Capital Market Day

Olivier Legrain (CEO)

25 September 2017
Introduction
Olivier Legrain, Chief Executive Officer, IBA

The role on proton therapy in oncology
Andrew K. Lee, MD, MPH, Medical Director, Texas Center for Proton Therapy

Testimony on the development of a state-of-the-art proton therapy center
Craig W. Stevens, MD, PhD, Chair of Radiation Oncology, Beaumont Health System

North America PT market dynamics
Beth Klein, Beth Klein - Executive Vice President, IBA North America

Question and answer

Optional tour of IBA’s booth, # 2135
Disclaimer

This presentation may contain forward-looking statements concerning industry outlook, including growth drivers; the company’s future orders, revenues, backlog, or earnings growth; future financial results; market acceptance of or transition to new products or technology and any statements using the terms “could,” “believe,” “outlook,” or similar statements are forward-looking statements that involve risks and uncertainties that could cause the company’s actual results to differ materially from those anticipated. The company assumes no obligation to update or revise the forward-looking statements in this release because of new information, future events, or otherwise.
In the US, 1.1M patients receive radiation therapy

- There are about 1.7M new cancer diagnoses per year in the US, and about 1.1M of patients receive radiation, often with curative intent.

### Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Thousand, 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>242</td>
</tr>
<tr>
<td>Breast</td>
<td>227</td>
</tr>
<tr>
<td>Lung</td>
<td>226</td>
</tr>
<tr>
<td>CRC</td>
<td>143</td>
</tr>
<tr>
<td>Melanoma</td>
<td>76</td>
</tr>
<tr>
<td>Bladder</td>
<td>74</td>
</tr>
<tr>
<td>NHL</td>
<td>70</td>
</tr>
<tr>
<td>Kidney</td>
<td>65</td>
</tr>
<tr>
<td>Corpus Uteri</td>
<td>47</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43</td>
</tr>
<tr>
<td>Liver</td>
<td>29</td>
</tr>
<tr>
<td>Ovary</td>
<td>22</td>
</tr>
<tr>
<td>Stomach</td>
<td>21</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>341</td>
</tr>
</tbody>
</table>

### External Beam Radiation Therapy Treatments, 2014

- 3DCRT: 42
- IMRT: 42
- SBRT: 11
- Other: 5

**Total**

- 1.7M diagnoses
- 1.1M radiation therapy
RT manufacturers capture a tiny slice of US Oncology market

- Despite nearly 1M patients treated per year, often with curative intent, RT manufacturers capture a tiny slice of the US Oncology market.

### US Annual Spend on Cancer Treatment, 2020

<table>
<thead>
<tr>
<th>Category</th>
<th>USD $B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Spend, 2020</td>
<td>216</td>
</tr>
<tr>
<td>Surgery, Inpatient, ED</td>
<td>38</td>
</tr>
<tr>
<td>Outpatient Eval &amp; Mgmt</td>
<td>71</td>
</tr>
<tr>
<td>Drugs</td>
<td>85</td>
</tr>
<tr>
<td>Imaging</td>
<td>10</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>12</td>
</tr>
</tbody>
</table>

**PRELIMINARY ESTIMATES**

- RT Mfr revenues (CapEx / Service Fees): ~$2 B

**CAGR, 2015-2010**

- 7-9
- 4-5
- 4-5
- 12-15
- 1-3
- 1-3

SOURCE: Team Analysis

These thoughts represent an initial working draft; they will be subject to appropriate legal and compliance review before any implementation takes place.
Proton therapy capacity gap - 2035

Estimation of RT and PT rooms needed by 2035

- Radiotherapy rooms needed by 2035 estimated by Lancet Oncology - [www.thelancet.com/oncology](http://www.thelancet.com/oncology)

- Proton Therapy rooms needed by 2035 extrapolated worldwide from the "Horizon Scanning : Proton Therapy" in the Netherlands [https://www.gezondheidsraad.nl/sites/default/files/proton%20radiotherapy200917E_0.pdf](https://www.gezondheidsraad.nl/sites/default/files/proton%20radiotherapy200917E_0.pdf)
Proton therapy capacity gap - today

PT capacity Gap
2252 rooms

Number of PT rooms sold [end 2016]
[of which 191 in operation]

Number of PT rooms needed

PT potential cases/year

RT cases/year

Diagnosed cancer cases/year

Population

Source: IBA internal modeling based on Model Based Approach developed in The Netherlands (https://www.gezondheidsraad.nl/sites/default/files/proton%20radiotherapy200917E_0.pdf)
Proton therapy catalysts

1. Cost efficient

2. Increasing publications and support

3. Innovations and new technologies

- Compact PT
- Adaptive PT
- Software
- Imaging
- Organ motion management
- Turnkey solutions
- Laser-based PT system

