Treating cancer with radiation :

a new approach with FLASH Therapy

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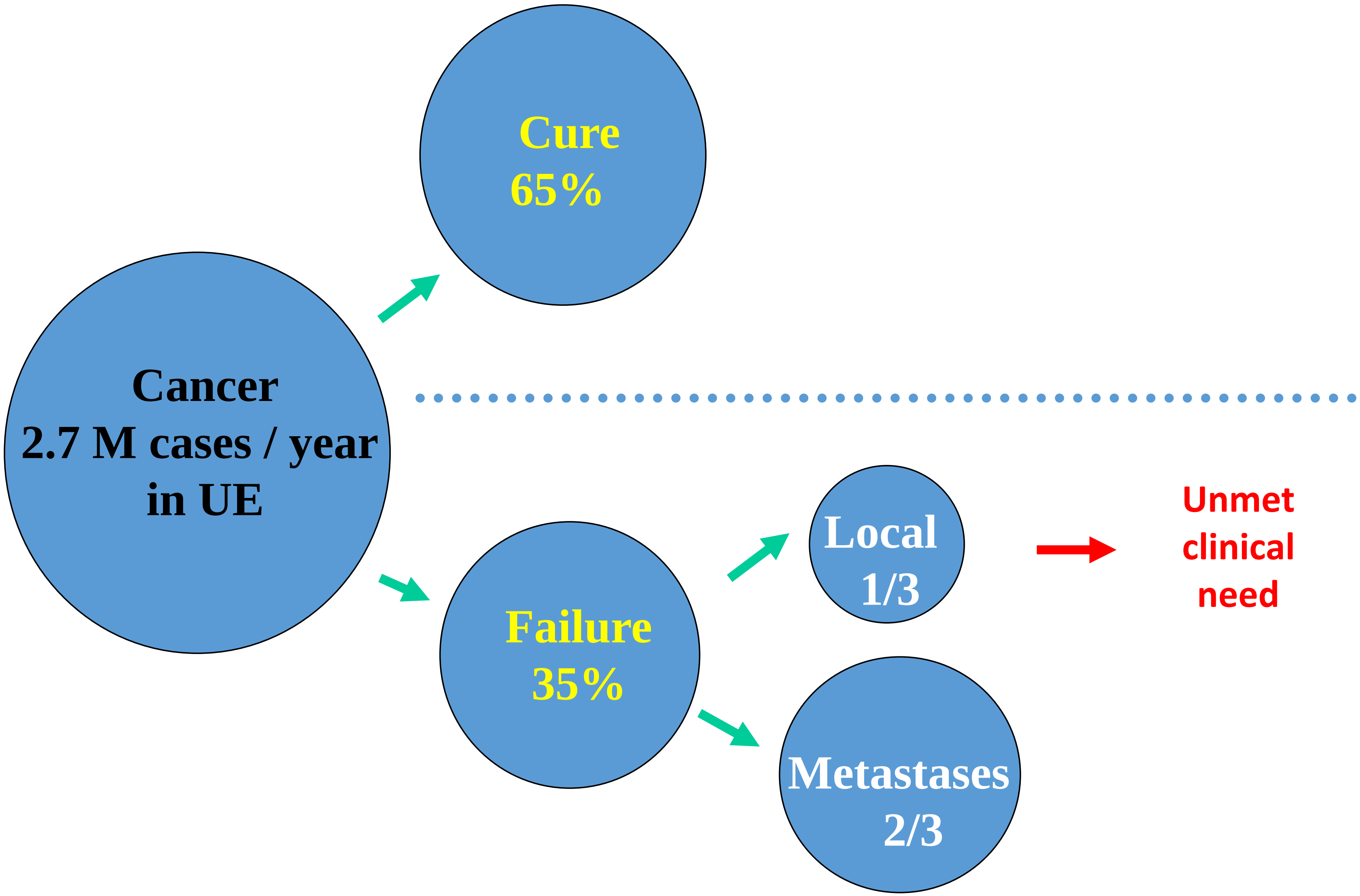
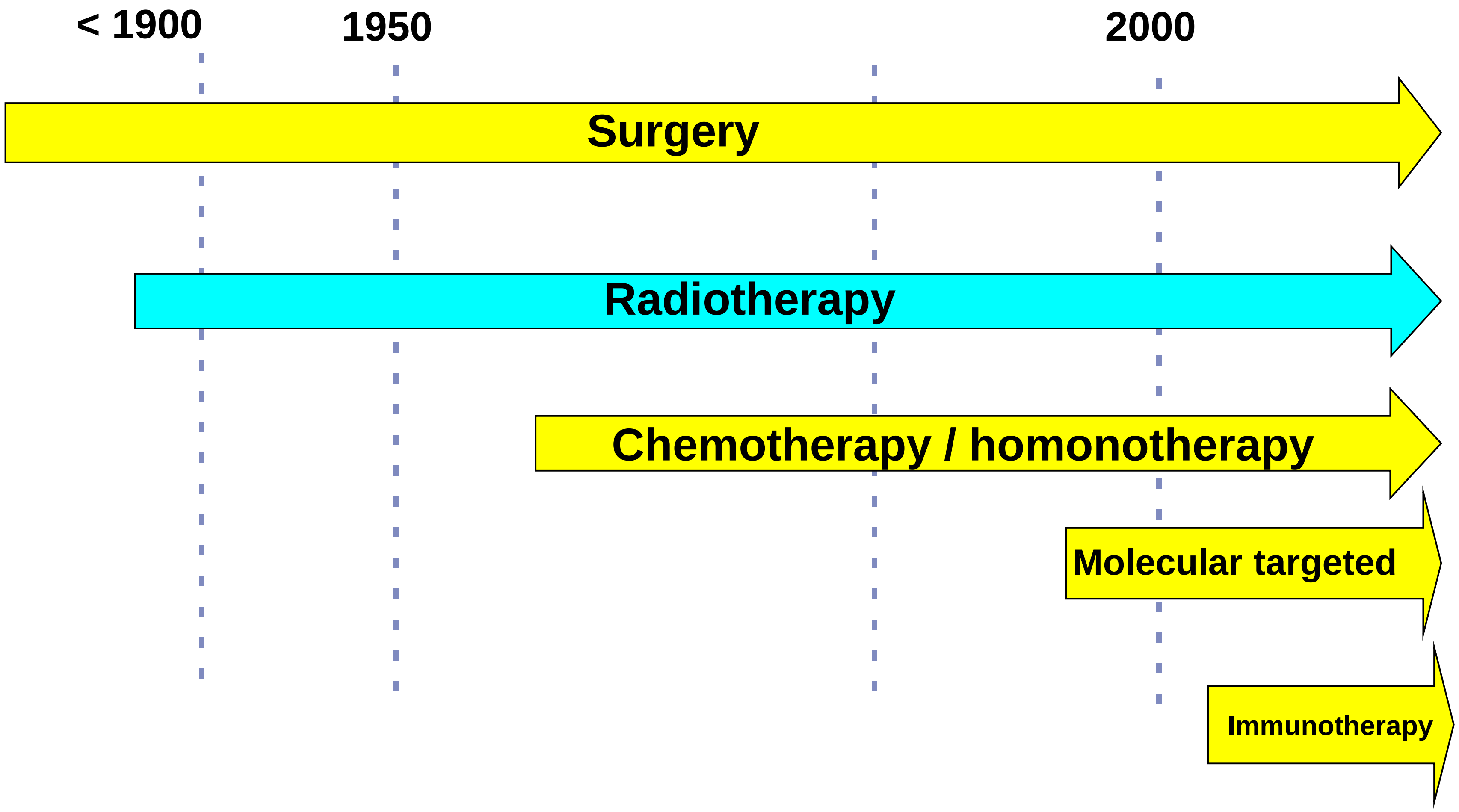
@ Lausanne University Hospital (CHUV) Switzerland

Cancer cure in 2021?



How do we fight cancer ?



What is FLASH therapy ?

