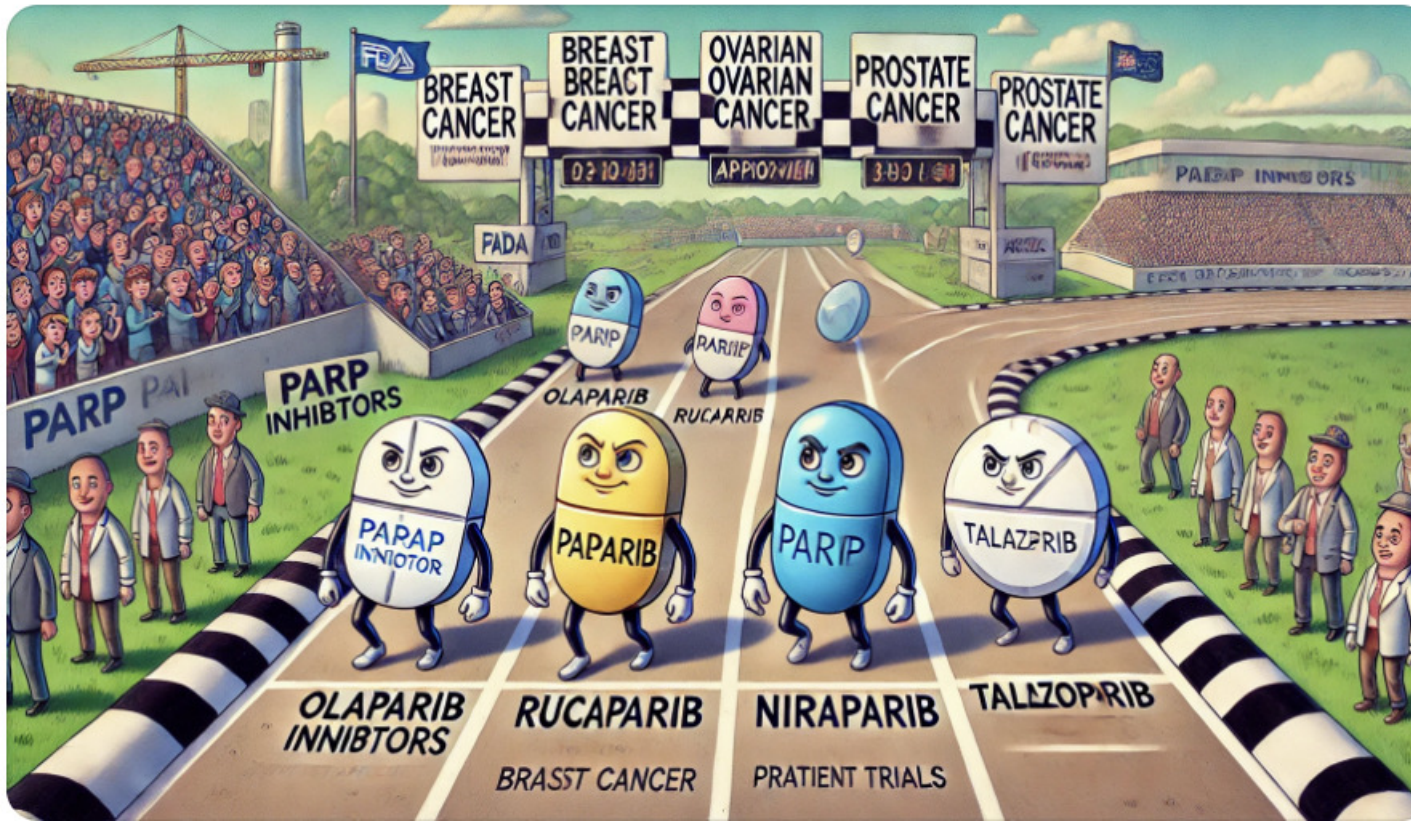
PARP (poly-ADP ribose polymerase) inhibit

歷史發展晴天與烏雲

Senior clinical pharmacist

Lihua Fang



PARP inhibitors 的發展

在1963年，由Chambon、Weill和Mandel首次識別出名為“PARP”的酶。最初PARP的功能並不十分清楚。198
代：研究闡明了PARP在DNA損傷反應中扮演著關鍵角色，特別是通過基礎切除途徑修復單股斷裂。在1990年
末，開始了 PARP抑制劑的概念化，科學家假設抑制PARP可以防止癌細胞中的DNA修復，從而增加它們對損
敏感性並導致細胞死亡。這對已經在DNA修復能力上受損的細胞中尤為重要，例如那些帶有BRCA1或BRCA2突
的細胞。

PARP抑制劑的早期開發

2000年代：PARP抑制劑的開發正式開始。最初的努力集中於證明阻斷PARP活性可以增強DNA損傷和放射治療
效果。2005年 第一種PARP抑制劑AG14361在前臨床模型中顯示出增強抗癌的潛力，引發了對該領域進一步
趣和開發。

臨床試驗與FDA批准

2009年：Olaparib（Lynparza）成為首批進入臨床試驗的PARP抑制劑之一。其在BRCA突變的卵巢癌中的有
特別引人注目，導致進一步的研究。2014年，Olaparib在歐洲和美國首次獲得針對BRCA突變卵巢癌的治療
，標誌著PARP抑制劑正式進入臨床腫瘤治療的領域。隨後幾年，其他PARP抑制劑如rucaparib、niraparib
talazoparib繼 Olaparib之後陸續上市，也獲得了包括卵巢癌、乳腺癌和前列腺癌等多種治療的批准。

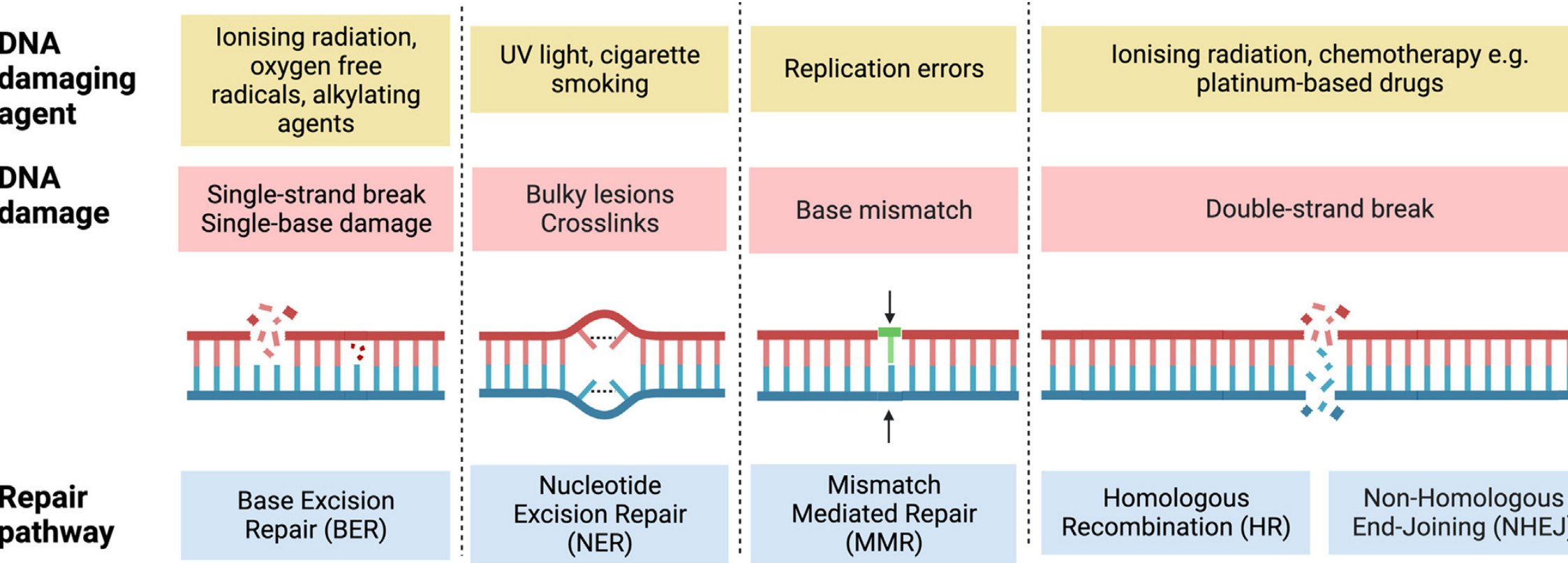
2010年代至今，研究持續探索PARP抑制劑的更廣泛應用，不僅限於BRCA突變，還包括其他DNA修復機制的缺
。研究也在檢視結合PARP抑制劑與化療和免疫療法的潛在協同效應。雖然PARP抑制劑已成為重大進展，其
並非沒有挑戰，包括藥物抗性和副作用問題。PARP抑制劑的歷史見證了從基礎生物學洞察到針對具有特定
背景的癌症病人治療策略的演變。

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

NA repair pathways according to the type of damage.
eficiency in DNA repair pathways has been identified as an Achilles heel of cancer cells BRCA1 and BRCA2 are tumor suppressor protei
at work at different stages in the DNA damage and repair pathways. Their loss of function leads to homologous recombination repair (HR
eficiency.



