

# PARP Inhibitors as radiosensitizers

## Could Particle therapy be the best irradiation modality?

ENLIGHT MEETING  
Caen, 07/02/2019



---

Dr Paul Lesueur, MD, PhD Student

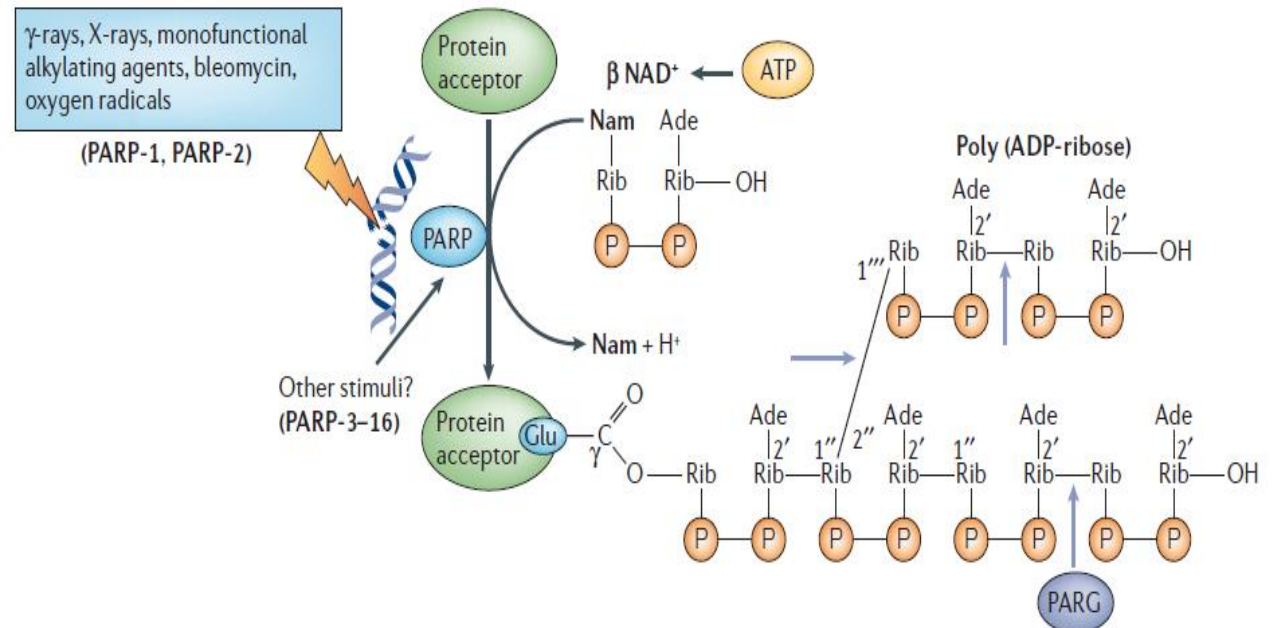
Radiation oncology and proton therapy Department

François Baclesse Center.

ISTCT Cyceron

# PARP: What are we talking about?

- ❑ PAR polymerases (PARPs also known as ADP-ribosyl transferases (ARTDs))
- ❑ SuperFamily of 17 cytoplasmic or nuclear proteins
- ❑ Few sub families: Tankyrase, CCCH-type zinc-finger PARP, Macro-PARP and **DNA-damage-dependent PARPs**
- ❑ Enzymes that generate ADPr modifications on to acceptor proteins
- ❑ Add negatively charged polymers of ADP-ribose (PAR), and recruits other proteins

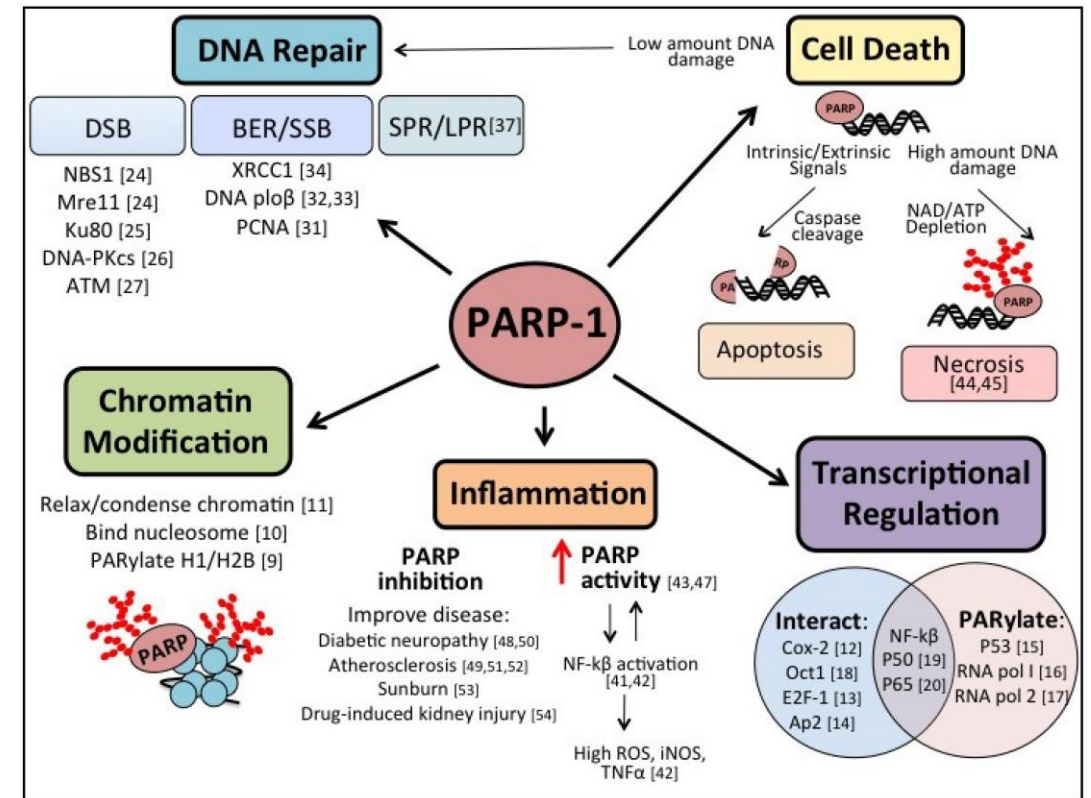


# PARP: What are we talking about?

□ Important roles in various cellular processes:

- modulation of chromatin structure
- Transcription
- replication
- recombination
- and DNA repair

