



# Physics and Medicine: the present and the future of Theragnostics

Conférence publique MEDICIS-Promed



Stefano Buono  
Advisor to Advanced Accelerator Applications, a Novartis Company  
March 14, 2018

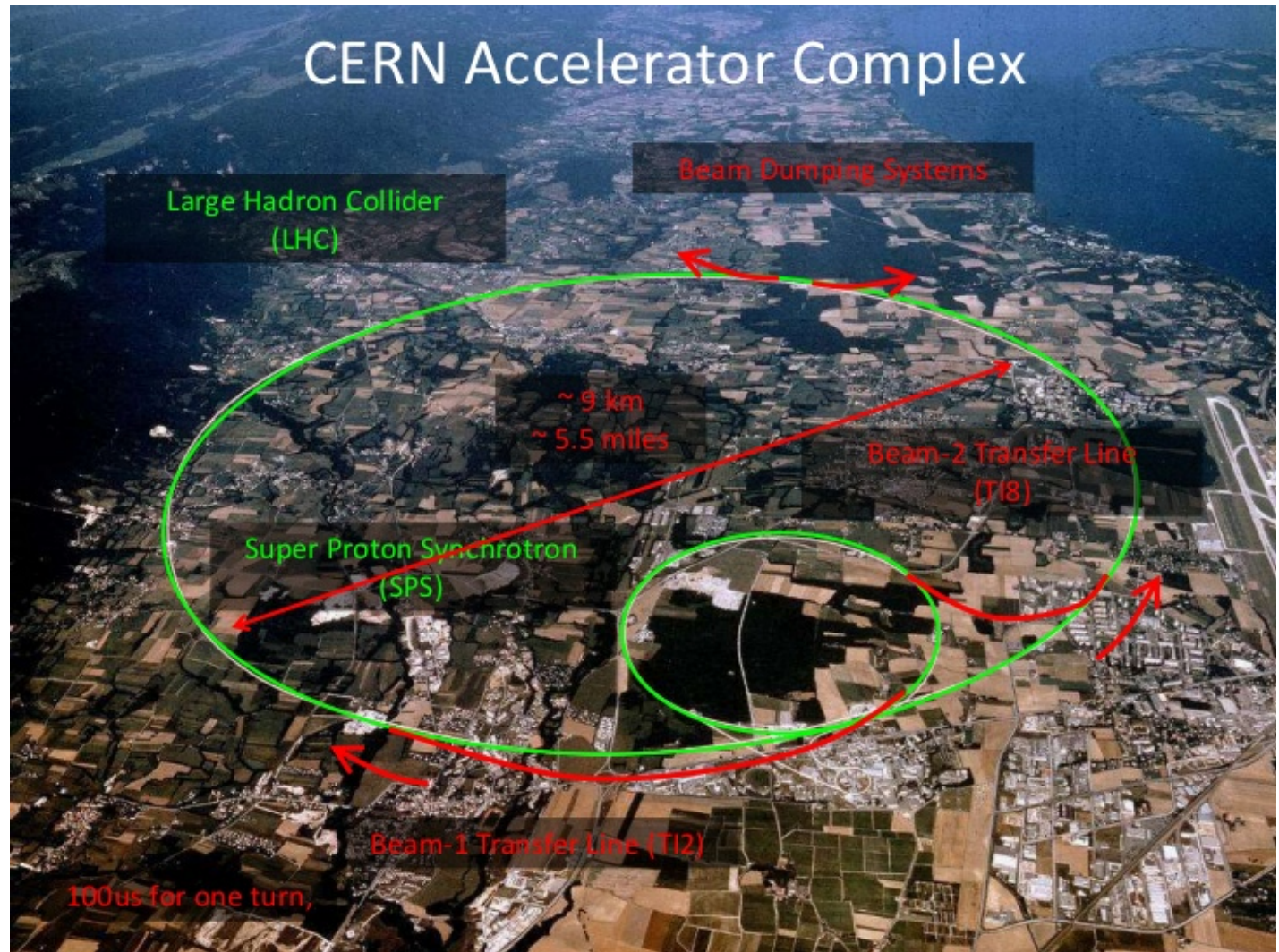


## Advanced Accelerator Applications: a Pioneer in Molecular Nuclear Medicine Theragnostics

- Advanced Accelerator Applications (AAA) is a radiopharmaceutical company founded by Stefano Buono in 2002 in France and acquired by Novartis on 19th January 2018 for €3.9b. In this period the company:
  - Registered 8 diagnostic drugs and one therapeutic drug
  - Registered first ever radiopharmaceutical theragnostic pairing for oncology based on radiolabeling of single targeting molecule with different radioisotopes for diagnosis (Ga-68) and therapy (Lu-177)
  - Established or acquired state-of-the-art manufacturing in 20 locations across 8 countries in Europe, the US, and Israel
  - Grew to over 630 employees in 13 countries (Belgium, Canada, France, Germany, Italy, Israel, The Netherlands, Poland, Portugal, Switzerland, Spain, UK & USA)
  - Completed 13 acquisitions (out of almost 200 Business Development opportunities analyzed), and reached €150m in sales prior to the launch of its first therapeutic
  - Listed on NASDAQ in November 2015; price appreciated over 300% from \$16 IPO to \$65 in September 2017 (prior to rumors of Novartis acquisition), with a take out price of \$82 per ADS



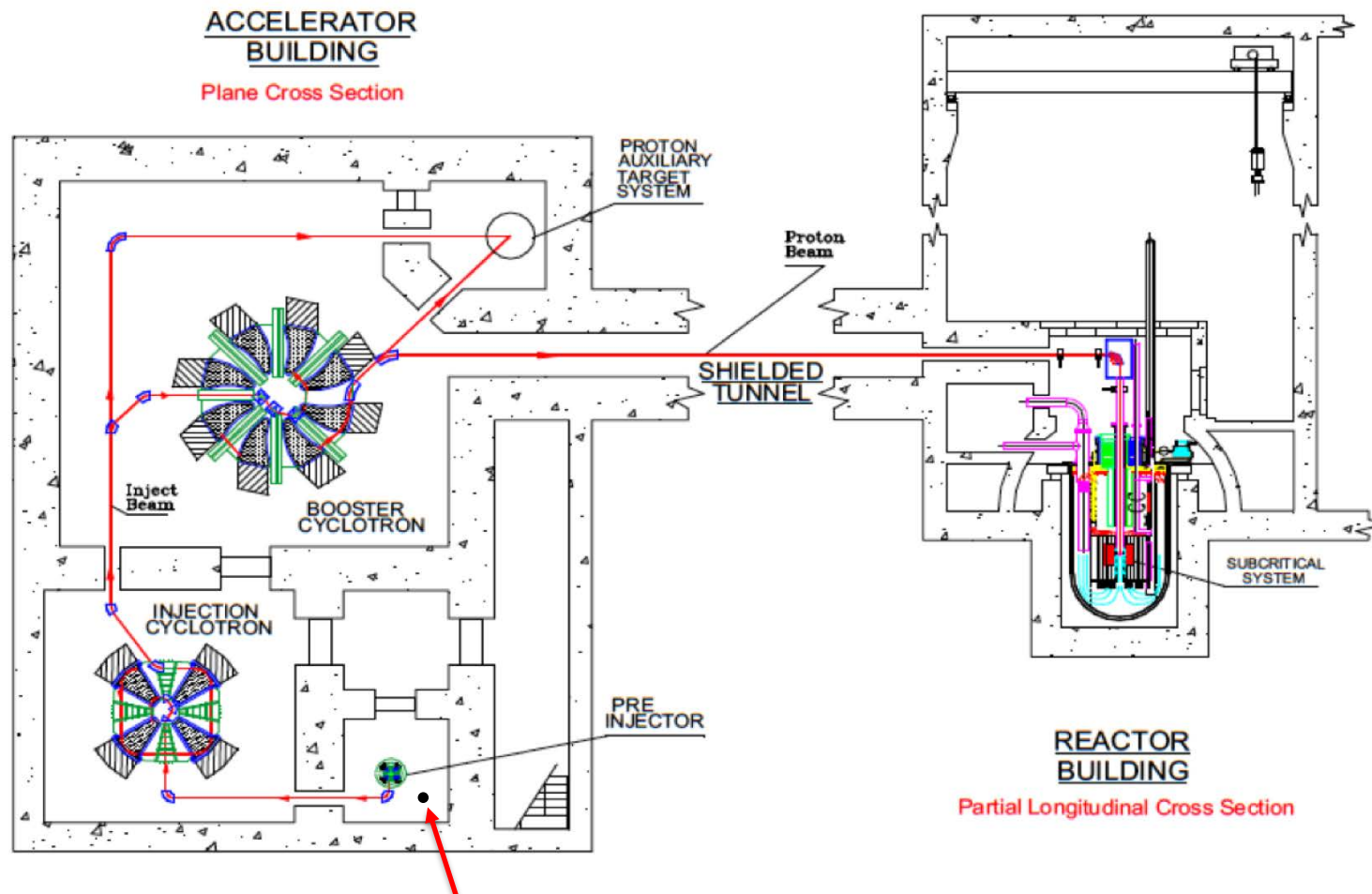
# The AAA journey started in 2002 at the European Center for Nuclear Research (CERN)



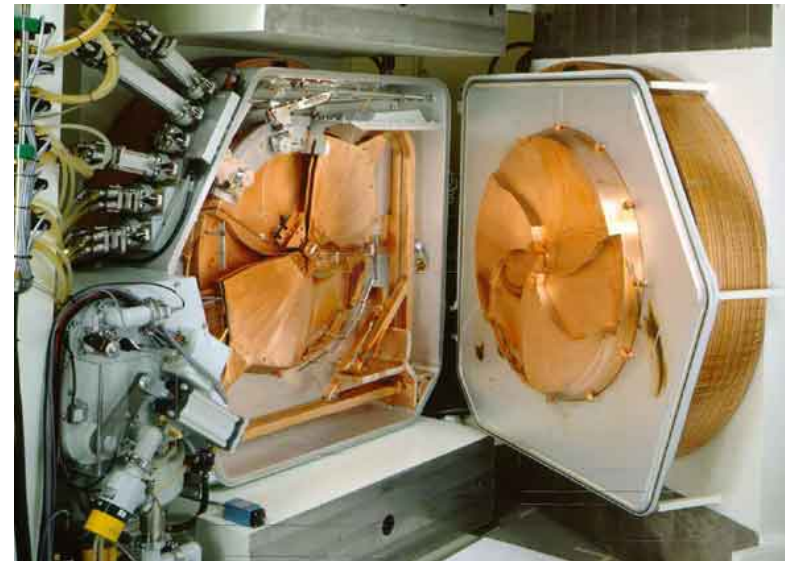
# I was searching for applications for particle accelerators



- This is the reason for the company name: **“Advanced Accelerator Applications”**
- This was my first project: an “Energy Amplifier”
- Energy seemed complicated to start...



## Much smaller commercial particle accelerators could produce short lived radioactive isotopes



# The original AAA business plan: thinking about applications of radioactivity

12 New York Tribune November 10, 1918

## Radium and Beauty

**HERE** are the first toilet preparations to embody Actual Radium, an astonishing new force for betterment, applied as an aid to Beauty. Learn how the amazing Energy of Radium has proved a boon to the human skin. Learn what Radium actually means to Beauty and how its power is employed in "Radium" Preparations. Study our \$5,000 guarantee. Then turn to "Radium" Toilet Requisites. When you have used, enjoyed and tested them you will adopt them as your own first aid to Beauty.

**PREHISTORIC** woman first discovered her image in some quiet jungle pool. Ever since Beauty has engaged the world's attention. Radium, though new to the world, is no less of abiding interest. Its marvels have amazed and thrilled us all. Who would have imagined that these two subjects would some day go hand in hand? Yet, in Radium, Science has discovered a revolutionary Beauty Secret.

Current health and Radioactivity. Any number of them are in any public library. They will show you that Radium possesses no more power for human betterment.

The finest particle of Radium throws, off a continuous stream of Energy Rays. An Energy wave diminishes every second, day or night, year in, year out. A force a million times more powerful than any other force.

These Radium Rays are particularly valuable in their uses on the human skin. Dr. Louis Wickham and Dr. Eugene specialists in the St. Louis and the St. Louis Hospital of Paris, have proved what Radium will do for even the most devoted skin disease.

Rays of Radium, in fact, energize and revitalize any living matter with which they come in contact. They are accepted by the human system so harmoniously as to be sought by the plant.

The wonderful force for betterment has now been embodied in "Radium" Toilet Requisites, thus placing the power of Radium at the command of every woman who uses a face cream or powder, hair tonic, or soap.

"Radium" Toilet Requisites are delightfully delectable and delicious. They have a exquisite and exclusive fragrance all their own, a perfume not for sale in any market. They are the first and only preparations for the toilet to contain Actual Radium—Nature's greatest aid to Beauty.

Every "Radium" Preparation is guaranteed, under \$5,000 penalty, to contain a definite amount of Actual Radium, and to retain its Radioactivity for at least twenty years. See Guarantee above.

In England, "Radium" Preparations are a source of several years' standing. They are used by most women of title and fashion. They are the rage in the leading shops.

We present them to the United States as the greatest boon ever offered—to those who value perfection of complexion, rounded, youthful facial outlines; a healthy skin and beautiful hair.

Each and every "Radium" Beauty Aid is the formula of a famous Parisian specialist. Entirely made from Radium, you would choose "Radium" Preparations for themselves alone—for the silky smoothness of the cream—the impalpable fineness of the powder and the tantalizing, haunting fragrance.

