies rather than economic analyses. Other publications are mentioning economic terminology without applying an economic framework in a thorough attempt for an economic assessment. With the absence of long term RCTs, it is perhaps less surprising that there are only few economic effectiveness studies on IMPT assessing its benefits for long-term outcome i.e. secondary cancer following radiation therapy. However, it is surprising that few or no economic models are built to assess short-term benefits assessing adverse events during or shortly after radiation.

Mounting evidence for short-term benefits of particle therapy for the treatment of head and neck cancer warrants a thorough economic analysis in order to identify whether a higher reimbursement price can be justified by health-economic models.

Up to 2016, there was no systematic review of cost effectiveness of IMPT available. Vivek Verma and colleagues published the first systematic review of eighteen original investigators across five cancer types. They found convincing evidence for paediatric brain cancer, loco regionally advanced tumours in non-small cell lung cancer. They also found favourable economic evidence in subgroups of breast cancer (left sided, to prevent cardio toxicity) and high-risk head and neck cancers. Prostate cancer treatment with IMPT was less convincing.

With respect to short term adverse events following radiation, the average morbidity for IMRT, according to the data described above were 71.8% for IMRT and 22.2% for IMPT. The average costs for grade I, grade II and grade III of all adverse events together, where $8,807, $13,134 and $14,965 respectively. While overall morbidity was significantly lower for IMPT, the grade distribution for adverse events for IMPT and IMRT respectively, Grade II 46% (IMRT) vs 50% (IMPT) and Grade III 22% (IMRT) vs 25% (IMPT). The average costs for grade I, grade II and grade III respectively were $1,762, $2,073 and $2,465.

The total average costs per patient across morbidity grades weighted by grading occurrence was $10,190 for IMRT and $4,869 for IMPT.
We found a number of studies, which illustrated useful costing analysis. However, none of these studies grouped costs according to morbidity grades according to mean occurrences from larger studies. The data of the above-mentioned costing analyses served as a basis for our economic model and adjustments for our assumptions on volume weighted morbidity grading.

The assessment of economic benefits over the short term is the main purpose of this analysis. We calculated the ICER based on the decision tree analysis illustrated below. Both trees were populated with costs and morbidity probabilities referenced above. The calculated costs were $74,624 and $50,950 for IMPT and IMRT respectively. The average utilities at baseline for patients in the IMPT arm and IMRT were 8.42 and 7.25 respectively over a 10-year period. However, adverse events from radiotherapy occurred either during irradiation or within one year since beginning of treatment.

We used morbidity costs from $14,965 to $8,807 as illustrated in the previous chapter and assumed that costs to be the same in both treatment arms with respect to comparable morbidity grading.

We used morbidity costs from $14,965 to $8,807 as illustrated in the previous chapter and assumed that costs to be the same in both treatment arms with respect to comparable morbidity grading.

CHART 35: Overall costs for the treatment of adverse events after irradiation of HNC

<table>
<thead>
<tr>
<th>Description</th>
<th>IMRT</th>
<th>IMPT</th>
<th>Costs/morbidity Grade/patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Morbidity Rates</td>
<td>71.8%</td>
<td>22.2%</td>
<td></td>
</tr>
<tr>
<td>Total Average Costs/patient across all morbidity grades</td>
<td>$10,190</td>
<td>$4,869</td>
<td>$8,807</td>
</tr>
<tr>
<td>Grade I - distribution and average costs</td>
<td>44%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Grade II - distribution and average costs</td>
<td>46%</td>
<td>50%</td>
<td>$13,134</td>
</tr>
<tr>
<td>Grade III - distribution and average costs</td>
<td>11%</td>
<td>14%</td>
<td>$14,965</td>
</tr>
</tbody>
</table>

Source: London School of Economics

CHART 36: IMPT decision tree – Short term benefit based on adverse events following irradiation

Expected costs and outcomes for IMPT treatment = Sum of the expected costs and outcomes of each branch

Expected QALY = 7.02 + 0.59 + 0.71 + 0.90 + 0.00 = 8.42
Expected costs = $38,991 + $11,701 + $12,453 + $11,479 + $0 = $74,624

Source: London School of Economics
**CHART 37: IMRT decision tree – Short term benefit based on adverse events following irradiation**

IMRT $17,500

### Expected costs and outcomes for IMRT treatment = Sum of the expected costs and outcomes of each branch

- **Grade 0**
  - Toxicity: 72%
  - Costs: EC $4,900 LE 10
  - Expected QALY: 2.52
- **Grade I**
  - Toxicity: 44%
  - Costs: EC $15,379 LE 10
  - Complicat: 44%
  - Costs: EC $8,807 LE 10
  - Expected QALY: 2.37
- **Grade II**
  - Toxicity: 46%
  - Costs: EC $16,914 LE 10
  - Complicat: 72%
  - Costs: EC $13,134 LE 10
  - Expected QALY: 2.13
- **Grade III**
  - Toxicity: 11%
  - Costs: EC £13,757 LE 10
  - Complicat: 11%
  - Costs: EC £14,965 LE 10
  - Expected QALY: 0.232

**Expected costs = $4,900 + $15,379 + $16,914 + $13,757 + $0 = $50,950**

**Expected QALY = 2.52 + 2.37 + 2.13 + 0.232 + 0.00 = 7.25**

**Expected costs and outcomes for IMRT treatment = $50,950**

Source: London School of Economics
The table below illustrates our ICER calculation for short-term economic costs. The ICER resulted in $20,362 for the use of IMPT in HNC. The morbidity ratio was 3.27 — i.e. IMRT showed 3.27 times higher morbidity treatment costs in the control arm compared with IMPT. While absolute costs may vary, the ratio and its effect on the ICER might be more resilient in relation to changes for morbidity treatments.

## CHART 38: Computation of and ICER on short term benefits of IMPT over IMRT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>Incremental cost</th>
<th>Effect</th>
<th>Incremental effect</th>
<th>C/E</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>$50,000</td>
<td></td>
<td>7.25</td>
<td>$7,024</td>
<td></td>
<td>$20,362</td>
</tr>
<tr>
<td>IMPT</td>
<td>$74,624</td>
<td>$23,673</td>
<td>8.42</td>
<td>$8,867</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: London School of Economics

The multi directional sensitivity analysis may prove useful for reimbursement bodies, when deciding on treatment recommendation and funding. The sensitivities capture morbidity rates, costs and irradiation costs of both IMPT and IMRT.

## CHART 39: Sensitivity analysis – IMPT treatment costs vs morbidity costs – vs. IMRT treatment costs

<table>
<thead>
<tr>
<th>Morbidity Cost</th>
<th>IMRT morbidity rate</th>
<th>IMRT</th>
<th>IMPT</th>
<th>IMRT morbidity cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>$9,000</td>
<td>10.0%</td>
<td>$30,000</td>
<td>$20,362</td>
<td>$40,000</td>
</tr>
<tr>
<td>$10,500</td>
<td>10.0%</td>
<td>$30,000</td>
<td>$20,362</td>
<td>$40,000</td>
</tr>
<tr>
<td>$12,000</td>
<td>10.0%</td>
<td>$30,000</td>
<td>$20,362</td>
<td>$40,000</td>
</tr>
<tr>
<td>$15,000</td>
<td>10.0%</td>
<td>$30,000</td>
<td>$20,362</td>
<td>$40,000</td>
</tr>
<tr>
<td>$18,000</td>
<td>10.0%</td>
<td>$30,000</td>
<td>$20,362</td>
<td>$40,000</td>
</tr>
</tbody>
</table>

Source: London School of Economics

The most sensitive parameter are the morbidity rates. If IMRT morbidity rates approximate IMPT rates, ICERs are at risk to become too high for cost acceptance under current thresholds. There is indeed a risk that improved software could lead to a better beam delivery for IMRT and morbidity rates could improve. In contrast, the IMPT reimbursement rates are likely to come down driven by lower technology costs over time.