= a new way of delivering radiotherapy

« FLASH » is a biological observation

= A reduction of radiation toxicity to normal healthy tissues,

while maintaining a similar effect on tumors

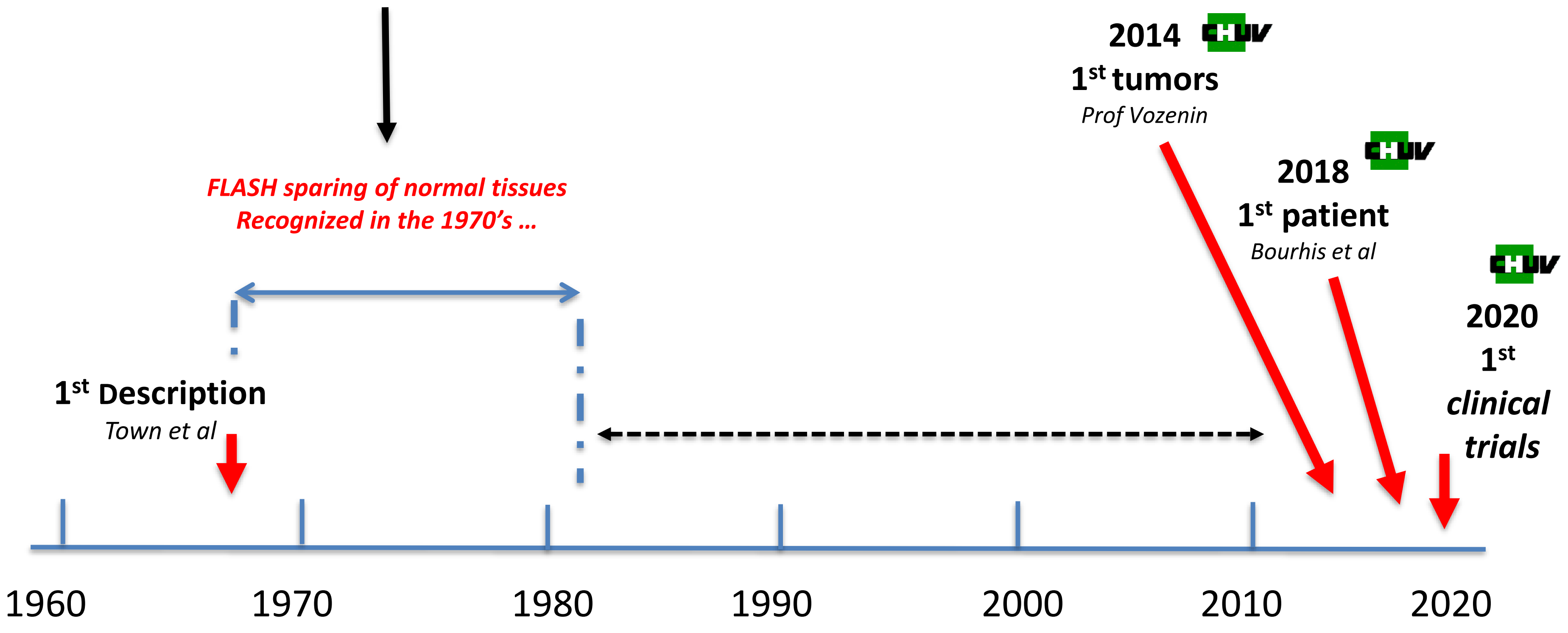
when comparing

ultra-high

to

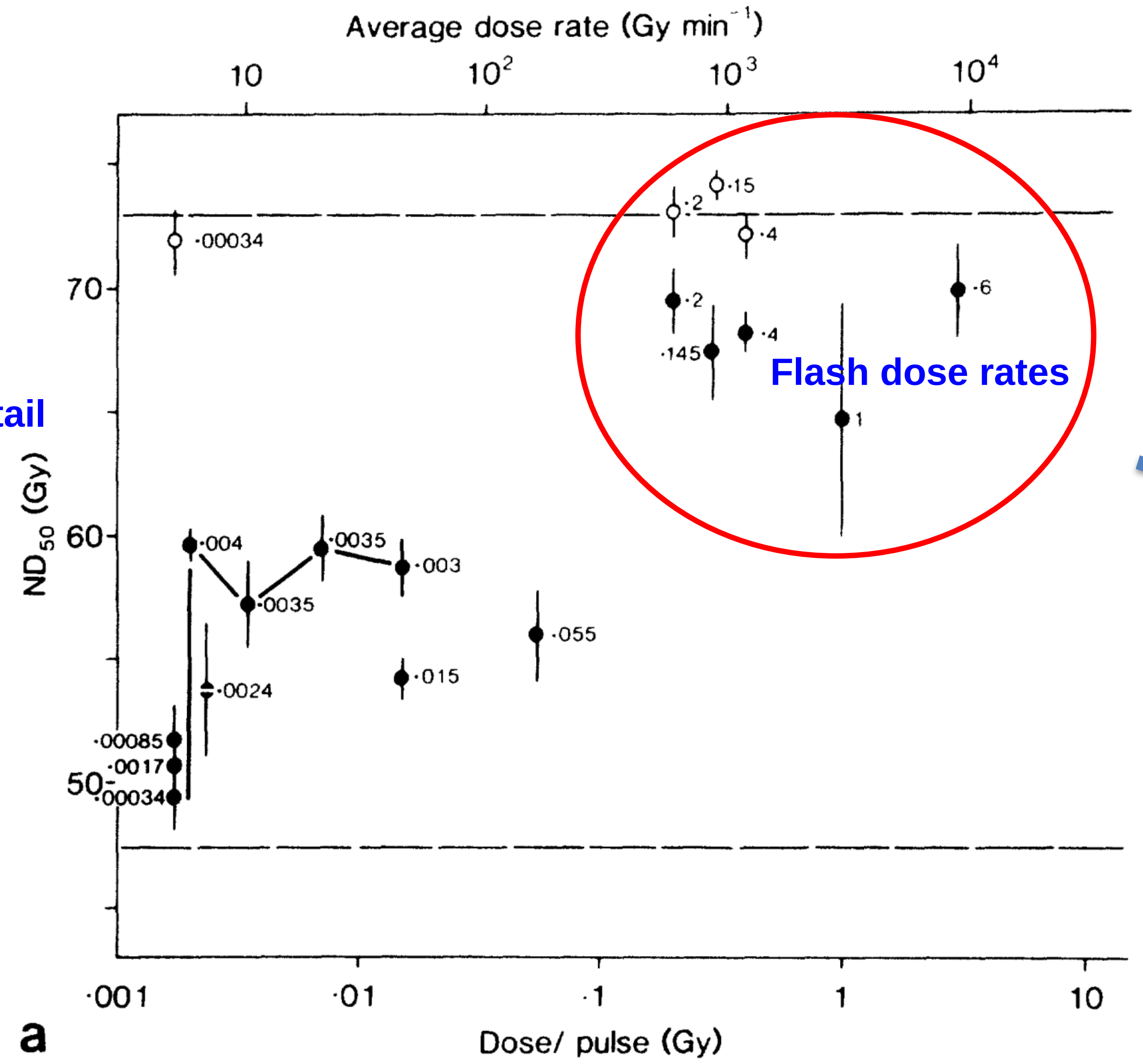
conventional dose rates

Historical perspective



Until 1982 :

Dose for inducing tail necrosis in mice



Jolyon H. Hendry
1982

FLASH sparing effect on normal tissues was recognized

2014 Re-discovery …

1) Sparing normal tissues

2) No sparing of tumors


Favaudon & Vozenin

RESEARCH HIGHLIGHTS

IN BRIEF

RADIOTHERAPY

FLASHing tumours

A new study in mice suggests that radiation delivered in short pulses at ultrahigh dose rates (FLASH) is as effective against lung tumours as conventional protracted single lower dose rates and has fewer side effects. Using both orthotopic lung tumours in immunocompetent mice and human lung tumour xenografts in nude mice, Favaudon *et al.* showed that FLASH irradiation caused less lung fibrogenesis and less apoptosis in normal tissue than conventional radiation. Although this technique was only tested in one tumour type, it suggests that delivery methods are crucial to minimizing radiation treatment side effects, and it has implications for therapeutic protocols.

ORIGINAL RESEARCH PAPER Favaudon, V. *et al.* Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci. Transl Med.* **6**, 245ra93 (2014)

NATURE REVIEWS | CANCER VOLUME 14 | SEPTEMBER 2014

What is the magnitude

of the sparing effect on

normal tissues ?

FLASH is consistently associated with a relative sparing of normal tissues

(compared to normal radiotherapy):

