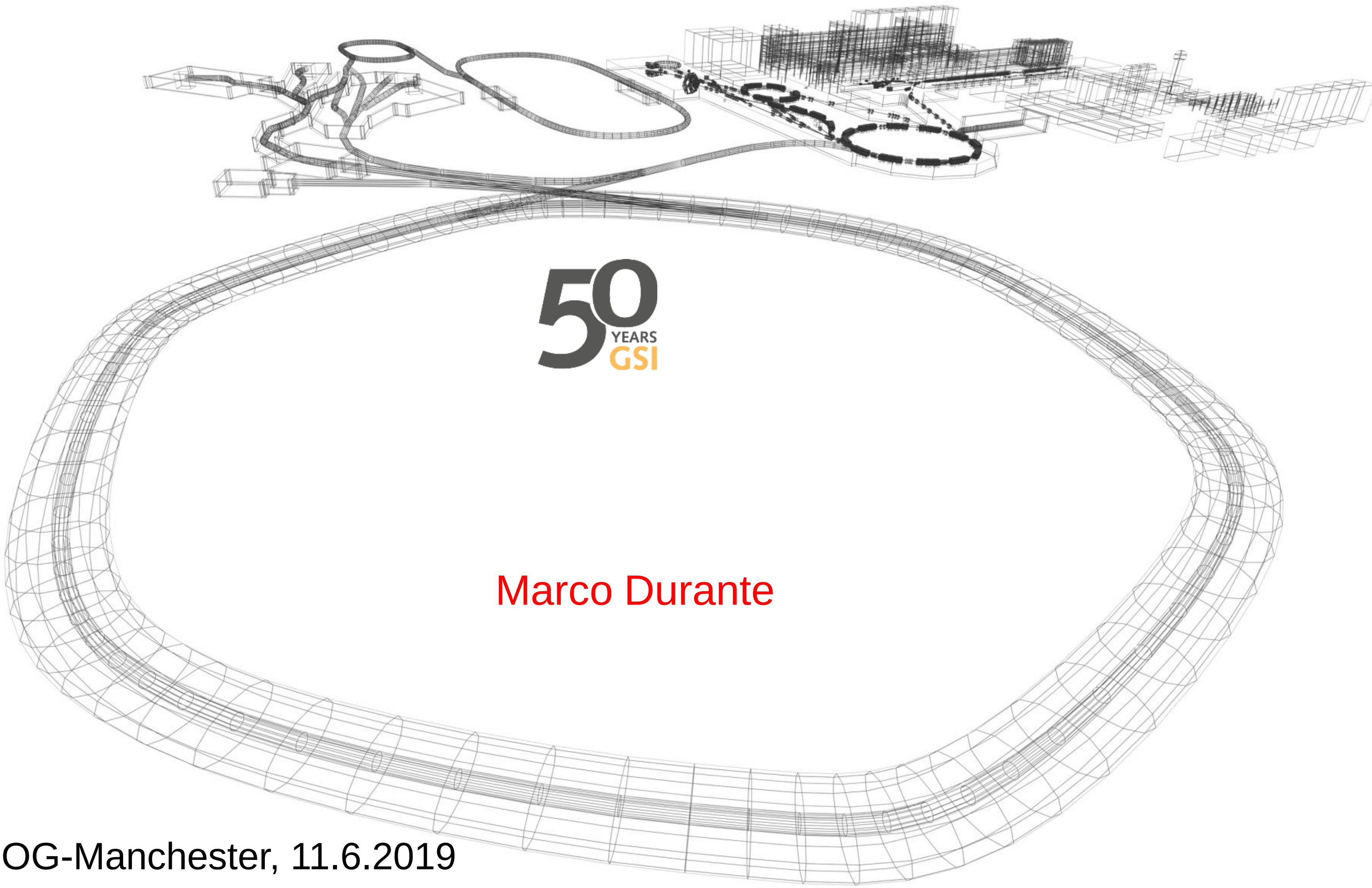
Research vision for particle therapy: European perspective



Marco Durante

PTCOG-Manchester, 11.6.2019

EU perspectives?


The last coal mine
Martin Fletcher on what the death of the mining industry says about Britain

John Sutherland
On the demon drink and life after alcohol

Tracey Thorn
on Bond themes

Alan Ryan
on Henry Kissinger

NewStatesman

Free thinking since 1913

6-12 November 2015/£3.95

The end of Europe

A political project in crisis

By Brendan Simms and Timothy Less

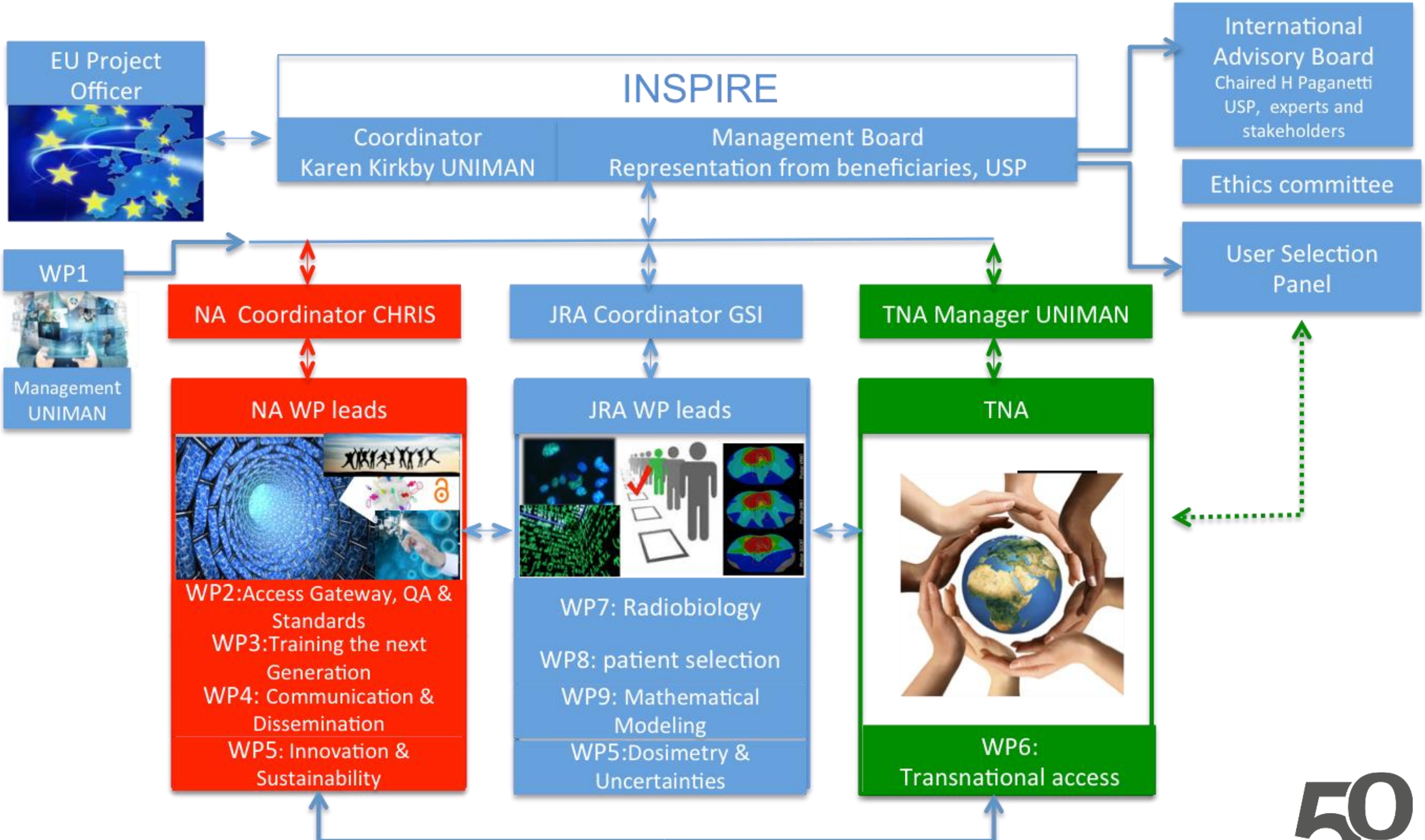
PLUS Hunter Davies: 13 reasons why Mourinho is failing

