RESISTENZA AI PARPi: BASI FARMACOLOGICHE E STRATEGIE DI SUPERAMENTO

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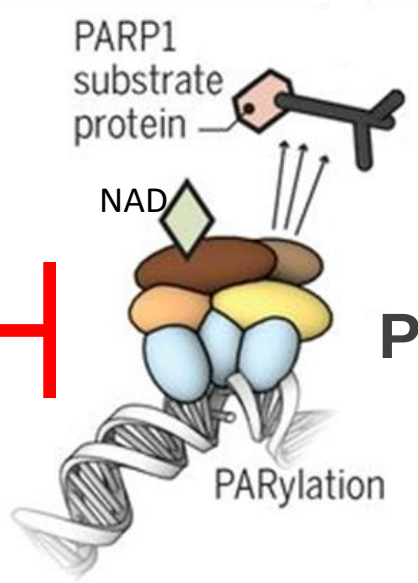
Mechanism of action of PARPi

PARP1 regulates multiple cellular processes

PARP inhibitor

off-target effects



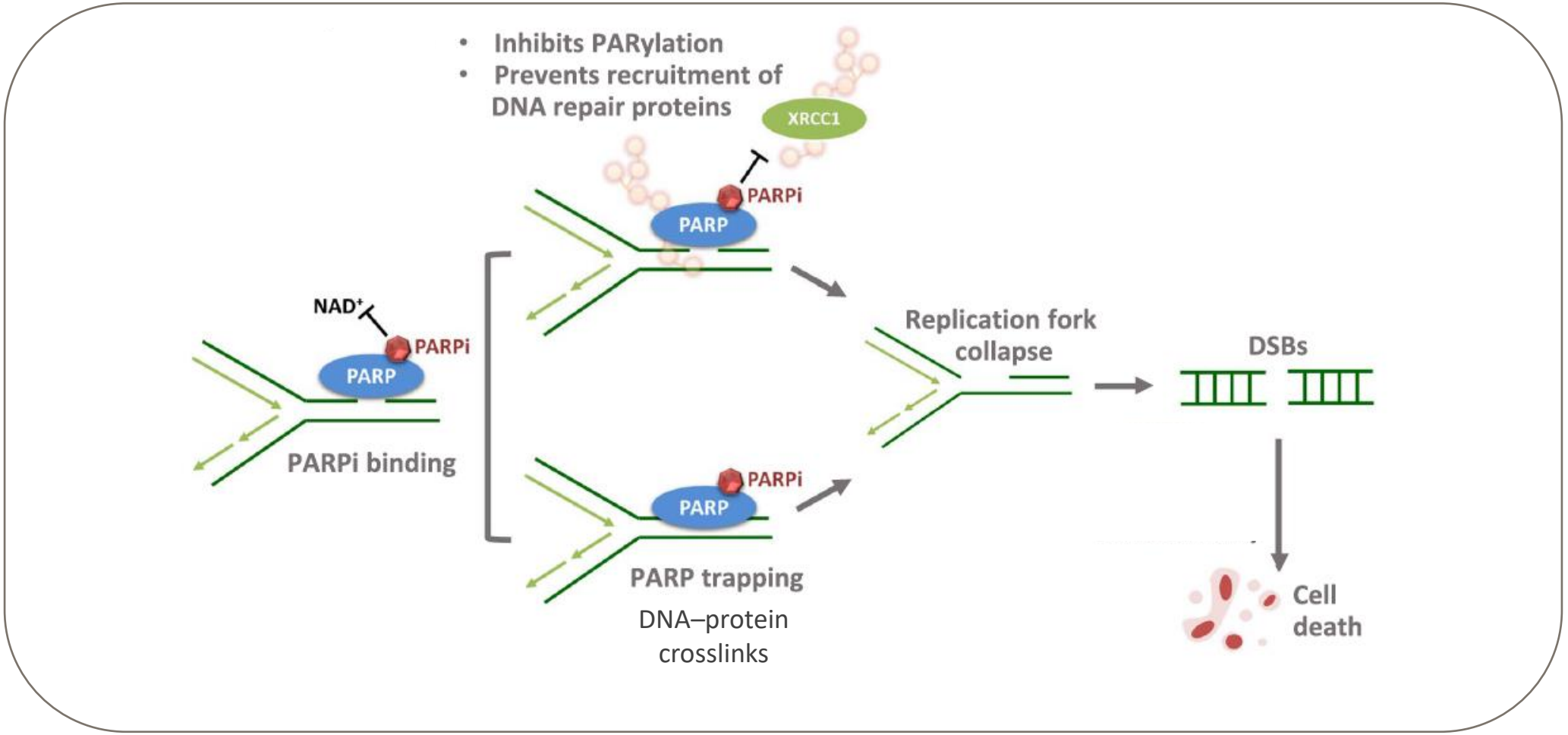
increased PARP1 expression in malignant tumors of various cancer types

PARP1

- DNA damage signalling
- chromatin remodelling
- transcription
- stabilization of replication forks
- sensing of unligated Okazaki fragments
- inflammation
- metabolism