K.D. Doig, A.P. Fellowes and S.B. Fox / Mod Pathol 36 (2023) 10

Homologous recombination pathways

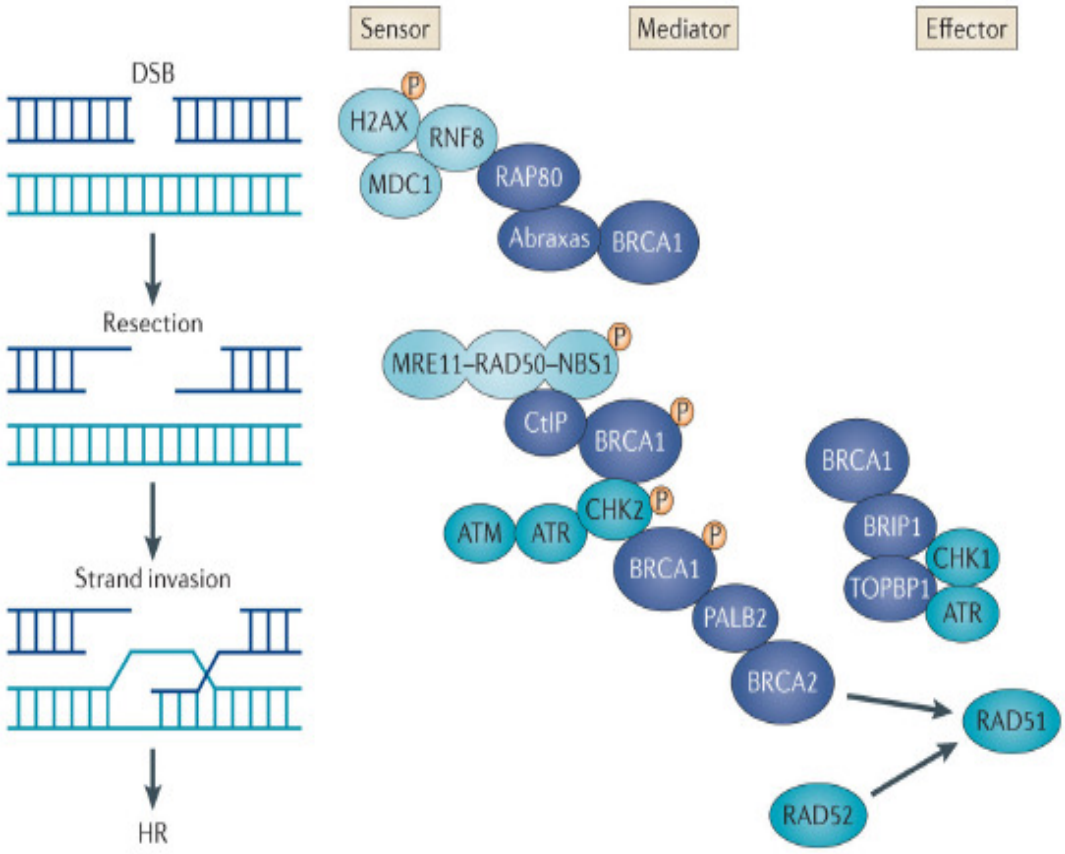
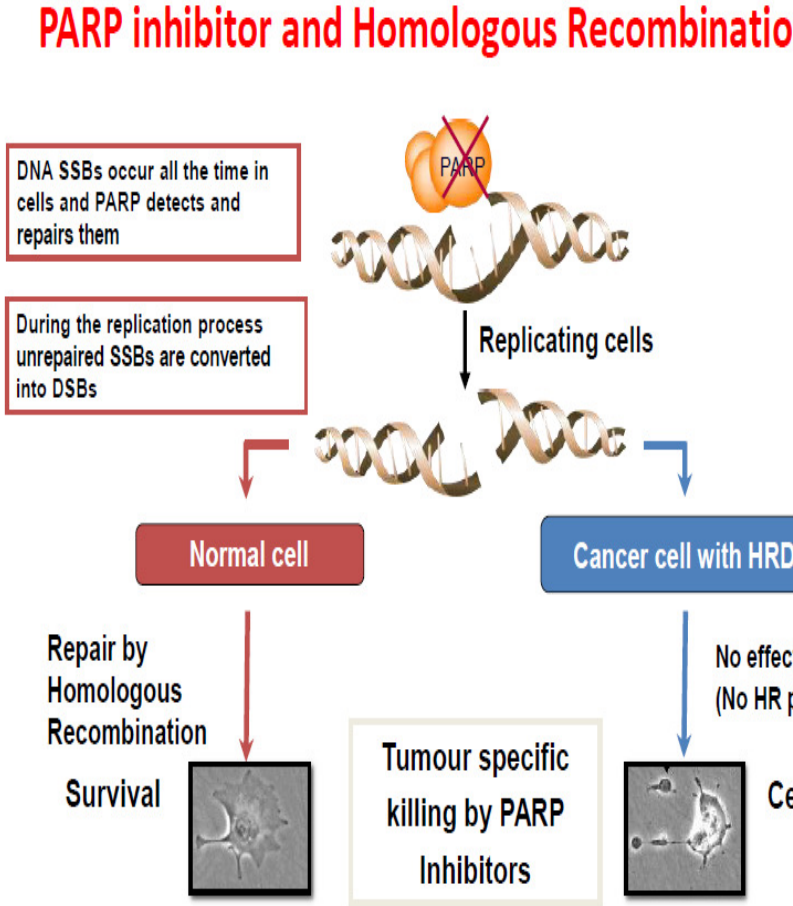


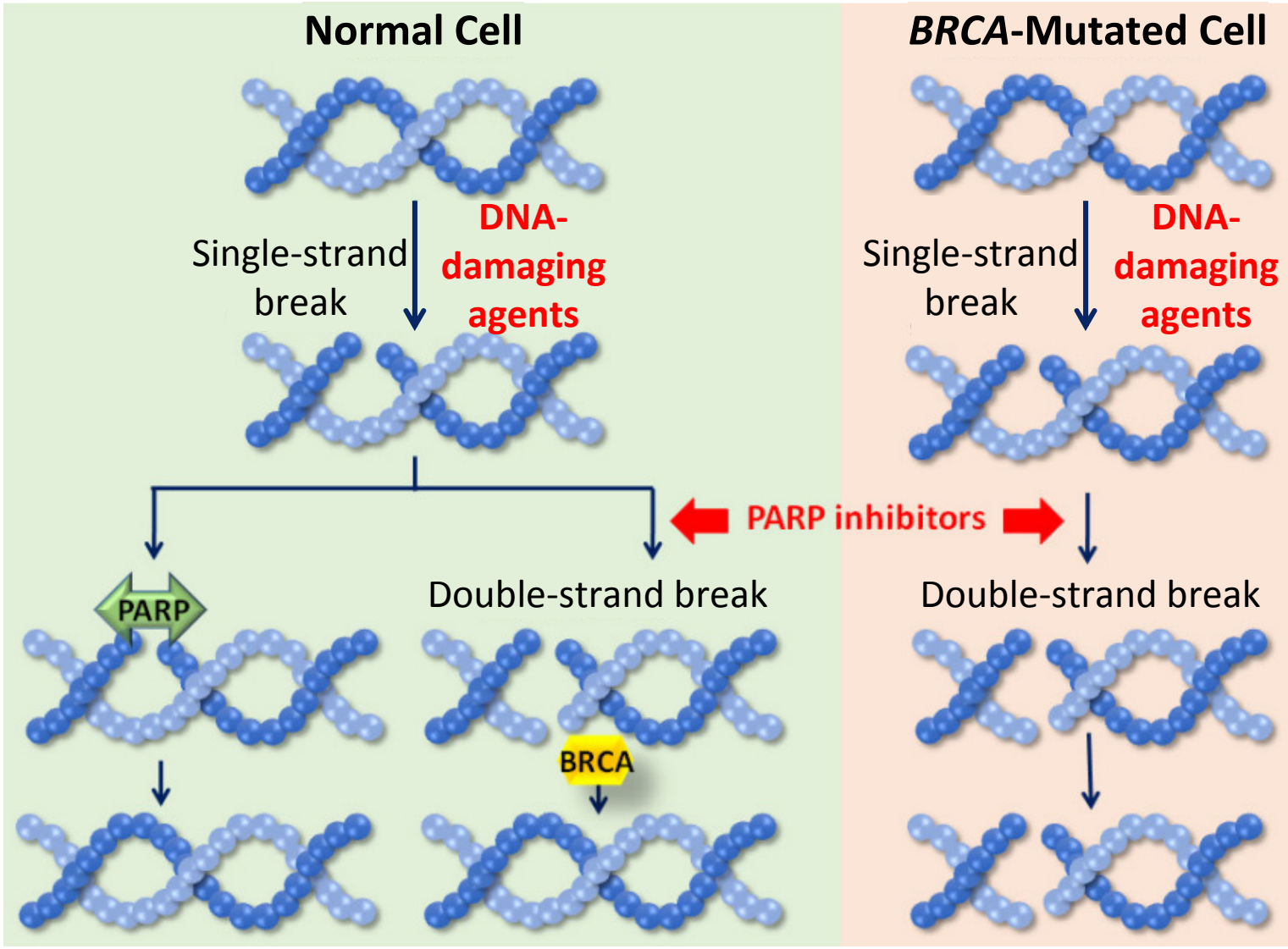
Figure 1. Molecular mechanisms of the DNA damage response