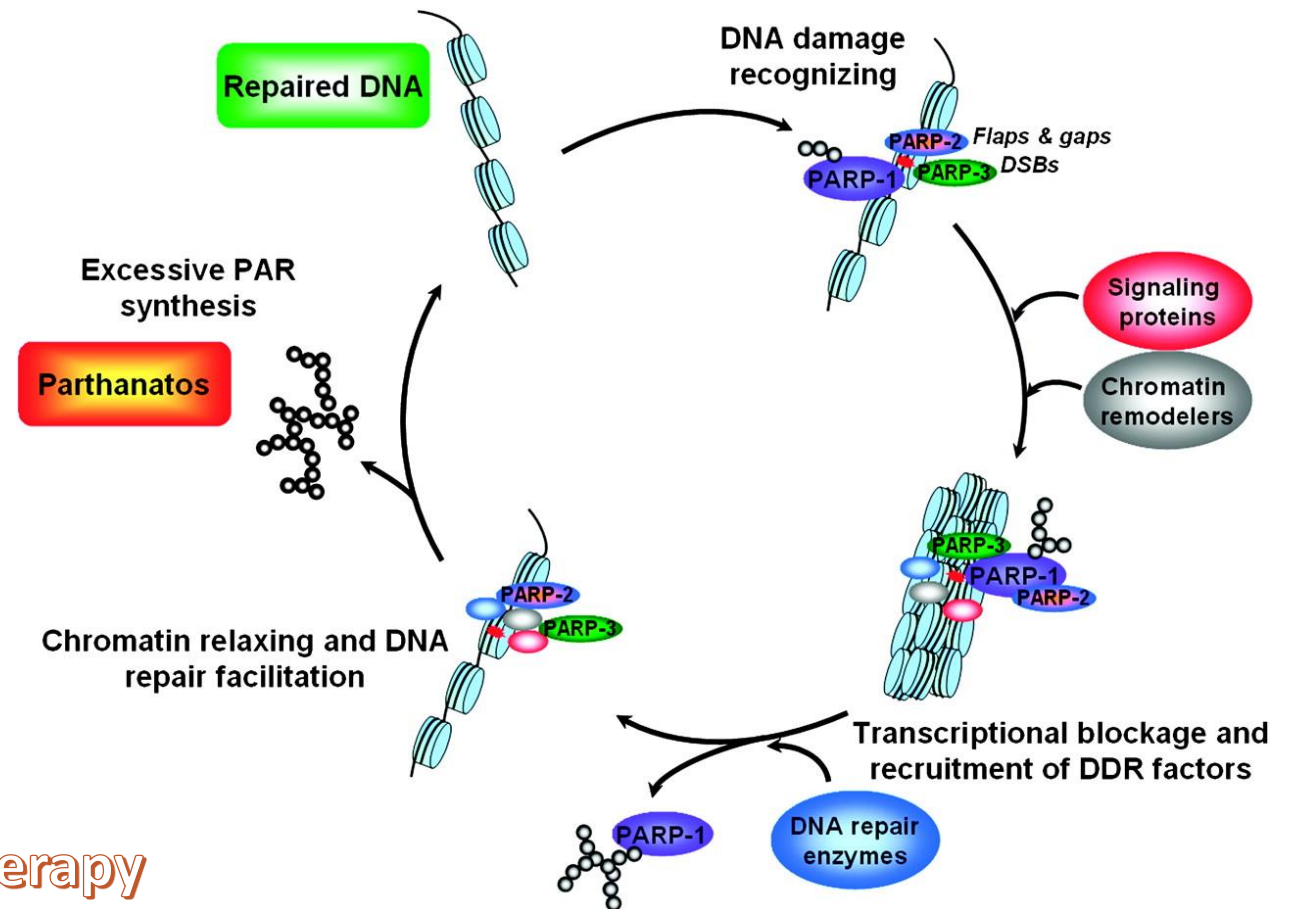
□ But...physiological function of the majority of PARPs have not been established



# Implication in DNA repair

- ❑ Recognize DNA damages
- ❑ Recruit DNA damages repair factors
- ❑ Activate Base excision repair and single strand break repair +++
- ❑ Facilitate Chromatin relaxation and access of DNA repair agents
- ❑ Favor accurate Homologous recombination instead of mutagenic NHEJ.
- ❑ PARP-1, PARP-2 and PARP-3

⇒ PARPi could potentiate the cytotoxic effect of chemotherapy



# Beginning of the story : 2005, the concept of synthetic lethality.

- ❑ “BRCA1 or BRCA2 dysfunction unexpectedly and profoundly sensitizes cells to the inhibition of PARP enzymatic activity, resulting in chromosomal instability, cell cycle arrest and subsequent apoptosis”
- ❑ Inhibition of PARP leads to the persistence of DNA lesions normally repaired by homologous recombination
- ❑ Concept of synthetic lethality appears
- ❑ the combined lethal effect of two genetic variations that are otherwise non-lethal when occurring in isolation