## CHART 40: Sensitivity analysis – IMPT morbidity rate vs. IMRT morbidity rate vs morbidity costs

<table>
<thead>
<tr>
<th>IMRT morbidity rate</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>72%</th>
<th>80%</th>
<th>Morbidity Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0%</td>
<td>$35,598</td>
<td>$21,584</td>
<td>$13,282</td>
<td>$6,908</td>
<td>$3,889</td>
<td>$5,000</td>
</tr>
<tr>
<td>17.5%</td>
<td>$66,151</td>
<td>$38,517</td>
<td>$24,407</td>
<td>$14,520</td>
<td>$10,094</td>
<td>$10,000</td>
</tr>
<tr>
<td>22.0%</td>
<td>$99,560</td>
<td>$53,814</td>
<td>$33,517</td>
<td>$20,336</td>
<td>$14,690</td>
<td>$15,000</td>
</tr>
<tr>
<td>25.0%</td>
<td>$136,243</td>
<td>$67,699</td>
<td>$41,115</td>
<td>$24,925</td>
<td>$18,230</td>
<td>$20,000</td>
</tr>
<tr>
<td>30.0%</td>
<td>$271,588</td>
<td>$102,604</td>
<td>$57,849</td>
<td>$34,280</td>
<td>$25,225</td>
<td>$25,000</td>
</tr>
</tbody>
</table>

Source: London School of Economics

Our findings on the ICER for the adoption of IMPT for selected HNC patient populations are $20,362 for short term. Those numbers can never be accurate; hence we believe rather than a single number once should assess a corridor of ICERs depending on robust ranges of critical input parameters. In our case, it would be around morbidity rates, treatment costs for induced morbidities and percentage of secondary cancer induced by IMRT and IMPT. The ICER corridor is realistically between $10,000 and $30,000 for both ST and LT time horizons, which is well within the range of the NICE threshold of $50,000 per QALY.
Market for Radiotherapy

Ion beam radiotherapy is rapidly growing worldwide. There are 23 centres operative in Europe and 4 for carbon ions, while another 23 are under construction or in the planning stage (as of 31st March 2018). The main advantage of charged particles over photons is represented by significantly lower energy deposition in the patient like a similar clinical target coverage combined to reduced dose to the normal tissues. Cyclotrons and synchrotrons are used to accelerate ion beams, while pencil beam scanning modality is replacing passive scattering.

We argue there is a delta in terms of utilising one modality over another for some specific tumour types. While this is only an estimate based some literature and expert opinions, the delta for Carbon over protons could be in the range of 15%, hence determines a market for carbon accelerators.

Besides protons and carbon ions, there is interest for fast helium ions, expected as beneficial for paediatric patients due to lower fragmentation tail and RBE than carbon ions and less lateral scattering.
Varian and IBA are at the forefront of industrialising the particle accelerator technology and launched an off-the-shelf product in their efforts. Software is a driving force of innovation especially in the more conventional RT technology, where we noticed that older RT machines could achieve equal or better results with a good TPS product when compared with the results from a last generation hardware and second tier TPS software, when products are bundled together from the hardware manufacturer.

Radiation therapy model and status for RT machines

The expectations for commercial particle market growth vary significantly. Our own assumptions and views are based on two models. In general, the need for cancer therapy is driven by cancer prevalence, clinical ability (staff requirements), clinical evidence, applicability for more tumour types and affordability.

- Firstly, we have built a global cancer / radiotherapy model and have taken a view on how many machines are going to be needed based on that. We applied different inputs for various regions based on data and interviews. The two variables for the regions are:
  - Average number of fractions per machine per year per region
  - The utilisation rate of radiotherapy in the different cancer types in the respective regions

- Secondly, from this cancer model we have driven our particle therapy model and have taken a view on how many radiotherapy units (rooms) will be replaced / taken over by particle therapy

- Thirdly, we assumed that heavy ions will take market share from proton therapy and also expand the market by tapping into cancer types for which neither conventional RT nor proton would achieve great success rates.

We have modelled all regions by cancer types and likely adoption rates for radiotherapy. In order to get a better understanding of treatment modalities, we review the main cancer types, which can be treated with RT. The biggest volume comes from prostate, lung, breast and colon rectal cancers. However, in some of the university clinics with high quality academic staff and state of the art equipment (UCLH, London), we note that some less prominent cancer types are treated (brain, head and neck, sarcoma and paediatric cancers). We refer to those as “Other cancer types”. Below we have illustrated North America as a very mature market, where we keep the availability of particle therapy.

Our assumptions and model drivers are based on the conclusion from literature and interviews with several clinics and their commercial and clinical directors. The number of fractions are between 20 and 25 the number of fractions per treatment room per annum is around 5,500 on average. The utilisation of radiotherapy as a percentage of all diagnosed cancers is the highest in the US with around 62%. The number of linacs per million inhabitants is also highest in the United States. The main reason was a reimbursement incentive for free RT treatment demand in the rural areas in the United States. While the incentive was good, it gradually led to both an overflow of linacs and freestanding clinics, which trended rapidly towards a second tier TPS software, when products are bundled together from the hardware manufacturer.
hyper-fractionation mode compared to hospitals with more standardised and academic treatment protocols.

![CHART 46: Global linac distribution - # of linacs per region](image)

North America 4,085
Europe 3,111
Russia 194
Apac -rest 613
Japan 833
China 1,117
India 213
MENA 254
AFRICA 102
Latam 746
Total 11,268

Source: goetzpartners Research

The result of this incentive also led to a high penetration of radiotherapy as a percentage of all diagnosed cancer types in the US. Thus, the utilisation of RT in the US is twice as high as in Europe.

![CHART 47: Number of linacs and utilisation rates as % of diagnosed cancers](image)

Radiations per machine/a 2015 4,818 4,818 4,818 7,709 4,818 7,227
Radiations per machine/a 2025 5,500 5,500 5,500 7,333 5,500 6,875
Radiations per machine/a 2035 6,000 6,000 6,000 7,846 6,000 6,000

<table>
<thead>
<tr>
<th>treatments/region/a</th>
<th>United States</th>
<th>Japan</th>
<th>Europe</th>
<th>Russia</th>
<th>APAC-rest</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elekta’s rate (IR pres)</td>
<td>62.4%</td>
<td>26.8%</td>
<td>33.6%</td>
<td>17.2%</td>
<td>9.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>patients on linac per year (Elekta)</td>
<td>1,003,758</td>
<td>200,677</td>
<td>885,435</td>
<td>108,670</td>
<td>102,142</td>
<td>275,889</td>
</tr>
<tr>
<td>implied utilisation of machines / radiations /m/a (Elekta)</td>
<td>4,914</td>
<td>4,529</td>
<td>5,692</td>
<td>11,203</td>
<td>3,333</td>
<td>4,940</td>
</tr>
<tr>
<td>implied utilisation of machines / patients /m/a (Elekta)</td>
<td>246</td>
<td>226</td>
<td>285</td>
<td>560</td>
<td>167</td>
<td>247</td>
</tr>
<tr>
<td>Utilisation rate calculated</td>
<td>61.2%</td>
<td>28.5%</td>
<td>28.4%</td>
<td>11.8%</td>
<td>13.0%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Radiated - linac treatment</td>
<td>984,114</td>
<td>200,677</td>
<td>749,468</td>
<td>74,778</td>
<td>147,677</td>
<td>403,643</td>
</tr>
</tbody>
</table>

