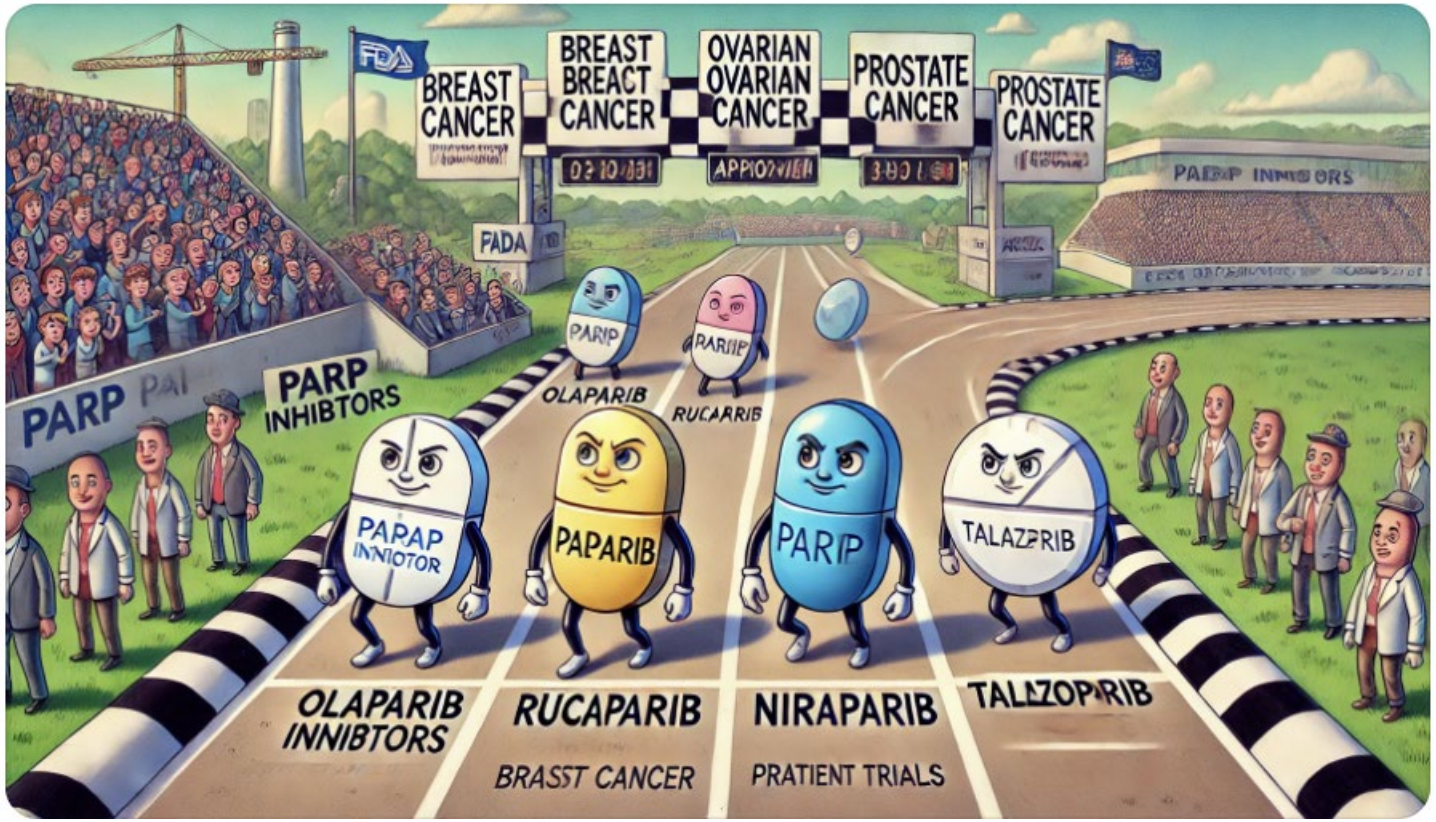
PARP (poly-ADP ribose polymerase) inhibitors

歷史發展晴天與烏雲

Senior clinical pharmacist

Lihua Fang

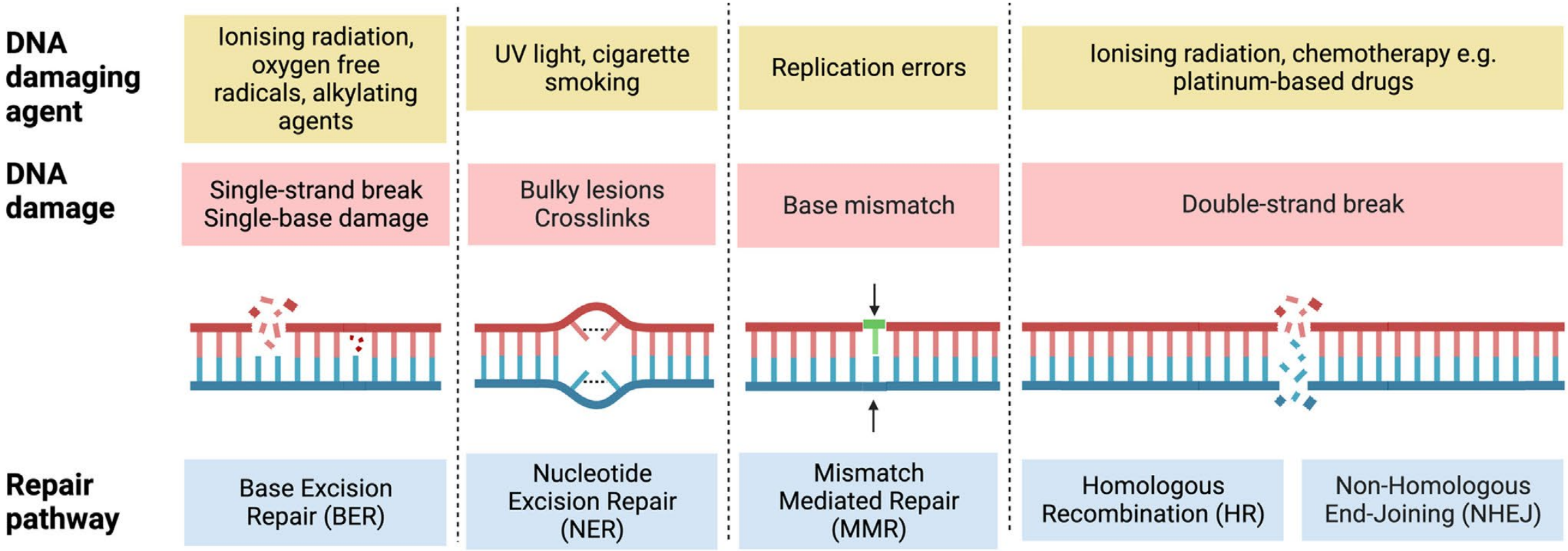


Outlines

- **Mechanism of Action**
  - Role of PARP (Poly ADP-ribose polymerase) in cellular functions
  - PARP inhibitors in cells deficient in other DNA repair pathways
- **Clinical Applications (trials)**
  - Ovarian cancer, Breast cancer, Prostate cancer, Pancreatic cancer
  - Comparative analysis of different PARP inhibitors based on clinical trial data.
- **Combination Therapies and Future Directions**
  - Exploration of combination strategies with other treatments (e.g., chemotherapy, radiation, immune checkpoint inhibitors).
- **Conclusion**
  - Summary of the impact of PARP inhibitors on cancer treatment.

DNA Damage Response

DNA repair pathways according to the type of damage.
Deficiency in DNA repair pathways has been identified as an Achilles heel of cancer cells BRCA1 and BRCA2 are tumor suppressor proteins that work at different stages in the DNA damage and repair pathways. Their loss of function leads to homologous recombination repair (HRR) deficiency.



K.D. Doig, A.P. Fellowes and S.B. Fox / Mod Pathol 36 (2023) 100049

Homologous recombination pathways

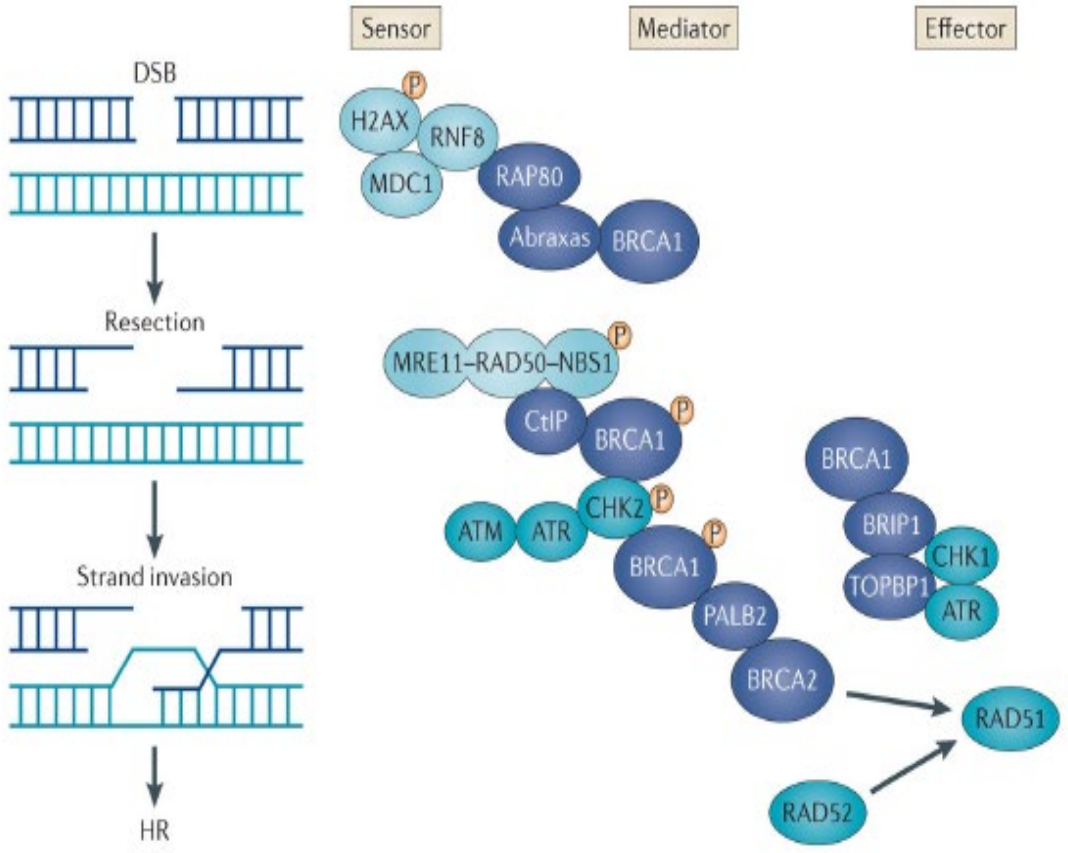
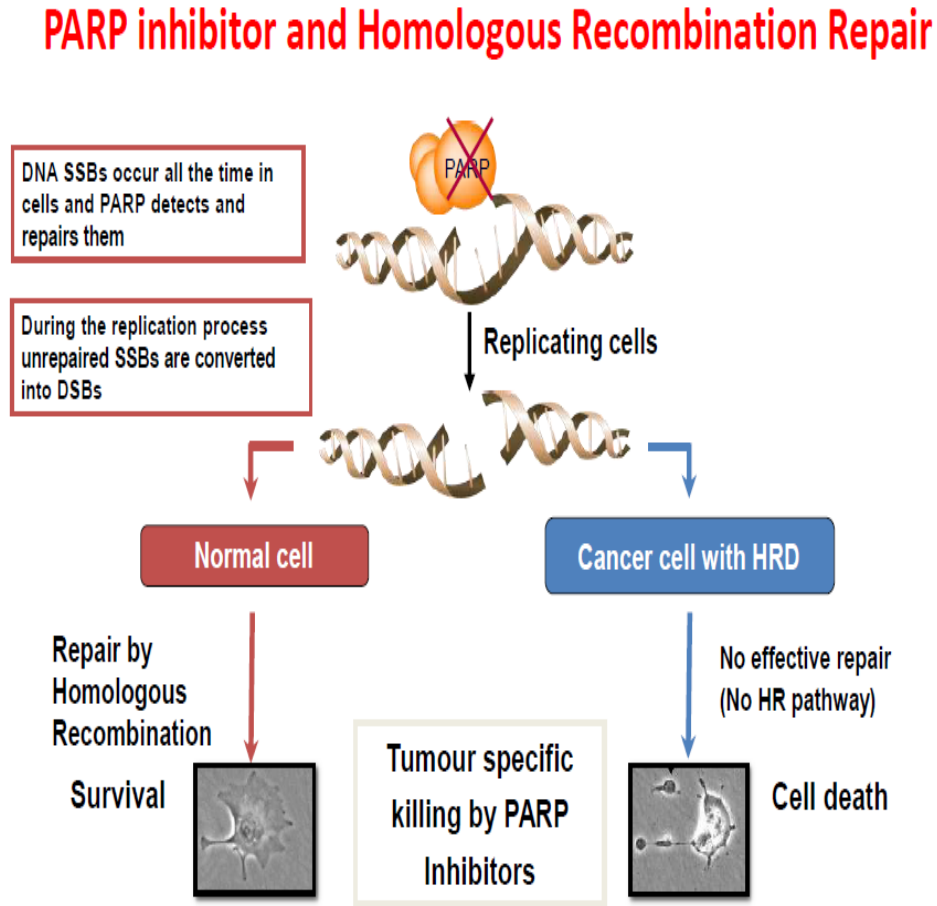


