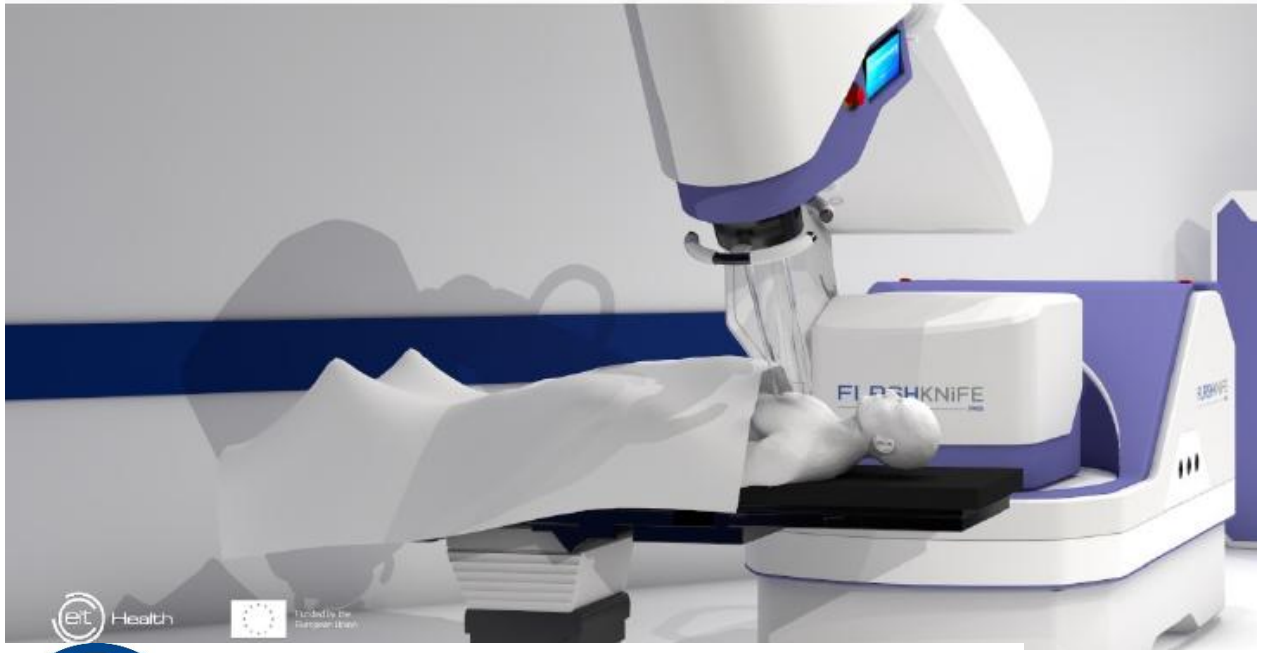
SPEED CONFERENCING

Traitements locaux et Phases Précoces

Modérateur : Christophe Le Tourneau
Avec la participation de : Eric Deutsch, Louis Kayitalire

Ultra-high dose-rate radiotherapy for skin cancers

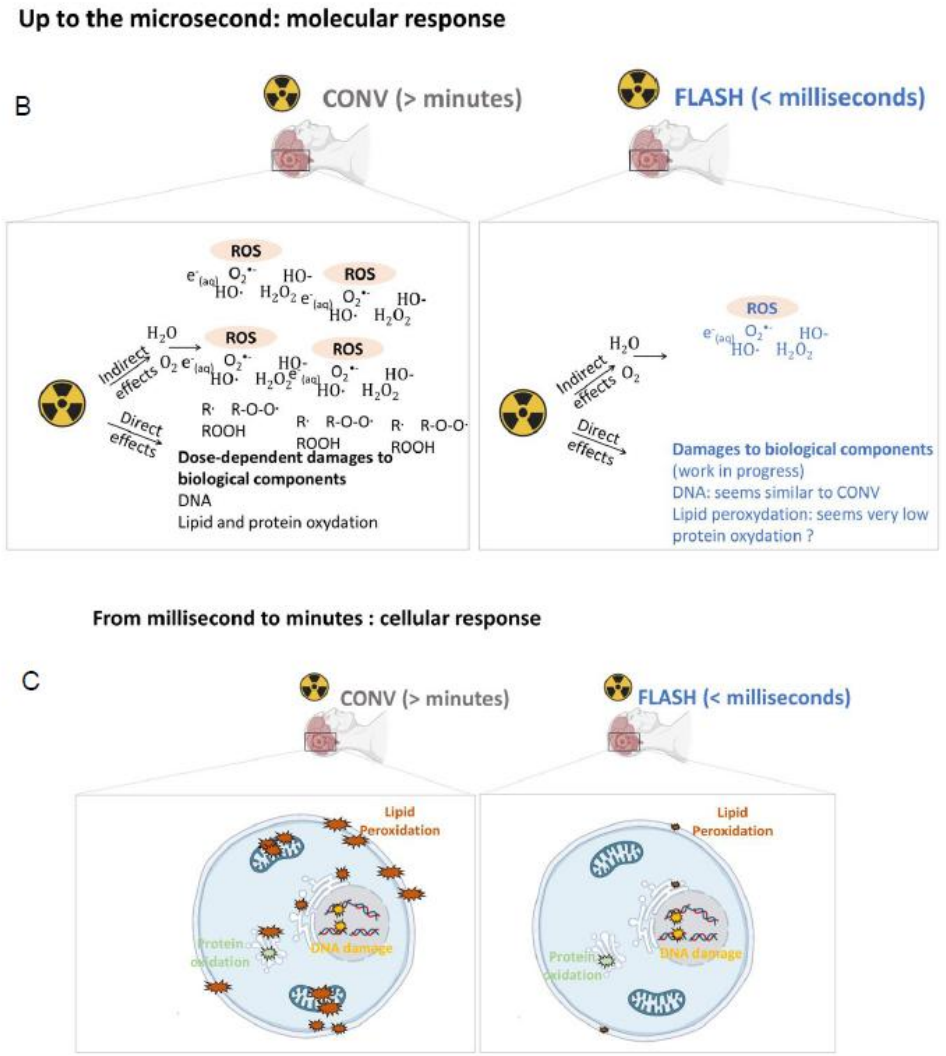


EIT Health is supported by the EIT, a body of the European Union

Eric Deutsch, Charlotte Robert, C Massard

Gustave Roussy, Villejuif, France

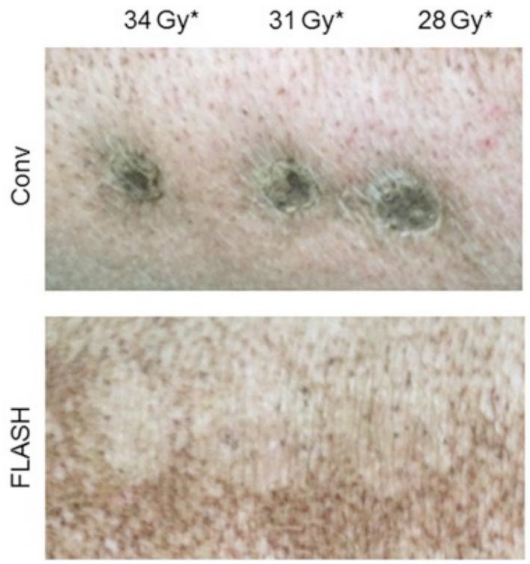
FLASH radiotherapy



FLASH Radiotherapy

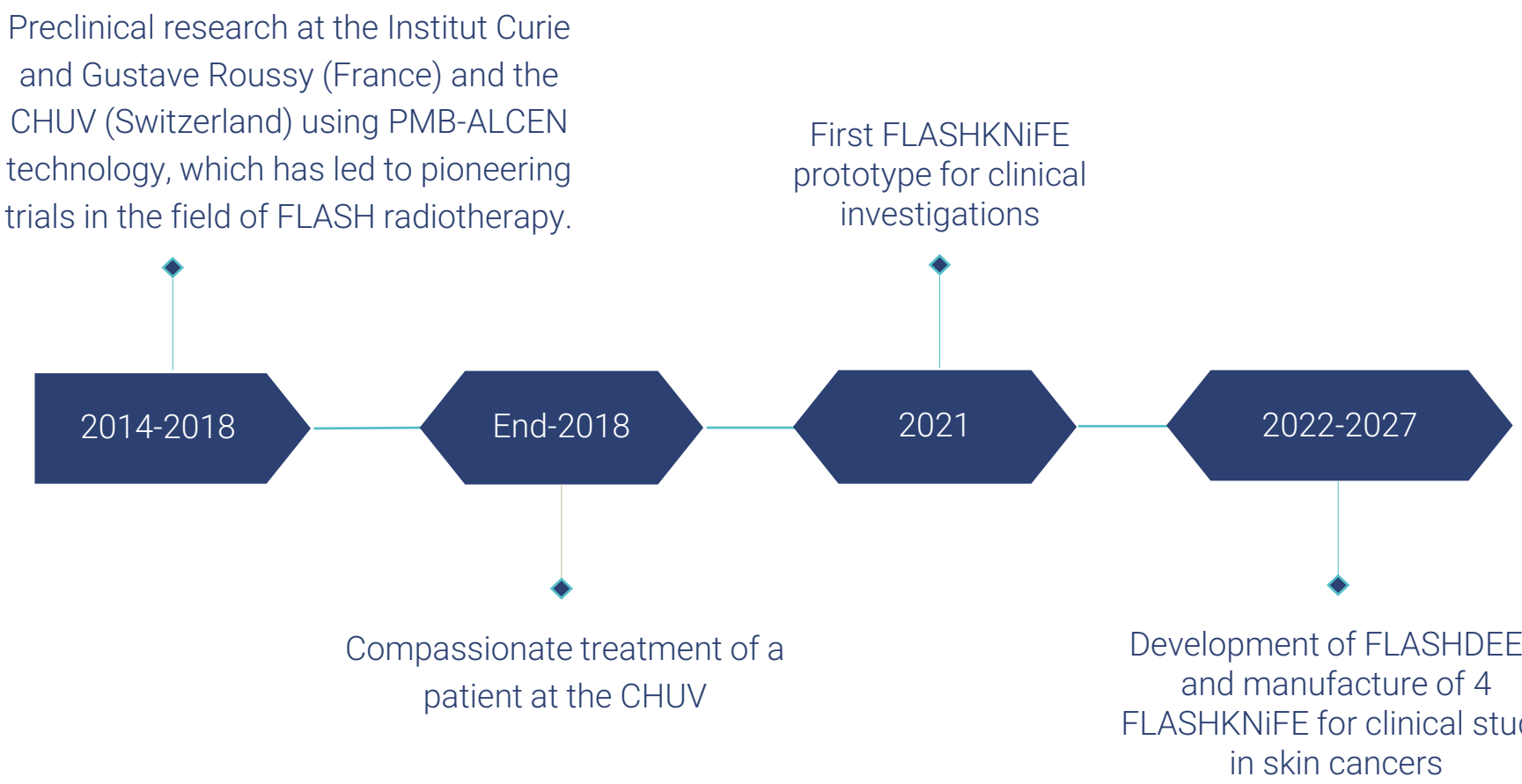
- Conventional radiotherapy >> **a few Gy/minute in multiple sessions of several minutes**
- **FLASH** mode >> an **ultra-high radiation dose (up to 350 Gy/s !)** of pulsed electron beam delivered in **a fraction of a second** and in **a single session**
- **FLASH** effect >> same destructive effect on the tumor as conventional radiotherapy, while **sparing normal tissue**

→ FLASHKNiFE



Thirty-six weeks postradiotherapy, macroscopic visualization showed severe fibronecrotic lesions in Conv-irradiated spots and the normal appearance of the skin in FLASH-irradiated spots.