Mechanism of action of PARPi

Main hypothesis



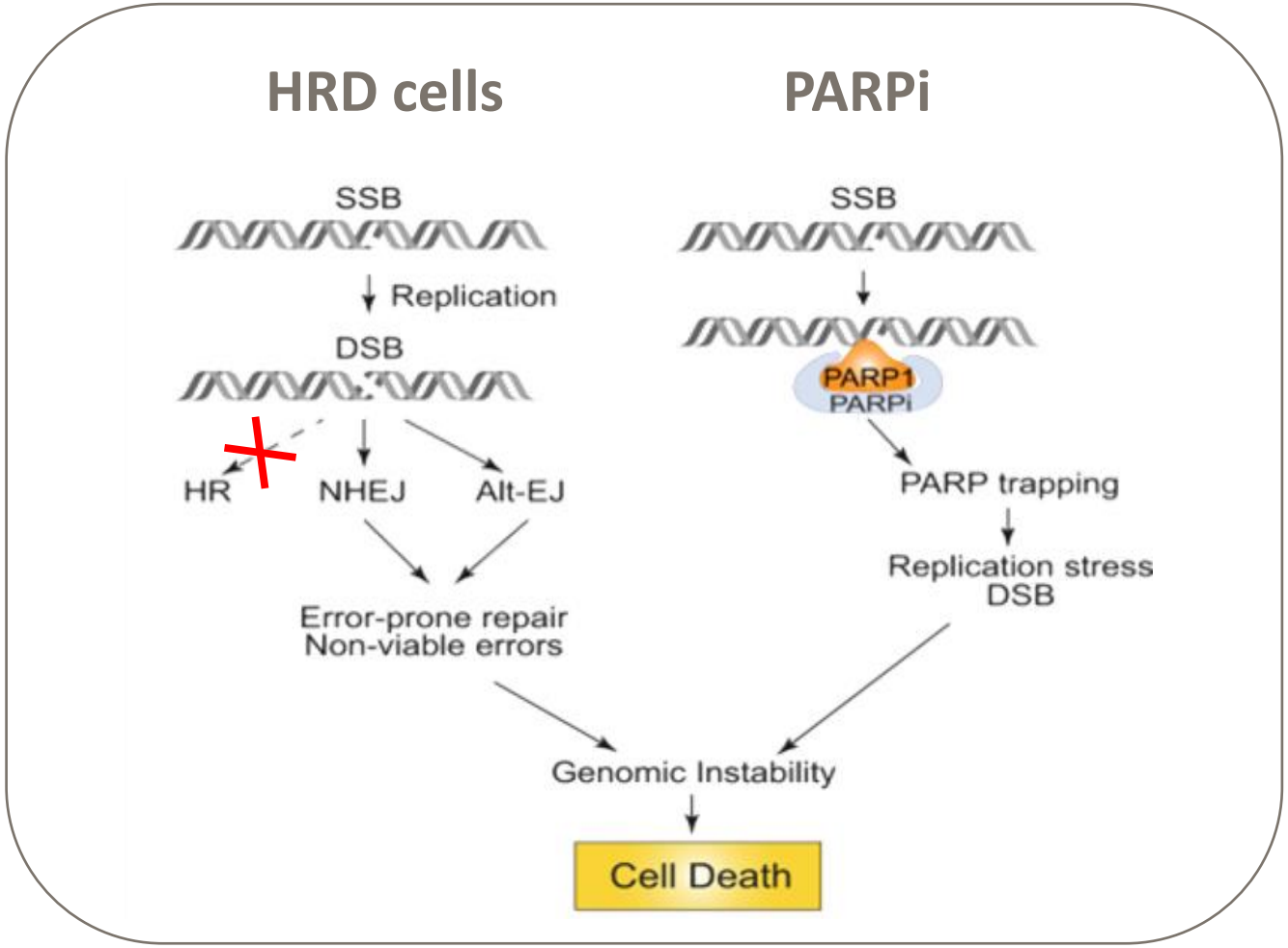
Chu et al. J Bio Science 2022

Mechanism of action of PARPi

Synthetic lethality

HRD tumors exhibit a pronounced level of sensitivity to DNA-damaging agents:

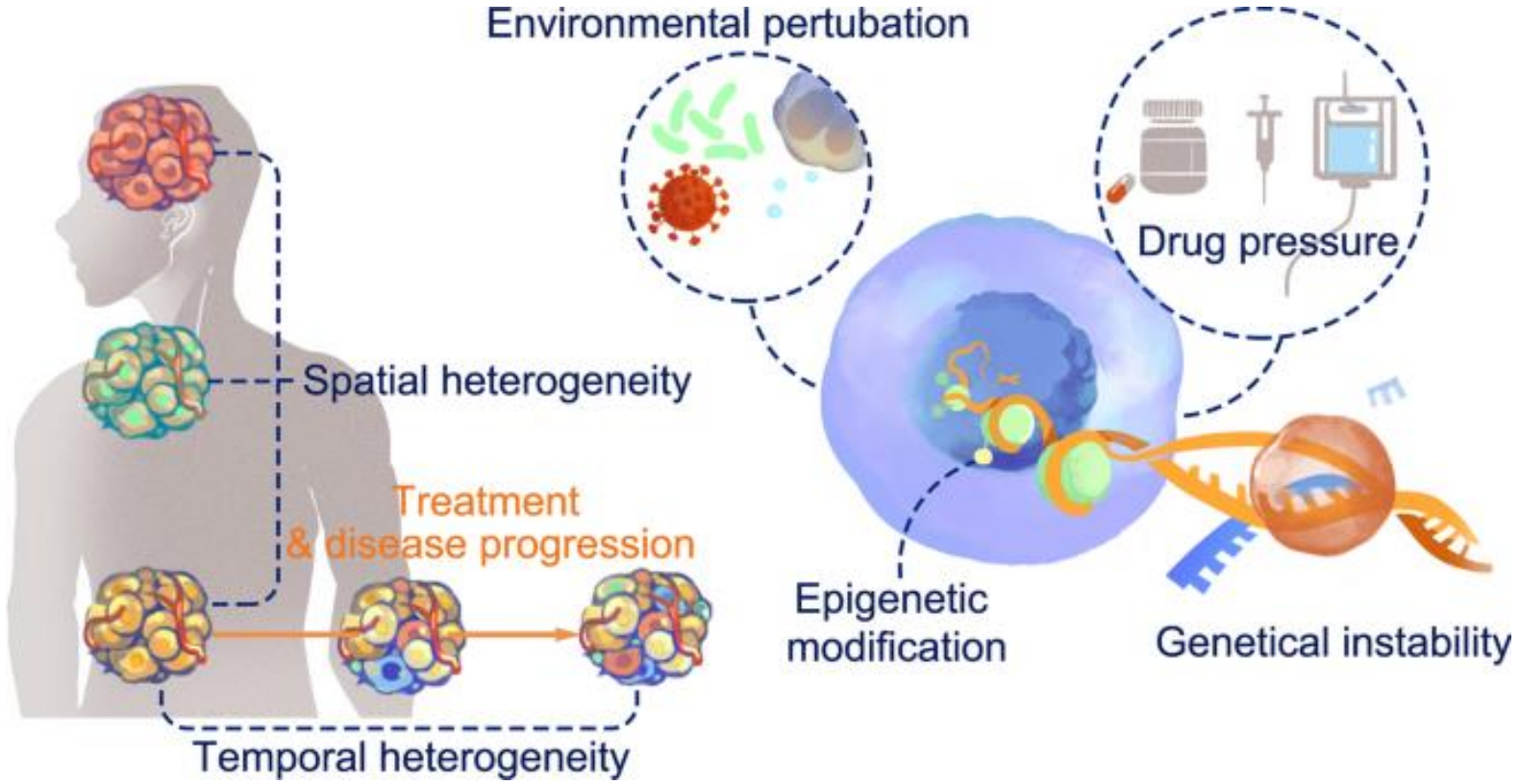
- platinum-based chemotherapies
- topoisomerase (TOP) inhibitors
- bifunctional alkylators
- PARP inhibitors



