WP on New Radiotherapies

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On behalf of the WP members

Milano
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WP bringing together members of 3 ICRP Committees

- C1 - Radiation effects
- C2 - Doses From Radiation Exposure
- C3 - RP in medicine

List of members

ANDERSSON Martin	Committee 2	**KRON Tomas**	Affiliated to TG 116 (C3)
BADIE Christophe	Committee 1	**M Mahesh**	Committee 3
GROS Sebastien	Affiliated to TG 116 (C3)	**SMALL Bill**	Committee 3
HOSONO Makoto	Committee 3	**WILLIAMS Ivan**	Committee 3 (WP leader)
ISAMBERT Aurelie	Committee 3 (WP leader)	**WOLOSCHAK Gayle**	Committee 1

Purpose

To monitor scientific presentations and publications on new radio therapies **with different radiobiological behavior than classic EBRT.**

Focus on key new therapies to include:
FLASH, Spatial fractionation, Alpha therapies, Heavy Ion Tx, and a few others (BNCT)

Ultimate goal - when might literature be mature for ICRP Guidance / Recommendations
(creation of a task group to be considered)

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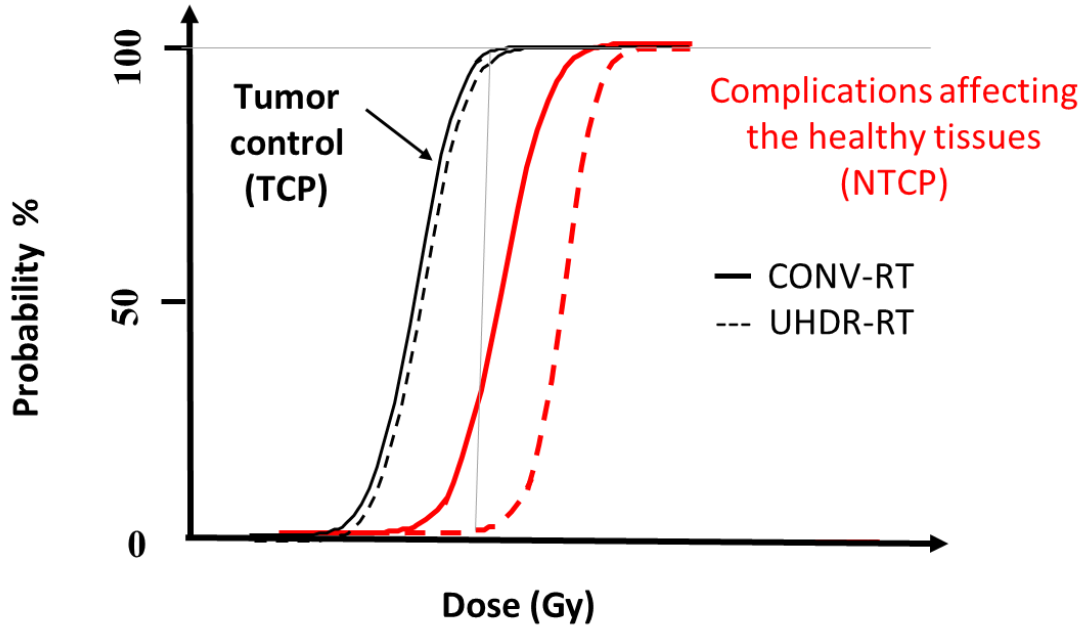
1/ FLASH : UHDR therapy

- FLASH effect is the radiobiological effect with the improvement of healthy tissues protection when delivering the prescribed dose at UHDR