29 centers in 2019 and 16 under construction

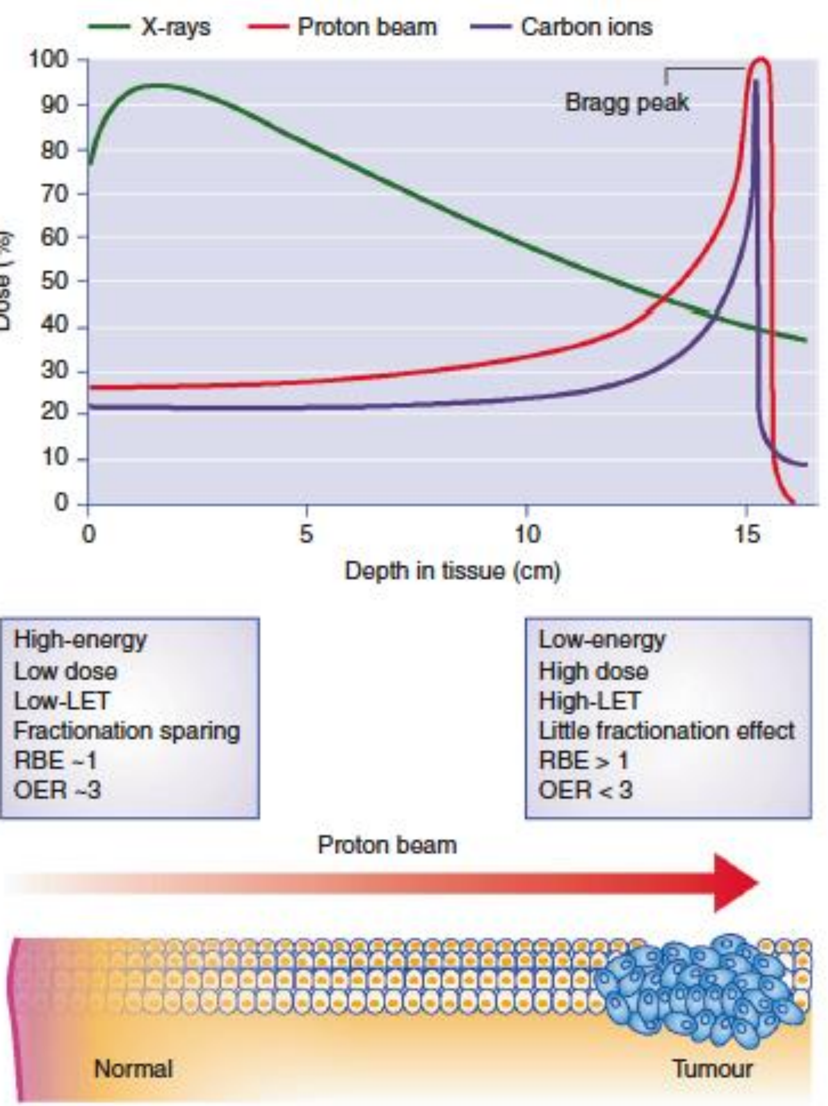
EU Integrating Activity INSPIRE

- €5M (Coordinated by **Manchester**)
- Integrating proton research across Europe
- 17 partners
- Networking, Transnational Access, Joint Research Activities
- 13 TNA providers
- 11 PBT centres; national hubs
- Varian and IBA

https://protonsinspire.eu/



Which research is planned at the EU centers?



