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MOVING FROM PARP INHIBITION TO TARGETING DNA REPAIR AND DNA DAMAGE RESPONSE IN CANCER THERAPY

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SELECTED HIGHLIGHTS

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DISCLAIMER

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DNA DAMAGE RESPONSE (DDR) IS OF CRUCIAL IMPORTANCE AS A CANCER TARGET

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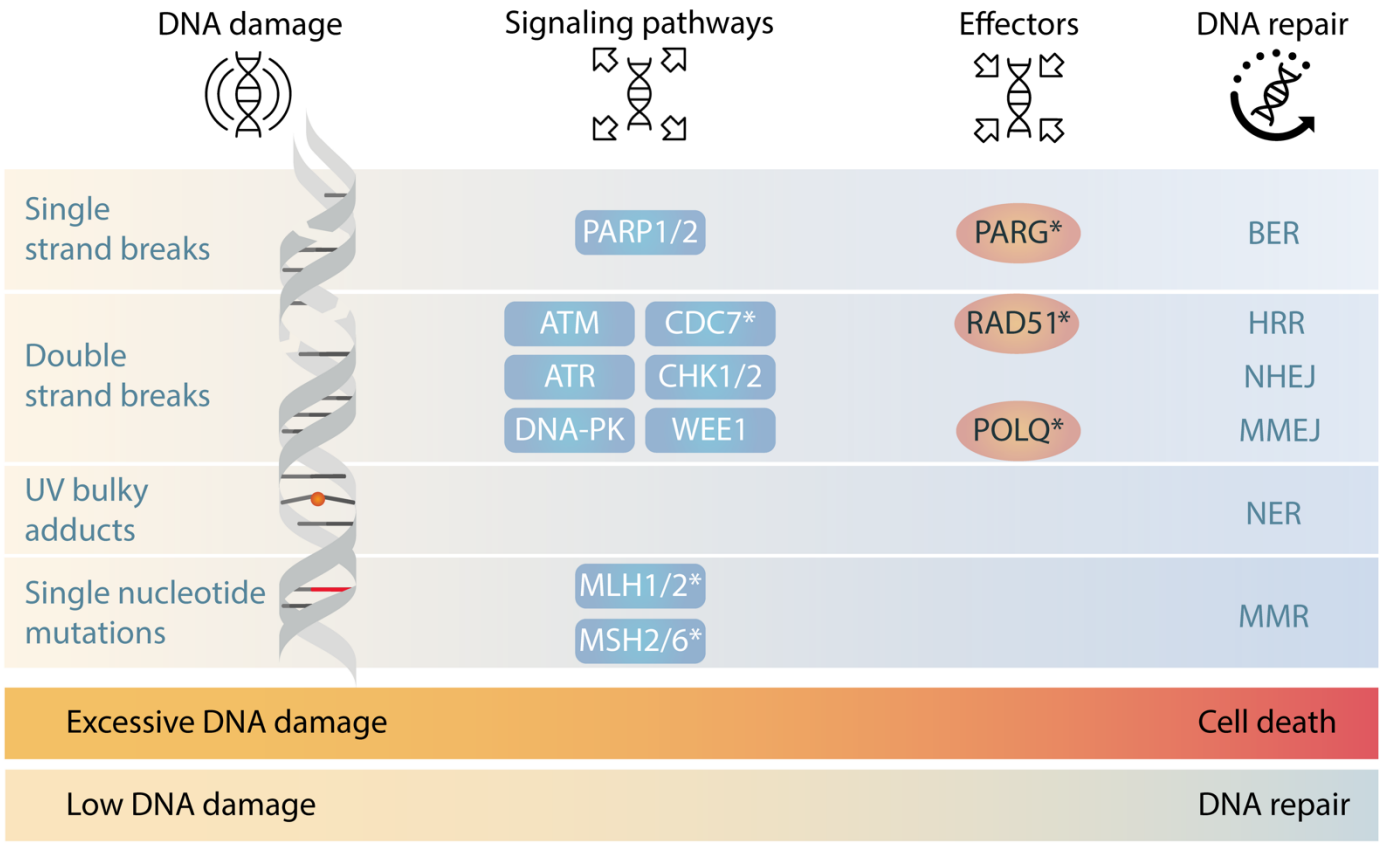
DDR coordinates the identification, signaling, and repair of DNA damage. PARP is the most well-known therapeutic target and several other targets are being investigated for the treatment of cancer



Pharmacologically targeted:

PARP1/2 Olaparib (AstraZeneca)
Rucaparib (Clovis)
Niraparib (Tesaro)
Talazoparib (Pfizer)
ATR AZD-6738 (AstraZeneca)
M-4344 (Merck)
DNA-PK Asi DNA (Onxeo)
CC-125 (Celgene)
LY-3023414 (Eli Lilly)
M-3814 (Merck)
WEE1 AZD-1775 (AstraZeneca)
CHK1/2 CBP-501 (CanBas)
Prexasertib (Eli Lilly)
GDC-0575 (Genentech)
SRA-737 (Sierra Oncology)
ATM AZD-0156 (AstraZeneca)

*Inhibitors in preclinical development

BER, base excision repair; DDR, DNA damage response; HRR, homologous recombination repair; MMEJ, micro-homology mediated end joining; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; PARP, poly (ADP-ribose) polymerase

PARP INHIBITION IN THE TREATMENT OF CANCER

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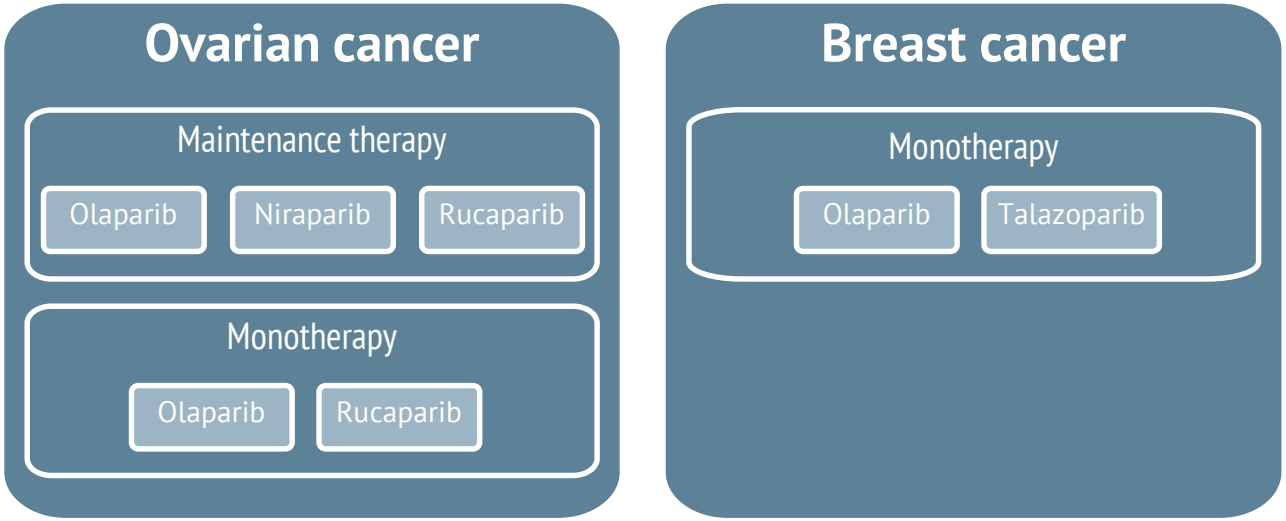
- Four PARP inhibitors have been approved for use in the treatment of **ovarian and breast cancer** in Europe and the USA



- The therapeutic reach of PARP inhibitors is expanding to **other cancer types**, many of which are associated with *BRCA* mutations
  - Trials are ongoing in pancreatic, endometrial, prostate, urothelial, colorectal, glioblastoma, small-cell and non-small-cell lung and gastroesophageal cancers

THE FUTURE ROLE OF PARP INHIBITION IN CLINICAL PRACTICE

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Selecting the right patients

- Patients whose tumors harbor *BRCA* mutations are likely to respond to PARP inhibition, and identifying these patients is now well established in the clinic
  - In ovarian cancer, platinum sensitivity functions as a surrogate marker for HRD
- Genomic scars and mutational signatures associated with an HRD phenotype can define a wider population that may benefit from DDR targeting agents
- Understanding innate tumor genomics prior to treatment and combining this knowledge with information from functional analysis assessing sensitivity to PARP inhibition may be applied to generate patient-personalized treatment plans

DDR, DNA damage response; HRD, homologous recombination repair defects

THE FUTURE ROLE OF PARP INHIBITION IN CLINICAL PRACTICE

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Understanding resistance

- Several mechanisms of acquired PARP inhibitor resistance have been described in pre-clinical settings
  - To date, only restoration of HRR and expression of hypomorphic forms of *BRCA1* have been shown to be clinically relevant
- It is likely that in different cancers, different mechanisms of resistance may emerge, likely depending on the germline or other mutational profile, or other factors such as origin of the disease or prior treatment
  - These mutations may include loss of PARP1 expression, compromised regulation of end-resection via loss of 53BP1, MAD2L2/Rev7 or the Shieldin complex, and activation of trans-lesion DNA synthesis through loss of CHD4, allowing less efficient HRR to proceed