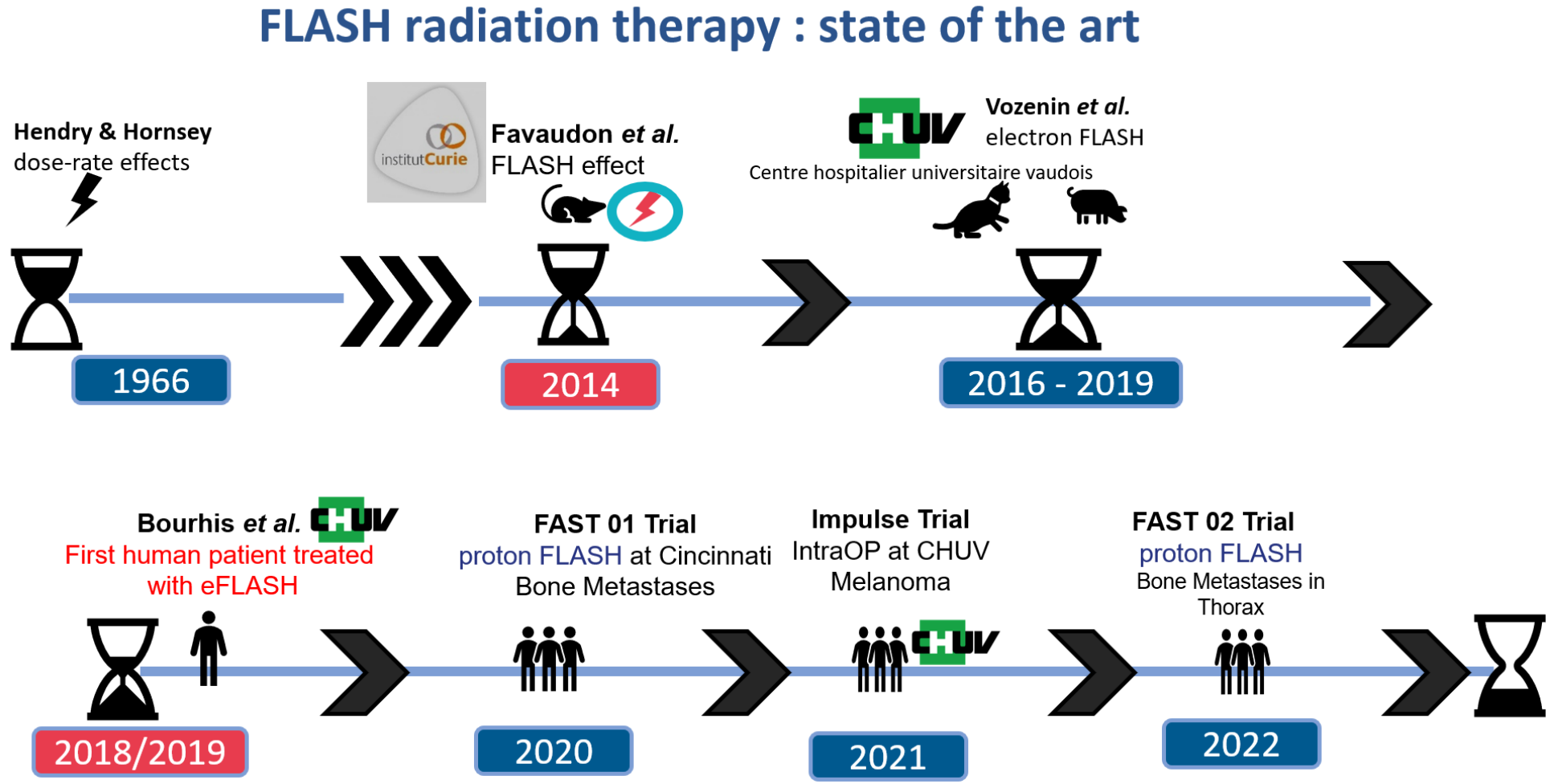
- UHDR-RT is the delivery of higher dose rates with a pulse of radiation (40-150+ Gy/s and irradiation times below 1s)

- Expected benefits compared to CONV-RT:
  - Low normal tissue toxicity
  - Iso-efficient tumor control



Chaikh et al. Cancer Radiother, in Press, 2024

FLASH : UHDR therapy *(courtesy, A. Chaikh)*



FLASH : UHDR therapy *(courtesy, A. Chaikh)*

Questions to be resolved …

- Dose fractionation schedules for clinical use : biological effect is not clear
- Physical parameters : optimal parameters to obtain the FLASH effect not clear
- Dosimeters for absolute dosimetry (ionization chamber, diamond, film, etc) : issue of saturation for most common reference dosimeters (IC)
- Quality Assurance (QA) tools for planning and dosimetric verification to be developed
- Robust dose planification to be developed
- In vivo dosimetry, imaging for patient positioning : on going developments
- Radiation protection shielding: patients, staff & public

… Very active domain

FLASH : UHDR therapy

With a call for caution and further investigations…

Dose- and Volume-Limiting Late Toxicity of FLASH Radiotherapy in Cats with Squamous Cell Carcinoma of the Nasal Planum and in Mini Pigs

Carla Rohrer Bley[1], Friederike Wolf[1], Patrik Gonçalves Jorge[2,3,4], Veljko Grilj[2,3,4], Ioannis Petridis[2,3], Benoit Petit[2,3], Till T. Böhlen[4], Raphael Moeckli[4], Charles Limoli[5], Jean Bourhis[2], Valeria Meier[1], and Marie-Catherine Vozenin[2,3]

Clin Cancer Res. 2022 Sep 1;28(17):3814-3823

Results: In cats, acute side effects were mild and similar in both arms. **The trial was prematurely interrupted due to maxillary bone necrosis**

The reported outcomes point to the caveats of translating single-high-dose FLASH-radiotherapy and emphasizes the need for caution and further investigations

EDITORIAL

Taking Care with FLASH Radiation Therapy

Jolyon Hendry, PhD, DSc

Medical Physics Department, Christie Hospital, Manchester, United Kingdom

Int J Radiat Oncol Biol Phys. 2020 Jun 1;107(2):239-242.