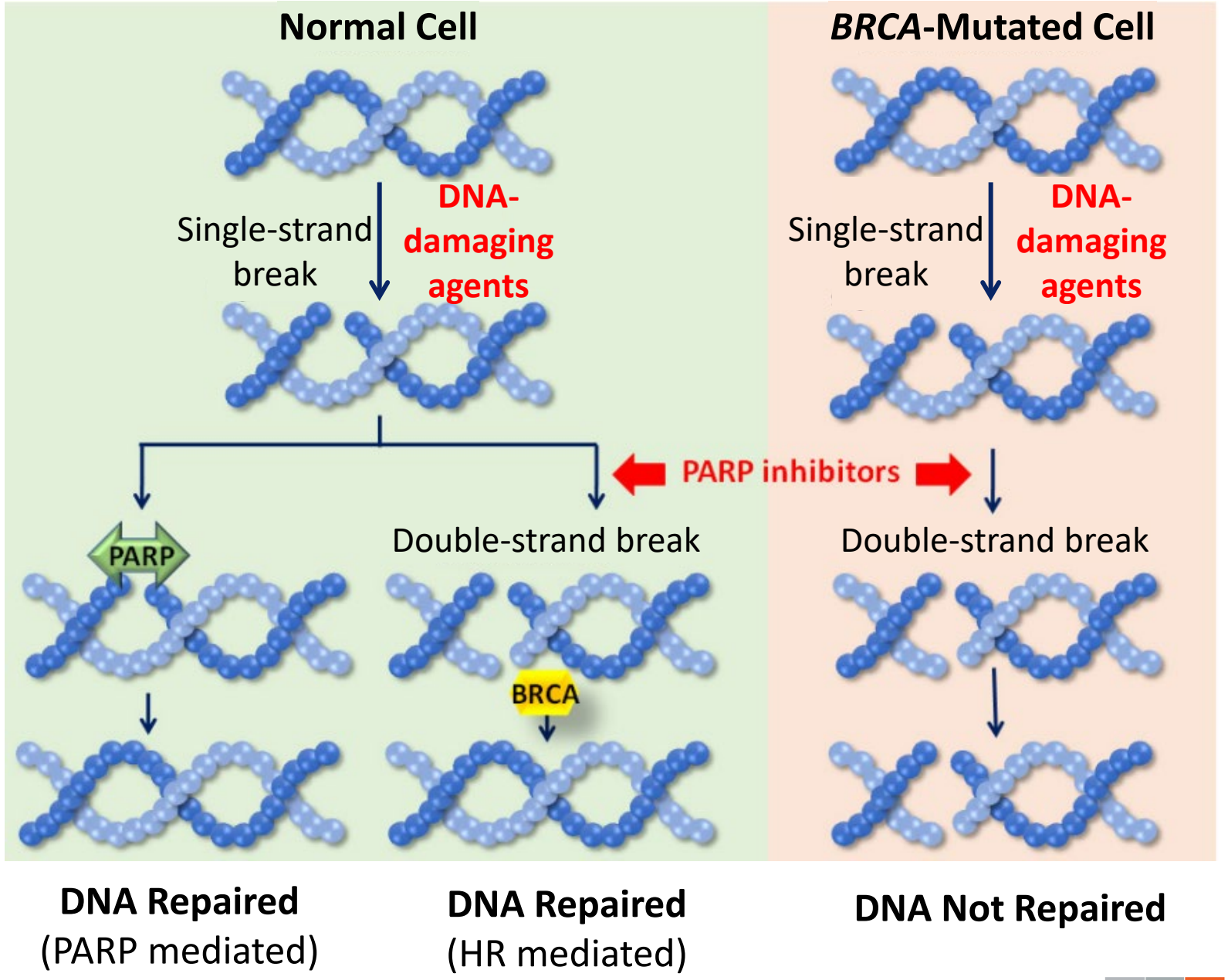
Figure 1. Molecular mechanisms of the DNA damage response



Nat Rev Cancer. 2012 Jan; 12(1): 68–78

Cells With HRD Are Sensitive to PARP Inhibition

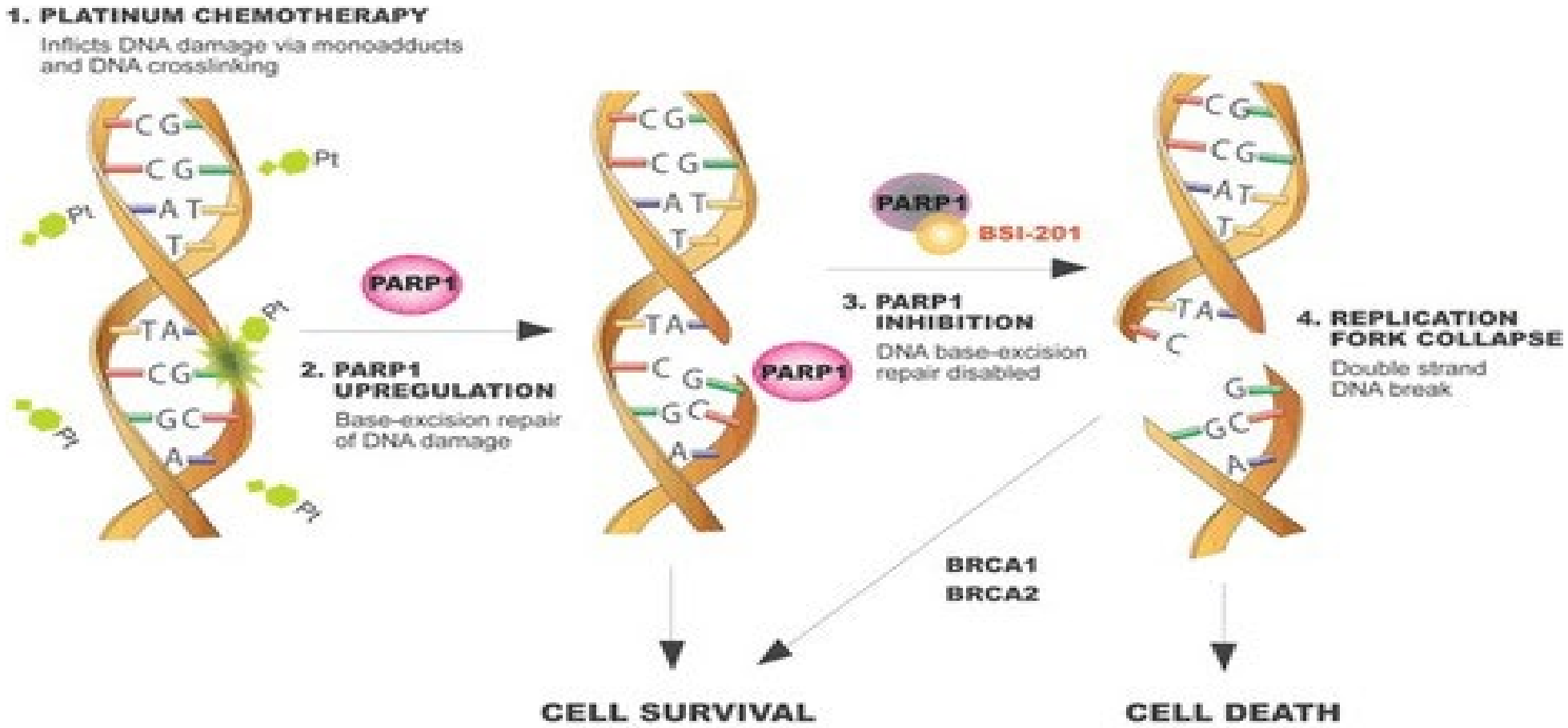
- Dual cytotoxic mechanisms of PARP enzyme inhibition by PARPi
  - Base excision repair blockade via catalytic inhibition
  - PARP trapping on DNA, which induces double-strand breaks
- Cells with HRD are unable to repair dsDNA breaks using homology-directed repair



Slide credit: clinicaloptions.com

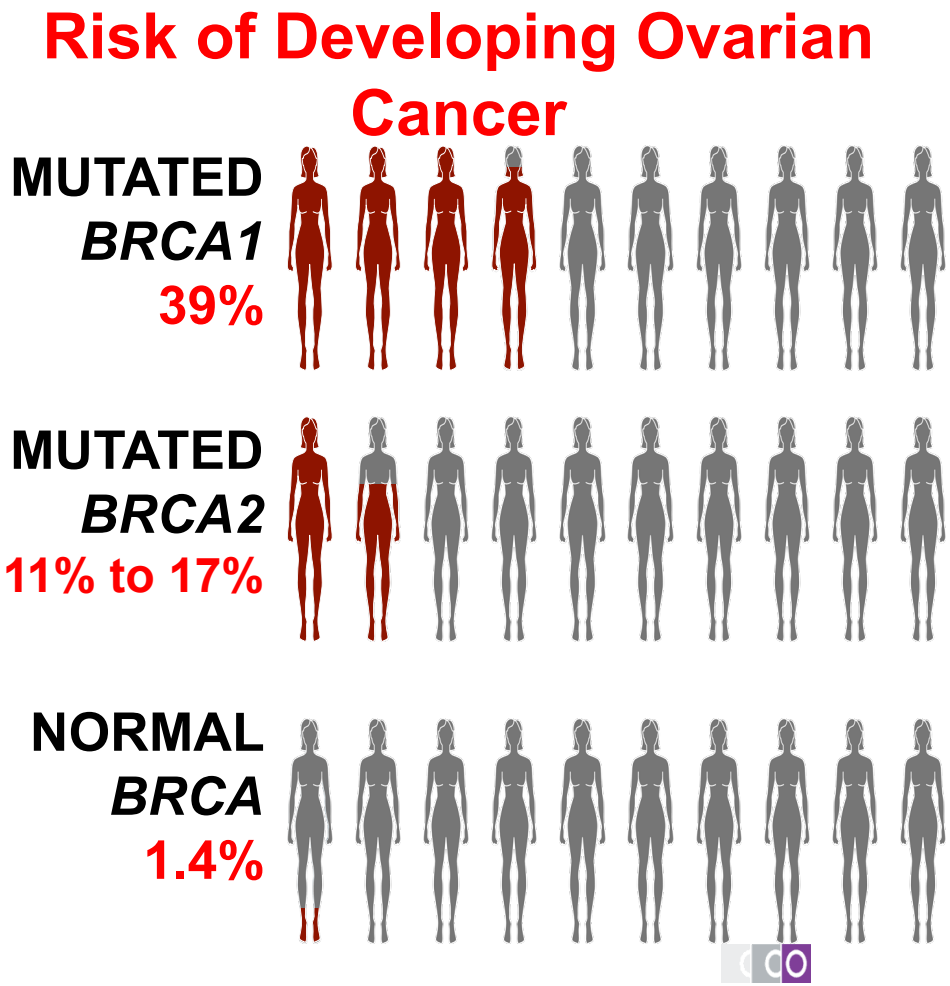
PARP (poly-ADP ribose polymerase)

Olaparib 2014, Niraparib 2016, Rucaparib 2017, Talazoparib 2018



Overview of BRCA1 and BRCA2

- Enzymes that repair double-stranded DNA breaks
- Mutations in *BRCA1* or *BRCA2*
  - Increased risk of breast and ovarian cancer
  - Prognostic marker
  - Predictive biomarker for PARP inhibitor activity