The history of FLASH radiotherapy



Genesis of the project

- Initial thoughts on the project and **creation of a European consortium**: 2020
- 2021: **approval of funding** for a European project by **EIT Health** (2022-2024)
- **Objective: Obtaining CE marking for the FLASHKNiFE machin thanks to a multicentre trial focusing on skin cancers** (MDR regulation)

Universitätsklinikum Erlangen

THERYQ

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

CENTRO HOSPITALAR LISBOA NORTE, EPE

HSM HPV

Establishment of a European consortium — 2020

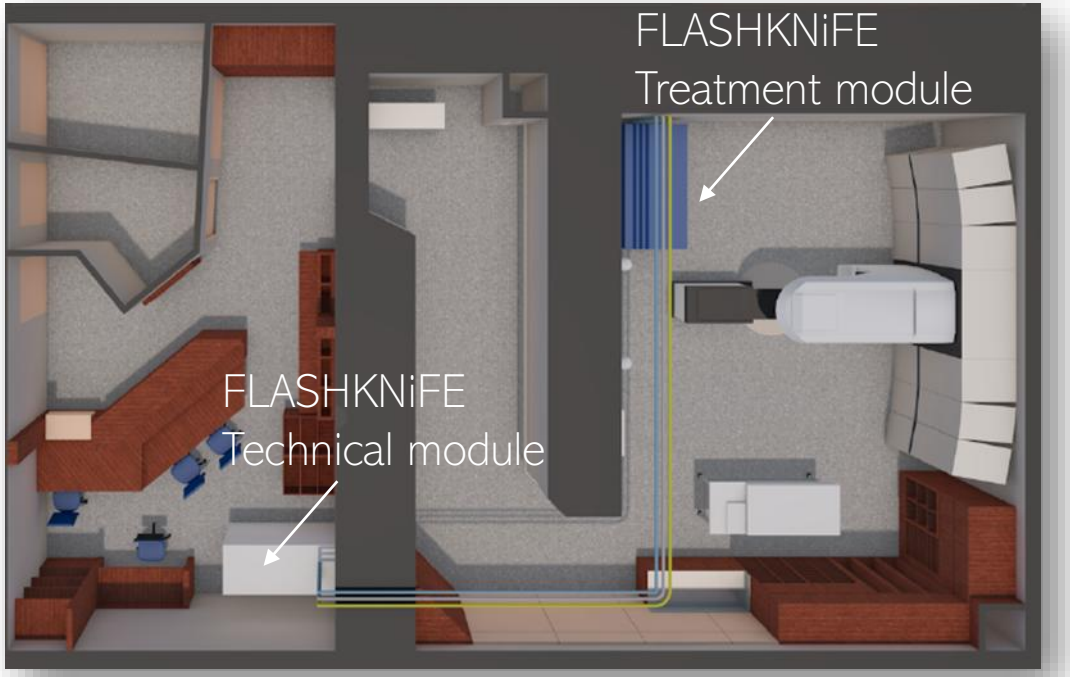
Official launch of the EITHealth project — Jan 2022

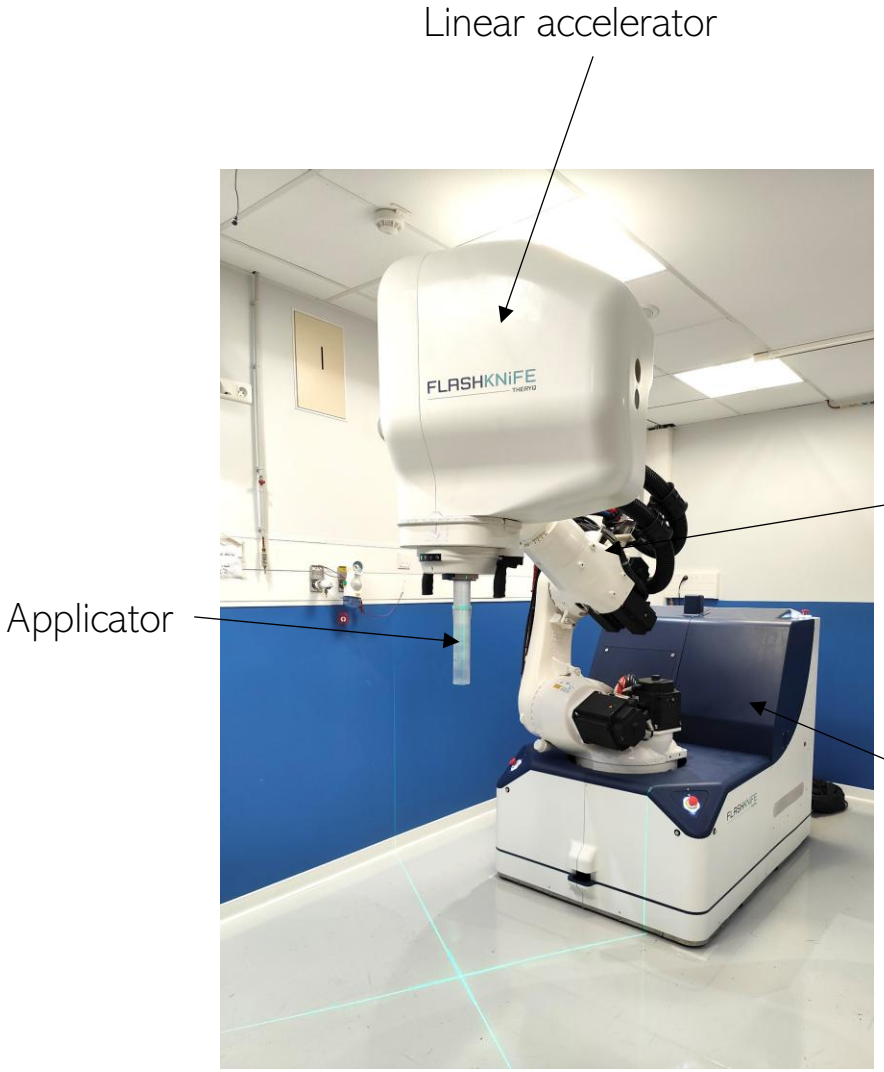
Arrival of the machine at Gustave Roussy — June 2023

Exhaustive characterization of the beam and start of preclinical experiments

Installation of the FLASHKNiFE system in the RT department

- Installation of the machine in **an existing bunker** in which a **LINAC is already present** (maximum energy 20 MeV)
- Renovation of the bunker to **accommodate electrical sockets, ventilation, and cable routine**
- Updating **safety systems** to meet French standards and regulatory requirements

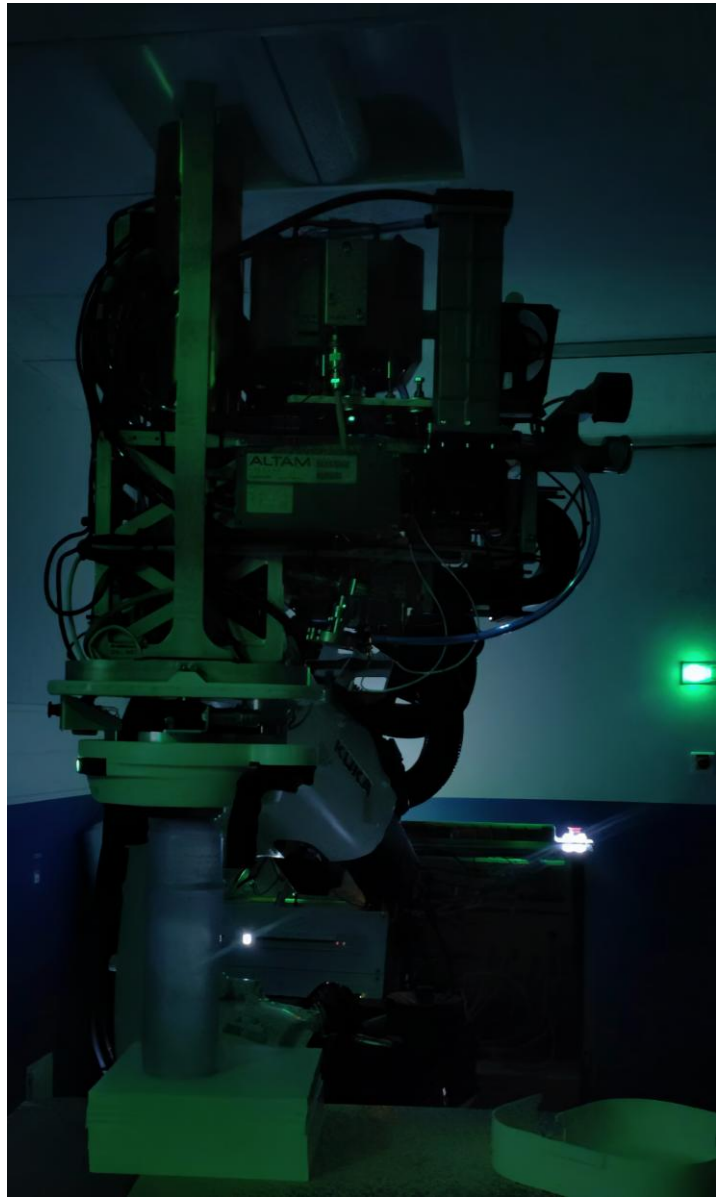




On-site installation time: 2 weeks

FlashKnife

10MeV
<3cm



Funded by the European Union
eit Health

Regulatory difficulties and … solutions!