When in the perfection as toilet preparations, is added the power of Actual Radium, the highest level of Beauty Culture is reached.

From velocity "Radium" Face Powder is hailed as "Radium" Skin Soap—our delighted "Radium" Face Powder is wonderful "Radium" Hair Tonic, "Radium" Toilet Requisites all contain actual Radium for Beauty's sake.

Space does not permit us to go into further details, but there are further facts concerning Radium and Beauty which every woman should know. They are contained in our booklet sent free on request.

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**Write Today for This Vitaly Interesting Booklet**



This is probably the most revolutionary booklet on the subject of Beauty ever published. You who have imagined that all had been done for Beauty which could be done should now be time in availing yourself of this "new knowledge." Investigate the subject of "Radium and Beauty."

The booklet is written from the book "Radium—Its Discovery and Power," by C. A. J. Any, one hundred and twenty thousand copies of which have been distributed in England. It is given with our compliments. To secure your copy before our first edition is exhausted, mail the coupon NOW.

RADIUM CO., LTD., of LONDON,  
235 Fifth Ave., New York.

Enclosure: Please mail me a copy of your booklet, "Radium and Beauty." I understand that this request places no burden or obligation upon me.

Name .....

Address .....

RADIUM TOILET REQUISITES OBTAINABLE AT  
Leading Department Stores of  
New York, Brooklyn and Newark  
and  
Liggett's Drug Stores

## Radium Toilet Requisites

Sole Manufacturers  
**Radium Co., Ltd., of London**  
235 Fifth Avenue, New York 167 Oxford St., London, W. 1.

If your Dealer cannot supply you communicate with us.

### Radium Toilet Requisites

"Radium" Toilet Requisites are necessarily higher in price. This must be expected in preparations containing the finest ingredients only, plus a definite quantity of Actual Radium. But the greater benefits obtained from "Radium" Preparations would justify an even higher price. The best is always the cheapest and goes further.

It is easy to prove the superiority of "Radium" Preparations. Try them. See how smoothly the Vanishing Cream rubs in.

Notice how your complexion improves with "Radium" Peau de Voleur (night cream).

See how imperceptibly the face powder blends with the skin. How smoothly it adheres. Appreciate the soothing comfort of the Talc. Note the effects produced by the Hair Tonic.

Enjoy the fit, elegant, elusive fragrance.

Remember that each preparation has the power to work for betterment—the power of Actual Radium. It is easy to apply these tests.


Purchase "Radium" Toilet Requisites at any of the leading department and drug stores. If you are not delighted with them, communicate with us and we will see that your money is refunded.



Radium Articles	
1 Peau de Voleur (Night Cream)	52
2 Soap (Compound)	51
3 Cream (Compound)	51
4 Vanishing Cream	51
5 Hair Tonic	51
6 Face Powder	51
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9 Face Powder	51
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11 Face Powder	52
12 Face Powder	52
13 Face Powder	52
14 Face Powder	52
15 Face Powder	52

## Cosmetics?

Perhaps this inspired  
Bayer's pipeline based on  
Thorium after it's first  
Radium drug: Xofigo ?



**LE RADIUM**  
AU SERVICE DE  
**LA BEAUTÉ**

●

**CRÈME**  
EMBELLISSANTE  
PARCE QUE  
**CURATIVE**


**THO-RADIA**

A BASE DE THORIUM ET DE RADIUM  
FORMULE DU D<sup>r</sup> ALFRED CURIE

Active la circulation  
raffermit les tissus  
élimine la graisse  
empêche la déformation  
des pores, prévient et  
supprime les rides.

CHEZ LES PHARMACIENS  
EXCLUSIVEMENT

Le Tube: 10 fr.  
Le Pot: 15 fr.



**guérit les brûlures du soleil**

Brochure gratuite sur demande à SECOR (Service 73) 20, Rue des Capucines - PARIS





Orthopedics?



Une saine et douce chaleur,  
**radio-active...**

Publ. André Hirsch - Paris

Une laine, souple, élastique, résistante, épaisse et confortable, qu'un traitement physico-chimique a doué d'un remarquable pouvoir : la radio-activité. Chacun connaît les extraordinaires effets de stimulation organique, d'excitation cellulaire, transmis par le radium. Une laine ainsi traitée allie aux avantages propres du textile une indéniable valeur hygiénique. Pour tricoter la layette de Bébé, les lainages des enfants, vos sous-vêtements et vos pull-over, utilisez la

# LAINÉ ORADIUM

Source précieuse de chaleur et d'énergie vitale, irrétrécissable, infeufrable. C'est un Produit de la LAINE MÉDICALE, 20, rue St-Georges, PARIS - Trud. 07-28

La LAINE ORADIUM est vendue chez votre pharmacien au prix imposé de frs : 8.50 la pelote de 50 grammes.

DEMANDEZ LA BROCHURE ET LA CARTE DES COLORIS

*Si votre pharmacien habituel n'est pas encore approvisionné ou n'a pas en stock le coloris que vous désirez, veuillez nous en aviser en nous donnant son adresse et nous nous ferons un plaisir de vous faire parvenir les pelotes de LAINE ORADIUM par son intermédiaire.*



## Reproductive technology? Nuclear medicine's answer to Viagra

**NEW ENERGY FOR WEAK,  
SAGGING MEN**



*Front View—Showing full, comfortable leg that entirely encloses and supports the scrotum. Wide, adjustable, comfortable tapes that hold suspensory in position with no chance for discomfort.*

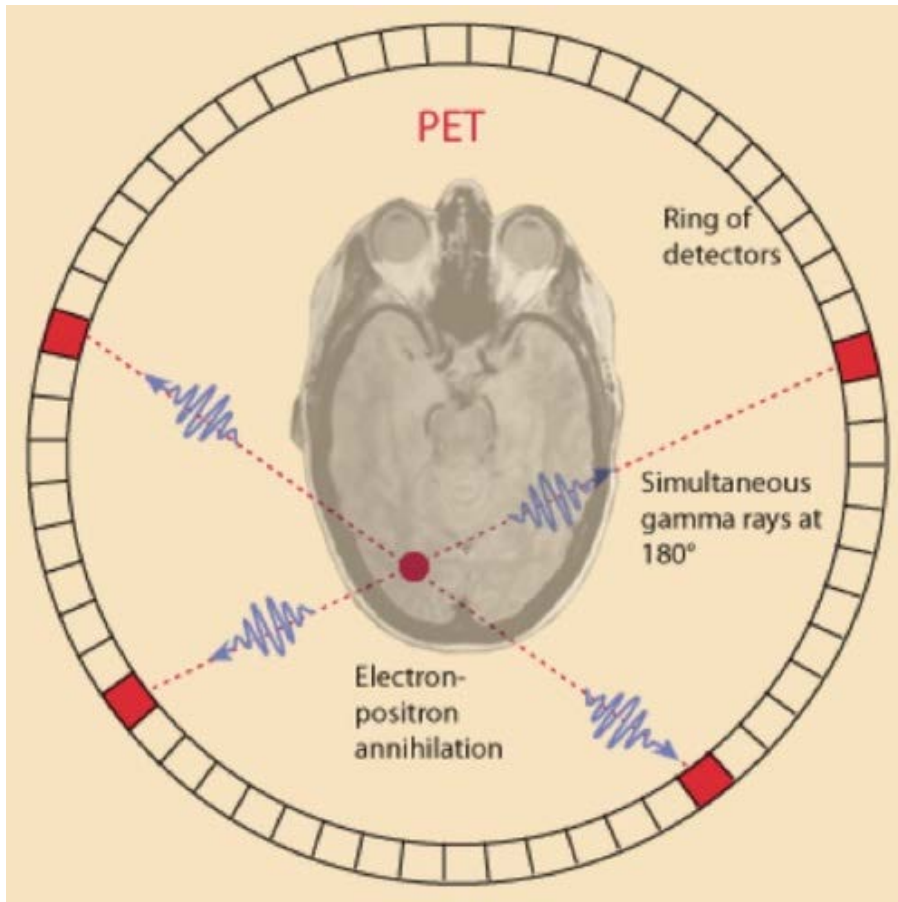
*Rear View—Shows radium pad, containing 20 micrograms of refined, measured radium. Size of pad, 4 in. wide, 3 in. deep. Size of suspensory, 4 in. deep, 8 in. wide. Very comfortable. Can't bleed.*

**Testone Radium Energizer and Suspensory**  
Contains 20 Micrograms Refined, Measured Radium

For that sagging, dragging weight that pulls you down and saps your energy—and for storing up and husbanding strength in that seat of all male activity—the testicles—this marvelous appliance has no equal!

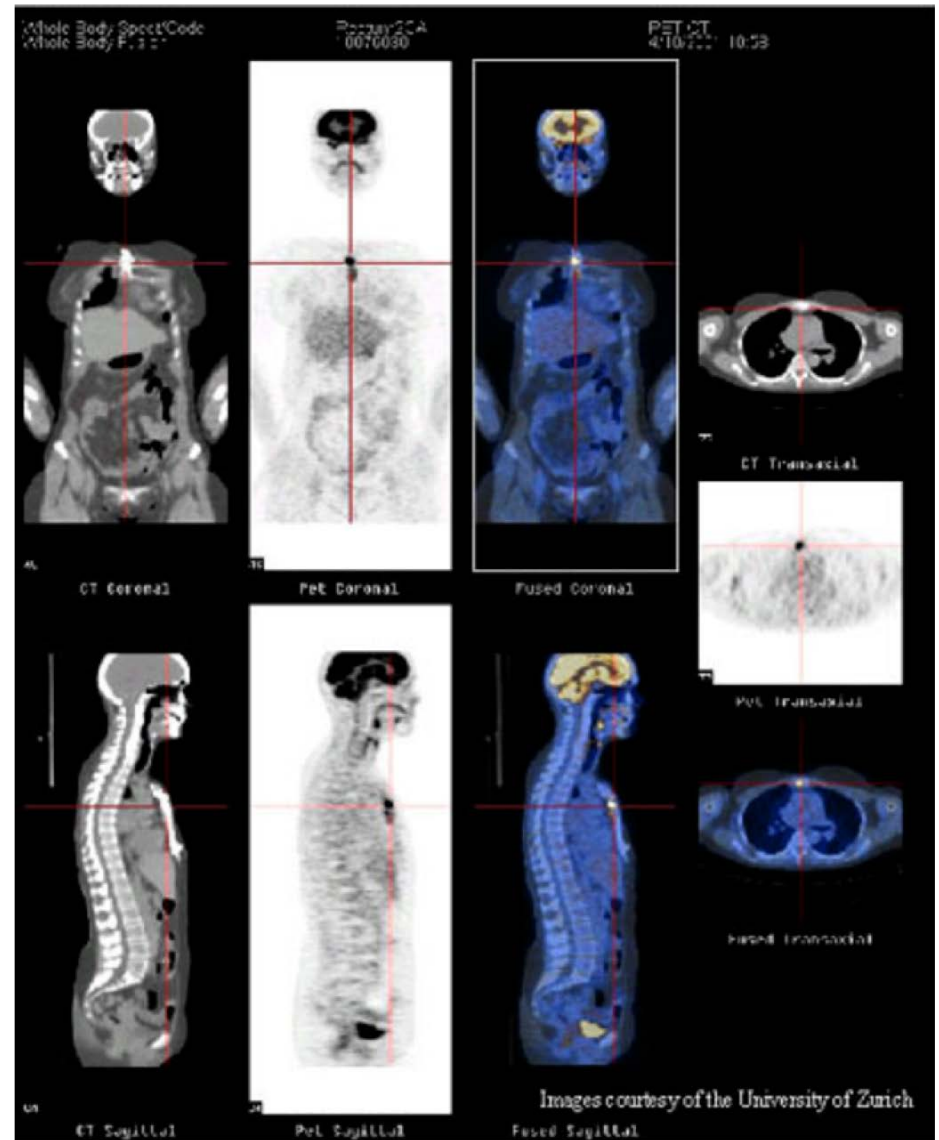
We GUARANTEE that the Testone Radium Appliance contains only purified, highly refined radium salts, free from all toxic metallic substances. Actually contains 20 micrograms of this precious sub-

## In 2002 Positron Emission Tomography (PET) started to expand in Europe



## Positron Emission Tomography (PET)

- In 2002, **PET** was the fastest growing state-of-the-art diagnostic tool using radioisotopes as consumables.
- PET cameras use short-life isotopes to achieve **non-invasive functional imaging diagnostics** (i.e. PET visualises on-going biochemical processes in living organs without damaging them).
- Allows for accurate diagnosis of complex diseases and **helps improve cost-effective patient management.**
- PET radiopharmaceuticals such as Fluoro DeoxyGlucose (**FDG**) are manufactured using particle accelerators (**cyclotrons**) and have a **shelf-life of only 10 hours !**



## Selling short lived radiopharmaceutical products: a complex business requiring unique know-how





# The “final” business plan of 2002



## AAA Mission

- **Advanced Accelerator Applications (AAA)** mission is to commercially exploit the fast growing demand of consumables and services originating from the increasing number of applications of particle accelerators in the medical, industrial and energy sectors.
- AAA initial **commercial focus** will be the **medical diagnostic radioisotopes market**.
- AAA **R&D focus** will be the **medical therapy radioisotopes market** and it will be pursued through the exploitation of a worldwide deposited **patent** developed at the European Organization for Nuclear Research (**CERN**) by Nobel laureate **Carlo Rubbia** and his team.