Relative cost

Guidelines ASTRO / NCCN

*US spending per year in cancer care

$12 B*

$38 B*

$85 B*

*US spending per year in cancer care
Growing acceptance of proton therapy

108 Trials Open and Recruiting

- Ocular: 3%
- Others: 4%
- Lymphoma, Hodgkins: 1%
- Pediatric: 16%
- Brain, CNS, skullbase: 16%
- Breast: 9%
- Head and neck: 5%
- Spine: 4%
- Liver: 8%
- Pancreas: 1%
- Esophagus: 4%
- Prostate: 12%
- Uterus, cervix: 2%
- Bone soft tissues: 4%
- Lung: 11%

End December 2016

Publications Statistics per Year

Number of publications up to end of 2016

Data from https://clinicaltrials.gov/
Growing acceptance of proton therapy

- New guidelines further endorse proton therapy as an important treatment option in the fight against cancer

- **American Society for Radiation Oncology (ASTRO)**
  - **5 new indications in Group 1**
    (frequently supported treatment with proton therapy)
    - Paranasal sinuses and other accessory sinuses
    - Non-metastatic retroperitoneal sarcomas
    - Malignant and benign primary Central Nervous System tumors
    - Advanced and/or unresectable head and neck cancers
    - Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)
  
  Source: www.astro.org

- **National Comprehensive Cancer Network (NCCN)**
  - **5 new indications**
    (where proton therapy is appropriate or may be appropriate in specific situations)
    - Central Nervous System Cancers
    - Head and Neck Cancers
    - Non-Small Cell Lung Cancer
    - Hepatocellular Carcinoma (Liver)
    - Eosophagial and Esophagogastric Junction Cancers
  
  Source: www.nccn.org
IBA - a global leader in proton therapy
IBA – a global leader in proton therapy

- 5 continents
- 20 countries
- 51 rooms in construction/installation
- 62 rooms treating

PROTEUS® PLUS  PROTEUS® ONE
IBA – a global leader in proton therapy

Global share of installed base in rooms

Share of installed base in NA in rooms

Share of installed base in Europe and ROW in rooms

Share of installed base in APAC in rooms
IBA lead over competition
IBA world-class innovative proton therapy solutions
Proteus ONE

COMPACT
Open Gantry & accelerator design

IMPT
Most precise treatments
Easy Workflow

INTEGRATED
Software, Dosimetry & Training
Proteus ONE

INSTANT 2D & CONE-BEAM CT
For Image-Guided PT

PROVEN PENCIL BEAM SCANNING
For highly conformal IMPT

PATIENT AND STAFF FRIENDLY
Open environment
IBA lead over competition

- Fastest from contract to patient treatment
- Largest software integration
- Best IMPT System
- Best image guided system
- Best workflow
- Unique value in the industry
IBA lead over competition

Largest Software integration

- RayCare
- RayStat
- Xio
- Monaco
- Mosaiq
- Eclipse
- Aria
- Pinnacle

IBA CONFIDENTIAL
Elekta and IBA agree on a comprehensive partnership

- Co-funding for all PT related software development
  - MOSAIQ and Monaco
- Competitive bundling of PT/Linac/SW vs competition
- Commercial collaboration
  - finder’s fee globally for PT deals Elekta initiate
  - finder’s fee globally for Elekta linac deals IBA initiate
- Co-marketing of each others products (but non-exclusive)

Jointly work towards an integrated offering to elevate user experience in improve patient care
IBA lead over competition

Fastest from Contract to Patient treatment

IBA  building 14 months | equipment 12 months

Competitor 1  building 23 months | equipment 19 months

Competition 2  building 22 months | equipment 22 months
IBA lead over competition

Best IMPT System

<table>
<thead>
<tr>
<th>Features</th>
<th>Customer gain</th>
<th>IBA</th>
<th>Competitor 1</th>
<th>Competitor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beam availability</td>
<td>Best treatment quality</td>
<td>&lt; 1s</td>
<td>3s</td>
<td>5s</td>
</tr>
<tr>
<td>Room matching</td>
<td>Best treatment quality</td>
<td>&lt; 1%</td>
<td>&lt; 3%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Room switching time</td>
<td>Best throughput</td>
<td>&lt; 10s</td>
<td>&lt; 30s</td>
<td>&lt; 45s</td>
</tr>
<tr>
<td></td>
<td>Patient confort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum range</td>
<td>Best conformity</td>
<td>3,1g/cm²</td>
<td>4,1g/cm²</td>
<td>4,1g/cm²</td>
</tr>
<tr>
<td>Accessory management</td>
<td>Best conformity for shallow tumors</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>a) H&amp;N snout supported</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>b) Dual motion</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Beam gatting</td>
<td>Motion management</td>
<td>Yes</td>
<td>Mono</td>
<td>Unknown</td>
</tr>
<tr>
<td>a) Universal</td>
<td>Right solution for each patient</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>b) Inputs</td>
<td>(no compromise)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## IBA lead over competition