Adapted from Patel et al. Oncogene 2021

The real issue

Cancer heterogeneity

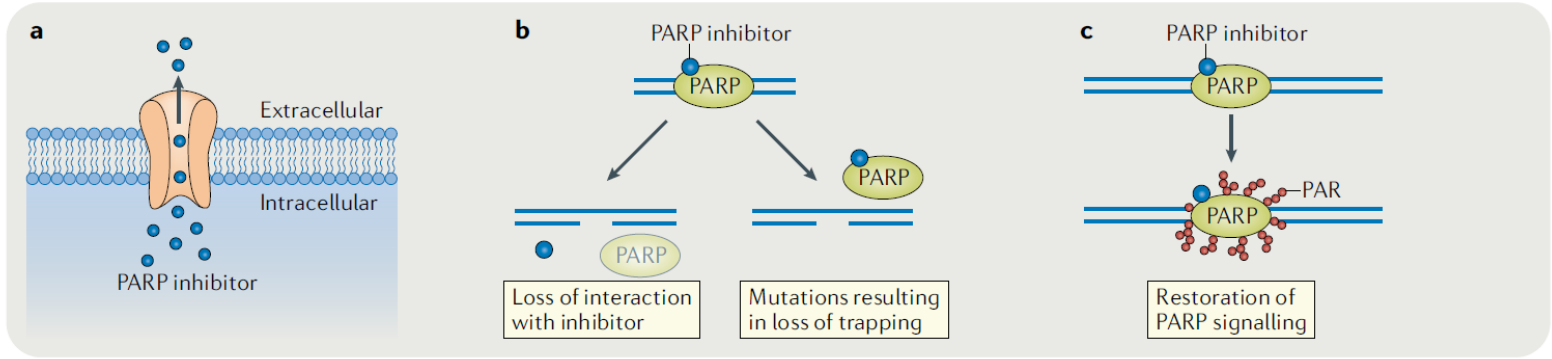


Jia et al. Exp Hematol Oncol 2022

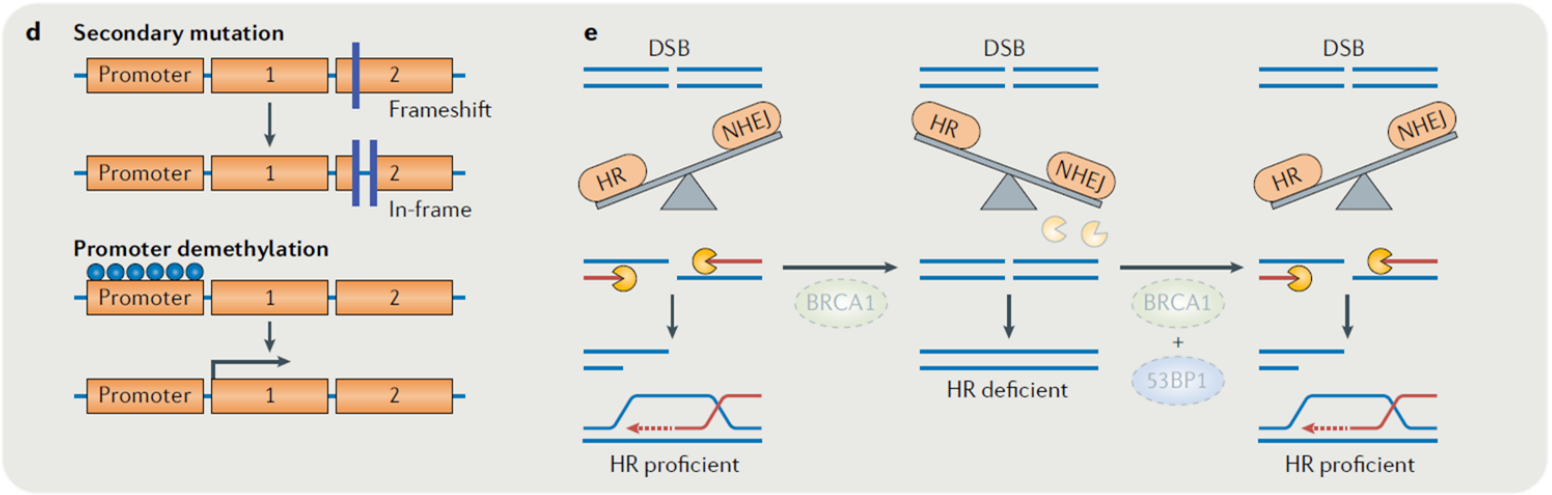
Mechanisms of resistance to PARPi

3 general mechanisms

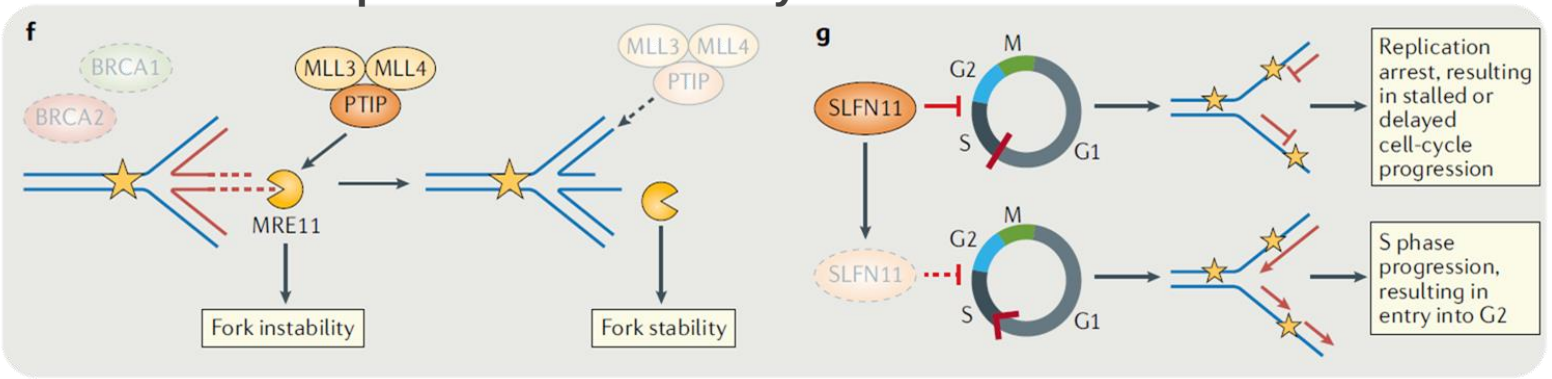
Drug-target related alterations



HR restoration



Restoration of replication fork stability

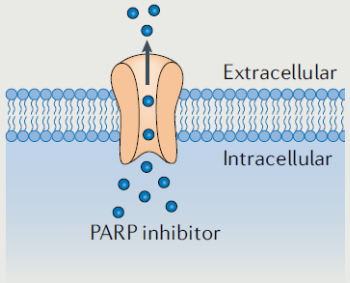


Paes Dias. Nat Rev Clin Oncol. 2021

Mechanisms of resistance to PARPi

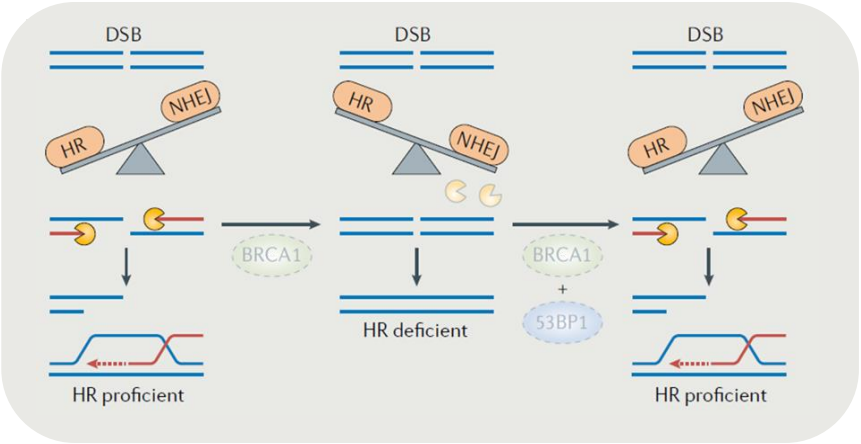
Clinical evidence

Upregulation of drug efflux pumps



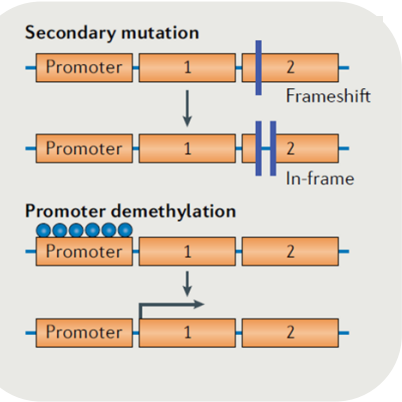
- Some PARPi are substrates for **MDR1**

BRCA-independent HR restoration



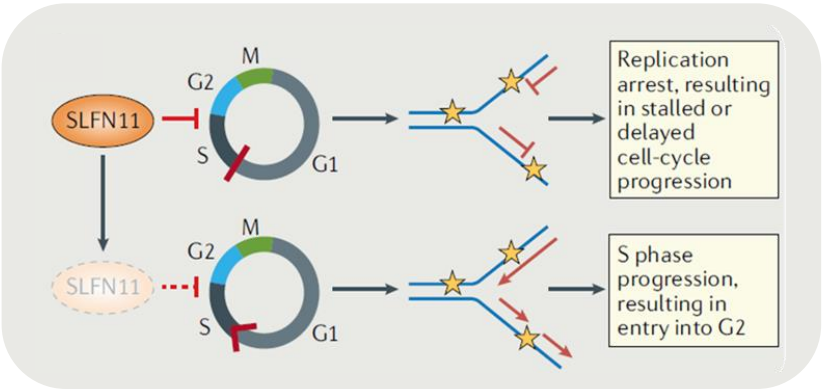
- Reversions in other **HR-related genes**: RAD51C, RAD51D, PALB2
- Mutations promoting **suppression of NHEJ** (e.g. loss of 53BP1)