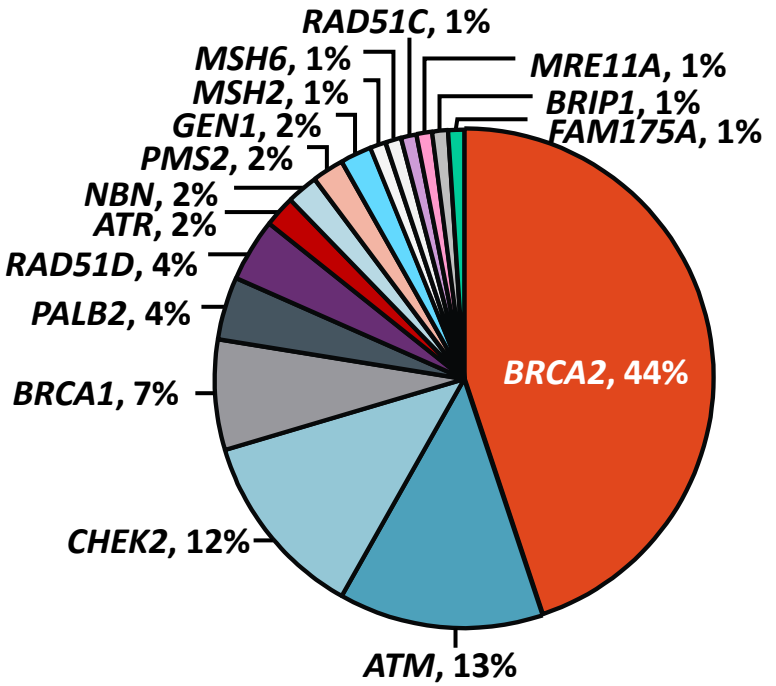
www.acog.org/Patients/FAQs/BRCA1-and-BRCA2-Mutations

Slide credit: clinicaloptions.com

DDR (DNA damage response) Mutations in Prostate Cancer

- Mutations may be either germline or somatic (tumor)
  - Somatic DNA testing results may change over time due to genetic instability of tumor DNA[1]
- 23% of metastatic castration-resistant prostate cancers have DNA repair alterations[2]
- 11.8% of 692 men with metastatic prostate cancer had germline DNA repair defects[3]

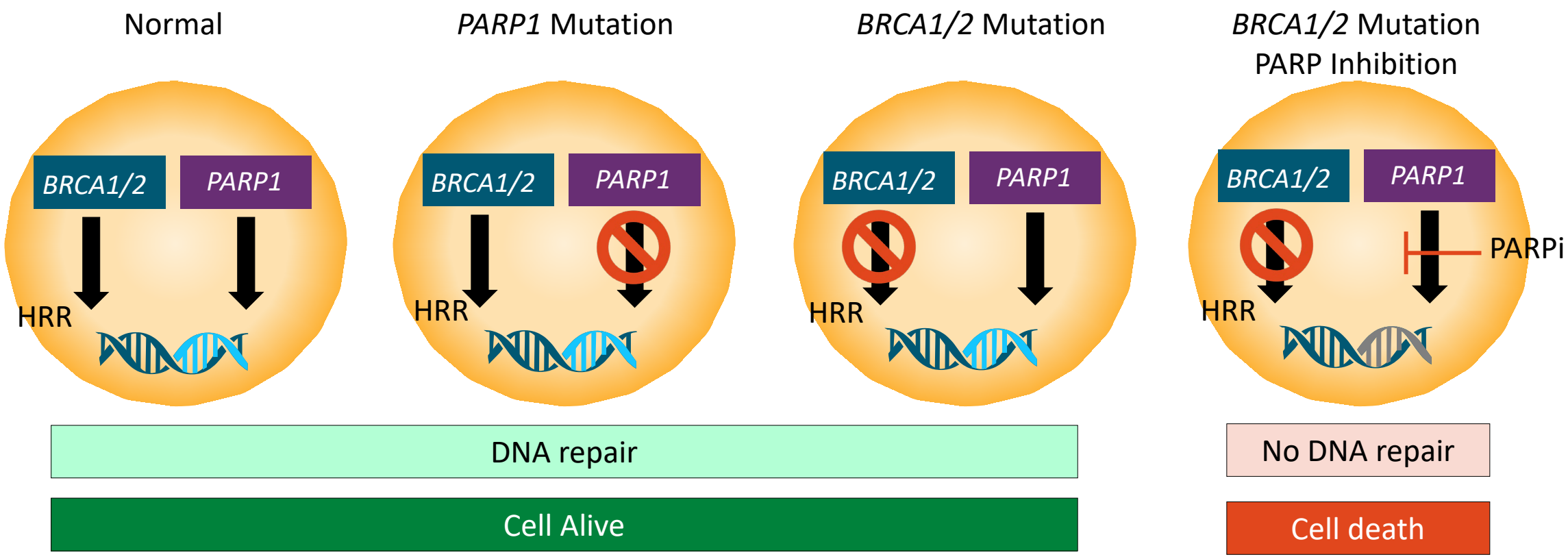
Distribution of Presumed Pathogenic Germline Mutations[3]



1. Friedlander. Am Soc Clin Oncol Edu Book. 2018;37:358.
2. Robinson. Cell. 2015;161:1215. 3. Pritchard. NEJM. 2016;375:443.

PARP Inhibitor mechanism: Synthetic Lethality (組合致死)

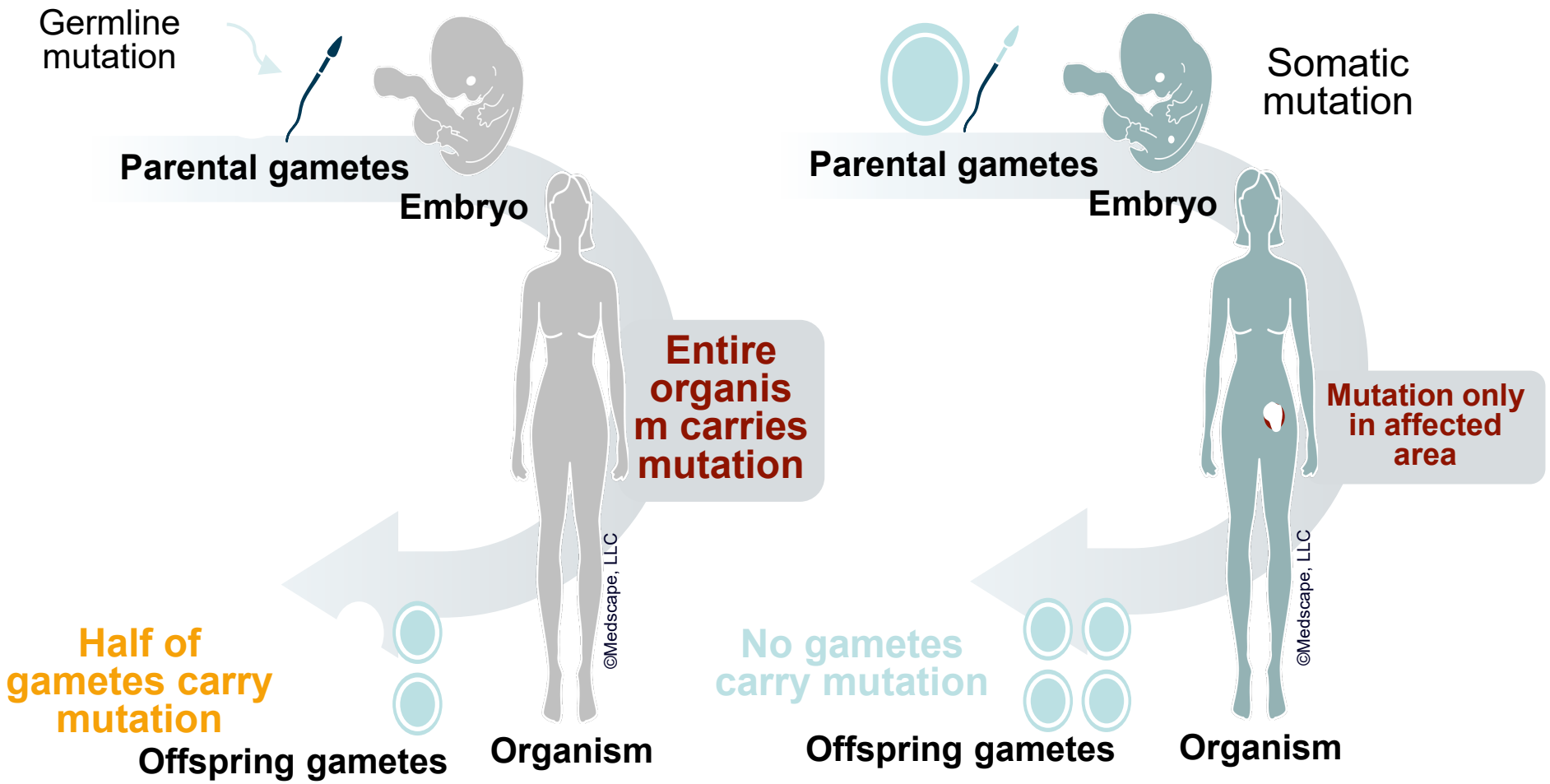
- Detection of DNA damage triggers activation of PI3K, ATM, ATR



Gourley. J Clin Oncol. 2019;37:2257.

Slide credit: clinicaloptions.com

Germline vs Somatic Mutations



Germline mutations are inherited and found in all cells
Somatic mutations are not inherited and are found within the tumor

Slide credit: clinicaloptions.com

Human cancers arising in *BRCA1* or *BRCA2* mutation carriers

Cancer type	*BRCA1* mutations	*BRCA2* mutations	Notes
Breast	70–80% lifetime risk	50–60% lifetime risk	Breast and ovarian cancer is the dominant cancer predisposition in *BRCA1* and *BRCA2* mutation carriers. *BRCA1* mutation carriers develop breast and ovarian cancer at a younger age than *BRCA2* mutation carriers[113]
Ovarian	50% lifetime risk	30% lifetime risk	Breast and ovarian cancer is the dominant cancer predisposition in *BRCA1* and *BRCA2* mutation carriers. LOH of the wild-type BRCA allele is always found
Prostate	Ashkenazi Jewish founder mutations are associated with increased risk	20-fold increased risk	<1% of *BRCA2* mutation carriers have prostate cancer. Prostate cancer is even rarer in *BRCA1* mutation carriers, except in members of the Ashkenazi Jewish population with *BRCA1* mutations
Pancreatic	Anecdotal evidence and case reports only	Tenfold increased risk	<1% of *BRCA2* mutation carriers have pancreatic cancer. No incidence has been clearly documented in *BRCA1* mutation carriers
Gastric	None reported	Limited reports	It is unclear whether stomach cancer is associated with *BRCA2* mutations
Others	None reported	Brain, medulloblastoma, pharyngeal, CLL and AML	Fanconi anaemia subtype D1 (caused by *BRCA2* mutations) is associated with cancer of the central nervous system
Fallopian tube	Observed, but rare	Rare	This cancer type is like ovarian cancer, but it is a rare cancer overall and is still uncommon in BRCA mutation carriers

AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; LOH, loss of heterozygosity.

Nat Rev Cancer. 2012 Jan; 12(1): 68–78

Characteristics of *BRCA1*- and *BRCA2*-mutation-associated breast cancers

Phenotype	*BRCA1*	*BRCA2*	Notes
ER expression	Negative in 80–90%	Positive in 60–65%	One of the major mysteries to be solved
PR expression	Predominantly negative	Positive in the majority of cases	Less complete data relative to ER expression
ERBB2 amplification	Usually absent	~15% have amplification	*ERBB2* amplification can occur in BRCA mutation carriers
Early onset	Highly prevalent between 30 and 50 years of age	Less prevalent between 40 and 70 years of age	
Lobular cancers	Less likely	As frequent as in sporadic breast cancer (~15%)	
High grade	Likely	Common	More common than sporadic cancers
Basal markers	Frequent	Less common	Tumours have cytokeratin profile of basal or myoepithelial markers
HR function	Defective	Defective	Some debate over the frequency of LOH for the wild-type allele
Prognosis relative to sporadic cancer at the same stage	No difference overall. Local recurrence in the breast is increased with conservative surgery and radiation therapy	No difference	

