COR2ED
THE HEART OF MEDICAL EDUCATION
DNA DAMAGE RESPONSE & PARP INHIBITION

FEBRUARY 2018
These slides summarize two BluePrint documents:

- DDR (DNA Damage Response): DDR BluePrint
- PARPi (PARP inhibition): PARPi BluePrint

These BluePrints have been developed under the guidance of a Steering Committee:

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DNA DAMAGE RESPONSE (DDR)
DNA damage can be sustained due to:

- **Endogenous factors**
  - Spontaneous or enzymatic reactions
  - Chemical modifications
  - Replication errors
  - Replication stress

- **Exogenous factors**
  - UV radiation
  - Ionizing radiation
  - Genotoxic chemicals

Repair pathways to overcome this are collectively referred to as: **DNA Damage Response**
## DNA REPAIR MECHANISMS

### THE MAIN DNA REPAIR PATHWAYS, THE TYPE OF DNA LESIONS THEY REPAIR AND THEIR FUNCTION

**DNA Repair Mechanisms:** the main DNA repair pathways, the type of DNA lesions they repair and their function

<table>
<thead>
<tr>
<th>DNA repair mechanism and type of lesion</th>
<th>Repair function</th>
</tr>
</thead>
</table>
| **Base Excision Repair (BER)** → Single strand breaks | • Spontaneous hydrolytic decay products  
• Oxidative and alkylating modifications to bases or the sugar phosphate backbone |
| **Nucleotide Excision Repair (NER)** → Bulky adducts | • Removes bulky DNA lesions formed by UV light, environmental mutagens and some cancer chemotherapeutic adducts (e.g. platinum compounds) |
| **Mismatch Repair (MMR)** → Mispaired bases | • Base-base mismatches and insertion/deletion mispairs generated during DNA replication and recombination or caused by oxidative DNA damage |
| **Homologous Recombination Repair (HRR)** → Double-strand breaks (DSB) → Inter/intra-strand cross links | • Repairs DSBs using as a template the undamaged homologous sequence provided by the “sister chromatid” (hence mostly error-free)  
• Involved in the recovery of stalled or broken replication forks during DNA replication |
| **Non-Homologous End Joining (NHEJ)** → Double-strand breaks | • Direct re-ligation of broken DNA molecules (without the requirement for a homologous template) |

BER, Base Excision Repair; NER, Nucleotide Excision Repair; MMR, Mismatch Repair; HRR, Homologous Recombination Repair; DSB, Double-strand breaks; NHEJ, Non-Homologous End Joining
REPLICATION STRESS: TYPE OF DNA DAMAGE OCCURRING DURING DNA REPLICATION

GENERATION OF ABBERRANT REPLICATION FORK STRUCTURES CONTAINING SINGLE-STRANDED DNA, MANIFESTED IN A NUMBER OF FORMS

- Limitation of essential replication factors
- Conflicts between replication and transcription
- Misincorporation of ribonucleotides
- DNA lesions
- Oncogene-induced replication stress
- Common fragile sites
- Nicks, gaps, and ssDNA
- Topoisomerase arrest
- Chromatin inaccessibility
- Unusual DNA structures

- If unrepaired, replication stress can lead to increased mutagenesis, ultimately resulting in genome instability – a hallmark of (pre-)cancerous cells

- Replication Stress Response: activation of DDR pathways preventing the collapse of the replication fork and subsequent generation of cytotoxic DNA Double Strand Breaks

DDR, DNA Damage Response; ssDNA, single-stranded DNA
DDR PLAYS AN IMPORTANT ROLE IN HEALTH AND DISEASE

Approximately 450 human DDR genes code for proteins with roles in physiological processes including:

- Immune receptor diversity
- Production of gametes for sexual reproduction
- Telomere homeostasis
- Aging

Deregulation of DDR is involved in the etiology of diseases such as:

- Genetic disorders
- Neurodegenerative disorders
- Immune pathologies
- Infertility
- Cardiovascular disease
- Metabolic syndrome
- Cancer
## EXAMPLES OF DDR GENES INVOLVED IN CANCER