Restoration of BRCA1/2 function



- **Reversion mutations or epigenetic alterations**
- Associated also with Pt resistance

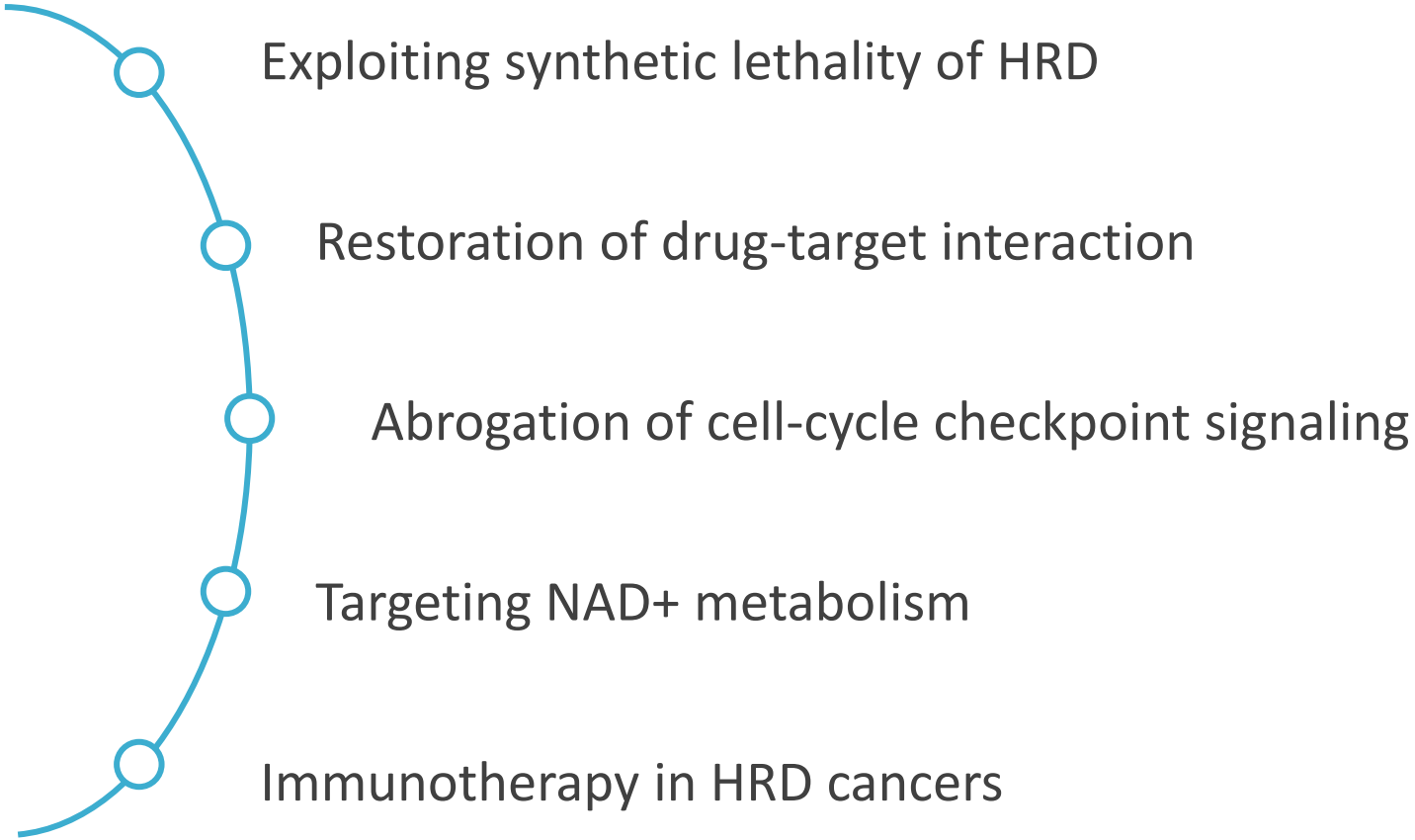
Restoration of fork stability



- **Loss of SLFN11** enables cells to progress through the S phase in the presence of replicative stress.
- SLFN11 is a strong determinant of response also to TOP1 inhibitors, TOP2 inhibitors, alkylating agents, DNA synthesis inhibitors.

Strategies to overcome PARPi resistance

Combinatorial strategies to amplifying the antitumor effects of PARPi



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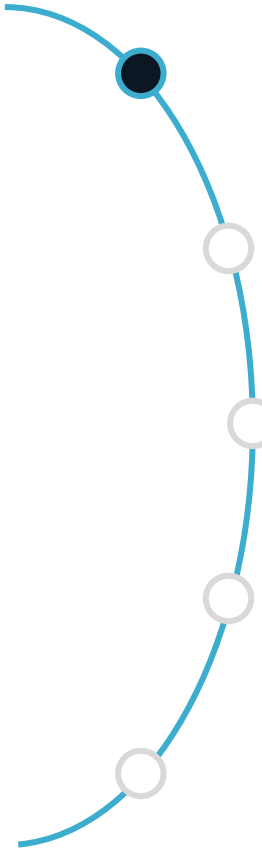


Exploiting synthetic lethality of HRD

Restoration of drug-target interaction

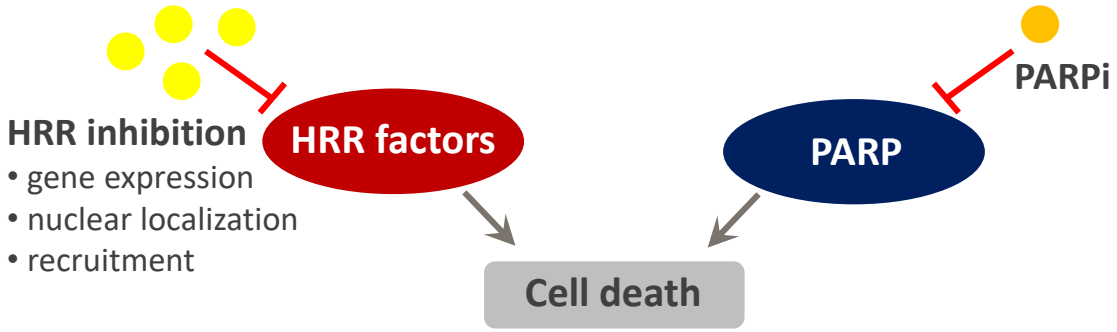
Abrogation of cell-cycle checkpoint signaling