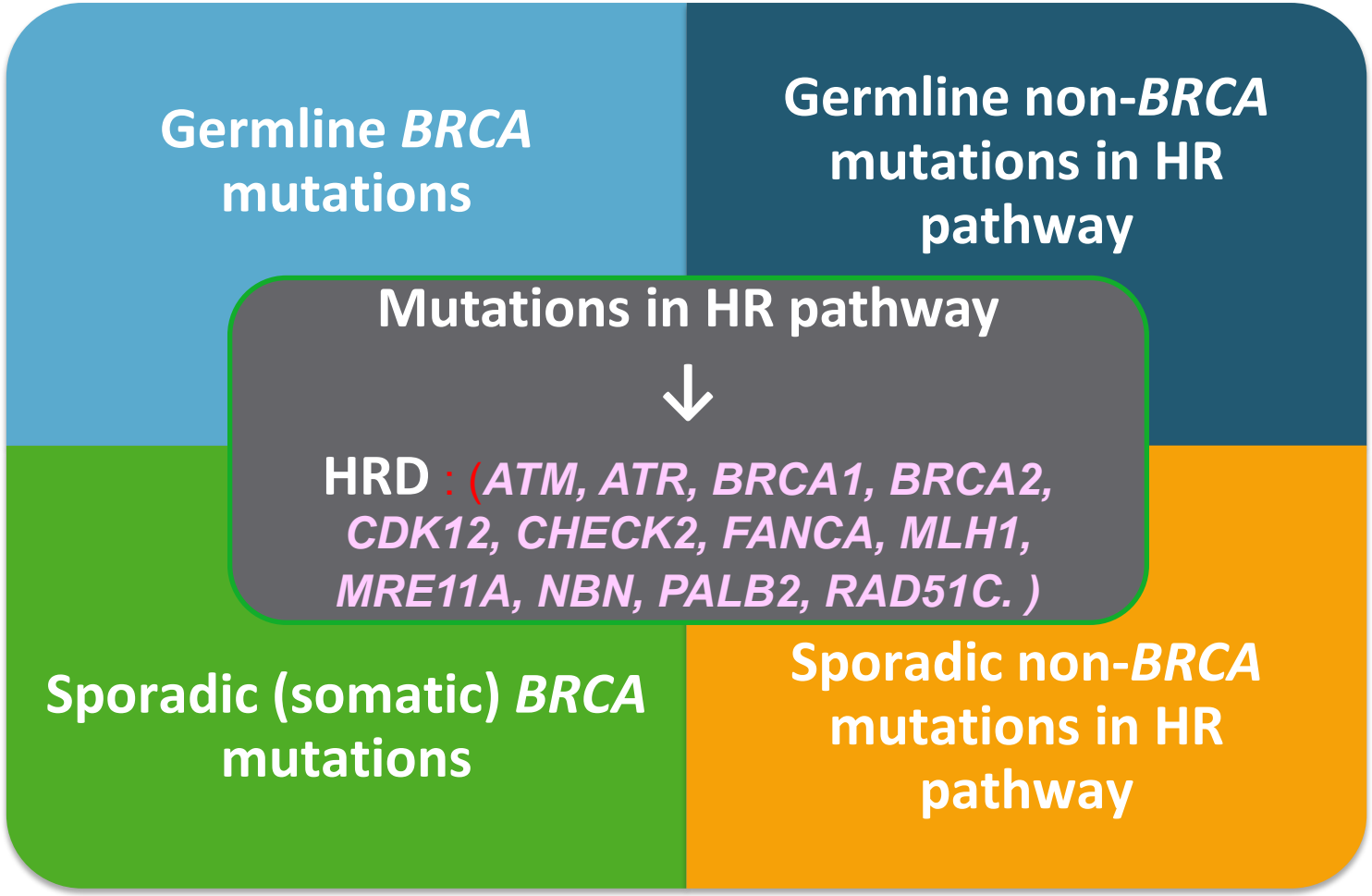
ER, oestrogen receptor; HR, homologous recombination; LOH, loss of heterozygosity; PR, progesterone receptor.

Nat Rev Cancer. 2012 Jan; 12(1): 68–78

Genetic Testing: Timing Recommendations

- Germline panel testing at diagnosis in all women with ovarian, peritoneal and fallopian tube cancer
- Somatic testing at recurrence
  - *BRCA*, HRD, MSI, etc

HRD and *BRCA* Mutations

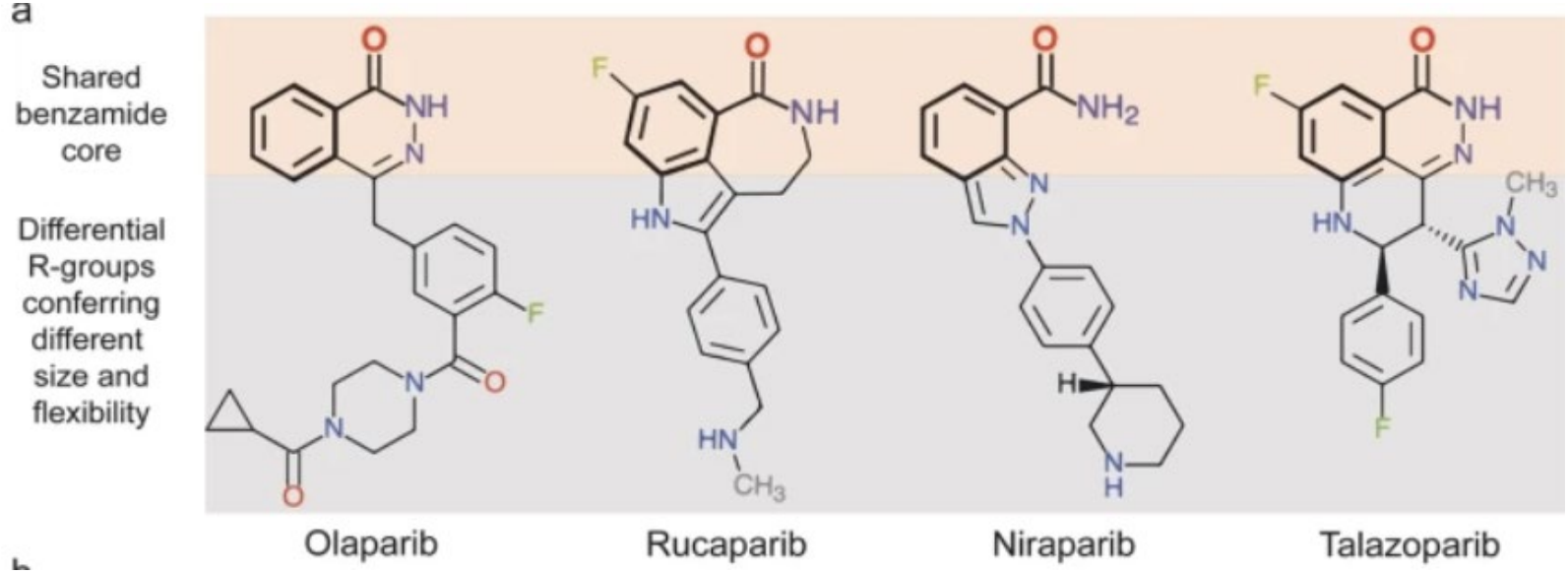


Slide credit: clinicaloptions.com

PARP inhibitors

Olaparib 2014, Niraparib 2016, Rucaparib 2017, Talazoparib 2018

- Olaparib has the broadest range of indications across different cancer types and was the first to market
- Rucaparib and Niraparib are mainly focused on ovarian cancer, with Niraparib also approved for prostate cancer in combination therapy.
- Talazoparib is specialized in breast cancer treatment and has a unique mechanism of action that enhances its potency.

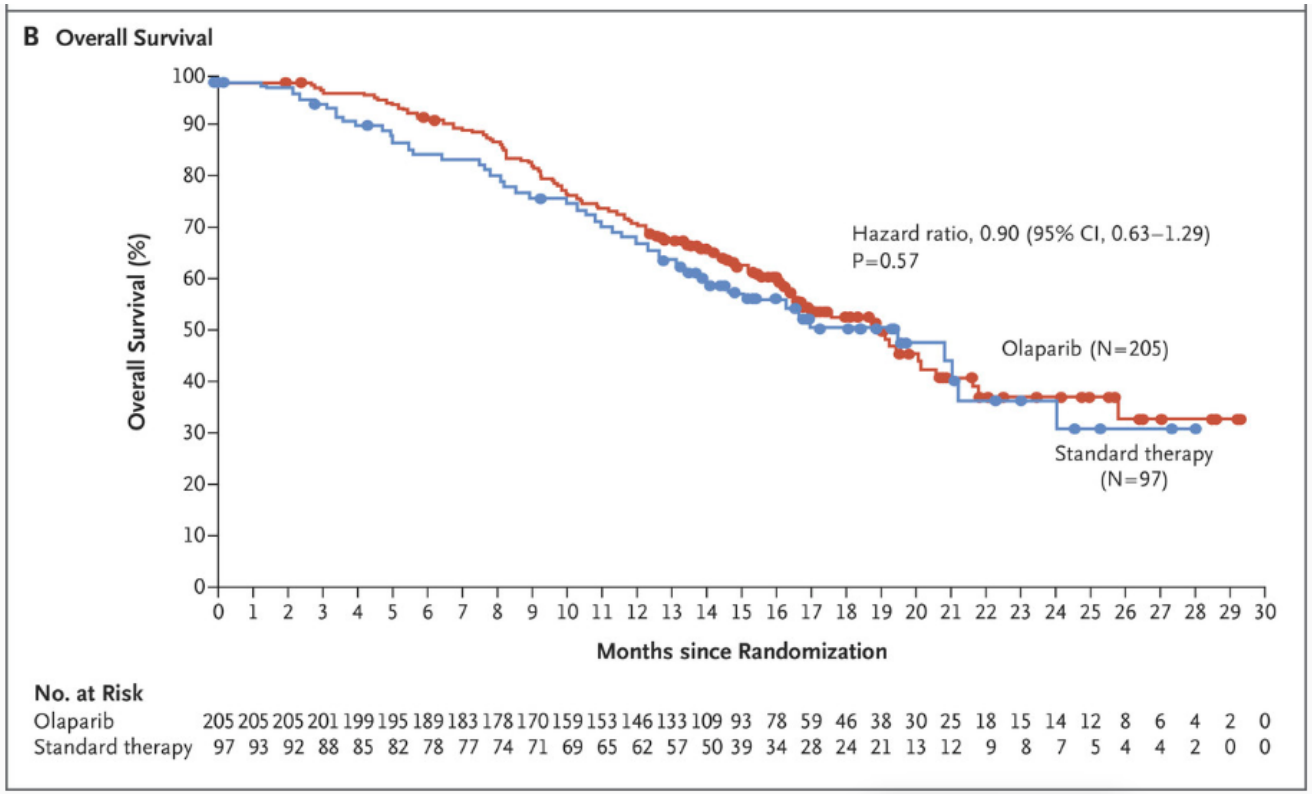


Sci Rep 10, 2585 (2020).

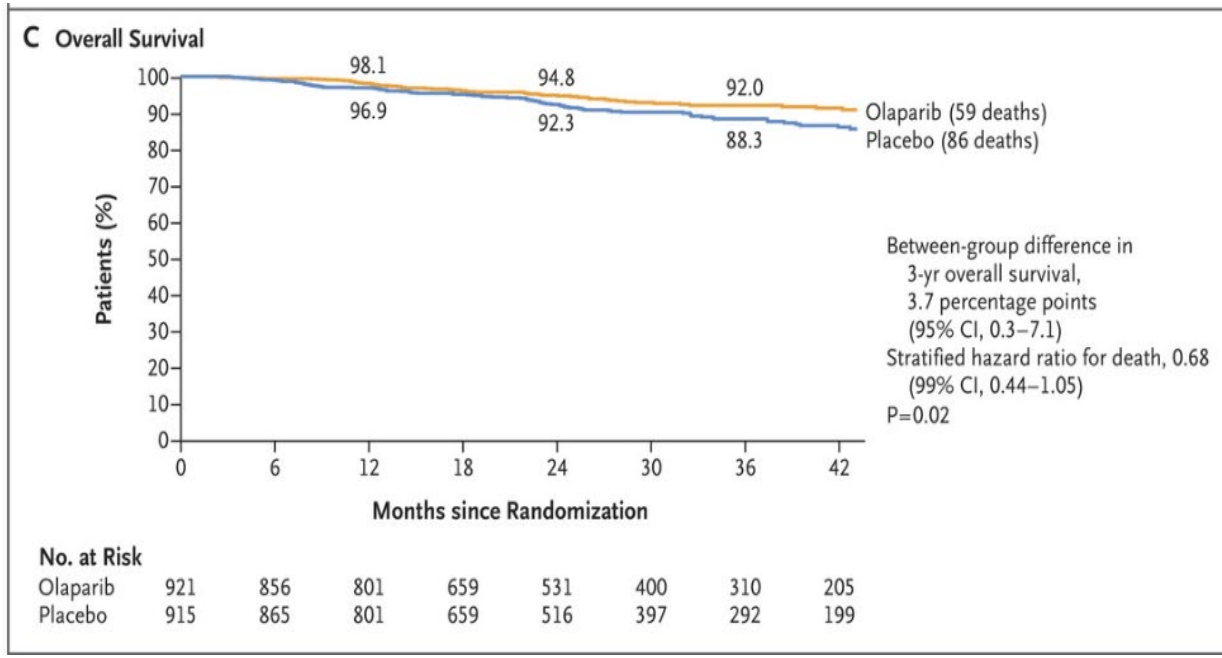
Olaparib (Lynparza, 令癌莎) 2014 先驅者
300 mg bid or 400mg bid