**nature**  
International journal of science

Letter | Published: 14 April 2005

Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy

**nature**  
International journal of science

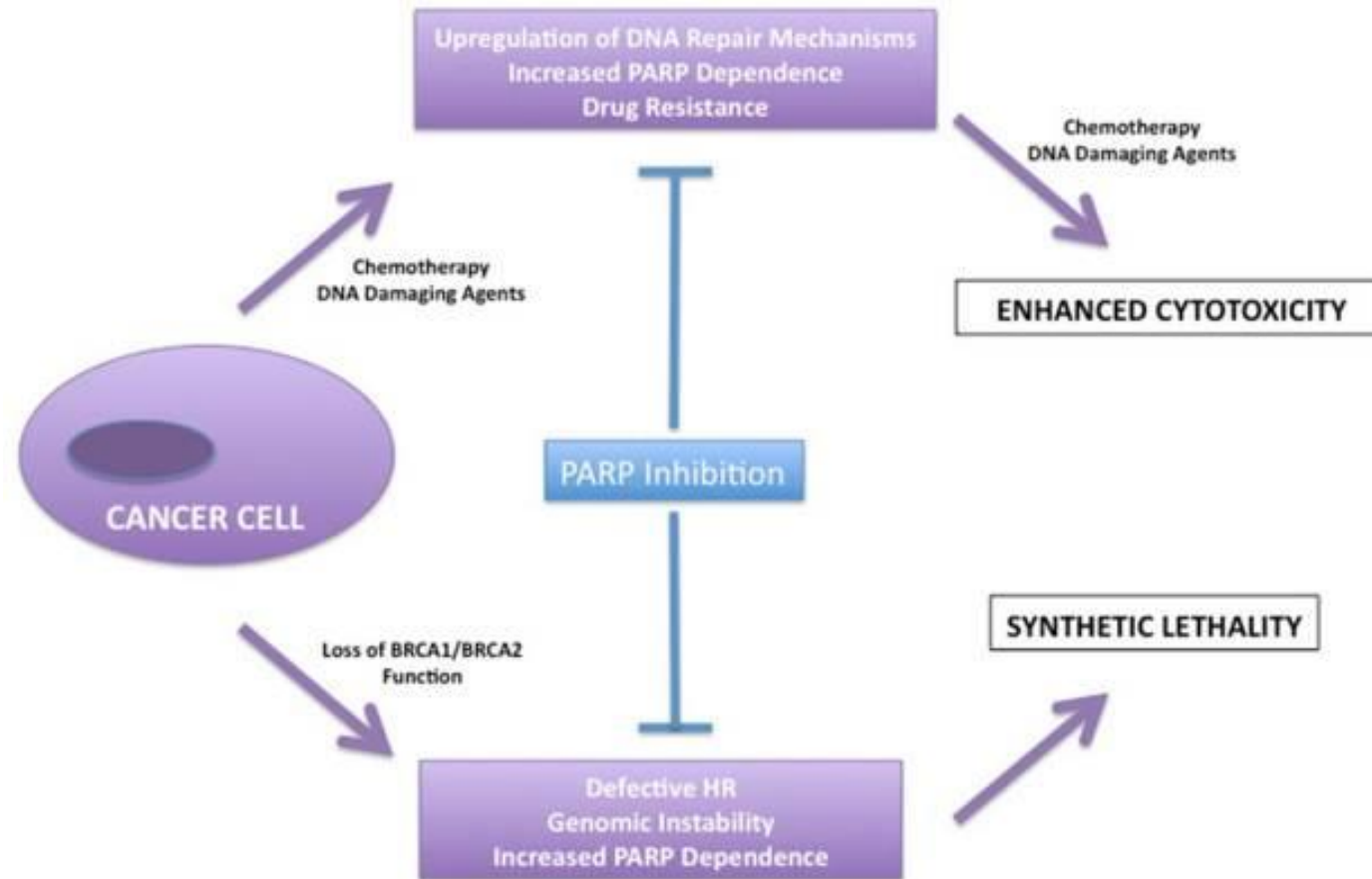
Letter | Published: 14 April 2005

Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Farmer et al ,Nature. 2005 Apr 14;434(7035):917-21

Bryant el al, Nature. 2005 Apr 14;434(7035):913-7.

# Treating cancer by the use of PARPi?



# From 2005 to 2019, PARP inhibitor in clinical practice.

ORIGINAL ARTICLE

## Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Catherine Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting...

ORIGINAL ARTICLE

## Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation

M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., ...  
Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck  
... Ph.D., *et al.*

ORIGINAL ARTICLE **FREE PREVIEW**

## Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Yun ...  
Ph.D., Giampaolo Tortora, M.D., ...

ORIGINAL ARTICLE

## DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Joaquin Mateo, M.D., Suzanne Carreira, Ph.D., Shahneen Sandhu, M.D., Susana Miranda, B.Sc., Helen Mossop, M.Math.Stat., Raquel Perez-Lopez, M.D., Daniel Nava Rodrigues, M.D., Dan Robinson, Ph.D., Aurelius Omlin, M.D., Nina Tunariu, M.D.Res., Gunther Boysen, Ph.D., Nuria Porta, Ph.D., *et al.*

ORIGINAL ARTICLE **FREE PREVIEW**

## Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

...ng-Gie Kim, M.D., Ph.D., Ana Oaknin, M.D., Ph.D., Michael ...  
..., Gabe S. Sonke, M.D., Ph.D., Charlie Gourley, M.D., Ph.D.,  
*et al.*

# So, Could PARPi interest radiation oncologists?

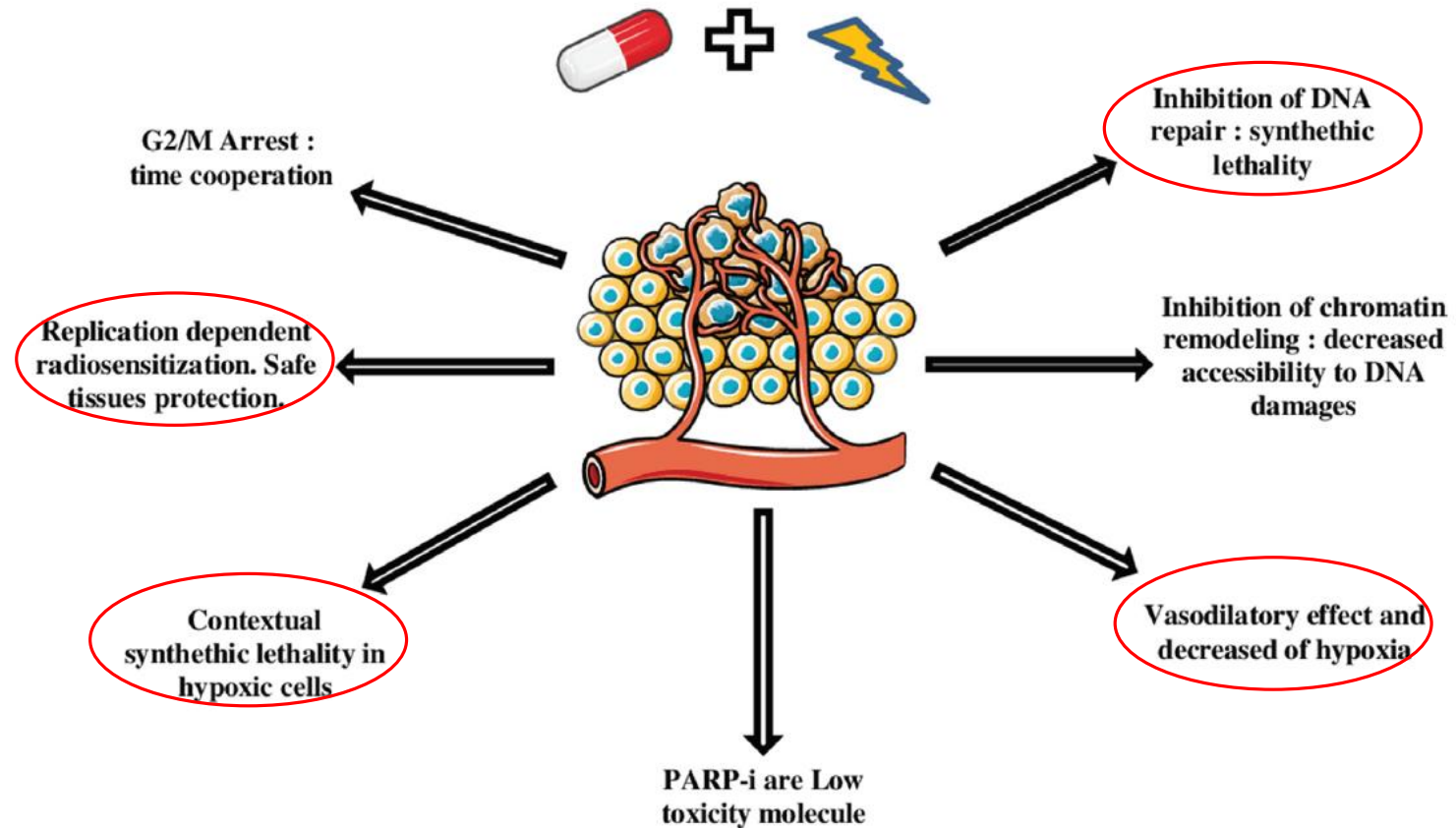
---

- Radiotherapy is a cytotoxic agent
- DNA damages is the main way of irradiation efficacy