✓ **Step 1:**

→ Authorization from the French Nuclear Safety Authority (ASN) for **use in research (Sept 2023)**

→ Has allowed/allows:

- Installation,
- Testing and commissioning,
- Research: radiobiology, exhaustive characterisation of the beam

Procedure duration: 1 year

Step 2 – still in progress:

→ Authorization **pending** with the French National Agency for the Safety of Medicines and Health Products (ANSM)

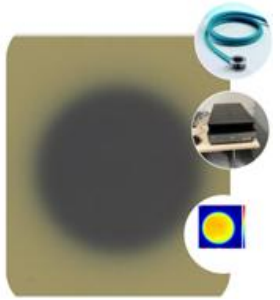
→ Must approve the clinical trial

Step 3:

→ application to obtain an Authorization from the French Nuclear Safety Authority **for clinical use**

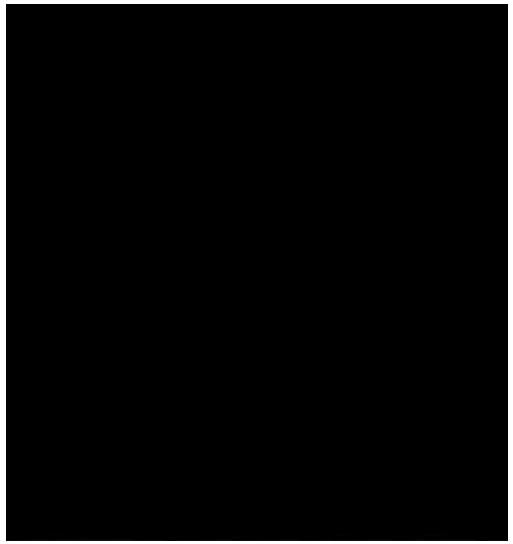
Beam commissioning

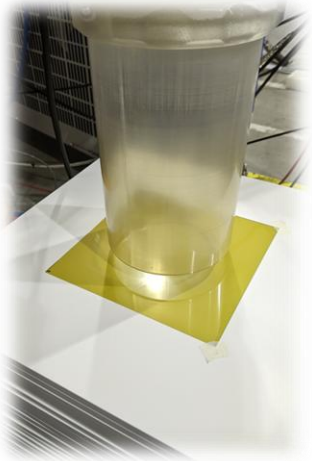
- Design of an experimental program to characterize:
  - **conventional beam properties** (absorbed dose, PDD, profiles, etc.)
  - the **impact of beam structure** (pulse width, repetition frequency) on beam properties
  - **stability of beam properties over time**



- Purchase/loan of **appropriate dosimetric equipment: EBT3, EBT-XD (Ashland) radiochromic films, FlashDiamond (PTW)**

Laboratoire National Henri Becquerel
LNE-LNHB





- Studies to characterize the response of **new detectors to UHDR electron beams** (OC-1 films (OrthoChromic), HYPERSCINT™ plastic scintillator (medscint))

Look again presentation of Julie Colnot on Saturday 4th of May in session “Proton and FLASH detectors, dose measurement and phantoms“

FLASHKNiFE Project objectives

01 PRODUCT

Bring an **innovative Medical Device to the Market**, therefore changing the way radiotherapy is administered today.

02 PATIENT

Improve the **patients' quality of life** by drastically reducing the number of sessions (1 vs 5-20) and giving a more tolerated and more efficient treatment.

03 COSTS

Provide **the healthcare system with a cost-saving solution**.

Objectives

- **Primary objective:**

  Acute safety profile of UHDR radiotherapy delivered to malignant lesions of the skin.

- **Secondary objectives:**

  To describe the overall safety profile of UHDR radiotherapy on malignant lesions of the skin and surrounding normal tissue.

  To evaluate the efficacy of UHDR radiotherapy delivered to malignant lesions of the skin.

  To evaluate the quality of life of patients treated with FLASHKNiFE.

- **Exploratory objectives:**

  To evaluate the impact of the use of the FLASHKNiFE device on the clinical workflow according to the radiation dose regimen.

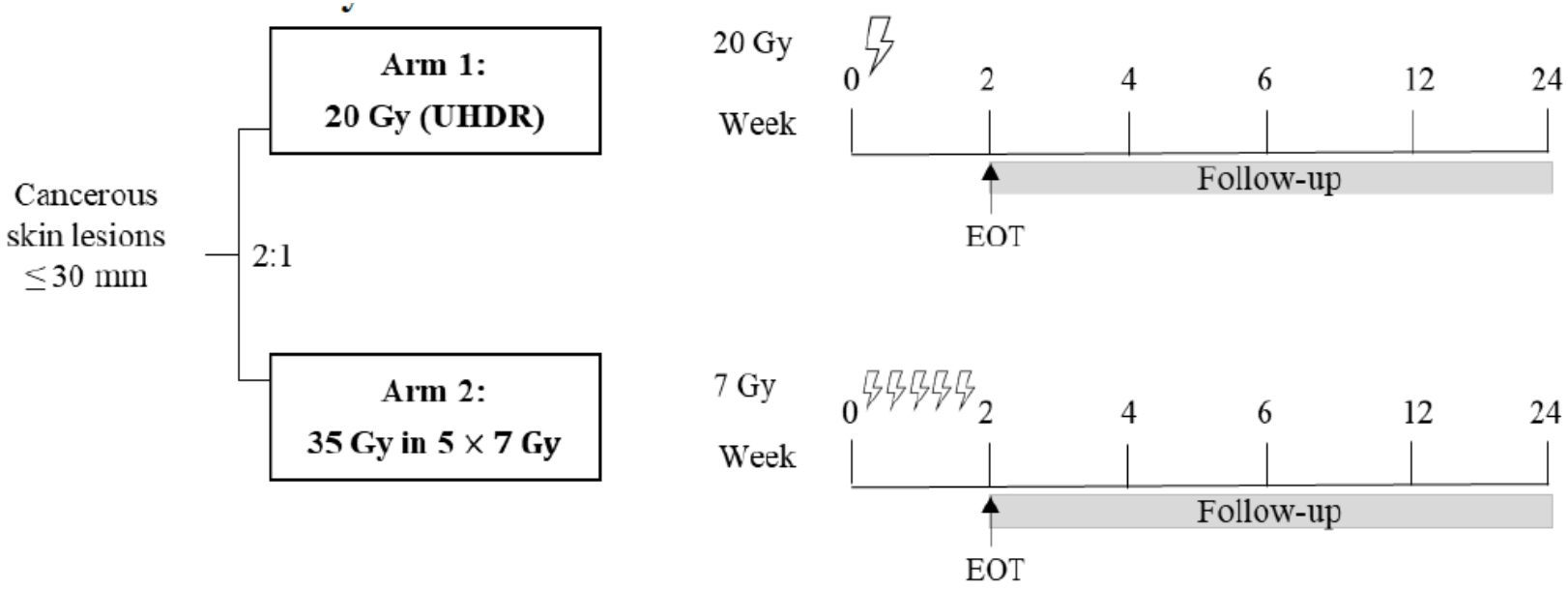
  To evaluate the cost-effectiveness of the use of the FLASHKNiFE device according to the radiation dose regimen.

- **Primary endpoint:**

  The **rate of patients experiencing Grade ≥ 3 radiation dermatitis from the start of treatment until 6 weeks post treatment,.**

Study Design

- Multi centric, open-label, non-comparative randomised clinical trial using a Bayesian approach.
- The aim will be to evaluate the safety and efficacy of UHDR radiotherapy in comparison to a standard-of-care regimen of radiotherapy for adult patients with cancerous lesion(s) of the skin.



Inclusion criteria:

1. Adult patients aged ≥ 18.

2. Patients with histopathologically proven cancer with one or more skin or superficial tissue lesions, for whom radical surgery is not a recommended option and radiation therapy appears as a valuable option.

- BCC, SCC, melanocytic tumours (melanoma), soft tissue tumours and neural tumours (Merkel);

-Secondary malignant tumours of the skin and superficial tissues such and cutaneous manifestations of haematological malignancies (cutaneous T-cell lymphoma).

3. Size of the treated lesion(s) ≤ 30 mm in its largest diameter and the planned treatment volume ≤ 40 mm depth.

Presentation of the FlashKnife machine

European project funded by EIT Health→ Installation at GR of the FlashKnife system (Theryq)

- Pulsed electron beams of 6 MeV or 10 MeV energy
- Mobile platform Robotic arm with manual and automatic movement
- Circular PMMA applicators
- Manual settings: pulse frequency, pulse duration, number of pulses
- Machine not CE marked yet

1/2 achieved Project Milestone to date

(M03) First unit installed (IGR-Villejuif)

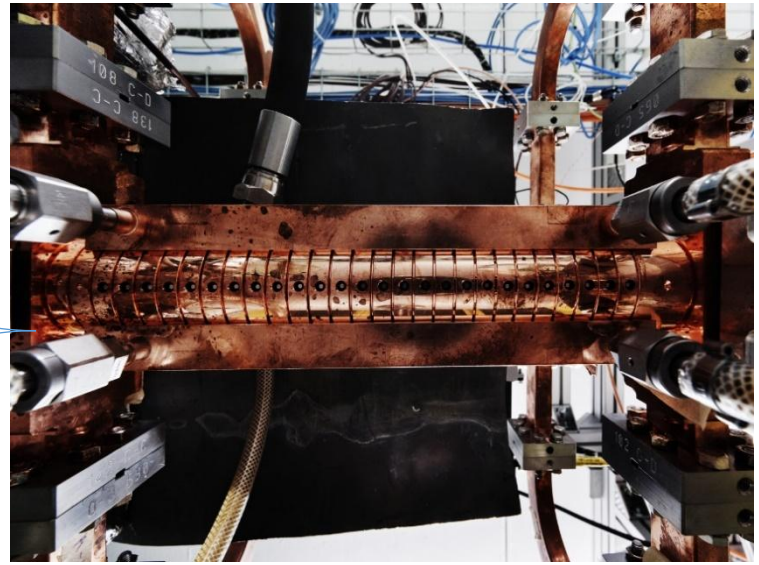
Developments in FLASH radiotherapy

- Electrons of 6-10 Mev
- Limited penetration
- Skin irradiation or IORT

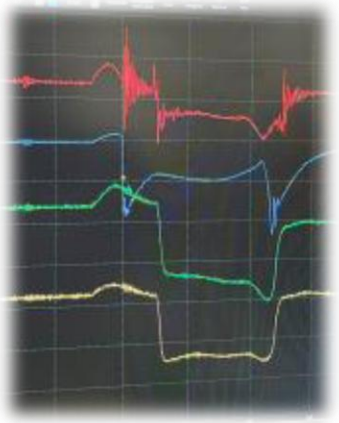
FLASHKNiFE

FLASH-DEEP

- Very high energy electrons ~150 MeV
- All types of tumour
- Implementation ~€12m