<table>
<thead>
<tr>
<th>DNA repair mechanism</th>
<th>Gene examples</th>
<th>Cancer predisposing syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>BER</td>
<td>OGG1</td>
<td>Renal, breast and lung cancer</td>
</tr>
<tr>
<td></td>
<td>XRCC1</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>NER</td>
<td>ERCC1</td>
<td>Lung and skin cancer, and glioma</td>
</tr>
<tr>
<td></td>
<td>XP</td>
<td>Xeroderma pigmentosum predisposing to skin cancer. Also increased risk of bladder and lung cancer</td>
</tr>
<tr>
<td>MMR</td>
<td>MSH2, MLH1</td>
<td>Lynch syndrome predisposing to colorectal cancer as well as endometrial, ovarian, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain and skin cancer</td>
</tr>
<tr>
<td>HRR</td>
<td>BRCA1, BRCA2</td>
<td>Increased risk of breast, ovarian, prostate, pancreatic, as well as gastrointestinal and haematological cancer, and melanoma</td>
</tr>
<tr>
<td></td>
<td>FANC</td>
<td>Group of proteins associated with Fanconi anaemia predisposing to squamous cell carcinomas and acute myeloid leukaemia (e.g. FANCA, FANCB)</td>
</tr>
<tr>
<td>NHEJ</td>
<td>KU70</td>
<td>Breast, colorectal and lung cancer</td>
</tr>
<tr>
<td></td>
<td>KU80</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Cell cycle checkpoints</td>
<td>ATM</td>
<td>Ataxia-telangiectasia predisposing to leukaemia, breast and pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td>ATR</td>
<td>Leukaemia, lymphoma, gastric and endometrial cancer</td>
</tr>
</tbody>
</table>

DDR, DNA Damage Response; BER, Base Excision Repair; NER, Nucleotide Excision Repair; MMR, Mismatch Repair; HRR, Homologous Recombination Repair; NHEJ, Non-Homologous End Joining
DDR DEREGULATION MAY LEAD TO CANCER THROUGH VARIOUS MECHANISMS

• **Dysregulation of one or more DDR pathways** driving genetic instability; e.g. by BRCA1/2 mutation

• **Increased levels of replication stress** leading to increased mutagenesis; e.g. by overexpression of oncogenes such as cyclin E, c-Myc or K-Ras

• **Increased levels of endogenous damage** generated by high ROS

• Any combination of the above, and/or sustained by the application of anticancer therapies
DDR CAN BE EXPLOITED IN CANCER THERAPY

CELL CYCLE AND DDR TARGETING: THREE KEY CELL CYCLE CHECKPOINTS AND ASSOCIATED PROTEINS ARE TARGETED BY SMALL MOLECULE INHIBITORS

**G2/M Checkpoint DDR Targets:** CHK1, MYT1, WEE1

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

**G1/S Checkpoint DDR Targets:** ATM, CHK2, p53

**Maximize Damage**

**Prevent Repair**

**Ensure the maximum amount of DNA damage is taken into mitosis**

**DDR-targeting agents:** maximize DNA damage in G1 and S-phase & prevent repair in G2

DDR, DNA Damage Response
SYNTHETIC LETHALITY

- When one DNA repair pathways is defective, cells can repair DNA damage by switching to an alternative repair mechanism.
- **Cells are unable to survive when** one mechanism is **defective** (e.g. BRCA mutation) and another is **blocked** by pharmacological inhibition (PARP inhibition).

BRCA, Breast Cancer Susceptibility Protein; PARP, Poly(ADP-ribose) Polymerase
DDR: RAPIDLY EMERGING AND PROMISING AREA FOR FUTURE ANTICANCER THERAPY

• Efficacy of DDR inhibitors may increase when combined with other DNA damaging agents
• The hope is that DDR inhibitors will find further use in clinical practice, in addition to or replacing chemotherapy
• Combinations of multiple DDR inhibitors or combining DDR inhibitors with antiangiogenic agents or immune checkpoint inhibitors pose interesting novel strategies
REFERENCES