2025 - Gap

<table>
<thead>
<tr>
<th>Radiation needed by 2020</th>
<th>United States</th>
<th>Japan</th>
<th>Europe</th>
<th>Russia</th>
<th>APAC-rest</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,188</td>
<td>1,405</td>
<td>5,259</td>
<td>700</td>
<td>755</td>
<td>2,039</td>
<td></td>
</tr>
<tr>
<td>targeted utilisation rate for diagnosed cancers</td>
<td>65%</td>
<td>45%</td>
<td>45%</td>
<td>25%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Percentag proton</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
<td>2%</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>of which could be proton</td>
<td>389</td>
<td>105</td>
<td>394</td>
<td>15.76</td>
<td>17</td>
<td>229.39</td>
</tr>
<tr>
<td>Machine Gap - 2025</td>
<td>1,103</td>
<td>572</td>
<td>2,148</td>
<td>506</td>
<td>142</td>
<td>922</td>
</tr>
</tbody>
</table>

2035 - Gap

<table>
<thead>
<tr>
<th>Radiation needed by 2034</th>
<th>United States</th>
<th>Japan</th>
<th>Europe</th>
<th>Russia</th>
<th>APAC-rest</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,420</td>
<td>2,119</td>
<td>7,935</td>
<td>878</td>
<td>1,052</td>
<td>2,840</td>
<td></td>
</tr>
<tr>
<td>targeted utilisation rate for diagnosed cancers</td>
<td>65%</td>
<td>65%</td>
<td>65%</td>
<td>30%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Percentag proton</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>5%</td>
<td>5%</td>
<td>25%</td>
</tr>
<tr>
<td>of which could be proton</td>
<td>1,355</td>
<td>530</td>
<td>1,984</td>
<td>44</td>
<td>53</td>
<td>710</td>
</tr>
<tr>
<td>Machine Gap - 2035</td>
<td>1,335</td>
<td>1,286</td>
<td>4,824</td>
<td>684</td>
<td>439</td>
<td>1,723</td>
</tr>
</tbody>
</table>

Source: goetzpartners Research estimates, Elekta IR

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Please see analyst certifications, important disclosure information, and information regarding the status of analysts on pages 53 - 55 of this research report.
The Linac need and market model is the basis for radiotherapy potential

Proton players erode the conventional photon market with single room offerings for mid-sized hospitals

The chart above summarises our linac model, which is the basis of our PARTICLE THERAPY forecast assumptions. We have modelled cancer prevalence and used the DIRAC database, which gives us a good indication of all installed linacs per country. We have clustered the machines per region.

The market shares are a rough estimate based on our views from the present situation. Mevion, Proteon and Hitachi have accelerated their commercialisation efforts and Varian appears to push more for growth in PT technology. Currently, only IBA and Mevion have sold single room products. We believe that the trend is going to single room systems and trending from currently 2.4x (sites vs. rooms) globally towards 1.3x in 2050E in a linear manner.

We have modelled the projected need of particle therapy machines by company. IBA will likely remain the market leader closely followed by Varian in PT. While we expect proton machine instalment to grow significantly as illustrated, we could see a strong demand for Carbon centres and potentially a threat to proton only machines. However, we felt that the current model for proton machines could serve as proxy for carbon demand in the mid to long term.

The above chart, illustrates our view of the annual order intake of proton systems per year and the market share of the current commercial particle players.

We believe that PT will end up being an oligopoly of manufacturers. While we believe that there are more than two credible technologies out there, it is likely that Commercial particle players will consolidate like the linac players (Varian, Elekta, Accuray). The model above does not consider those. However, consolidated or not, the penetration of PT shown above is rather independent on M&A dynamics.

However, in the case of heavier particles, we believe that the hurdle for current commercial players is too high and they end up running into a similar problem as Siemens and Elekta. Both companies have a conflict of interest that could affect the objectivity of this research report. Investors should consider this research report as only a single factor in making their investment decision. goetzpartners Research has a client relationship with Advanced Oncotherapy Plc.

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## Chart 51: Europe – Cancer model and radiotherapy

### Table: Europe 2017e - 2035e

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Systems with 4 rooms</th>
<th>2017e</th>
<th>2019e</th>
<th>2021e</th>
<th>2023e</th>
<th>2025e</th>
<th>2027e</th>
<th>2029e</th>
<th>2031e</th>
<th>2033e</th>
<th>2035e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td>362,032</td>
<td>382,589</td>
<td>404,314</td>
<td>427,273</td>
<td>451,535</td>
<td>477,175</td>
<td>504,271</td>
<td>532,906</td>
<td>563,166</td>
<td>595,145</td>
</tr>
<tr>
<td>% of total</td>
<td></td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>381,526</td>
<td>403,190</td>
<td>426,085</td>
<td>450,280</td>
<td>475,849</td>
<td>502,869</td>
<td>531,424</td>
<td>561,601</td>
<td>593,491</td>
<td>627,191</td>
</tr>
<tr>
<td>% of total</td>
<td></td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>334,183</td>
<td>353,160</td>
<td>373,213</td>
<td>394,406</td>
<td>416,802</td>
<td>440,469</td>
<td>465,481</td>
<td>491,913</td>
<td>519,846</td>
<td>549,365</td>
</tr>
<tr>
<td>% of total</td>
<td></td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>12.0%</td>
</tr>
<tr>
<td>All PBL</td>
<td></td>
<td>1,077,741</td>
<td>1,138,939</td>
<td>1,203,613</td>
<td>1,271,959</td>
<td>1,344,186</td>
<td>1,420,514</td>
<td>1,501,177</td>
<td>1,586,419</td>
<td>1,676,503</td>
<td>1,771,701</td>
</tr>
<tr>
<td>Penetration/F/B/L</td>
<td></td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>38.7%</td>
</tr>
<tr>
<td>PBL - particle</td>
<td></td>
<td>15,783</td>
<td>29,392</td>
<td>46,143</td>
<td>66,440</td>
<td>90,733</td>
<td>103,771</td>
<td>131,503</td>
<td>156,223</td>
<td>184,248</td>
<td>215,926</td>
</tr>
<tr>
<td>Penetration/F/B/L</td>
<td></td>
<td>2.8%</td>
<td>4.6%</td>
<td>6.4%</td>
<td>8.2%</td>
<td>10.0%</td>
<td>11.0%</td>
<td>12.0%</td>
<td>14.0%</td>
<td>14.0%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>

### Difficult-to-treat cancers or difficult cases

Common cancers could open a significant market for heavy ions in the European market.

### The main cancers for radiation therapy today are prostate, breast, and lung cancers

The chart above illustrates the penetration of radiotherapy in the treatment of these three cancer types in Europe, which is close to 50%. Other cancer types are c.20% penetrated, which results in a total penetration of c.31%. While utilisation of RT in EU countries is heterogeneous, no European country is as highly penetrated as the United States. However, we assume as described above that penetration for RT will rise overall.

### The need for heavy ion systems in Europe

Below we illustrate with the example of the European market how much heavy ion particle could be used. We assume that robust commercial patient throughput models in some of the larger centres will set examples on how heavy particle systems could both be commercially and clinically viable.

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**Source:** goetzpartners Research estimates

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**Please see analyst certifications, important disclosure information, and information regarding the status of analysts on pages 53 - 55 of this research report.**
The North American Market could potentially create a need for more than 2035e.