### Best Image Guided System

<table>
<thead>
<tr>
<th>Features</th>
<th>Customer gain</th>
<th>IBA</th>
<th>Competitor 1</th>
<th>Competitor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray direction VS beam direction</td>
<td>Best treatment quality, Best workflow</td>
<td>BEV</td>
<td>45°</td>
<td>45°</td>
</tr>
<tr>
<td>Orthogonal kV-kV</td>
<td>In combination with BEV, faster and better setup</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CBCT LFOV</td>
<td>Best imaging quality</td>
<td>50cm</td>
<td>38cm</td>
<td>38cm</td>
</tr>
<tr>
<td>CBCT longitudinal FOV</td>
<td>Best imaging quality</td>
<td>34cm</td>
<td>24cm</td>
<td>24cm</td>
</tr>
<tr>
<td>Virtual topogram</td>
<td>Guarantees proper imaging acquisition</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Sticky settings / window level prop.</td>
<td>Best workflow</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Beam gating for X-Ray</td>
<td>Best organ motion</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
## IBA lead over competition

### Best Workflow

<table>
<thead>
<tr>
<th>Features</th>
<th>Customer gain</th>
<th>IBA</th>
<th>Competitor 1</th>
<th>Competitor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambient experience solution</td>
<td>Reduced anesthesia for pediatrics, best throughput</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wireless hand pendant</td>
<td>More seamless operation, more freedom of movement, best throughput</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Beam eye view imaging</td>
<td>Most intuitive way for human to interpret patient images</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dual motion of accessory</td>
<td>Best throughput</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fast irradiation delivery</td>
<td>Patient confort</td>
<td>45s (high range)</td>
<td>60s (low range)</td>
<td>60s</td>
</tr>
<tr>
<td>Fast room switching</td>
<td>Patient confort</td>
<td>&lt; 10s</td>
<td>&lt; 30s</td>
<td>&lt; 45s</td>
</tr>
</tbody>
</table>
## Unique Value in the Industry

<table>
<thead>
<tr>
<th>Features</th>
<th>IBA</th>
<th>Competitor 1</th>
<th>Competitor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upgradeability</td>
<td>Proven at 10+ centers</td>
<td>No proven track record</td>
<td>No proven track record</td>
</tr>
<tr>
<td>Open architecture</td>
<td>Proven at 48 centers</td>
<td>Optimized for own SW only</td>
<td>Yes, limited experience</td>
</tr>
<tr>
<td>Experience</td>
<td>&gt; 30 years in Proton Therapy</td>
<td>Recently acquired technology</td>
<td>No worldwide experience</td>
</tr>
<tr>
<td>Size and depth of the service organization</td>
<td>&gt; 250 trained and certified service engineers in USA</td>
<td>Limited PT service organization</td>
<td>No worldwide experience</td>
</tr>
<tr>
<td>Motion management solutions</td>
<td>Multiple solutions in clinical use</td>
<td>Mono gating solution</td>
<td>Unknown</td>
</tr>
<tr>
<td>Imaging software</td>
<td>Designed to move in the future of Adaptive PT</td>
<td>Limited to image guidance</td>
<td>3rd party, limited to image guidance</td>
</tr>
<tr>
<td>Training program</td>
<td>First to offer comprehensive &amp; formal training; faster ramp up</td>
<td>Basic and limited</td>
<td>Limited</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Experience allows IBA to be first to offer advanced technology (prompt gamma, eye treatment, range verification, etc)</td>
<td>Limited focus on PT</td>
<td>Limited focus on PT</td>
</tr>
<tr>
<td>Gantry ocular solution</td>
<td>Innovative patent pending solution</td>
<td>Traditional solution under development</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dosimetry</td>
<td>In-house &amp; integrated to improve workflow efficiency</td>
<td>3rd party</td>
<td>3rd party</td>
</tr>
</tbody>
</table>

**Unique Value in the Industry**
The future of proton therapy
Largest and most experienced community in proton therapy
# IBA’s worldwide research collaboration

## North America
### Clinical partners
- Massachusetts General Hospital Burr Proton Therapy center [US]
- University of Florida Health Proton Therapy Institute [US]
- University of Pennsylvania Roberts Proton Therapy Center [US]
- Hampton University Proton Therapy Institute [US]
- Oklahoma Proton Treatment Center [US]
- Northwestern Medicine Chicago Proton Therapy Center [US]
- New Jersey Proton Treatment Center [US]
- Seattle Cancer Care Alliance Proton Therapy Center [US]
- Provision Center for Proton Therapy [US]
- Willis-Knighton Cancer Center [US]
- Texas Center for Proton Therapy [US]
- Beaumont Health System [US]
- Miami Cancer Institute – Baptist Health South Florida [US]

### Research partners
- Massachusetts General Hospital Burr Proton Therapy Center [US]
- University of Pennsylvania Roberts Proton Therapy Center [US]
- Massachusetts Institute of Technology [US]
- Northwestern Medicine Chicago Proton Therapy Center [US]
- Seattle Cancer Care Alliance Proton Therapy Center [US]
- Willis-Knighton Cancer Center [US]
- Texas Center for Proton Therapy [US]
- Beaumont Health System [US]
- Miami Cancer Institute – Baptist Health South Florida [US]
- MD Anderson Cancer Center [US]
- Memorial Sloan Kettering Cancer Center [US]
- Fermilab [US]