AAA, Advanced Accelerator Applications

Stefano Buono



## AAA strategy: R&D

- The **ARC (Adiabatic Resonance Crossing)** patent allows to produce with **particle accelerators** those isotopes that it was only previously possible to produce in **nuclear reactors**. The advantages are:
  - The **costs** are **lower** and the facility is **easier** to **build** and **operate**.
  - The **production** is **easier** and **products** have **better quality**.

The method has been **experimentally proven** at **CERN** between 1995 and 1997 and a worldwide **patent** has been taken in 1999.



AAA, Advanced Accelerator Applications

Stefano Buono

## Inspiring colleagues at AAA's first office at CERN

EMERGING ENERGY TECHNOLOGIES		
864 D 01	F. SALDANA	
864 D 02	Computer Room	
864 D 03	L. SARCHIAPONE	A. MARTINEZ M. DAHLFORS
864 D 04	Computer Room (Printers & Scanner)	
864 D 05	A. FERRARI	
864 D 08	S. BUONO	O. SESSANO
864 D 11	P. CENNINI	S. ANDRIAMONJE
864 D 12	L. MACIOCCO	P. MANDRILLON
864 D 13	G. CHARPAK	A. DIRAT I. GIOMATARIS
864 D 14	A. MENGONI	
864 D 17	Library & Meeting Room	
864 D 18	V. VLACHOUDIS	
864 D 21	E. CHIAVERI	Group Leader
864 D 22	Y. KADI	
864 D 23	A. MOLAT-BERBIERS	Group's Secretariat
864 D 24	Archives	
864 D 25	C. RUBBIA	
864 D 26	Rubbia's Secretariat	
864 D 28	P. PAVLOPOULOS	C. GELES
865 2B 21	G. BER HEINZ MAUSLI	PH. DASSE E. DE MARIA
865 2B 15	V. KETTEROV	V. KONOVALOV



## While we were waiting for the construction of our first lab to proceed...



...and proceed



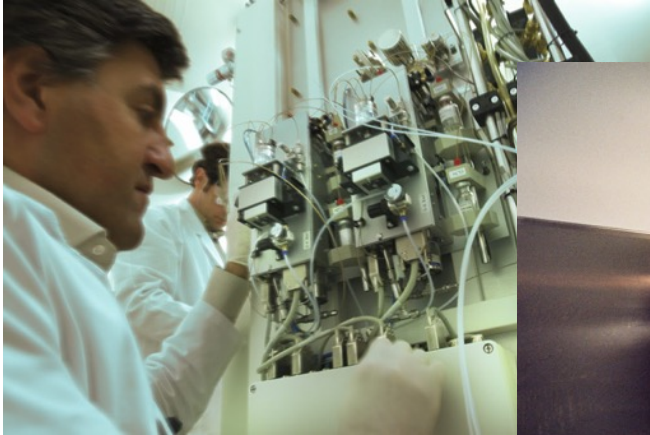
...and proceed



Until finally our first lab was ready!



# A GMP lab for radiopharmaceuticals required a lot of new technology and processes



...and we were always working at the forefront of  
technology





Advanced  
Accelerator  
Applications

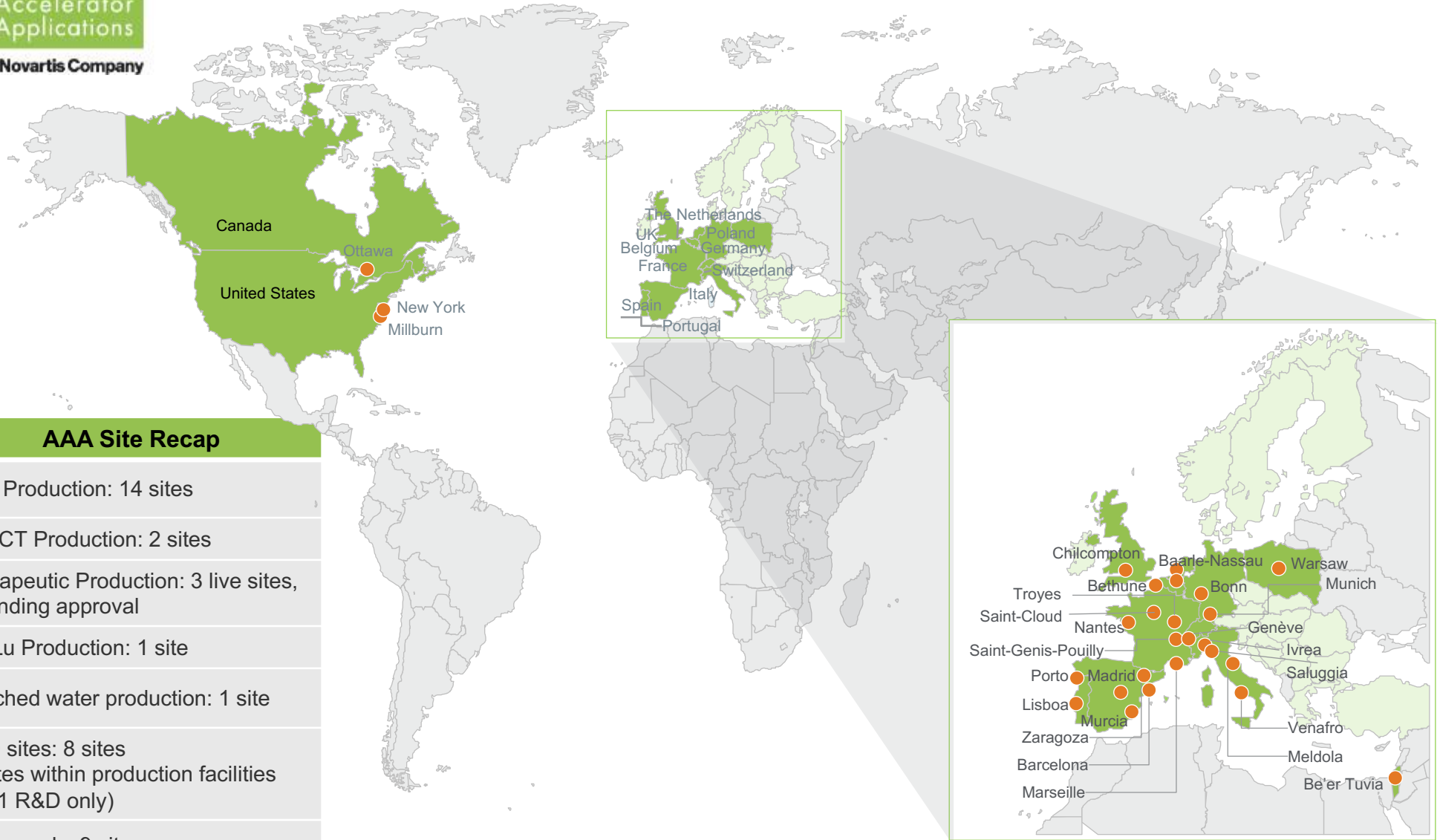
A Novartis Company

## The new administrative building





# Our presence: 630 employees in 13 countries

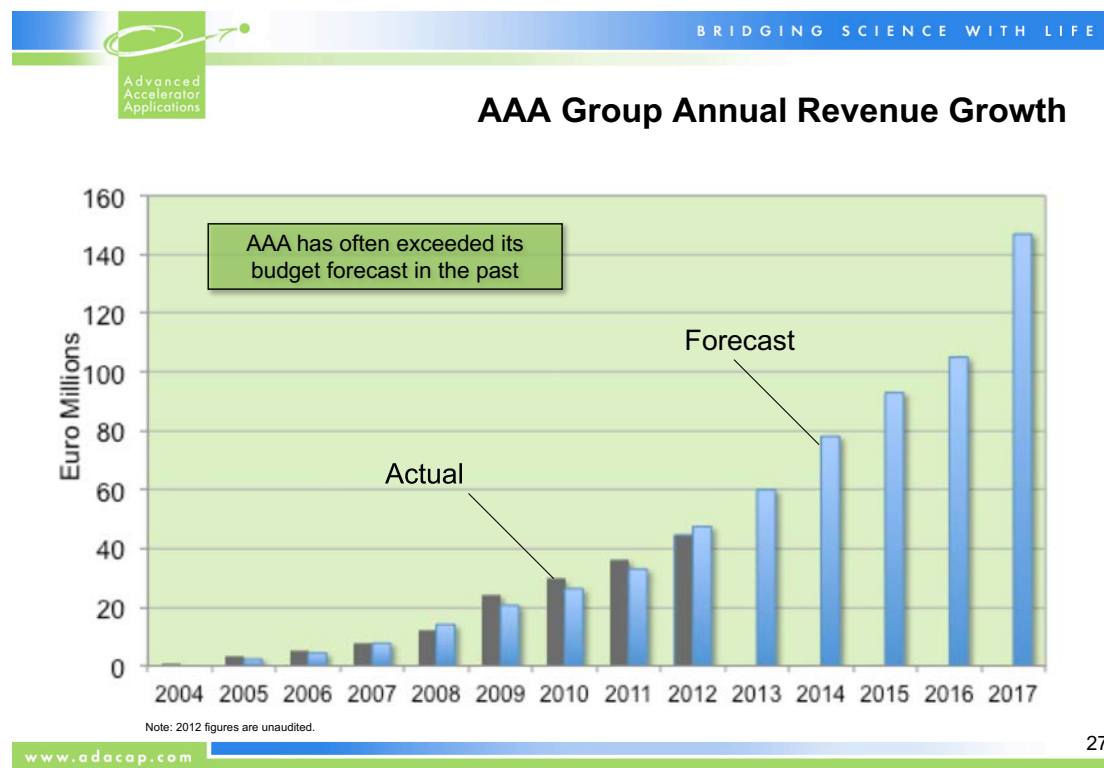


AAA Site Recap
PET Production: 14 sites
SPECT Production: 2 sites
Therapeutic Production: 3 live sites, 1 pending approval
<sup>177</sup> Lu Production: 1 site
Enriched water production: 1 site
R&D sites: 8 sites (7 sites within production facilities and 1 R&D only)
Offices only: 9 sites



## PET has been our unique business for many years

- PET business has been a **cash cow** allowing to develop a pipeline of products using the **alternative model** of an **EBITDA positive biotech company**
- PET was a **difficult business** to understand for investors:
  - Capital Intensive
  - Local
  - Generic
  - Declining prices
  - Unclear Margins
  - Logistic costs



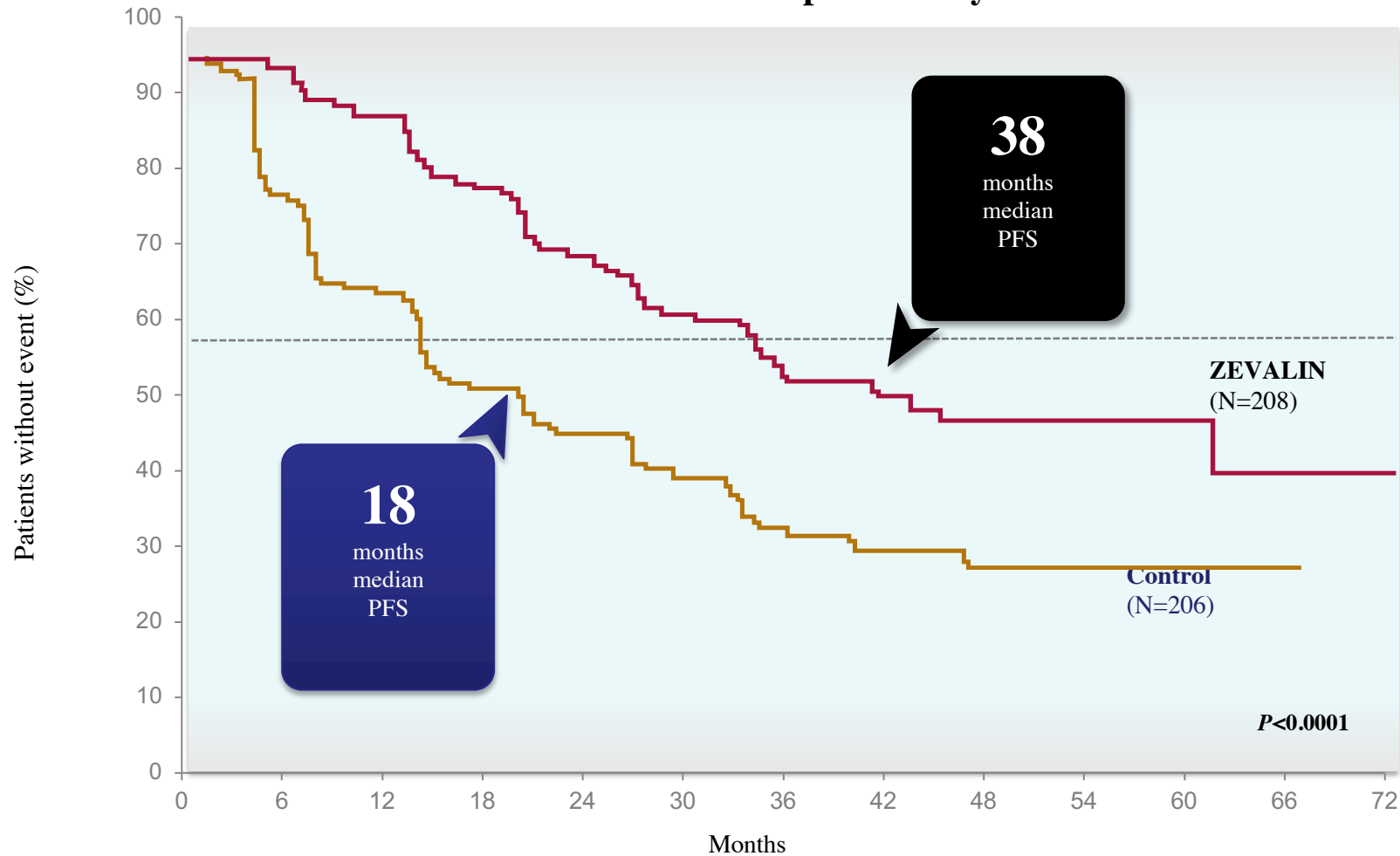


## 2002-2015: An “alternative” financial model as a private-public company

- Before IPO (2015), AAA Collected €150m from about 240 shareholders:
  - No institutional investor signed any investment agreement other than the original shareholders agreement
  - No investor had significant weight: independent management
  - Acquisitions:
    - Paid in shares to keep management of acquired companies engaged
    - Companies kept independent
  - A significant turnover happened during the “private” phase (about 25-30 shareholders exited)
  - Used maximum legal amount of free shares and stock options for employees
  - Executed 41 capital increases