HRR, homologous recombination repair

MOVING FROM PARP TO DDR INHIBITION IN THE CLINIC

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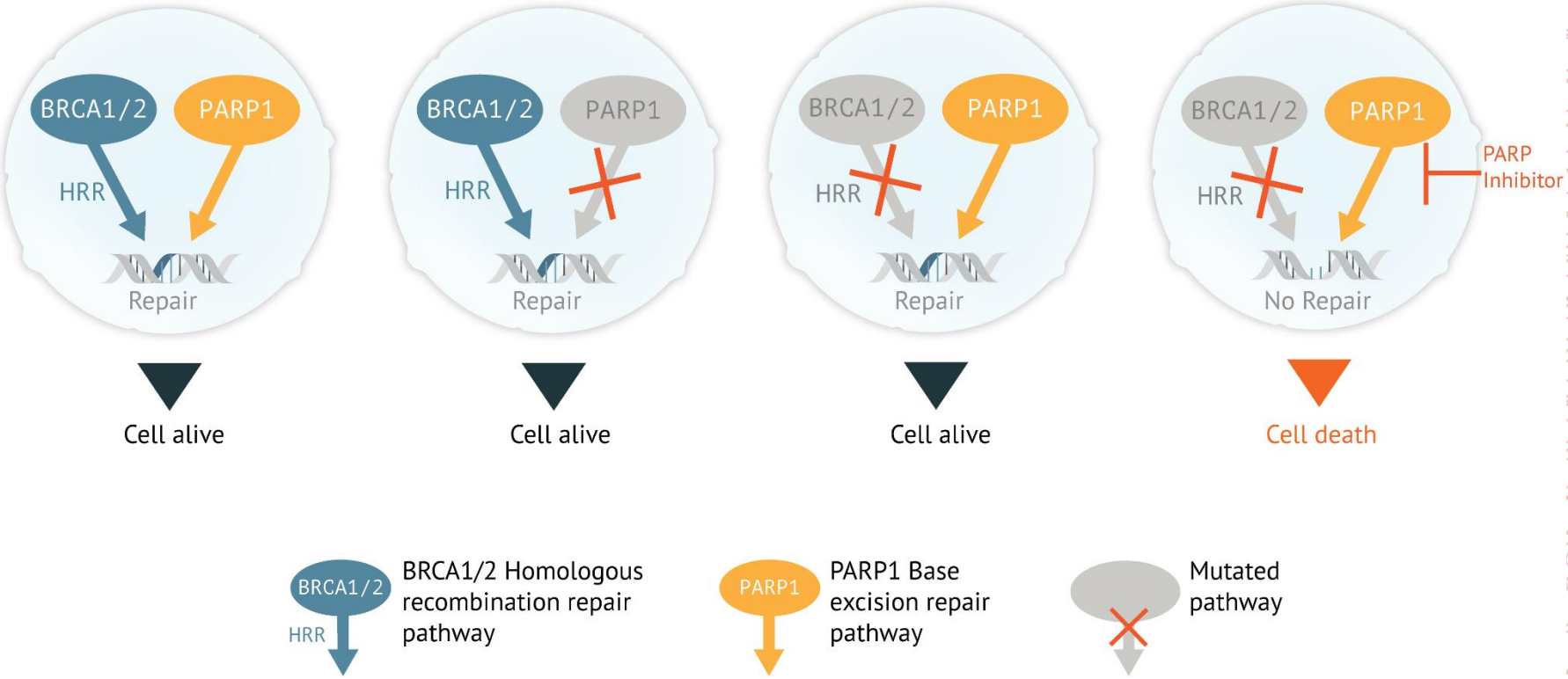
Trapping PARP on DNA following its inhibition confers lethality to HRR deficient cells. This concept has been exploited in the clinic and can be applied to other molecules in the DDR pathway.



HRR, homologous recombination repair

FUTURE DDR TREATMENT STRATEGIES

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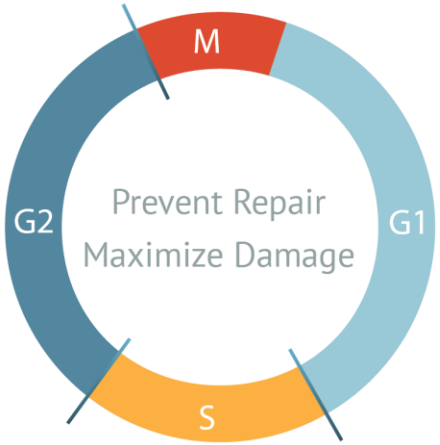
The three key cell cycle checkpoints are being targeted by small molecule inhibitors in clinical trials. Cancer cells have increased susceptibility to S-phase-induced DNA damage that in turn may lead to either replication catastrophe or apoptosis (unsustained levels of S-phase DNA damage), or mitotic catastrophe (double strand breaks carried into mitosis).