<table>
<thead>
<tr>
<th>North America</th>
<th>2017e</th>
<th>2019e</th>
<th>2021e</th>
<th>2023e</th>
<th>2025e</th>
<th>2027e</th>
<th>2029e</th>
<th>2031e</th>
<th>2033e</th>
<th>2035e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>1,902,091</td>
<td>2,010,099</td>
<td>2,124,341</td>
<td>2,244,863</td>
<td>2,372,336</td>
<td>2,507,046</td>
<td>2,649,407</td>
<td>2,799,850</td>
<td>2,958,837</td>
<td>3,126,852</td>
</tr>
<tr>
<td>New Machines</td>
<td>403</td>
<td>412</td>
<td>421</td>
<td>491</td>
<td>515</td>
<td>471</td>
<td>483</td>
<td>495</td>
<td>508</td>
<td>520</td>
</tr>
<tr>
<td>Installed Base</td>
<td>4,049</td>
<td>4,178</td>
<td>4,303</td>
<td>4,529</td>
<td>4,763</td>
<td>4,889</td>
<td>5,018</td>
<td>5,149</td>
<td>5,283</td>
<td>5,420</td>
</tr>
<tr>
<td>Treatments/patient</td>
<td>19</td>
<td>19</td>
<td>18.0</td>
<td>17.7</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Treatment per linac</td>
<td>5,341</td>
<td>5,420</td>
<td>5,500</td>
<td>5,571</td>
<td>5,643</td>
<td>5,714</td>
<td>5,786</td>
<td>5,857</td>
<td>5,929</td>
<td>6,000</td>
</tr>
<tr>
<td>Patients treated</td>
<td>1,118,437</td>
<td>1,213,101</td>
<td>1,314,909</td>
<td>1,424,368</td>
<td>1,542,018</td>
<td>1,629,580</td>
<td>1,722,114</td>
<td>1,819,903</td>
<td>1,923,244</td>
<td>2,032,454</td>
</tr>
<tr>
<td>Prostate</td>
<td>275,803</td>
<td>291,464</td>
<td>308,015</td>
<td>325,505</td>
<td>343,989</td>
<td>363,522</td>
<td>384,164</td>
<td>405,978</td>
<td>429,031</td>
<td>453,394</td>
</tr>
<tr>
<td>% of total</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Breast</td>
<td>275,803</td>
<td>291,464</td>
<td>308,015</td>
<td>325,505</td>
<td>343,989</td>
<td>363,522</td>
<td>384,164</td>
<td>405,978</td>
<td>429,031</td>
<td>453,394</td>
</tr>
<tr>
<td>% of total</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Lung</td>
<td>254,880</td>
<td>269,353</td>
<td>284,648</td>
<td>300,812</td>
<td>317,893</td>
<td>335,944</td>
<td>355,020</td>
<td>375,180</td>
<td>396,484</td>
<td>418,998</td>
</tr>
<tr>
<td>% of total</td>
<td>12.4%</td>
<td>13.4%</td>
<td>13.4%</td>
<td>13.4%</td>
<td>13.4%</td>
<td>13.4%</td>
<td>13.4%</td>
<td>13.4%</td>
<td>13.4%</td>
<td>13.4%</td>
</tr>
<tr>
<td>All PBL</td>
<td>806,486</td>
<td>852,282</td>
<td>900,678</td>
<td>951,822</td>
<td>1,005,870</td>
<td>1,062,988</td>
<td>1,123,348</td>
<td>1,187,137</td>
<td>1,254,547</td>
<td>1,325,785</td>
</tr>
<tr>
<td>PenetrationP/B/L</td>
<td>84.5%</td>
<td>85.4%</td>
<td>85.4%</td>
<td>84.5%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>PBL - particle</td>
<td>19,078</td>
<td>33,123</td>
<td>48,704</td>
<td>65,949</td>
<td>84,956</td>
<td>98,805</td>
<td>113,908</td>
<td>130,407</td>
<td>148,413</td>
<td>168,043</td>
</tr>
<tr>
<td>PenetrationP/B/L</td>
<td>2.8%</td>
<td>4.6%</td>
<td>6.4%</td>
<td>8.2%</td>
<td>10%</td>
<td>11%</td>
<td>12%</td>
<td>15%</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Other Cancer types</td>
<td>1,095,604</td>
<td>1,157,817</td>
<td>1,223,563</td>
<td>1,293,041</td>
<td>1,366,465</td>
<td>1,444,059</td>
<td>1,526,058</td>
<td>1,612,714</td>
<td>1,704,290</td>
<td>1,801,067</td>
</tr>
<tr>
<td>% of total</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
<td>57.6%</td>
</tr>
<tr>
<td>Other - Radiotherapy</td>
<td>437,087</td>
<td>493,027</td>
<td>553,910</td>
<td>620,117</td>
<td>692,058</td>
<td>731,356</td>
<td>772,885</td>
<td>816,772</td>
<td>863,152</td>
<td>912,165</td>
</tr>
<tr>
<td>Penetration other cancer</td>
<td>39.9%</td>
<td>42.6%</td>
<td>45.3%</td>
<td>48.0%</td>
<td>50.6%</td>
<td>50.6%</td>
<td>50.6%</td>
<td>50.6%</td>
<td>50.6%</td>
<td>50.6%</td>
</tr>
<tr>
<td>Other - particle</td>
<td>16,609</td>
<td>32,540</td>
<td>52,067</td>
<td>75,654</td>
<td>103,809</td>
<td>117,017</td>
<td>131,390</td>
<td>147,019</td>
<td>163,999</td>
<td>182,433</td>
</tr>
<tr>
<td>% of total</td>
<td>3.8%</td>
<td>6.6%</td>
<td>9.4%</td>
<td>12.2%</td>
<td>15%</td>
<td>16%</td>
<td>17%</td>
<td>18%</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>Total - particle</td>
<td>35,687</td>
<td>65,663</td>
<td>100,771</td>
<td>141,603</td>
<td>188,805</td>
<td>215,822</td>
<td>245,298</td>
<td>277,426</td>
<td>312,412</td>
<td>350,476</td>
</tr>
<tr>
<td>% of total</td>
<td>1.9%</td>
<td>3.3%</td>
<td>4.7%</td>
<td>6.0%</td>
<td>8.0%</td>
<td>9.3%</td>
<td>9.9%</td>
<td>10.6%</td>
<td>11.2%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Source: Goetzpartners Research estimates

Utilisation for North American cancer patients – The chart above illustrates the penetration of radiotherapy in the treatment of three cancer types in the US, which is close to 85%. Other cancer types are close to 85% penetrated, which results in a total penetration of 57.5%. This could be seen as being already fully penetrated. The biggest driver there is the conversion of other cancer types from currently 37% to 50% or more. We believe that especially the other cancer type segment could drive the particle therapy market, in which we see tumour types where RT is currently not being used due to toxicity.

Below we illustrate with the example of the mature North American market how much heavy-ion particle therapy could be used. Large systems will likely be installed in cancer centres such as MD Anderson, Massachusetts General Hospital in Boston, Memorial Sloan Kettering Cancer Centre, New York City, etc.
Asia is a promising market for Advanced Oncotherapy

China has six proton centres, two carbon centres and c.1,120 linacs installed. As such China has a very well-developed oncotherapy market. We believe that some of these linacs should be converted into particle accelerators. The Chinese government has initiated a program to install 25 PT rooms by 2020.

Given that Chinese hospitals and some oncology centres are enormous and outpace even the biggest cancer centres in the US, the demand for heavy ion particle accelerators could be significant.

The cancer prevalence is comparable to that of Europe and the US. In China the number of cancer cases have increased by more than 75% in the last ten years. However, only 15% of diagnosed cancer cases undergo radiotherapy, which is less than a quarter in the US and less than half in Europe. The survival rates in China are also only 30% the US with 60% for all diagnosed patients.