2/ Alphatherapies *(courtesy, M. Mahesh)*

- Targeted α-therapy (TAT) is one of the most promising fields in novel targeted cancer therapy, with several early and late-stage clinical trials for neuroendocrine tumors and metastatic prostate cancer, e.g. :
  - 223Ra-dichloride, for treatment of bone metastases in castration-resistant prostate cancer (mCRPC) is the first US FDA approved α-therapy
  - 225Ac-PSMA-617 for treatment of prostate cancer

- Significant interest & investment in additional early-phase studies

Feuerecker et al, J Nucl Med 2023; 64:685–692

Alphatherapies : on going clinical trials

Overview of ongoing (2022) TAT clinical trials

TABLE 1 Overview of ongoing targeted alpha therapy clinical trials.

Radiopharmaceutical	Ligand	Cancer type	Special notes	Clinical trial*
^{211}At-BC8-B10	BC8-B10, antibody targeting CD45	Different types of acute leukemia or myelodysplastic syndrome		NCT03128034, phase I/II, recruiting (2017) NCT03670966, phase I/II, recruiting (2019) NCT04083183, phase I/II, recruiting (2020)
^{225}Ac-Lintuzumab	Lintuzumab, antibody targeting CD33	Acute myeloid leukemia	In combination with other chemotherapeutic agents	NCT03441048, phase I, recruiting (2018) NCT03867682, phase I/II, recruiting (2020) NCT03932318, phase I/II, not yet recruiting (2023)
^{212}Pb-DOTAMTATE	DOTAMTATE, somatostatin analog	Somatostatin positive neuroendocrine tumors		NCT03466216, phase I, recruiting (2018) NCT05153772, phase II, recruiting (2021)
BAY2315497 (^{227}Th)	Antibody targeting PSMA	Metastatic castration resistant prostate cancer	In combination with darolutamide	NCT03724747, phase I, active but not recruiting (2018)
^{225}Ac-FPI-1434	FPI-1175, antibody targeting insulin-like growth factor-1 receptor (IGF-1R)	Advanced solid tumors		NCT03746431, phase I/II, recruiting (2019)
BAY2701439 (^{227}Th)	Antibody targeting HER2	Advanced cancers expressing the HER2 protein		NCT04147819, phase I, recruiting (2020)
JNJ-69086420 (^{225}Ac)	H11B6, antibody targeting human kallikrein-2 (hk2)	Advanced and metastatic prostate cancer		NCT04644770, phase I, recruiting (2020)
^{225}Ac-J591	J591, monoclonal antibody against PSMA	Hormone-sensitive metastatic prostate cancer	In combination with androgen deprivation therapy	NCT04946370, phase I/II, recruiting (2021) NCT05567770, phase 1, not yet recruiting (2022)

Pallares et al, Front. Med. 9:1020188, 2022

Clinical trials (2024) of novel RN therapeutics for mCRPC

Table 1 – Clinical trials of novel targeted radionuclide therapeutics for metastatic castration-resistant prostate cancer [a]

