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Synergistic activity of DNA damage response kinase inhibitors in combination with the targeted alpha therapy radium-223 dichloride for metastatic castration-resistant prostate cancer

Victoria Dunne, PhD

The 1st International Electronic Conference on Cancers: Exploiting Cancer Vulnerability by Targeting the DNA Damage Response

Tuesday 2nd February, 2021

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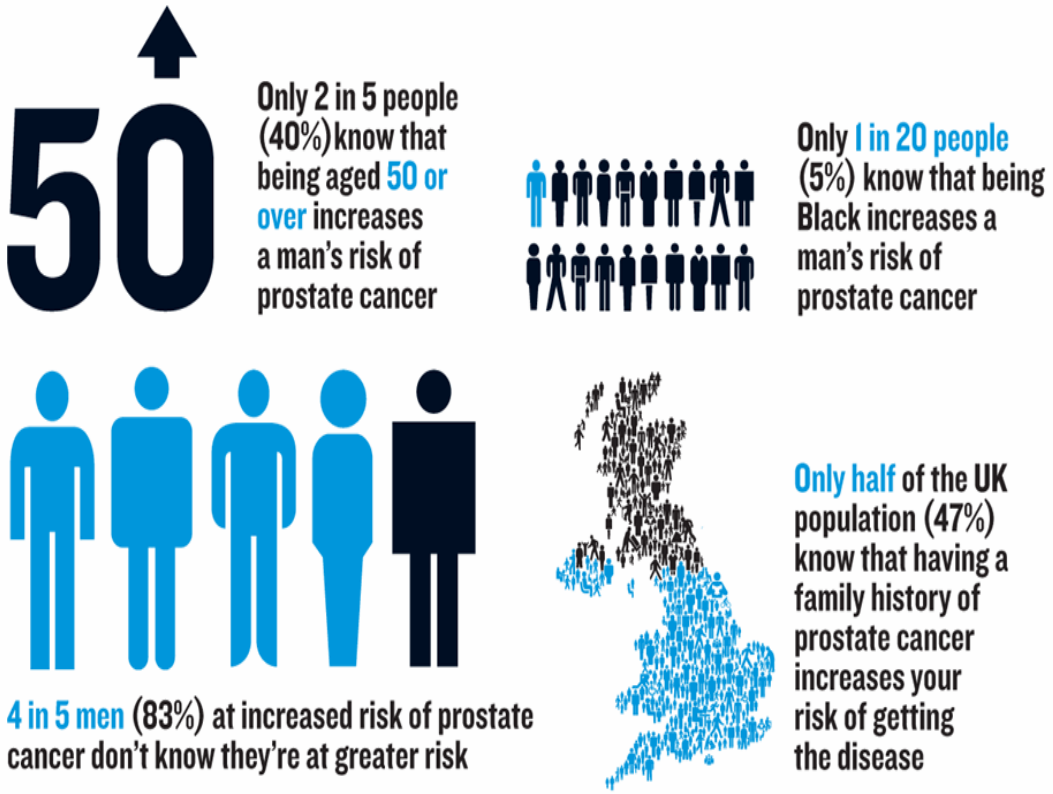
Prostate Cancer- UK



- Prostate cancer is the most common cancer in men.
- More than 47,500 men are diagnosed with prostate cancer every year.
- Every 45 minutes one man dies from prostate cancer.
- 1 in 8 men will be diagnosed with prostate cancer in their lifetime.
- Approximately 400,000 men are living with and after prostate cancer.