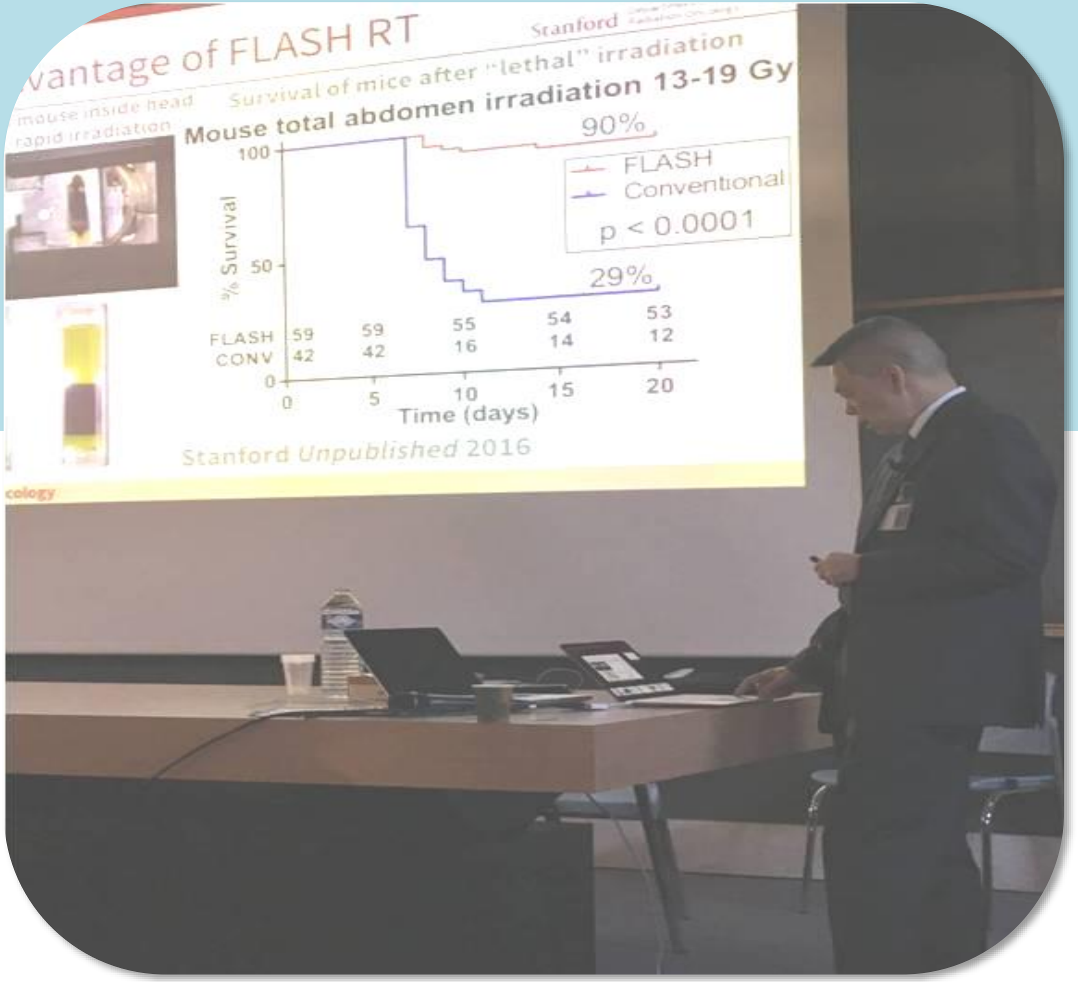
1) **in several types of tissues (brain, skin, lung, GI …)**

2) **in several** animal **species (cat, mouse, pig, Z-fish)**

3) with **several** types of **beam and energy (electrons, X-rays, protons)**

4) **accross a few Institutions (Europe, USA)**

Results of the CHUV were first confirmed @ Stanford University



"... Pre-clinical data indicate a marked reduction of normal tissues side effects while maintaining the destruction of tumor cells.

This could revolutionize the field of radiation oncology ...*"

Pr. Billy LOO MD PhD,
Thoracic radiation oncology program
Stanford Cancer Institute

Stanford MEDICINE

* Experimental Platform for Ultra-high Dose Rate FLASH Irradiation of Small Animals Using a Clinical Linear Accelerator, IJRO. Juin 2016. Bill Loo, (Stanford University

canton de vaud

Unil UNIL | Université de Lausanne

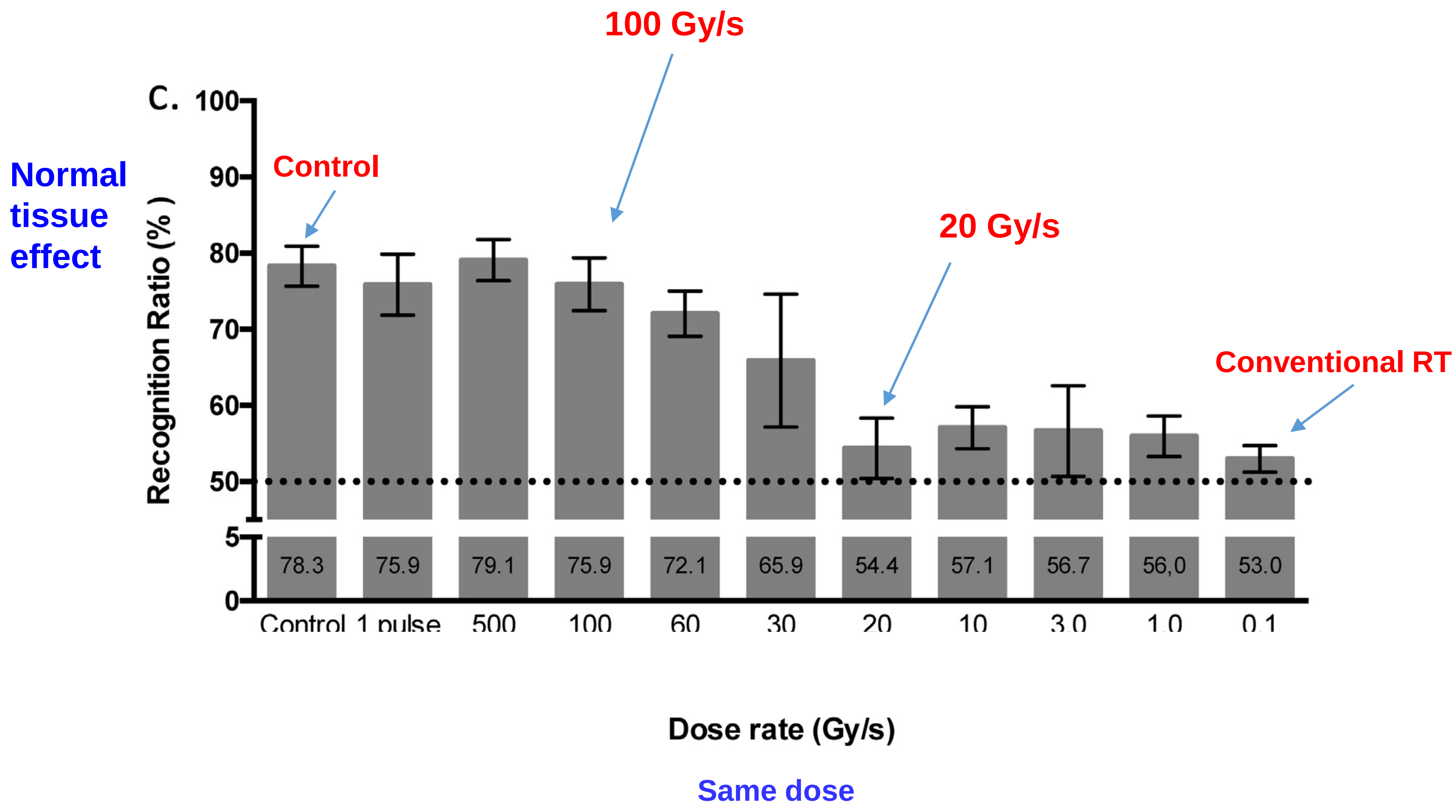
CHUV

Example N° 1 : FLASH effect on the skin (Pig)

(skin of a pig, @ 9 months post-RT)