BJC British Journal of Cancer www.nature.com/bjc

EDITORIAL

Proton beam therapy in Europe: more centres need more research

British Journal of Cancer https://doi.org/10.1038/s41416-018-0329-x

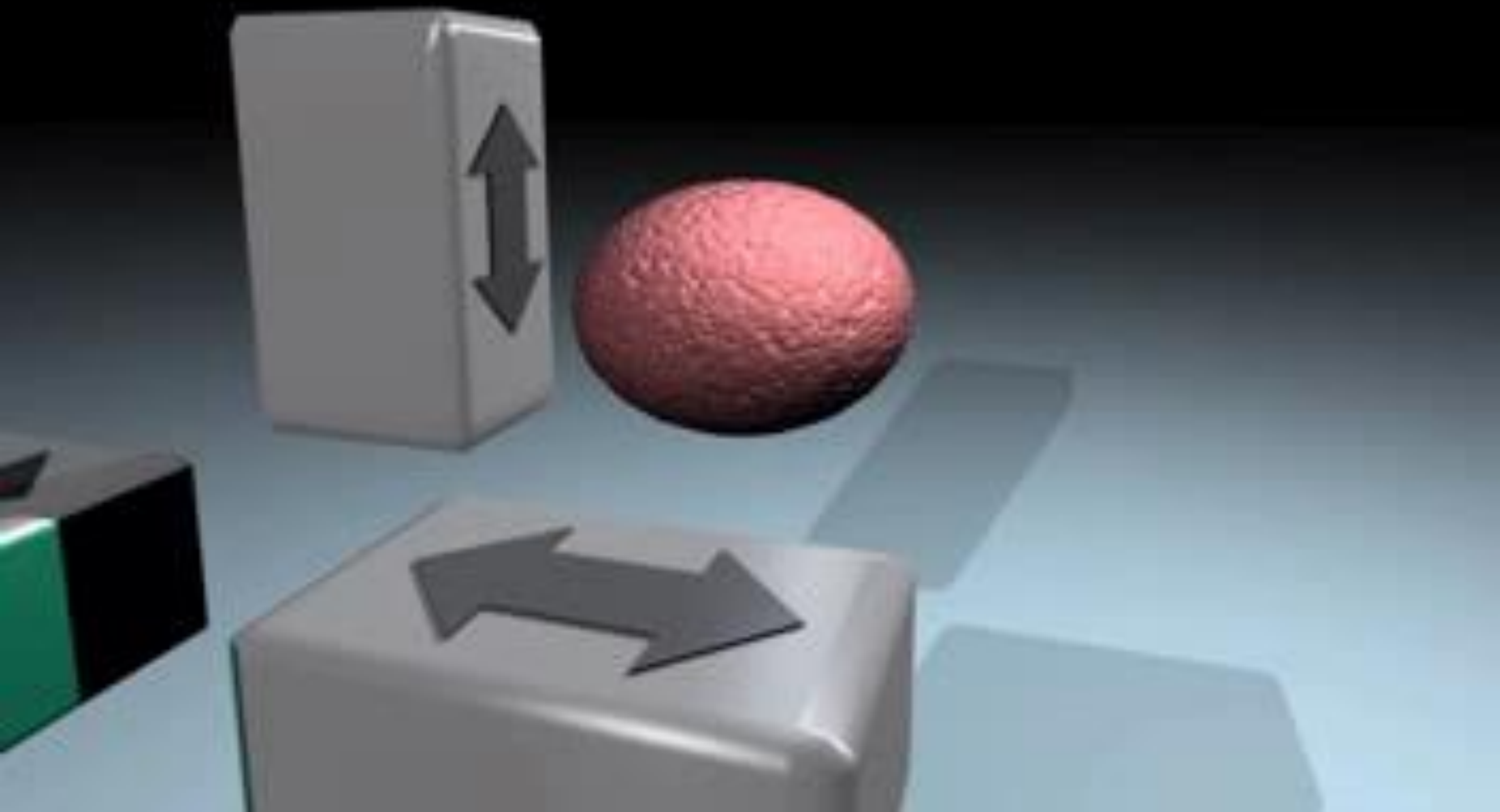
„Hot topics“ in EU centers

Physics
Range uncertainty
Beam delivery

Biology
Radiogenomics
Hypoxia
Combination with immunotherapy

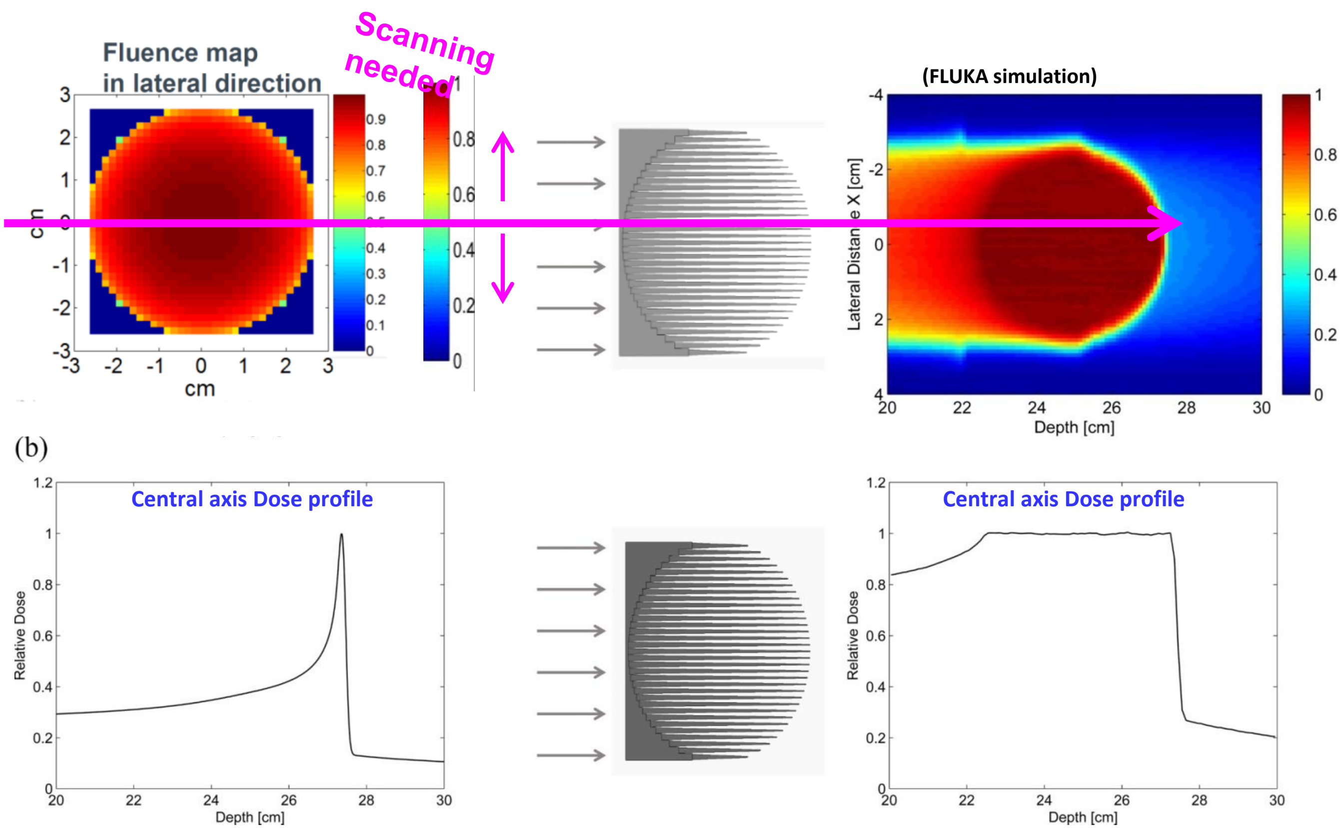
Clinical
Phase-III RCT

Beam delivery: faster and more accurate



3D Modulator: functional principle

Example for a spherical target volume, 5cm diameter, ^{12}C, E=400 MeV/u



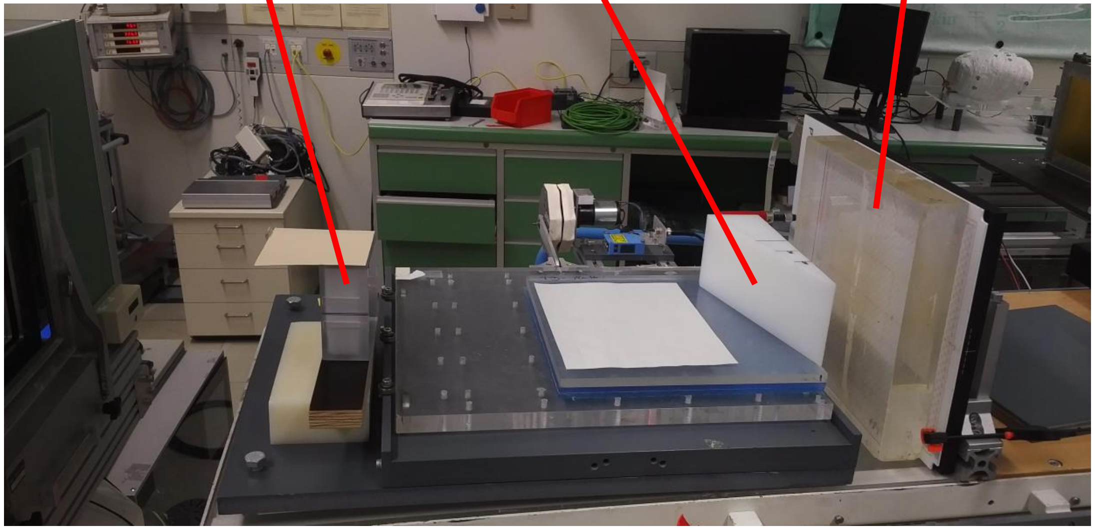
Simeonov *et al.*, *Phys. Med. Biol*. 2017

Ultrafast irradiation with 3D-printed beam modulators at GSI/FAIR – February 2019

3D printed SOBP modulator (having extremely filigree structures)

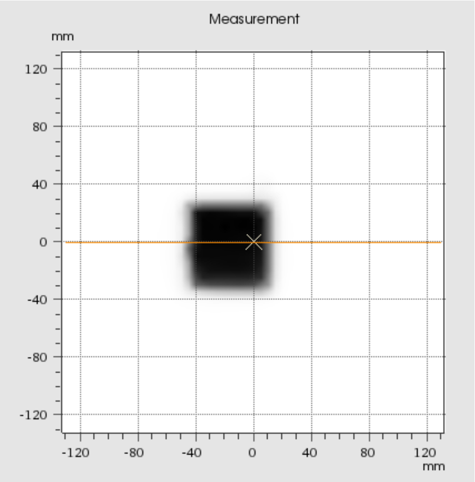
Absorber and Multi-Ionization chamber Array Octavius (1500 chambers)

Oscillating PE-wedge for simulation of the range fluctuations in the body

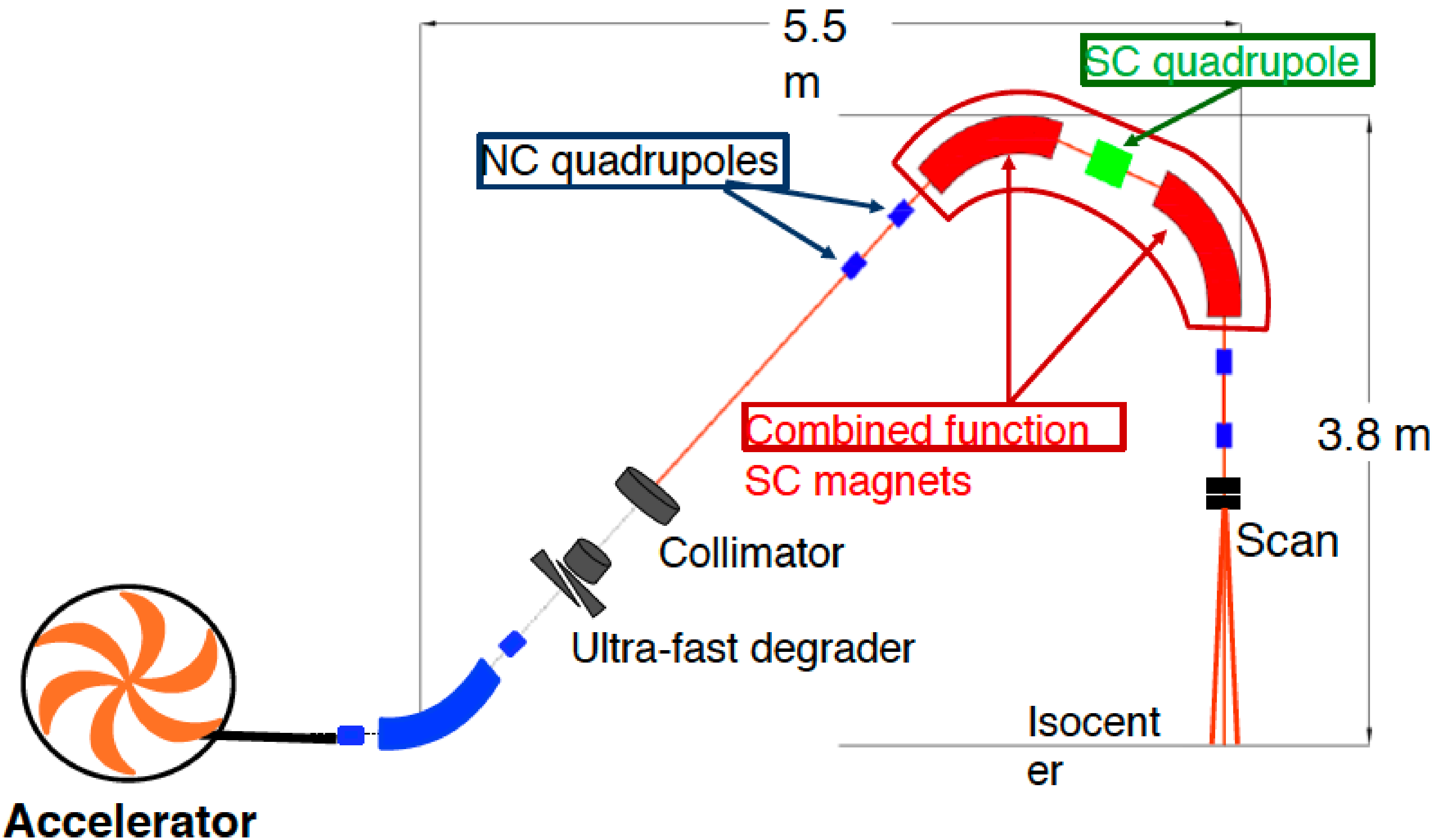


M. Durante, C. Graeff, U. Weber et al.

Result:
Robust dose field inside the target without interplay effects, due to ultrafast irradiation using the SOBP modulator