Next steps



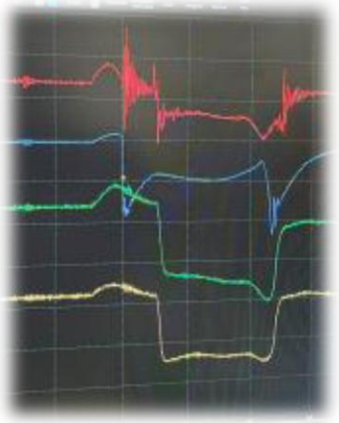
- **FLASHKNiFE:**
  - Post-processing of ACCT (Current Transformers) signals is being optimized to facilitate on-line dose control
  - Radiobiology experiments in progress
  - Ongoing work to characterize detectors
  - Start of clinical trial planned for late 2024

- **Next step: making it possible to irradiate deep targets by producing high-energy UHDR electron beams = FLASHDEEP project**

CLEAR and CLIC technologies, CERN

bpifrance

Next steps



- **FLASHKNiFE:**
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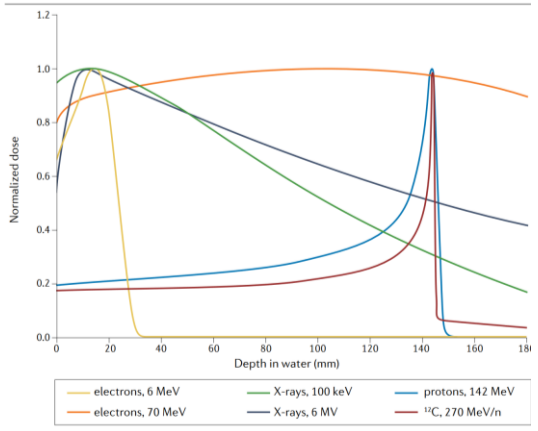
  - Start of clinical trial planned for late 2024

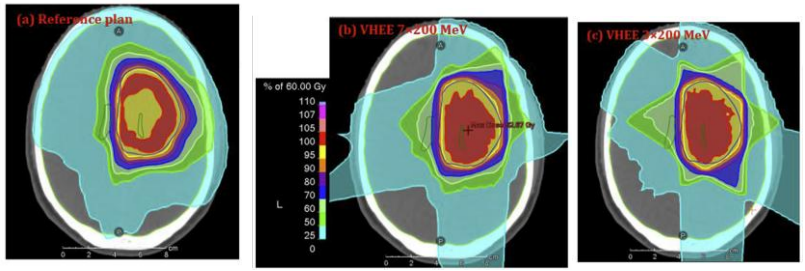
- **Next step: making it possible to irradiate deep targets by producing high-energy UHDR electron beams = FLASHDEEP project**

CLEAR and CLIC technologies, CERN

Up to 140 MeV UHDR electrons



Vozenin M.C. et al., Nature Reviews Clinical Oncology 2022



3D-conformal very-high energy electron **therapy** as candidate modality for FLASH-RT: A **treatment planning** study for glioblastoma and lung cancer.
Böhlen TT, Germond JF, Traneus E, Vallet V, Desorgher L, Ozsahin EM, Bochud F, Bourhis J, Moeckli R.
Med Phys. 2023 Sep;50(9):5745-5756. doi: 10.1002/mp.16586. Epub 2023 Jul 10.
PMID: 37427669


THEAYU

THERYQ IGR news : Public support for innovation - FLASHDEEP

- Programme: France 2030 (DGE)/ Operator Bpifrance "Accelerating the transformation of key sectors of our economy through innovation".
- Project: "FLASHDEEPDuration: 7 years (07/2023-06/2030)
- Total cost of the project: €84m
- Estimated amount of aid: €38m
- THERYQ: €30MInstitut / Gustave Roussy: €8m

SPEED CONFERENCING

Traitements locaux et Phases Précoces

Modérateur : Christophe Le Tourneau
Avec la participation de : Eric Deutsch, Louis Kayitalire

Traitement locaux et Phases Precoces

Intratumor Nanotherapy with NBTXR3: A First-In-Class Radioenhancer

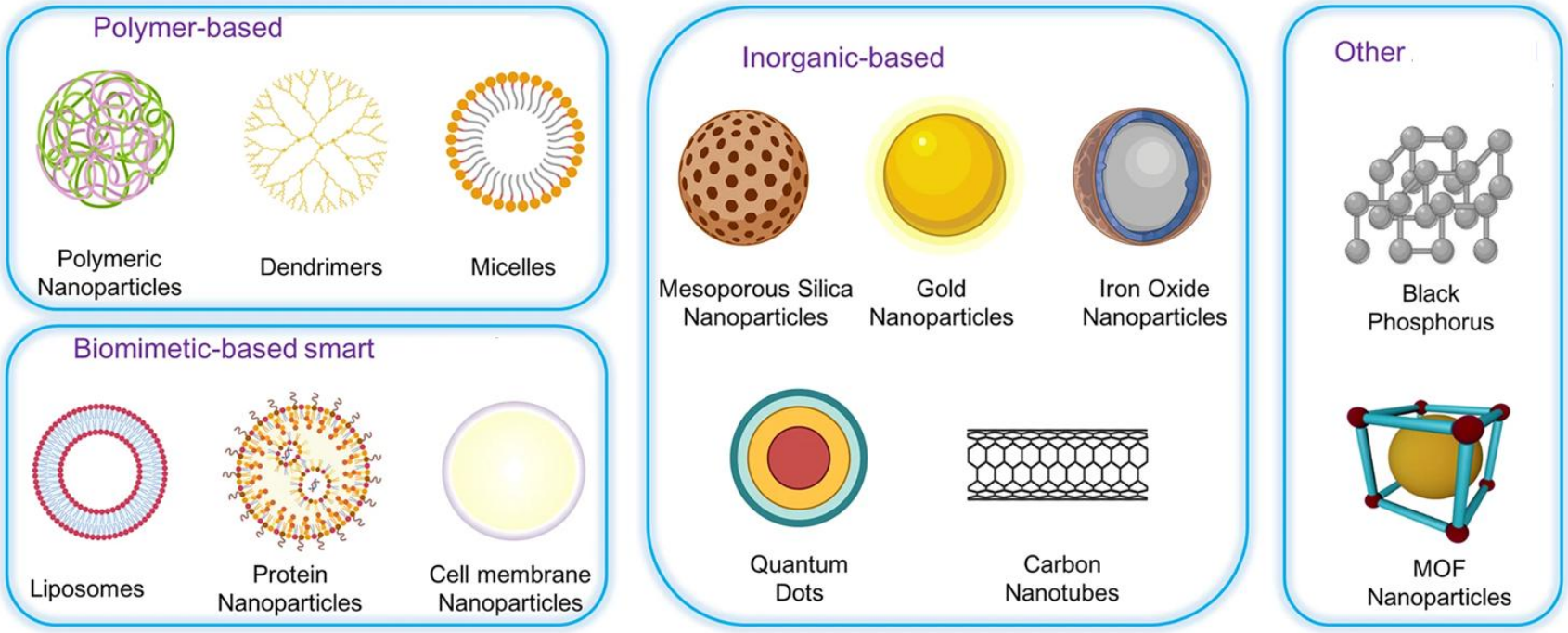
NANOBIOTIX

Louis Kayitalire, MD

Chief Medical Officer
Nanobiotix

Nanostructures

- At least one dimension in the 1–100 nm range
- Small size confers several advantages compared to traditional therapeutics
- Can accumulate in the tumor by passive or active mechanisms
- Large surface area-to-volume ratio of can enable high drug loading and multimodal functionality
- Areas of investigation include: targeted drug delivery, thermal ablation, gene therapy, MRI contrast enhancement, fluorescence imaging, theranostics, and photo-acoustic imaging



At Nanobiotix we have sought to develop a radiation enhancing nanoparticle

Elabed et al., 2025; Danhier et al., 2010; Bertrand et al., 2014; Sun et al., 2023

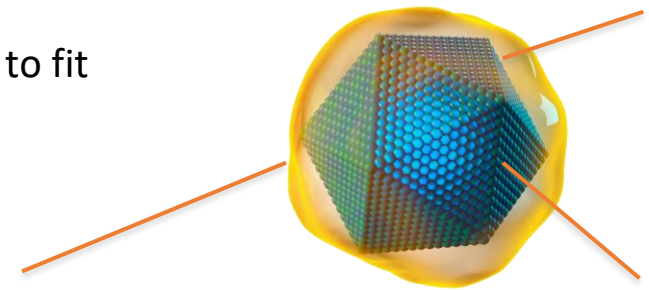
NBTXR3 a new Nanotherapy

NBTXR3 is a Suspension of Nano-sized Particles for One-Time Intratumoral Injection

NBTXR3: A First-In-Class Radioenhancer

NANOMETER SCALE

Mean size centered on 50 nm to fit into the cell



HAFNIUM OXIDE CORE

High atomic number (Z=72) and high electron density to increase absorption of ionizing radiation and cell damage

AMORPHOUS COATING

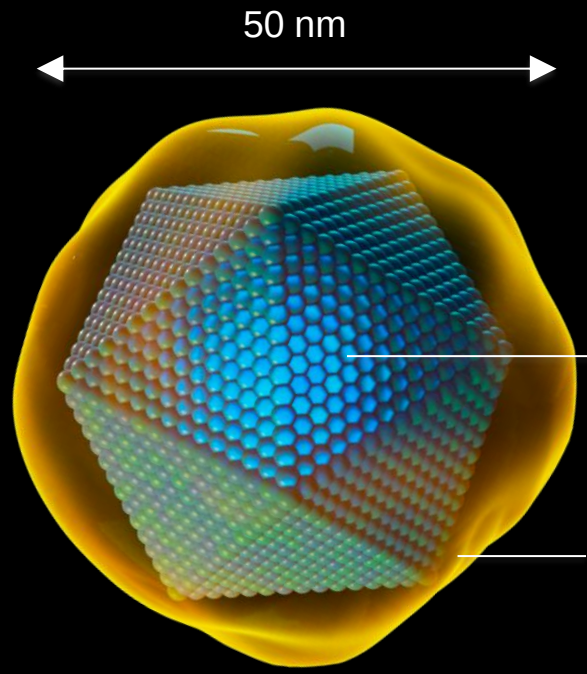
Negative surface charge for stability at neutral pH in aqueous medium and to facilitate tumor cell entry