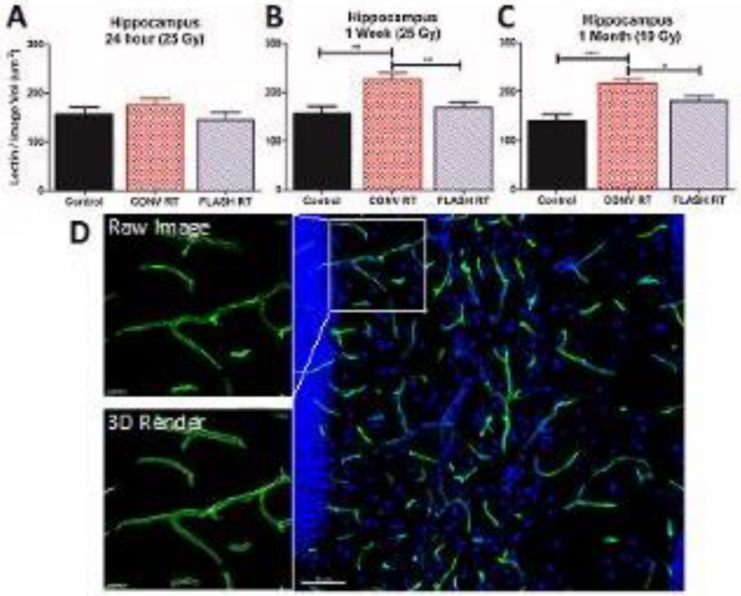
Vozenin et al
Clin Cancer Res
2018

Example N°2 in normal brain *(mice)*



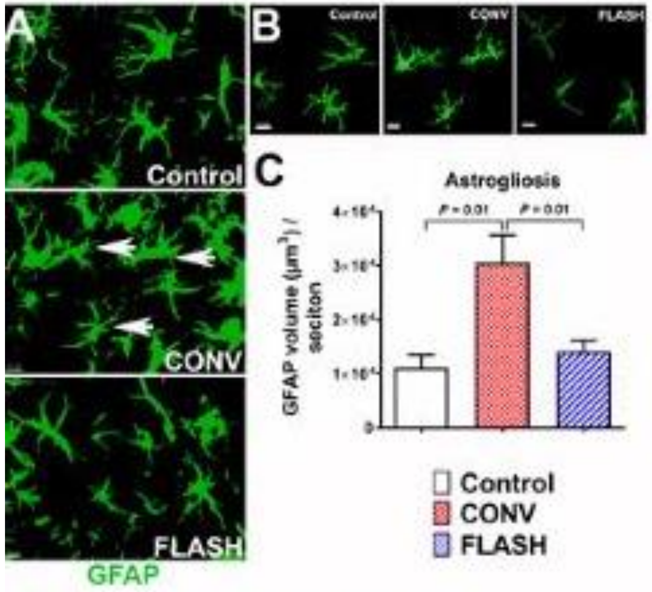
Montay-Gruel Radiother Oncol 2017

FLASH versus Normal RT in mouse brain



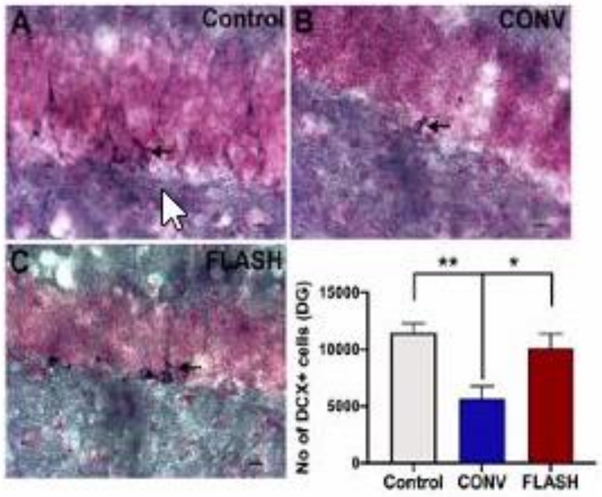
Allen et al, Rad Res, 2020

Less inflammation



Montay-Gruel et al, Rad Res, 2020

Blood vessel protection



Alaghband et al, Cancers, 2020

Protection of juvenile brain

What is the effect of FLASH

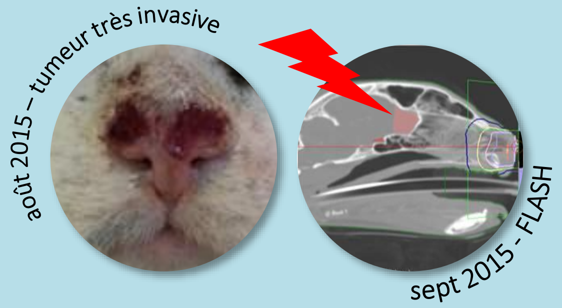
on tumors ?

So far … no sparing effect for tumors with FLASH-RT :

1) **in mouse :** breast, H/N, glioma, lung, GI xenografts and orthotopic models

2) **in a phase I veterinarian clinical trial** in SCC of cat-patients

High cure rate in cat cancer patients
(a veterinarian clinical trial @ CHUV)



6 cats with spontaneous cancers treated with FLASH

⊕ Minimal mucosal toxicity swallowing preserved

⊕ 84% tumor control rate at 1 year

* *Vozenin et al Clinical Cancer Research* 2019

How does it works ?

Potential mechanisms ?

Lower production of H2O2/contribution of O2
(Montay-Gruel, 2019; Adrian, 2019)

Lower level of persistent DNA damages and senescent cells
(Fouillade, 2019)

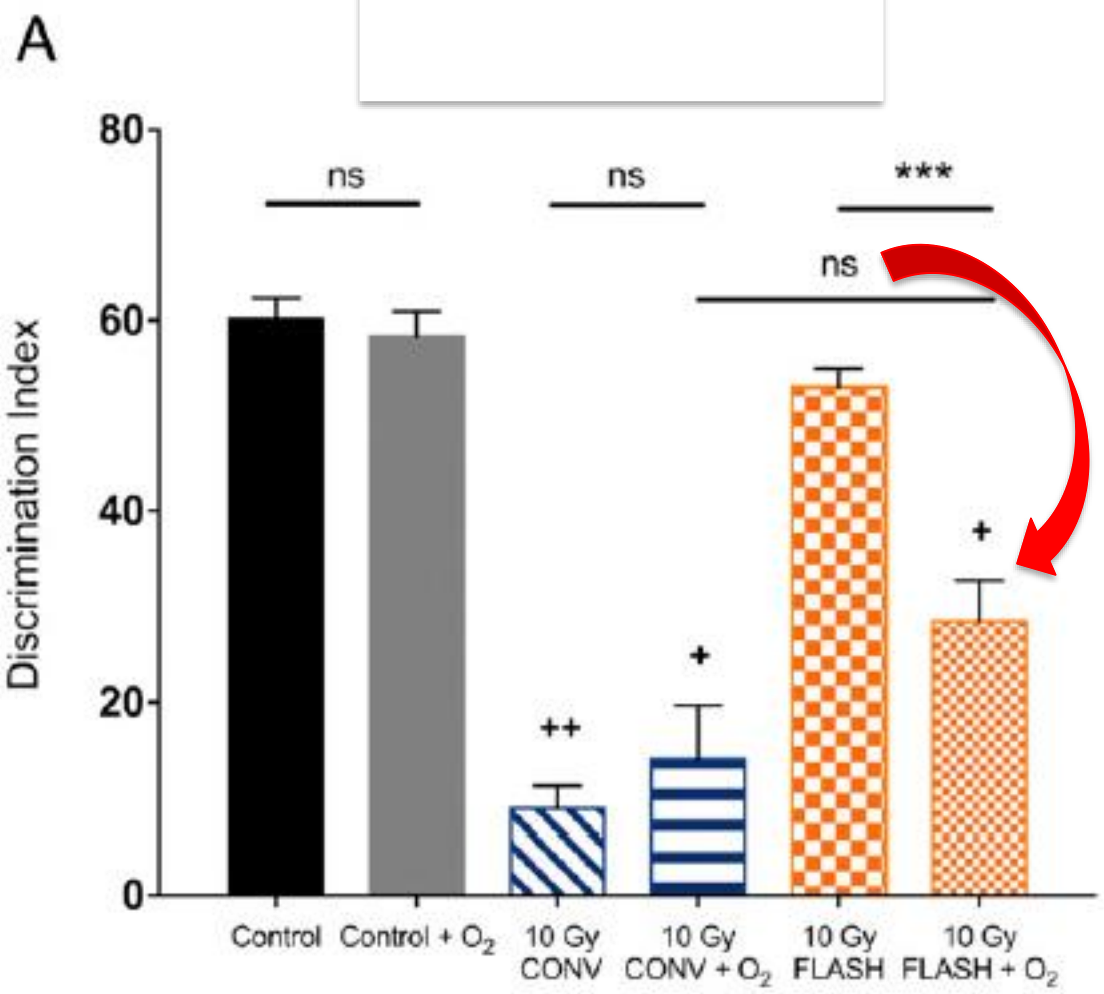
Metabolism including redox (Spitz, 2019)

Inflammation/Immune system
(Favaudon, 2014; Montay-Gruel, 2019; Simmons, 2019; Diffenderfer, 2019)

Signaling pathways/Stem cells protection
(Montay-Gruel, 2017, Fouillade, 2019, Alaghband, 2010)

Vascular protection
(Montay-Gruel, 2020; Allen, 2020)