• O’Connor MJ. Targeting the DNA Damage Response in Cancer. Mol Cell. 2015;60(4):547-60
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ATM</td>
<td>Ataxia telangiectasia mutated kinase</td>
</tr>
<tr>
<td>LOH</td>
<td>Loss of heterozygosity</td>
</tr>
<tr>
<td>ATR</td>
<td>Ataxia-and Rad-related kinase</td>
</tr>
<tr>
<td>LST</td>
<td>Large-scale state transitions</td>
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<tr>
<td>ATRi</td>
<td>Ataxia-and Rad-related kinase inhibitor</td>
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<td>MLH1</td>
<td>MutL homologue 1</td>
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<td>BER</td>
<td>Base excision repair</td>
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<tr>
<td>MMR</td>
<td>Mismatch repair</td>
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<tr>
<td>BIR</td>
<td>Break-induced replication</td>
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<tr>
<td>MSH2</td>
<td>MutS protein homolog 2</td>
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<td>BRCA1/2</td>
<td>Breast cancer 1/2 susceptibility protein</td>
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<tr>
<td>NER</td>
<td>Nucleotide excision repair</td>
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<td>Chk1/2</td>
<td>Checkpoint kinase 1/2</td>
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<tr>
<td>NHEJ</td>
<td>Non-homologous end joining</td>
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<td>c-MYC</td>
<td>Myc proto-oncogene</td>
</tr>
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<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
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<td>Chk2</td>
<td>Checkpoint kinase 2</td>
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<td>OGG1</td>
<td>8-Oxoguanine glycosylase</td>
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<tr>
<td>DDR</td>
<td>DNA damage response</td>
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<td>PARP</td>
<td>Poly(ADP-ribose) polymerase</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<td>PARPi</td>
<td>Poly(ADP-ribose) polymerase inhibitor</td>
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<td>DNA-PK</td>
<td>DNA-dependent protein kinase</td>
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<td>RAD51</td>
<td>DNA repair protein</td>
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<tr>
<td>DSBs</td>
<td>Double strand breaks</td>
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<td>ROS</td>
<td>Reactive Oxygen Species</td>
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<tr>
<td>ERCC1</td>
<td>ERCC excision repair 1</td>
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<tr>
<td>RPA</td>
<td>Replication protein A</td>
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<td>FANC</td>
<td>Fanconi anemia complementation groups</td>
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<td>SCLC</td>
<td>Small cell lung cancer</td>
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<td>G1 (phase)</td>
<td>Gap/growth phase 1</td>
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<tr>
<td>ssDNA</td>
<td>Single-stranded DNA</td>
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<td>G2 (phase)</td>
<td>Gap/growth phase 2</td>
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<tr>
<td>TAI</td>
<td>Telomeric allelic imbalance</td>
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<tr>
<td>H2AX</td>
<td>Variant of histone H2</td>
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<tr>
<td>TLS</td>
<td>Translesion synthesis</td>
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<tr>
<td>HRR</td>
<td>Homologous recombination repair</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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<td>IHC</td>
<td>Immunohistochemistry</td>
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<td>WEE1</td>
<td>WEE1 G2 checkpoint kinase</td>
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<td>K-Ras</td>
<td>Ras proto-oncogene</td>
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<td>XP</td>
<td>Xeroderma pigmentosum</td>
</tr>
<tr>
<td>XRCC1</td>
<td>X-ray repair cross-complementing protein 1</td>
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</table>
PARP INHIBITION
(PARPi)
DNA damage is detected by PARP1, triggering its activation and cleavage of NAD+ generating nicotinamide and ADP-ribose.

Successive addition of ADP-ribose units results in PAR polymers adjacent to the DNA breaks.

These highly negatively charged polymers form a scaffold that recruits critical proteins for DNA repair.
PARP inhibitors act by **inhibiting** the enzymatic activity, and by **trapping** PARP on DNA.

In HRR deficient cells, trapped PARP results in **replication fork collapse** and finally **cell death**.
THREE PARP INHIBITORS APPROVED FOR CLINICAL USE IN OVARIAN CANCER

<table>
<thead>
<tr>
<th>PARPi</th>
<th>Approval Indication</th>
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</table>
| Olaparib*        | • **EMA (Dec 2014)**: As monotherapy for maintenance treatment of platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous ovarian cancer patients who are in response (complete response or partial response) to platinum-based chemotherapy.  
• **FDA (Dec 2014)**: As monotherapy for the treatment of germline BRCA1/2 mutated (as detected by an FDA-approved test) advanced ovarian cancer patients that have been treated with three or more prior lines of chemotherapy (capsule formulation).  
• **FDA (Aug 2017)**: As maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy (tablet formulation).  
• **FDA (Jan 2018)**: For use in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been previously treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR+ breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Patients are selected for therapy based on an FDA-approved CDx. |
| Rucaparib        | • **FDA (Dec 2016)**: As monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated with advanced ovarian cancer who have been treated with two or more chemotherapies (patient selection using an FDA-approved CDx for Rubraca™).                                                                                                                                                                                                 |
| Niraparib        | • **FDA (Mar 2017)**: As monotherapy for maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, whose tumours have a complete or partial response to platinum-based chemotherapy.  
• **EMA (Sept 2017)**: As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. |