BIOLOGICALLY INERT

NBTXR3 is inert (“off” status) in the absence of ionizing radiation. It is activated by ionizing radiation and increases energy dose deposit within cells (“on” status)

NANOBIOTIX
EXPANDING LIFE

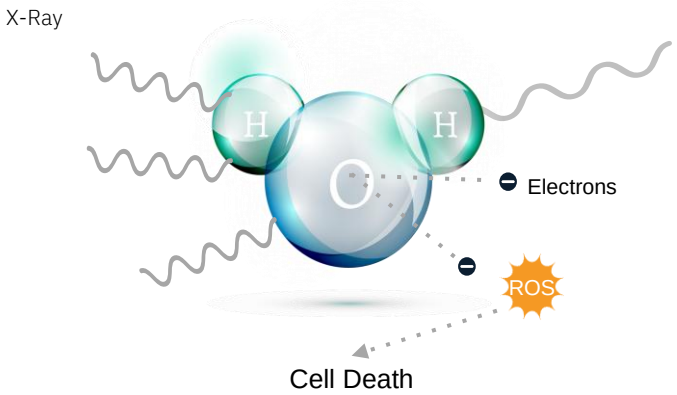
NBTXR3

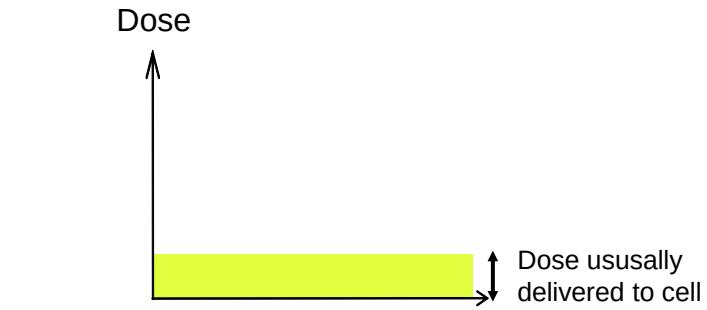


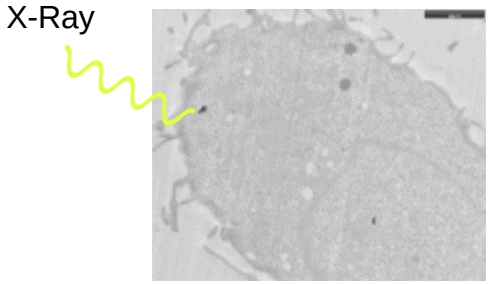
For intratumoral injection

NBTXR3 Radio-enhancement

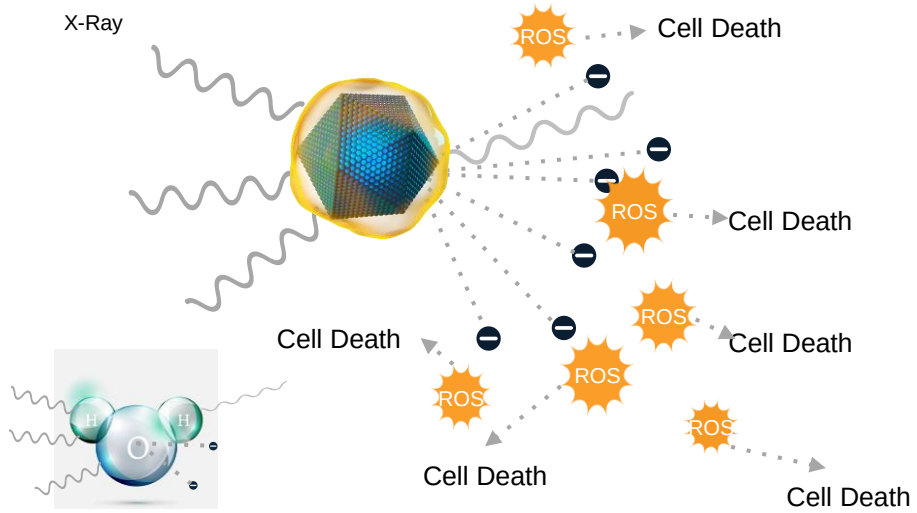
RT

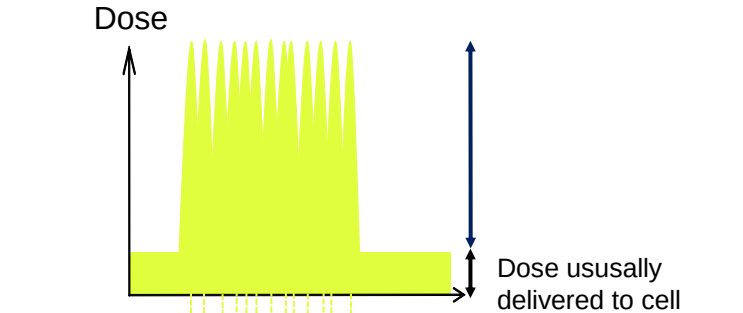


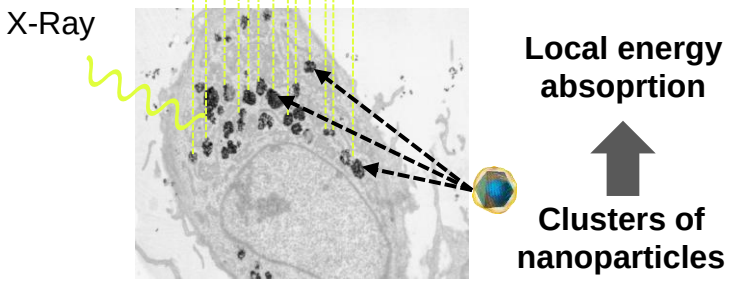




RT + NBTXR3

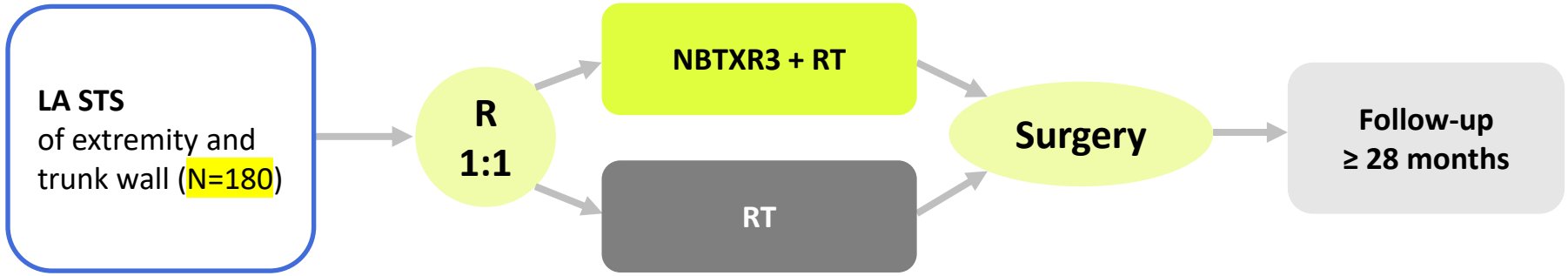






Proof-of-Concept in Sarcomas

- **Phase II/III Act.In.Sarc study (NCT02379845):** A prospective randomized, two-arm, multi-center, open-label and active-controlled study in patients with LA STS of the extremity or trunk wall.



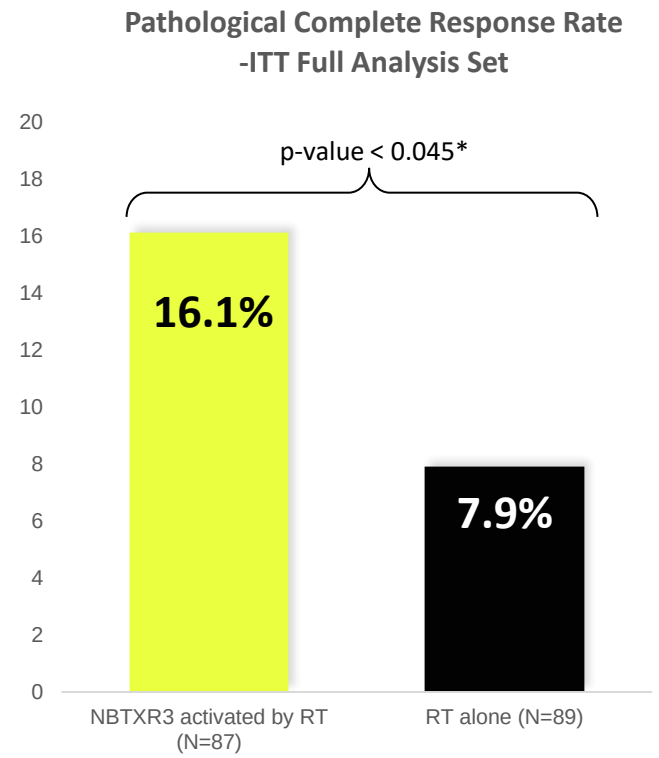
Primary endpoint:
Pathological complete response rate* (pCRR)

Secondary endpoints:
Safety Profile
Wound complications
Oncologic resection Amputation rate

* Pathological Response evaluated by an independent central Pathological Review Board following EORTC guidelines

Proof-of-Concept in Locally Advanced Soft Tissue Sarcoma

Doubling of Pathological Complete Response in Phase II/III



Results

- Achieved its primary endpoint of pathological CRR
- Achieved its secondary endpoint in quality of margins (R0)
- Demonstrated long-term persistent bioavailability
- No impact on patient ability to receive planned dose of RT
- European marketing authorization (CE mark)

Published in Lancet Oncol. 2019

NBTXR3, a potential first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2-3, randomised, controlled trial.