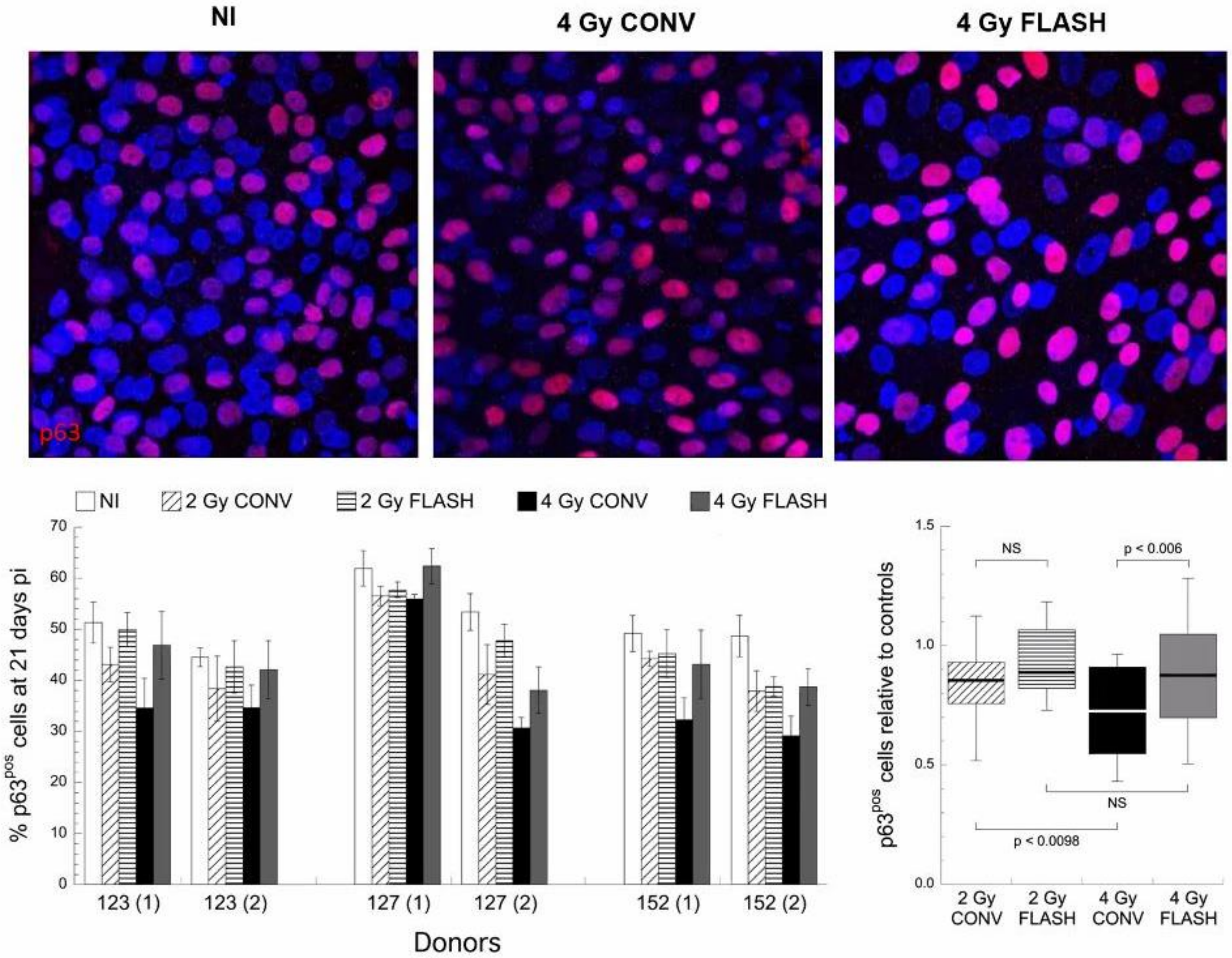
Mechanisms ? Some level of O2 dependency



Hyper-oxygenation with carbogen breathing abolishes the FLASH effect

Montay Gruel PNAS 2019

FLASH-RT spares lung basal stem cells *in vitro*



Fouilhade
Curie institute

- Increased proportion of remaining of human basal stem cells after FLASH-RT

Are there

potential limitations

for clinical use ?

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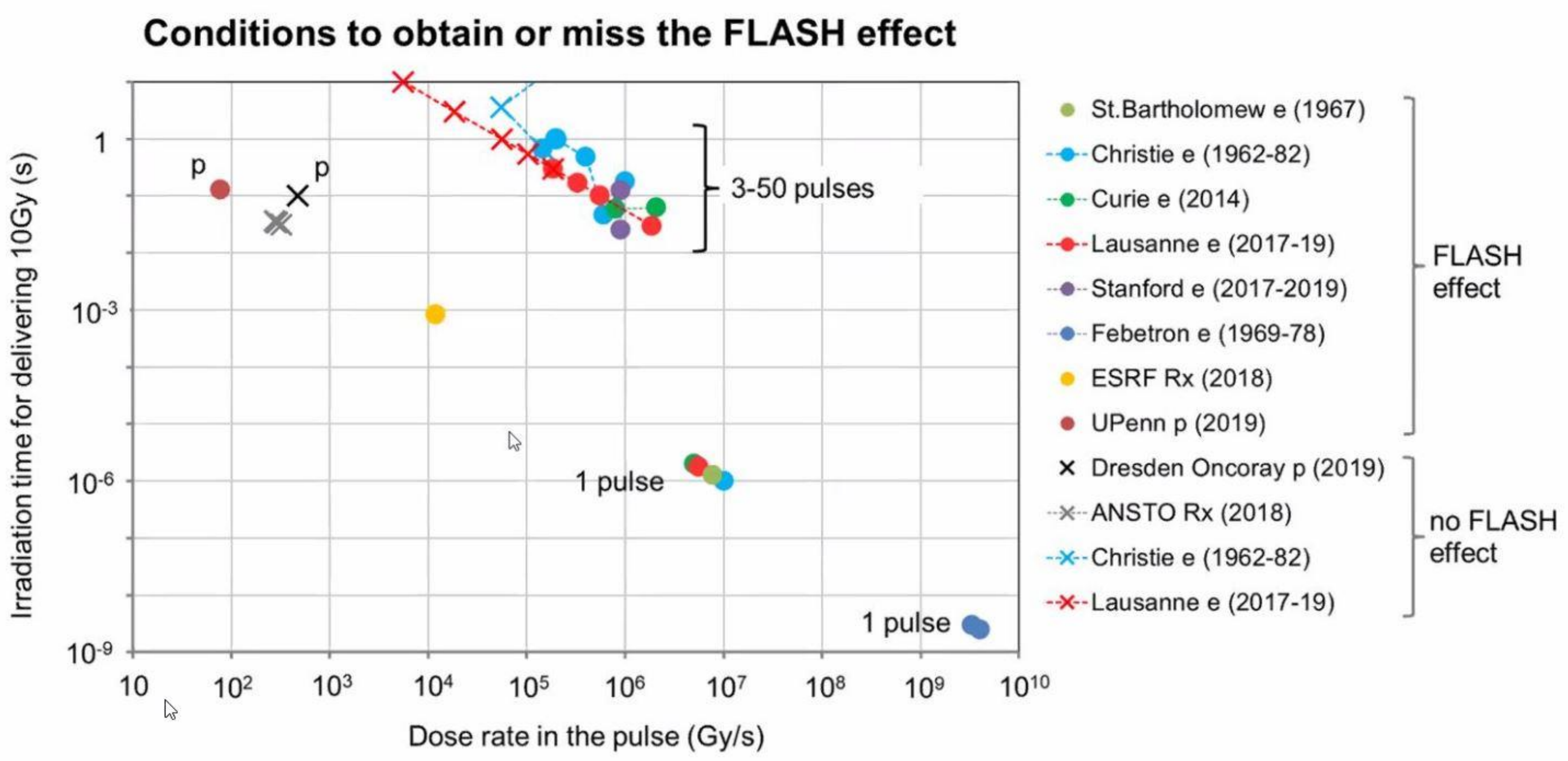
How high should be the dose rate to observe a FLASH effect ?

(for small volumes / with electrons)

Possible :	**30-40 Gy/s** ***(Favaudon et al 2014)***
Likely :	**> 100-150 Gy/s** ***(Montay-Gruel et al 2017)***
Reproducible :	**Dose / pulse** ***(> 1.5 Gy and very few pulses)***
	Dose rate in the pulse ***(>= 10^6 Gy /s)***
	Overall time ***(< 100 ms)***
	(Vozenin et al 2019, Montay Gruel 2019, Bourhis et al, 2019)



JF Germond, CHUV

Potential limitations for the clinical translation ?

The experimental **conditions to observe a FLASH effect were essentially** :

- **Small** volumes of normal tissues (a few cc)
- Mainly (but not only) with **single** dose (7-10 Gy or higher)
- Overall Treatment Time **< 100-200 ms**

Is the magnitude of the benefit clinically meaningful ?

Example for the pig's skin

Conventional | FLASH

25 Gy no necrosis

28 Gy

31 Gy

34 Gy

28 Gy

31 Gy

34 Gy, no necrosis

Potential DMF between 1.25 and 1.36

(late effects @ 9 months post-RT)

Vozenin et al
Clin Cancer Res 2019

… Clinical translation

is ongoing …

Great interest in the radiation oncology community

1) **Promizing, reproducible and consistent pre-clinical observations**

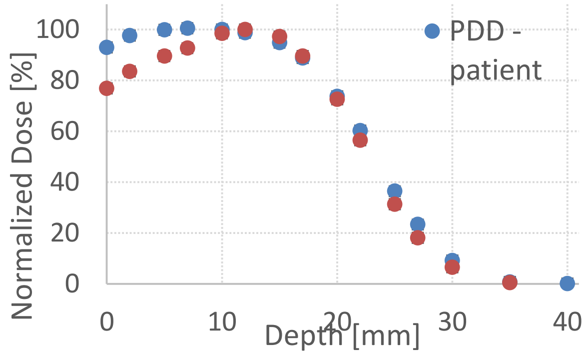
2) **Potentially less toxic, more efficient treatments for the radio-resistant tumors**

3) **Numerous projects initiated world wide**

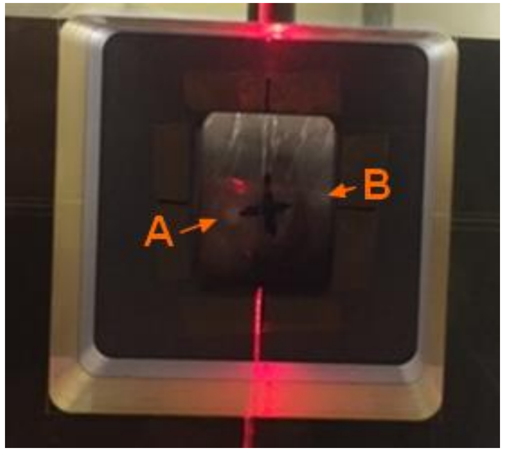
For clinical translation : additional safety measures are needed …