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

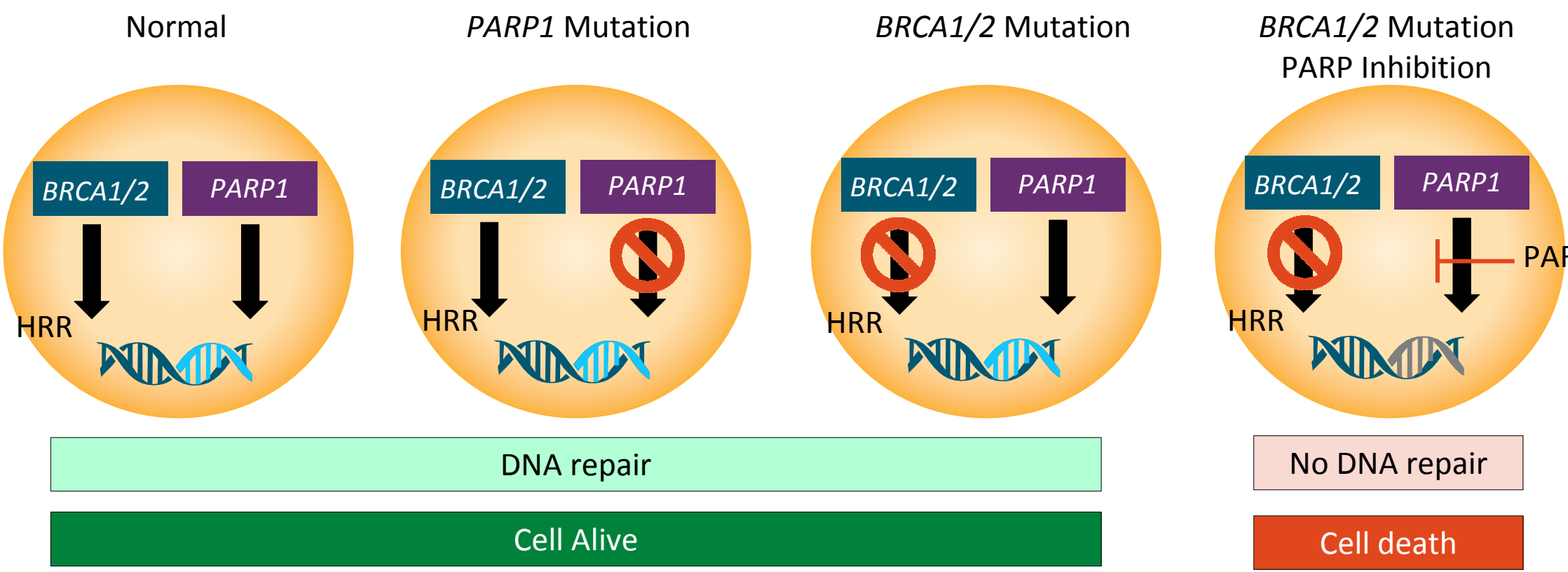


mier. Sci Transl Med. 2016;8:362ps17. Ocana. Oncotarget. 2017;8:22218.

Slide credit: clinicaloptions.com

PARP Inhibitor mechanism: Synthetic Lethality (組合致死

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

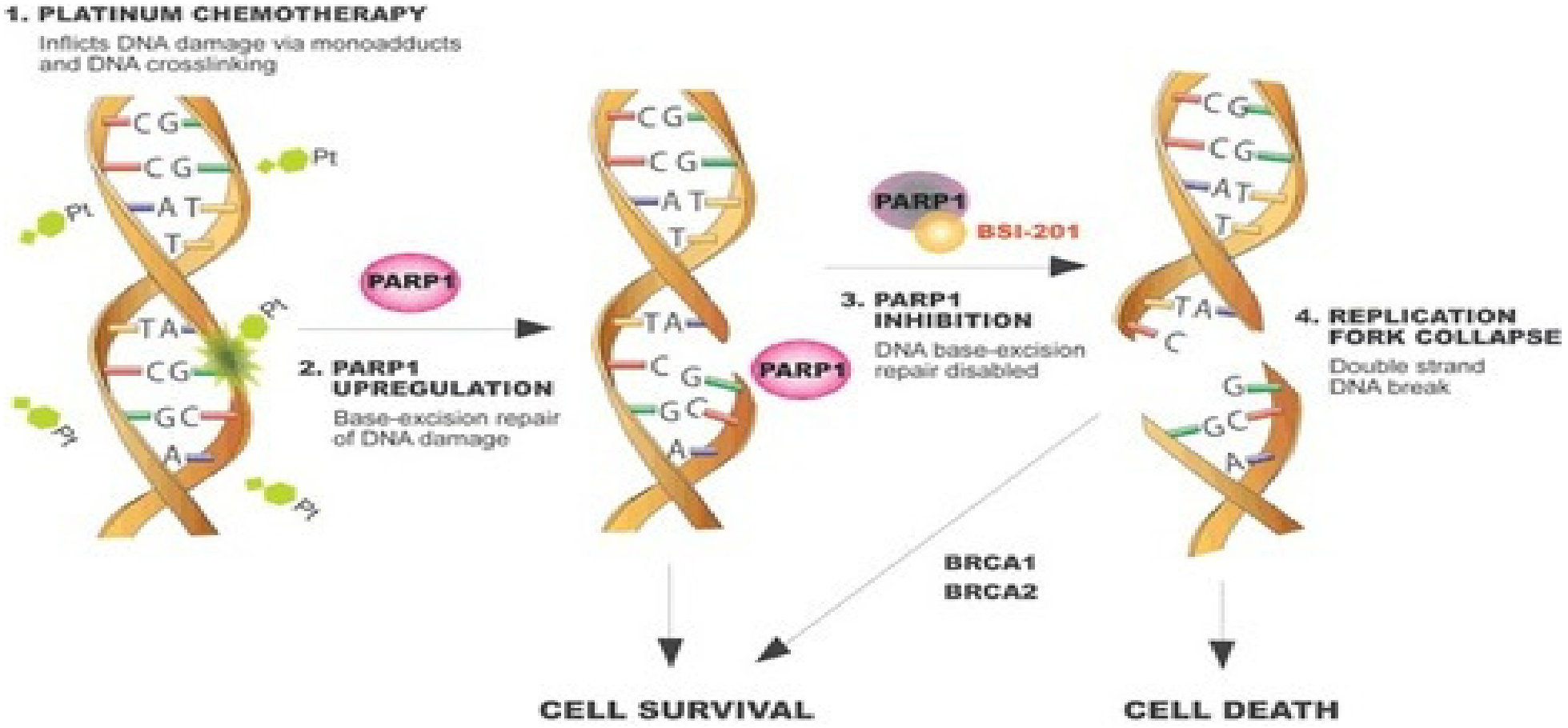


rley. J Clin Oncol. 2019;37:2257.

Slide credit: clinicaloptions.com

PARP (poly-ADP ribose polymerase)