- Breast cancer, metastatic, HER2 (-), germline BRCA mutated
- Breast cancer, early, high risk, HER2 (-), germline BRCA mutated, adjuvant therapy
- Ovarian cancer, recurrent, BRCA mutated, maintenance therapy
- Ovarian cancer, advanced, BRCA mutated, first-line maintenance therapy
- Ovarian cancer, advanced, homologous recombination deficient positive, first-line maintenance therapy
- Pancreatic cancer, metastatic, germline BRCA mutated, first-line maintenance therapy
- Prostate cancer, metastatic, castration resistant, homologous recombination repair gene mutated
- Prostate cancer, metastatic, castration resistant, BRCA mutated (in combination with abiraterone and prednisone or prednisolone

Indication	Trial Name	Comparative Protocol	ORR	PFS	OS	ADR	Source
Breast Cancer (Metastatic, HER2-, gBRCA mutated)	OlympiAD Phase 3	Olaparib (pt :205) vs. Physician's choice chemotherapy (pts : 97)	59.9% (Olaparib) vs. 28.8% (Chemotherapy)	Median: 7.0 months (Olaparib) vs. 4.2 months (Chemotherapy)	not significantl between groups (P=0.57)	Nausea, anemia, fatigue, neutropenia, leukopenia	N Engl J Med. 2017;377(6):523-533.
Breast Cancer (Early, High Risk, HER2-, gBRCA mutated, Adjuvant)	OlympiA	pts :1836 Olaparib 1yr vs. Placebo		3-year invasive IDFS: 86% (Olaparib) vs. 77% (Placebo)	3-year OS: 87.5% (Olaparib) vs. 80.4% (Placebo) P<0.001	Nausea, fatigue, anemia, vomiting, headache, diarrhea, leukopenia, neutropenia	N Engl J Med 2021;384:2394-2405



N Engl J Med. 2017;377(6):523-533



N Engl J Med 2021;384:2394-2405

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

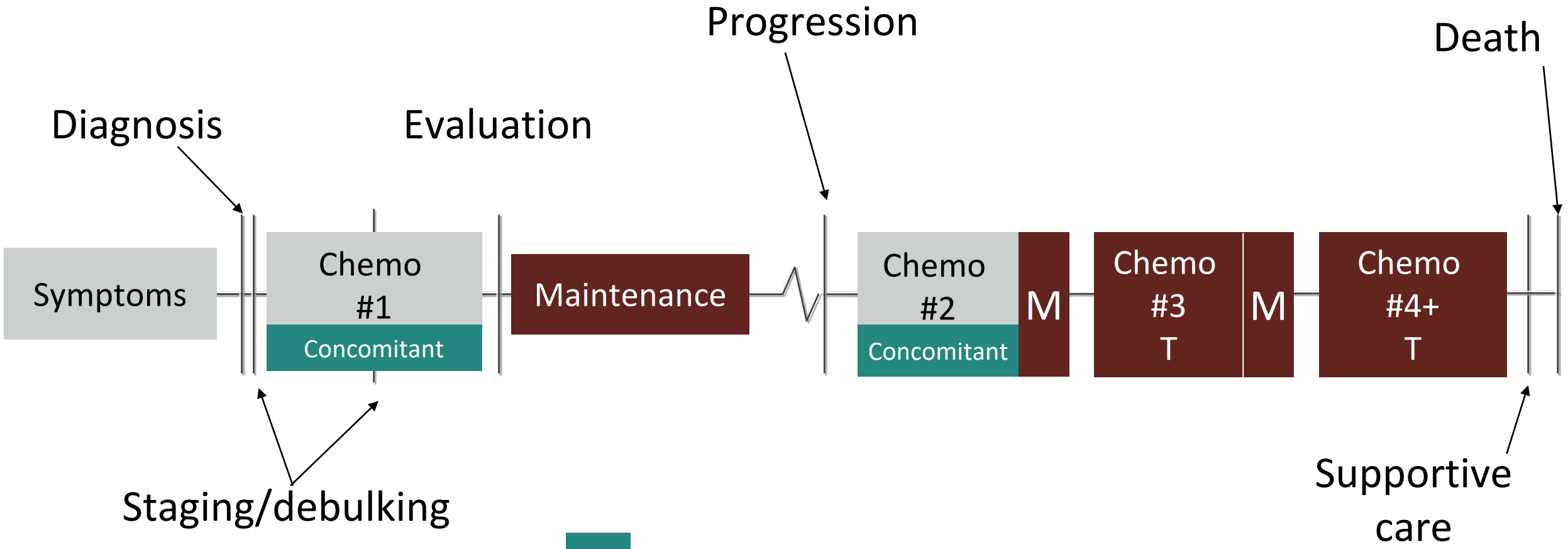
Adverse Events

Table 2. Summary of Adverse Events.*

Variable	Olaparib Group (N = 205)		Standard-Therapy Group (N = 91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

N Engl J Med 2017; 377:523-533

Current Treatment Landscape for PARPi in Ovarian Cancer



LaFargue. Lancet Oncol. 2019;20:e15.

Slide credit: clinicaloptions.com

Indication	Trial Name	Comparative Protocol	PFS (months)	OS	ADR	Source
Ovarian Cancer (Recurrent, BRCA mutated, Maintenance): Platinum-Sensitive	Study 19 Pts : 326	Olaparib 400mg bid vs. Placebo	Median: 8.4 (Olaparib) vs. 4.8 (Placebo)	No overall survival benefit P=0.75	Nausea, fatigue, vomiting, anemia	N Engl J Med 2012;366:1382-1392
Ovarian Cancer (Advanced, Homologous recombination deficient, First-line maintenance)	PAOLA-1 Pts: 806	Olaparib + Bevacizumab vs. Placebo + Bevacizumab 2 yrs	37.2 months (Olaparib) vs. 17.7 months With BRCA (HRD) mutation Without BRCA mutations (HRD) 28.1 vs. 16.6 months 5-year PFS 72% vs 28% with bevacizumab	5 yrs OS 88% vs 61%, (HR 0.31) No benefit HRD (-)	Hypertension, fatigue, anemia, nausea	N Engl J Med 2019;381:2416-2428 . Int J Gynecol Cancer 2023;0:1–9.
Ovarian Cancer (Advanced, BRCA mutated, First-line maintenance)	SOLO-1 Pts: 391 Platinum-based chemotherapy to maintenance for up to 2 years.	Olaparib 2 ys. (260 pts) vs Placebo (131 pts)	Median PFS : 56 months (Olaparib) vs. 13.8 months (Placebo) at 5 yrs	7 years OS 67.0% olaparib vs 46.5% (placebo)	Nausea, fatigue, anemia, abdominal pain, vomiting	J Clin Oncol 2023 Jan 20;41(3):609-617

PARP Inhibitors May Yield Rational Combination Strategies in prostate cancer

- Monotherapy

  Synthetic lethality

  - Post ARPi (ie, abiraterone, enzalutamide) +/- docetaxel in selected mCRPC (HRR+, particularly effective in *BRCA*m)

  PARP/AR crosstalk

- Combination with ARPi (abi + olaparib, abi + niraparib, enza + talazoparib) in 1st line mCRPC with HRR+ *and possibly all comers*
- Combination with radiation or radioligand therapy
- Combination with immunotherapy

  Other MOA

Agarwal. Eur J Cancer. 2023;192:113249. Marchetti. Cancers (Basel). 2022;14:907.
Maiorano. Crit Rev Oncol Hematol. 2023;192:104157.

FDA Indications for PARP Inhibitor Monotherapy in Prostate Cancer

Olaparib	Rucaparib
Deleterious/suspected deleterious germline or somatic **HRR gene–mutated** mCRPC that progressed following prior enzalutamide or abiraterone ▪Select using approved companion diagnostic **Approved HRR genes:** *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*	Deleterious ***BRCA* mutation–associated mCRPC** treated with AR-directed tx and taxane-based chemotherapy *(accelerated approval)* ▪Select using approved companion diagnostic **Approved genes:** *BRCA1* *BRCA2*

- Patients also should receive GnRH analogue or have had bilateral orchiectomy
- Continue PARP inhibitor until PD or unacceptable toxicity

Olaparib PI. Rucaparib PI. NCCN. Clinical practice guidelines in oncology: prostate cancer. v.4.2023. nccn.org.

FDA Indications for PARP Inhibitor Combinations in Prostate Cancer

Niraparib + AAP	Olaparib + AAP	Talazoparib + Enzalutamide
Adults with deleterious or suspected deleterious ***BRCA*-mutated mCRPC** ▪ Select using approved companion diagnostic **Approved genes:** *BRCA1* *BRCA2*	Adults with deleterious or suspected deleterious ***BRCA*-mutated mCRPC** ▪ Select using approved companion diagnostic **Approved genes:** *BRCA1* *BRCA2*	Adults with **HRR gene–mutated mCRPC** ▪ Select based on presence of HRR gene mutations ▪ Approved diagnostic <u>not</u> currently available **Approved HRR genes:** *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*

- Patients also should receive GnRH analogue or have had bilateral orchiectomy
- Continue PARP inhibitor until PD or unacceptable toxicity

Niraparib and abiraterone acetate PI. Olaparib PI. Talazoparib PI.

Slide credit: clinicaloptions.com

Indication	Trial Name	Comparative Protocol	Progression-Free Survival (PFS)	Overall Survival (OS)	Adverse Effects	Source
Pancreatic Cancer (Metastatic, germline BRCA (gBRCA) mutated, First-line maintenance)	POLO pts: 154	Pts: Olaparib vs. Placebo	Median: 7.4 months (Olaparib) vs. 3.8 months(Placebo) P =0.004	18.9 months vs. 18.1 months; P=0.68	Fatigue, nausea, abdominal pain, anemia	NEJ M 2019;381:317-327
Prostate Cancer (Metastatic, Castration resistant **Cohort A (pt 245) : at least one alteration in BRCA1, BRCA2, or ATM; cohort B (142 patients) had alterations in any of 12 other prespecified gene**	PROfound Pts: 384	Olaparib vs. Enzalutamide or Abiraterone	Median: 7.4 months (Olaparib) vs. 3.6 months; P<0.001)	Median: 18.5 months (olaparib vs 15.1 months in the control in Cohort A	Anemia, nausea, fatigue, decreased appetite	NEJM 2020;382:2091-2102
olaparib, with abiraterone and prednisone, for BRCA-mutated metastatic castration-resistant prostate cancer	PROpel 399 pts abiraterone+prednisolone ±olaparib (399 vs 397 pts (placebo)	Olaparib+abiraterone / prednisone vs Abiraterone+prednisolone		Median OS 42.1 (not reached) months vs 34.7 months (placebo) ; p=0.054).	anemia, fatigue, nausea, diarrhea, decreased appetite, lymphopenia, dizziness, and abdominal pain	Lancet Oncol . 2023 Oct;24(10):1094-1108

Treatment Options Across Disease States for Radiographic Metastatic Prostate Cancer

Hormone Sensitive ("Castration Sensitive")

ADT
Abiraterone
Enzalutamide
Apalutamide
Docetaxel + Abiraterone
Docetaxel + Darolutamide
Radiation

Hormone Resistant ("Castration Resistant")

ADT	
Cabazitaxel	Niraparib + Abiraterone (1L)
Docetaxel	Olaparib + Abiraterone (1L)
Sipuleucel-T	Talazoparib + Enzalutamide (1L)
Radium-223	Olaparib
177-Lu-PSMA-617	Rucaparib
Abiraterone	Pembrolizumab (for dMMR/MSI-H or TMB-H)
Enzalutamide	

Selected based on genomic markers

Not selected based on genomic markers

Ajmera. J Natl Compr Canc Netw. 2023;21:548.