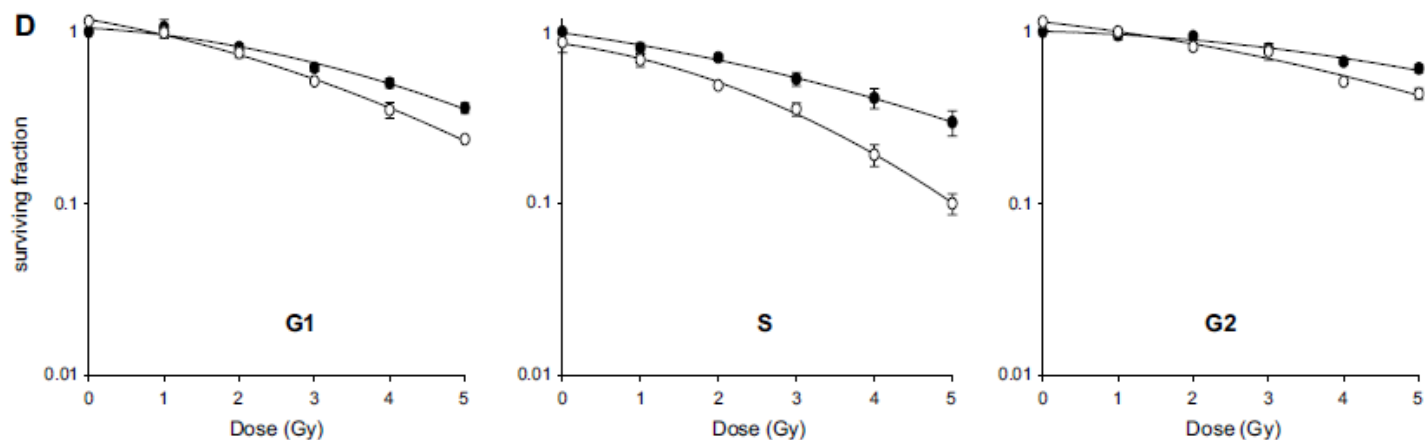
So... For sure, PARP-I should be investigated as radiosensitizer!



# So, Could PARPi interest radiation oncologists?



# Replication-dependent radiosensitization

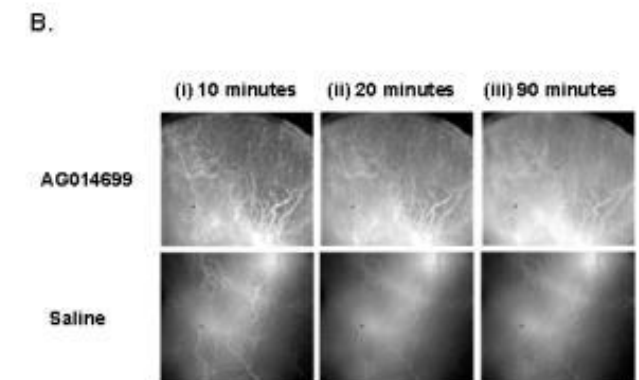
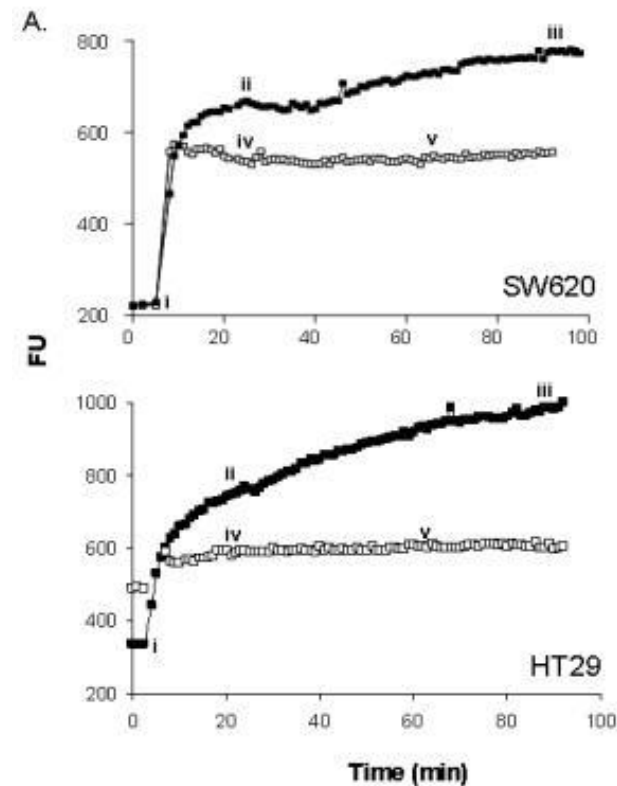


Experiment	Cell line	Mean plating efficiency (%)	SER <sub>50</sub>	SER <sub>37</sub>	S phase (%)	Figure
Exponential phase	U373-MG	50	1.25	1.28	24	1
	T98G	43	1.32	1.30	23	
	U87-MG	48	1.17	1.08	19	
	UVW	66	1.38	1.36	33	
Replication inhibition	T98G		1.34	—	23	2B
	T98G + APH		1.09	—	23	
Synchronization	T98G, G <sub>1</sub>		1.27	1.24	14	2D
	T98G, S		1.60	1.56	73	
	T98G, G <sub>2</sub> /M		1.33	1.30	16	
Fractionation	T98G, single dose		1.27	1.26	23	3A
	T98G, fractionated		1.55	1.56	23	

- Increase radiosensitivity in exponential growth population
- Radiosensitizing effects of PARP inhibition are replication dependent and likely to be tumor specific in the context of the brain.
- Increase differential effect between the tumor and late reactions tissues

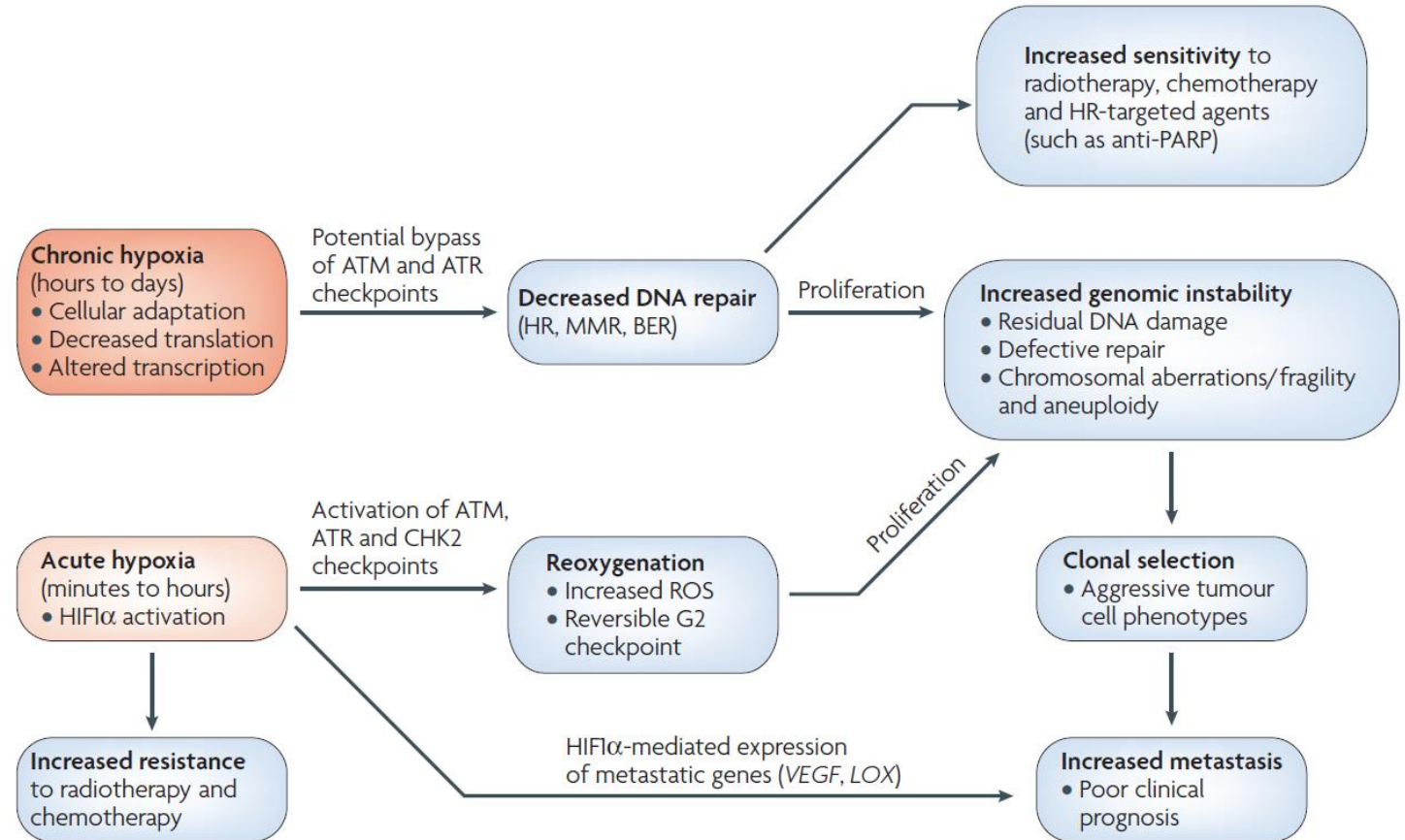
# Radiosensitizing hypoxic radioresistant cancer cells