Targeting NAD+ metabolism

Immunotherapy in HRD cancers

Amplifying the antitumor effects of PARPi

Exploiting synthetic lethality of HRD



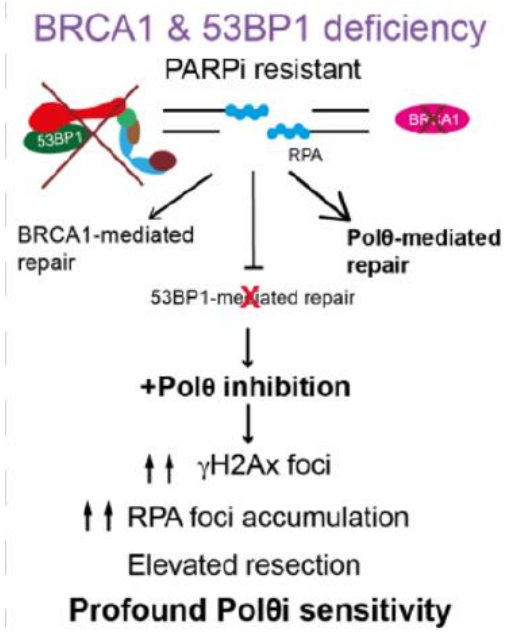
ACTIVE CLINICAL TRIALS

HDAC inhibitors	• **NCT04703920 - Phase 1** **Belinostat +** Talazoparib for breast, prostate and EOC
AsiDNA	oligonucleotide mimicking DSBs • **REVOCAN - Phase 1/2** **AsiDNA** + PARPi for relapsed Pt-sensitive EOC already treated with PARPi
mTOR inhibitors	• **NCT02208375- Phase 1/2** **Vistusertib** (mTORC1/2 Inhibitor) + Olaparib for recurrent EOC
MEK inhibitors	• **NCT03162627- Phase 1** **Selumetinib** + Olaparib for solid tumors • **NCT05554328 – Phase 2** **Selumetinib** + Olaparib for RAS pathway mutant recurrent or persistent EOC and endometrial cancers
Inhibition of VEGF/PDGF signaling	• **NCT05494580 - Phase 1/2** **Surufatinib** + Pamiparib for Pt-resistant EOC • **ANLOLA - Phase 2** **Anlotinib** + Olaparib for Pt-sensitive EOC • **ICON9 - Phase 3** **Cediranib** + Olaparib for Pt-sensitive EOC • **NRG-GY005/COCOS - Phase 2/3** **Cediranib** + Olaparib for Pt-resistant or -refractory EOC
AKT inhibitors	• **NCT02208375 - Phase 1/2** **Capivasertib** + Olaparib for recurrent EOC
PI3 kinase inhibitors	• **EPIK-O - Phase 3** **Alpelisib** + olaparib against BRCAwt, platinum-resistant EOC

Amplifying the antitumor effects of PARPi

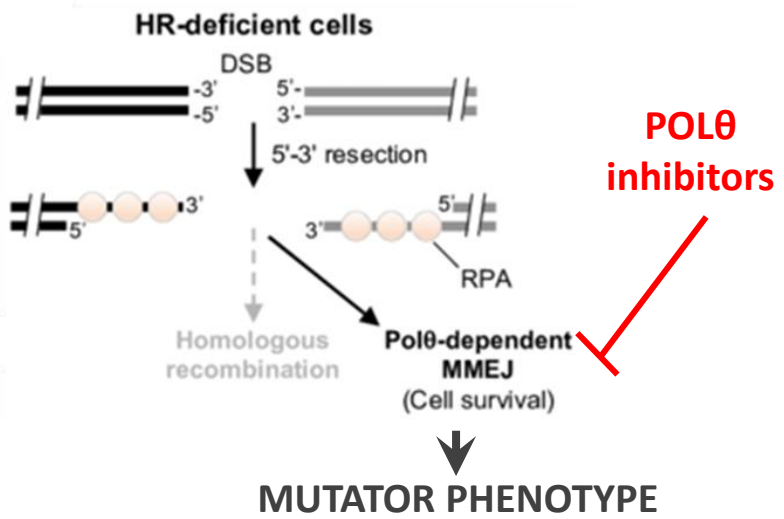
Exploiting synthetic lethality of HRD

1) **POLθ inhibitors elicit BRCA-gene synthetic lethality** and PARP inhibitor synergy, as well as targeting a biomarker defined mechanism of PARPi-resistance.



2) POLθ inhibitors can **delay emergence of resistance** by suppressing the mutator phenotype.

HRD cells upregulate **microhomology-mediated end-joining** (**MMEJ**) as a compensatory mechanism. **MMEJ is an error-prone repair pathway**, driven by the low-fidelity DNA polymerase θ.



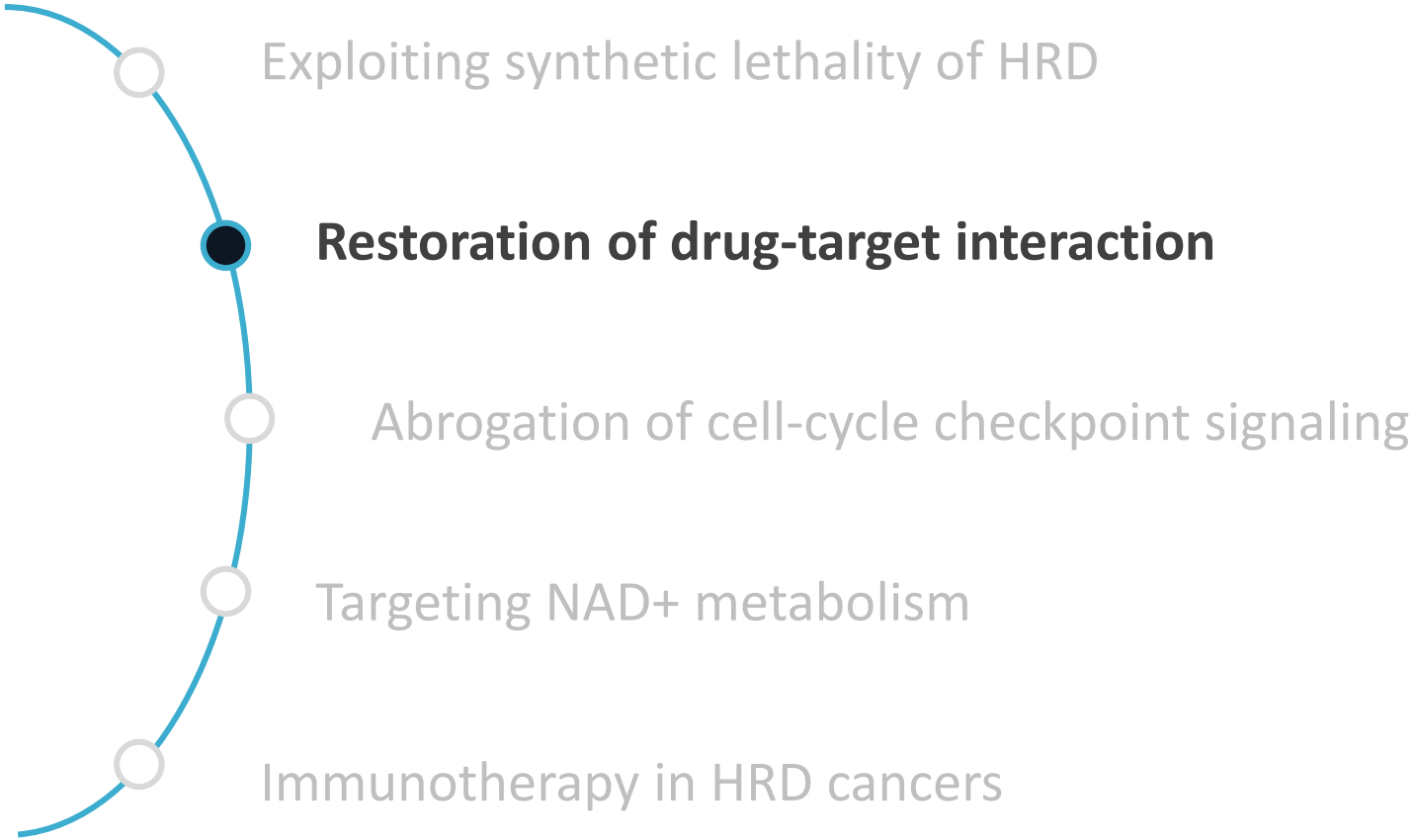
ACTIVE CLINICAL TRIALS

- **NCT04991480 - Phase 1/2**
  ART4215 + talazoparib or as monotherapy for solid tumors