Niraparib (Zejula, 截永樂) : (2016) 專注與突破者

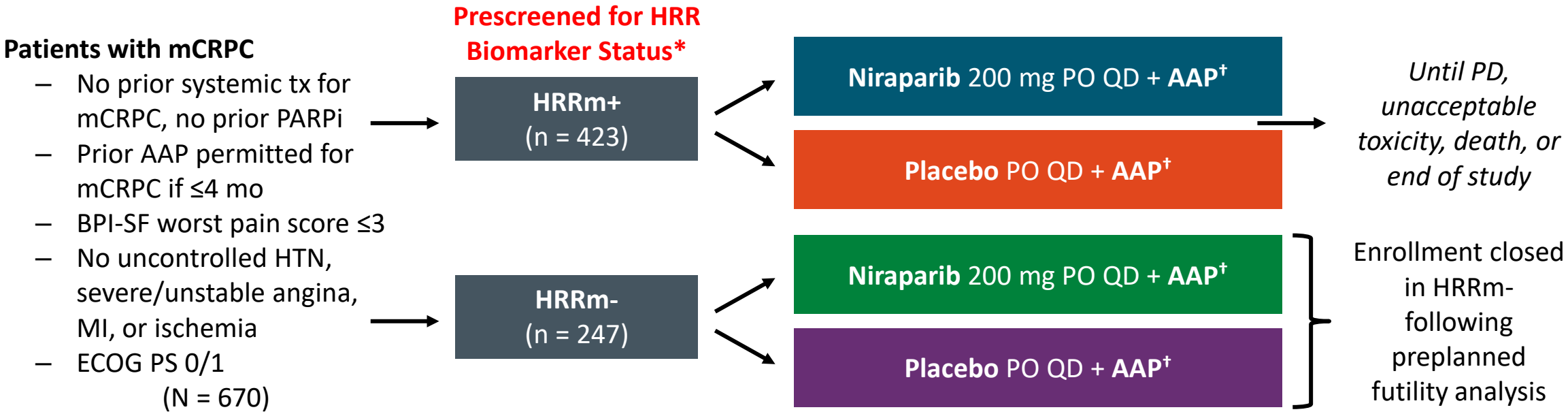
200-300mg qd

- Ovarian, fallopian tube, or primary peritoneal cancer:
  - Recurrent Ovarian Cancer First-line maintenance treatment of advanced epithelial ovarian cancer in adults who are in a complete or partial response to first-line platinum-based chemotherapy.(2017)
  - for Late-line Treatment for Women with Recurrent Ovarian Cancer (2019)
  - Once-Daily PARP Inhibitor in First-Line Monotherapy Maintenance Treatment for Women with Platinum-Responsive Advanced Ovarian Cancer Regardless of Biomarker Status (2020)
- BRCA-mutated castration-resistant prostate cancer (mCRPC)
  - The fixed dose combination of niraparib and abiraterone acetate with prednisone (2023)

indication	Trial Name	Comparative Protocol	Progression-Free Survival (PFS)	Overall Survival (OS)	Adverse Effects	Source
Ovarian Cancer (Recurrent, platinum-sensitive, maintenance)	NOVA Pts: 553 gBRCA cohort (with 138 (niraparib) and 65 (placebo), and 350 (non-gBRCA 234 (niraparib) and 116 (placebo)	Niraparib vs. Placebo	gBRCA+: 21.0 months (Niraparib) vs. 5.5 months non-gBRCA with homologous recombination deficiency (HRD) 12.9 months vs. 3.8 months Overall Non-gBRCA: 9.3 (Niraparib) vs. 3.9 months	NORA : ≥2 prior lines) gBRCAm: 56 vs 47.6 months Non-gBRCAm; 46.5 vs 46.9 months All : 51.5 vs 47.6 months	thrombocytopenia (33.8%), anemia (25.3%), neutropenia (in 19.6%),	N Engl J Med 2016;375:2154-2164 EClinicalMedicine. 2024 May 7;72:102629. NORA study
First-line maintenance treatment of advanced ovarian cancer in a complete or partial response to first-line platinum-based chemotherapy.	PRIMA Pt 733, 373 (50.9%) with homologous-recombination deficiency. (HRD)	Niraparib 300mg qd 36 months or disease in progression vs. Placebo	HRD-positive: 21.9 months (Niraparib) vs. 10.4 months (Placebo) P<0.001; Overall population: 13.8 months (Niraparib) vs. 8.2 months (Placebo)	84% in the niraparib group vs 77% (the placebo) at the 24-month (hazard ratio, 0.70)	> grade 3 or higher were anemia (in 31.0%), thrombocytopenia (in 28.7%), and neutropenia (in 12.8%).	N Engl J Med 2019;381:2391-2402
Prostate Cancer (Metastatic, castration-resistant, mBRCA)	MAGNITUDE niraparib and abiraterone acetate plus prednisone (niraparib + AAP) in patients with (HRD, n = 423) or without (HRD, n = 247)	Niraparib 200mg +qd Abiraterone 1gm+prednisolone 10mg qd vs. Placebo + Abiraterone	16.6 months (Niraparib + Abiraterone) vs. 10.9 months (Placebo + Abiraterone) in BRCA1/2 subgroup (P = .001). niraparib + AAP vs placebo + AAP group (16.5 v 13.7 months; P = .022) in HRD	Median OS: 30.4 months (Niraparib + Abiraterone) vs. 28.6 months (Placebo + Abiraterone) HR: 0.663 , P = .0237	Anemia, hypertension, thrombocytopenia, nausea	J Clin Oncol . 2023 Jun 20;41(18):3339-335

MAGNITUDE: First-line Niraparib vs Placebo in Combination With AAP in mCRPC

- International, randomized, double-blind phase III trial



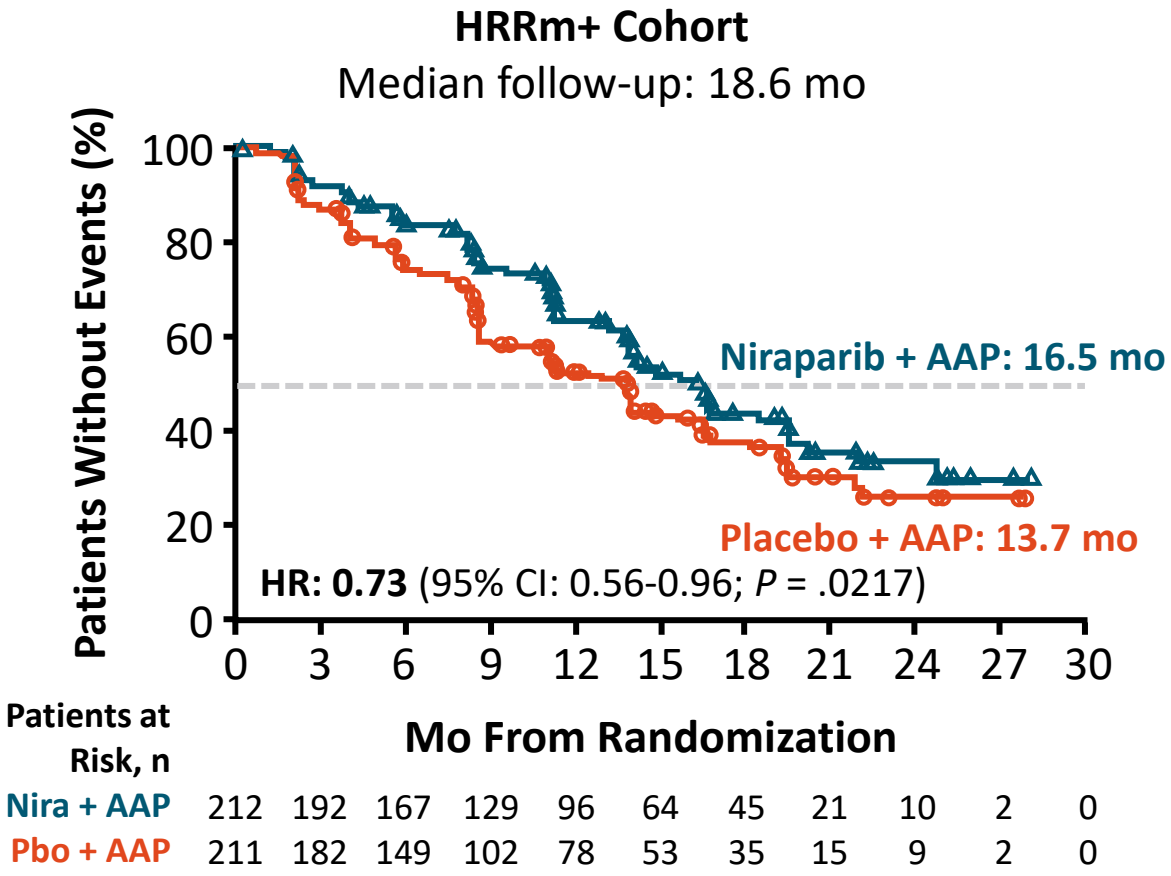
*HRRm+ per tissue and/or plasma assays for ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***.

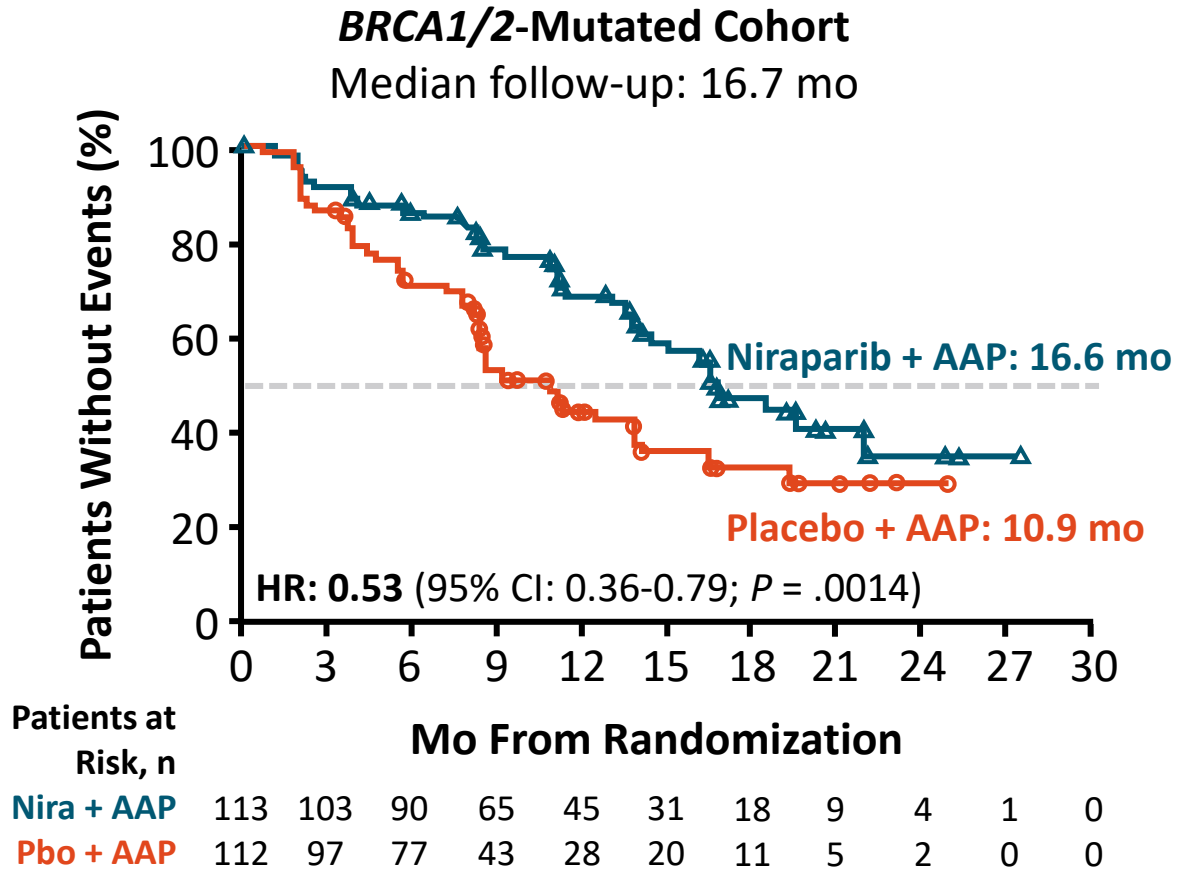
†AAP: abiraterone acetate 1000 mg PO QD + prednisone 10 mg PO QD.

- **Primary endpoint:** rPFS by central review
- **Secondary endpoints:** OS, time to cytotoxic CT, time to symptomatic progression
- Prior taxane in 19.3%-25.9%, prior AAP for 1L mCRPC in 22.7%-26.5%, prior ARPI for nmCRPC/mHSPC in 2.4%-5.3%

Chi. ASCO GU 2022. Abstr 12. Chi. JCO. 2023;41:3339.