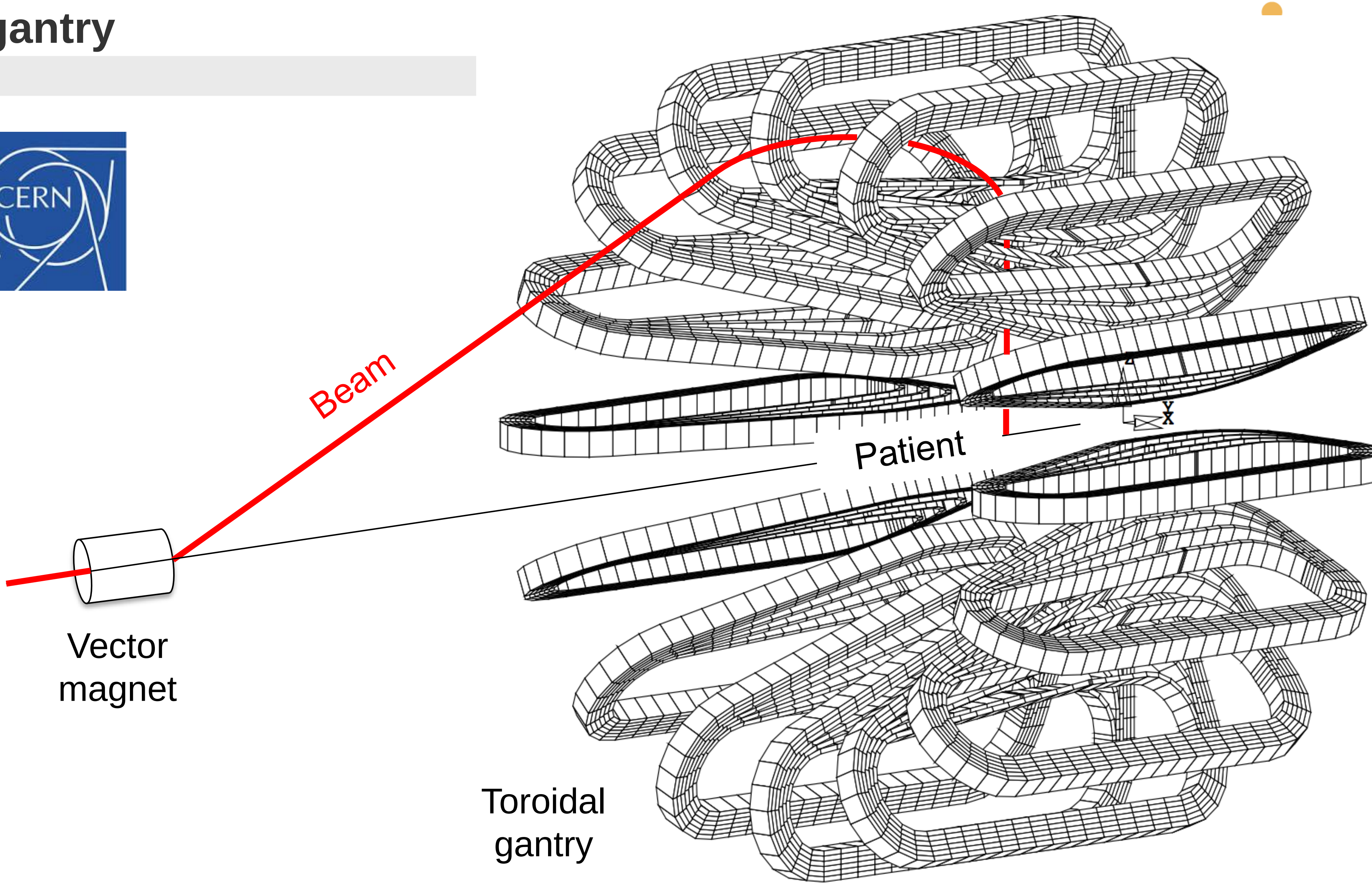


Scheme of the PSI SC Gantry



K. Nesteruk et al.: ACCEPTED by PMB: https://arxiv.org/abs/1901.01821

A toroidal magnet superconducting gantry

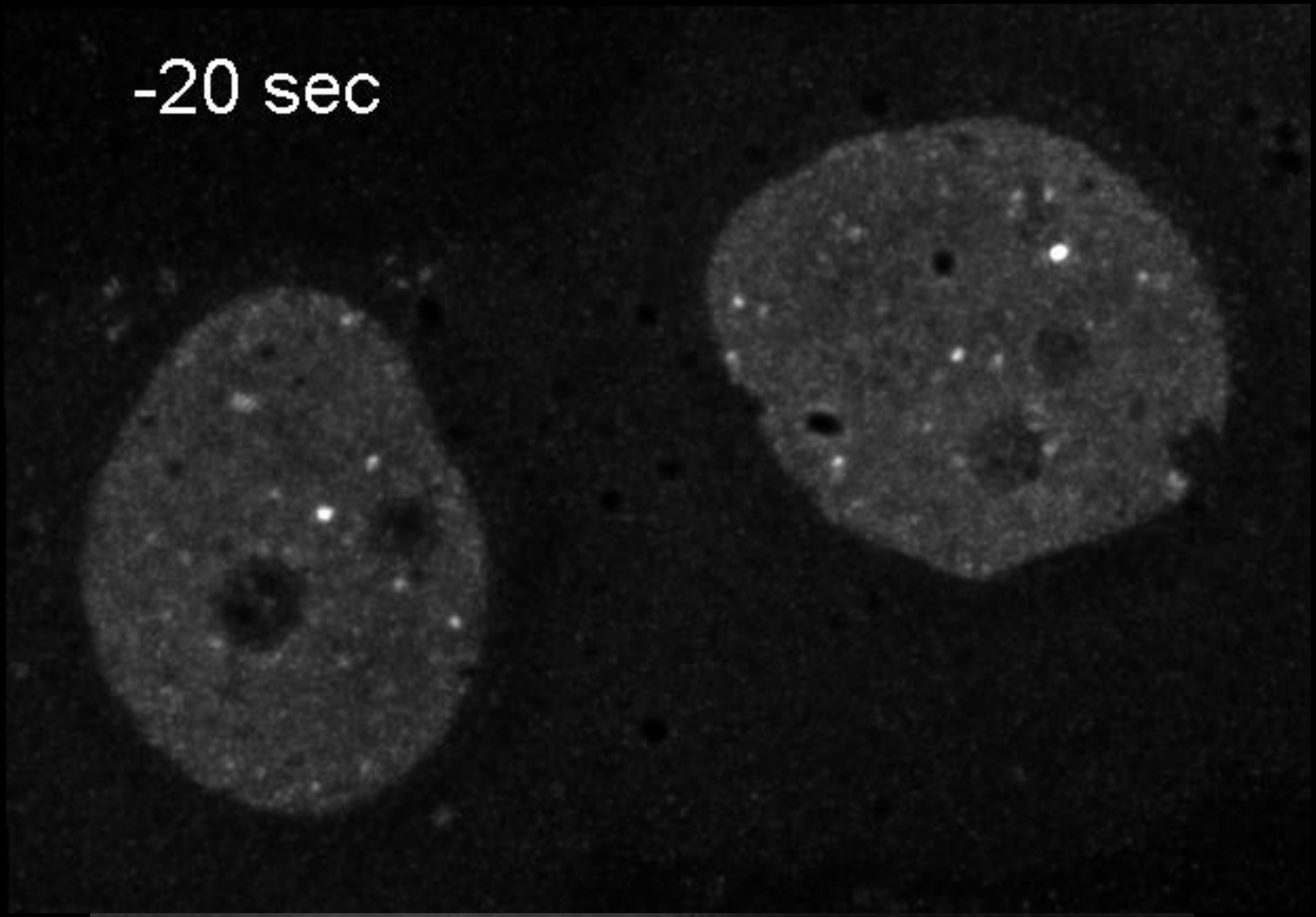


Courtesy of Luca Bottura

Gantry-free DDS for charged particles?

Keall *et al., Med. Phys*. 2019

Improving the benefit: radiobiology research



Jakob *et al., Proc. Natl. Acad. Sci. USA* 2009; *Nucl. Acids Res*. 2011

Weill Cornell Medicine

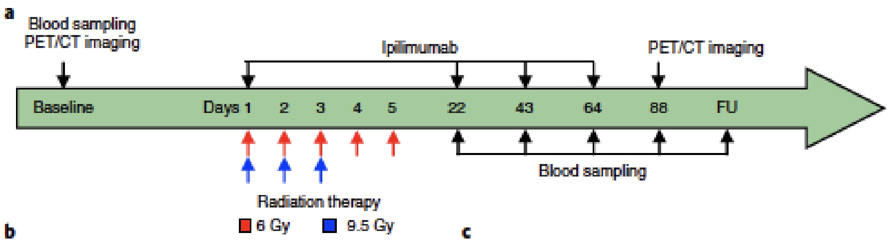
nature medicine

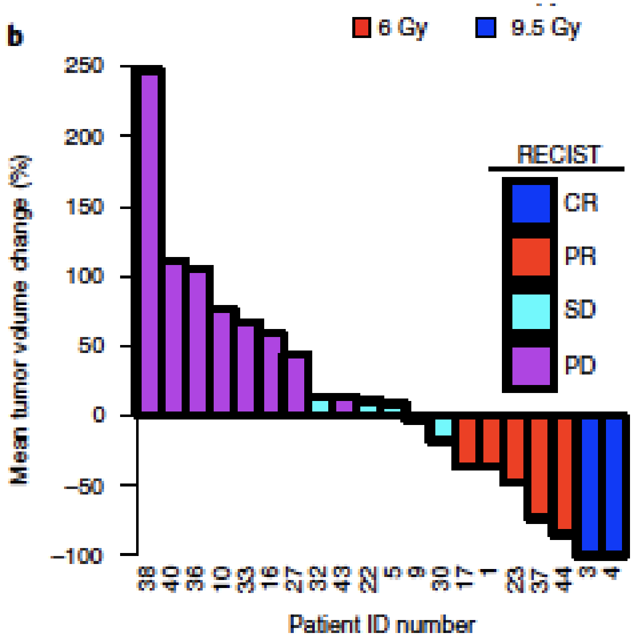
LETTERS

https://doi.org/10.1038/s41591-018-0232-2

Radiotherapy induces responses of lung cancer to CTLA-4 blockade

Silvia C. Formenti[1*], Nils-Petter Rudqvist[1,15], Encouse Golden[1,14,15], Benjamin Cooper[2], Erik Wennerberg[1], Claire Lhuillier[1], Claire Vanpouille-Box[1], Kent Friedman[3], Lucas Ferrari de Andrade[4,5], Kai W. Wucherpfennig[4,5], Adriana Heguy[6,7], Naoko Imai[8], Sacha Gnjatic[8], Ryan O. Emerson[9], Xi Kathy Zhou[10], Tuo Zhang[11], Abraham Chachoua[12] and Sandra Demaria[1,13*]





~30%

Particle therapy + immunotherapy

Does Heavy Ion Therapy Work Through the Immune System?