Olaparib 2014, Niraparib 2016, Rucaparib 2017, Talazoparib 2018

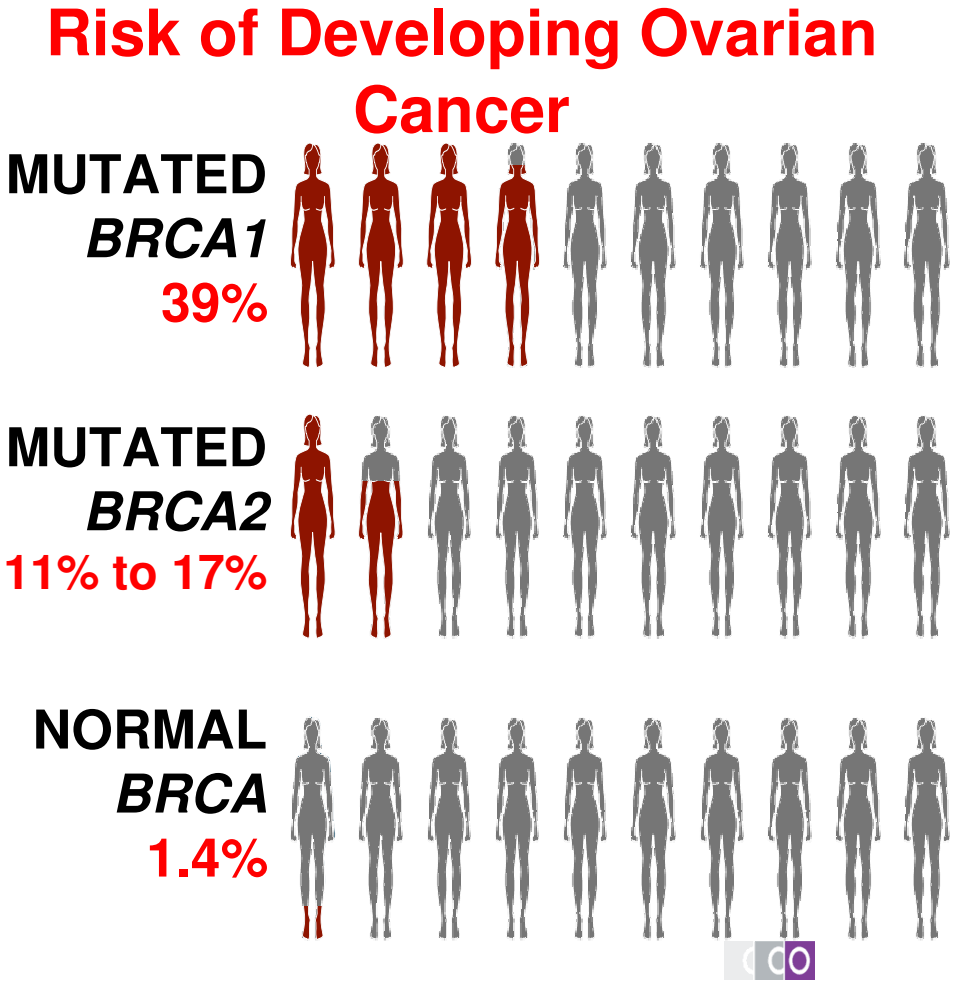


Overview of BRCA1 and BRCA2

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



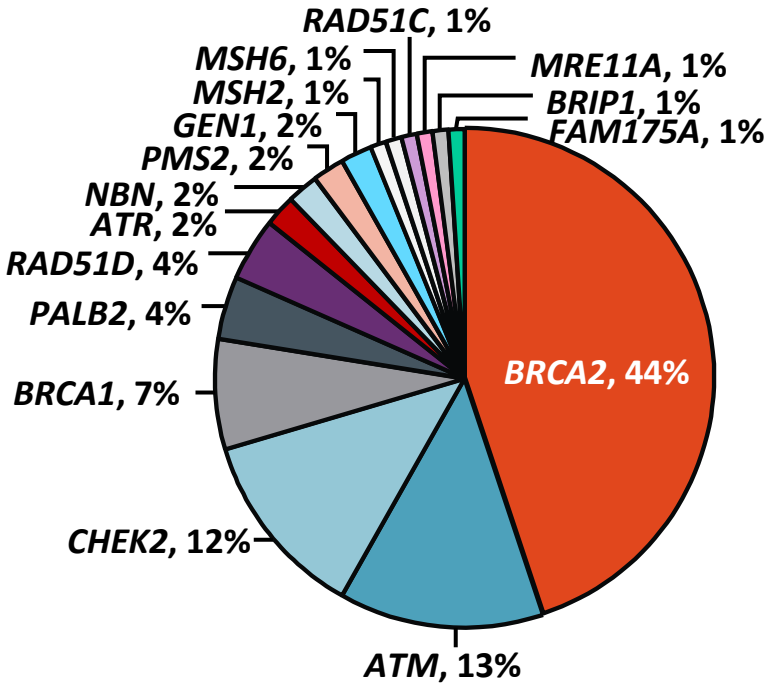
www.acog.org/Patients/FAQs/BRCA1-and-BRCA2-Mutations

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]

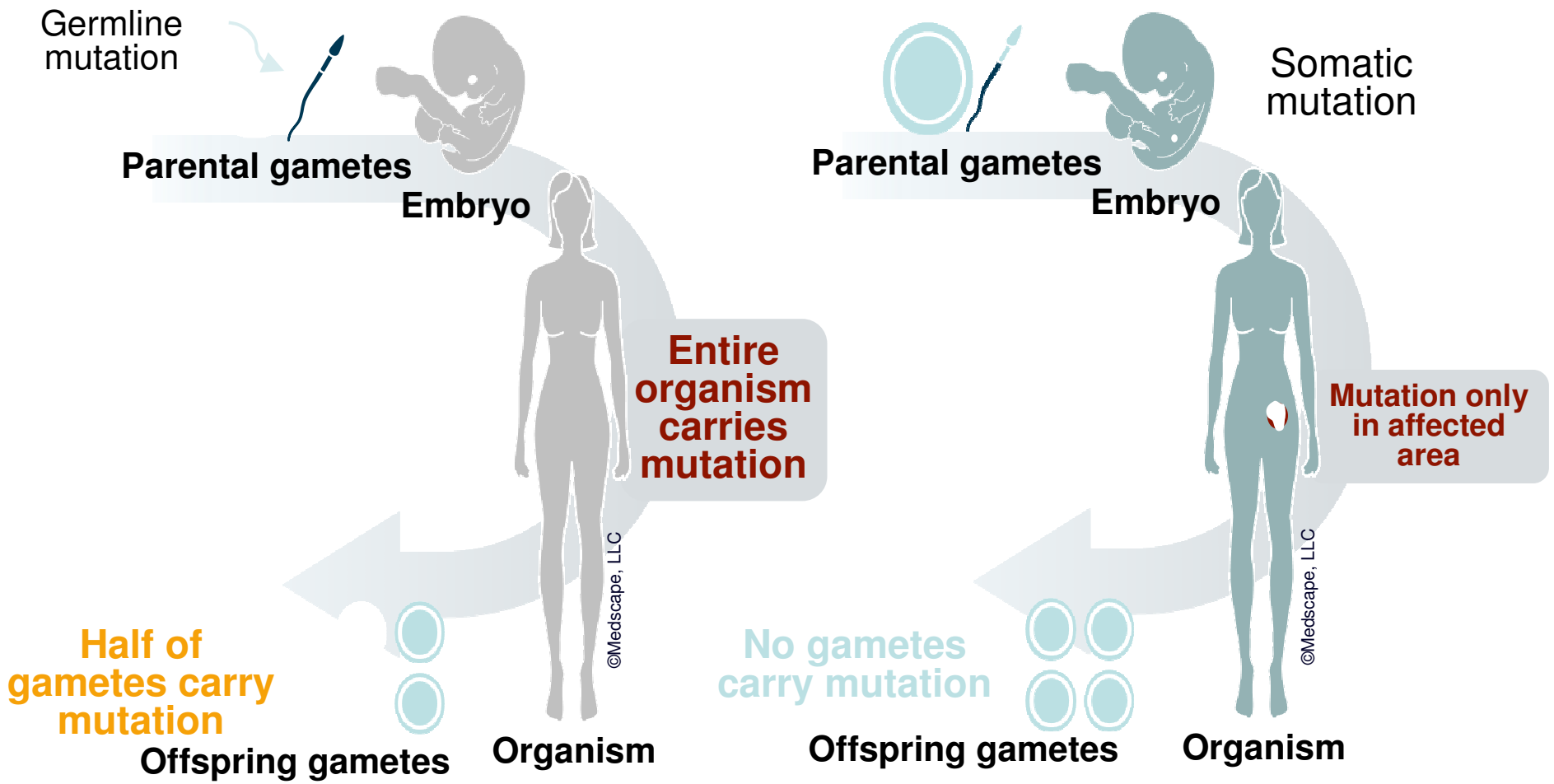
Distribution of Presumed Pathogenic Germline Mutations[3]



riedlander. Am Soc Clin Oncol Edu Book. 2018;37:358.
obinson. Cell. 2015;161:1215. 3. Pritchard. NEJM. 2016;375:443.

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	

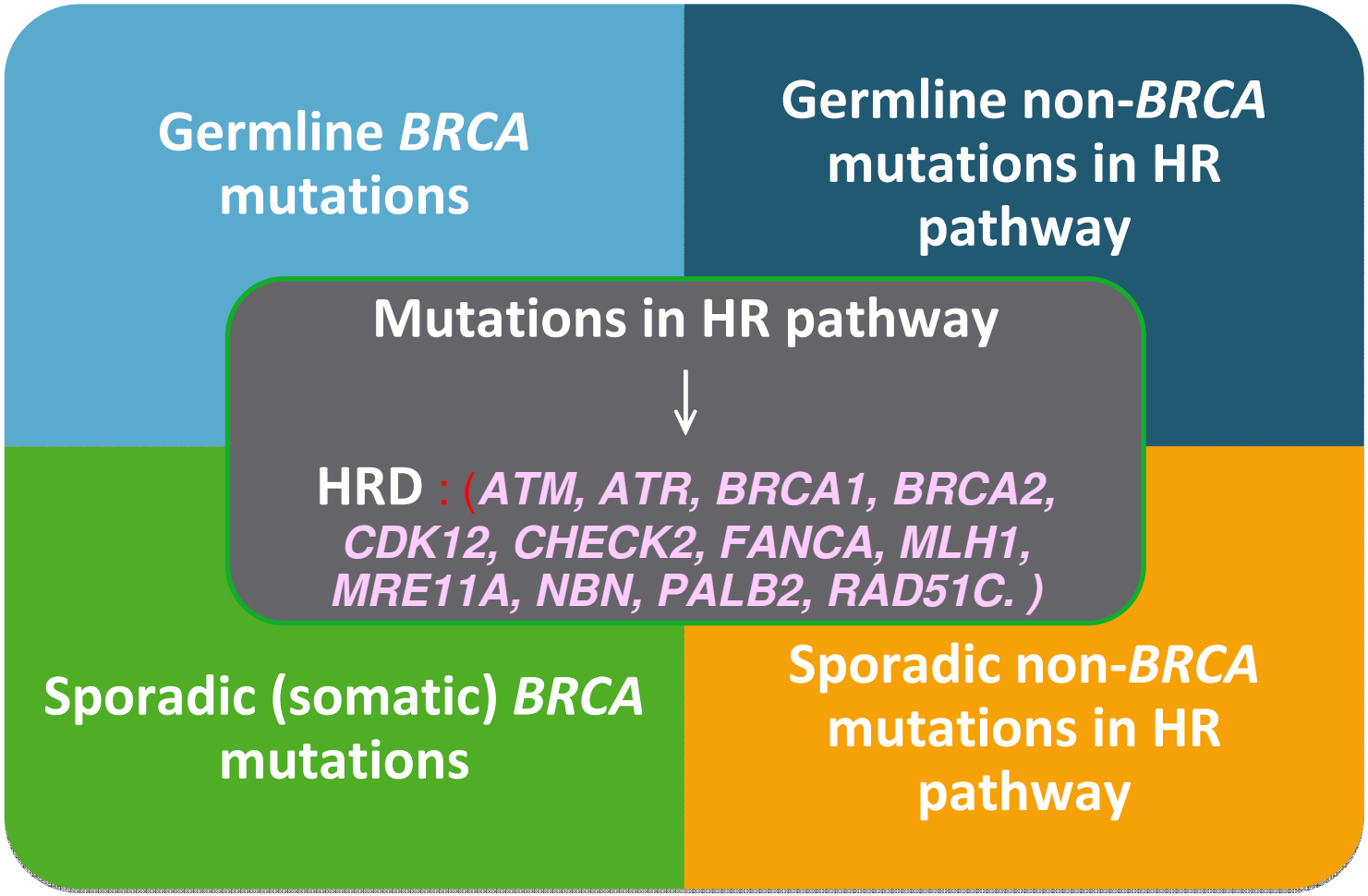
ER, oestrogen receptor; HR, homologous recombination; LOH, loss of heterozygosity; PR, progesterone receptor.