## Outstanding data for Zevalin in 2003: the first nuclear medicine therapeutic to run a randomized phase III study

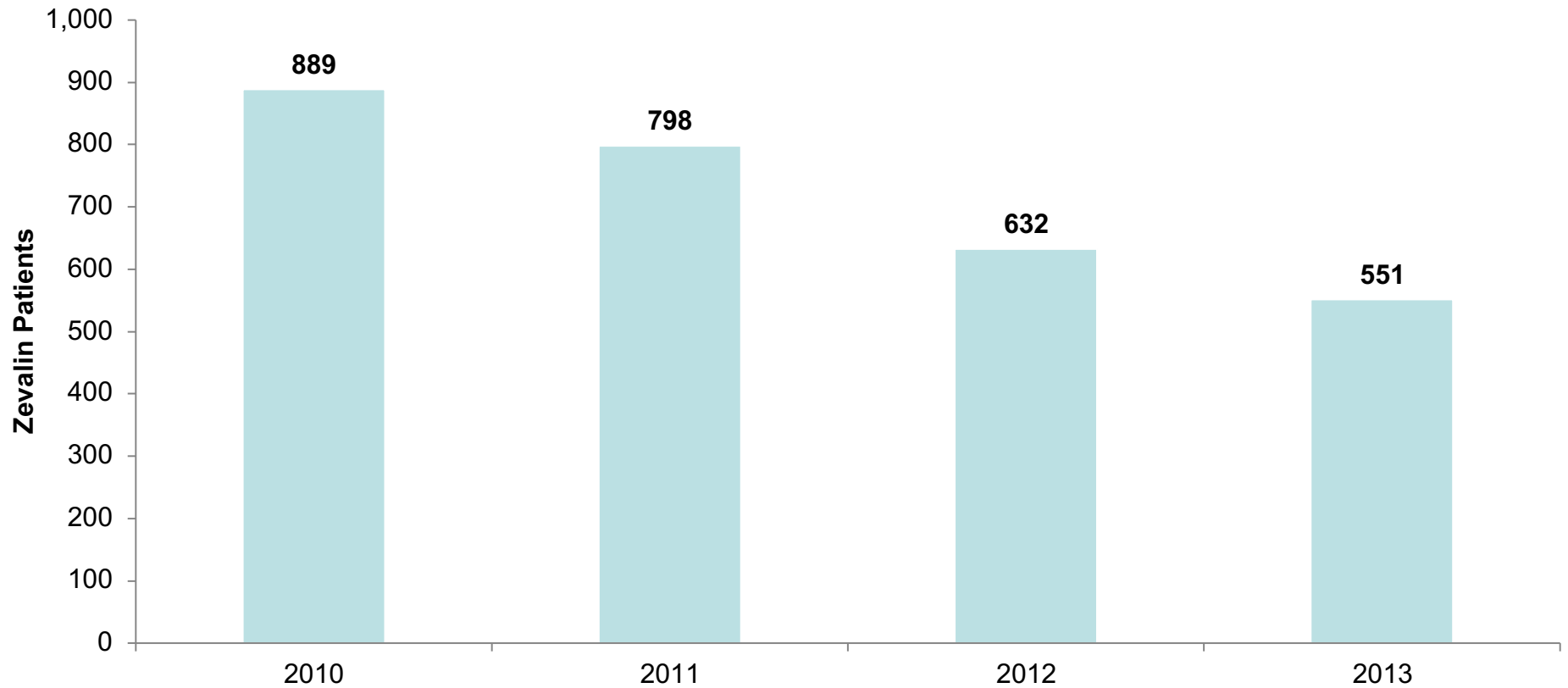
**PFS measured from time of randomization (months)**  
**Median observation period 3.5 years.**





## Zevalin has been a commercial failure in non-Hodgkin's lymphoma

# of Zevalin Patients Treated by Year





# Paving the way for commercial nuclear medicine therapeutics



BRIDGING SCIENCE WITH LIFE

## Production of new radiopharmaceuticals for therapy

- AAA is applying its know-how on FDG to the set up of a process to produce **therapy radiopharmaceuticals** labelled with **Y-90** or **Lu-177**.
- Today such radiopharmaceuticals are sold in **kits**: the precursor and the radioisotope are sold **separately** and the doctor has to make a **complex process** to label it **in-house**. Only few nuclear medicine departments can do it.
- AAA believes that if these radiopharmaceuticals are sold already in injectable form (like FDG), their success will be stronger.
- Therapy products can be either "**generics**", like FDG (interesting patents are expiring starting from 2007), or "**patented**" (contacts have started with Sigma-Tau, Bracco and Berna Biotech).

www.adacap.com

18

2005

2006



BRIDGING SCIENCE WITH LIFE

## RMT: from a local to a global market

- **Therapy radiopharmaceuticals** labelled with **Y-90** or **Lu-177** (produced in nuclear reactors) can be used within a **few days** from production and not a **few hours**.
- This allows to go from a **local (regional) market** to a **global (European) market** with only 1-2 similar production units.
- Therapy production units are smaller than FDG (no cyclotron), are less costly, but have the same capacity (in excess of 100 doses/day).
- Marketing authorisations are more difficult to obtain: investments can reach 10 M€ over 5 years.
- Prices can easily overcome 10-20 k€/treatment (few injected doses).

www.adacap.com

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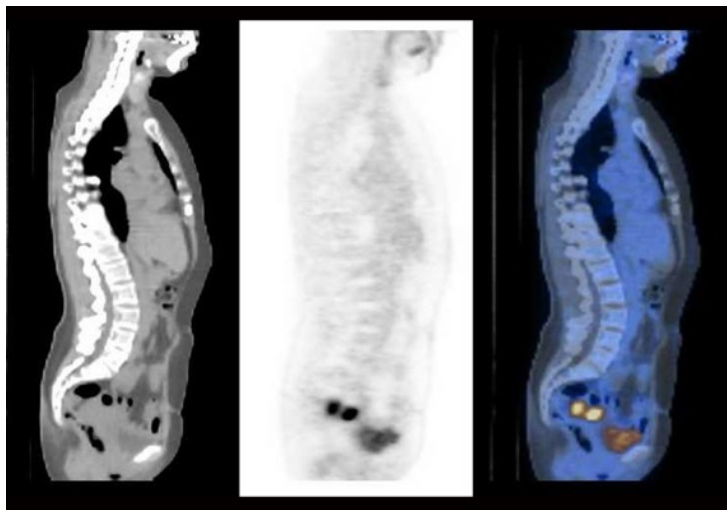
# The molecular nuclear medicine market

## Molecular Nuclear Medicine (MNM)

- Uses trace amounts of radioactive substances called radiopharmaceuticals to reveal specific biochemical processes (functional imaging) or treat disease
- Used in: oncology (65%), cardiology (33%), others (2%)
- Global market expected to reach US\$26 billion by 2030

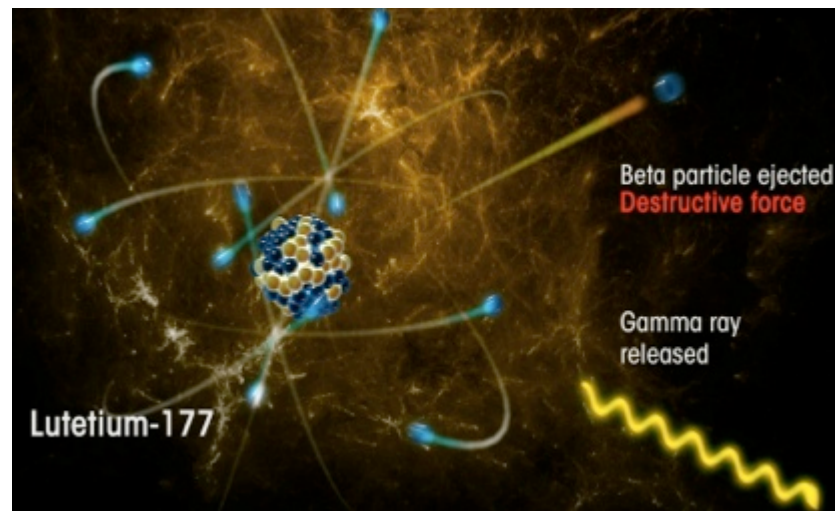
## Molecular Nuclear Diagnostics (MND)

- Allows for accurate diagnosis of complex diseases and helps improve **cost-effective patient's management**
- Patients are imaged with PET (Positron Emission Tomography) or SPECT (Single-Photon Emission Computed Tomography) cameras
- Accounted for 88% of total MNM market in 2016

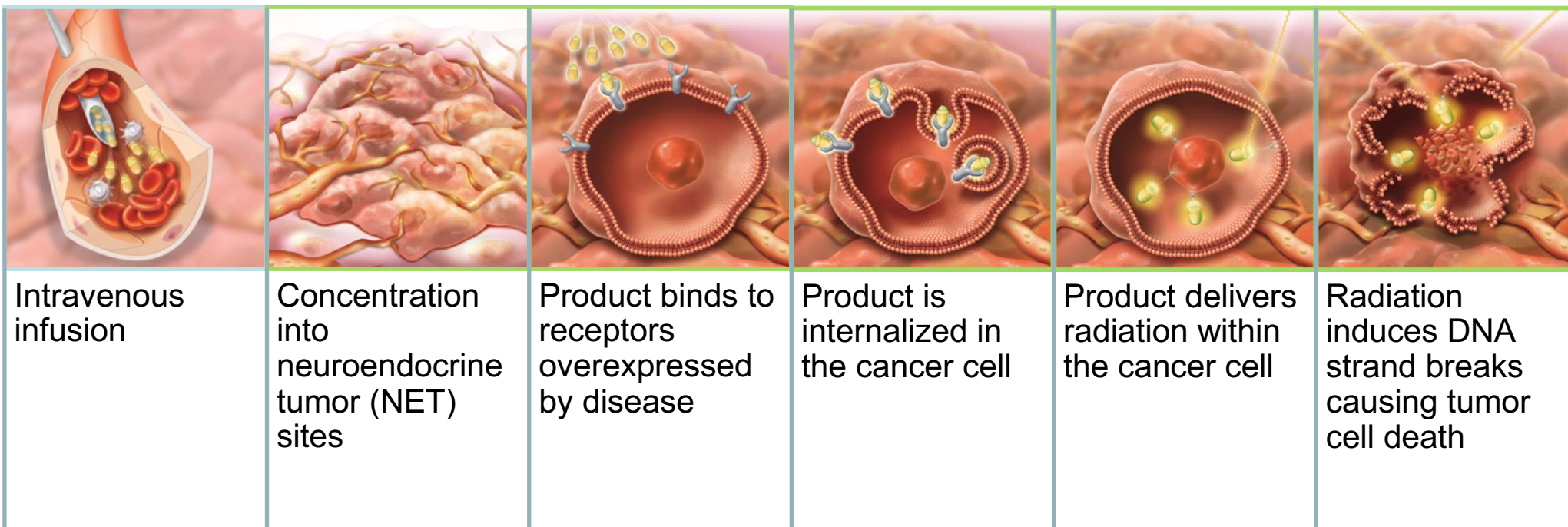


## Molecular Nuclear Therapeutics (MNT)

- Innovative therapeutic modality that combines two approaches: **tumor targeting** and **radiation**
- PK, toxicity and mechanism of action are quite simple
- Accounted for 12% of total MNM market in 2016; expected to represent 60% of MNM market by 2030



## Targeted Radiotherapy mechanism of action



# The theragnostic opportunity

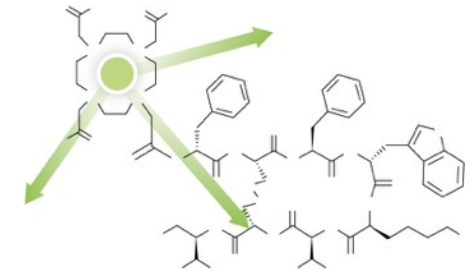
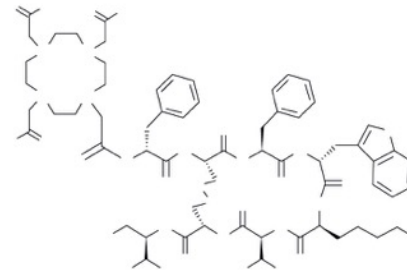
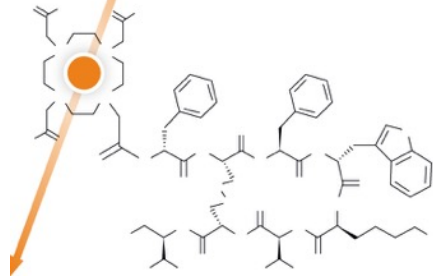