G2/M Checkpoint
DDR Targets
CHK1, WEE1



S phase Checkpoint
DDR Targets
ATR, CHK1, DNA-PK, WEE1

G1/S Checkpoint
DDR Targets
ATM, CHK2, p53

DDR TARGET	AGENT (MANUFACTURER)	ACTIVITY IN CELL CYCLE
ATR	AZD-6738 (AstraZeneca) M-4344 (Merck) M6620 (Merck)	Kinase activated by replication stress and required to coordinate replication fork stabilisation and restart
DNA-PK	Asi DNA (Onxeo) CC-125 (Celgene) LY-3023414 (Eli Lilly) M-3814 (Merck)	DNA double strand break responsive kinase important for DNA repair by non-homologous end joining
WEE1	AZD-1775 (AstraZeneca)	Kinase that negatively regulates the G2-M transition and entry into mitosis
CHK1/2	CBP-501 (CanBas) Prexasertib (Eli Lilly) GDC-0575 (Genentech) SRA-737 (Sierra Oncology)	DNA damage responsive effector kinases, which work downstream of ATR and ATM, respectively
ATM	AZD-0156 (AstraZeneca)	Kinase that initiates the checkpoint response to DNA double strand break required to signal to the DNA repair and cell cycle machineries

FUTURE DDR TREATMENT STRATEGIES

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Compounds targeting DDR in clinical development (other than PARP1/2 inhibitors)

DDR Target	Compound Name	Company Name	Highest Development Stage	Indication
CHK1/2	CBP-501	CanBas Co Ltd	Phase II	NSCLC
	Prexasertib	Eli Lilly and Company	Phase II	SCLC, Ovarian Cancer, Triple Negative Breast Cancer, Metastatic Castrate Resistant Prostate Cancer
	GDC-0575	Genentech	Phase I	Solid tumors
	SRA-737	Sierra Oncology Inc	Phase I	Solid tumors
WEE1	AZD1775	AstraZeneca	Phase II	SCLC, Squamous Cell Lung Cancer, Ovarian Cancer, Triple Negative Breast Cancer, Advanced Acute Myeloid Leukaemia or Myelodysplastic Syndrome, Gastric Cancer, Head and Neck Cancer, Pancreatic Cancer
ATR	AZD6738	AstraZeneca	Phase I	Various solid malignancies
	M-4344	Merck KGaA	Phase I	Various solid malignancies
	M6620 (VX-970)	Merck KGaA	Phase II	Various solid malignances
DNA-PK	CC-115	Celgene Corp	Phase II	Glioblastoma
	LY-3023414	Eli Lilly and Company	Phase II	SCLC, Endometrial Cancer, Prostate Cancer, Pancreatic Cancer, Lymphoma
	AsiDNA	Onxeo SA	Phase I	Various solid malignancies
	M-3814	Merck KGaA	Phase I	Various solid malignancies
ATM	AZD0156	AstraZeneca	Phase I	Various solid malignancies

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

OPPORTUNITIES FOR COMBINATION THERAPY WITH DDR-TARGETING COMPOUNDS

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Trials are underway combining compounds targeting DDR, including PARP inhibitors, with:

Other DDR-targeting agents, including:

- ATR inhibitors
- WEE1 inhibitors

Angiogenesis inhibitors, including:

- VEGF and VEGF-A inhibitors

Immunotherapy, including:

- Anti-PD-1 antibodies
- Anti-PD-L1 antibodies

PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor

OVERCOMING CHALLENGES IN DDR INHIBITION

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- The optimal treatment sequence of DDR inhibitors with other agents is still being determined
  - Results from the SOLO 1 trial suggest moving PARP inhibitors/DDR agents earlier in the treatment course may be appropriate for certain patients
- Understanding the differences between the mechanisms of action for different PARP inhibitors and the influence of specific *BRCA* mutations on efficacy will be important to support the future development of DDR inhibitors
- DDR-targeting agents will be tailored for specific patient populations and for specific innate and acquired mechanisms of resistance

Key questions for the near future:		
Defining the genetic and epigenetic level of HRD	How to incorporate predictive biomarkers of HRD and PARP inhibitor sensitivity into clinically relevant platforms	How will the molecular heterogeneity within tumors impact treatment regimens and resistance mechanisms

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