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

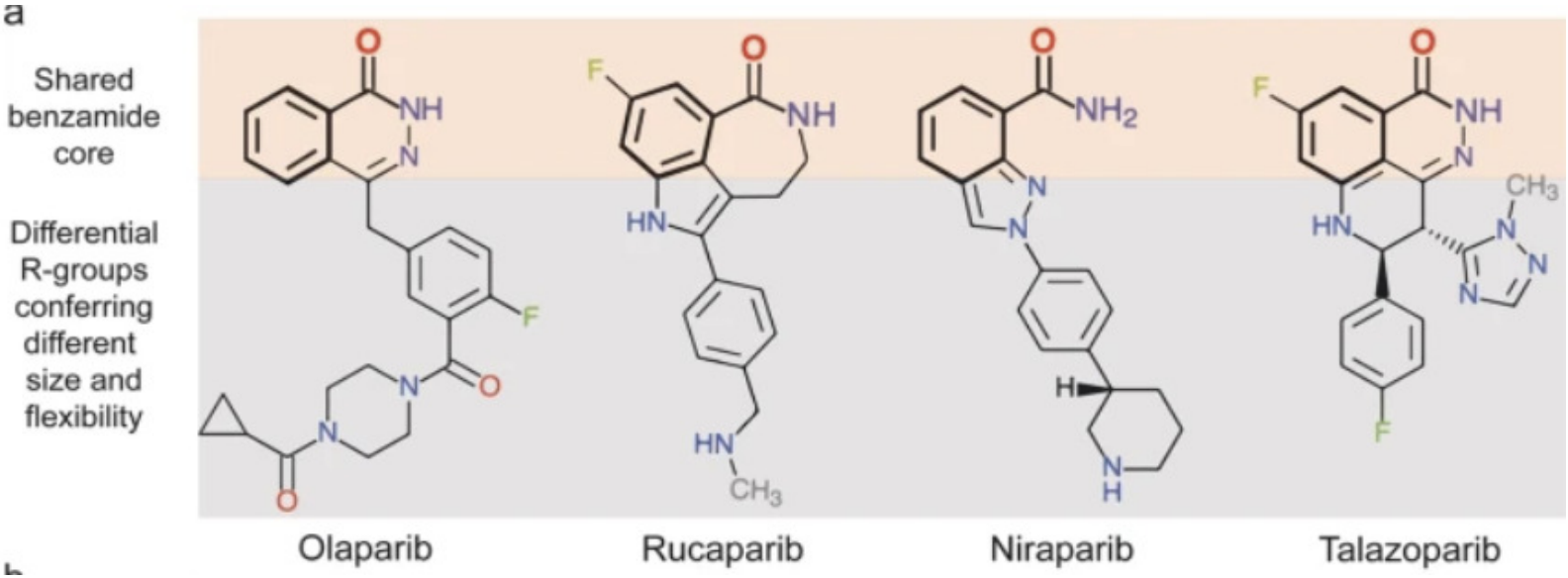


Slide credit: clinicaloptions.

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

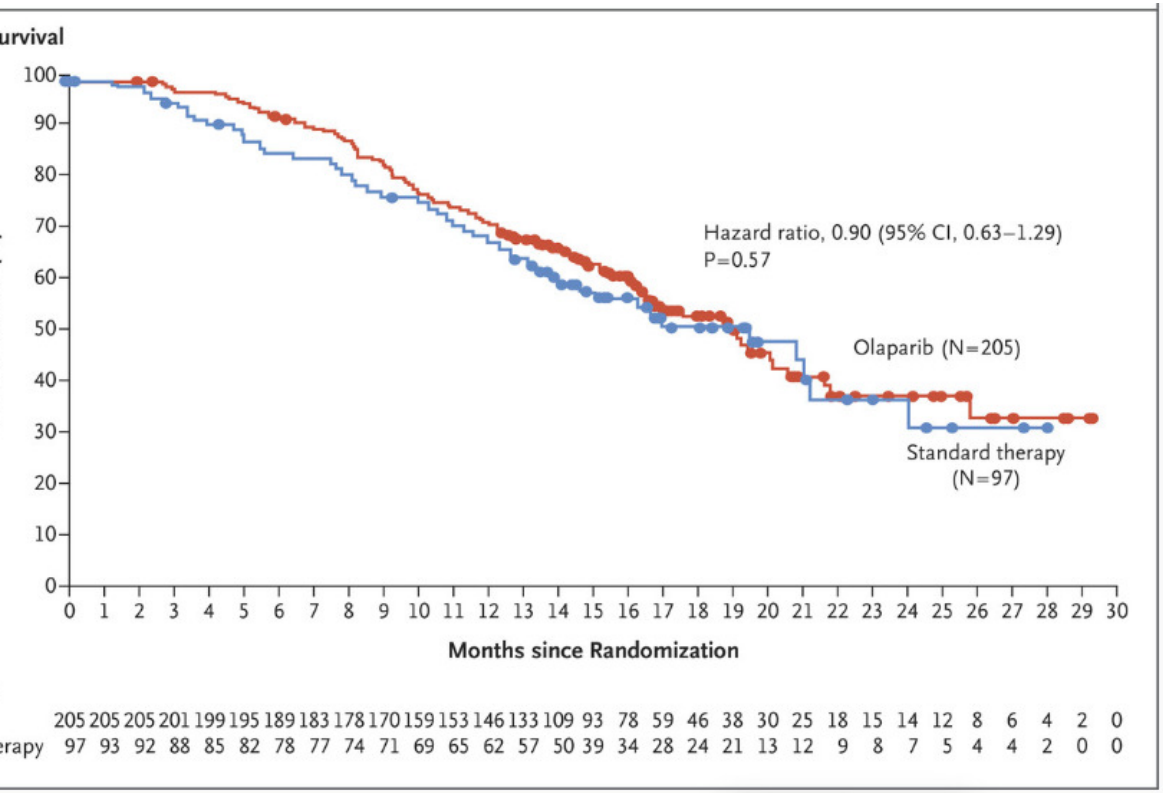
Ovarian cancer, advanced, homologous recombination deficient positive, first-line maintenance therapy

Pancreatic cancer, metastatic, germline BRCA mutated, first-line maintenance therapy

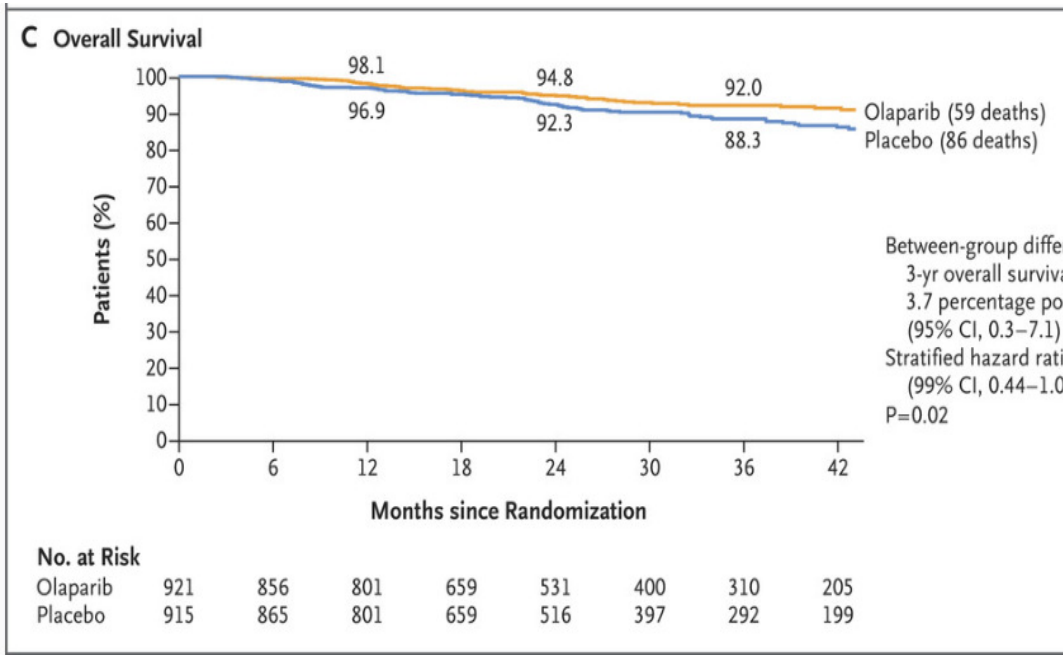
Prostate cancer, metastatic, castration resistant, homologous recombination repair gene mutated