<table>
<thead>
<tr>
<th>CHART 55: China – Cancer model and radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>China</strong></td>
</tr>
<tr>
<td><strong>2017e</strong></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
</tr>
<tr>
<td><strong>New Machines</strong></td>
</tr>
<tr>
<td><strong>Installed Base</strong></td>
</tr>
<tr>
<td><strong>Particle facilities</strong></td>
</tr>
<tr>
<td><strong>Heavy particle - facilities</strong></td>
</tr>
<tr>
<td><strong>Treatments/patient</strong></td>
</tr>
<tr>
<td><strong>Treatment per linac</strong></td>
</tr>
<tr>
<td><strong>Patients treated</strong></td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
</tr>
<tr>
<td><strong>Breast</strong></td>
</tr>
<tr>
<td><strong>Lung</strong></td>
</tr>
<tr>
<td><strong>All PBL</strong></td>
</tr>
</tbody>
</table>

| **Prost/Breast/Lung** | 264,022 | 292,066 | 322,443 | 355,328 | 390,908 | 429,630 | 471,488 | 516,715 | 565,559 | 618,283 |
| **Penetration** | 21.1% | 22.0% | 23.0% | 24.0% | 25.0% | 26% | 27% | 28% | 29% | 30% |
| **Other Cancer types** | 1,985,817 | 2,098,580 | 2,217,745 | 2,343,678 | 2,476,761 | 2,617,402 | 2,766,028 | 2,923,094 | 3,089,079 | 3,264,490 |
| **Penetration** | 61.3% | 61.3% | 61.3% | 61.3% | 61.3% | 61.3% | 61.3% | 61.3% | 61.3% | 61.3% |
| **Other** | 174,414 | 183,813 | 193,717 | 204,154 | 215,151 | 210,844 | 205,354 | 198,561 | 190,334 | 180,532 |
| **Penetration** | 8.8% | 8.8% | 8.7% | 8.7% | 8.7% | 8.1% | 7.4% | 6.8% | 6.2% | 5.5% |

Source: goetzpartners Research estimates
Market Position of Advanced Oncotherapy

While Varian and IBA are on the forefront of accelerator technology and launched an off-the-shelf product in their efforts to industrialise the PT technology, AVO believes that there is a need to invest in software technology, in TPS and Oncology information software (“OIS”). Software is a driving force of innovation especially in the more conventional RT technology, where we noticed that older RT machines could achieve equal or better results with a good TPS product when compared with the results from last generation hardware and second-tier TPS software, when products are bundled together from the hardware manufacturer.

Types of accelerators presently used in radiotherapy

Linear accelerators for photon therapy

X-rays are produced by accelerating electrons using a high frequency linear accelerator (linac), and letting them collide with high-density targets, usually made of tungsten. This converts their energy into photon beams that can be redirected at the patient. Modern radiotherapy linacs are capable of accelerating electrons up to 18 MeV - 20MeV, over a relatively short length of 1.5m. Electron linacs with energies between 6 MeV - 10MeV are also used in Stereotactic Surgery and Intra Operative Radio-Therapy applications.

Cyclotrons & synchrotrons for proton therapy

Cyclotrons

In cyclotrons, charged particles are accelerated outwards from the centre along a spiral path (CHART 59). The injection point lies at the centre of the accelerator and the extraction point at the extremity. The particles are accelerated every time they pass a constant frequency electric field, and as the proton’s energy increases, the centrifugal force increases and it moves further away from the centre. Once the particle gains enough energy, it will spiral out towards the extraction point. Consequently, the maximum energy is fixed and related to the number of turns the beam makes prior to exit. Cyclotrons are capable of accelerating protons with energy up to 250MeV.

Synchrotrons

In contrast to cyclotrons, synchrotrons accelerate particles in a fixed closed-loop path (CHART 60), where the magnetic field that keeps the particle beam confined to its path increases as the particle accelerates, thus being synchronised with the increasing kinetic energy of the particles within the beam. Synchrotrons are the most powerful modern particle accelerators, with the largest one being the Large Hadron Collider near Geneva.
Limitations of current systems

Given their superior clinical properties, it is evident that charged particles would be the treatment of choice if the cost was more comparable with that of photons. While cyclotrons and synchrotrons provide the technology to generate these particles, their cost and installation complexity are the biggest factors slowing adoption. Due to the circular nature of both cyclotrons and synchrotrons, particles are more likely to collide with the periphery, thereby creating radioactive energy. As a result, these systems require excessive shielding, further driving up cost. AVO is now developing a system that generates a proton beam using a linear accelerator, which reduces installation costs and shielding requirements, thus making installation more convenient, while maintaining the benefit of using protons for therapy.

<table>
<thead>
<tr>
<th>CHART 61: Features of accelerators currently used in radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclotron</strong></td>
</tr>
<tr>
<td>Trajectory</td>
</tr>
<tr>
<td>Radiofrequency</td>
</tr>
<tr>
<td>Magnetic field</td>
</tr>
<tr>
<td>Beam emittance</td>
</tr>
<tr>
<td>Energy modulation</td>
</tr>
<tr>
<td>Modularity</td>
</tr>
<tr>
<td>Proton loss</td>
</tr>
<tr>
<td>Spot size regulation</td>
</tr>
<tr>
<td>Shielding requirements</td>
</tr>
<tr>
<td>Construction</td>
</tr>
<tr>
<td>Electrical power</td>
</tr>
<tr>
<td>Gantry requirements</td>
</tr>
</tbody>
</table>

Source: goetzpartners Research
The AVO Technology and its advantages

LIGHT is a next-generation PT system, developed to provide a more compact and more affordable approach to PT, while improving machine reliability. In addition to technological superiority, the modularity of LIGHT makes the system suitable for installation in urban settings where space is the main limitation, bringing the technology closer to the patient.

**CHART 62: LIGHT technology**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Proton Source generates up to 200 pulses of protons per second from a source of hydrogen gas.</td>
</tr>
<tr>
<td>2</td>
<td>RFQ increases velocity of proton from 40keV to 5MeV using a design developed at CERN.</td>
</tr>
<tr>
<td>3</td>
<td>SCDTL units match increasing velocity of the protons and accelerate protons from 5MeV to 37.5MeV.</td>
</tr>
<tr>
<td>4</td>
<td>CCL controls beam energy and accelerates beam to up to 230MeV and 60% of the speed of light.</td>
</tr>
<tr>
<td>5</td>
<td>BTL measures and directs the proton beam to the gantry where it is integrated with the PPS for treatment.</td>
</tr>
</tbody>
</table>

Abbreviations: RFQ: Radio Frequency Quadrupole; SCDTL: Side Coupled Drift Tube Linac; CCL: Coupled Cavity Linac; BTL: Beam Transport Line; MeV: Mega Electron Volts; PPS: Patient Positioning System

Source: Company data, goetzpartners Research

**LIGHT overcomes key limitations of first-generation PT systems**

AVO’s LIGHT system has a number of advantages over other PT systems. On top of high costs, the installation and the maintenance of PT systems are highly challenging projects. Furthermore, the majority of PT systems are cyclotrons that produce significant stray radioactivity, requiring manufacturers and healthcare facilities to plan for expensive and complex shielding. The LIGHT system is a linear accelerator and produces far less of the unwanted radioactivity. In addition, it has a number of other advantages:

- **Superior proton beam:** The LIGHT system uses an innovative linear accelerator rather than a cyclotron / synchrotron. This means that particle collision with structures within the accelerator is reduced, thus creating less radioactive energy. The results are increased safety and lower shielding requirements, reducing overall installation time and cost.

- **Precision:** LIGHT’s proton beam can be moved up to 200 times per second, allowing for more accurate temporal and spatial targeting of moving tumours. Furthermore, spot scanning allows a more confocal dose that can be altered to meet individual needs, and beam energy can be adjusted at source, requiring no absorbers or energy reduction devices. This is a unique feature of linear accelerators such as LIGHT and cannot be achieved with commercially available systems. Prompt Gamma may provide a novel method for live imaging during irradiation, thus more precision.

- **Compact, modular and easy to install:** While other systems come in one size, LIGHT can be customised due to its modularity. This offers clinics an opportunity to expand their offering to other rooms and / or to increase system strength step by step as clinical needs develop. The fact that new modules can be added to increase output energy at any point reduces the commitment by healthcare providers to high upfront costs for systems that may not be fully utilised.

- **Affordability:** Due to the modular nature of the system and mass-production manufacturing, LIGHT is well positioned to compete with other PT systems currently available. LIGHT is associated with lower capital-, operational-, and decommissioning costs.