- ❑ Help to bypass the hypoxia-induced radioresistance
- ❑ Structural similarities with nicotinamide, a vaso-dilatory component
- ❑ Increasing tumor bloodflow, enhancing drug penetration, and increasing oxygen concentrations



# Radiosensitizing hypoxic radioresistant cancer cells

- Contextual synthetic lethality: HR is altered by hypoxia
- Hypoxic cells can acquire a mutator phenotype that consists of decreased DNA repair
- Defects in Homologous recombination and MMR have been documented in tumour cells that are exposed to chronic hypoxia.



# In 2019, Do radiation therapists use PARPi-in routine such as medical oncologists?

---

- ❑ 80-90 published studies (in vitro, in vivo...) evaluating combination of PARP and ionizing irradiation.
- ❑ Enhancement ratio comprised between 1,04 and 2,87 for *in vitro* data
- ❑ But only few phase I trials published:
  - ❑ Inflammatory or recurrent breast cancer
  - ❑ Locally advanced rectal cancer
  - ❑ Locally advanced pancreatic cancer
  - ❑ Brain metastases
  - ❑ Ovarian cancer
  - ❑ H&N HPV+ cancer

→ The association is safe

→ Late toxicity have to be monitored

# At Caen, we believe in PARPi!

Lesueur et al. *BMC Cancer* (2019) 19:198  
<https://doi.org/10.1186/s12885-019-5413-y>


BMC Cancer

STUDY PROTOCOL

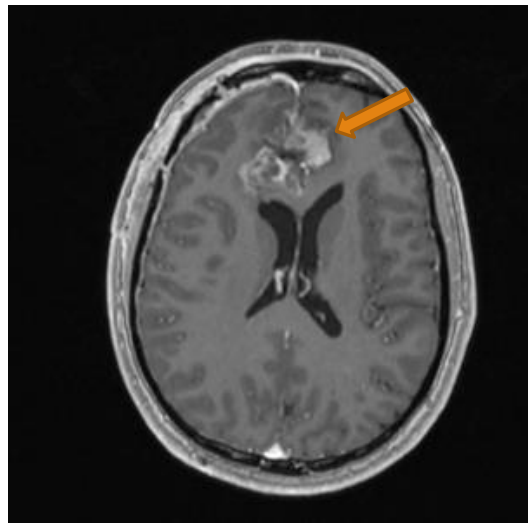
Open Access

## Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable or partially resectable glioblastoma: OLA-TMZ-RTE-01 trial protocol

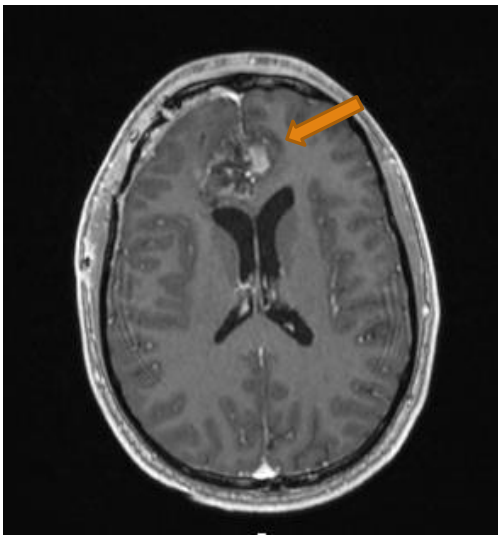


Paul Lesueur<sup>1,2\*</sup> , Justine Lequesne<sup>3</sup>, Jean-Michel Grellard<sup>3</sup>, Audrey Dugué<sup>3</sup>, Elodie Coquan<sup>3,4</sup>, Pierre-Emmanuel Brachet<sup>3,4</sup>, Julien Geffrelot<sup>1</sup>, William Kao<sup>1</sup>, Evelyne Emery<sup>2,5</sup>, David Hassanein Berro<sup>2,5</sup>, Laurent Castera<sup>6</sup>, Nicolas Goardon<sup>6</sup>, Joëlle Lacroix<sup>7</sup>, Marie Lange<sup>3,8</sup>, Aurélie Capel<sup>3</sup>, Alexandra Leconte<sup>3</sup>, Benoit Andre<sup>9</sup>, Angélique Léger<sup>10</sup>, Anaïs Lelaidier<sup>11</sup>, Bénédicte Clarisse<sup>3</sup> and Dinu Stefan<sup>1</sup>