## Europe, Middle East, Africa
### Clinical partners
- Institut Curie [FR]
- Proton Therapy Center Czech [CZ]
- Westdeutsches Protonentherapiezentrum Essen [DE]
- AIPS Azienda Provinciale per i Servizi Sanitari [IT]
- Universitätsklinikum Carl Gustav Carus [DE]
- Bronowice Cyclotron Center (IFJPAN) [PL]
- Centre Léon Kollip [BE]
- Cyclotron – Cyclotron for Hadron Therapy [FR]
- Universitario Medico Centrum Groningen – UMC [NL]
- Universitario Ziekenhuis Luene[BE]
- Centre Oscar Lambret [FR]
- Universitario Medico Centrum Groningen – UMC [NL]
- Universitario Ziekenhuis Luene[BE]
- University College London Hospital [UK]
- University Catholique de Louvain [BE]
- Université Libre de Bruxelles [BE]
- University of Liege [BE]
- Erasmus Medisch Centrum [NL]
- Heidelberg Ion Therapy [DE]

### Research partners
- LMU [DE]
- MedAustron [AT]
- Paul Scherrer Institute [CH]
- CNAO [IT]
- INFN [IT]
- ...
The future of proton therapy

- Irradiation in one breath hold
- Volumetric imaging for replanning
- Eye treatment in a Gantry
- On-Line QA
- On-Line adaptive
The future of personalized precision

- Log-based patient QA
- Virtual CT
- Prompt Gamma
- Proton Radiography
- MR Guided Proton Therapy
- Automated re-planning
- Fast Irradiation
- Motion Reduction
- Online adaptive workflow
- Others

Anatomical changes
Range uncertainties
Moving targets
Lung
H&N
Breast
Pediatrics

Others
API based architecture to be fast and flexible

Treatment Session Manager manages adaptive workflows in the PT treatment room
Strong worldwide pipeline

654 Leads

100 Qualified leads

50 Closing (24 months)

IBA global leads

PERSPECTIVE ON RADIATION THERAPY PATIENTS RECEIVING PROTON THERAPY AS PART OF THEIR TREATMENT

1% Today

20% Following reports & policies

45% Following clients’ experiences
Our strategy is to create a virtuous circle in PT

- Enhance market penetration
- Develop regionalization
- Leverage partnership

- Invest in clinical affairs initiatives
- Focus on product roadmap

- Increase clinical relevance
- Reduce cost of modality
The role on proton therapy in oncology
Andrew K. Lee, MD, MPH, Medical Director, Texas Center for Proton Therapy
The role of proton therapy in oncology and future evolution

Andrew K. Lee, M.D., MPH
Medical Director
Texas Center for Proton Therapy
Clinical benefits of proton therapy

- Higher radiation doses to tumor
- Minimizes dose to normal tissues
- Better tumor control
- Decreased side effects: early and late
- Preserve organ function
- Better tolerance of multi-modality therapy
  e.g. Chemotherapy and/or surgery

“One cannot have a radiation-induced side effect in tissue that receives no radiation.”
What cases to consider for protons therapy?

- Pediatric
- Adults w/ projected longevity >20 years

- Primary CNS
  - Skull base
  - Para-nasal sinus
  - Nasopharynx
  - Oropharynx (especially younger HPV+)

- Left-sided breast + lymphatics
- Anterior/Posterior mediastinum
- Lymphoma
- NSCLC (stage II-III, non-operative)
- Distal esophagus (definitive, preop)
- Liver

- Prostate
- Recurrent rectal
- Sarcomas
Proton Rx: Advances and future directions

Pencil beam scanning
Intensity modulated proton therapy
Better treatment planning software
PBS with apertures for sharper edges
Smaller (and less expensive) proton units
On-board volumetric imaging (CBCT)
Advances in technology have expanded clinical indications
Increased utilization of SBRT/Hypofxn regimens with x-rays will benefit particle therapy
More protons users have resulted in increased advocacy

** Better CT imaging would be cost-effective method to improve proton therapy
How are protons different from X-rays?
Proton is hydrogen atom without electron (Heavy particle)
Protons are **accelerated** to almost light speed for treatment

Hyper-speed protons are used like “smart bullets” to kill cancer cells.
Key components

**Cyclotron**
Using electric fields, the cyclotron can accelerate hydrogen protons to two-thirds the speed of light.

**Electromagnets**
Magnets focus and steer proton beam to gantries.

**Gantry**
Giant gantries provide the beam pathway to treatment nozzle, utilizing series of steering and focusing magnets.
Diameter ~ 33 feet
Weight > 100 tons