gBRCAm, germline BRCA-mutated; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; CDx, companion diagnostic
Clinical trials with PARPi have implemented intermediate clinical endpoints, complementing PFS in determining efficacy of therapies in settings with prolonged PFS or with post-progression survival benefit in multiple subsequent lines of therapies.

PFS, Progression Free Survival; TFST, Time to First Subsequent Therapy; PFS2, Progression Free Survival 2; TSST, Time to Second Subsequent Therapy; OS, Overall Survival; PARPi, Poly(ADP-ribose) Polymerase inhibitor; Tx, treatment

Diagram adapted from Matulonis et al., Cancer 2015
In advanced ovarian cancer olaparib, niraparib and rucaparib display similar efficacy, the magnitude of this benefit may depend on:

- In the **maintenance setting**: existence of a germline/somatic BRCA1/2 mutation versus absence of any homologous recombination deficiency

- In the **monotherapy setting**: on number of previous lines of treatment received

PARP, Poly(ADP-ribose) Polymerase; BRCA, Breast Cancer Susceptibility Protein
Efficacy of PARP inhibitors in breast cancer

OlympiAD: OLAPARIB IN METASTATIC BREAST CANCER PATIENTS WITH gBRCA MUTATION

<table>
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<tr>
<th></th>
<th>ORR (%)</th>
<th>Median PFS (months)</th>
<th>PFS2 (months)</th>
<th>Grade ≥3 AEs (%)</th>
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</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>59.9</td>
<td>7.0</td>
<td>13.2</td>
<td>36.6</td>
</tr>
<tr>
<td>Treatment of Physician's Choice</td>
<td>28.8</td>
<td>4.2</td>
<td>9.3</td>
<td>50.5</td>
</tr>
<tr>
<td>HR</td>
<td>–</td>
<td>0.58; P=0.0009</td>
<td>0.57; P=0.0033</td>
<td>–</td>
</tr>
</tbody>
</table>

In January 2018, the FDA approved olaparib as monotherapy for the treatment of patients with germline BRCA1/2 metastatic breast cancer after chemotherapy or endocrine treatment using an FDA-approved companion diagnostic.

AEs, Adverse Events; HR, Hazard Ratio; ORR, Objective Response Rate; PFS, Progression Free Survival; TPC, Treatment of Physician’s Choice; gBRCA, germline Breast Cancer Susceptibility Protein; FDA, US Food and Drug Administration

Robson et al., N Engl J Med 2017
ALL APPROVED PARPi CARRY A SIMILAR SAFETY PROFILE

<table>
<thead>
<tr>
<th>AE Preferred Term</th>
<th>Olaparib Study 19(1) (400 mg bid capsule)</th>
<th>Niraparib SOLO2(2) (300 mg bid tablet)</th>
<th>Niraparib NOVA(3) (300 mg od)</th>
<th>Rucaparib ARIEL2(4) (600 mg bid)</th>
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<tbody>
<tr>
<td>Anaemia</td>
<td>21 (6)</td>
<td>44 (20)</td>
<td>50 (25)</td>
<td>37 (19)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (4)</td>
<td>20 (5)</td>
<td>30 (20)</td>
<td>18 (7)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>4 (1)</td>
<td>8 (0)</td>
<td>61 (34)</td>
<td>28 (5)</td>
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<tr>
<td>Nausea</td>
<td>71 (2)</td>
<td>76 (3)</td>
<td>74 (3)</td>
<td>75 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>63 (9)</td>
<td>66 (4)</td>
<td>60 (8)</td>
<td>69 (7)</td>
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<tr>
<td>Vomiting</td>
<td>35 (2)</td>
<td>37 (3)</td>
<td>34 (2)</td>
<td>37 (4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>27 (2)²</td>
<td>33 (1)</td>
<td>32 (1)</td>
<td></td>
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<tr>
<td>Dysgeusia</td>
<td>–</td>
<td>27 (0)</td>
<td>10 (0)</td>
<td>39 (0)</td>
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<tr>
<td>Headache</td>
<td>–</td>
<td>25 (1)</td>
<td>26 (0)</td>
<td>18 (&lt;1)</td>
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<tr>
<td>Decreased appetite</td>
<td>–</td>
<td>22 (11)</td>
<td>25 (0)</td>
<td>23 (1)</td>
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<tr>
<td>Constipation</td>
<td>–</td>
<td>21 (0)</td>
<td>40 (1)</td>
<td>37 (2)</td>
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<td>Transaminase elevation</td>
<td>–</td>
<td>5</td>
<td>–</td>
<td>34 (10)</td>
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<tr>
<td>Hypertension</td>
<td>–</td>
<td>–</td>
<td>19 (8)</td>
<td>–</td>
</tr>
<tr>
<td>Hypotension</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>MDS/AML</td>
<td>2⁶</td>
<td>2⁷</td>
<td>1⁸</td>
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</table>