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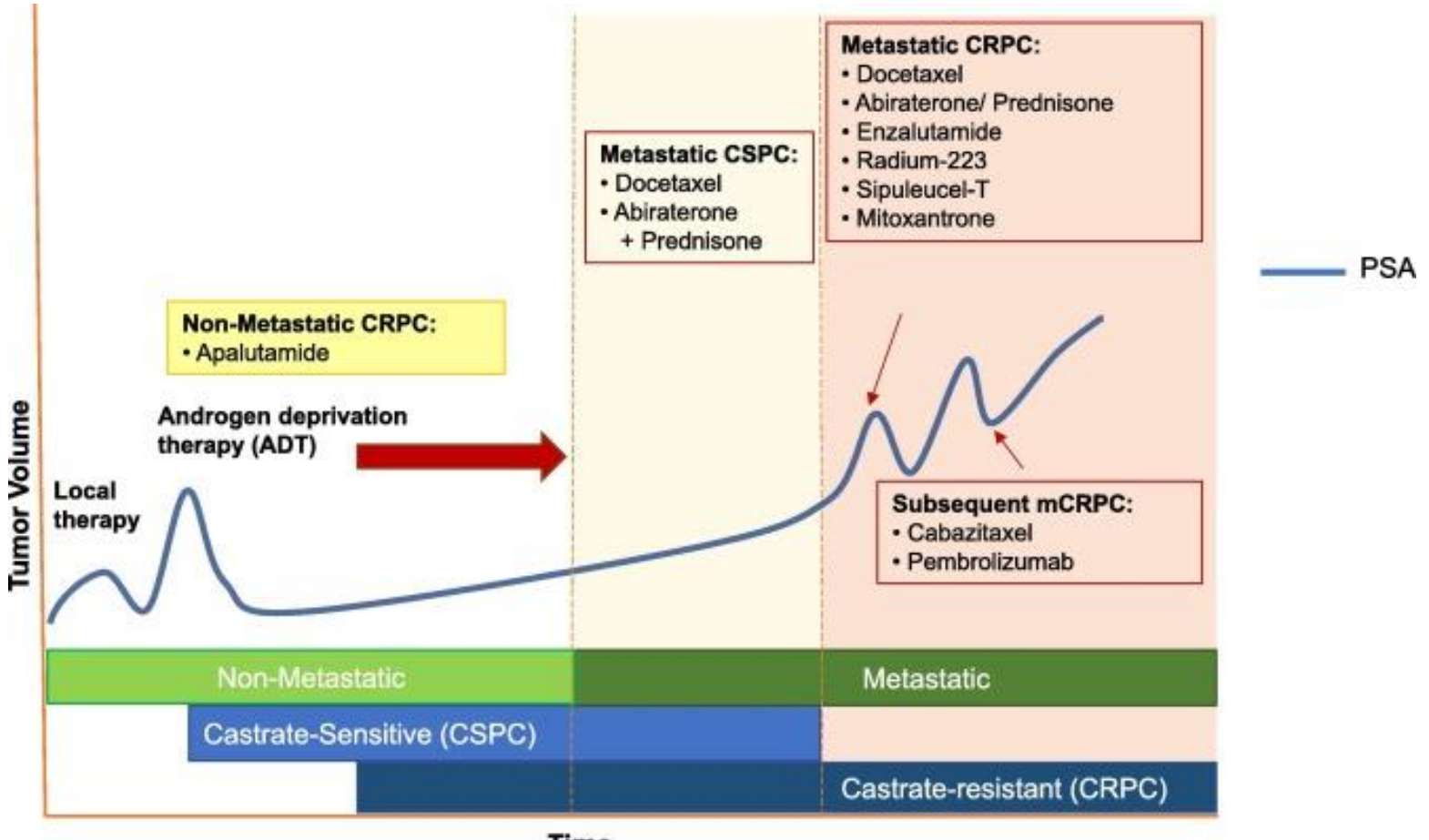
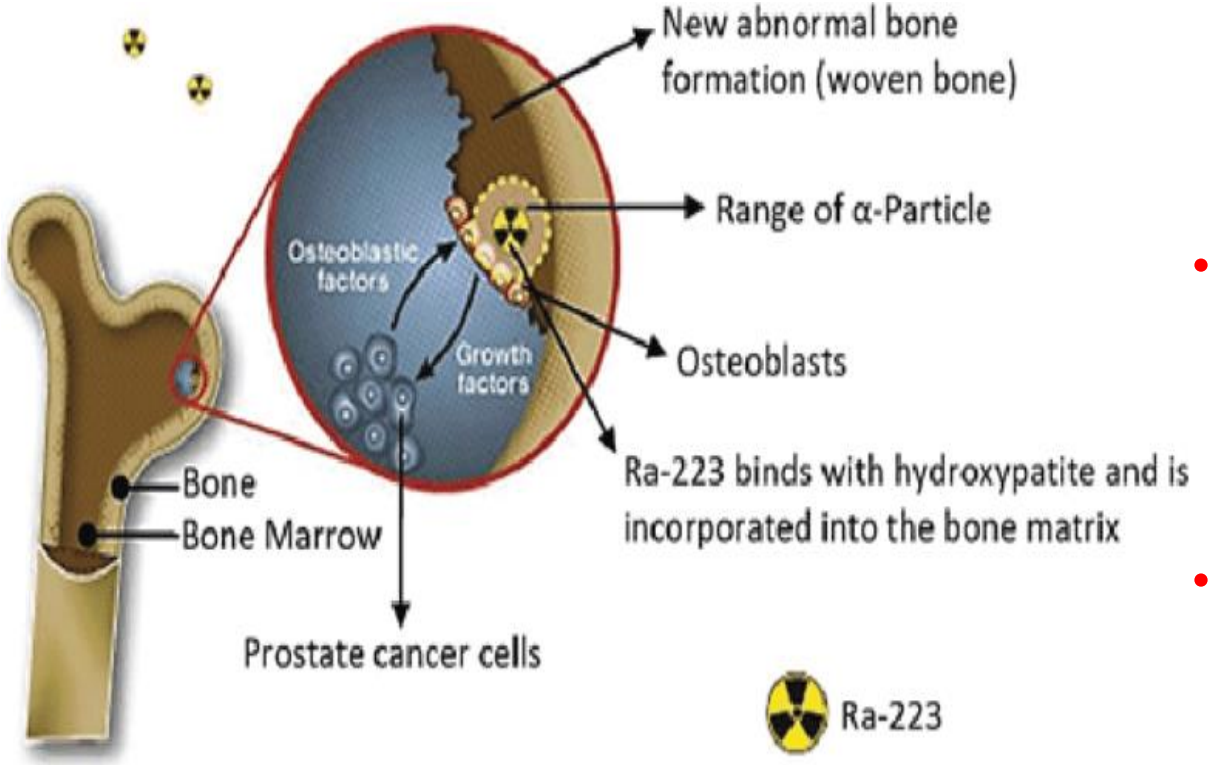
Prostate Cancer Development



^{223}Ra Treatment for mCRPC



Cha, T-L., *et al.* (2017). Optimal usage of radium-223 in metastatic castration-resistant prostate cancer. *Journal of the Formosan Medical Association.* **116**(11)*:* 825-836.

- Metastatic castrate-resistant prostate cancer (mCRPC) stops responding to hormone treatment and is found in other parts of the body including the bones.
- Bone metastases often leads to pain or skeletal events and, therefore, may decrease the patients' quality of life.
- Radium-223 (^{223}Ra; Xofigo®) is an α-emitting radionuclide that can incorporate into newly formed bone in areas of osteoblast activity and increase bone turnover surrounding prostate cancer bone metastases.