Marco Durante, PhD,* David J. Brenner, PhD,† and Silvia C. Formenti, MD‡

**Trento Institute for Fundamental Physics and Applications-National Institute for Nuclear Physics, University of Trento, Trento, Italy; †Center for Radiological Research, Columbia University Medical Center, New York, New York; and ‡Department of Radiation Oncology, Weill Cornell Medical College, New York, New York*

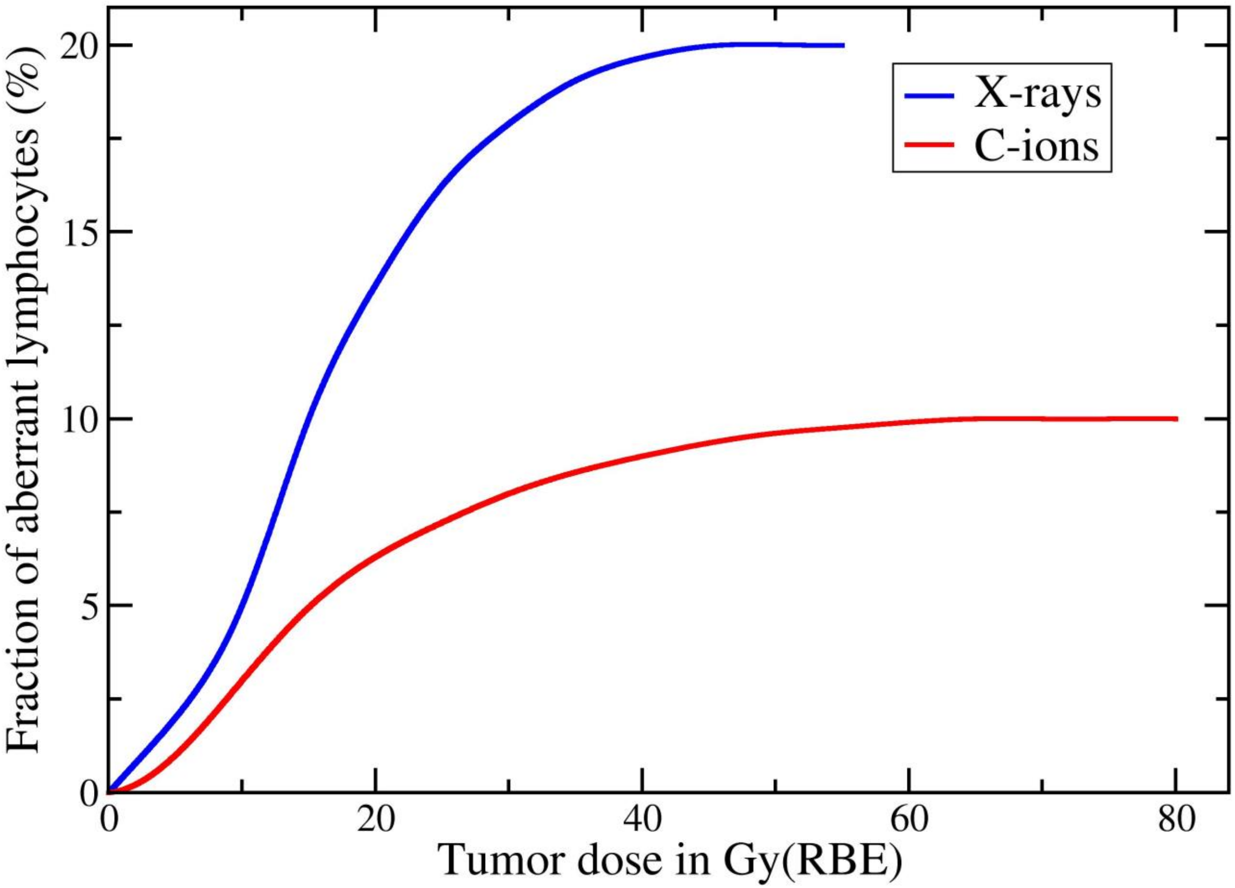
Received Aug 10, 2016, and in revised form Aug 21, 2016. Accepted for publication Aug 25, 2016.

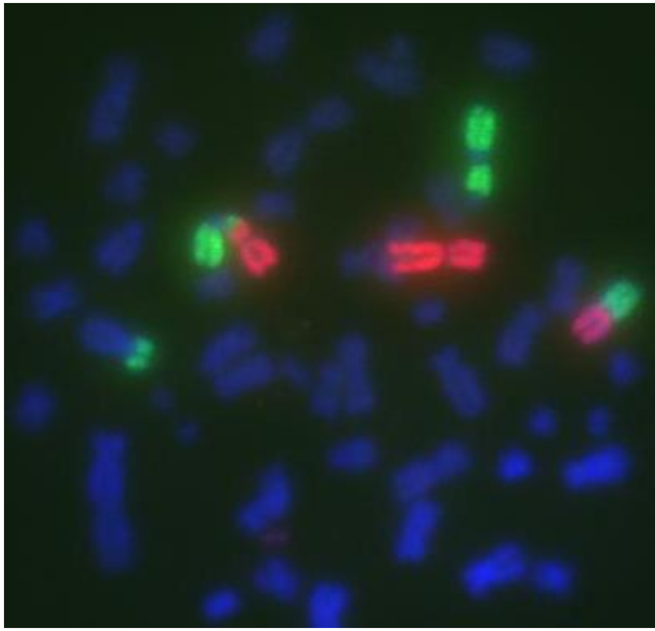
CrossMark

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Physical advantages of particle therapy for immunology