AI

Ga-68 labeled

Same Targeting Molecule

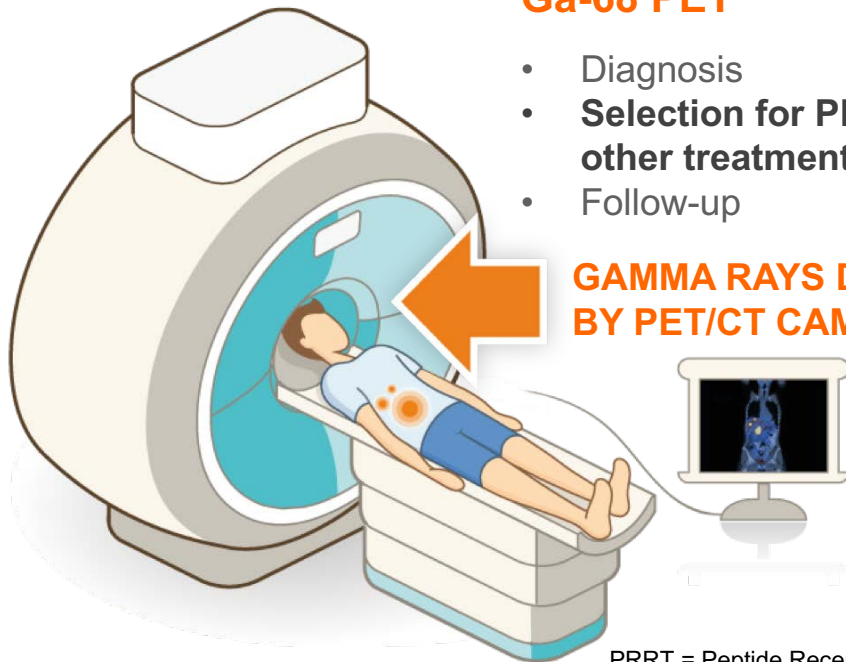
Lu-177 labeled



Ga-68 PET

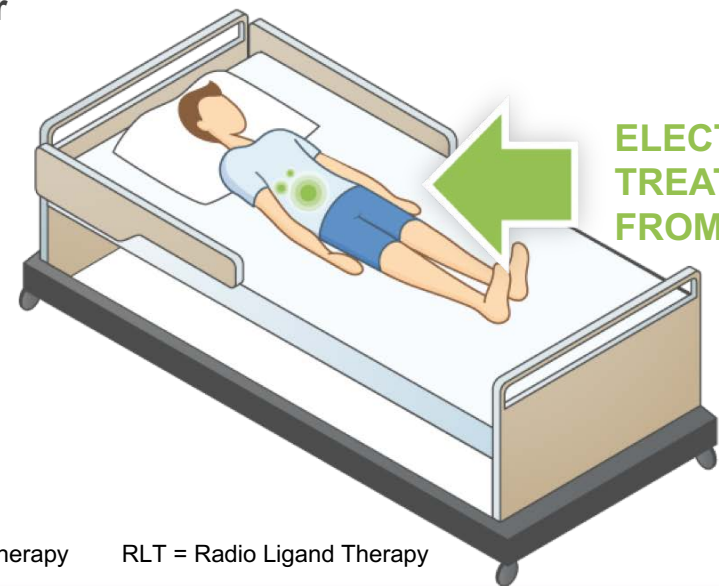
- Diagnosis
- **Selection for PRRT / RLT or other treatment**
- Follow-up

GAMMA RAYS DETECTED BY PET/CT CAMERA



Lu-177 PRRT / RLT

ELECTRONS TREAT TUMORS FROM WITHIN



PRRT = Peptide Receptor Radionuclide Therapy

RLT = Radio Ligand Therapy





## What is theragnostics for the pharma-biotech world?

- Theragnostics is considered a patient management strategy involving the **integration of diagnostic kits and therapeutic drugs**
    - The term “**diagnostic drug**” is already a novelty for pharma-biotech stakeholders: “diagnostics” terminology is associated with lab tests, devices, not drugs
    - The idea of using the **same molecule** for developing a **pair of drugs** (a diagnostic and a therapeutic drug) is then completely **unknown**; is a new concept that requires a clear explanation
    - Pharma-biotech experts are astonished to discover that a company can develop 2 different drugs from the same molecule that will have the same pharmacokinetics leading to 2 completely different uses (and independent marketing authorizations) of this compound
  - This is the **unique value** of nuclear medicine that will lead to a significant expansion of our sector
-

## Impact of Theragnostics

### Patients

- More effective care through personalized interventions
- Reduce or eliminate unnecessary treatment

### Physicians

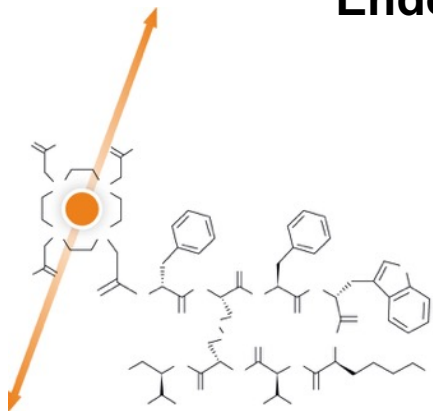
- Better diagnose and stage disease
- Select optimal therapies
- Monitor treatment response and disease progression

### Payors

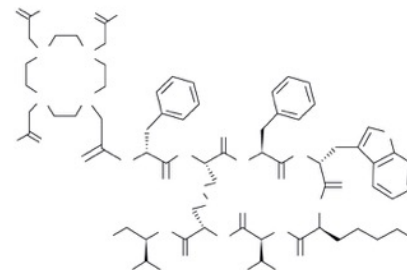
- Reduce costs from unnecessary treatments
- Improve patient management & outcomes

# AAA has been the first company in the world to develop theragnostic pairing using Ga-68 and Lu-177

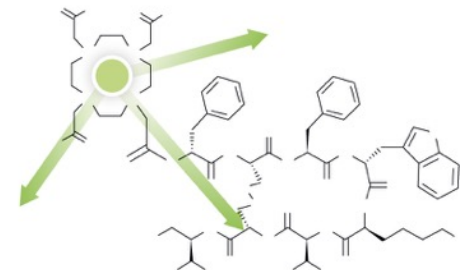
**Dotatate** is an analog of Somatostatin, targeting receptors with high binding affinity. Somatostatin receptors are overexpressed in **Neuro Endocrine Tumours (NET)**



Ga-68 labeled  
Diagnostic



dotatate



Lu-177 labeled  
Therapy

## NETSPOT®

First-in-class drug  
4 hour shelf-life

## LUTATHERA®

First-in-class drug  
3 day shelf-life



**NETSPOT<sup>®</sup> approved by FDA June 2016  
only 23 months from pre-IND meeting**

FOR PATIENTS WITH ADVANCED NEUROENDOCRINE TUMORS (NETs)

## **SPOT WHAT OTHERS MAY FAIL TO SEE**

A new era of NET detection  
and management



**INDICATION:** NETSPOT<sup>®</sup>, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

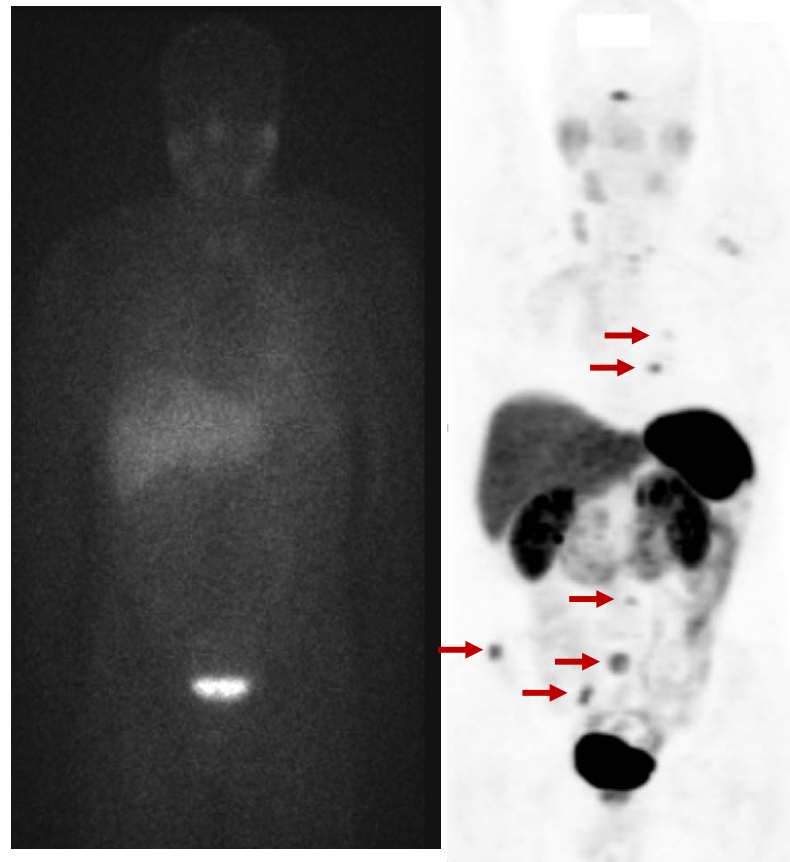


# NETSPOT<sup>®</sup> impacts all aspects of NET management, from diagnosis to clinical decisions

<p><b>Diagnostics</b></p>	<ul style="list-style-type: none"> <li>• <b>NETSPOT<sup>®</sup></b> (PET) is a significant improvement vs existing diagnostic tools             <ul style="list-style-type: none"> <li>- Imaging allows detection of 30% more lesions than Octreoscan<sup>™</sup></li> <li>- Improved sensitivity and accuracy</li> <li>- 100 times higher affinity for SSTR2 than Octreoscan<sup>™</sup></li> </ul> </li> </ul>
<p><b>Management</b></p>	<ul style="list-style-type: none"> <li>• 71% of patients scanned with <b>NETSPOT<sup>®</sup></b> (PET) had experienced an impact on their disease management             <ul style="list-style-type: none"> <li>- Less futile surgery</li> <li>- <b>NETSPOT<sup>®</sup></b> helps predict clinical response to somatostatin receptor-mediated therapies (including PRRT)</li> </ul> </li> </ul>
<p><b>Dose Reduction</b></p>	<ul style="list-style-type: none"> <li>• <b>NETSPOT<sup>®</sup></b> (PET) has a lower effective dose and higher typical injected activity compared to Octreoscan<sup>™</sup> <ul style="list-style-type: none"> <li>- The effective dose per activity unit for Octreoscan<sup>™</sup> is approximately 3 to 5 times higher</li> </ul> </li> </ul>
<p><b>Convenience</b></p>	<ul style="list-style-type: none"> <li>• <b>NETSPOT<sup>®</sup></b> is a convenient option for hospitals, with better patient acceptability             <ul style="list-style-type: none"> <li>- 2 hour vs 24 to 48 hour protocol</li> <li>- No bowel cleansing</li> <li>- Fewer examinations, reduced hospitalization time</li> </ul> </li> </ul>
<p><b>Cost Savings</b></p>	<ul style="list-style-type: none"> <li>• Ga-DOTA-peptides reduce cost and time for the institution             <ul style="list-style-type: none"> <li>- Lower cost of materials vs Octreoscan<sup>™</sup></li> <li>- The higher patient throughput of <b>NETSPOT<sup>®</sup></b> (PET) lowers the cost per examination vs Octreoscan<sup>™</sup></li> </ul> </li> </ul>