MAGNITUDE: Radiologic PFS by Central Review (Primary Endpoint)

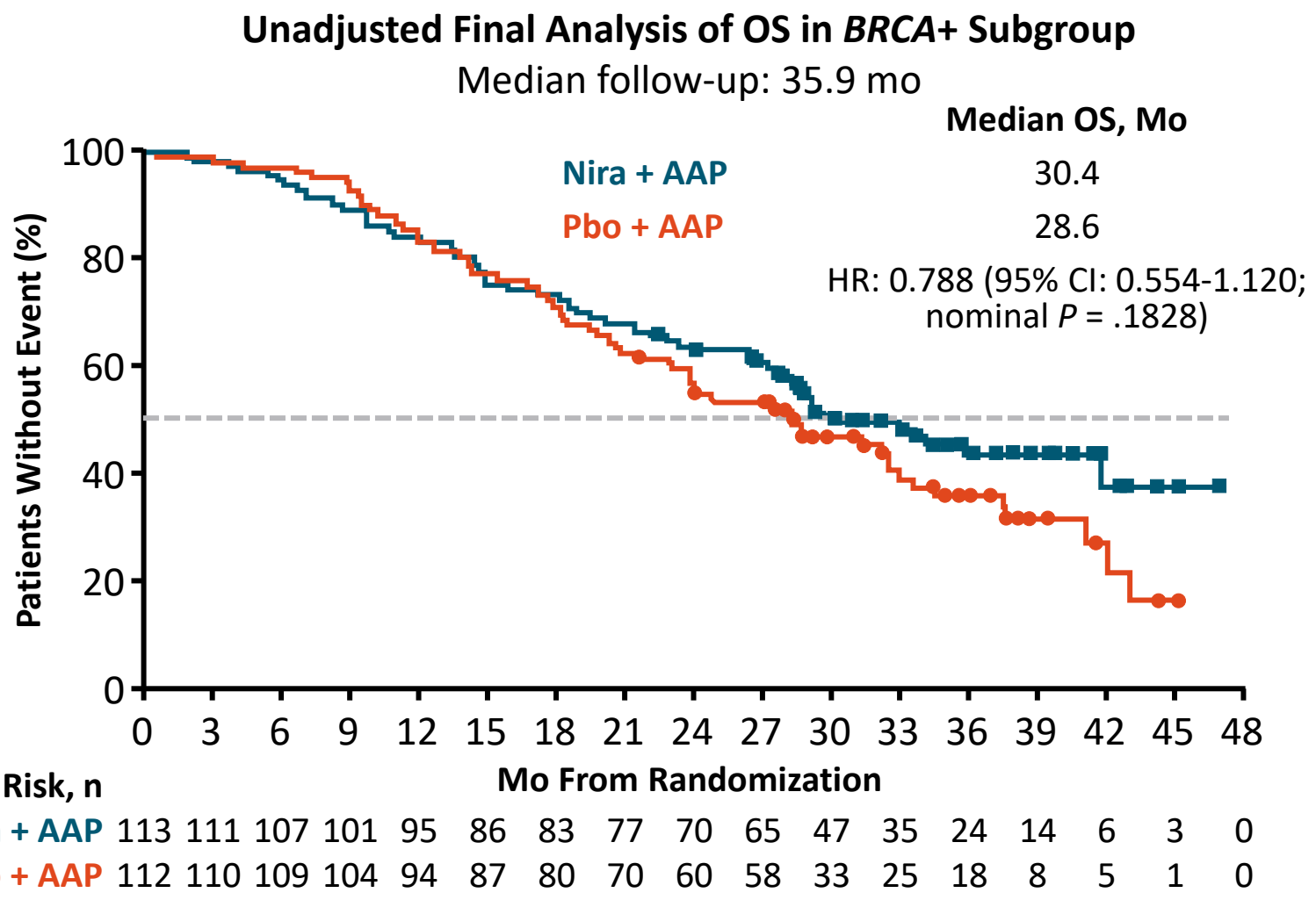




Chi. ASCO GU 2022. Abstr 12. Chi. JCO. 2023;41:3339.

Slide credit: clinicaloptions.com

MAGNITUDE: Final OS Analysis in *BRCA*+ Subgroup

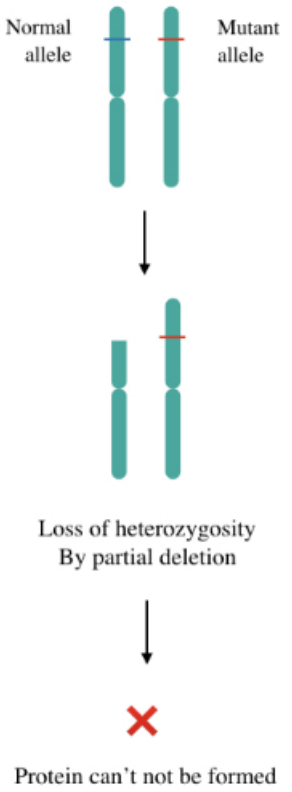


- Unadjusted OS analysis numerically favored niraparib + AAP
- In preplanned multivariate analysis incorporating prognostic factors, OS improved with niraparib + AAP
  - HR: 0.663 (95% CI: 0.464-0.947; nominal *P* = .0237)

Chi. ESMO 2023. Abstr LBA85.

Rucaparib 2017 創新不足

- Clovis filed for bankruptcy in 2023
- Ovarian cancer (epithelial ovarian, fallopian tube, or primary peritoneal cancer)
  - Maintenance treatment with recurrent who are in a complete or partial response to platinum-based chemotherapy.
  - BRCA mutation (germline and/or somatic) have been treated with two or more chemotherapies based on an FDA-approved companion diagnostic for Rubraca. (Clovis voluntarily withdrew in 2022)
- Prostate Cancer :
  - BRCA mutation (germline and/or somatic) associated mCRPC have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. (accelerated approval)



genomic loss of heterozygosity

Indication	Trial Name	Comparative Protocol	Overall Response Rate	Median Progression-Free Survival (PFS)	Adverse Effects	Source
Advanced Ovarian Cancer (BRCA mutated) genomic loss of heterozygosity (LOH) (phase 2)	ARIEL2 pt:204 HRD (BRCA mutant, wild-type and LOH high /low	Rucaparib 600 mg bid (single-arm)	54% (gBRCA)	12·8 months BRCA mutant subgroup, 5.7 months in the LOH high subgroup, and 5.2 months in the LOH low subgroup.	Anemia and elevations in GOT/GPT elevated, abdominal pain	Lancet Oncol . 2017 Jan;18(1):75-87.
Recurrent Ovarian Cancer (Maintenance) HRD (BRCA mutant or BRCA wild-type and high loss of heterozygosity),	ARIEL3 (pt 564)	Rucaparib vs. Placebo	Not specified	BRCA mutation 16·6 vs 5·4 months (placebo) p<0·0001). In HRD : 13.6 vs 5.4 months (p<0·0001). In the intention-to-treat population, 10.8 vs 5.4 months (p<0·0001) OS: 45.9 months (BRCA-mutant) vs 47.8 months (placebo) OS : 40.5 (HRD) vs 47.8 months (placebo) .	Anemia (19%) and increased alanine or aspartate aminotransferase (10%.	Lancet . 2017 Oct 28;390(10106):1949-1961.
Relapsed ovarian cancer and a deleterious *BRCA1* or *BRCA2* *m*utation rucaparib should no longer be used for third-line cancer treatment in new patients	ARIEL 4 (pt 349, rucaparib (n=233) or chemotherapy (n=116).	Rucaparib versus standard-of-care chemotherapy		7.4 (rucaparib) vs 5.7 months (chemotherapy) p=0·0010) OS : 19.6 months vs 27.1 (chemotherapy), hazard ratio of 1.550. (p=0.0507)	Clovis voluntarily withdrew in 2022	Lancet Oncol . 2022 Apr;23(4):465-478

Indication	Trial Name	Comparative Protocol	Overall Response Rate	Median Progression-Free Survival (PFS)	Adverse Effects	Source
Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (FDA未核准)	(ATHENA-MONO/GOG-3020/ENGOT-ov45) Pt 427 vs 111 (placebo)	oral rucaparib 600 mg bid vs placebo.		28.7 vs 11.3 months (placebo) in the HRD population (P = .0004) 12.1 vs 9.1 months in HRD (-) (HR, 0.65)		J Clin Oncol . 2022 Dec 1;40(34):3952-3964
Metastatic Castration-Resistant Prostate Cancer (mCRPC, BRCA mutated)	TRITON2 (pt 115)	Rucaparib (single-arm)	43.5% (BRCA) by radiology review ORRs were similar gBRCA or sBRCA, BRCA1 or BRCA2 alteration,	Not specified	Anemia, nausea, fatigue, thrombocytopenia	J Clin Oncol . 2020 Nov 10;38(32):3763-3772

FDA-Approved Indications and Withdrawals for PARP Inhibitors in Ovarian Cancer

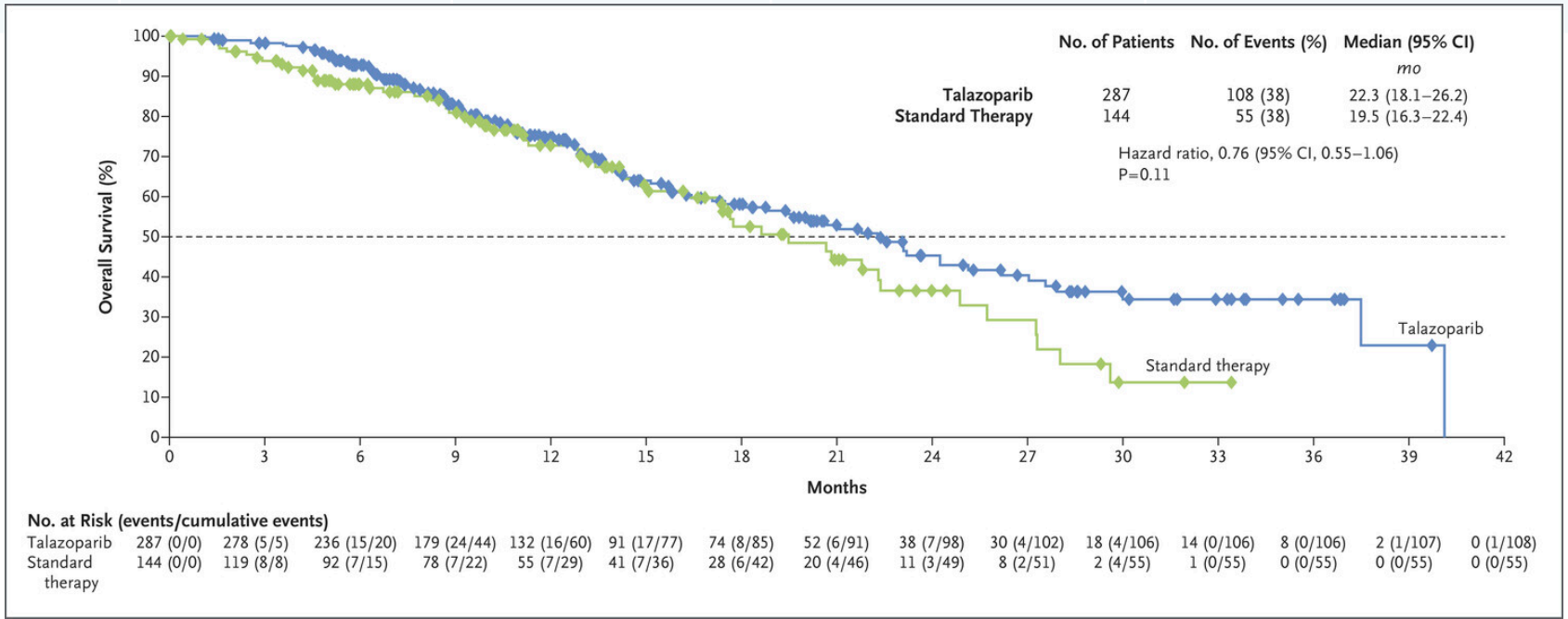
Medication	Approval date	Withdrawal date	US FDA indications	Effect size at initial approval
Olaparib	5/8/2020	-	First-line maintenance with bevacizumab, HRd	HR 0.33 (95% CI, 0.25-0.45)
	5/19/2018	-	First-line maintenance, *BRCA* variant	HR 0.30 (95% CI, 0.23-0.41)
	8/17/2017	-	Recurrent maintenance, *BRCA* variant	HR 0.30 (95% CI, 0.22-0.41)
		9/12/2023	Recurrent maintenance, non-*BRCA* variant	HR 0.34 (95% CI, 0.025-0.49)
	12/19/2014	8/26/2022	Monotherapy treatment, >3rd-line, g*BRCA* variant	ORR 34% (95% CI, 23%-42%)
Niraparib	4/29/2020	-	First-line maintenance , all	HR 0.62 (95% CI, 0.50-0.76)
	10/23/2019	9/14/2022	Recurrent maintenance, >3rd-line, HRd	ORR 24% (95% CI, 16%-34%)
	3/27/2017	-	Recurrent maintenance, g*BRCA* variant	HR 0.45 (95% CI, 0.34-0.61)
		11/11/2022	Recurrent maintenance, non-g*BRCA* variant	HR 0.27 (95% CI, 0.17-0.41)
Rucaparib	4/6/2018	-	Recurrent maintenance, *BRCA* variant	HR 0.23 (95% CI, 0.16-0.34)
		12/12/2022	Recurrent maintenance, non-*BRCA* variant	HR 0.36 (95% CI, 0.3-0.45)*
	12/19/2016	6/10/2022	Monotherapy treatment, >2nd-line, *BRCA* variant	ORR 54% (95% CI, 44%-64%)

Gynecologic Oncology 187 (2024) 204–211

Talazoparib (Talzenna, 達勝癌) 2018 (模仿改進者)

- Once daily
- For gBRCAm HER2-Negative Locally Advanced or Metastatic Breast Cancer (2018)
- in Combination with Xtandi (enzalutamide) for HRR Gene-Mutated Metastatic Castration-Resistant Prostate Cancer (2023)

FDA Approval Indication	Phase 3 Trial Name	Comparison Protocol	Overall Response Rate	Progression Free Survival	Adverse Effects	Source of Journal
HER2-negative, BRCA-mutated locally advanced or Metastatic breast cancer	EMBRACA pts: 431	Compared to physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine in 21-day cycles)	62.6% vs. 27.2%; (P<0.001).	8.6 months (talazoparib) vs. 5.6 (chemotherapy) (P<0.001).	primarily anemia : 55% (talazoparib) and 38% (placebo) fatigue, anemia, nausea, neutropenia, thrombocytopenia, alopecia, headache, vomiting, diarrhea, decreased appetite	N Engl J Med 2018;379:753-763
Breast Cancer (Metastatic, HER2-, gBRCA mutated)	Olaparib (pt :205) vs. Physician's choice chemotherapy (pts : 97) OlympiAD	Olaparib vs. Chemotherapy	59.9% vs. 28.8%	Median: 7.0 months (Olaparib) vs. 4.2 months (Chemotherapy) P<0.001	Nausea, anemia, fatigue, neutropenia, leukopenia	N Engl J Med. 2017;377(6):523-533.