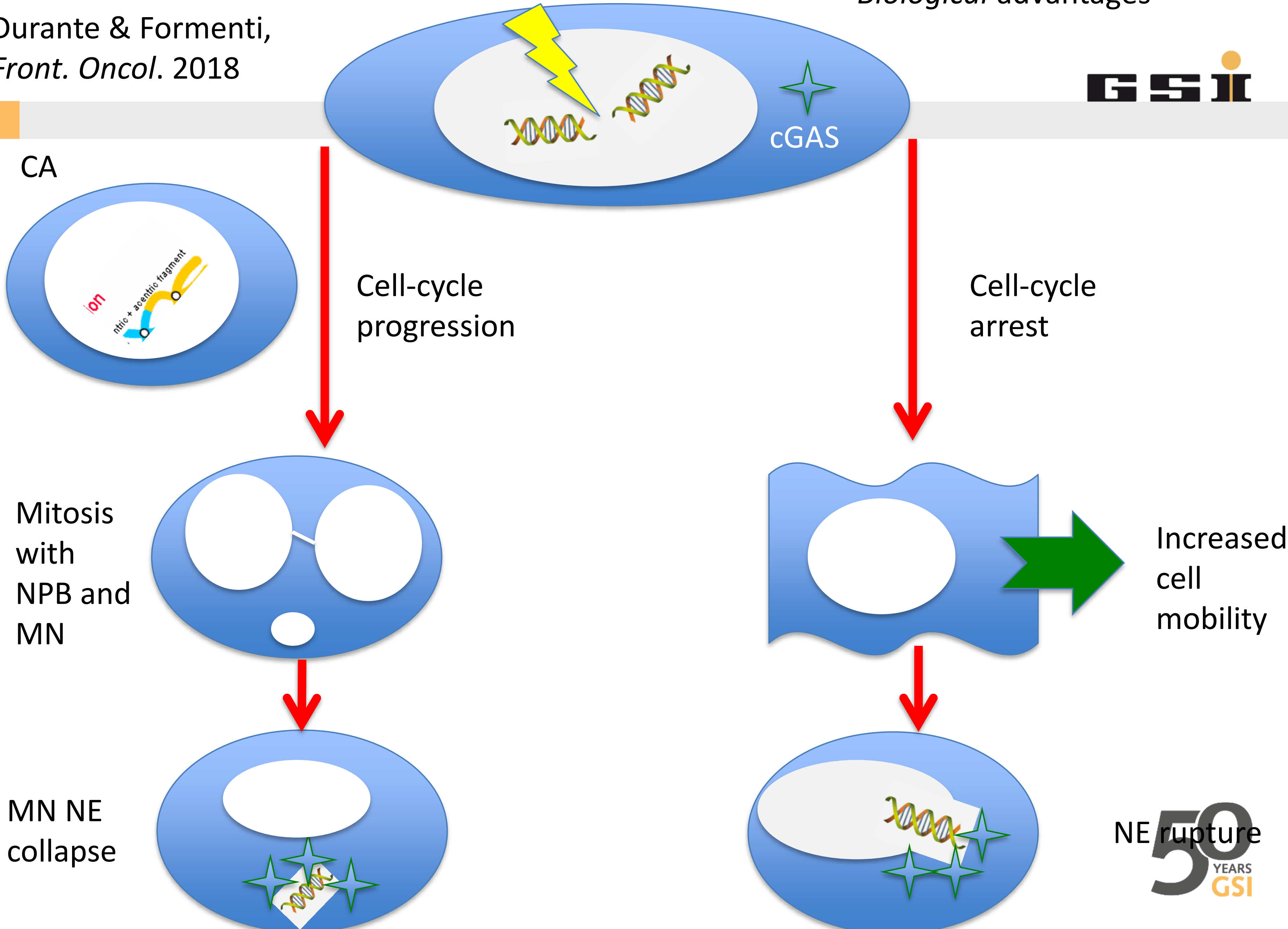




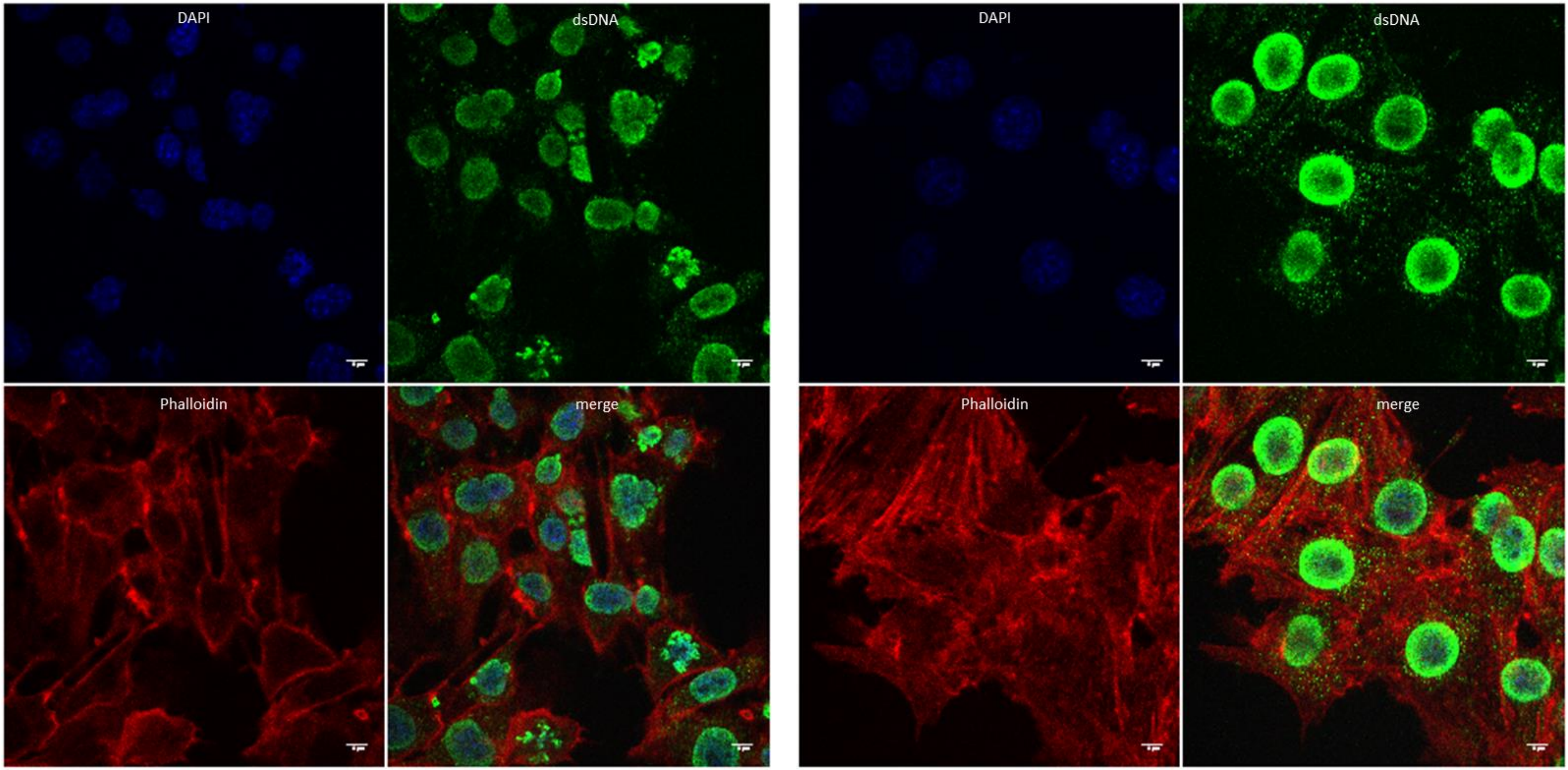
Durante *et al.*, *Int. J. Radiat. Oncol. Biol. Phys*. 2000

Durante & Formenti, *Front. Oncol.* 2018

Biological advantages



Cytosolyc dsDNA foci after C-ions



0 Gy – control

4 Gy

Averbeck et al., February 2019

Table 1 | Ongoing randomized clinical trials comparing different radiation modalities for the same disease

Study	Institution	Phase	Condition	Radiation arm 1	Radiation arm 2
R03CA188162: IMPT vs IMRT	MDACC	III	Oropharyngeal cancer (head and neck cancer)	Protons*	X-rays*
PARTIQoL (NCT01617161): proton therapy vs IMRT	MGH	III	Low-risk or intermediate-risk prostate cancer	Protons	X-rays
NCT01512589: proton-beam therapy vs IMRT	MDACC	III	Oesophageal cancer	Protons*	X-rays*
RADCOMP (NCT02603341): pragmatic randomized trial of proton vs photon therapy	PTCORI	III	Post-mastectomy stage II or III breast cancer	Protons	X-rays
NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation	NRG Oncology	II	Newly diagnosed glioblastoma	Protons*	X-rays*
NRG 1542: proton radiation vs conventional photon radiation‡	NRG Oncology	III	Hepatocellular carcinoma	Protons	X-rays
NCT01182753: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Low-grade and intermediate-grade chondrosarcoma of the skull base	Protons	Carbon ions
NCT01182779: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	Carbon ions
CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Primary gioblastoma	Protons*§	Carbon ions*§
IPI (NCT01641185): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Prostate cancer	Protons	Carbon ions
ISAC (NCT01811394): proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	Carbon ions
ETOILE (NCT02838602): carbon-ion radiotherapy vs IMRT	Lyon University Hospital, France	III	Radioresistant adenoid cystic carcinoma and sarcomas	Carbon ions	IMRT
BAA-N01CM51007-51: prospective trial of carbon-ion therapy vs IMRT	NCI	I/III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*
CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy	UTSW	III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*

Convincing the non-believers: phase-III clinical trials

Durante *et al.*, *Nat. Rev. Clin. Oncol.* 2017

Problems in CPT phase-III randomized trials

Loeffler & Durante, *Nat. Rev. Clin. Oncol*. 2013

Table 3 | Comparison of IMRT, SBRT, protons, and carbon ions for prospective clinical trials*

Radiation type	Physical dose distribution	Fractionation	RBE
IMRT	Excellent target conformality, high integral dose to normal tissue	Conventional to hyperfractionation	1 (low LET)
SBRT	Excellent target conformality, very high integral dose to normal tissue	Hypofractionation to oligofractionation	1 (low LET)
Protons	Excellent target conformality, ~60% lower integral dose to normal tissue compared with X-rays	Conventional to hypofractionation	1.1 (possibly higher in the distal part of the SOBP)
Heavy ions	As for protons, but with smaller lateral penumbra (reduced lateral scattering) and fragmentation tail beyond the Bragg peak	Conventional to oligofractionation	1 to 4 (depending on depth in the tissue, energy, tissue radiosensitivity, fractionation and so on)

*These modalities differ in physical dose distribution, fractionation regimens, and radiation quality or LET. Abbreviations: IMRT, intensity-modulated radiotherapy; LET, linear energy transfer; RBE, relative biological effectiveness; SBRT, stereotactic body radiotherapy; SOBP, spread-out Bragg-peak.

1. Compare only 1 variable: e.g. IMRT vs. protons different physical dose distribution same RBE same fractionation
2. Compare “best possible schedule”

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer

Zhongxing Liao, J. Jack Lee, Ritsuko Komaki, Daniel R. Gomez, Michael S. O'Reilly, Frank V. Fossella, George R. Blumenschein Jr, John V. Heymach, Ara A. Vaporciyan, Stephen G. Swisher, Pamela K. Allen, Noah Chan Choi, Thomas F. DeLaney, Stephen M. Hahn, James D. Cox, Charles S. Lu, and Radhe Mohan

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on January 2, 2018.

Clinical trial information: NCT00915005.

Corresponding author: Zhongxing Liao, MD, Department of Radiation Oncology, Unit 1422, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Houston, TX 77030; e-mail: zliao@mdanderson.org.

0732-183X/18/3699-1/$20.00

ABSTRACT

Purpose
This randomized trial compared outcomes of passive scattering proton therapy (PSPT) versus intensity-modulated (photon) radiotherapy (IMRT), both with concurrent chemotherapy, for inoperable non–small-cell lung cancer (NSCLC). We hypothesized that PSPT exposes less lung tissue to radiation than IMRT and thereby reduces toxicity without compromising tumor control. The primary end points were grade ≥ 3 radiation pneumonitis (RP) and local failure (LF).

Patients and Methods
Eligible patients had stage IIB to IIIB NSCLC (or stage IV NSCLC with a single brain metastasis or recurrent lung or mediastinal disease after surgery) who were candidates for concurrent chemoradiation therapy. Pairs of treatment plans for IMRT and PSPT were created for each patient. Patients were eligible for random assignment only if both plans satisfied the same prespecified dose-volume constraints for at-risk organs at the same tumor dose.