# NETSPOT® Image vs Octreoscan™

Same Patient



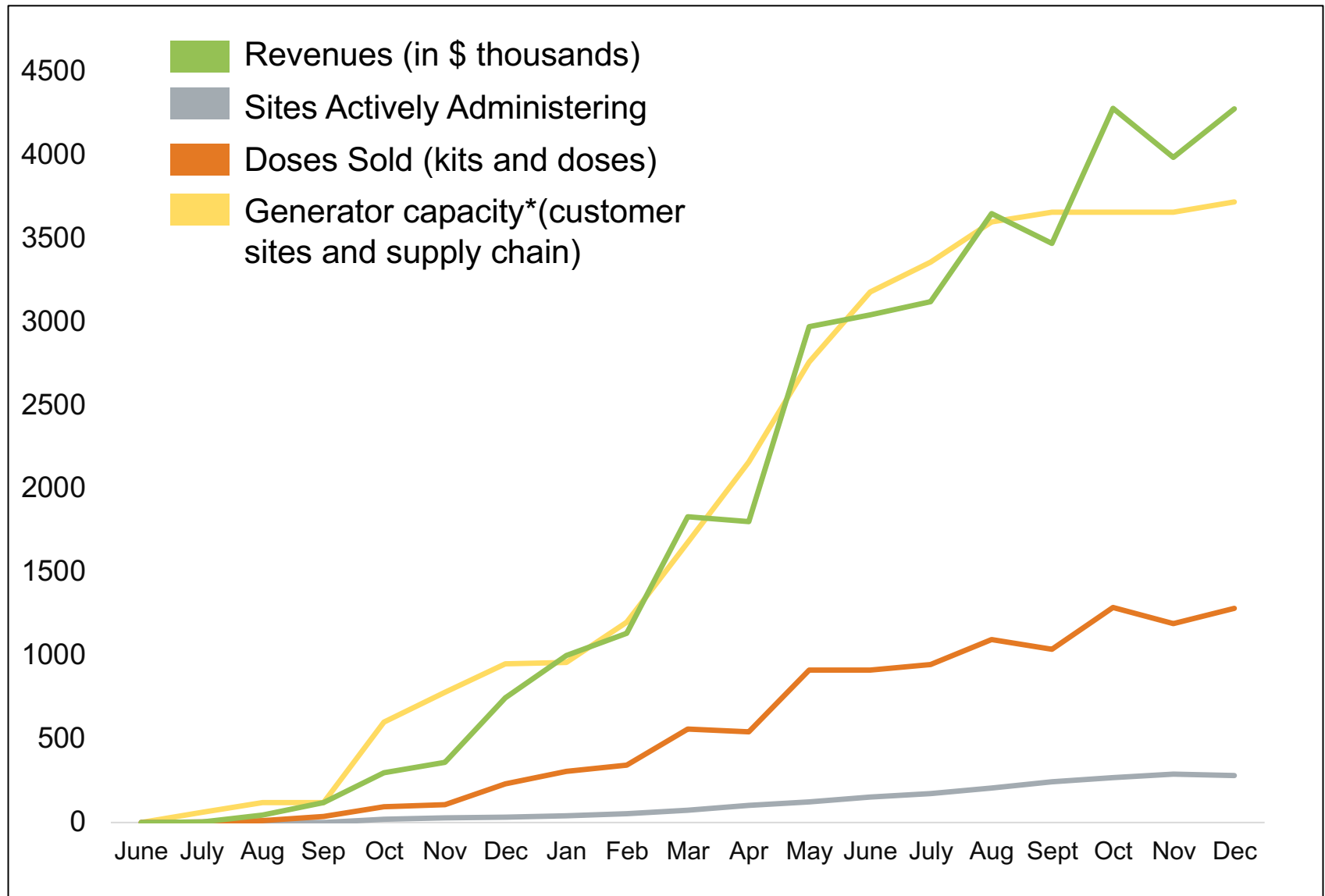
Octreoscan™  
SPECT image

68Ga-DOTATATE  
PET/CT image

\*Courtesy of Ron Walker, Vanderbilt University, Nashville TN



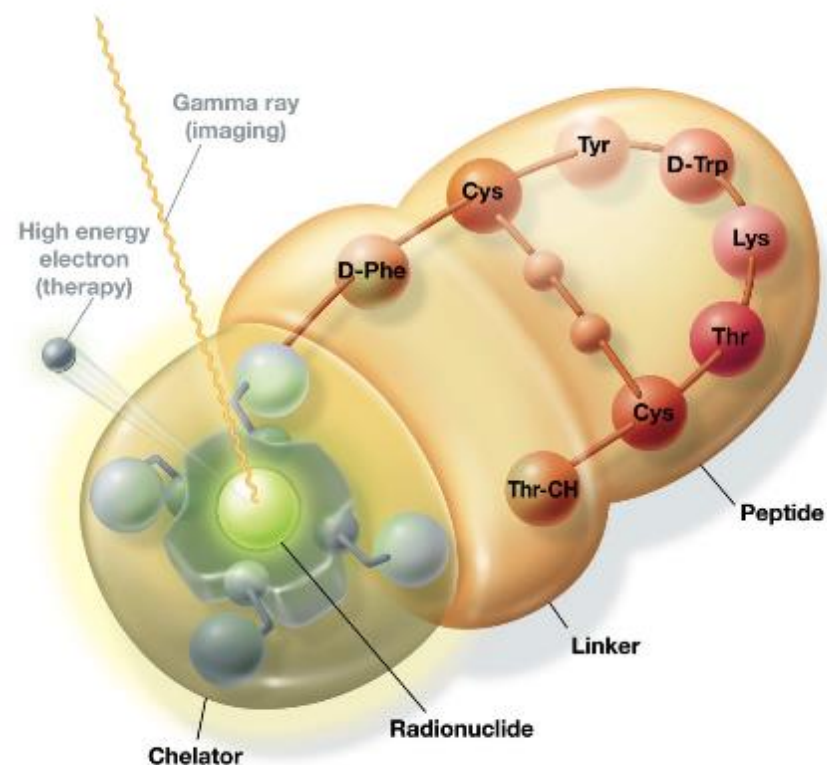
# NETSPOT® Ramp-up: 2017



\*Assumes 1 generator produces 60 doses/month

## AAA acquired LUTATHERA<sup>®</sup> (lutetium Lu 177 dotatate\*) in 2010

- LUTATHERA<sup>®</sup> belongs to an innovative drug category called PRRT (Peptide Receptor Radionuclide Therapy). PRRT involves the **systemic administration** of a targeted radiopharmaceutical to deliver cytotoxic radiation to a tumor.
- LUTATHERA<sup>®</sup> is composed of a **lutetium radionuclide chelated to a peptide**. Lutetium emits high energy electrons (therapy) and gamma rays (imaging).
- The peptide is designed to **target somatostatin receptors** with high binding affinity.

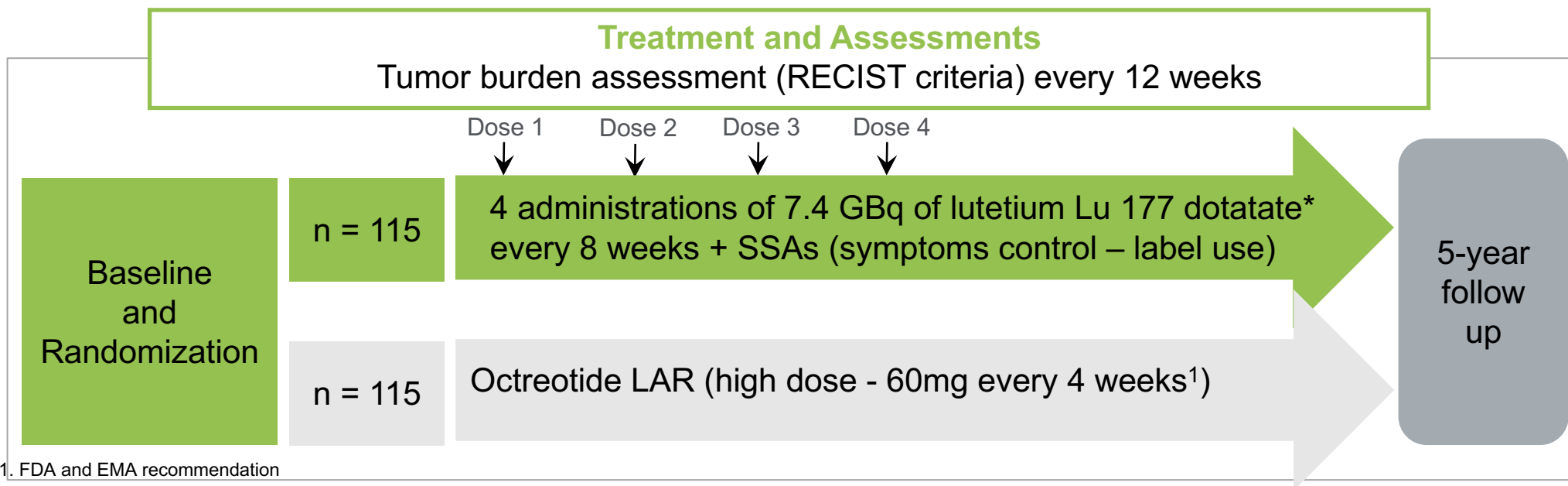


The affinity for SSTRs and the specificity of binding enables a high level of specificity in the delivery of radiation to the tumor



## NETTER-1: Phase III Study

- **Aim:** Evaluate the efficacy and safety of lutetium Lu 177 dotatate\* + SSAs (symptom control) compared to Octreotide LAR 60mg (off-label use)<sup>1</sup> in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
- **Design:** International, multicenter, randomized, comparator-controlled, parallel-group - 51 sites (36 in Europe and 15 in the US)
- **Primary endpoint:** Progression-Free Survival (PFS)
- **Secondary endpoints:** Safety, Objective Response Rate (ORR), Time to Tumor Progression (TTP), Overall Survival (OS) and Quality of Life (QoL)
- Phase 3 results presented for the first time at the ESMO Congress in Vienna on 27 September 2015.



1. FDA and EMA recommendation



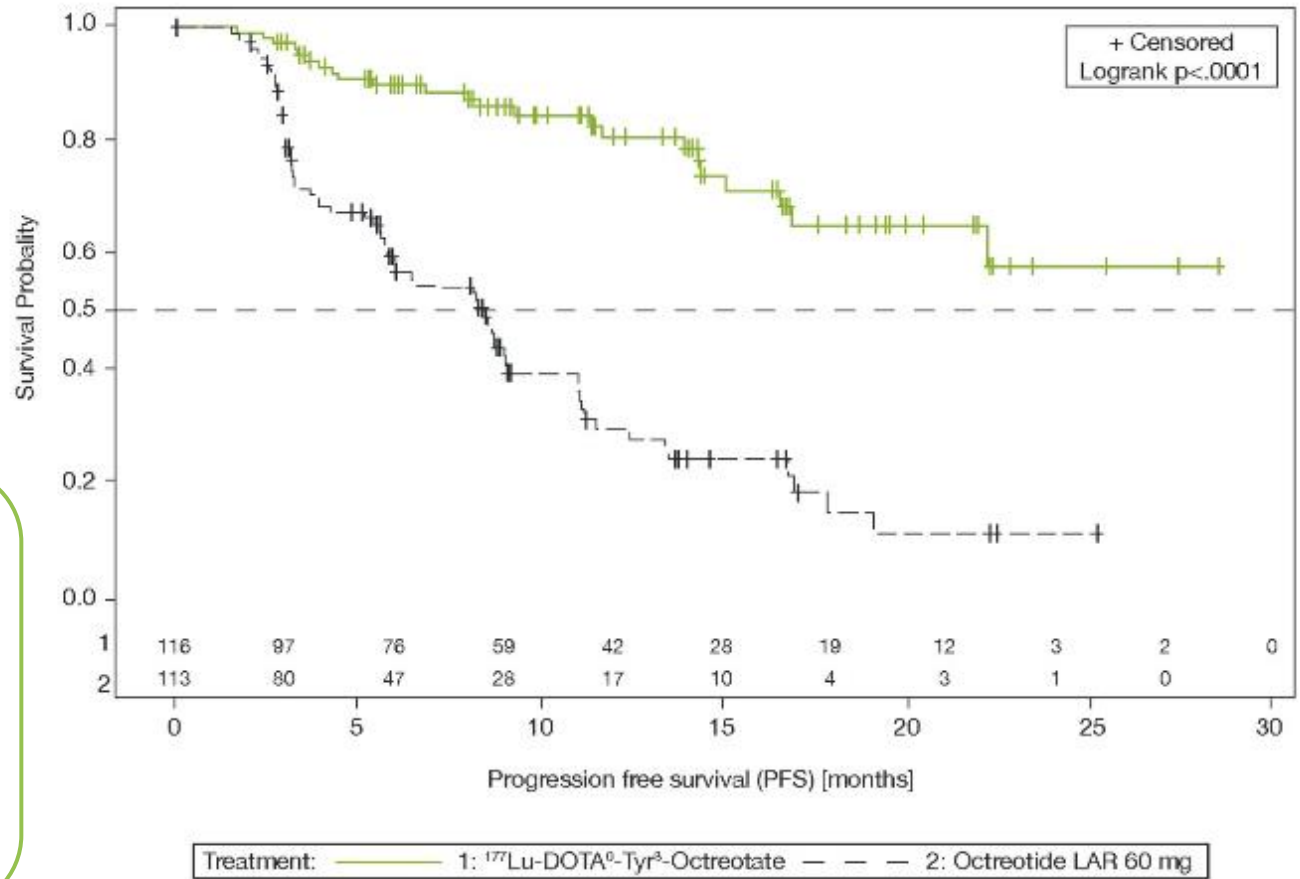
# NETTER-1 Final Analysis: Progression-Free Survival Published in *The New England Journal of Medicine*

N = 229 (ITT)  
Number of events: 91  
LUTATHERA® arm : 23  
Oct 60 mg LAR: 68

Hazard ratio: **0.21**  
[0.13 – 0.33]  
**p < 0.001**



79% reduction in the risk of  
disease progression/death



All progressions centrally confirmed and  
independently reviewed for eligibility (SAP)