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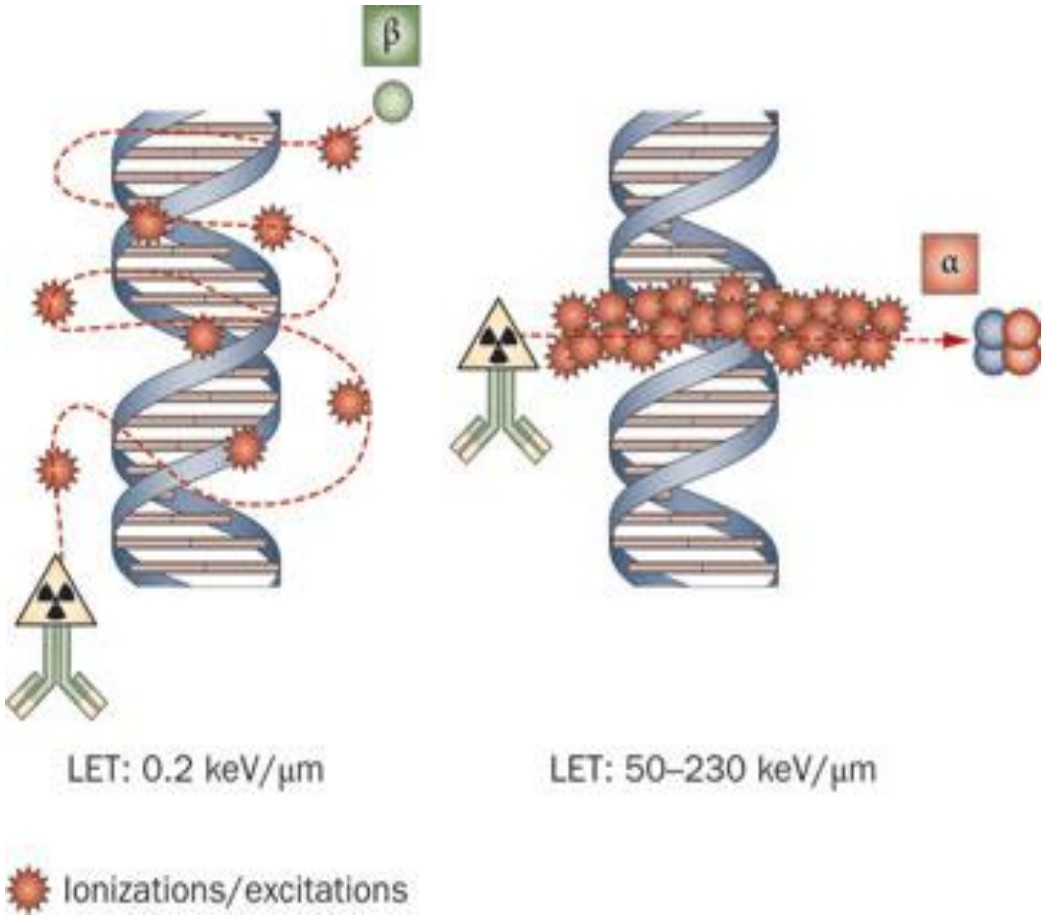
Low LET Radiation versus High LET Radiation



Adapted from Pouget, J-P, *et al.* (2011). Clinical radioimmunotherapy-the role of radiobiology. *Nature Reviews Clinical Oncology.* **8***:* 720-734.

- High LET particles have a 3-5 times greater relative biological effectiveness compared to X-rays, γ-rays or β-emitters.
- Low LET radiation produces sparse ionization and individual DNA lesions whereas high LET radiation produces clusters and more complex DNA damage.
- The high cytotoxicity of high-LET particle emitters is independent of the dose rate.
- Alpha particles have a high energy and an intermediate path length in biological tissues.

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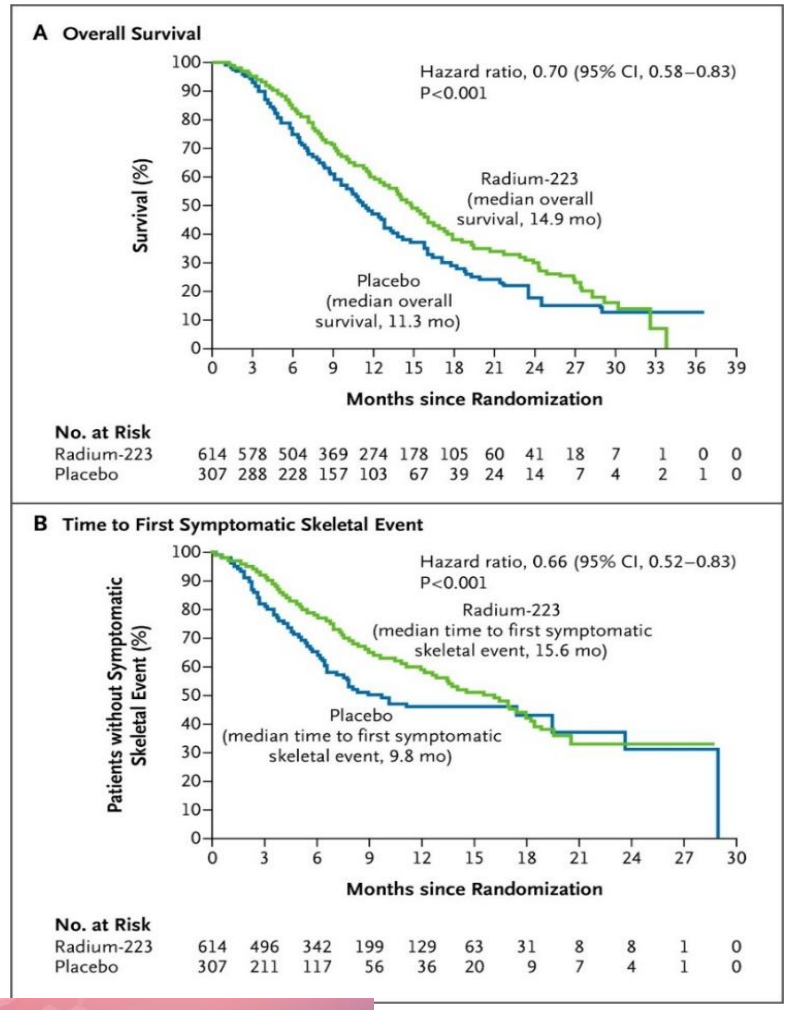
^{223}Ra Bone Metastasis- Phase 3 ALSYMPCA Trial



- The ALSYMPCA randomized Phase III trial compared ^{223}Ra efficacy versus placebo in 921 patients with CRPC and symptomatic bone metastases.
- ^{223}Ra showed an overall survival benefit in patients with CRPC and symptomatic bone metastases treated with ^{223}Ra compared with patients who received placebo (14.9 months vs 11.3 months).
- Patients treated with ^{223}Ra also had a longer time to symptomatic skeletal events (15.6 months vs 9.8 months) and a better biological response.

Parker, S, *et al.* (2013). Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. *The New England Journal of Medicine.* **369**(3): 213-223

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Relative prevalence of DNA repair mutations in prostate cancer patients

- Currently, it is reported that the prevalence of Homologous Recombination (HR) mutations in primary prostate cancer is likely between 8–10% and in mCRPC is likely between 20–25%.
- The HR pathway genes commonly mutated include BRCA1, BRCA2, CHEK2, ATM, RAD51D, AND PALB2.