Zatreanu et al. Nat Commun. 2021

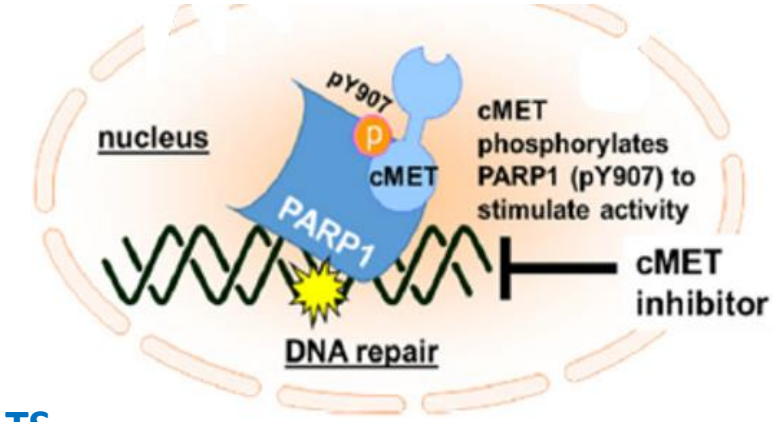
Strategies to overcome PARPi resistance

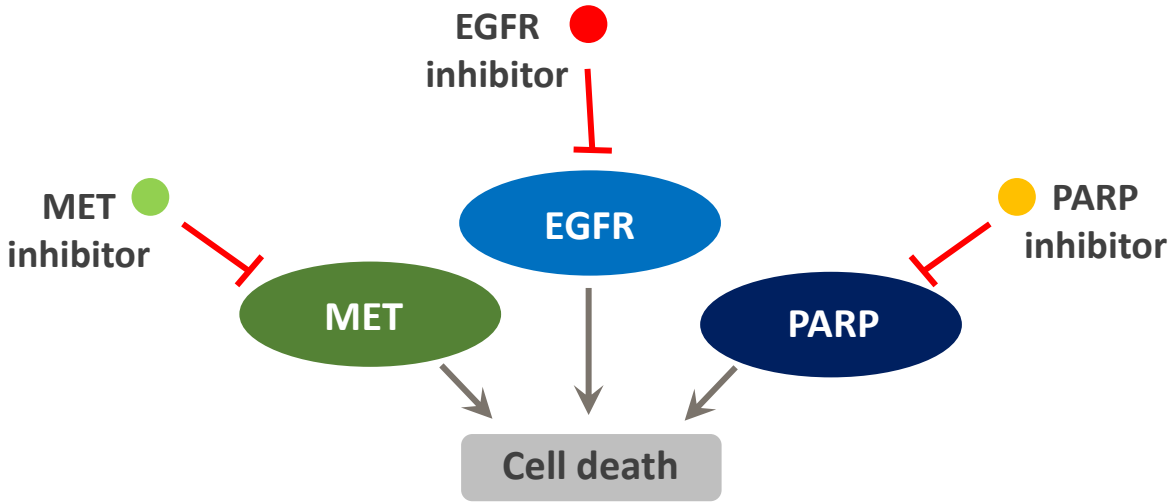
Combinatorial strategies to amplifying the antitumor effects of PARPi



Amplifying the antitumor effects of PARPi

Restoration of drug-target interaction





PRECLINICAL RESULTS

- **c-MET** phosphorylates PARP1 at Y907 residue.
- The phosphorylation of Y907-PARP1 upregulates the enzymatic activity of PARP1 and **prevents the binding of PARPi** (resistance to PARPi).
- **Combination of c-METi and PARPi** synergistically suppresses the growth of xenograft tumors which have high c-MET and p-Y907 PARP expression.

[breast, ovarian, pancreatic cancer]

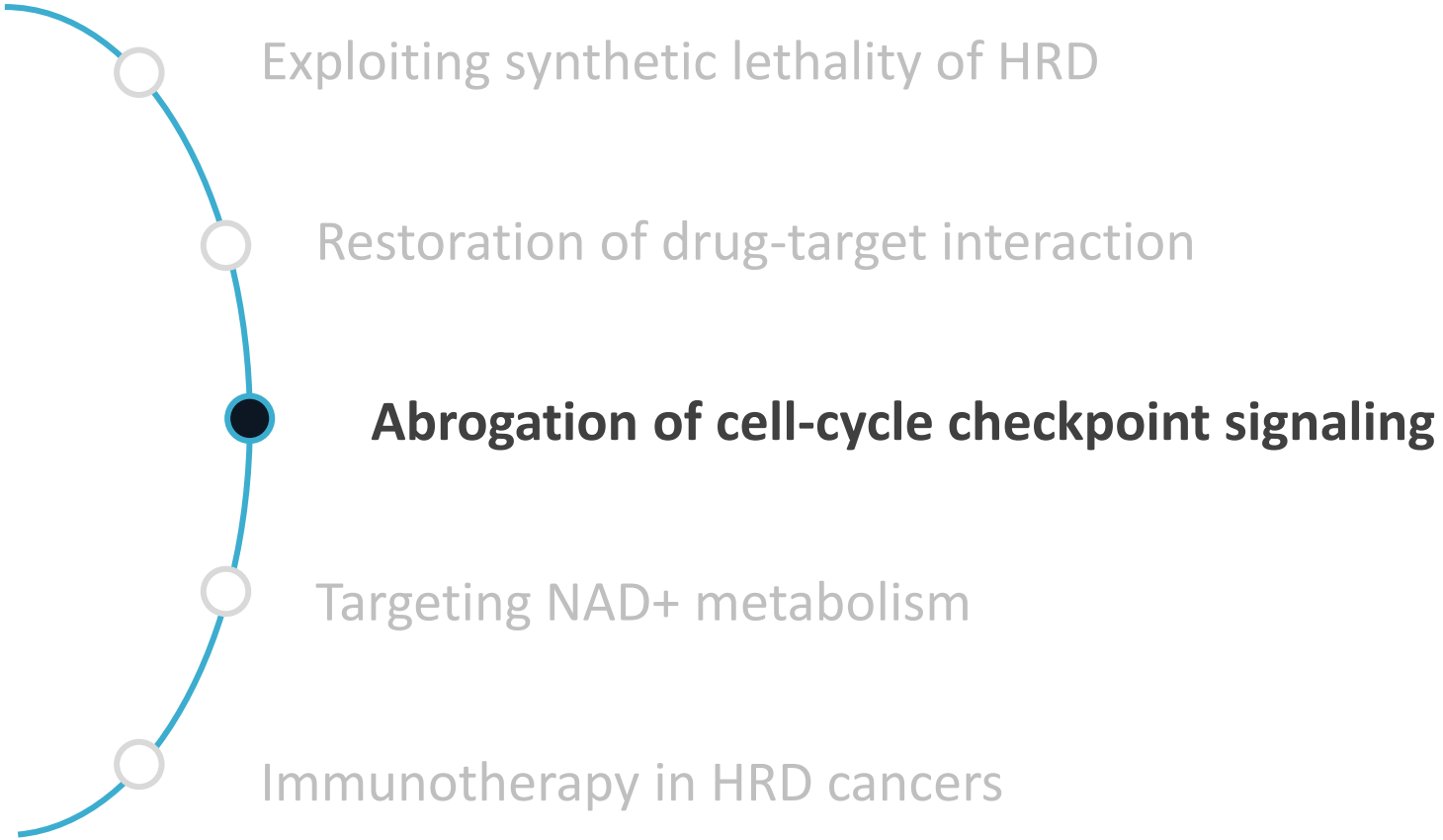
- **EGFR** interacts with c-MET and phosphorylate PARP-Y907 [HCC cells].
- **Simultaneous inhibition of both EGFR and c-MET significantly increases the antitumor activity of PARPi**.