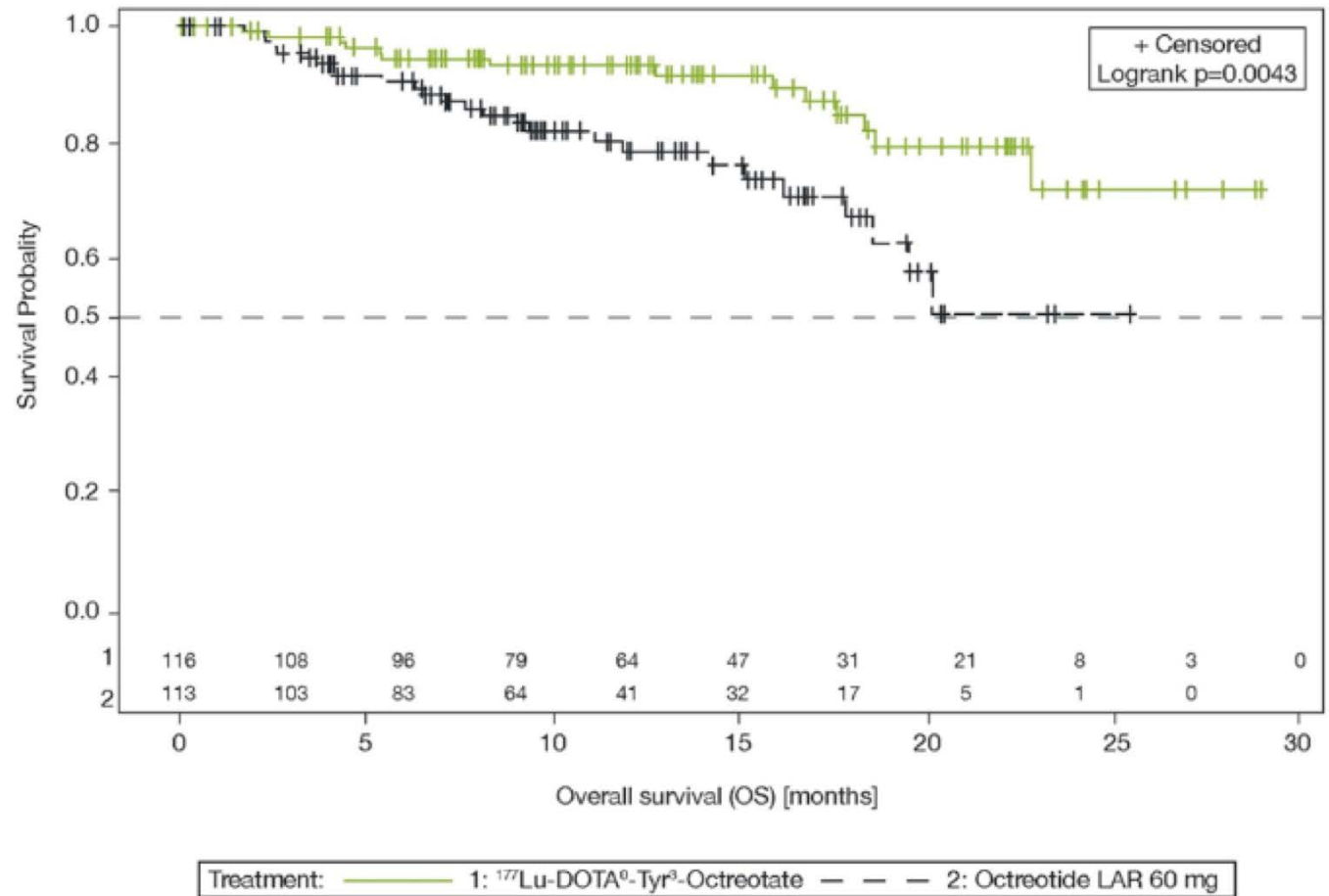
# NETTER-1 Results: Overall Survival (pre-planned interim analysis)

N = 229 (ITT)  
 Number of deaths: 40  
 LUTATHERA® arm: 14  
 Oct 60 mg LAR: 26

Hazard ratio: **0.40**  
 [0.21 – 0.77]  
**P = 0.004**



60% reduction in  
 estimated risk of death



All cases independently reviewed for eligibility (SAP)



# Netter-1 presentation at ESMO 2016 presidential session

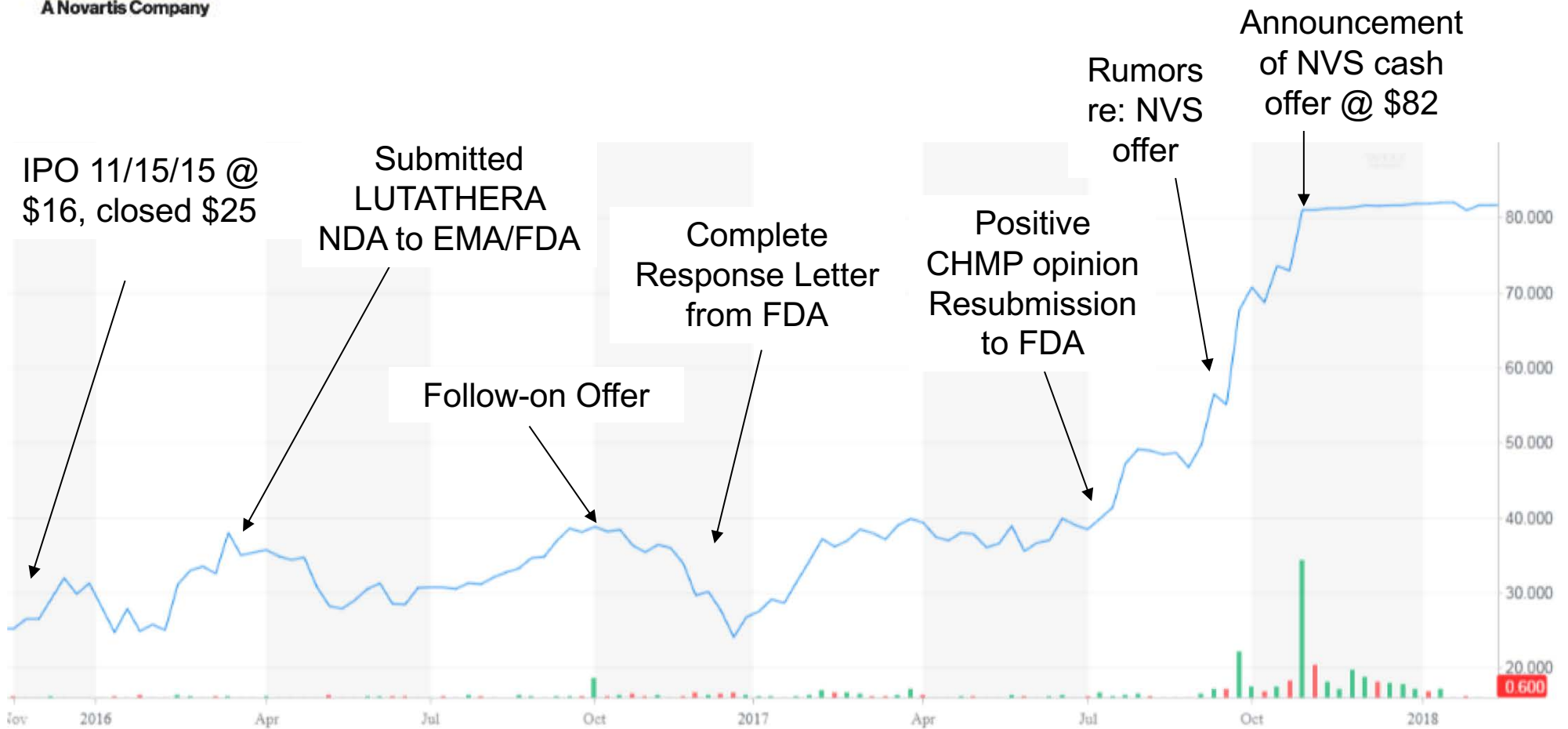


... boosted success of AAA IPO on Nasdaq, just one month after (November 2015)





# AAAP metrics during the period as a public company



## AAA Culture: all about the patients

***“Knowing that our daily efforts directly impact the lives of patients inspires me.”***

Olaya Argülles,  
Qualified Person (Spain)



***“As a part of AAA, I feel strongly that I am empowered to take responsibility for improving the lives of patients on a daily basis.”***

Axel Gillan,  
Pharmacist and Site  
Manager (France)

***“I am moved every day by our team’s dedication to serving our patients.”***

Kristina Maximenko,  
Director Human  
Resources (US)





## LUTATHERA® compassionate use

- **1,964 EU patients / 348 US patients** injected as of the end of January 2018
- 76 centers across 10 European countries from 2012:
  - Austria, Denmark, Estonia, Finland, France, Greece, Portugal, Spain, Switzerland, and the United Kingdom
- 42 centers across the United States from 2017:
  - Arizona, California, Colorado, Florida, Georgia, Illinois, Iowa, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Texas, Utah, Virginia and Washington





# January 26, 2018: FDA decides LUTATHERA® is ready to fly!



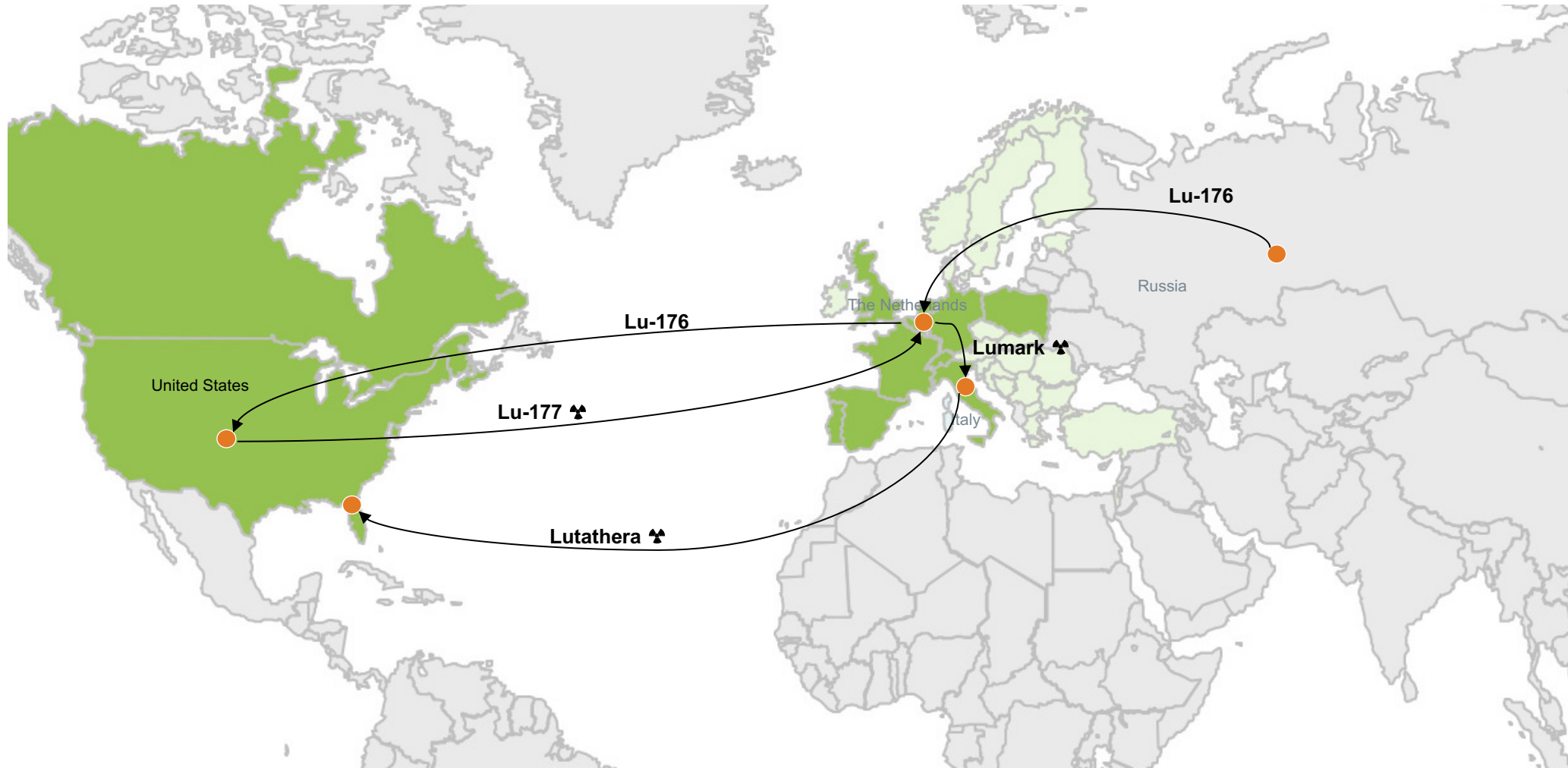
**INDICATION:** NETSPOT<sup>®</sup>, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

# LUTATHERA® U.S. Commercial Introduction

- Price per dose: US wholesale acquisition cost for each individually produced dose of Lutathera is \$47,500 (cost for total 4-doses is \$190,000)
- 1<sup>st</sup> US commercial dose administered on February 22, 2018 at Excel Diagnostics in Houston, TX



# The manufacturing of Lutathera





## Proven and reliable supply chain has been key for our success

- **PET:** Proven track record in managing short shelf life of PET products (10 hours) :
  - Manufactured and sold over **40,100 batches** of F-18 PET diagnostic products to date
  - Delivered and injected over **1,079,400 doses** of F-18 PET diagnostic products
- **SPECT** know-how founded on more than **2.2 million vials**
- **Therapy:** Proven track record in managing short shelf life of therapeutic products (3 days):
  - Produced over **770 batches** of lutetium Lu 177 dotatate (Lutathera®)
  - Delivered over **5,400 doses** of lutetium Lu 177 dotatate (Lutathera®) to 1,900 patients for compassionate/named patient use with NET across 99 centers in Europe and the US