- **City-centre focus:** LIGHT’s unique properties allow for implementation in existing clinical sites and densely populated areas where space is scarce. This means making the technology more accessible to patients, ensuring that as many people as possible can benefit from it.

- **An integrated system:** Full workflow-integration from patient intake, over treatment planning, through to beam delivery, ensures a seamless patient treatment experience.
AVO’s commercial potential and the adoption rate of PT

IBA is currently ahead of its competition with an off-the-shelf product, which is not only more economical for both manufacturer and customer, but much quicker to produce and install. We believe that AVO has the potential to introduce another competitive product, which could be ahead of Mevion’s single room approach.

We compare AVO’s LIGHT system with its closest competitor Mevion. AVO aims to reduce costs dramatically in order to expand the adoption rate for PT. Although this is only a bullish scenario in our valuation section and our base case assumes a significantly lower price per room, we think that this could indeed be a more realistic scenario, if the industry plays its cards well. We compare the success of the pharmaceutical industry to justify its highly priced drugs and PT, which has still a tough battle ahead.

We should not forget that particle therapy has become a highly topical subject in the oncology community. It is fuelled by discussions concerning questionable superiority to photon treatment with regard to survival or local control, higher costs and cost effectiveness, better tolerance for patients due to fewer side effects, and, last but not least, continuous patient inquiries regarding the therapy.

The big commercial question is will PT remain a commercial niche or will it become the gold standard for the majority of cancers that are radiated today, plus the radio resistant tumour types for photons.
## LIGHT SYSTEM - SOFTWARE

<table>
<thead>
<tr>
<th></th>
<th>2020e</th>
<th>2021e</th>
<th>2022e</th>
<th>2023e</th>
<th>2024e</th>
<th>2025e</th>
<th>2026e</th>
<th>2027e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of rooms (accumulated)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Market Share base (4,500 by 2035)</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.6%</td>
<td>0.9%</td>
<td>1.4%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Sales</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
<td>2.1</td>
<td>4.4</td>
<td>8.7</td>
<td>15.3</td>
<td>30.5</td>
</tr>
<tr>
<td>COGS/3rd party payout</td>
<td>-</td>
<td>-</td>
<td>0.8</td>
<td>1.7</td>
<td>3.5</td>
<td>7.0</td>
<td>12.2</td>
<td>24.4</td>
</tr>
<tr>
<td>Gross Profit</td>
<td>0.2</td>
<td>0.4</td>
<td>0.9</td>
<td>1.7</td>
<td>3.1</td>
<td>6.1</td>
<td>10.3</td>
<td>16.8</td>
</tr>
<tr>
<td>gross margin</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Source: goetzpartners Research estimates

## LIGHT SYSTEM - TOTAL

<table>
<thead>
<tr>
<th></th>
<th>2020e</th>
<th>2021e</th>
<th>2022e</th>
<th>2023e</th>
<th>2024e</th>
<th>2025e</th>
<th>2026e</th>
<th>2027e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales</td>
<td>6.2</td>
<td>13.0</td>
<td>21.3</td>
<td>40.9</td>
<td>67.4</td>
<td>128.1</td>
<td>213.7</td>
<td>318.1</td>
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<tr>
<td>COGS</td>
<td>-</td>
<td>6.7</td>
<td>7.1</td>
<td>15.1</td>
<td>27.1</td>
<td>41.3</td>
<td>88.6</td>
<td>125.6</td>
</tr>
<tr>
<td>Gross Profit</td>
<td>-</td>
<td>0.6</td>
<td>5.9</td>
<td>6.3</td>
<td>13.8</td>
<td>26.0</td>
<td>39.5</td>
<td>88.1</td>
</tr>
<tr>
<td>gross margin</td>
<td>-9%</td>
<td>45%</td>
<td>29%</td>
<td>34%</td>
<td>39%</td>
<td>31%</td>
<td>41%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Source: goetzpartners Research estimates

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Please see analyst certifications, important disclosure information, and information regarding the status of analysts on pages 53 - 55 of this research report.
Valuation Scenario

We have tested our DCF model around a few variables (market share of proton technology and market share of AVO in proton therapy market). The penetration rates are dependent on clinical factors and on cost factors. In the next sections, we will review clinical data. We believe the cost factor will not be the only decisive factor, but certainly a major one, whether PT will become a mass product or remain a niche product. Hence, we have come up with four scenarios for AVO’s PT rooms. Proton rooms are on average below $25m today. We have assumed prices will reduce to $15m by 2020 on average across the PT industry including AVO. However, we believe AVO could potentially lower the price to $7.5m. This allows a long-term penetration rate of 15% for the PT industry with a c.15% potential market share for AVO.

Our DCF results in £246m enterprise value for AVO’s business on these assumptions. This would result in an equity value of £230m (net debt 15.5m – consideration of £25m debt facility from Metric). This results in a fair value of 155 GBP / share representing a c.340% upside from its current trading levels.

We have modelled pricing assumptions by 2020E per PT room ($15m and $7.5m) to test our valuation and its resulting potential for AVO. As expected, the results do not differ that much. A higher market share results in higher volumes at the expense of lower absolute profit per machine assuming only a moderate gross margin contraction. It seems that variable room pricing almost results in a balancing NPV figure, unless the company manages to get costs down and margins up at the same time. Given the labour intense installation and manufacturing coupled with wage inflation of highly skilled personnel, significant margin expansion beyond our long term 25% is unlikely.

However, we see a significant potential with pricing of maintenance fees. While the industry charges between 6% and 8% (resulting at >$1.0m) – we assume that AVO could charge 10% or more given their instrument price is likely to be significantly higher than their competitors. Margins on maintenance contracts are typically high and therefore accelerate earnings growth.

However, we believe that based on current and expected favourable clinical evidence, prices could be justifiable at $20m and still achieve a market penetration of 15% - 20% long term. If PT is as successful as the pharmaceutical industry with its high-end oncology drugs, a high price / high market share scenario could be possible. This could result in an NPV for AVO in a range between £90m and £400m. This results in an equity range of 75GBP / share (80% upside) – 400GBP / share (950% upside).

We discuss the rational of cancer therapy pricing and the evolution of high-end drugs in immune oncology in the next section of the note. Although, we highlight that this is not our base case, we believe the investment case in PT and AVO in particular should not only hinge on the company’s ability and / or willingness to lower installation cost per room.