(equivalent to Boeing 757 with passengers and cargo)
What patient sees

- Robotic couch
- Snout
- Nozzle
- kV imagers
  IGRT, CBCT
- Screens
- Pendant

TExAS CENTER for PROTON THERAPY
Single room units are a fraction of cost of multi-room centers but… Typically partial gantries & not as cost-effective if > 2 rooms
X-rays pass through tissue. Protons STOP
X-RAYS

Tumor

Exit dose

PROTONS

NO Exit dose

Exit dose

NO exit dose

100% dose

40% dose
Medulloblastoma

Exit dose $\sim 50\%$

No exit dose

X-rays

Protons
IMRT or Protons?
Or Gamma Knife
Or Cyber Knife
Or Tomo Therapy
Or True Beam

All X-rays
IMRT vs. Protons:
Maximize tumor dose **conformity** and **minimize** normal tissue exposure
Prostate cancer

*25 Gy (25 Sv) of Unnecessary Radiation =*

<table>
<thead>
<tr>
<th>IMRT</th>
<th>Protons</th>
<th>Unnecessary radiation with IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="IMRT Image" /></td>
<td><img src="image2" alt="Protons Image" /></td>
<td><img src="image3" alt="Unnecessary Radiation Image" /></td>
</tr>
</tbody>
</table>

- **2,500** Pelvic CTs
  - (10 mSv)
- **20,833** Pelvic X-Rays
  - (1.2 mSv)
- **25,000x** General Public Annual Limit
  - (1.0 mSv)
- **1.83x** Additional Cancer Risk*
  - (CTs, 65 yo)

*Source: Matt Palmer*  
*http://www.xrayrisk.com/calculator/calculator-normal-studies.php*
Longer waits result in more second cancers

<table>
<thead>
<tr>
<th></th>
<th>Latency 5-9 years</th>
<th>Latency 10-14 years</th>
<th>Latency ≥15 years</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/pharynx</td>
<td>1.12 (0.99 to 1.27)</td>
<td>1.14 (0.95 to 1.38)</td>
<td>0.95 (0.74 to 1.22)</td>
<td>0.34</td>
</tr>
<tr>
<td>Rectum*</td>
<td>1.13 (0.94 to 1.35)</td>
<td>1.33 (1.03 to 1.70)</td>
<td>0.91 (0.64 to 1.27)</td>
<td>0.54</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.57 (1.08 to 2.36)</td>
<td>1.04 (0.66 to 1.70)</td>
<td>1.29 (0.75 to 2.30)</td>
<td>0.45</td>
</tr>
<tr>
<td>Lung (non-small cell)</td>
<td>1.12 (0.98 to 1.27)</td>
<td>1.37 (1.12 to 1.65)</td>
<td>1.62 (1.23 to 2.09)</td>
<td>0.0079</td>
</tr>
<tr>
<td>Female breast</td>
<td>1.17 (1.05 to 1.30)</td>
<td>1.42 (1.24 to 1.62)</td>
<td>1.56 (1.34 to 1.81)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Cervix (external beam)*</td>
<td>1.18 (0.79 to 1.75)</td>
<td>1.55 (1.00 to 2.40)</td>
<td>2.59 (1.84 to 3.68)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Endometrium (external beam)*</td>
<td>1.30 (1.08 to 1.56)</td>
<td>1.99 (1.60 to 2.47)</td>
<td>2.18 (1.78 to 2.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prostate (external beam)*</td>
<td>1.39 (1.29 to 1.50)</td>
<td>1.59 (1.41 to 1.80)</td>
<td>1.91 (1.53 to 2.38)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Thyroid*</td>
<td>0.89 (0.49 to 1.55)</td>
<td>1.03 (0.47 to 2.14)</td>
<td>1.21 (0.64 to 2.17)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Relative risk of second cancer at 10-14 years = 1.6, at 15 years RR = 1.9

Source: de Gonzalez et al., Lancet Oncol, Mar 2011
Types of proton therapy delivery

- Passive scattered (most common)
- Spot-scanning (pencil-beam scanning)
- Intensity modulated proton therapy (IMPT)
Spot scanning (pencil-beam scanning)
“Conventional” proton therapy (Right lateral beam’s eye view)
The pencil-beam scanning mode of proton beam delivery

Proton therapy in 1980’s vs. Modern era

**FIG. 1.** Sagittal CT reconstruction shows perineal proton boost technique and how beam high dose region incorporates prostate, prostatic urethra and bladder neck.
Any randomized trials between IMRT vs. Protons should be done with PBS (IMPT)

<table>
<thead>
<tr>
<th></th>
<th>2 D X-rays</th>
<th>3 D X-rays</th>
<th>IMRT</th>
<th>CONVENTIONAL PROTONS (Passive-scattered)</th>
<th>IMPT - Intensity modulated proton therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformity</td>
<td>+</td>
<td>++</td>
<td>++++</td>
<td>+++1/2</td>
<td>++++</td>
</tr>
<tr>
<td>Normal tissue exposure</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Highly conformal but less tissue exposure
Beyond tumor sites like CNS & HN, how can pencil beam scanning proton therapy (IMPT) expand the clinical utility of proton therapy?
Breast + lymph nodes w/ pencil-beam proton therapy
For breast cancer, linear risk of coronary events…
7.4% increase per mean Gy to heart