	Localized PCa	MPCa
Homologous Recombination Pathway		
BRCA2	2-3%	7-8%
ATM	2-4%	5-6%
PALB2	<1%	1-2%
BRCA1	1%	1%
CHEK2	<1%	1-2%
RAD51	1-2%	3-4%
CDK12	1-2%	5-6%
Mismatch Repair Pathway		
MLH1	<1%	1%
MSH2	<1%	2-3%
MSH6	<1%	1%
PMS2	<1%	<1%
Overall	**8-10%**	**20-25%**

Teply and Antonarakis *et al.*, (2017). Treatment strategies for DNA repair-deficient prostate cancer. Expert Rev Clin Pharmacol. **10**(8): 889-898.

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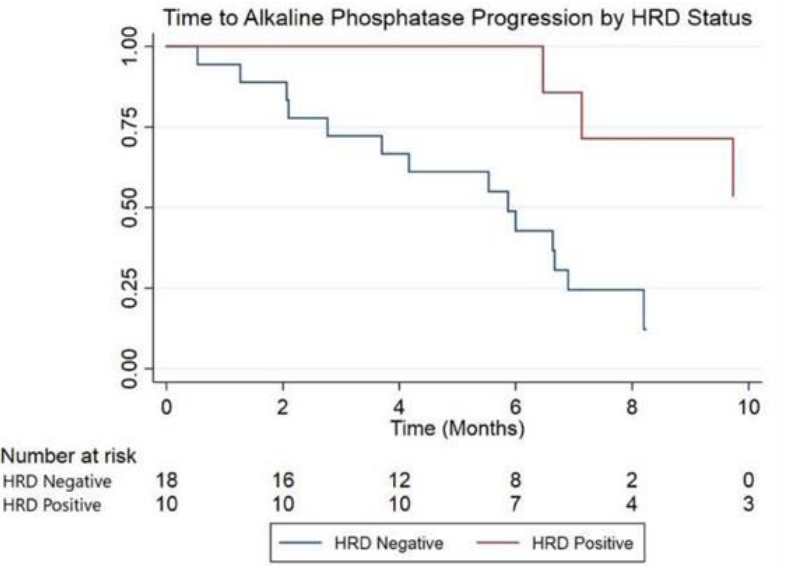
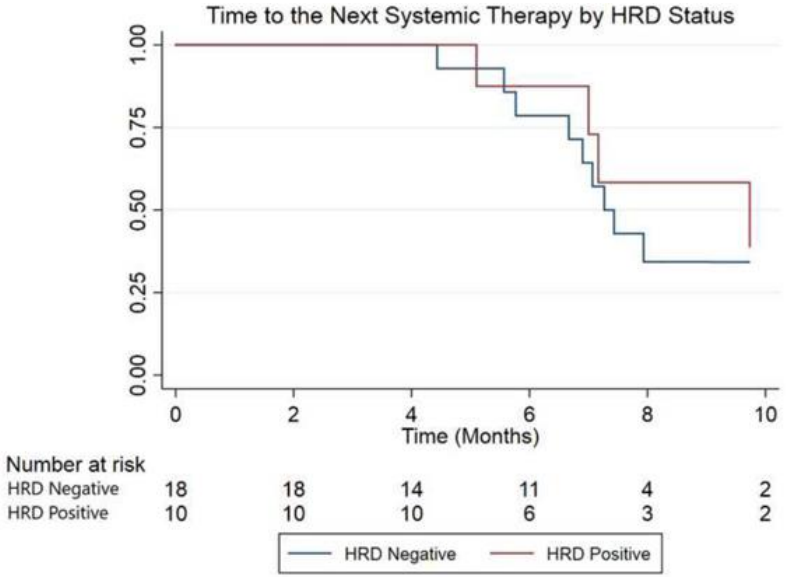
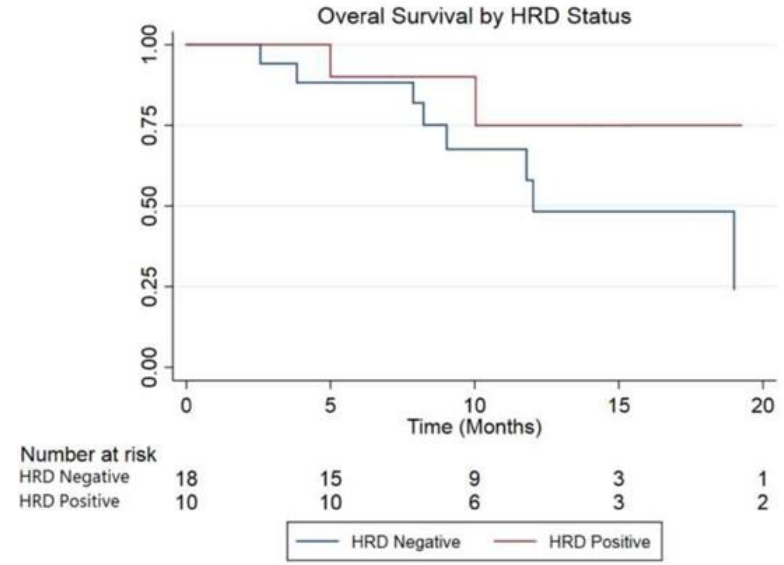
Efficacy of ^{223}Ra in mCRPC with and without Homologous Repair Gene Defects







Velho, P.I, *et al.* (2019). Efficacy of Radium-223 in Bone-metastatic Castration-resistant Prostate Cancer with and Without Homologous Repair Gene Defects. *European Association of Urology*. **76**(2): 170-176.

- Patients who harbour homologous recombination mutations may have a greater clinical benefit from ^{223}Ra.
- Patients with homologous recombination mutations showed greater ALP responses (80% vs 39%), longer time to ALP progression (median 10.4 vs 5.8 months) and longer overall survival (median 36.9 vs 19.0 months).