[HCC, TNBC]

Han et al. Am J Cancer Res. 2019; Du et al. Nat Med. 2016

Strategies to overcome PARPi resistance

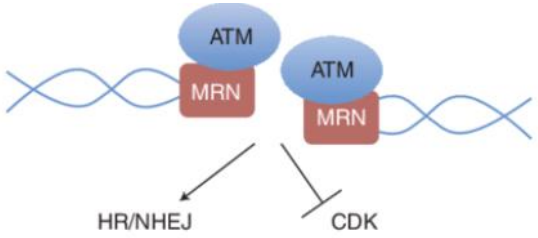
Combinatorial strategies to amplifying the antitumor effects of PARPi



Amplifying the antitumor effects of PARPi

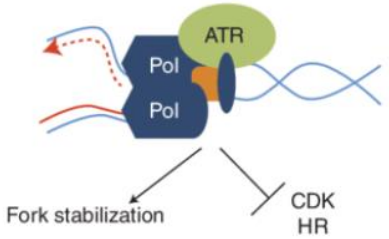
Abrogation of cell-cycle checkpoint signaling

ATR promotes RAD51 loading onto DSBs and stalled forks



ATR inhibitors + PARPi

ATM kinase activity is required for the early stages of HR



ATM inhibitors + PARPi

WEE1 kinase
↓
inhibits CDK1 and CDK2
↓
activates the G2/M cell-cycle checkpoint
↓
cell-cycle arrest
↓
provides time for DNA damage repair

WEE1 inhibitors + PARPi

Multiple inhibitors of cell-cycle checkpoint kinases (ATR, ATM, CHK1, WEE1) + PARPi

Proteins controlling cell-cycle checkpoint activation can induce arrest of cells in response to DNA damage

↓

After removal of replication stress, stalled **replication forks can be restarted**

ACTIVE CLINICAL TRIALS

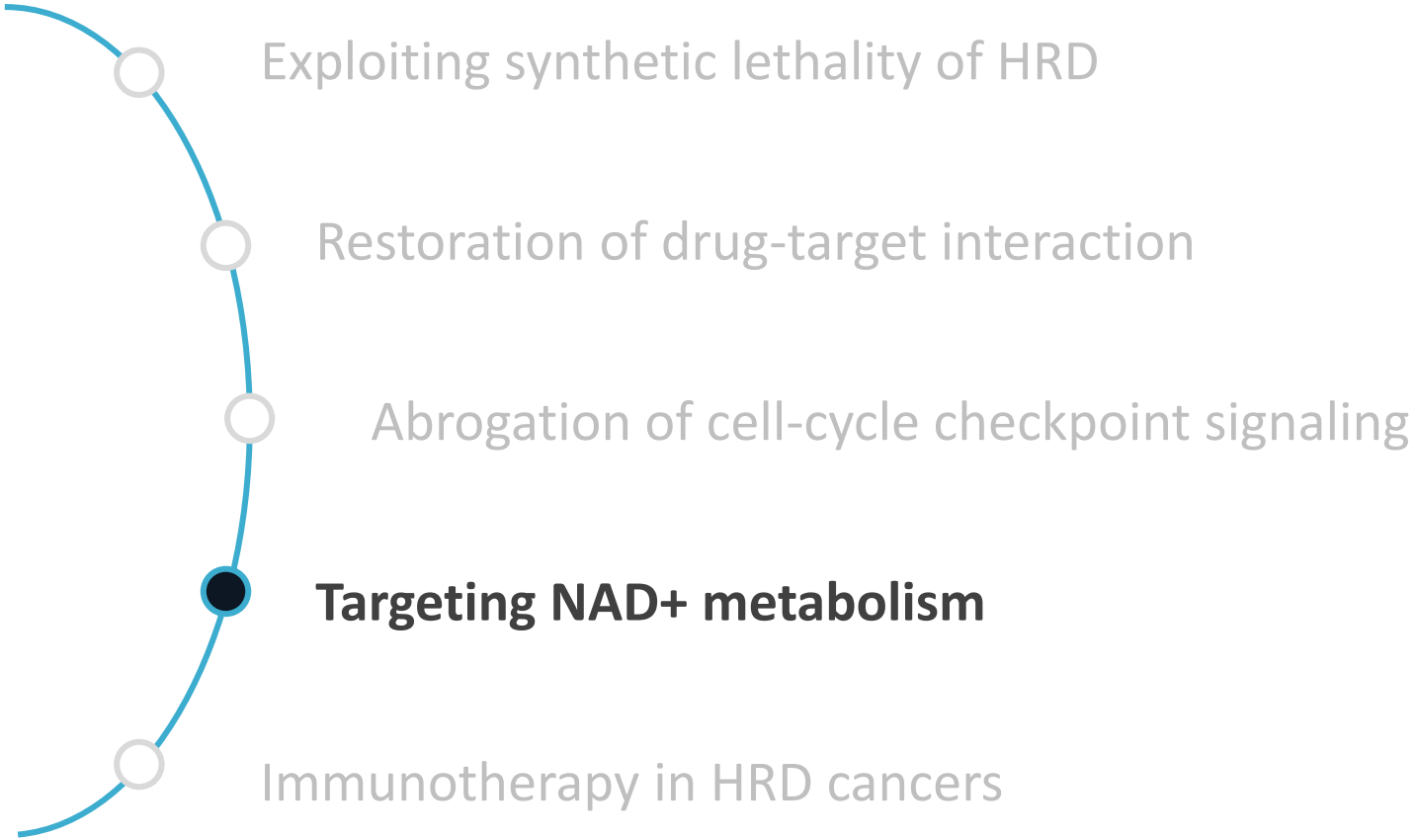
- **NCT04267939 - Phase 1**
  Elimusertib (ATRi) + Niraparib for EOC

PARP-resistant tumors

- **NCT04149145 - Phase 1**
  M4344 (ATR/ATMi) + Niraparib
- **NCT04826341 - Phase 1/2**
  Berzosertib (ATRi) + Sacituzumab Govitecan
- **CAPRI - Phase 2**
  Ceralasertib (ATRi) + Olaparib for recurrent Pt-sensitive or Pt-resistant EOC