Darby et al. NEJM 2013;368.
Proton therapy for lung cancer represents particular challenge (e.g. moving target, density changes, etc)

PROTON ADVANCES IN LUNG CANCER

Better target delineation

Management of respiratory motion

On-board image guidance (CBCT)

Better treatment planning techniques

Better delivery techniques

Understanding importance of heart dose
Anterior tumors (e.g. lung, thymoma, lymphoma)
Protons can keep dose anteriorly
Same risk for Hodgkin lymphoma survivors

F. Van Nimwegen et al. J Clin Oncol 2015;34
As systemic therapy improves, so must local-regional Rx...Case example: Advanced NSCLC

- 59 yo woman w/ stage IIIB NSCLC (T1N3, ALK +)
- RLL primary with extensive bilateral mediastinal, hilar, S/C disease
- Neoadjuvant chemoRx and crizotinib
- Good metabolic response but gross residual disease
- Plan for consolidative chemo-XRT
Axial Comparison

The Proton plan spares more normal LUNG than the IMRT plan.
Coronal Comparison

Protons

Photons (IMRT)

Dark Blue
Yellow
Gold

60 GyE
30 GyE
15 GyE
RTOG 0617
Overall survival multivariable analysis
Heart dose was independent factor

Supplemental Table 2. Multivariable Cox model for overall survival*

<table>
<thead>
<tr>
<th>Co-variates</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT technique</td>
<td>3D-CRT (RL) vs. IMRT</td>
<td>1.05 (0.83, 1.34)</td>
<td>0.682</td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>1.012 (0.999, 1.026)</td>
<td>0.08</td>
</tr>
<tr>
<td>% of PTV covered by 100% of Rx dose</td>
<td>Continuous</td>
<td>0.996 (0.992, 1.001)</td>
<td>0.107</td>
</tr>
<tr>
<td>Heart V40</td>
<td>Continuous</td>
<td>1.012 (1.005, 1.02)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Site accrual volume</td>
<td>Low volume (RL) vs. high volume</td>
<td>0.75 (0.59, 0.96)</td>
<td>0.021</td>
</tr>
<tr>
<td>PET-staging</td>
<td>No (RL) vs. yes</td>
<td>0.78 (0.54, 1.15)</td>
<td>0.207</td>
</tr>
</tbody>
</table>

Potential to improve survival with particle therapy by reducing cardiac doses

Courtesy of Dr. Stephen Chun. J Clin Oncol 34, 2016
Lymphopenia Association With Gross Tumor Volume and Lung V5 and Its Effects on Non-Small Cell Lung Cancer Patient Outcomes

Chad Tang, MD, MS, Zhongxing Liao, MD, Daniel Gomez, MD, Lawrence Levy, MS, Yan Zhuang, MD, Rediet A. Gebremichael, BS, David S. Hong, MD, Ritsuko Komaki, MD, and James W. Welsh, MD

Graph showing the relationship between absolute lymphocyte count and date from RT start.
Esophageal Cancer
Improved perioperative pulmonary complications with proton therapy

- **444 patients who had surgery after CRT**
- **3D** (n=208, 1998-2008); **IMRT** (N=164, 2004-2011), and **PBT** (n=72, 2006-2011)
- Evaluated Pulmonary, GI, cardiac, wound healing within 30 days of surgery

- **Pulmonary complications** (ARDS, pleural effusion, RI, PNA) most predictive based on radiation type
  - **IMRT vs 3D** (OR 0.50, 95% CI 0.27-0.91)
  - **PBT vs 3D** (OR 0.32, 95%CI 0.14-0.73)
  - **IMRT vs PBT** (OR 1.56, 95%CI 0.68-3.60)

Value of proton therapy in esophageal cancer

Protons reduces average hospital stay by > 2 days and max hospital days

Mean Length of Hospital Stay 2007-2013

- PBT: n=111, 9.3 days (95%CI 8.2-10.3)
- IMRT: n=252, 11.6 days (95%CI 10.9-12.7)
- 3D: n=214, 13.2 days (95%CI 11.7-14.7)

Source: Lin SH et al., ASTRO 2015
Proton Therapy (IMPT)  
X-Ray Therapy (IMRT)  
Added Radiation with X-Rays
Value Proposition - Head and Neck Cancer

Cumulative Cost of Care During Radiation Therapy

Equivalent at 21 Days

Number of patient treatments

Cumulative cost

Protons
IMRT

Protons just 6% more at end
IMRT loses 3x more body weight
Re-planning due to weight loss
Feeding tube

Thaker N et al. Oncology Payers 2014
What is “new” in proton therapy?