Prostate cancer, metastatic, castration resistant, BRCA mutated (in combination with abiraterone and prednisone or prednisolone

dication	Trial Name	Comparative Protocol	ORR	PFS	OS	ADR	S
ancer tic, HER2-, nutated)	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 E 201 23-
ancer (Early, k, HER2-, nutated,)	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 E 202 240



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

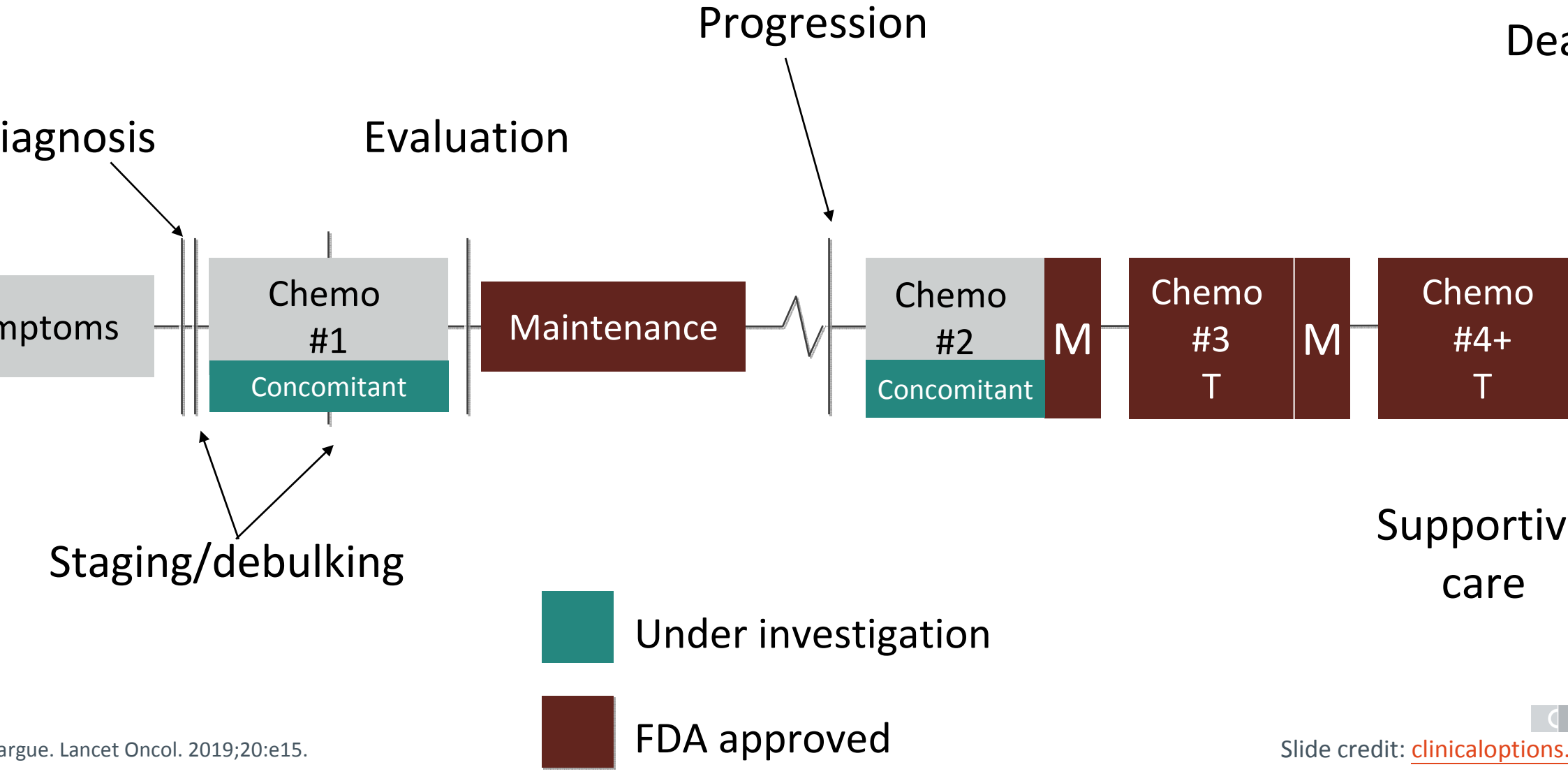
Adverse Events

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

J Med 2017; 377:523-533

Current Treatment Landscape for PARPi in Ovarian Cance



Slide credit: clinicaloptions.

ndication	Trial Name	Comparative Protocol	PFS (months)	OS	ADR	So
Cancer ent, BRCA d, Maintenance): m-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 2012;3 1392
Cancer ced, gous ination t, First-line nance)	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 2019;3 2428 . Int J C Cancer 9.
Cancer ced, BRCA d, First-line nance)	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 C 2023 J 20;41(3

ARP 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

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

Slide credit: clinicaloptions.com

FDA Indications for PARP Inhibitor Monotherapy in Prostate Cancer

Olaparib

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	*BRIP1*	*FANCL*	*RAD51D*
BARD1	*CDK12*	*PALB2*	*RAD54L*
BRCA1	*CHEK1*	*RAD51B*	
BRCA2	*CHEK2*	*RAD51C*	

Rucaparib

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

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

Slide credit: clinicaloptions.com

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	Adults with deleterious or suspected deleterious ***BRCA*-mutated mCRPC** ▪Select using approved companion diagnostic	Adults with **HRR gene–mutated mCRPC** ▪Select based on presence of HRR gene mutations ▪Approved diagnostic not currently available
Approved genes: *BRCA1* *BRCA2*	**Approved genes:** *BRCA1* *BRCA2*	**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

aparib 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	Sour
atic Cancer atic, germline gBRCA) mutated, ne 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;381:3 327
e Cancer atic, Castration nt A (pt 245) : at ne alteration in , BRCA2, or ATM; B (142 patients) erations in any of r prespecified	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;382:2 2102
b, with abiraterone ednisone, for mutated metastatic ion-resistant e 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 On . 2023 Oct;24(10) 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
- Docetaxel
- Sipuleucel-T
- Radium-223
- 177-Lu-PSMA-617
- Abiraterone
- Enzalutamide
- Niraparib + Abiraterone (1L)
- Olaparib + Abiraterone (1L)
- Talazoparib + Enzalutamide (1L)
- Olaparib
- Rucaparib
- Pembrolizumab (for dMMR/MSI-H or TMB-H)

Selected based on genomic markers

Not selected based on genomic markers

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

Slide credit: clinicaloptions.com

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)

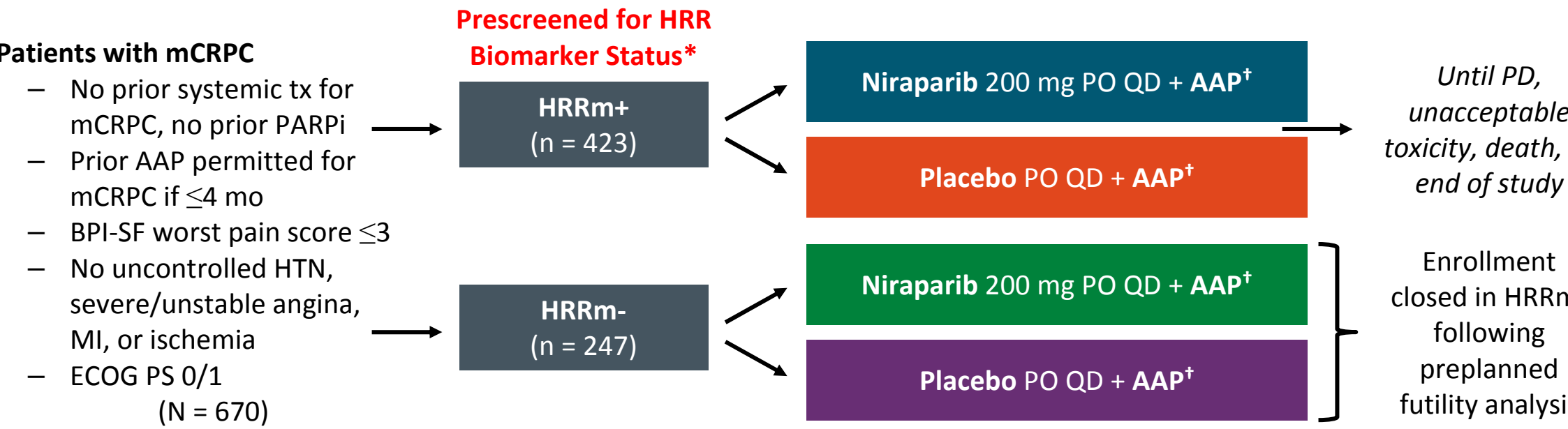
BRCA-mutated castration-resistant prostate cancer (mCRPC)