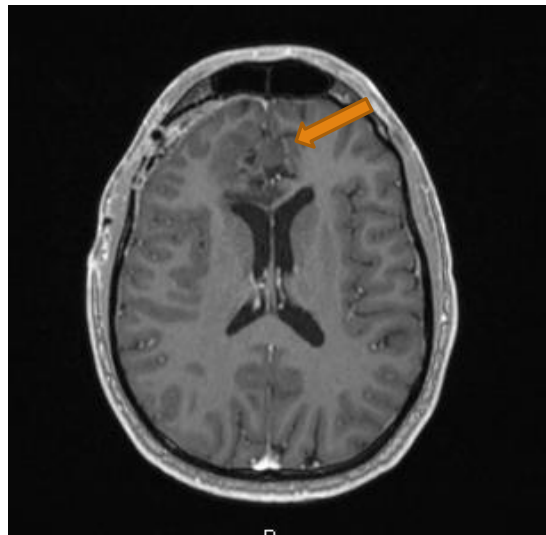




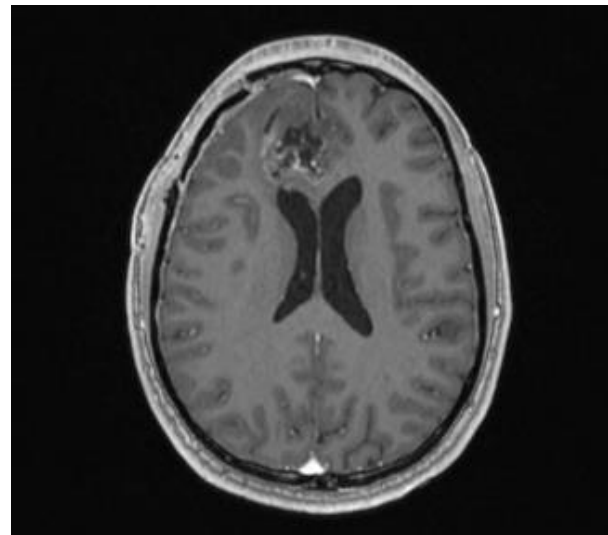
Baseline : Before radiotherapy



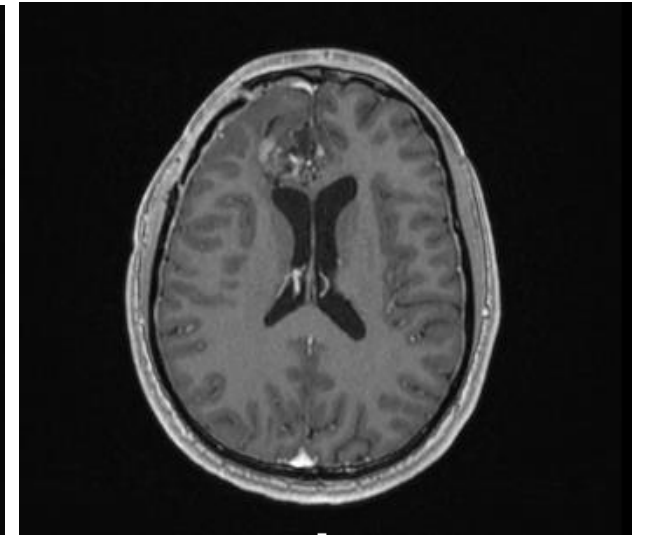
Last day of irradiation



+ 1 month



+ 3 months



+ 5 months

# Could we increase the therapeutic ratio with the use of particle irradiation?

---

## MAIN RATIONALE:

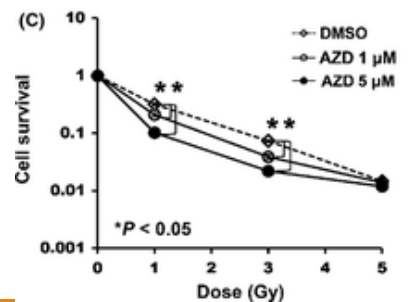
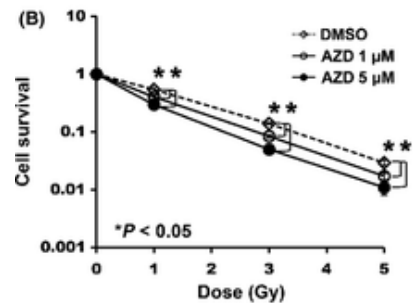
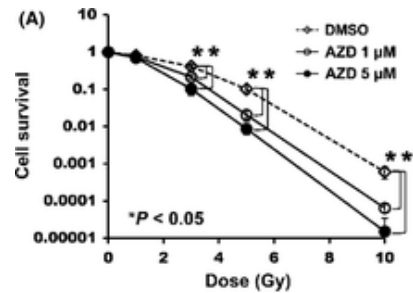
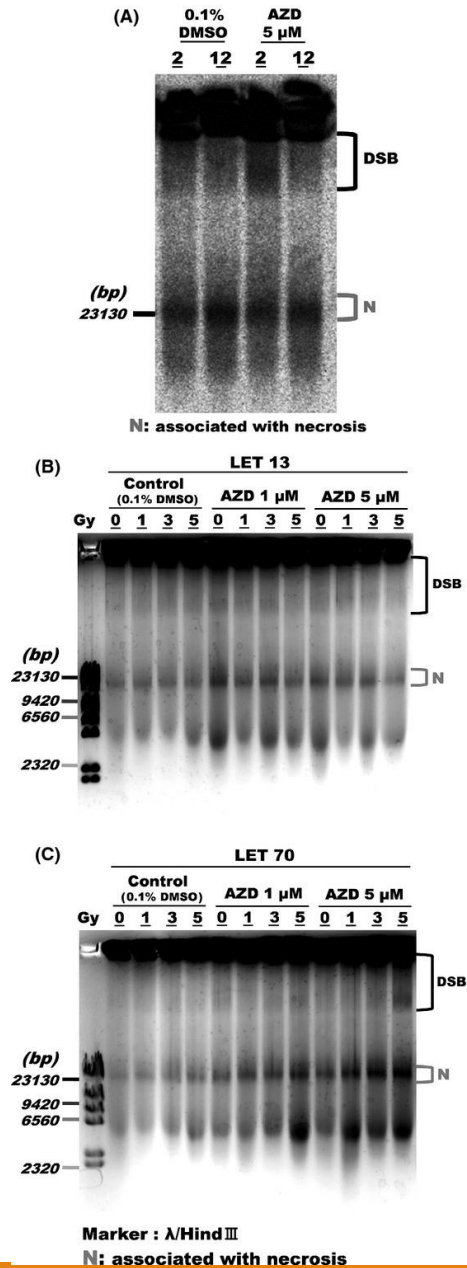
The ballistic advantage of particle

But...

Only few studies exploring combination of particle therapy and PARPi...