(ex @ CHUV :)

Pre-treatment

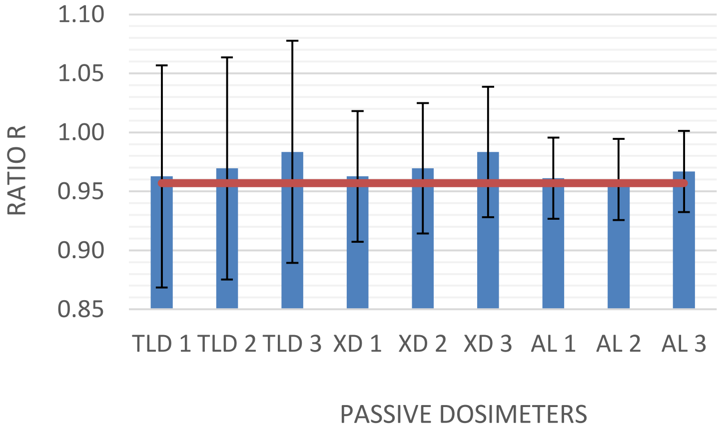


Treatment



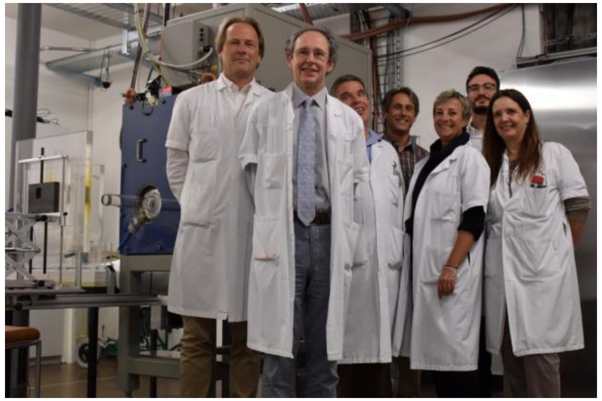
Dosimetry check

	Pre-treatment [Gy]	Alanine A [Gy]	Alanine B [Gy]
Dose [Gy]	14.9	14.9	14.9



→ **Independent pulses and time counter device <u>for beam stopping</u>**

Bourhis et al 2019



First treatment of a patient with FLASH

(CHUV, Oct 2018)

Multiresistant
T cell lymphoma

150 Gy/s
Overall time
90 ms

Day 0

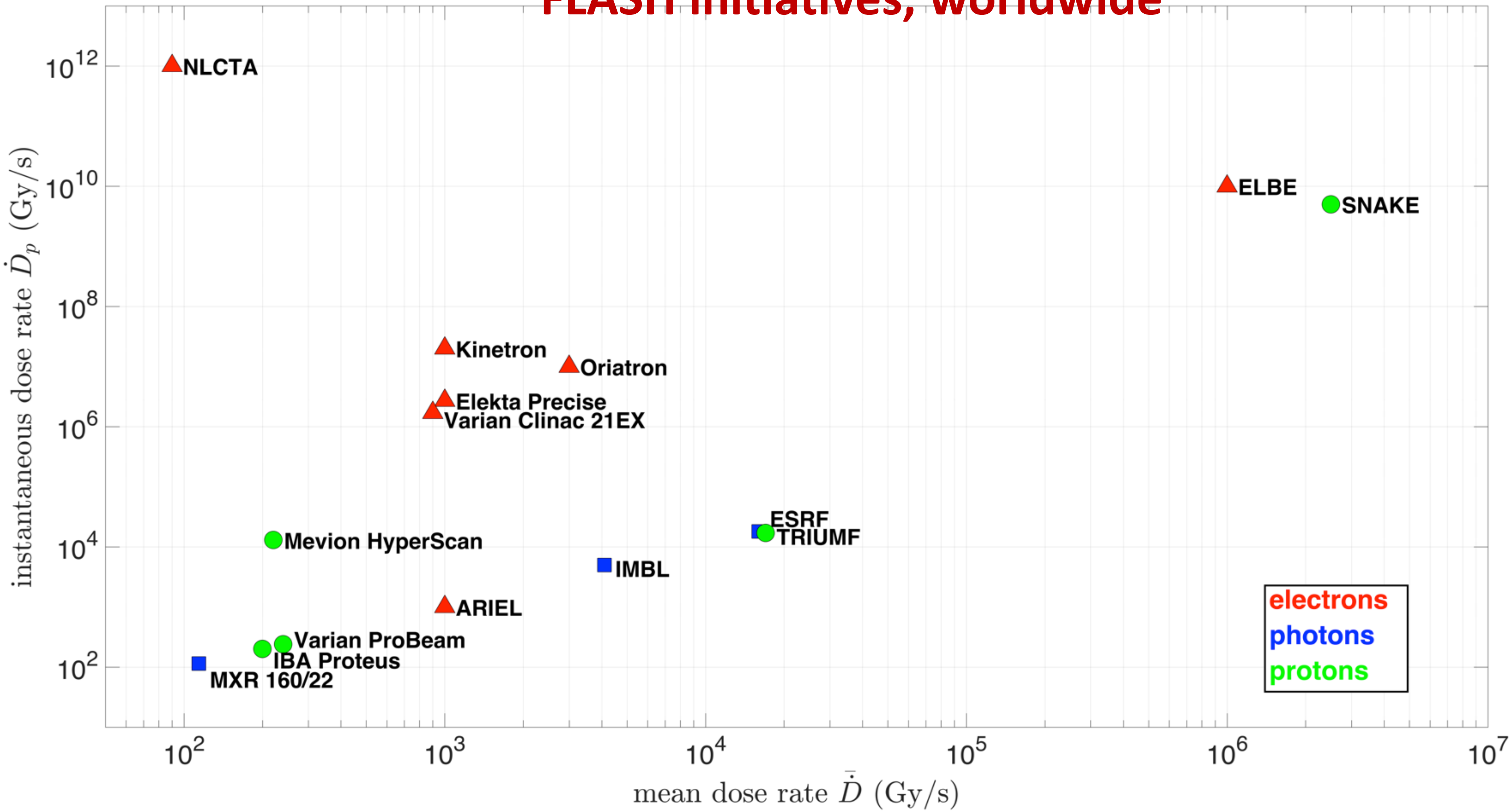
5 months

→ **Feasible**

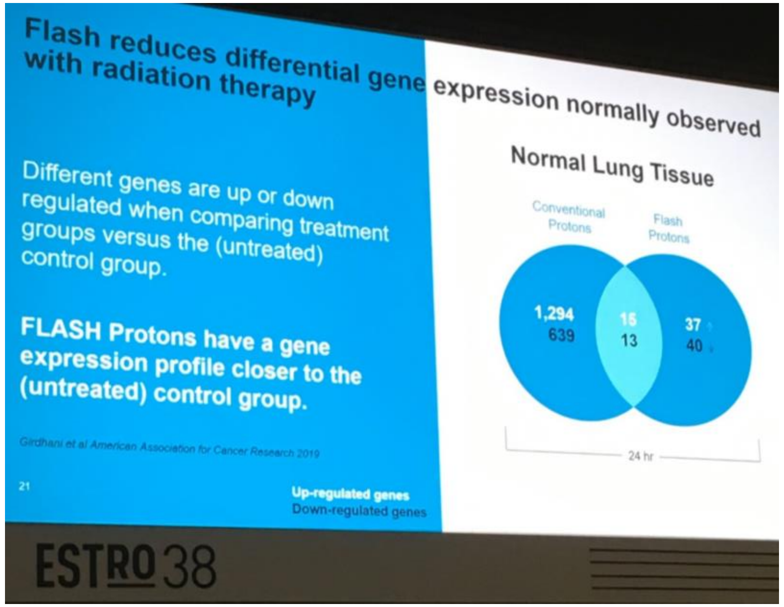
Safe

(Bourhis et al 2019)

FLASH initiatives, worldwide



FLASH with Protons (broad beam)



Varian and the Cincinnati Children's/UC Health Proton Therapy Center Announce Initial Patient Treated in the FAST-01 First Human Clinical Trial of FLASH Therapy for Cancer

- First patient in the world to participate in a clinical trial of FLASH therapy
- Physicians and researchers at Cincinnati's Children's/UC Health Proton Therapy Center are using a Varian ProBeam® proton therapy system modified to deliver radiation treatment at ultra-high dose rates