- The fixed dose combination of niraparib and abiraterone acetate with prednisone (2023)

ndication	Trial Name	Comparative Protocol	Progression-Free Survival (PFS)	Overall Survival (OS)	Adverse Effects	S
Cancer nt, platinum- e, 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 Eng 2016;3 2164 EClini e. 202 7;72:1 NORA
e maintenance t of advanced cancer in a e or partial e to first-line -based erapy.	PRIMA Pt 733, 373 (50.9%) with homologous-recombination deficiency. (HRD)	Niraparib 300mg qd 36 months or disease in progression vs. Placebo	HRD (+) : 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 Eng 2019;3 2402
Cancer tic, castration- , 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 . 2023 20;41(335

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

- International, randomized, double-blind phase III trial



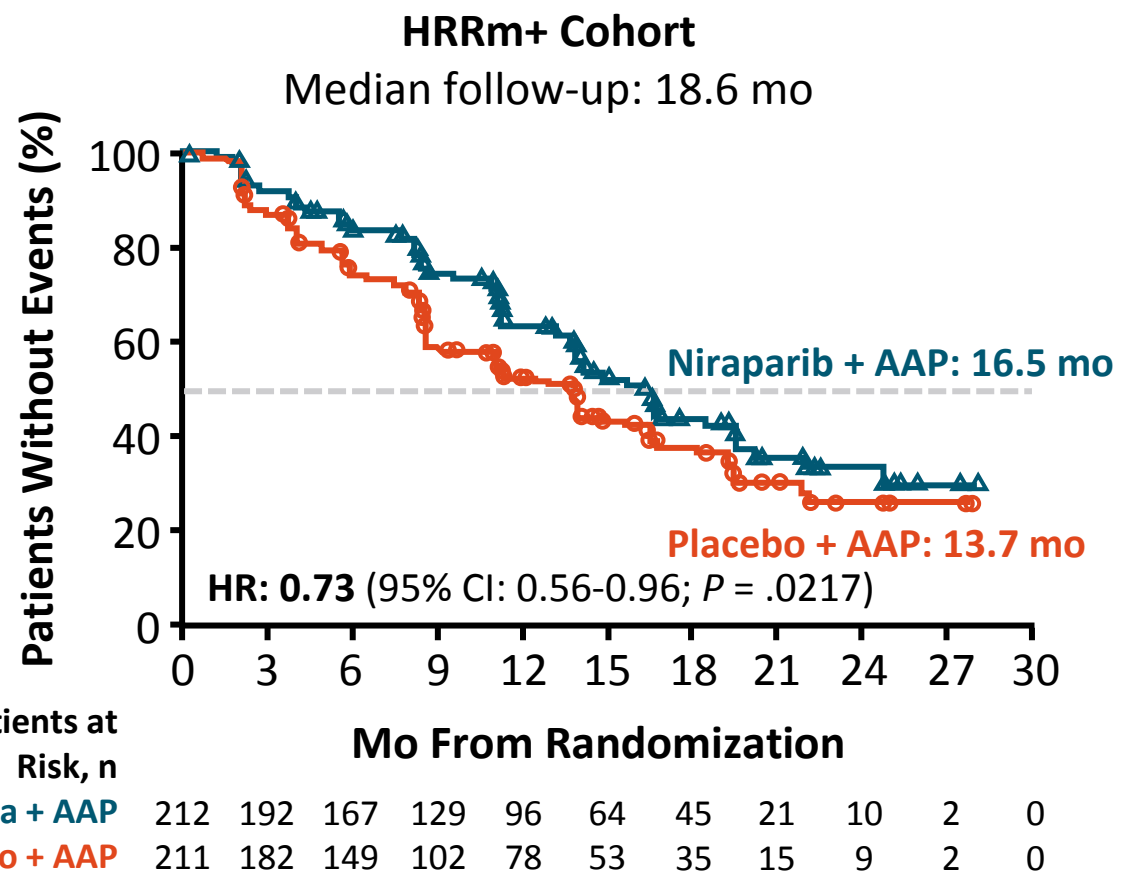
*HRRm+ per tissue and/or plasma assays for ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***.
†AAP: abiraterone acetate 1000 mg PO QD + prednisone 10 mg PO QD.

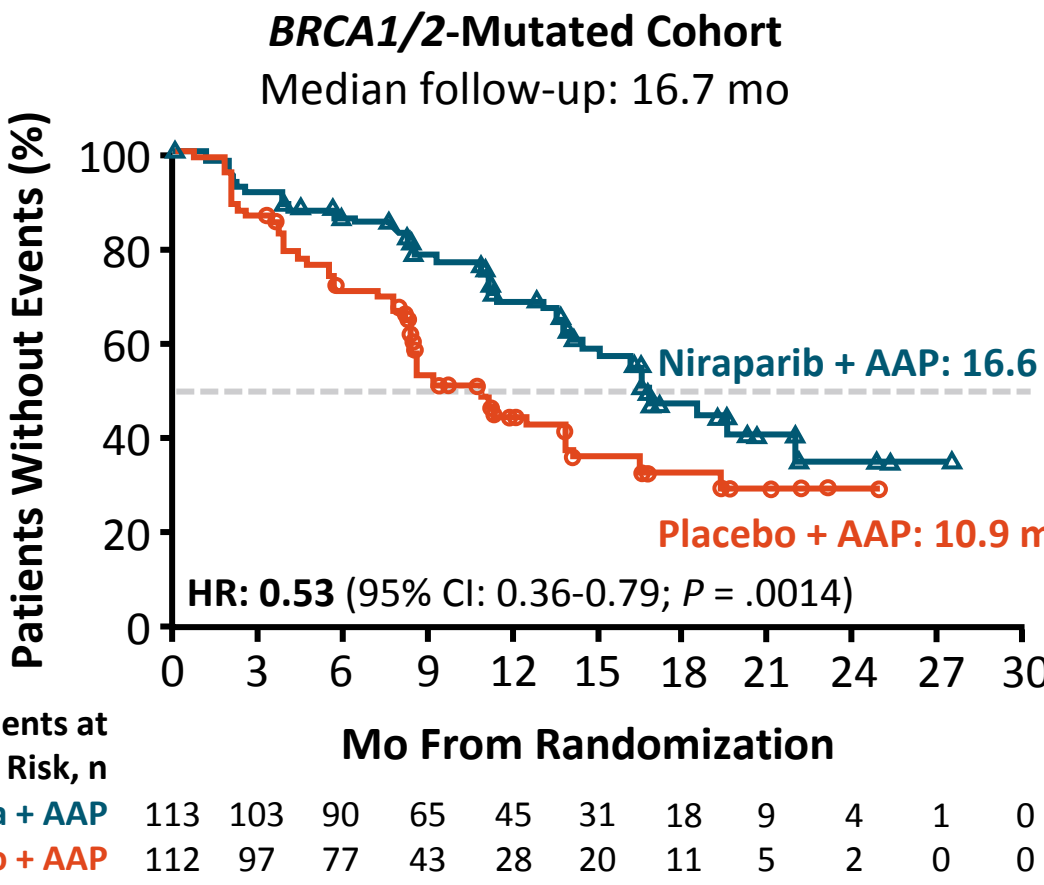
- **Primary endpoint:** rPFS by central review
- **Secondary endpoints:** OS, time to cytotoxic CT, time to symptomatic progression
- Prior taxane in 19.3%-25.9%, prior AAP for 1L mCRPC in 22.7%-26.5%, prior ARPI for nmCRPC/mHSPC in 2.4%-5.3%

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

Slide credit: clinicaloptions.com

MAGNITUDE: Radiologic PFS by Central Review (Primary Endpoint)