Sylvie Bonvalot, Piotr L Rutkowski, Juliette Thariat, Sébastien Carrère, Anne Ducassou, Marie-Pierre Sunyach, Peter Agoston, Angela Hong, Augustin Mervoyer, Marco Rastrelli, Victor Moreno, Rubi K Li, Béatrice Tiangco, Antonio Casado Herraez, Alessandro Gronchi, László Mangel, Teresa Sy-Ortin, Peter Hohenberger, Thierry de Baère, Axel Le Cesne, Sylvie Helfre, Esma Saada-Bouzid, Aneta Borkowska, Rodica Anghel, Ann Co, Michael Gebhart, Guy Kantor, Angel Montero, Herbert H Loong, Ramona Vergés, Lore Lapeire, Sorin Dema, Gabriel Kacso, Lyn Austen, Laurence Moureau-Zabotto, Vincent Servois, Eva Wardelmann, Philippe Terrier, Alexander J Lazar, Judith V M G Bovée, Cécile Le Péchoux, Zsusanna Papai

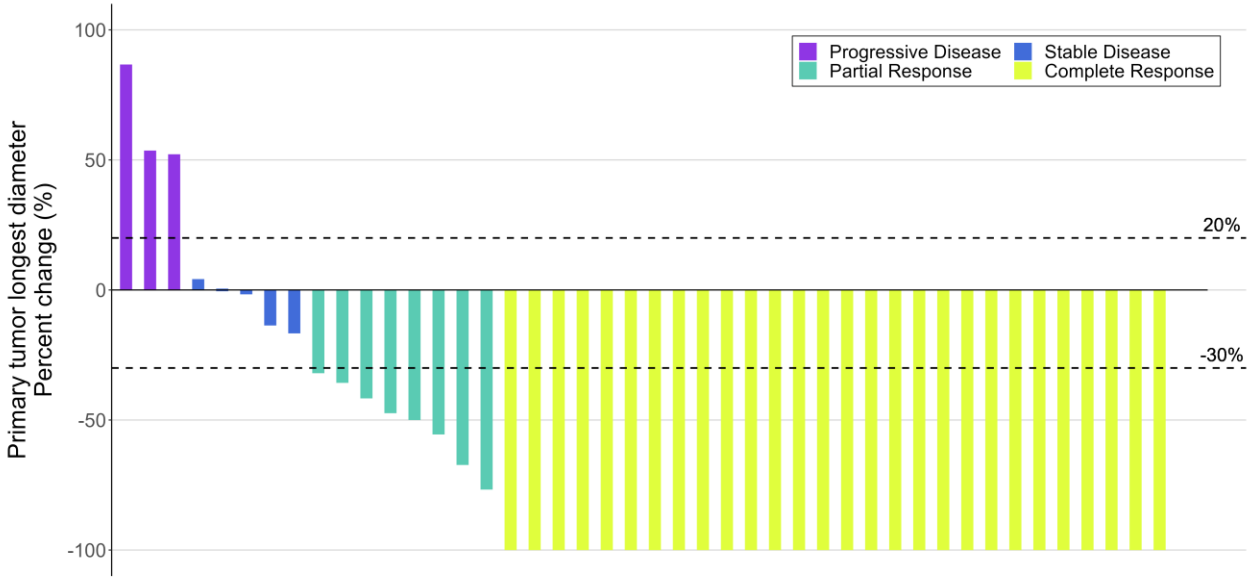
Summary

Background Pathological complete response to preoperative treatment in adults with soft-tissue sarcoma can be achieved in only a few patients receiving radiotherapy. This phase 2–3 trial evaluated the safety and efficacy of the hafnium oxide (HfO_2) nanoparticle NBTXR3 activated by radiotherapy versus radiotherapy alone as a pre-operative treatment in patients with locally advanced soft-tissue sarcoma.

Lancet Oncol 2019
Published Online
July 8, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30326-2

** ITT FAS = Intention to Treat Full Analysis Set; statistically significant at a threshold of 0.04575.*

Phase I of NBTXR3 in LA HN (Study 102)



- **Evaluable patients for Objective Tumor Response**

Underwent at least one post-treatment assessment, and received at least 80% of the planned dose of NBTXR3 and 60 Gy of IMRT

- **12 patients were non-evaluable:**
  - Did not receive 60 Gy of IMRT: 4 patients (3 TEAE, 1 consent withdraw)
  - No post treatment assessment: 8 early deaths

Best Overall Response Based on Investigator Assessment

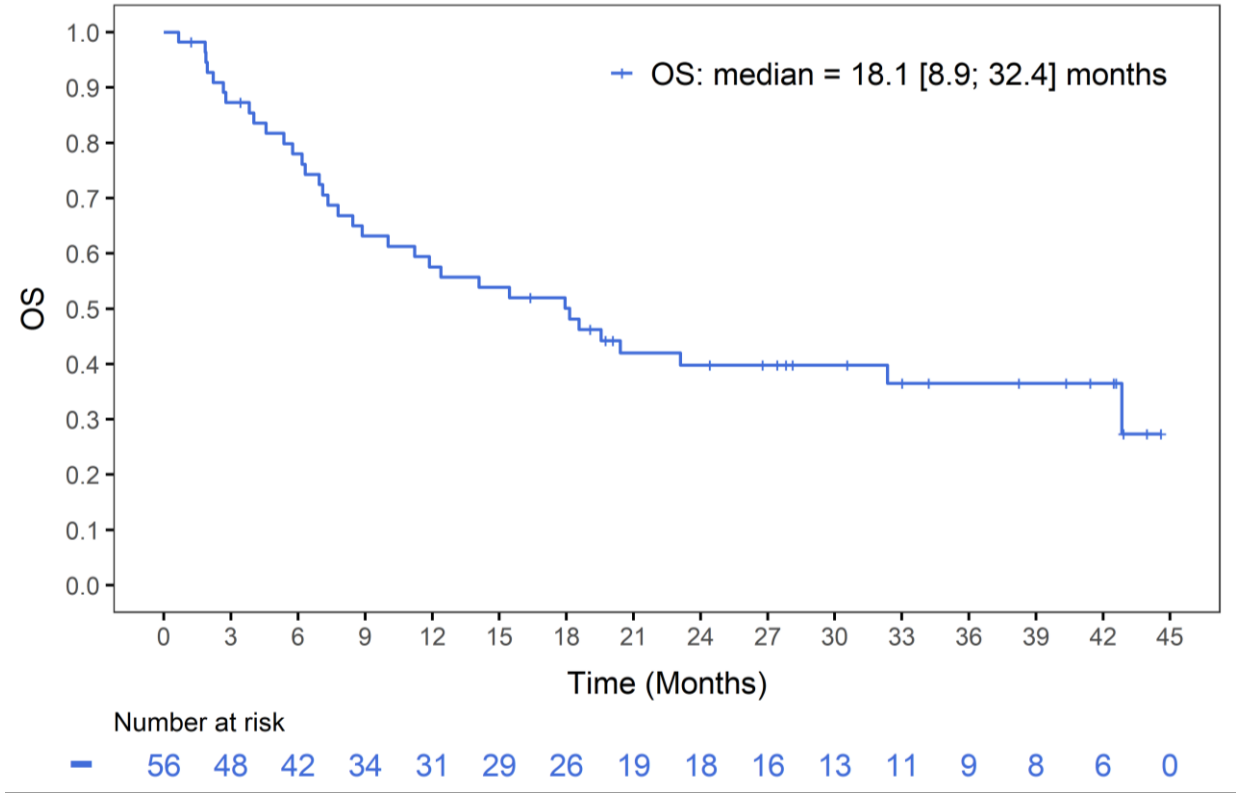
Measurement of tumor change as per RECIST v1.1

NBTXR3 Injected Lesion	Evaluable Patients (n=44)
Best Overall Response, n(%)	
CR	28 (63.6%)
PR	8 (18.2%)
SD	5 (11.4%)
PD	3 (6.8%)
ORR (CR + PR)	**36 (81.8%)**

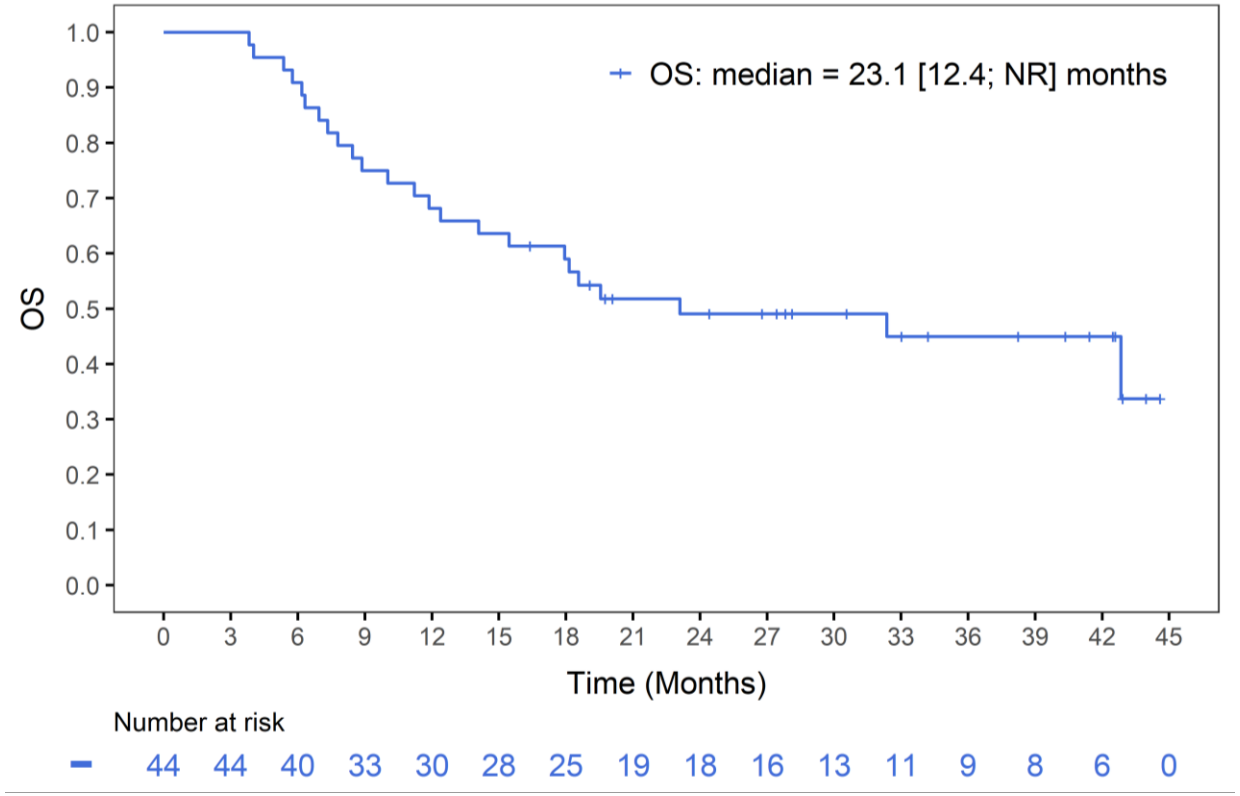
Injected and Non-Injected Lesion	Evaluable Patients (n=44)
Best Overall Response, n(%)	
CR	23 (52.3%)
PR	12 (27.3%)
SD	4 (9.1%)
PD	5 (11.4%)
ORR (CR + PR)	**35 (79.5%)**