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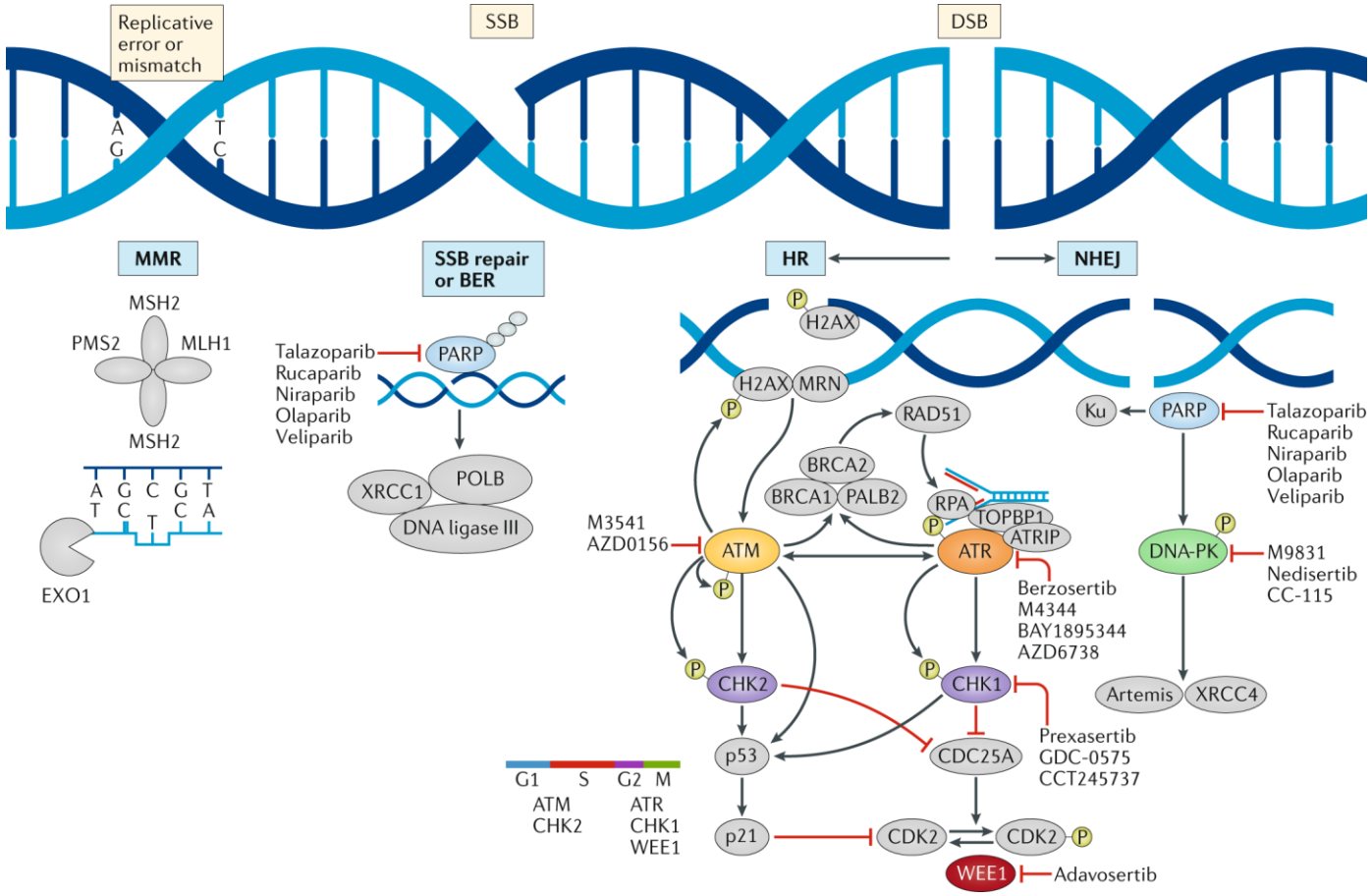
DNA damage response pathways and targets for inhibition



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Aims

1. To determine the response of prostate cancer cell lines to different types of radiation (X-rays, and ^{223}Ra) and whether an ATR inhibitor increases this response.

2. Determine the response of prostate cancer cells with HRD mutations to ^{223}Ra and whether the addition of DDR inhibitors increases this response.

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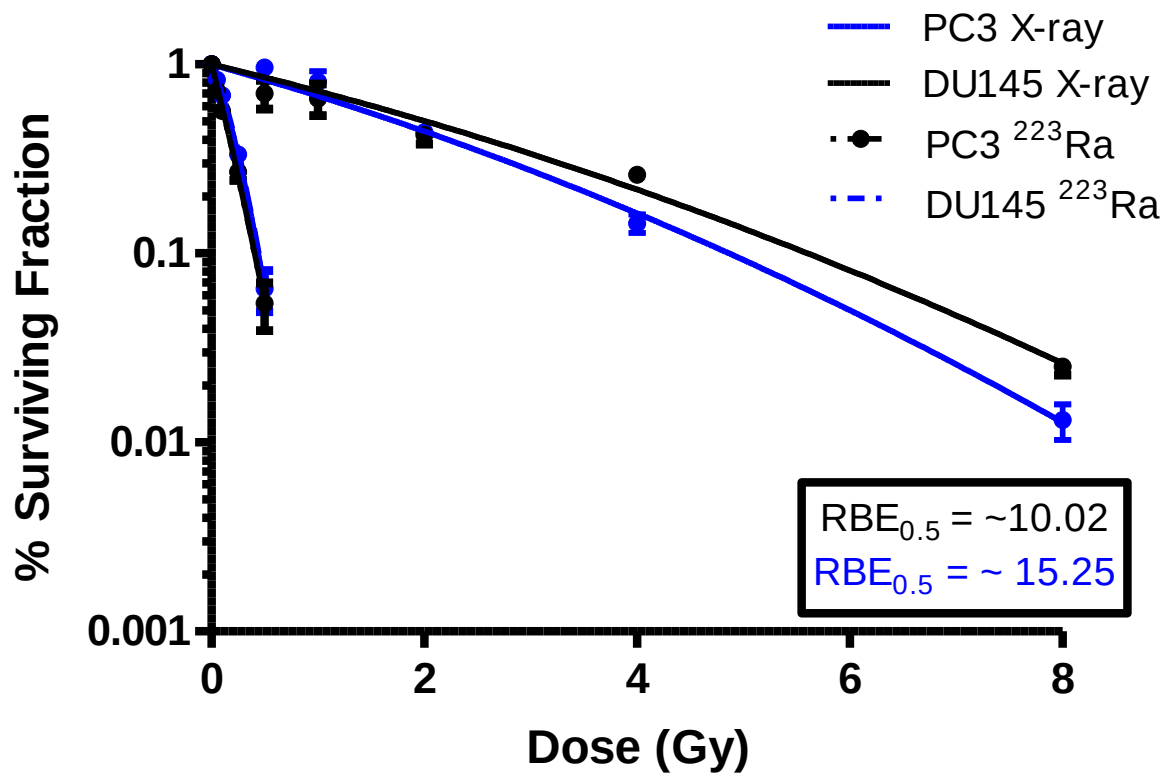
Radiosensitivity of prostate cancer cell lines to different doses of X-rays and ^{223}Ra



RBEs at **50%** survival of Radium-223 (High LET) are **> 5** times more effective in inducing cell death compared to X-rays (Low LET).