- Proton therapy has improved as technology has advanced (just like X-ray therapy)
- Imaging (OBI and CBCT)
- Treatment planning (software)
- Treatment delivery systems
- Intensity modulation
- Immobilization
THANK YOU

Andrew.Lee@USOncology.com
TexasCenterForProtonTherapy.com
Development of a state-of-the-art proton therapy center
Craig W. Stevens, MD, PhD, Chair of Radiation Oncology, Beaumont Health System
Beaumont Proton Therapy Center

Craig W. Stevens, M.D., Ph.D.
Professor and Chair
Department of Radiation Oncology
Thanks!

• IBA

• Team at Beaumont
  – Too many people to count but
  – Xuanfeng Ding, PhD
  – Peyman Kabolizadeh, MD PhD
  – Tom Lanni
  – Patti Cardoze
Summary

• We successfully installed and commissioned the first proton center in MI
• We met critical C.O.N. timeline requirements
• This allowed us to
  – Treat the first proton patient in MI
  – Increase our overall consults by almost 10%
  – Treat the first pediatric patient with protons in MI
• Impossible without STRONG commitment from IBA
Beaumont Proton Therapy Center
Physics of Proton Therapy

- Photons

- Protons
Disease sites

Less integral dose

Head, Neck and Brain

Lung

Prostate
For Pediatric patient

Photon VMAT

Proton PBS
Beaumont Journey

• Initial plan for Proton Center dates from ~2007
  – The 5 room plan was tabled due to the financial crisis
• When I was being recruited to Beaumont in 2013, PTC was reintroduced.
• Board approval in January of 2014
• CON requirements were daunting
  – CON commission had NEVER overseen the construction of a successful center
  – Penalties could be severe if we failed
CON Requirements

Red: C.O.N. Requirement Dates
Black: Completed Milestones
Grey: Design and Construction
Green: IBA Target Dates

- IBA Term Sheet Signed 15-Aug-14
- IBA Contract Signed 7-Nov-14
- Construction Start 7-Jan-15
- 1-Oct-14
- 1-Jan-15
- 1-Apr-15
- 1-Jul-15
- 1-Oct-15
- 1-Jan-16
- 1-Apr-16
- 1-Jul-16
- 1-Oct-16
- 1-Jan-17
- 1-Apr-17
- 1-Jul-17
- Install Equipment Complete 28-May-17
- FIRST PATIENT 9-Jun-17
- FIRST PATIENT 11-Jul-17
- IDB Received 18-Aug-14
- IBA CONTRACT SIGNED 19-Nov-14
- CONSTRUCTION CONTRACT EXECUTED 19-May-15
- CONSTRUCTION START 19-Nov-15
- INSTALL EQUIPMENT (to include technical commissioning) 19-Nov-16
- COMMENCEMENT OF TREATMENT 9-Mar-17
- Building Complete 8/4/2016
- Equipment Ship from Belgium 13-Mar-16
- Cyclotron Delivery 25-May-16
- BOD 29-Apr-16
- Install Equipment Complete 4/28/2017
- First Patient 11-Jul-17
Beaumont Journey

• Request for Proposals Drafted
  – With help from Proton International
  – IMPT, CBCT, FDA approved, install by March 2017

• Sent to 7 vendors
  – 6 responded

• Three vendors were chosen for site visit
  – One couldn’t deliver IMPT
  – One had a compact cyclotron that would reduce the cost of construction and operations so…….

• IBA was selected July 2014
Beaumont Journey

• In November 2016, clear we would miss the last two milestones
  – One because it was never reasonable
  – One because of weather and other construction delays
• We restated the time line with a plan to treat the first patient by June 30, 2017
Beaumont Journey

• In February 2017, the schedule slipped again
• We reached out to IBA and other partners to develop an aggressive new schedule
• Plan for first patient to be a patient with a brain tumor
Collaborate and synchronize the team schedule

- Combine the beam data acquisition procedure with acceptance test (IBA & Beaumont)
  - Lock beam optics settings
- Beam modeling and validations (Beaumont & RaySearch America & Sweden)
  - Dry run with current data format
  - Communicate with the RaySearch team
- Mosiaq integration and on-site therapist training
  - Address the bugs and workflow issues
- Independent Physics Check/IROC TLD check
  - Dr. Gao from Chicago Proton Center
  - IROC team (Beaumont commission and treatment schedule)
- Took 16 week process and condensed it to 7
Beaumont Commissioning Timeline

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
</table>
|      | - Beam Optics Acceptance  
     - Beam Data Acquisition  
     (Double shifts)          | - Imaging Acceptance  
     - Safety Acceptance  
     - Patient position system  
     - Beam Modeling          | - Beam Model Validation  
     - OIS/TPS Integration  
     - Quality Assurance  
     - IROC TLD check  
     (Double shifts)          | - Therapist training  
     - End to End test  
     - Treatment protocol  
     - Independent Physics check |

Ding et al. NA-PTCOG 2017
Protons
Beaumont Proton Therapy Center

100 tons

4,131 miles by sea

190 feet

5,300 cubic yards concrete

10,500 cubic yards sand & stone
ProteusONE treatment room

- 220 degree Compact Gantry
- Superconducting Synchrocyclotron
- Stereotactic imaging system
  And CBCT
- Pencil Beam Scanning Technique
- Phillips Ambience light system
- 6 degree robotic couch
- Rolling floor
Treatment Room

Exam Room

Lobby
Protons

• Our center has IMPT and 3 options for daily imaging
  – Very precise delivery of dose to tumor
  – Reduce uncertainties, and so reduce the target volume
  – This further reduces normal tissue doses

  – Better dose to tumor with less side effects!!!