Strategies to overcome PARPi resistance

Combinatorial strategies to amplifying the antitumor effects of PARPi

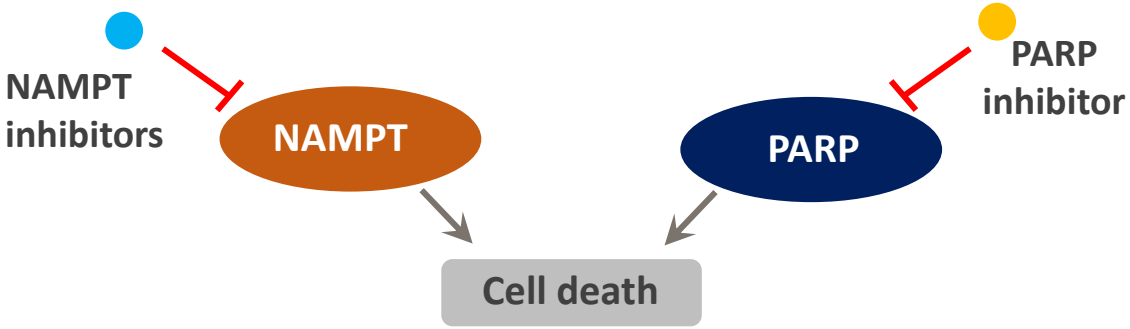


Amplifying the antitumor effects of PARPi

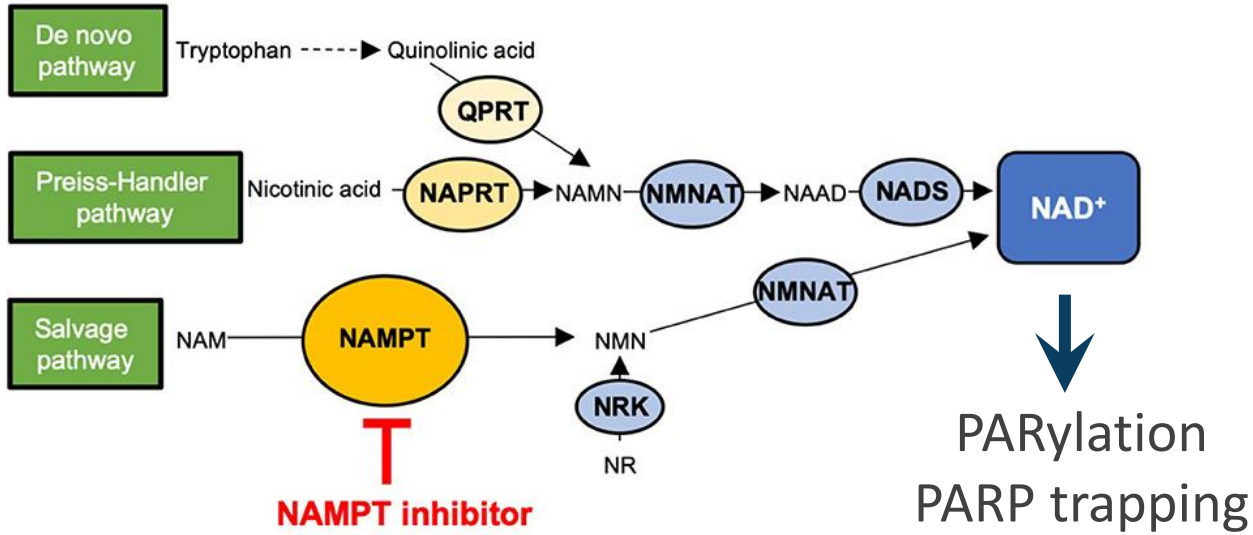
Targeting NAD+ metabolism

Excessive PARP activation (e.g. excessive DNA damage) can deplete the cellular pool of NAD+, used as substrate for PARylation.

To maintain NAD+ levels, cells are reliant on salvage pathways, in which **nicotinamide phosphoribosyltransferase (NAMPT)** is a rate-liming enzyme.

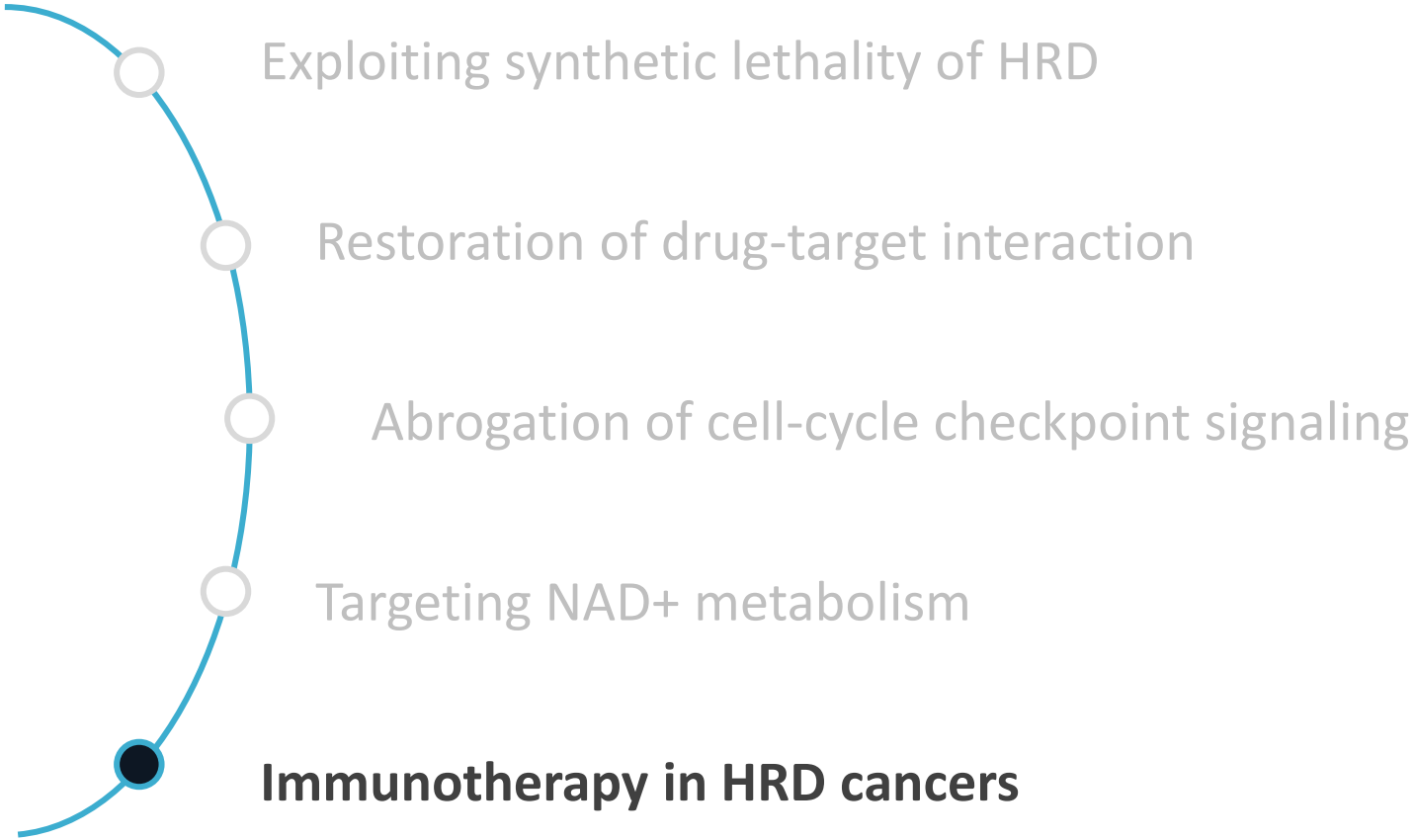


PRECLINICAL RESULTS



Strategies to overcome PARPi resistance

Combinatorial strategies to amplifying the antitumor effects of PARPi



Amplifying the antitumor effects of PARPi

Immunotherapy in HRD ovarian cancers

HRD cancers

- increased mutational burden → increased availability of **tumor-specific neoantigens**
- cytosolic accumulation of unrepaired DNA fragments → activation of **cGAS–STING signaling** → activation of the **IFN pathway**

PARPi

- induces **PD-L1 expression**
- induces **cGAS–STING signalling**

→ increased **CD8+ T cell infiltration** and **activation**

Immune-checkpoint inhibitors + PARPi

ACTIVE CLINICAL TRIALS

- **ANITA - Phase 3**
  Pt-based chemotherapy + Atezolizumab followed by Niraparib + **Atezolizumab** for Pt-sensitive **EOC**
- **ATHENA - Phase 3**
  Nivolumab + Rucaparib for Pt-sensitive EOC
- **NCT04673448 - Phase 1**
  Niraparib + Dostarlimab
- **NCT02571725 - Phase 1/2**
  Olaparib + Tremelimumab
- **NCT04034927 - Phase 2**
  Olaparib + Tremelimumab in Pt-sensitive EOC

Concluding remarks

What shall we do now?

More research will allow to

- **improve our knowledge** about the **mechanism of action** and possible **sources of resistance** to PARPi.
  - **Liquid biopsy**
  - **New experimental models** of PARPi resistance
  - **Genetic** and **pharmacological screens** to identify compounds that specifically target resistant cancer cells.
- **develop better biomarkers to predict**
  - response (including long-term responses) and resistance,
  - the risk of side effects,
  - potential synergism with other therapeutics.
- **develop rational combination treatment strategies** to prevent, delay and/or counteract the onset of resistance.