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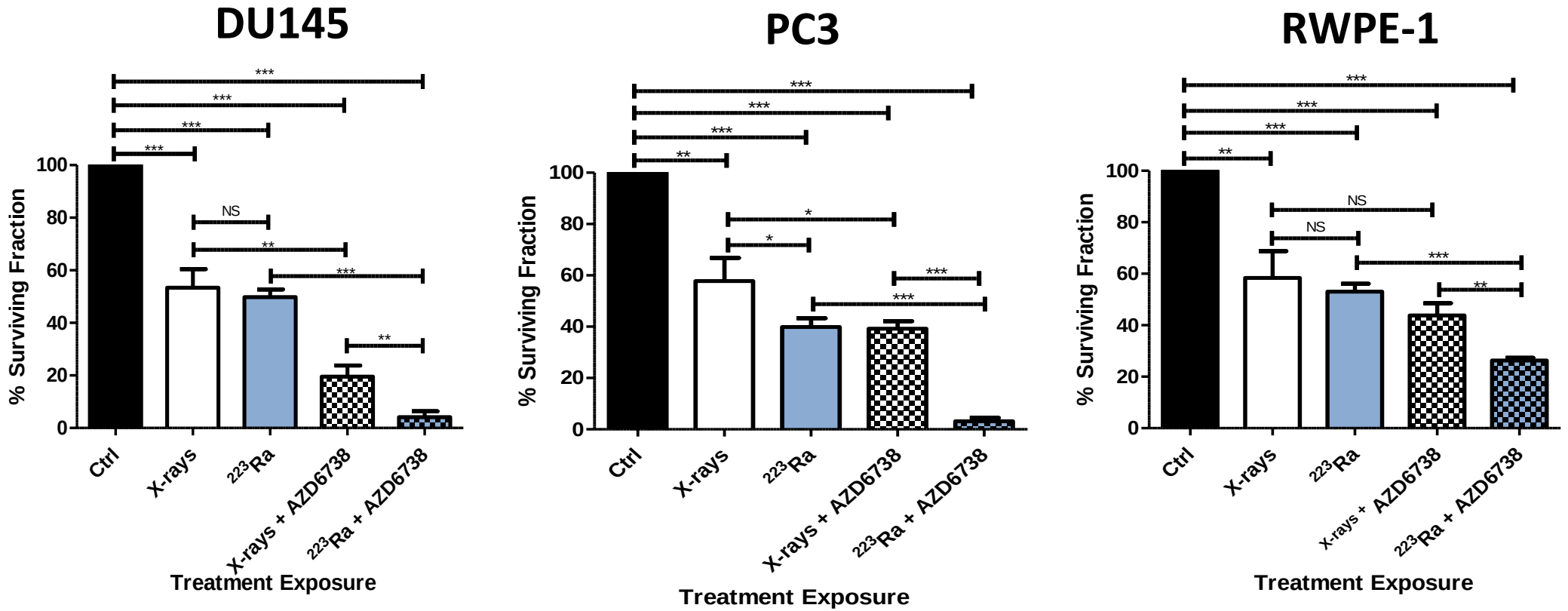
Radoisensitsation response to ^{223}Ra or X-rays in combination with ATR kinase inhibition



Cell Line	PC3		DU145		RWPE-1	
Treatment Group	X-Rays vs X-Rays + AZD6738	^{223}Ra vs ^{223}Ra + AZD6738	X-Rays vs X-Rays + AZD6738	^{223}Ra vs ^{223}Ra + AZD6738	X-Rays vs X-Rays + AZD6738	^{223}Ra vs ^{223}Ra + AZD6738
RER	1.33	12.83	2.74	12.09	1.33	2.01

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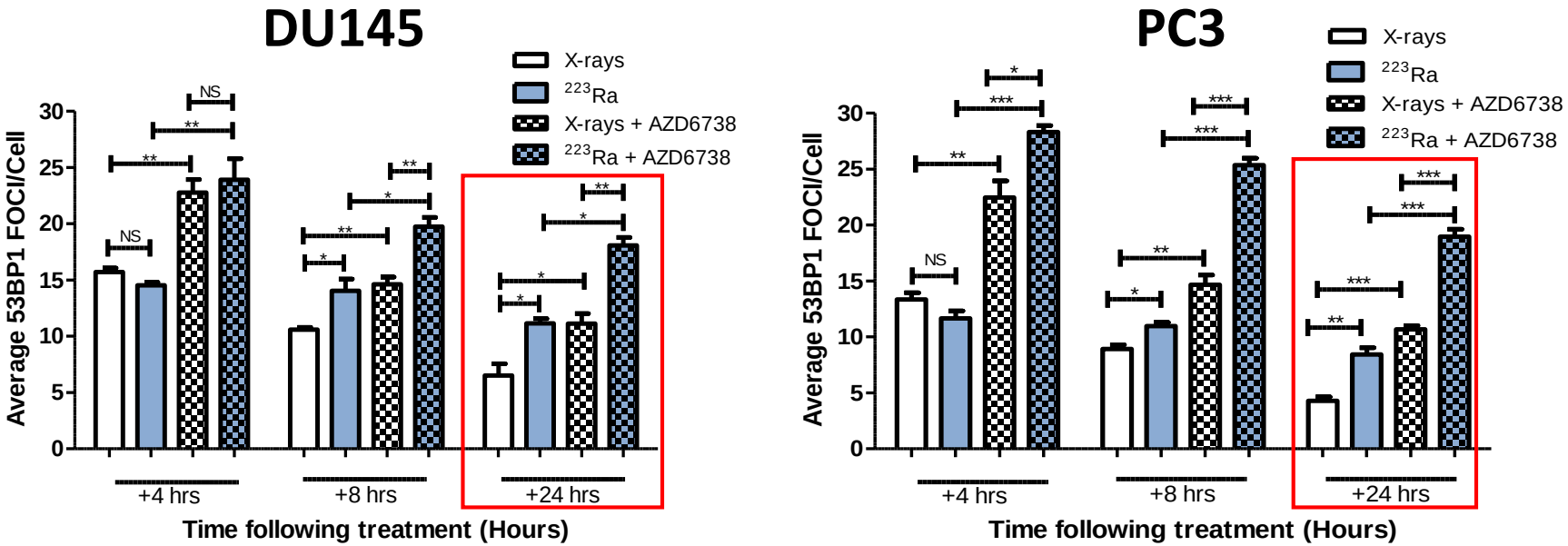
DNA damage response to ^{223}Ra or X-rays in combination with ATR kinase inhibition