• Pediatric Oncology relocated to second floor of PTC
  – More than doubles space for pediatrics
Proton Center 1st Patient Treatment
June 28, 2017
Treatment mix

Case Mix - In Treatment

- Astrocytoma
- Brain
- Breast-LT
- Breast-RT
- Colon CA
- Cholangiocarcinoma
- Chordoma
- CNS
- Fibrosarcoma
- Glioblastoma
- Glioma
- Head & Neck
- Hemangioma
- Hodgkins
- Liposarcoma
- Liver
- Lung CA
- Meningioma
- Parotid/Thyroid
- Prostate
- Synovial Sarcoma
- Thymoma
• CNS – done
• Tumors with stable soft tissue component - done
  – Sarcomas
  – Prostate
• Tumors without stable soft tissue component – mostly done
  – Immobile lung cancers- done
  – Chest wall – almost done
  – H&N – almost done
• Anesthesia – November
• Mobile tumors - ~November
• Eyes - 2020
During this time we also

- Dr. Ding has developed a process for rotational IMPT with PBS
  - SParc
- Developed a sponsored research program with IBA
- Submitted R03 for technology development
- Published extensively
- Developed and opened a Patient Access Center to facilitate referrals and coordinate care
- Enhanced authorization and billing process
  - Only one patient ultimately failed authorization
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Questions?
North American Market Dynamics
Beth Klein - Executive Vice President, IBA North America
PT market dynamics in North America

Softer near term market
Chapter 11 concerns
Reimbursement/Payor uncertainties still exist
Competitive dynamics resulting in more aggressive pricing

NA predicted to grow to 46 centers by 2020
More centers opening, strong pipeline
Wider acceptance of PT, NCCN / ASTRO guidelines
The Alliance for Proton Therapy Access good efforts educating patients/payer's
Canada looking to establish PT presence
Lower entry barriers due to compact proton therapy
Mature technology, expanding clinical indications (PBS, CBCT,…)
Strong IBA North America market leadership position

Share of installed base in NA in rooms

- IBA: 45%
- Varian: 23%
- Hitachi: 21%
- Mevion: 7%
- Protom: 4%
Newest additions to IBA’s league of PT experts

INOVA

Miami Cancer Institute

UFHealth

Beaumont Health

Texas Center for Proton Therapy
Proton Therapy functions co-located in Reston:

- Sales & Marketing
- Sales support
- Product specialists
- Project management
- Install seams
- Service delivery
- Operations
- Finance
- EHS, Legal, Information Technology

>250 PT Experts focused on serving our Customers better and faster!
Value of IBA’s experience

- Clinical Impact
- Security of Investment
- Fastest Throughput
- 98% Availability
- Proven Upgradability
- 30+ Years
- Fastest Install/Ramp-up
- Smooth Operation
- Improved ROI

- Improved ROI
IBA’s unique value in the industry

<table>
<thead>
<tr>
<th>Features</th>
<th>IBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upgradeability</td>
<td>Proven at 10+ centers</td>
</tr>
<tr>
<td>Open architecture</td>
<td>Proven at 48 centers</td>
</tr>
<tr>
<td>Experience</td>
<td>&gt; 30 years in Proton Therapy</td>
</tr>
<tr>
<td>Size and depth of the service organization</td>
<td>&gt; 250 trained and certified service engineers in USA</td>
</tr>
<tr>
<td>Motion management solutions</td>
<td>Multiple solutions in clinical use</td>
</tr>
<tr>
<td>Imaging software</td>
<td>Designed to move in the future of Adaptive PT</td>
</tr>
<tr>
<td>Training program</td>
<td>First to offer comprehensive &amp; formal training; faster ramp up</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Experience allows IBA to be first to offer advanced technology (prompt gamma, eye treatment, range verification, etc)</td>
</tr>
<tr>
<td>Dosimetry</td>
<td>In-house &amp; integrated to improve workflow efficiency</td>
</tr>
</tbody>
</table>
Conclusion
Olivier Legrain, Chief Executive Officer, IBA
Conclusion

- Strong perspectives for the proton therapy market
  - Growing acceptance of proton therapy
    - Increasing amount of scientific data
    - Recent update of ASTRO and NCCN guidelines
  - Strong pipeline

- IBA technological lead over competition
  - IBA world-class innovative proton therapy solutions
  - Strong partnerships
  - IBA experience in installing equipment clearly established
Question and Answer