Trial	Vector	Isotope	Target	Phase	ECD	Sponsor
NCT05458544 LUCIDA	Ludotadipep	^{177}Lu	PSMA	1/2a	June 2025	FutureChem
NCT03822871	CTT1403	^{177}Lu	PSMA	1	Completed	Cancer Targeted Technology
NCT05413850	Radiohybrid-PSMA-10.1	^{177}Lu	PSMA	1/2	Oct 2026	Blue Earth Therapeutics
NCT06343038 PROGNOSTICS	Sibu-DAB	^{161}Tb	PSMA	1	June 2028	University Hospital Basel
NCT04868604 SECURE	SAR-bis-PSMA (Abefolastat)	^{67}Cu	PSMA	1/2a	Sept 2026	Clarity Pharmaceuticals
NCT05633160 COMBAT	SAR-BBN	^{67}Cu	GRPR	1	May 2026	Clarity Pharmaceuticals
NCT04597411 ACTION	PSMA-617	^{225}Ac	PSMA	1	Jan 2027	Endocyte
NCT05983198 SATISFACTION	PSMA-R2	^{225}Ac	PSMA	1/2	Aug 2026	Novartis
NCT06217822 PANTHA	PSMA-Trillium (BAY3563254)	^{225}Ac	PSMA	1, FIH	June 2027	Bayer
NCT06052306	Macropa-pelgifatamab (BAY3546828)	^{225}Ac	PSMA	1, FIH	June 2027	Bayer
NCT05219500 TATCIST	FPI-2265 (PSMA-I&T)	^{225}Ac	PSMA	2	Dec 2025	Fusion Pharmaceuticals
NCT06402331 ALPHABREAK	FPI-2265 (PSMA-I&T)	^{225}Ac	PSMA	2/3	Jan 2031	Fusion Pharmaceuticals
NCT05725070	NG001	^{212}Pb	PSMA	0/1	July 2023	ARTBIO
NCT03724747	BAY2315497	^{227}Th	PSMA	1, FIH	Nov 2024	Bayer

ECD = estimated completion date; FIH = first in human.

[a] Ongoing trials and trials that have completed recruitment complete with results pending, excluding trials at the most advanced clinical stage such as for [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-I&T. Data retrieved from ClinicalTrials.gov in May 2024.

K. Hébert et al, New Drugs for Targeted Radionuclide Therapy in Metastatic Prostate Cancer, Eur Urol Focus (August 2024)

Alphatherapies

Ac225-PSMA - Results of the WARMTH Act study (2024)

- **488 patients** from **7 centres** in Australia, India, Germany, and South Africa.
- Mostly administered as a **last-line compassionate treatment** in patients who have not responded to or are unfit for other lines of therapy
- The investigation of the safety of ^{225}Ac-PSMA RLT was limited to the **assessment of salivary gland, bone marrow, and renal toxicities** as they are the most commonly known side-effects of this treatment modality
- **Conclusion of the study :** ^{225}Ac-PSMA RLT shows a substantial antitumour effect in mCRPC and represents a viable therapy option in patients treated with previous lines of approved agents. Xerostomia is a common side-effect. Severe bone marrow and renal toxicity are less common adverse events.
- **The optimum dosing** of [^{225}Ac]Ac-PSMA-617 **is being investigated further** in the ongoing phase 1 dose-escalation AcTION trial (NCT04597411)

Sathekge M et al – The Lancet Oncology Vol 25, Feb 2024

Alphatherapies *(courtesy, M. Mahesh)*

- “Field of TAT is currently one of the most promising in innovative targeted cancer therapy”
- “Despite profound excitement and incredible clinical potential, it is also important to emphasize **need to understand short- and long-term toxicity** of TAT and identification of suitable therapeutic combination partners”

Feuerecker et al, J Nucl Med 2023; 64:685–692

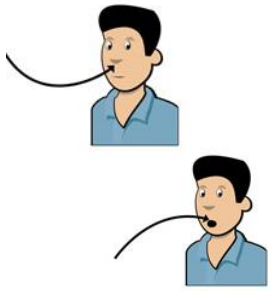
Alphatherapies *(courtesy, M. Mahesh)*

Challenges and special care

- **Scarcity** of alpha emitters + at a reasonable cost * but should be solved in the coming years **

- **Patient - Precise dosimetry calculations** are still challenging, particularly due to the difficulty *:
  - to perform Ac225-**imaging** by SPECT
  - to consider the impact of the **daughter radionuclides** on the dose distribution

- **Occupational and Public exposures** : external exposure is low



However, **special care needed** such as:

- While administering doses, avoid skin contamination, inhalation and ingestion
- Keep family members and children away from patients soon after treatment
- In case patients after administration requires hospital-admission or surgery or die careful considerations to be given to staff exposures and contamination of crematoriums or burial places

Pallares et al, Front in Med 2022 * / Zimmerman, Is Actinium Really Happening? 2023 **

Unanswered questions and pleading for …

- What is the relative biological effectiveness endpoint being considered for any of these approaches?
- RBE for Nuclear Medicine is related to the irradiating nuclei and the carrier molecule, how do we engage with this?
- How should the dose, a historically macroscopic parameter, for theranostics be calculated ?
- FLASH RT has a number of unresolved questions around minimum dose, integrated dose rate compared with local dose rate

- Results of the studies deeply rely on the parameters used to deliver the doses (eg beams characteristics/structures, delivered dose etc)

→ Need for publications to contain the necessary information ***to be able to replicate the results*** within or appended to the article

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Thank you !