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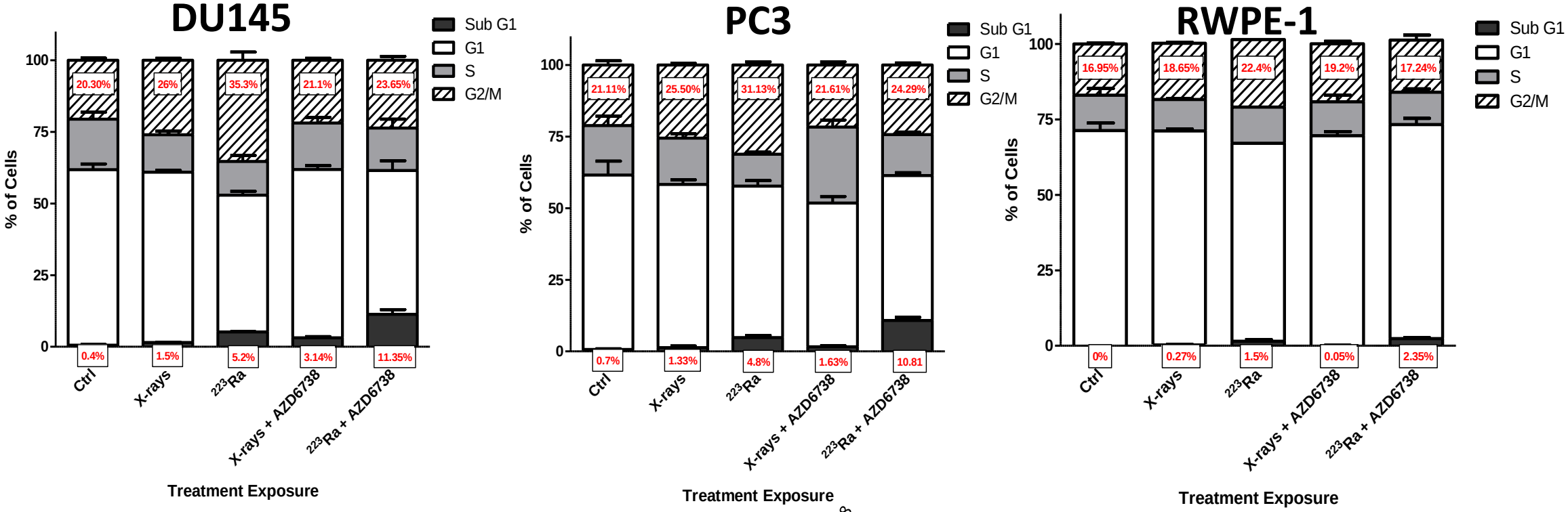
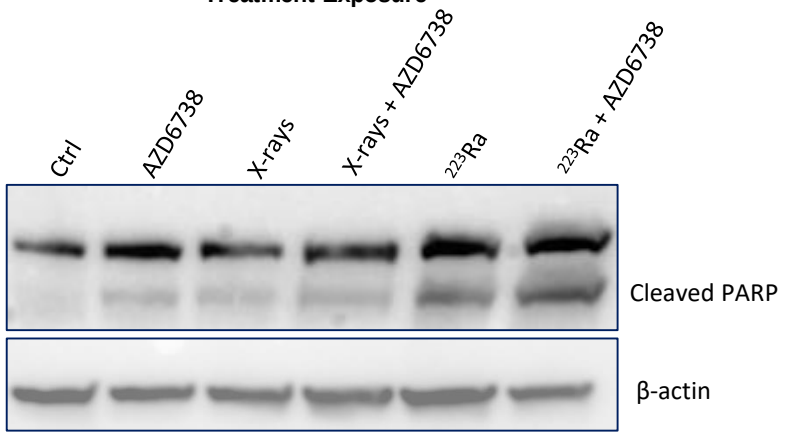
The effect of ^{223}Ra or X-rays in combination with ATR kinase inhibition on cell cycle distribution





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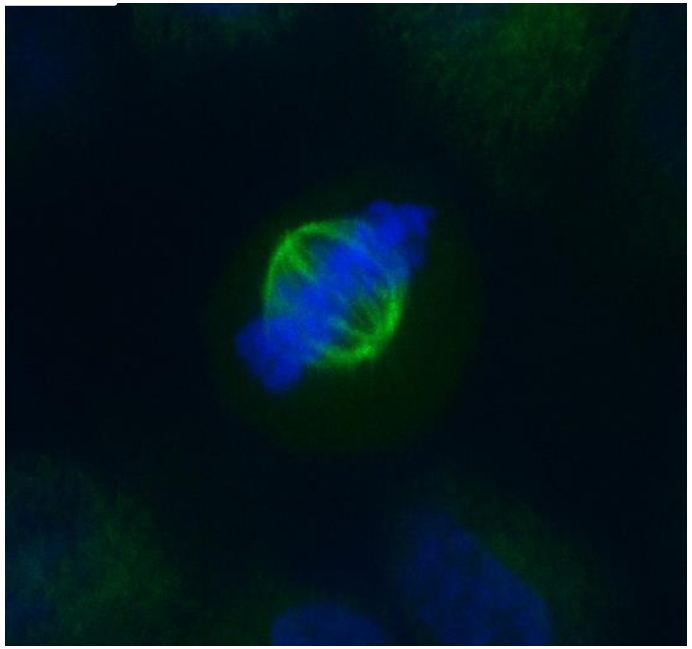
The effect of ^{223}Ra or X-rays in combination with ATR kinase inhibition on mitotic catastrophe