PARPi HAVE SHOWN ACTIVITY IN CANCER TYPES OTHER THAN OVARIAN CANCER

PARP, Poly(ADP-ribose) Polymerase
PARPi ARE FIRMLY ESTABLISHED AS EFFECTIVE THERAPIES FOR SELECTED PATIENTS WITH OVARIAN CANCER

- The first PARP inhibitor is now also approved for the treatment of breast cancer.

- The therapeutic reach of PARPi is likely to expand to include other cancer types in the near future (prostate cancer).

- Evolving biological insight within the overall context of DDR, replication stress, and immunological responses will allow us to use these agents in the most appropriate clinical setting to improve patient care.

PARPi, Poly(ADP-ribose) Polymerase inhibitor
REFERENCES

# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia telangiectasia mutated kinase</td>
</tr>
<tr>
<td>ATR</td>
<td>Ataxia-and Rad-related kinase</td>
</tr>
<tr>
<td>BER</td>
<td>Base excision repair</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>Breast cancer 1/2 susceptibility protein</td>
</tr>
<tr>
<td>CDx</td>
<td>Companion diagnostic</td>
</tr>
<tr>
<td>Chk2</td>
<td>Checkpoint kinase 2</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
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<tr>
<td>DDR</td>
<td>DNA damage response</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DSB</td>
<td>Double strand break</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (US)</td>
</tr>
<tr>
<td>gBRCA</td>
<td>Germline BRCA1 and/2 mutation</td>
</tr>
<tr>
<td>g/sBRCA</td>
<td>Germline/somatic BRCA1 and/2 mutation</td>
</tr>
<tr>
<td>HRD</td>
<td>Homologous Recombination Deficiency</td>
</tr>
<tr>
<td>HRR</td>
<td>Homologous Recombination Repair</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>LOH</td>
<td>Loss of heterozygosity</td>
</tr>
<tr>
<td>MMEJ</td>
<td>Microhomology-mediated end joining</td>
</tr>
<tr>
<td>NAD+</td>
<td>Nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NHEJ</td>
<td>Non-homologous end joining</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective Response Rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PALB2</td>
<td>Partner and localizer of BRCA2</td>
</tr>
<tr>
<td>PAR</td>
<td>Poly(ADP-ribose)</td>
</tr>
<tr>
<td>PARPi</td>
<td>Poly(ADP-ribose) polymerase inhibitor</td>
</tr>
<tr>
<td>pCR</td>
<td>Pathological complete response</td>
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<tr>
<td>PD-1</td>
<td>PDCD1, programmed cell death protein 1</td>
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<tr>
<td>PD-L1</td>
<td>Programmed cell death protein-ligand 1</td>
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<td>PFS</td>
<td>Progression free survival</td>
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<td>pgP</td>
<td>P-glycoprotein</td>
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<td>RAD51</td>
<td>RAD51 recombinase</td>
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<tr>
<td>TFST</td>
<td>Time to first subsequent therapy or death</td>
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<tr>
<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
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<tr>
<td>TLS</td>
<td>Translesional synthesis</td>
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<td>TSST</td>
<td>Time to second subsequent therapy or death</td>
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