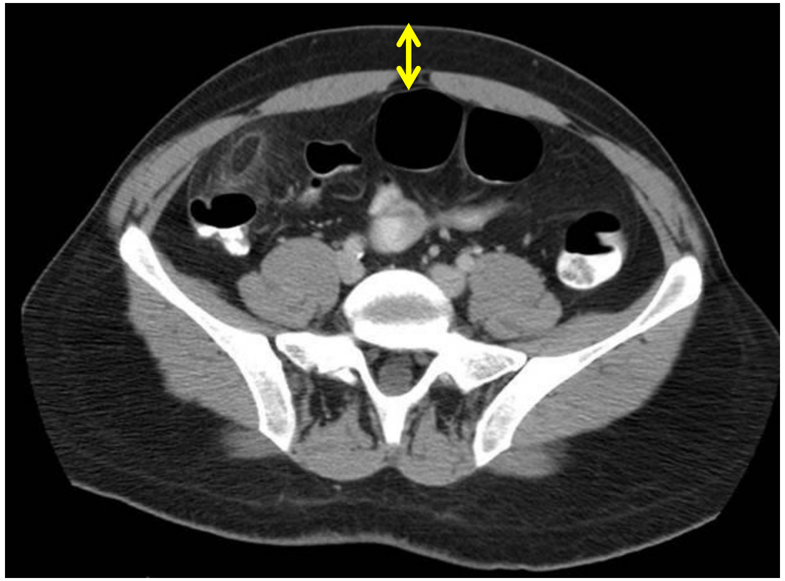
Menu CHUV

- FLASH therapy delivers radiation at ultra-high dose rates up to 100 times faster compared to conventional radiation therapy

Transfert clinique au CHUV (I)

FLASH-Mobetron

Only for superficial skin cancers



Press release — Lausanne, Switzerland & Sunnyvale, USA , June 18 2020 — 1

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IntraOp and Lausanne University Hospital Announce Collaboration in FLASH

A collaborative R&D agreement will advance FLASH radiotherapy for cancer patients

The Lausanne University Hospital (CHUV) and IntraOp Medical Corporation have announced a research and development collaboration to accelerate the development of FLASH radiotherapy toward first human trials.

First Investigational Trials Planned with Mobetron FLASH HDR

Lausanne University Hospital Clinical Translation Initiatives:

CHUV

Impulse Trial:

Phase I dose escalation study for multiresistant melanoma skin metastases (Mobetron-FLASH @ CHUV)

Classical 3 x 3 dose escalation : 22 Gy to 34 Gy

First cohort	Second Cohort
Small fields	**Larger fields**
< 30 cc	30-100 cc

Primary Endpoint : DLT / MTD with independent blinded photograph review

Status : Enrollment expected to start in 2020

NMSC Trial:

Randomized phase II trial for BCC and SCC of the skin (Mobetron-FLASH @ CHUV)

Randomisation volumes < 30 cc → **FLASH with Electrons single dose 22 Gy**

Randomisation volumes < 30 cc → **SOC 5 x 7 Gy**

Primary Endpoint : composite (toxicity / tumor control) with independent blinded review

Status : Enrollment expected to start in 2021

Courtesy of Prof. Jean Bourhis

Transfert clinique @ CHUV (II) : intra-operative FLASH-THERAPY

With
Pr Simon,
Pr Demartines,
Pr Mathevet

For cancers not amenable to
A complete resection

t-

What about large tumor volumes and deep seated tumors ?

- **Unmet clinical need :** this is where we have most of the tumor failures …

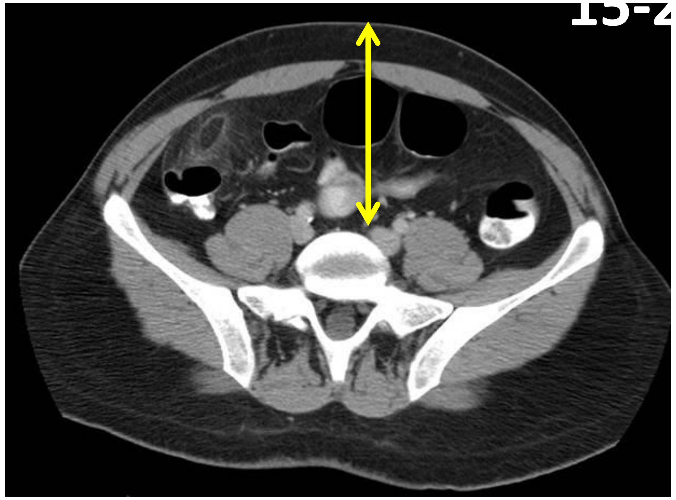
- **So far no FLASH** pre-clinical data mimicking these clinical situations

- **No FLASH** irradiating device is currently **available** : technical challenges

- **FLASH characteristics may not help for its use in such large volumes ?**

Next step : CHUV-CERN project

For deep seated tumors



Press Release Lausanne and Geneva, September 15th 2020

Lausanne University Hospital and CERN collaborate together on a pioneering new cancer radiotherapy facility

Lausanne University Hospital (CHUV) and CERN, in Switzerland, are collaborating to develop the conceptual design of an innovative radiotherapy facility, used for cancer treatment. The facility will capitalise on CERN breakthrough accelerator technology applied to a technique called FLASH radiotherapy, which delivers high-energy electrons to treat tumours. The result is a cutting-edge form of cancer treatment, highly targeted and capable of reaching deep into the patient's body, with less side-effects. The first phase of the study comes to a conclusion this September.

In radiotherapy, the FLASH effect appears when a high dose of radiation is administered almost instantaneously - in milliseconds instead of minutes. In this case, the tumour tissue is damaged in the same manner as with conventional radiotherapy, whereas the healthy tissue appears to be less affected, meaning that less side effects are expected.

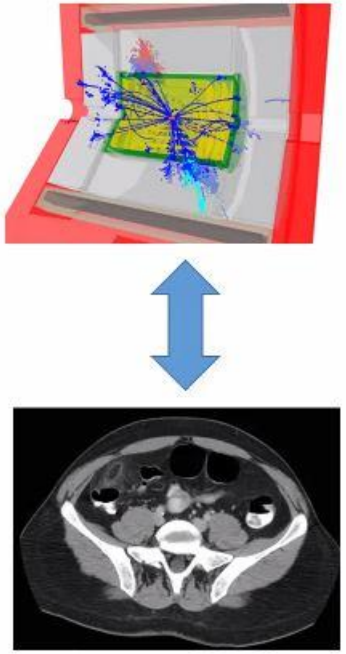
CERN-CHUV collaboration

- CHUV and CERN are actively collaborating on the realization of a clinical FLASH facility for large, deep-seated tumors.
- We have worked intensively and are now confident that the facility is feasible and are establishing the design.
- We are now working towards the next steps of t
project, with the target of a clinical facility.

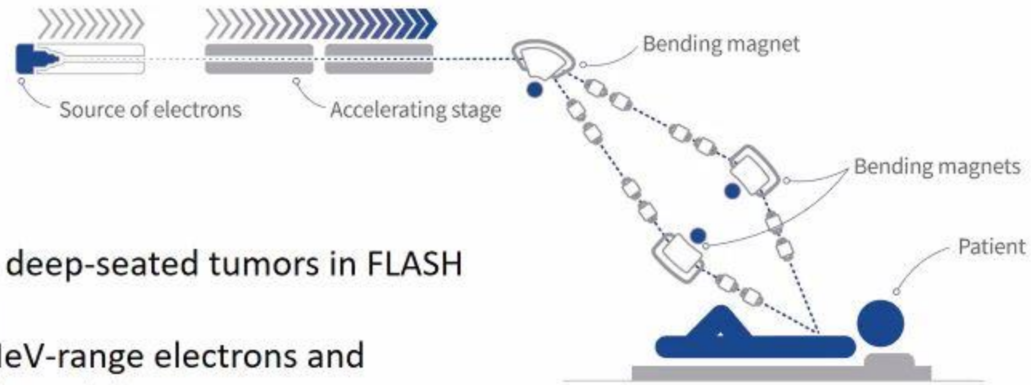
The remarkable connection between CLIC and FLASH

Both need:

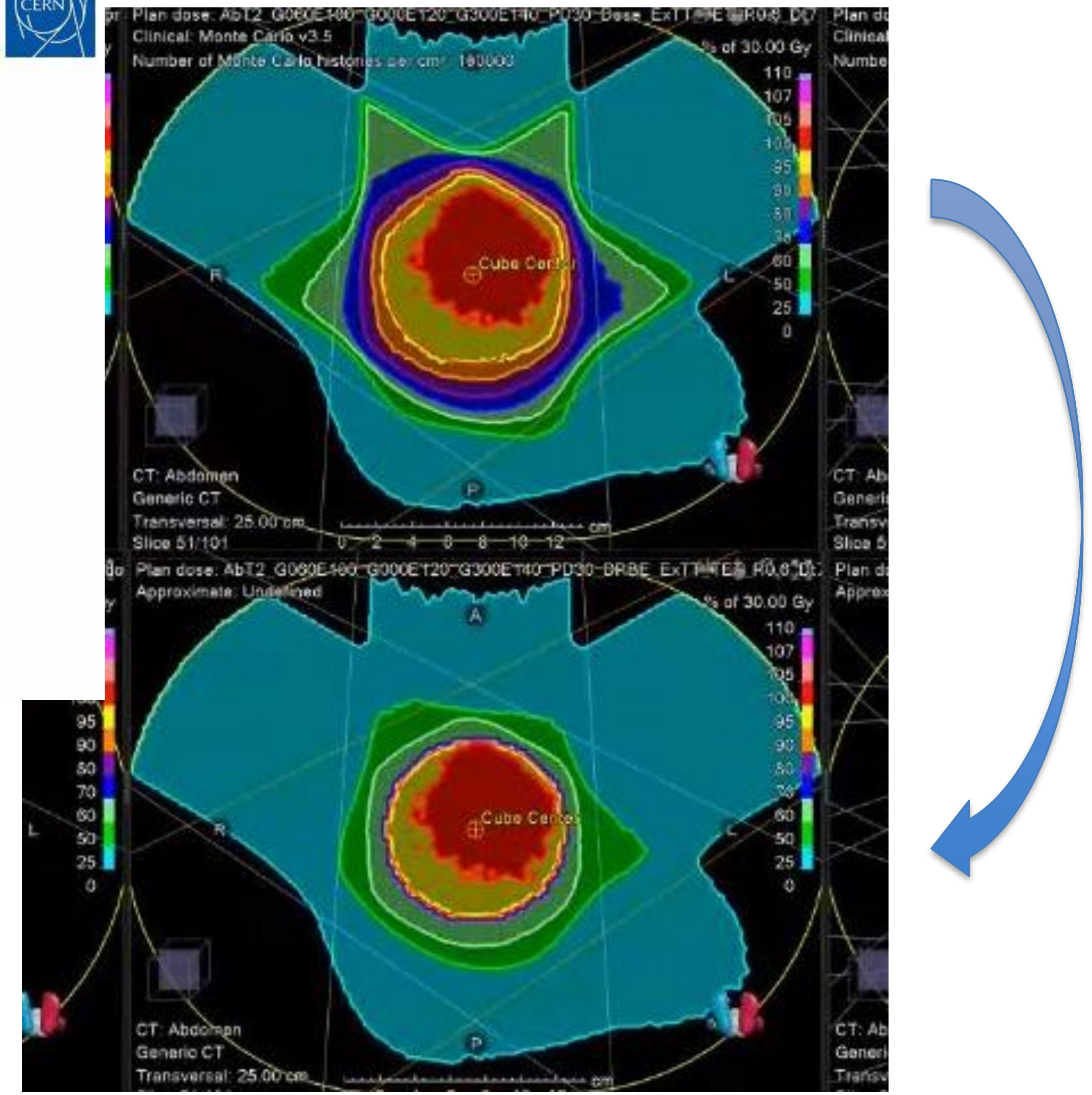
- Very intense electron beams
  - CLIC – to provide luminosity for experiments
  - FLASH – to provide dose fast for biological FLASH effect
- Very precisely controlled electron beams
  - CLIC – to reduce the power consumption of the facility
  - FLASH – to provide reliable treatment in a clinical setting
- High accelerating gradient
  - CLIC – fit facility in the Geneva area and limit cost
  - FLASH – fit facility on a typical hospital campus and limit cost of treatment



CLIC technology for a FLASH facility being designed in collaboration with CHUV



Treat large, deep-seated tumors in FLASH conditions.
Uses 100 MeV-range electrons and optimized dose delivery.
Compact to fit on a typical hospital campus.



Which tumor type first ? : glioblastoma ? one of the most non-curable cancer

Proc Natl Acad Sci U S A.
2019 May 28; 116(22): 10943–10951.
Published online 2019 May 16. doi: 10.1073/pnas.1901777116

PNAS

Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species

Pierre Montay-Gruel, Munjal M. Acharya, Kristoffer Petersson, et al

Less toxicity

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Hypofractionated FLASH-RT as an Effective Treatment against Glioblastoma that Reduces Neurocognitive Side Effects in Mice

Pierre Montay-Gruel[1], Munjal M. Acharya[2], Patrik Gonçalves Jorge[1,3], Benoît Petit[1], Ioannis G. Petridis[1], Philippe Fuchs[1], Ron Leavitt[1], Kristoffer Petersson[1,3], Maude Gondré[1,3], Jonathan Ollivier[1], Raphael Moeckli[3], François Bochud[3], Claude Bailat[3], Jean Bourhis[1], Jean-François Germond[3], Charles L. Limoli[2], and Marie-Catherine Vozenin[1]

More efficacy

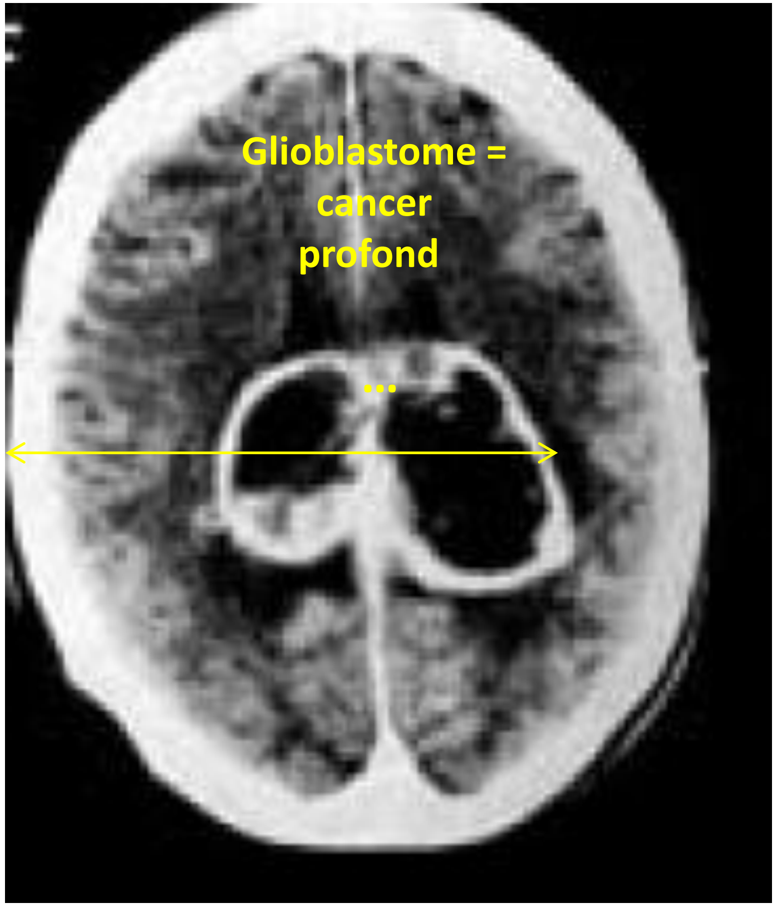
FLASH therapy CERN–CHUV project

ISREC & BILTEMA Foundations

Construction of the prototype

Installation 2023

First patient 2024-25



Conclusions

1) FLASH :

- Increases the **differential** effect between normal tissues & tumors
- Operates at **high dose / fraction,** delivered in few **milliseconds**
- Mechanisms **?**

2) Clinical translation :

- Optimal parameters for obtaining a FLASH effect **in large fields needs to be investigated**
- **Both** FLASH & high conformal delivery are needed : *technical challenges (CERN +++)*

Remerciements

L'équipe FLASH therapy
du CHUV

Pr Vozenin
(cheffe de laboratoire)

Pr Bochud et l'IRA

UNIL & CHUV : Pr P Eckert, Mr O Peters, Pr JD Tissot, Pr PF Leyvraz,
DO : Pr Coukos, Pr Kandalaft & l'équipe du CTE
Sponsors : ISREC & Fondation Biltema, Fondation CePO, Fond'Action, FNS, ANR, PO1, Fondation CHUV
Partenaires : PMB, CERN, IntraOp, RaySearch
Recherche de nouveaux partenaires en cours pour le projet CERN-CHUV

Table 5. Characteristics reported in the literature for electron UHDR devices.

Device	**Mobetron (IntraOp)**	**Oriatron eRT6 (PMB Alcen)**	**Kinetron (CGRMeV)**	**Modified Elekta**	**Modified Varian**	**Novac7 (Sordina)**
Reference	This publication	Jaccard [14] Petersson [26]	Lansonneur [16]	Lempart[15]	Schüler[8,17]	Felici [25]
Available beam energy [MeV]	6 and 9	6	4.5	10	9, 16 and 20	7
Maximum average dose rate [Gy/s]	> 700 @ 6 MeV > 800 @ 9 MeV	1000	NA*	≥ 300	74 @ 9 MeV 300 @ 16 MeV 200 @ 20 MeV	540
Maximum dose per pulse [Gy]	> 8 @ 6 MeV > 9 @ 9 MeV	10	1	1.9	1.67 @ 16 MeV 1.85 @ 20 MeV	18.2
Max. beam size @ max. dose rate [cm]	4 @ 90%	NA	NA	2 (5% flatness)	1 (90% isodose)	0.5 (FWHM)
Short term stability [%]	0.8	< 1	NA	1 to 4***	NA	NA
Long term stability	1.8 @ 6 MeV 2.3 @ 9 MeV	4.1%	NA	NA	NA	NA

* NA: data not available; ** during 10 mins; 7 to 11 for > 10 mins