A



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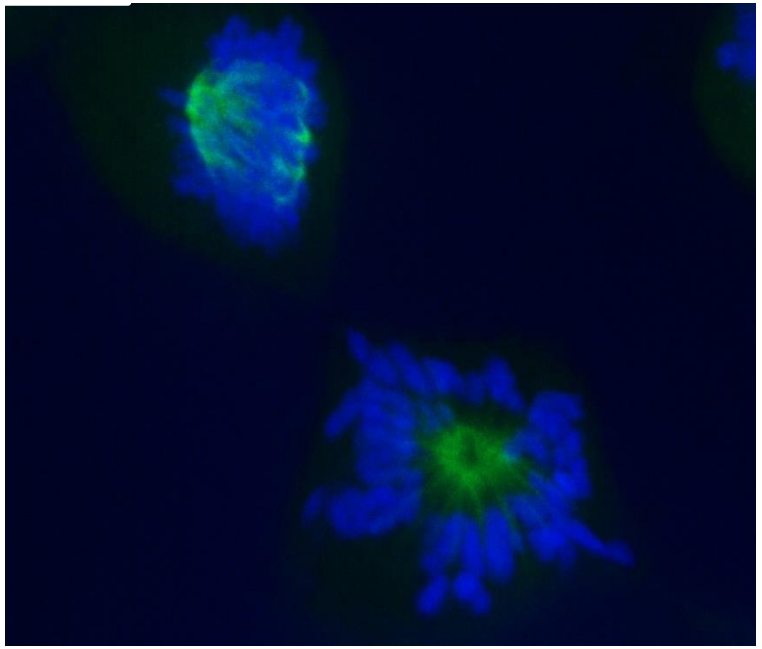

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Kalamida *et al.*
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Summary

- This study evaluates the impact of combining the ATR inhibitor AZD6738 with ^{223}Ra to investigate whether a greater radiosensitisation response occurs in comparison to standard X-rays.

- DDR inhibitors in combination with ^{223}Ra significantly enhanced radiosensitivity ($p < 0.001$) response in comparison to combined treatment with X-rays in prostate cancer cell lines and to a lesser extent in a normal epitheial prostate cell line. Additionally, a greater quantity of residual DSBs at 24 hours post combination treatment was observed after ^{223}Ra exposure in comparison to X-ray exposure in PC3 and DU145 cells but not normal RWPE-1 cells ($p < 0.001$).

- Cell cycle analysis indicates that either X-ray or ^{223}Ra treatment combined with AZD6738 abrogated the G2/M cell cycle checkpoint, with ^{23}Ra in combination with AZD6738 inducing a large Sub G1. Further analysis indicates that cell death was apoptotic as evidenced by PARP cleavage.

- Our findings strongly support the combination of DNA damage induction by ^{223}Ra with an ATR inhibitor as a novel potential treatment option for mCRPC patients in order to improve clinical outcome.

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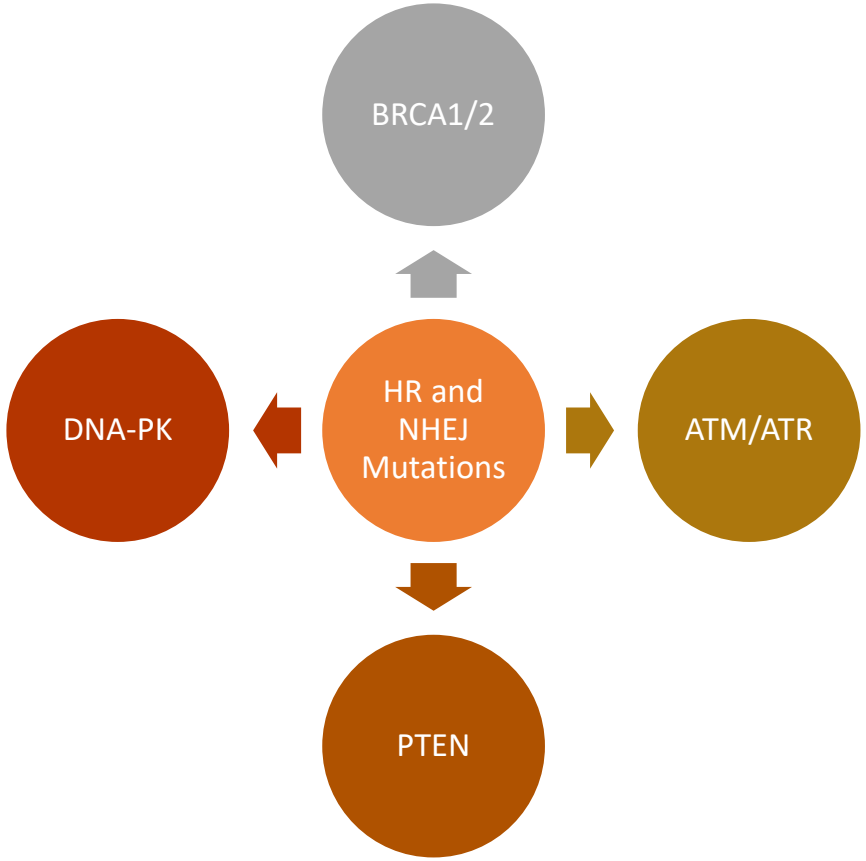
Future work



Aim: Determine the response of prostate cancer cells with HRD mutations to ^{223}Ra and whether the addition of DDR inhibitors increases this response.

In vitro

- Clonogenics, DNA damage kinetics, cell cycle distribution, mitotic catastrophe

In vivo

- Subcutaneous implant to investigate response to different radiation modalities in combination with DDR kinase inhibitors

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