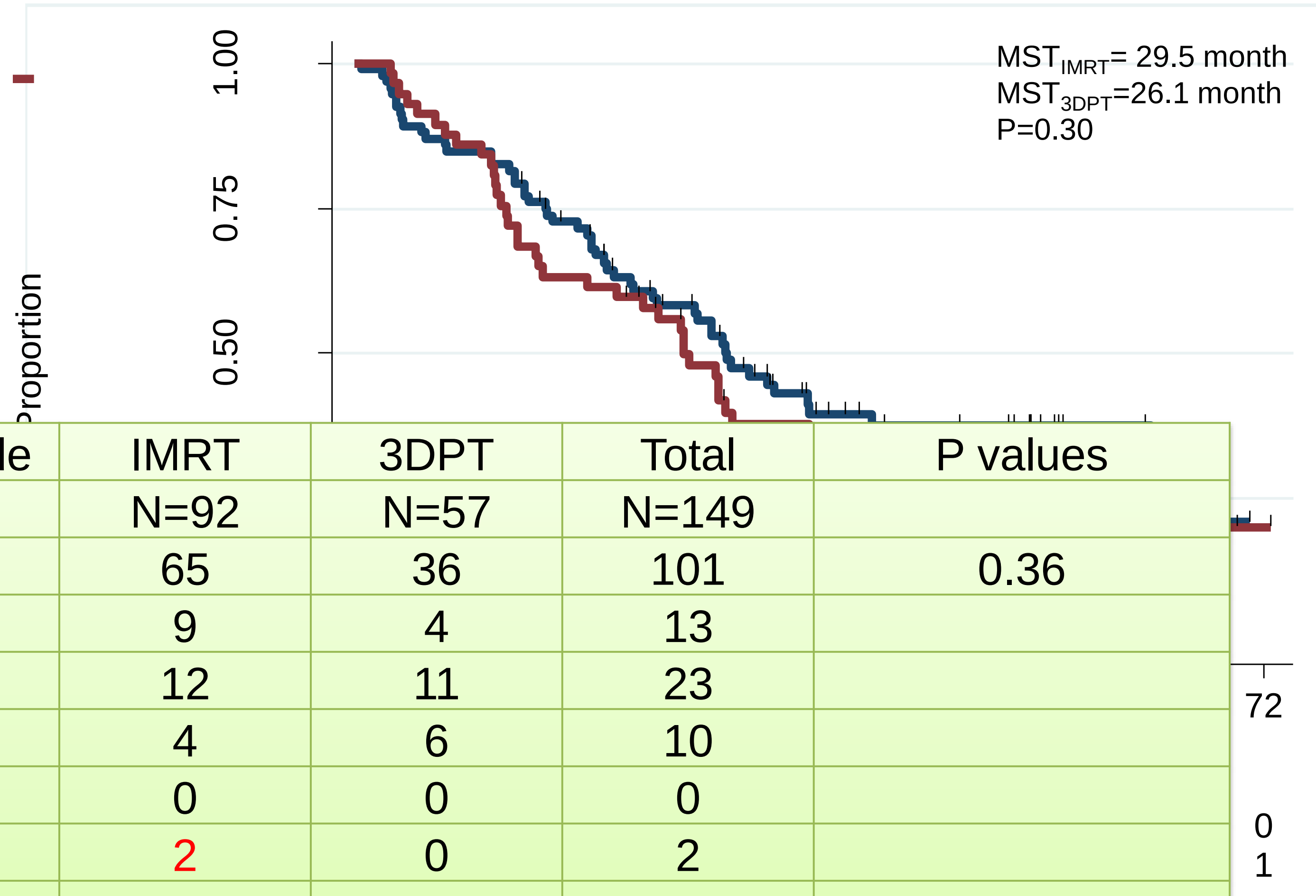
Results
Compared with IMRT (n = 92), PSPT (n = 57) exposed less lung tissue to doses of 5 to 10 Gy(RBE), which is the absorbed Gy dose multiplied by the relative biologic effectiveness (RBE) factor for protons; exposed more lung tissue was exposed to $ 20 Gy(RBE), but exposed less heart tissue at all dose levels between 5 and 80 Gy(RBE). The grade $ 3 RP rate for all patients was 8.1% (IMRT, 6.5%; PSPT, 10.5%); corresponding LF rates were 10.7% (all), 10.9% (IMRT), and 10.5% (PSPT). The posterior probability of IMRT being better than PSPT was 0.54. Exploratory analysis showed that the RP and LF rates at 12 months for patients enrolled before versus after the trial midpoint were 21.1% (before) versus 18.2% (after) for the IMRT group (P = .047) and 31.0% (before) versus 13.1% (after) for the PSPT group (P = .027).

Conclusion
PSPT did not improve dose-volume indices for lung but did for heart. No benefit was noted in RP or LF after PSPT. Improvements in both end points were observed over the course of the trial.

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

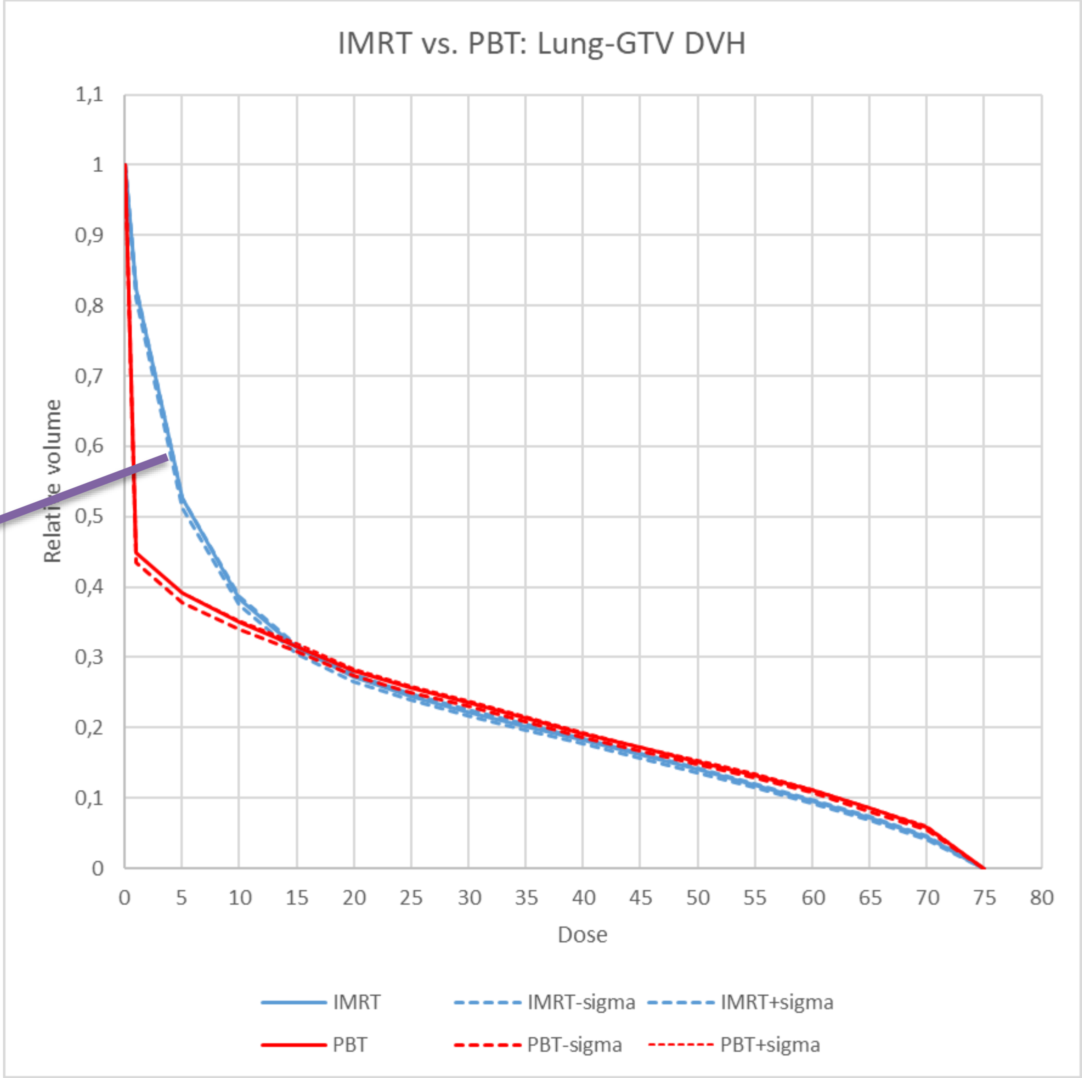
50 YEARS GSI

IMRT vs. PSPT

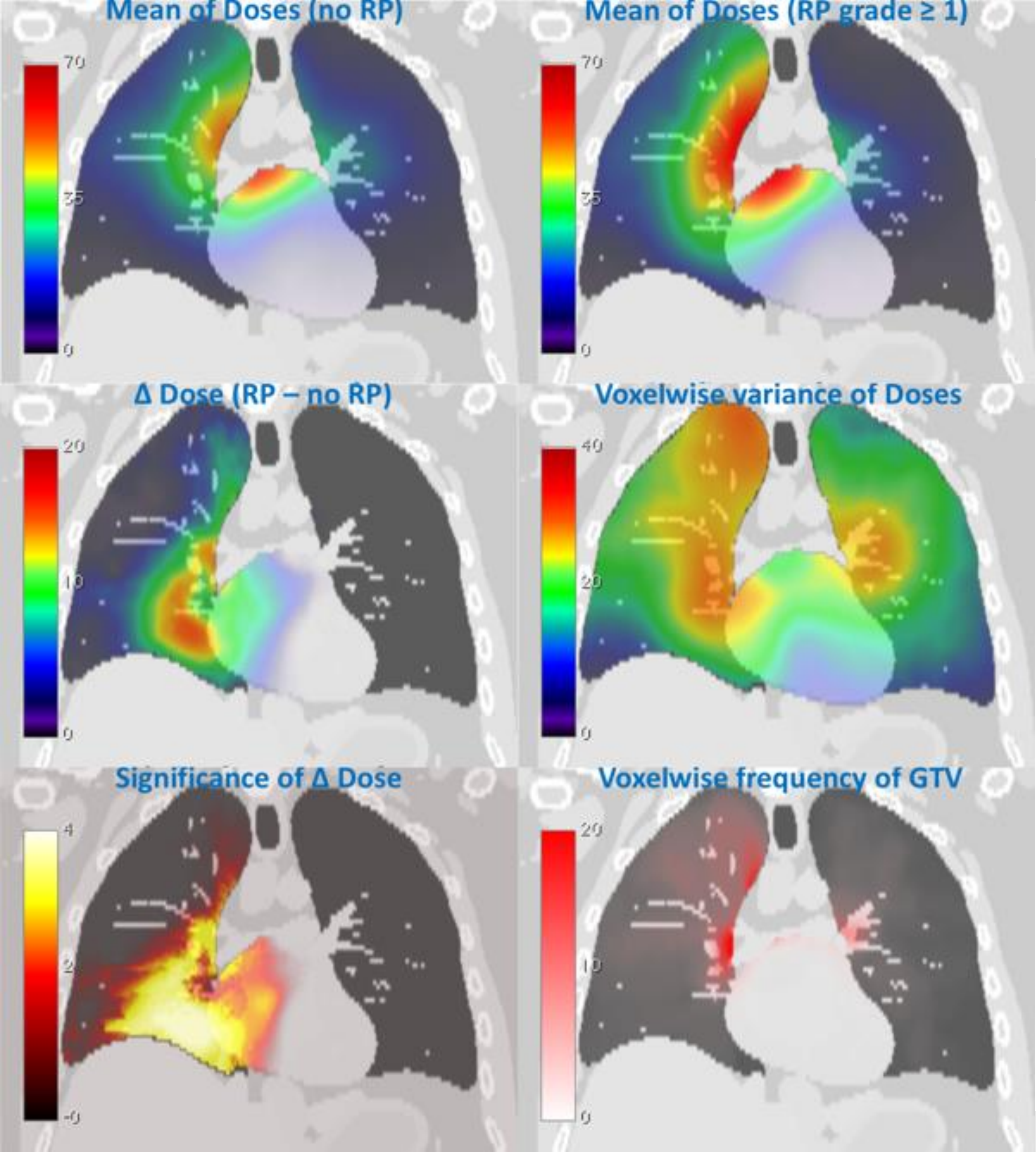


RP Grade	IMRT	3DPT	Total	P values
	N=92	N=57	N=149	
0	65	36	101	0.36
1	9	4	13	
2	12	11	23	
3	4	6	10	
4	0	0	0	
5	2	0	2	
Gr 0-2	86	51	137	0.54
Gr 3-5	6 (6.5%)	6 (10.5%)	12 (8.1%)	

DVH technique analysis



How can this low-dose difference fit the inverse RP incidence between the 2 techniques?