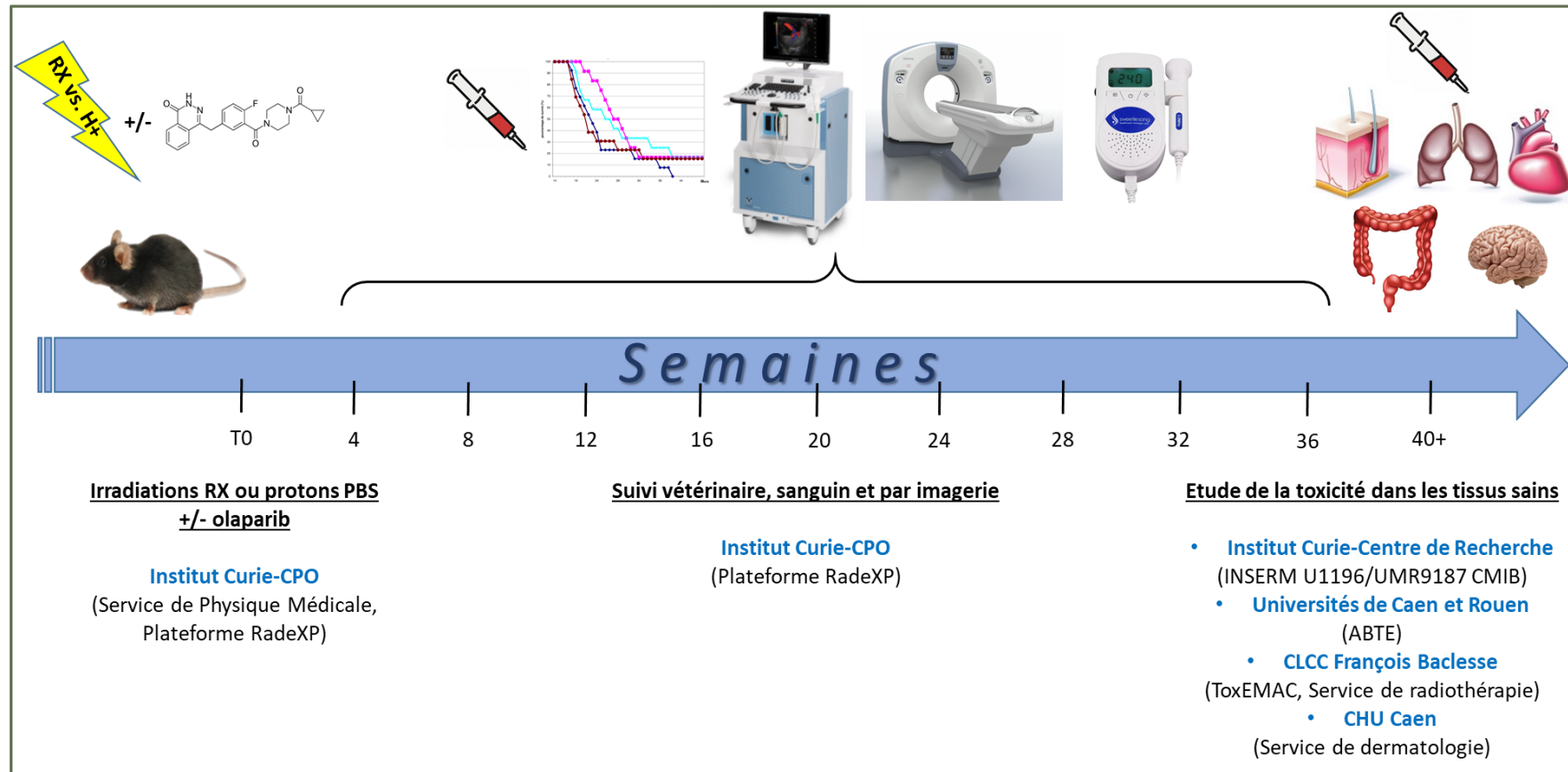
# First study published



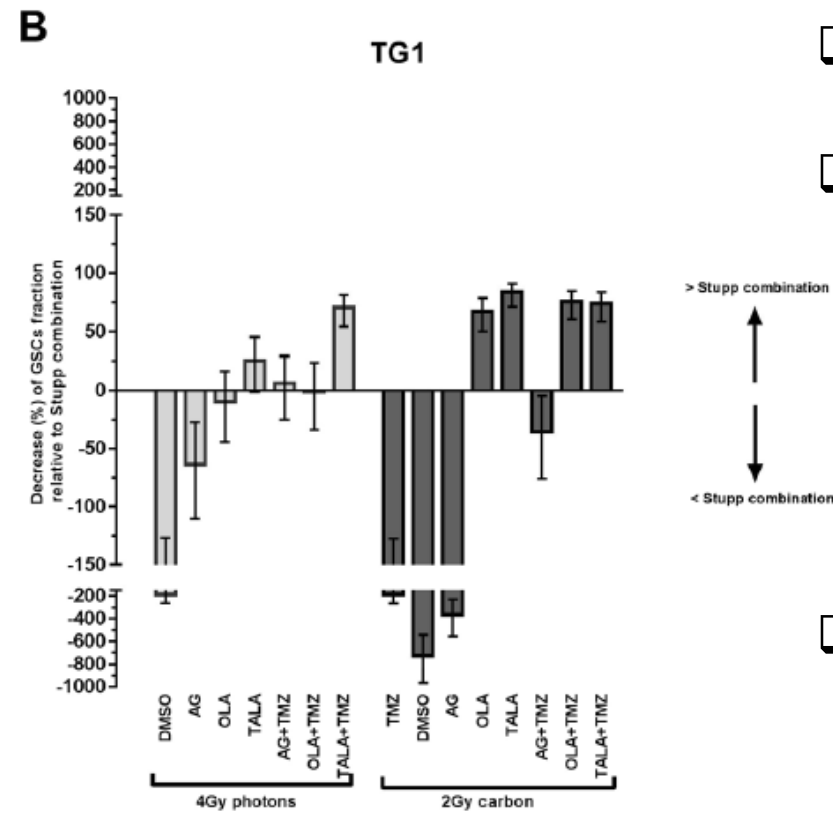
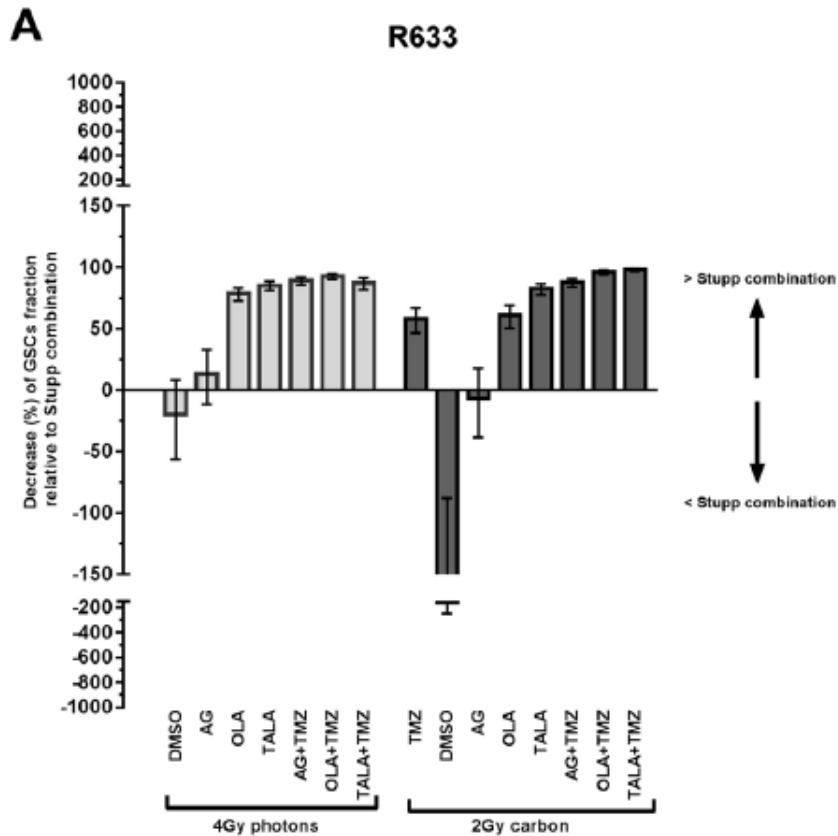
	$\gamma$ -ray	Carbon-ion beam	
		LET 13 keV/ $\mu$ m	LET 70 keV/ $\mu$ m
AZD2281 1 $\mu$ M	1.4	1.2	1.4
AZD2281 5 $\mu$ M	1.7	1.5	2.5