## AAA opens first U.S. production and distribution site in Milburn, New Jersey





# Nuclear medicine theragnostics gets a boost

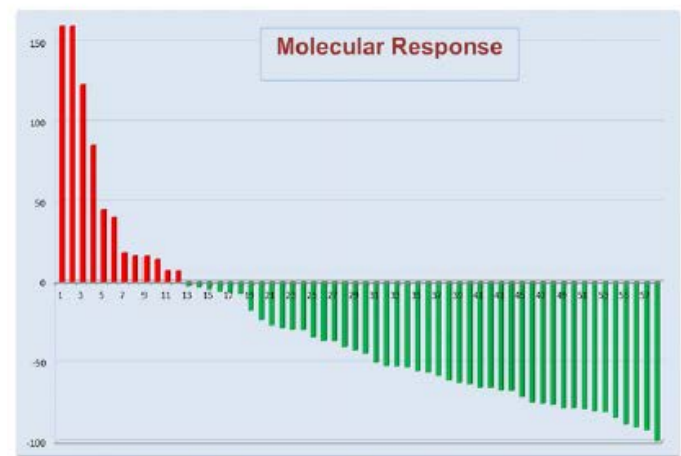
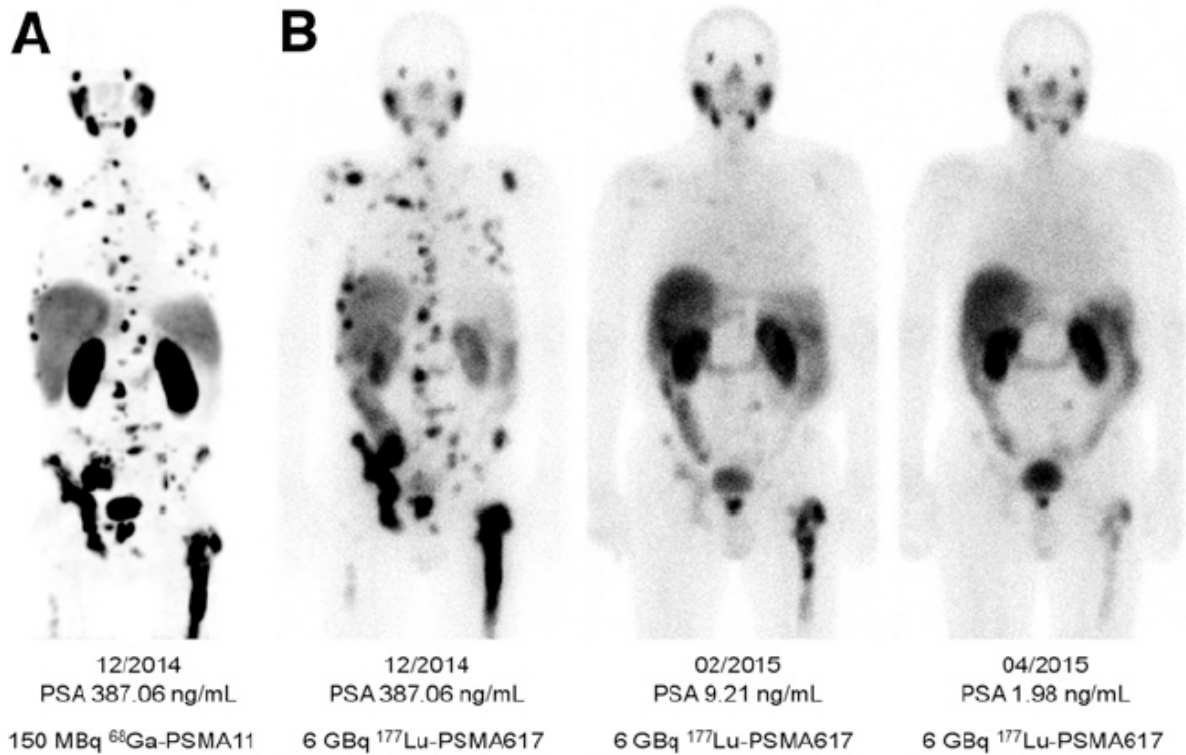


Product	Indications	Preclinical	Phase I	Phase II	Phase III	Filing	Marketed	Status	
	Gastroenteropancreatic Neuroendocrine tumors (GEP-NETs)	LUTATHERA® (USAN lutetium Lu 177 dotatate / INN: lutetium ( <sup>177</sup> Lu) oxodotreotide): Therapeutic							<ul style="list-style-type: none"> <li>Phase III Netter-1 study in NETs</li> <li>Orphan Drug Designation</li> <li>Approved in US and EU</li> </ul>
	Gastroenteropancreatic Neuroendocrine tumors (GEP-NETs)	NETSPOT® (gallium Ga 68 dotatate): PET Diagnostic							<ul style="list-style-type: none"> <li>PET diagnostics for localization</li> <li>Orphan Drug Designation</li> <li>Approved in US and EU</li> </ul>
		SOMAKIT-TOC® (gallium ((Ga 68) edotreotide): PET Diagnostic							

<b>177Lu PSMA-R2</b>	Prostate cancer	Therap.	<ul style="list-style-type: none"> <li>Exclusive license from John's Hopkins for series of candidates in prostate cancer</li> <li>Clinical studies planned for 2018</li> </ul>
<b>68Ga PSMA-R2</b>	Prostate cancer	PET Diag.	<ul style="list-style-type: none"> <li>Exclusive license from John's Hopkins for series of candidates in prostate cancer</li> <li>Clinical studies planned for 2018</li> </ul>
<b>177Lu NeoBOMB1</b>	GIST Prostate cancer Breast cancer	Therapeutic	<ul style="list-style-type: none"> <li>GRPR antagonist</li> <li>Exclusive license from Erasmus MC and Demokritos University</li> <li>Clinical studies planned for 2018</li> </ul>
<b>68Ga NeoBOMB1</b>	GIST Prostate cancer Breast cancer	PET Diagnostic	<ul style="list-style-type: none"> <li>GRPR antagonist</li> <li>Exclusive license from Erasmus MC and Demokritos University</li> <li>Clinical studies planned for 2018</li> </ul>

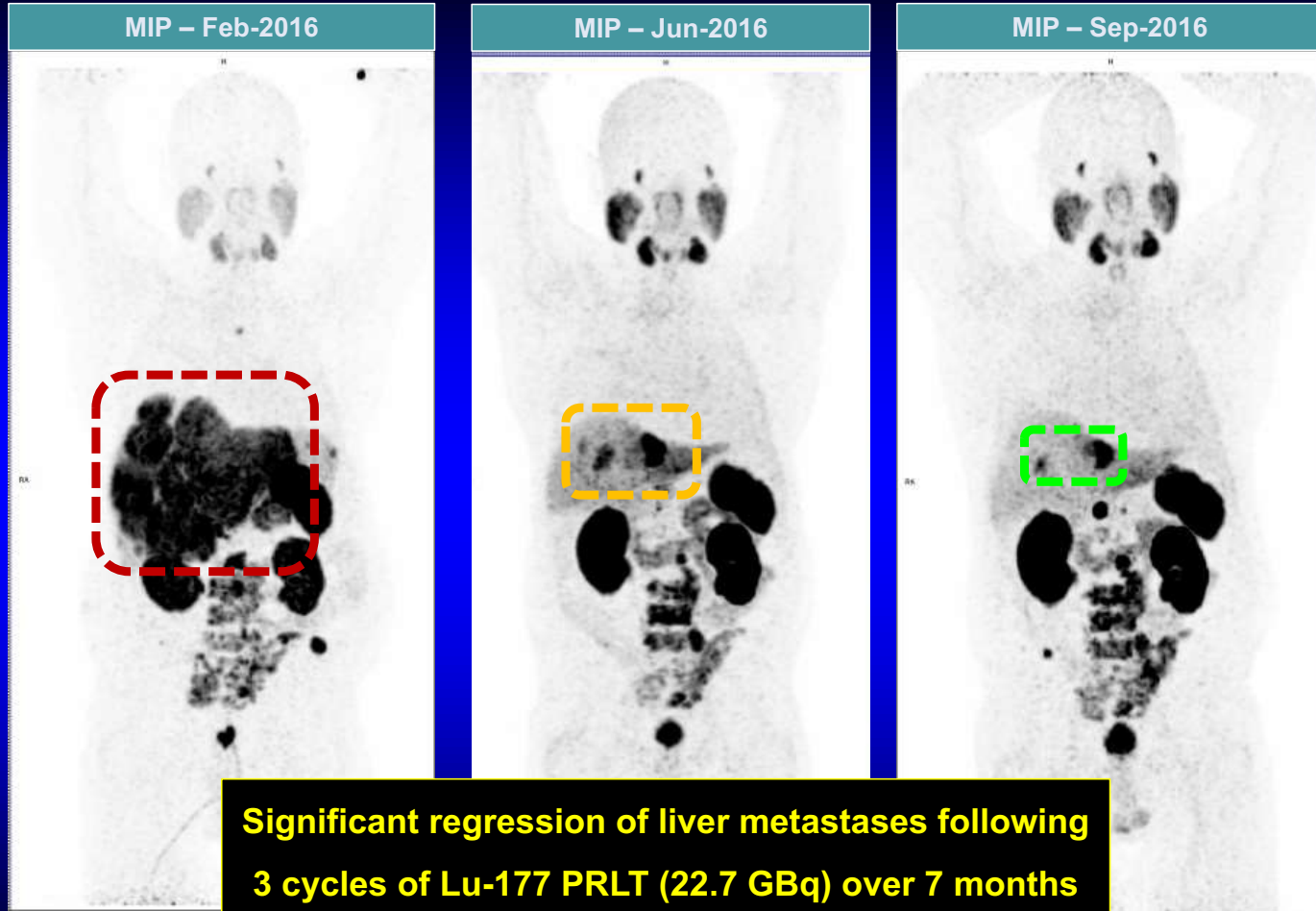
\*

# Peptide Radio Ligand Therapy (PRLT) targeting PSMA



Kratochil C. (JNM 2016); Kulkarni H. (J Nucl Med 2016)

## Ga-68 PSMA PET/CT – Restaging – EXCELLENT RESPONSE TO THERAPY



474858\_2016\_FB



## AAA's current leadership



**Stefano Buono**  
AAA Advisor



**Susanne Schaffert**  
Chairperson and President  
of AAA



**Gérard Ber**  
AAA Advisor



## Our mission to reimagine medicine



**Unique radiopharmaceutical experience, products and pipeline**



**Novartis resources, scale and expertise** will help realize the full benefit of the AAA portfolio

AAA and Novartis partnership attributes

## Key priorities to continue shaping our future

### Operational Execution



- Successfully enter the theragnostic market with the **launch of Lutathera** and build a leadership position in theragnostics

### Breakthrough Innovation



- Position AAA as a **core player in oncology with another theragnostic drug** pairing registered within 5 years

### Data / Digital Leadership



- Develop **Data/Digital strategy** for all units and functions

### Trust & Reputation



- Shape the role of **nuclear medicine** in the oncology market

### Culture & Organization



- **AAA remains distinct entity** in Novartis
- **Inspired employees** are the most productive



## Keeping patients at the center of everything we do

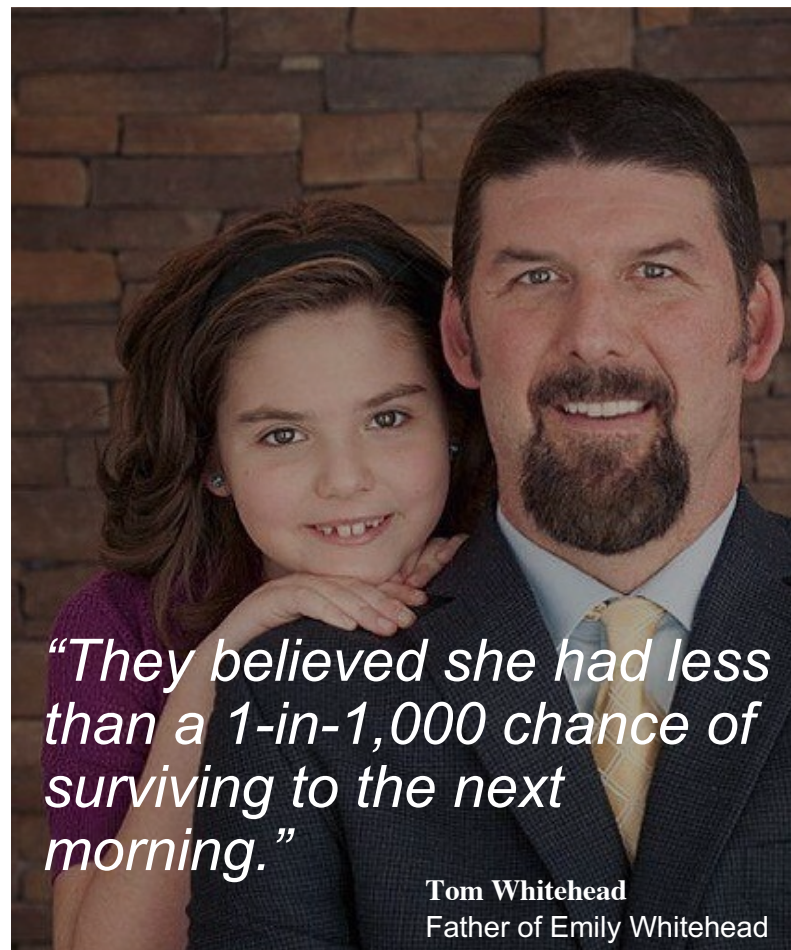
*"I was given three to six months to survive and I'm 16 months in remission ... I'm a walking miracle."*

**Scott McIntyre,**  
Patient



*"They believed she had less than a 1-in-1,000 chance of surviving to the next morning."*

**Tom Whitehead**  
Father of Emily Whitehead







**Thanks for your attention**