FDA Approval Indication	Phase 3 Trial Name	Comparison Protocol	Progression Free Survival	Overall survival	Adverse Effects	Source of Journal
Metastatic castration-resistant prostate cancer (mCRPC) with DDR defects (investigational)	TALAPRO-2 pts : 805	enzalutamide 160 mg ± talazoparib 0·5 mg oral once daily.	radiographic (rPFS) 27·5 months-not reached) talazoparib plus enzalutamide vs 21·9 months for placebo + enzalutamide (p<0·0001)		Primarily anemia : 55% (talazoparib) and 38% (placebo) fatigue, anemia, nausea, neutropenia, thrombocytopenia, alopecia, headache, vomiting, diarrhea, decreased appetite	Lancet . 2023 Jul 22;402(10398):291-303
olaparib, with abiraterone and prednisone, for BRCA-mutated metastatic castration-resistant prostate cancer	PROpel 399 pts abiraterone+ prednisolone ±olaparib (399 vs 397 pts (placebo)	Olaparib+abiraterone / prednisone vs Abiraterone+prednisolone		Median OS 42.1 (not reached) months vs 34.7 months (placebo) ; p=0·054).	anemia, fatigue, nausea, diarrhea, decreased appetite, lymphopenia, dizziness, and abdominal pain	Lancet Oncol . 2023 Oct;24(10):1094-1108

DNA Damage and Repair (DDR)

HRR gene alterations: ***ATM, ATR, BRCA1, BRCA2, CDK12, CHECK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C.***

Considerations When Selecting Patients for PARP Inhibitor Combination Regimen in prostate cancer

- **Genomic status**
  - For *BRCA*m: niraparib + AAP, olaparib + AAP, talazoparib + enzalutamide
  - For HRRm (including *BRCA*m): talazoparib + enzalutamide
- **Prior therapy**
  - Clinical trials were designed for first-line population with no prior NHA (~5% had prior NHA in MAGNITUDE and TALAPRO-2)
- **Safety considerations**
  - Differences in safety profile of NHA (AAP vs enzalutamide)
  - No known differences in safety between PARP inhibitors
  - Combination regimens have manageable but increased toxicities compared with monotherapy

Select Studies in mCRPC of PARP Inhibitors in Combination With Agents Targeting Potentially Synergistic Pathways

	AR Therapy	Immunotherapy		Cotargeting Other Pathways		
Olaparib	Ph III PROpel ***Met primary endpoint***	Ph III KEYLYNK-010 ***Negative results***	Ph II NCT03810105	Ph I/II COMRADE* NCT03317392	Ph I LuPARP* NCT03874884	Ph II NCT02893917
	Abiraterone	**Pembrolizumab**	**Durvalumab**	**Radium-223**	**^{177}Lu-PSMA-617**	**Cediranib (VEGFRi)**
Talazoparib	Ph III TALAPRO-2 ***Met primary endpoint***			Ph II† NCT04824937	Ph I* NCT04846478	Ph I* NCT04703920
	Enzalutamide			**Telaglenastat (GLSi)**	**Tazemetostat (EZH2i)**	**Belinostat (HDACi)**
Rucaparib	Ph III CASPAR NCT04455750	Ph II CheckMate 9KD NCT03338790		Ph II PLATI-PARP NCT03442556	Phase I/II NCT04253262	
	Enzalutamide	**Nivolumab**		**Chemotherapy**	**Copanlisib (PI3Ki)**	
Niraparib	Ph III MAGNITUDE ***Met primary endpoint***	Ph I/II QUEST NCT03431350		Ph I NiraRad NCT03076203		
	Abiraterone	**Cetrelimab**		**Radium-223**		

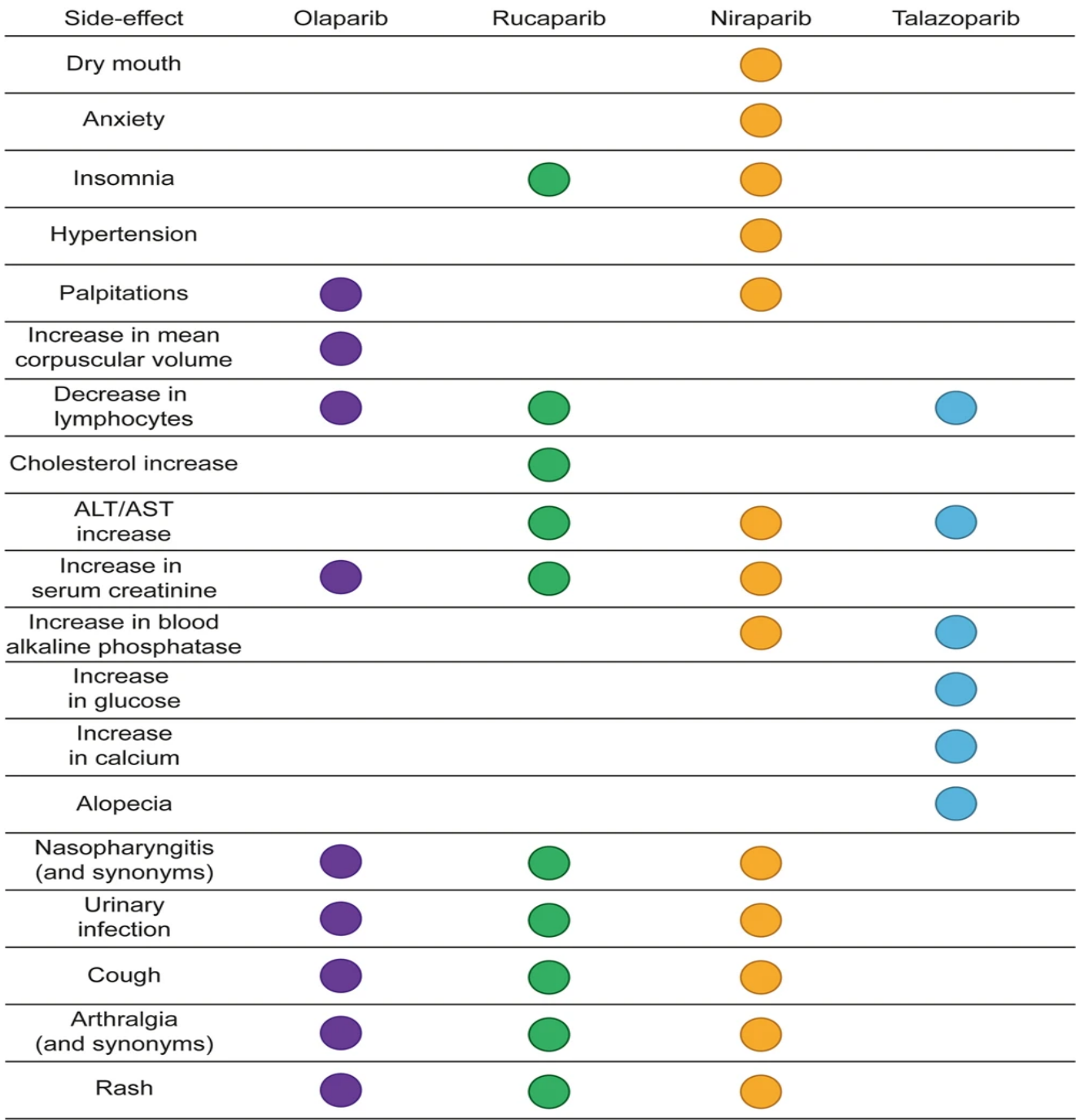
Phase III

Early phase

Trials active as of January 2024. *Recruiting. †Not yet recruiting.

Slide credit: clinicaloptions.com

Differential adverse reactions between FDA-approved clinical PARP inhibitors



Sci Rep 10, 2585 (2020).

PARP Inhibitor Dosing and Administration

	Olaparib	Rucaparib	Niraparib	Talazoparib
Dosing	300 mg PO BID (150-mg, 100-mg tablets)	600 mg PO BID (300-mg, 250-mg, 200-mg tablets)	300 mg PO daily (100-mg capsules)	1mg PO qd (0.1, 0.25,0.35, 0.5,0.75,1mg)
How to take	With/without food (taking at bedtime or 30-60 min after meal may help with nausea)			
Renal impairment (baseline dosing)	200 mg PO BID for CrCl 31-50 mL/min	—	—	CrCl 30 -59 mL/min: 0.75 mg qd CrCl 15- 29 mL/min: 0.5 mg qd
CYP interactions	Inhibits CYP3A and induces CYP2B6; metabolized by CYP3A4	Inhibits CYP2C19, 2C9, 3A4, 1A2; metabolized by CYP2D6, lesser extent 1A2 and 3A4	Other hepatic metabolism* Carboxylesterases	minimum
PARP inhibitor dose reductions for CYP interactions	Avoid strong CYP3A inhibitors 150 mg PO BID with moderate CYP3A inhibitors 100 mg PO BID with strong CYP3A inhibitors	No dose reductions	No dose reductions	No dose reduction

LaFargue. Lancet Oncol. 2019;20:e15. Olaparib PI. Rucaparib PI. Niraparib PI.Talazoparib PI

Managing Key AEs and Safety Considerations With PARP Inhibitors

- **Cytopenias:** monitor using monthly CBC with differential
  - If occur, dose hold until recovery; discontinue if not resolved after 28 days
- **Fatigue:** exercise, massage, CBT; rule out anemia or other causes
- **GI:** prophylactic antiemetics, loperamide as needed for diarrhea
- **Hypertension:** Routine BP monitoring, exercise, DASH diet, antihypertensives
- **Rare but serious AE:** pulmonary embolism/DVT or MDS/AML
  - Activity, no role for prophylactic anticoagulation
  - MDS particular concern for younger patients treated for longer time periods

Parameter	Niraparib	Olaparib	Rucaparib	Talazoparib
Starting dose	200 mg PO QD	300 mg PO BID	600 mg PO BID	0.5 mg PO QD
Dose modification	▪ First: 100 mg QD	▪ First: 250 mg BID ▪ Second: 200 mg BID	▪ First: 500 mg BID ▪ Second: 400 mg BID ▪ Third: 300 mg BID	▪ First: 0.35 mg QD ▪ Second: 0.25 mg QD ▪ Third: 0.1 mg QD

Manage AEs with dose holds and reductions; permanently discontinue for recurrent/high-grade AEs

Abiraterone acetate PI. Niraparib PI. Olaparib PI. Rucaparib PI. Talazoparib PI.

Slide credit: clinicaloptions.com

Take home message

- Platinum sensitivity predicts the response to PARP inhibitors.
- Germline and/or somatic BRCA1/BRCA2 mutations are key players in HRD (homologous recombination deficiency) in ovarian, breast, pancreatic, and prostate cancers . Other HRR genes do not show strong indicators.
- PARP inhibitors have an overall survival benefit in frontline therapy for breast and ovarian cancers.
- The FDA has restricted indications to patients with gBRCAm PSROC (platinum-sensitive relapsed ovarian cancer).
- Combined therapies in immunotherapy and co-targeting other pathways are ongoing.