VB analysis of dose differences (RP grade ≥ 1)

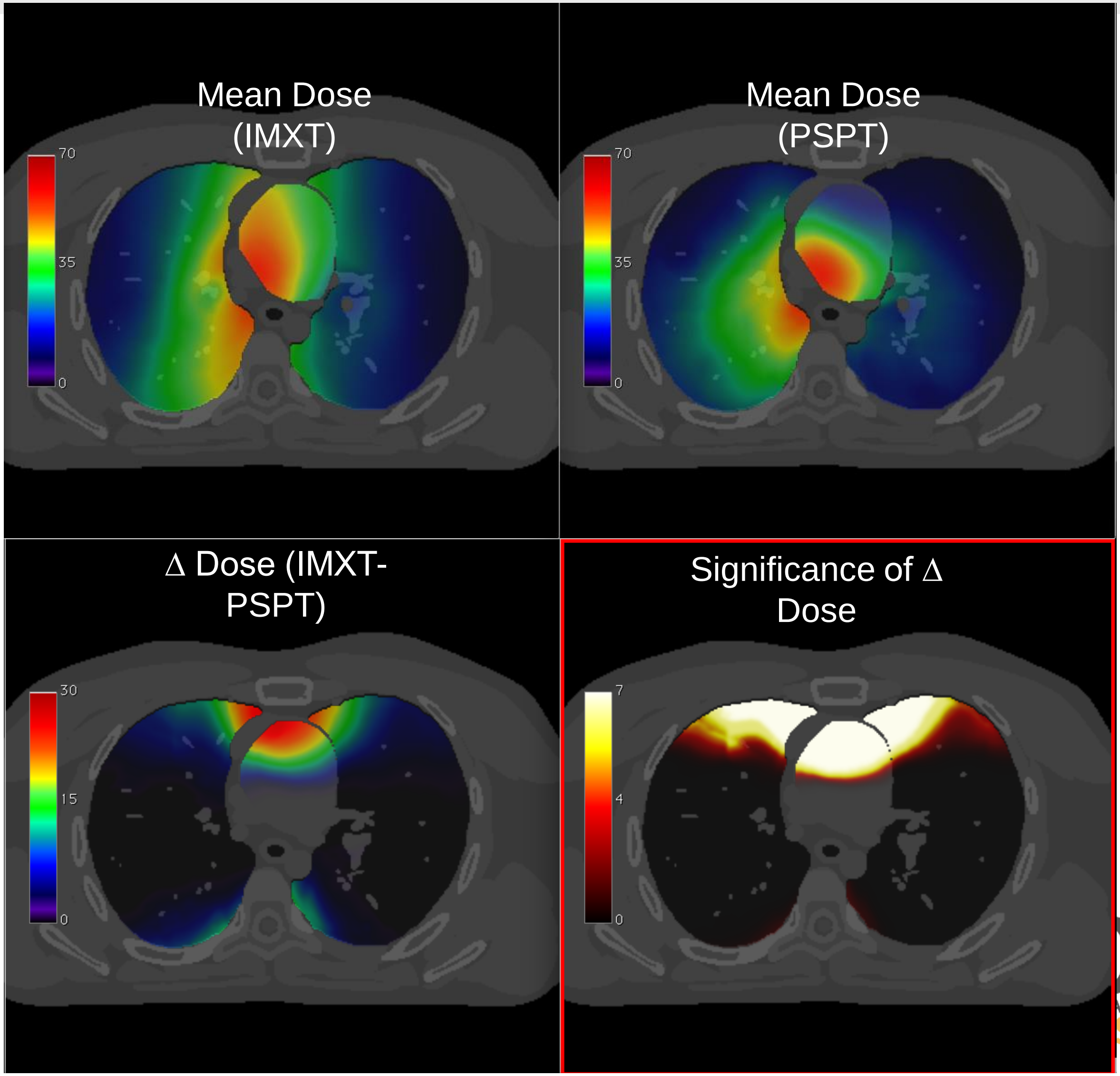
Conclusion 1:

the lower parts of the lungs and the heart play a prominent role in the development of RP

VB analysis: IMXT vs PSPT

Conclusion 2

The dose difference between X-rays and protons was mostly localized in the upper region of the lungs,which is not correlated to RP



Palma *et al., Int. J. Radiat. Biol. Oncol. Phys.* 2019

„Futuristic“ research

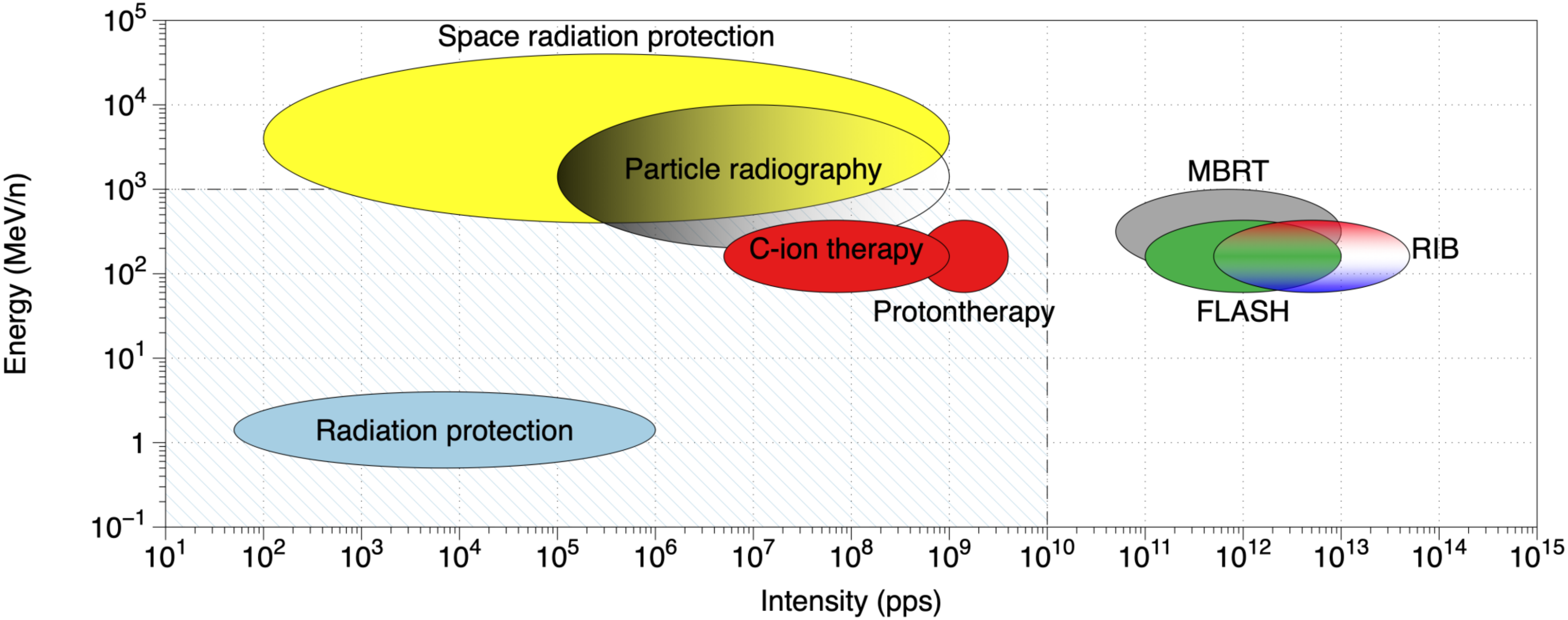
- FAIR-phase-0
- New accelerators under construction (NICA, RAON, ELI, SPES, SPIRAL2, FRIB, ...)

Biophysik

50 YEARS GSI

- 250 participants from 27 countries in 5 continents

Biomedical applications at particle accelerators



Conclusions

- By 2021, EU (+UK+Switzerland+Russia) will have as many centers as US (and 4 heavy ions centers)
- Unlike US, many of these centers have rooms dedicated to research and are research-oriented
- Research programs cover medical physics and radiobiology, and they have a substantial overlap
- EU-funded project INSPIRE is an important tool to coordinate these research efforts
- Moreover, new high-energy and –intensity accelerators in construction in Europe will contribute with high-rik/high-gain research for future develpments of particle therapy

Thanks you very much!

www.gsi.de/biophysik