Phase I of NBTXR3 in LA HN (Study 102)

All Treated Population N=56



Evaluable Population* N=44



*Patients who underwent at least one post-treatment assessment, and received at least 80% of the planned NBTXR3 dose and 60 Gy

Early stage Development of NBTXR3

Specifics

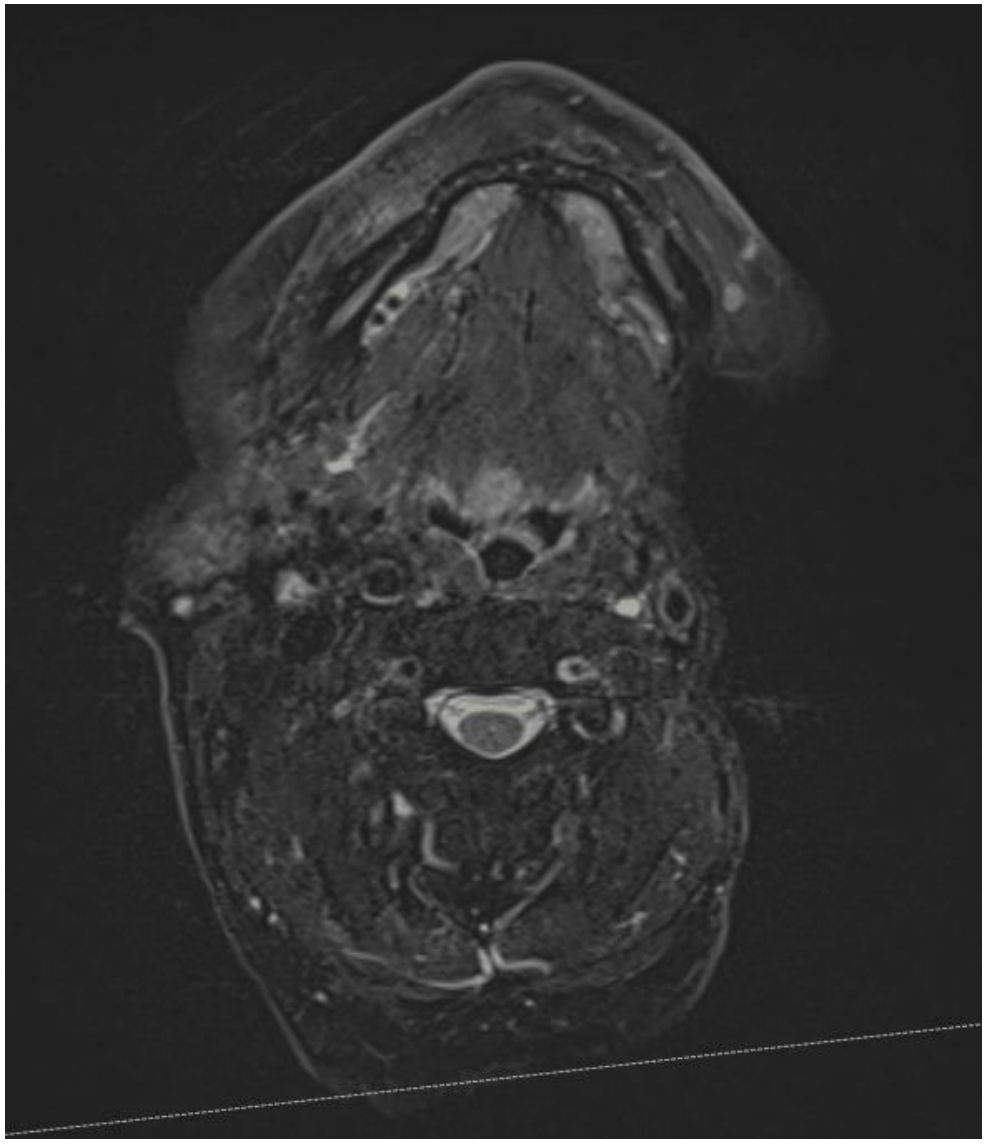
NANOBIOTIX

Dose and dose escalation in phase mg/m² ? Flat dosing ? Or ..

NANOBIOTIX

Gross Tumor Volume (GTV) is used to determine the dosing

Determined through imaging



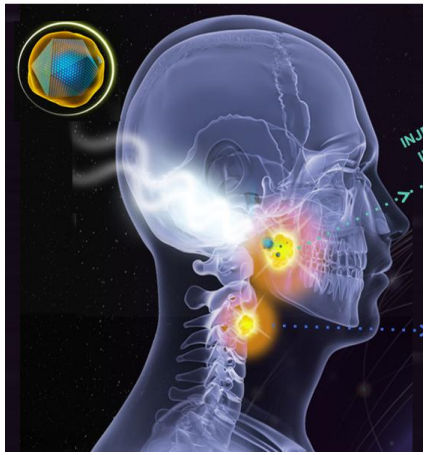
- The dose is a % of the GTV

- Different Dosing % tested in the dose escalation phase

Ex : Total volume of NBTXR3 to be injected = TV x 0.33 = …ml for a dose of 33 %

Expert Injector is needed

A multidisciplinary team as the pillar of Study Successful execution



Surgeon / Interventional radiologist

- Pre-operative tumor control
- Improved surgical resection outcomes
- Improved resectability rates
- Preserving organ integrity and function

Radiation Oncologist

- Local tumor control
- Enhancing dose of radiation 9x within the tumor
- Limiting toxicity to normal tissue (therapeutic ratio)
- Signs of efficacy across multiple radiation modalities

Medical Oncologist

- Feasible and safe in combination with chemotherapy

Immunotherapy specialist

- Systemic tumor control
- Priming immune response to increase response rate to immunotherapy
- Overcoming resistance to checkpoint inhibitors

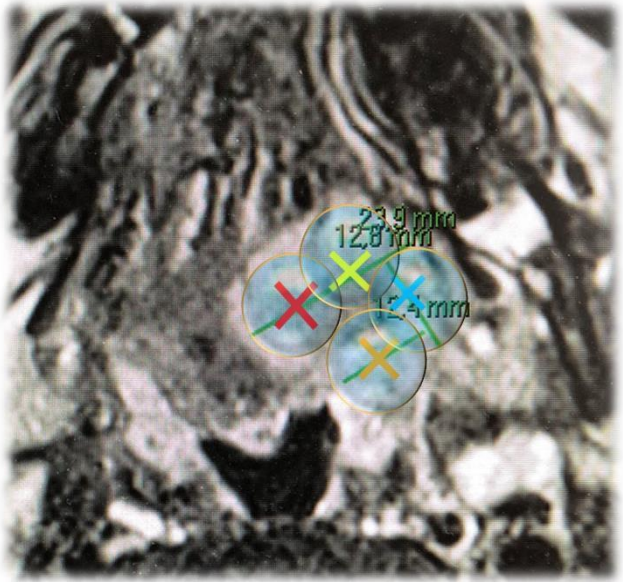
Cross functional modalities to be anticipated at very early stage in all sites settings =
Expanding the oncology playing field leads to in depth analysis of sites org

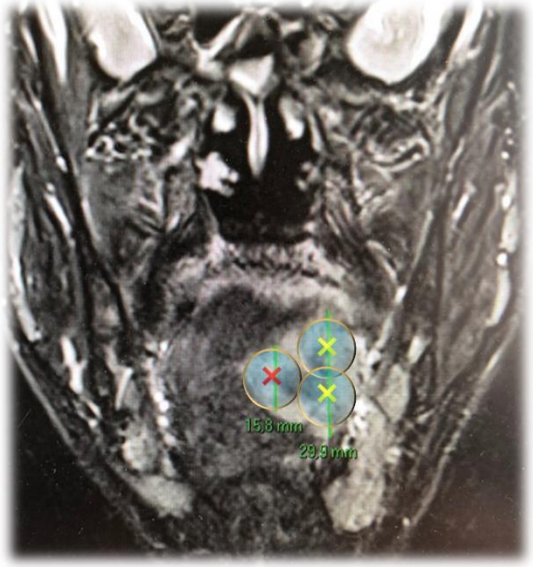
How to ensure optimal administration?

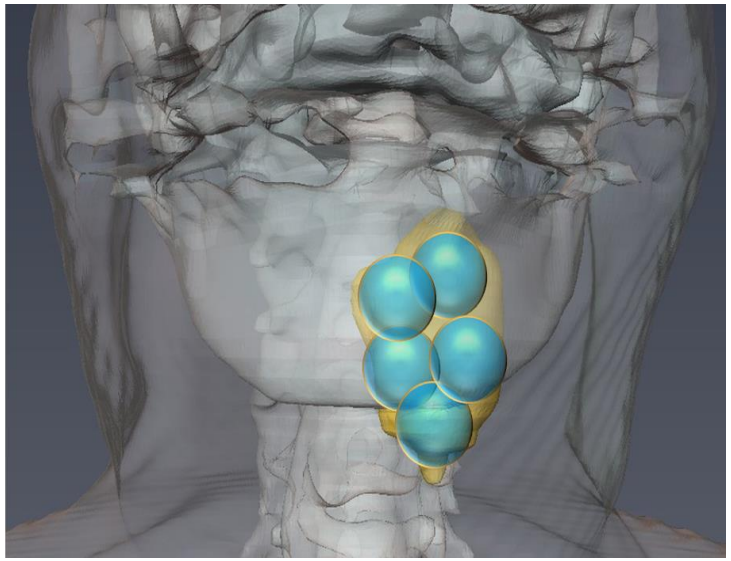
Injection Planning Example

Planning NBTXR3 IT injection on the pre-treatment imaging

Target areas: defined as spheres with a diameter of 1.5 cm within the tumor volume, for NBTXR3 to disperse as evenly as possible within the tumor





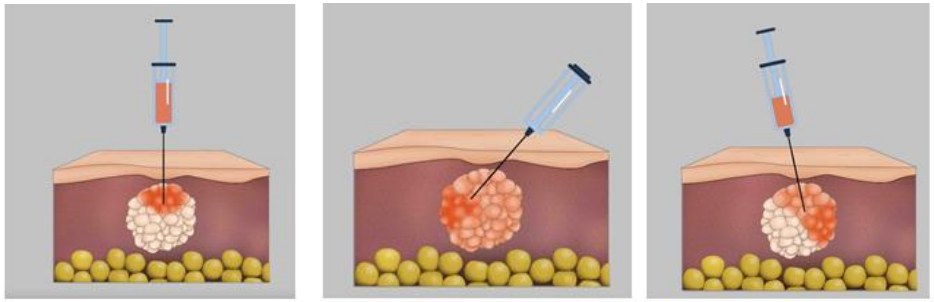


Needle tip

Target area

Injection Execution

- For some areas, a single puncture point can access multiple target areas.
- This can be accomplished by either **inserting the needle deeply and pulling back** as each area is injected or by **fanning the needle** to access multiple areas (or a combination of them both)