The four scenarios are based on our DCF model, which is conservative, in our view. While we appreciate that investors want to see sales to be confident enough to invest in AVO, we would point out that the reward could be high given the current share price weakness and the upside after the successful prototype experiment in Q3.
<table>
<thead>
<tr>
<th>CHART 69: DCF model for AVO (£m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIGHT SYSTEM - TOTAL</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Sales</th>
<th>COGS</th>
<th>Gross Profit</th>
<th>gross margin</th>
<th>R&amp;D</th>
<th>SG&amp;A</th>
<th>As % of sales</th>
<th>growth</th>
<th>EBIT</th>
<th>Tax</th>
<th>tax rate</th>
<th>NOPAT</th>
<th>DA</th>
<th>CAPEX</th>
<th>% of sales</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018e</td>
<td>0.5</td>
<td>-</td>
<td>0.5</td>
<td>0%</td>
<td>19.0</td>
<td>0.2</td>
<td>30%</td>
<td>413%</td>
<td>-18.65</td>
<td>-</td>
<td>16%</td>
<td>-18.65</td>
<td>0.22</td>
<td>0.03</td>
<td>6.00%</td>
<td>(18.46)</td>
</tr>
<tr>
<td>2019e</td>
<td>3.1</td>
<td>6.7</td>
<td>3.1</td>
<td>-9%</td>
<td>15.4</td>
<td>0.8</td>
<td>25%</td>
<td>80%</td>
<td>-13.10</td>
<td>-</td>
<td>16%</td>
<td>-13.10</td>
<td>0.22</td>
<td>0.12</td>
<td>4.00%</td>
<td>(13.00)</td>
</tr>
<tr>
<td>2020e</td>
<td>6.2</td>
<td>7.1</td>
<td>6.2</td>
<td>45%</td>
<td>11.8</td>
<td>1.4</td>
<td>23%</td>
<td>106%</td>
<td>-13.76</td>
<td>-</td>
<td>16%</td>
<td>-13.76</td>
<td>0.22</td>
<td>0.24</td>
<td>3.91%</td>
<td>(11.58)</td>
</tr>
<tr>
<td>2021e</td>
<td>13.0</td>
<td>15.1</td>
<td>13.0</td>
<td>29%</td>
<td>8.2</td>
<td>2.9</td>
<td>22%</td>
<td>35%</td>
<td>-5.17</td>
<td>-</td>
<td>16%</td>
<td>-5.17</td>
<td>0.37</td>
<td>0.50</td>
<td>3.82%</td>
<td>(4.47)</td>
</tr>
<tr>
<td>2022e</td>
<td>21.3</td>
<td>27.1</td>
<td>21.3</td>
<td>34%</td>
<td>4.6</td>
<td>3.8</td>
<td>18%</td>
<td>60%</td>
<td>-2.20</td>
<td>-</td>
<td>16%</td>
<td>-2.20</td>
<td>0.39</td>
<td>0.80</td>
<td>3.72%</td>
<td>(2.26)</td>
</tr>
<tr>
<td>2023e</td>
<td>40.9</td>
<td>41.3</td>
<td>40.9</td>
<td>39%</td>
<td>1.0</td>
<td>6.1</td>
<td>15%</td>
<td>48%</td>
<td>15.24</td>
<td>-</td>
<td>16%</td>
<td>15.24</td>
<td>1.49</td>
<td>1.49</td>
<td>3.63%</td>
<td>4.93</td>
</tr>
<tr>
<td>2024e</td>
<td>67.4</td>
<td>88.6</td>
<td>67.4</td>
<td>31%</td>
<td>1.7</td>
<td>9.1</td>
<td>14%</td>
<td>69%</td>
<td>20.93</td>
<td>16%</td>
<td>16%</td>
<td>20.93</td>
<td>2.28</td>
<td>2.38</td>
<td>3.45%</td>
<td>11.91</td>
</tr>
<tr>
<td>2025e</td>
<td>128.1</td>
<td>125.6</td>
<td>128.1</td>
<td>41%</td>
<td>3.2</td>
<td>15.4</td>
<td>12%</td>
<td>46%</td>
<td>60.30</td>
<td>16%</td>
<td>16%</td>
<td>60.30</td>
<td>4.88</td>
<td>4.42</td>
<td>3.36%</td>
<td>15.44</td>
</tr>
<tr>
<td>2026e</td>
<td>213.7</td>
<td>188.0</td>
<td>213.7</td>
<td>41%</td>
<td>5.3</td>
<td>22.4</td>
<td>9%</td>
<td>28%</td>
<td>93.54</td>
<td>16%</td>
<td>16%</td>
<td>93.54</td>
<td>6.91</td>
<td>7.17</td>
<td>3.26%</td>
<td>48.36</td>
</tr>
<tr>
<td>2027e</td>
<td>318.1</td>
<td>241.3</td>
<td>318.1</td>
<td>41%</td>
<td>8.0</td>
<td>28.6</td>
<td>8%</td>
<td>16%</td>
<td>157.61</td>
<td>16%</td>
<td>16%</td>
<td>157.61</td>
<td>10.35</td>
<td>10.38</td>
<td>3.17%</td>
<td>75.11</td>
</tr>
<tr>
<td>2028e</td>
<td>443.2</td>
<td>241.3</td>
<td>443.2</td>
<td>46%</td>
<td>11.1</td>
<td>33.2</td>
<td>3%</td>
<td>8%</td>
<td>132.40</td>
<td>16%</td>
<td>16%</td>
<td>132.40</td>
<td>13.05</td>
<td>14.06</td>
<td>3.17%</td>
<td>128.69</td>
</tr>
</tbody>
</table>

**Source:** goetzpartners Research estimates. **Warning Note:** Forecasts are not a reliable indicator of future performance or results.
While, the above model appears to be critical of a wider utilisation of PT in cases, it is a firm step towards a much wider adoption of PT as it is used today. The NTCP model suggests that 11% of diagnosed cancers are eligible for PT. Our model below shows a PT adoption rate of close to 11% of radiated cancers by 2027 running up to 15% in 2030 as per our DCF assumptions.

The market shares are a rough estimate based on our views from the present situation. Mevion and Hitachi have accelerated their commercialisation efforts and Varian appears to push more for growth in PT technology. Currently, only IBA and Mevion have sold single room products. We believe that the trend is going to single room systems and trending from currently 2.4x (sites vs. rooms) globally towards 1.3x in 2050 in a linear manner.

The above chart, illustrates our view of the annual instalment of proton systems per year and the market share of the current PT players. We believe this model is rather conservative. However, we refer to our sensitivity analysis above.

We believe that PT will end up being an oligopoly, potentially even a duopoly of manufacturers. While we believe that there are more than two credible technologies out there, it is likely that PT players will consolidate like the linac players (Varian, Elekta, Accuray). The model above does not take that into account. However, consolidated or not, the penetration of PT shown above is rather independent on M&A dynamics.
Management

AVO’s management team has been substantially reinforced by appointment of high calibre industry veterans, significantly changing the equity story compared to 2016. While the patents and the promising technology were already in place then, the company has managed to attract veterans of the PT industry from science, engineering, installation, application experience and compliance. We feel that the success of the industrialisation is entirely hinging on the top professionals like Prof Myers, Ed Lee, Dr Jonathan Farr and Dr Michel Baelen, supported by a team that has the right credentials to implement an attractive funding and execution strategy such as Dr Mike Sinclair or Nicolas Serandour.

Leadership Team

Dr Michael Sinclair - Executive Chairman
Dr Michael Sinclair has more than 40 years of experience in the healthcare sector and previously held Chief Executive positions at Nestor Healthcare and Allied Medical Group Limited. In addition, he is Chairman and Founder of Lifetime Corporation Inc, a Member of the Board of Overseers of the Tufts University School of Medicine, and Chairman and Founder of US based Atlantic Medical Management LLP.

Nicolas Serandour - Chief Executive Officer
Mr Serandour joined Advanced Oncotherapy in September 2014 as Chief Operating and Financial Officer, and now holds the position of Chief Executive Officer. Having worked at JPMorgan, Lehman Brothers and Lazard he has accumulated over 15 years of experience in the investment banking industry, providing strategic and financial advice to senior executives at leading healthcare companies.

Ed Lee - Chief Operating Officer
Mr Lee is responsible for the coordination of operations and program/project management to bring the LIGHT system to market. Over the last 20 years he has accumulated extensive manufacturing and operations experience in a variety of industries including Automotive, Aerospace, Military/Defence, Nuclear, and Medical Devices. Mr Lee previously led the Production and Technical Field Service teams for Optivus Proton Therapy. Mr Lee holds a BSc in Mechanical Engineering from the Christian Brothers University in Memphis.

Prof Steve Myers - ADAM Executive Chairman
Prof Steve Myers is an electronic engineer who works in high-energy physics, and became Executive Chairman of ADAM in January 2016. In 2008, he was appointed Director of Accelerators at CERN, and in 2014 Head of CERN Medical Applications. Prof Steve Myers is an honorary member of the European Physical Society and of the Royal Irish Academy, won the Duddell Medal and Prize of the Institute of Physics and the International Particle Accelerators Lifetime Achievement Prize, and was jointly awarded the EPS Edison Volta Prize and the Prince of Asturias Prize of Spain. He completed his Ph.D at Queen’s University, Belfast, in 1972 after earning his bachelor’s degree in electrical and electronic engineering in 1968.