- ☐ DDR and DSB processing, which leads to increased S phase arrest and a subsequent arrest at the G2/M phase
- ☐ X / C Let13 / C Let 70 + olaparib
- ☐ doses <5 Gy of LET 70 carbon-ion irradiation could be the appropriate range of radiosensitization with a blockade of DNA repair by PARP inhibitor

# At Caen...



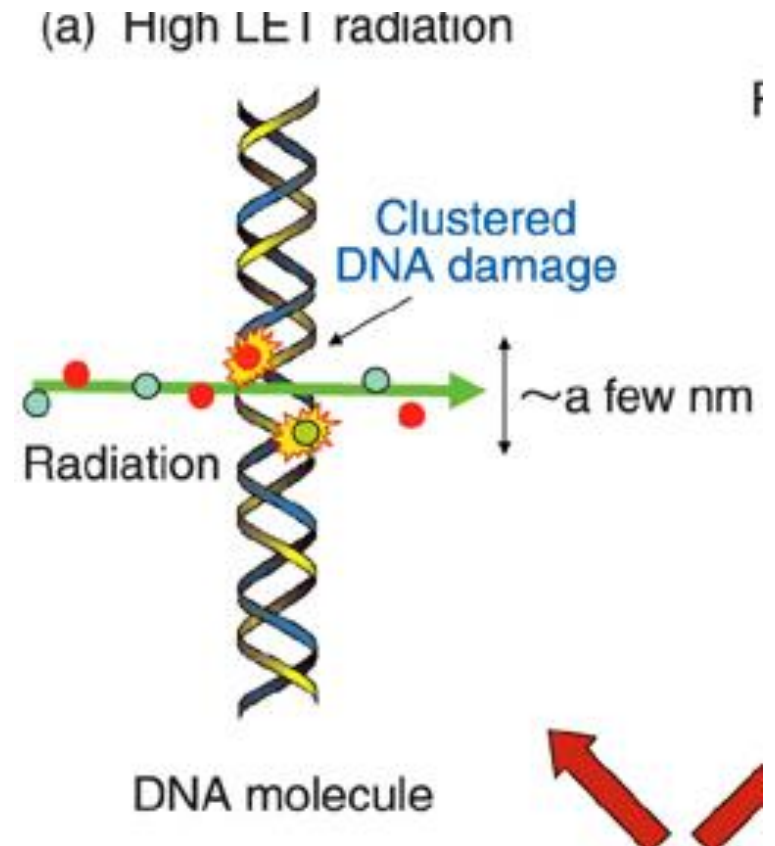
# Our experience: PARPi +/- TMZ + Photons Or Carbon irradiation on GSC.



- ❑ First study to evaluate talazoparib as a radiosensitizer
- ❑ Particle irradiation combined with PARPi decreases the GSC fraction further compared with photonic irradiation:
  - ❑ Ex : the GSC fraction was markedly reduced by 98% for Carbon + talazoparib in comparison with carbon alone or carbon + TMZ.
- ❑ Talazoparib appears to be the better radiosensitizer

# Why Radiosensitizing effect of PARPi is higher with high LET irradiation?

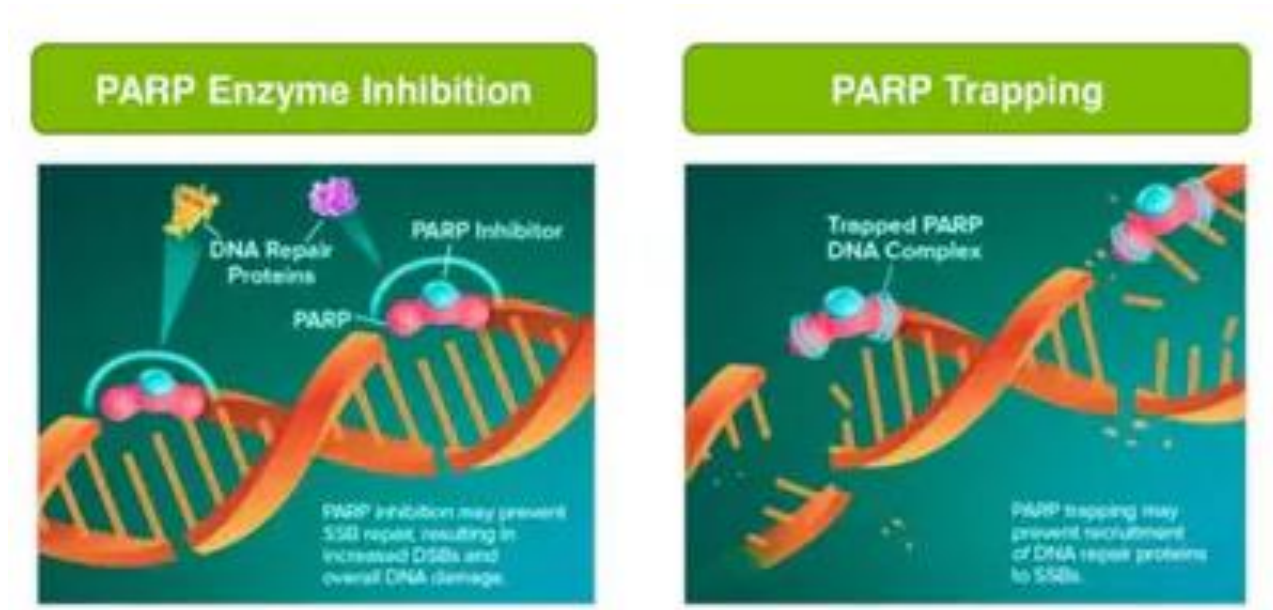
- ❑ High LET irradiations induce more complex DNA damages than photons: oxidative clustered DNA lesions (OCDLs).
- ❑ OCDLs include oxidized bases, apurinic-apyrimidinic sites, and SSBs.
- ❑ Repaired mainly by BER, in which PARP plays a significant role !
  - ➔ Decrease of OCDL repair
  - ➔ Conversion of OCDL to lethal DSB by binding of the PARP inhibitor to PARP at strand break ends



# To choose the best PARPi

We should favor inhibitors with :

- ❑ Specific ability to stay bound to the PARP1-DNA complex, increasing the DSB rate while the replication fork progresses
- ❑ Anti PARP-3 activity :
  - ❑ >>> G4 quadruplex
  - ❑ inhibition of c-NHEJ
  - ❑ Inhibition EMT



# Conclusion

---

- PARPi are now well known radiosensitizers for Low and high LET irradiation
- High LET irradiation probably a best partner:
  - Ballistic advantage
  - Type of DNA damages induced
- In vivo studies and phase I studies have to be proposed
- Radiation therapist should appropriate themselves PARPi.
- So PARPi... The new cisplatin? ( Dinu Stefan, MD)

Thank you for your attention!