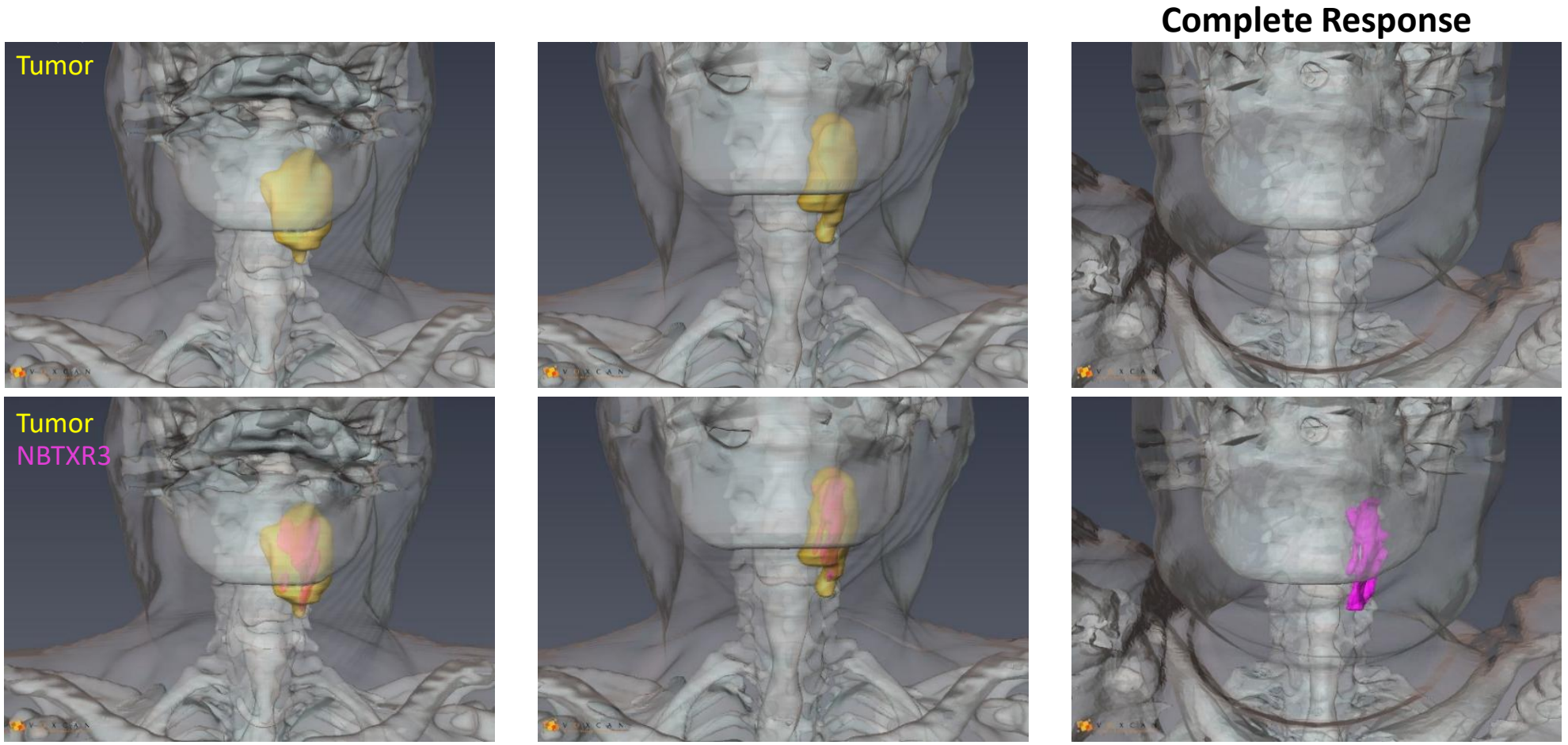


One single puncture point reaching multiple target areas

Liem X, et al., Head & Neck (2024)

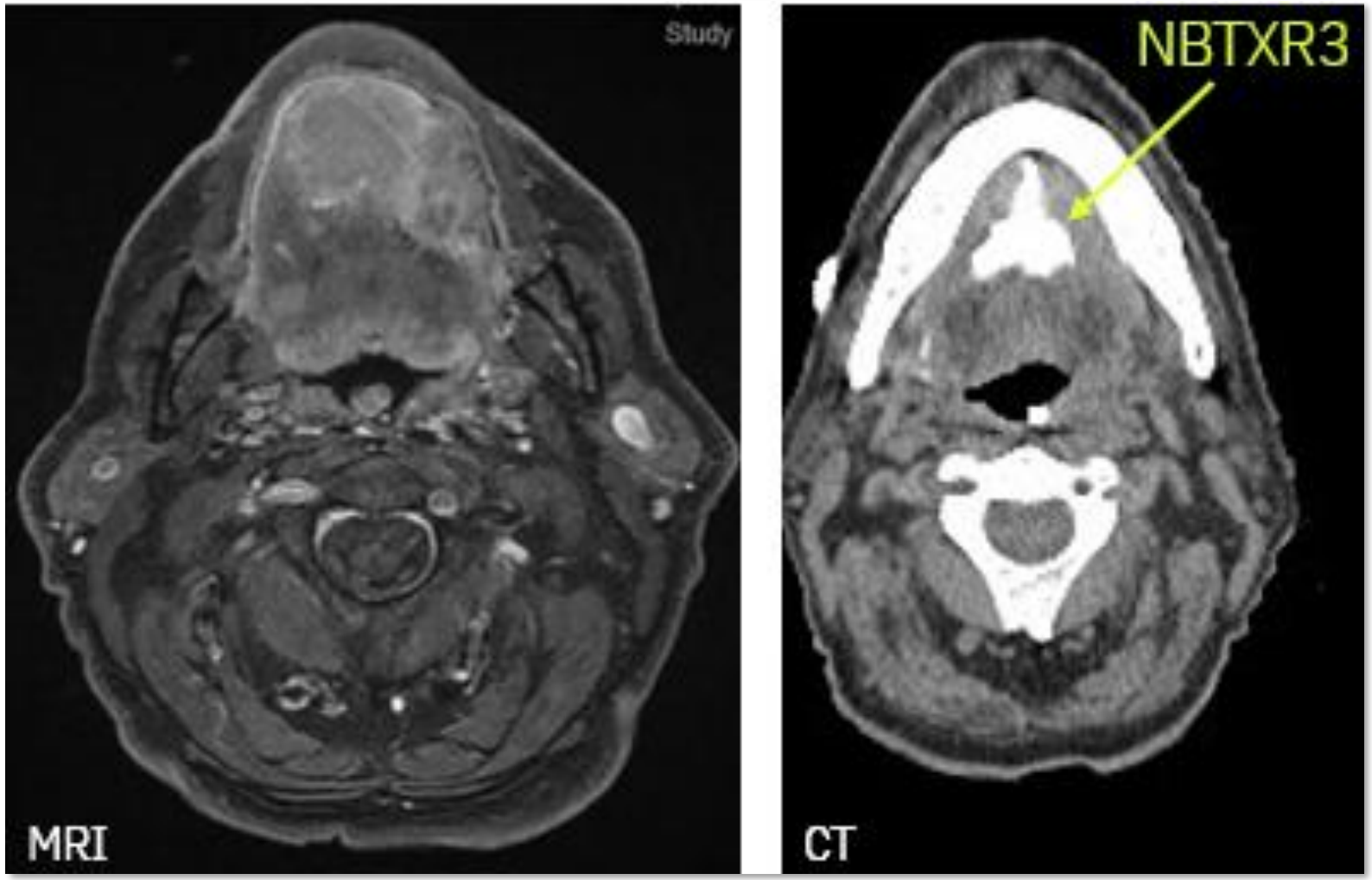
How the efficacy looks like

Complete response visualized via 3-D reconstruction in a patient with HNSCC



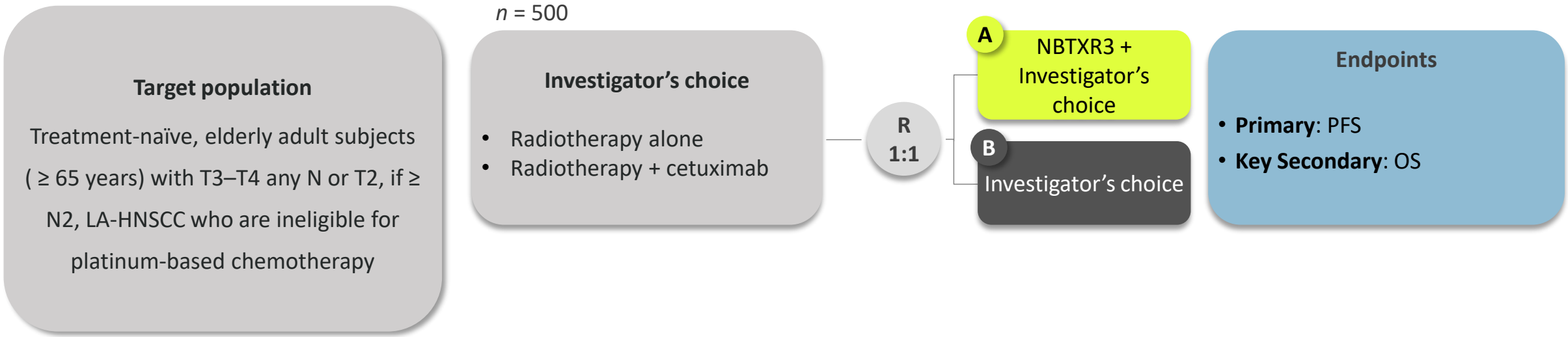
Hoffmann et al. (2020) Eur J Cancer. PMID: 33607477

NBTXR3 IS RADIOPAQUE- Visible on CT, not MRI



Phase III in Local advanced Head and Neck cancers (Nanoray-312)

A Phase III Study of NBTXR3 Activated by Investigator's Choice of Radiotherapy Alone or Radiotherapy in Combination With Cetuximab for Platinum-based Chemotherapy-ineligible Elderly Patients With LA-HNSCC (NCT04892173)




Merci
pour votre
attention