Dr Michel Baelen - Director, Regulatory Affairs
Mr Baelen is responsible for product compliance during the regulatory assessment by the notified body/regulated authority. Previously, he worked as Quality Coordinator at the University Hospital Saint-Luc at the Catholic University of Louvain in Brussels and as Vice President Group Regulatory and Quality Assurance Affairs at IBA, before joining AVO as Head of Regulatory Affairs in March 2016. Mr Baelen holds an MBA, an MSc in electrical engineering and a doctor in management sciences from IAE in Lille (France).

Dr Jonathan Farr - Director of Medical Physics
Dr Jonathan Farr is responsible for the clinical application and ongoing medical physics development of the LIGHT system. Previously, Dr Farr has served as Chief of Medical Physics at the Westdeutsches Protonentherapiezentrum, Essen, Germany, and at the St. Jude Children’s Research Hospital, USA. He received his PhD degree from Wayne State University in 2003 and completed an advanced postgraduate qualification (Habilitation) in novel radiation oncology techniques at the Universitätsklinikum Essen-Duisburg, Germany in 2012.
Financial Statements

Sales Model – Gross margin model

### CHART 71: Sales Model (£m)

<table>
<thead>
<tr>
<th>(in £m)</th>
<th>2017e</th>
<th>2018e</th>
<th>2019e</th>
<th>2020e</th>
<th>2021e</th>
<th>2022e</th>
<th>2023e</th>
<th>2024e</th>
<th>2025e</th>
<th>2026e</th>
<th>2027e</th>
<th>2028e</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIGHT SYSTEM - Accelerator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Room (price)</td>
<td>10.6</td>
<td>10.3</td>
<td>10.1</td>
<td>9.9</td>
<td>9.6</td>
<td>9.4</td>
<td>9.2</td>
<td>9.0</td>
<td>8.7</td>
<td>8.5</td>
<td>8.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Room (production cost)</td>
<td>17.5</td>
<td>15</td>
<td>14</td>
<td>5.9</td>
<td>5.8</td>
<td>5.6</td>
<td>5.5</td>
<td>5.4</td>
<td>5.2</td>
<td>5.1</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>COGS as % of sales</td>
<td>-66%</td>
<td>-45%</td>
<td>-39%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>LIGHT SYSTEM - Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance/room</td>
<td>1.1</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
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<td>Systems (personal + spare parts)</td>
<td>2.1</td>
<td>0.9</td>
<td>0.6</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>COGS as % of sales</td>
<td>-99%</td>
<td>14%</td>
<td>45%</td>
<td>39%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td><strong># of rooms ordered</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>13</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td><strong>market share PT rooms sold/a</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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Source: goetzpartners Research estimates, Company data. Warning Note: Forecasts are not a reliable indicator of future performance or results.
## Profit & Loss Statement

**CHART 72: Profit & Loss account (£m)**

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<th>2019e</th>
<th>2020e</th>
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Source: goetzpartners Research estimates, Company data. Warning Note: Past performance and forecasts are not a reliable indicator of future performance or results.
## Balance Sheet

### CHART 73: Balance Sheet (£m)

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<th>2019e</th>
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Source: goetzpartners Research estimates, Company data. Warning Note: Past performance and forecasts are not a reliable indicator of future performance or results.
## Cash Flow Statement

### CHART 74: Cash Flow Statement (£m)

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Source: goetzpartners Research estimates, Company data. Warning Note: Past performance and forecasts are not a reliable indicator of future performance or results.
## Appendix

### CHART 75: List of PT sites – global

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<th>last data</th>
<th>MeV</th>
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Source: goetzpartners Research
### Chart 76: List of PT sites – global

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Please see analyst certifications, important disclosure information, and information regarding the status of analysts on pages 53 - 55 of this research report.
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COMPANY DESCRIPTION
Advanced Oncotherapy plc, together with its subsidiaries, focuses on providing radiotherapy systems for cancer treatment through the use of a novel proton therapy technology to healthcare providers and hospitals. It is developing Linac Image Guided Hadron technology, a next generation of proton therapy system for treating cancer. The company was formerly known as CareCapital Group plc and changed its name to Advanced Oncotherapy plc in September 2012. Advanced Oncotherapy plc was incorporated in 2005 and is headquartered in London, the United Kingdom.

SCENARIOS

Base Case - GP Investment Case
Proton therapy penetrates the conventional radiation therapy market by 15% in 2030. AVO will be able to get a market share of around 15%. Price per treatment room will come down to $7.5m and accelerates sales growth.

Bluesky Scenario
Proton therapy penetrates at a faster pace and goes up to 30% or higher. AVO will maintain or increase market share in an oligopolistic market. Price per treatment rooms will be as high as $15m - scale effects improve margins.

Downside risk
Proton therapy penetrates at a slower pace and goes up to only 10% by 2030. AVO may have significant delays and its market share in PT remains low as a result (10%) in 2030. Competitors could develop a competing linac with a modular system.

SWOT

Strength - AVO has a promising modular system, which could be cheaper and faster installed in hospitals.
Weakness - The company is small in size, early stage and has a limited financial strength compared to its competitors IBA, Varian, Hitachi, etc.
Opportunity - Growing clinical evidence and patient driven demand could accelerate adoption rate more than expected.
Threat - Capital constraints on healthcare budgets and underwhelming evidence for PT could be replaced by carbon ion RT. Partnerships are instrumental for AVO’s success and there is a significant risk of terminations or delays.

INDUSTRY EXPECTATIONS
The industry is expected to benefit from a higher adoption rate for proton therapy fuelled by growing clinical evidence. Prices for treatment rooms are not that high when broken down on a per patient basis vs. modern drug therapy. Thus, prices for PT treatment rooms are expected to come down only moderately. Software and better of imaging is expected to improve beam delivery and help adoption rates.
Important Disclosures: Non-Independent Research

Analyst Certification

I, Martin Brunninger, hereby certify that the views regarding the companies and their securities expressed in this research report are accurate and are truly held. I have not received and will not receive direct or indirect compensation in exchange for expressing specific recommendations or views in this research report.

I, Martin Piehlmeier, hereby certify that the views regarding the companies and their securities expressed in this research report are accurate and are truly held. I have not received and will not receive direct or indirect compensation in exchange for expressing specific recommendations or views in this research report.

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OUTPERFORM - Describes stocks that we expect to provide a relative return (price appreciation plus yield) of 15% or more within a 12-month period.

NEUTRAL - Describes stocks that we expect to provide a relative return (price appreciation plus yield) of plus 15% or minus 10% within a 12-month period.

UNDERPERFORM - Describes stocks that we expect to provide a relative negative return (price appreciation plus yield) of 10% or more within a 12-month period.

NON-RATED – Describes stocks on which we provide general discussion and analysis of both up and downside risks but on which we do not give an investment recommendation.

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- BRISTOL-MYERS SQUIBB CO (BMY US)
- CIRCLE HEALTH LTD (PRIVATE COMPANY)
- DECONSTRUCT (PRIVATE COMPANY)
- ELEKTA AB (EKTA SS)
- HITACHI LTD (6501 JP)
- ION BEAM APPLICATIONS (IBAB BB)
- MEDAUSTRON (PRIVATE COMPANY)
- MEVION MEDICAL SYSTEMS (PRIVATE COMPANY)
- MITSUBISHI CORP (8058 JP)
- P-CURE (PRIVATE COMPANY)
- PROTEOME SCIENCES PLC (PRM LN)
- SCANDINOVA (PRIVATE COMPANY)
- SIEMENS AG (SIE GR)
- SUMITOMO CORP (8053 JP)
- THALES SA (HO FP)
- TOSHIBA CORP (6502 JP)
- VARIAN MEDICAL SYSTEMS INC (VAR US)
- Advanced Oncotherapy Plc (AVO-GB)
- Healthcare (HLTH)
- Medical Technology (MT)

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