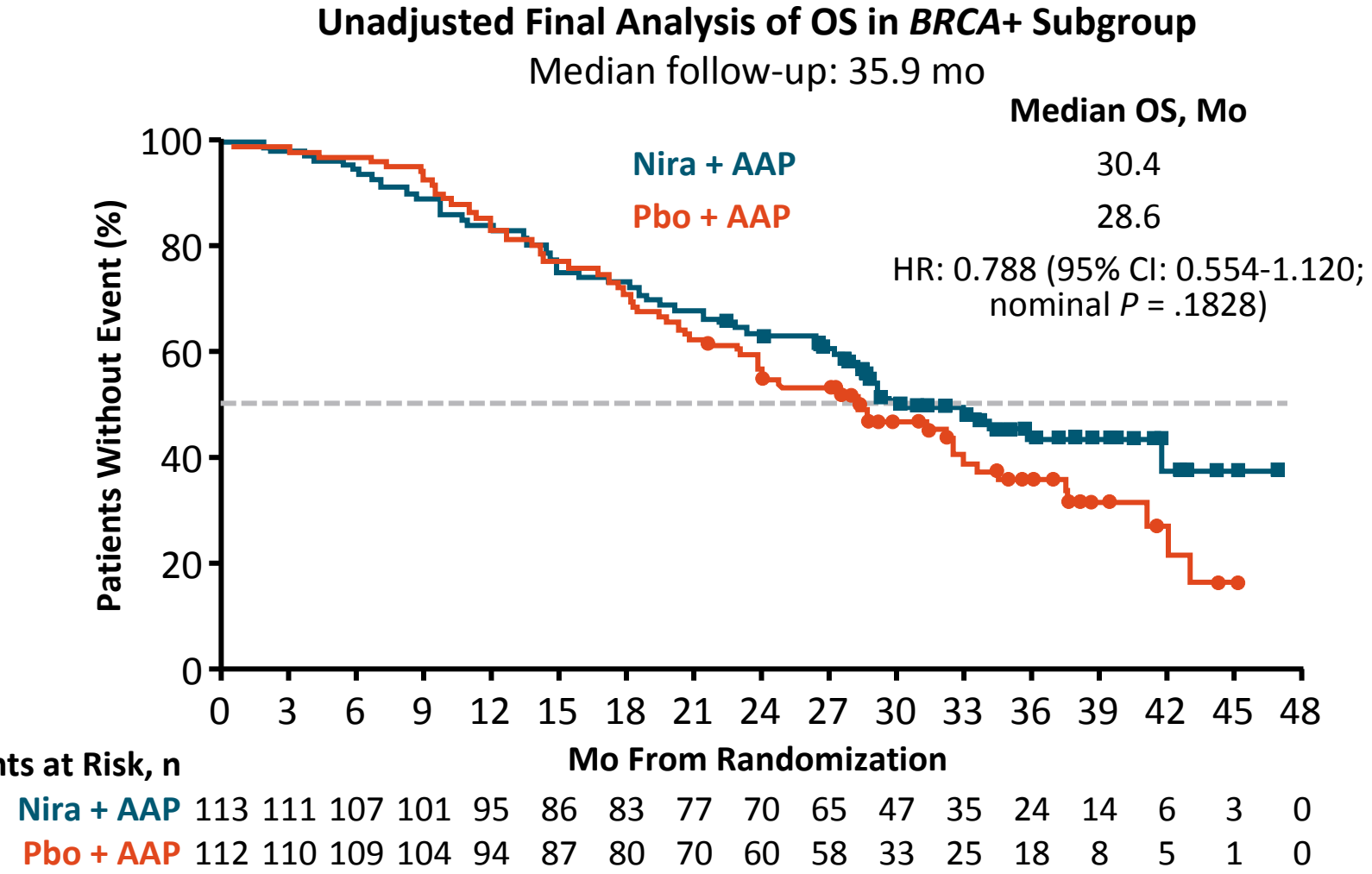




ASCO GU 2022. Abstr 12. Chi. JCO. 2023;41:3339.

Slide credit: clinicaloptions.com

MAGNITUDE: Final OS Analysis in *BRCA*+ Subgroup



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

ESMO 2023. Abstr LBA85.

Slide credit: clinicaloptions.com

Rucaparib 2017 創新不足

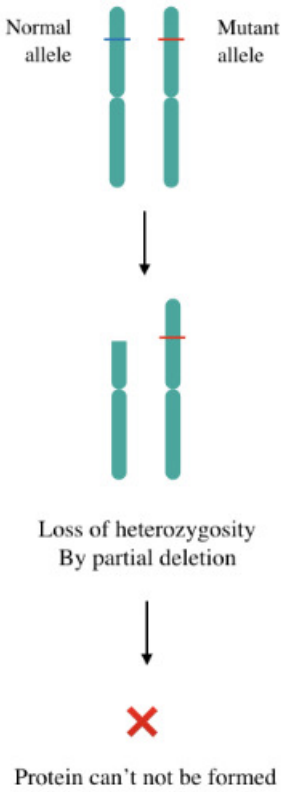
lovis filed for bankruptcy in 2023

varian cancer (epithelial ovarian, fallopian tube, 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)

rostate 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

ndication	Trial Name	Comparative Protocol	Overall Response Rate	Median Progression-Free Survival (PFS)	Adverse Effects	So
d Ovarian BRCA mutated) loss of gosity (LOH))	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 . 2017 Jan;18(
nt Ovarian Maintenance) CA mutant or ld-type and high eterozygosity),	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 28;390 949-19
ovarian cancer eterious r *BRCA2* rucaparib should be used for third- er treatment in ents	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 2022 Apr;23(478

dication	Trial Name	Comparative Protocol	Overall Response Rate	Median Progression-Free Survival (PFS)	Adverse Effects	Sc
erapy as ance Treatment nts With Newly ed Ovarian (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 . 2022 1;40(3 3964
tic Castration-nt Prostate (mCRPC, BRCA)	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 . 2020 10;38(3772

DA-Approved Indications and Withdrawals for PARP Inhibitors in Ovarian Canc

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

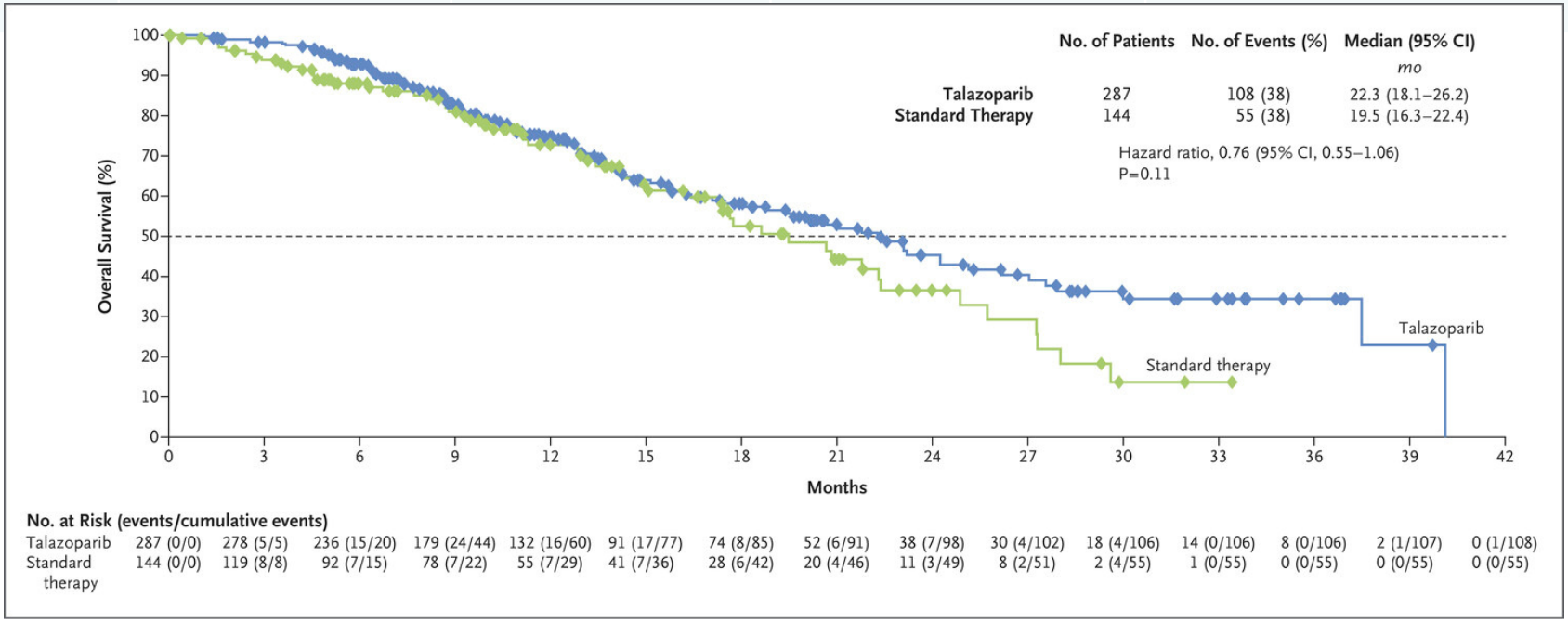
Talazoparib (Talzenna, 達勝癌) 2018 (模仿改進者)

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)

A Approval dication	Phase 3 Trial Name	Comparison Protocol	Overall Response Rate	Progression Free Survival	Adverse Effects	Sou Jo
negative, -mutated advanced or atic breast	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 2018;37
Cancer static, HER2-, A 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 2017;37



Approval ication	Phase 3 Trial Name	Comparison Protocol	Progression Free Survival	Overall survival	Adverse Effects	Sou Jou
tatic tion- ant te cancer PC) with defects tigational)	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 Ju 22;402(1 303
ib, with erone and sone, for -mutated tatic tion- ant te cancer	PROpel 399 pts abiraterone+ prednisolone ±olaparib (399 vs 397 pts (placebo)	Olaparib+abirater one / prednisone vs Abiraterone+pred nisolone		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 . 2023 Oct;24(-1108

A Damage and Repair (DDR)

R 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		
arib	Ph III PROpel ***Met primary endpoint***	Ph III KEYLYNK-010	Ph II NCT03810105	Ph I/II COMRADE* NCT03317392	Ph I LuPARP* NCT03874884	Ph II NCT02893
	Abiraterone	**Pembrolizumab**	**Durvalumab**	**Radium-223**	**^{177}Lu-PSMA-617**	**Cediranib (V**
arib	Ph III TALAPRO-2 ***Met primary endpoint***			Ph II† NCT04824937	Ph I* NCT04846478	Ph I* NCT04703
	Enzalutamide			**Telaglenastat (GLSi)**	**Tazemetostat (EZH2i)**	**Belinostat (H**
arib	Ph III CASPAR NCT04455750	Ph II CheckMate 9KD NCT03338790		Ph II PLATI-PARP NCT03442556	Phase I/II NCT04253262	
	Enzalutamide	**Nivolumab**		**Chemotherapy**	**Copanlisib (PI3Ki)**	
arib	Ph III MAGNITUDE ***Met primary endpoint***	Ph I/II QUEST NCT03431350		Ph I NiraRad NCT03076203		
	Abiraterone	**Cetrelimab**		**Radium-223**		

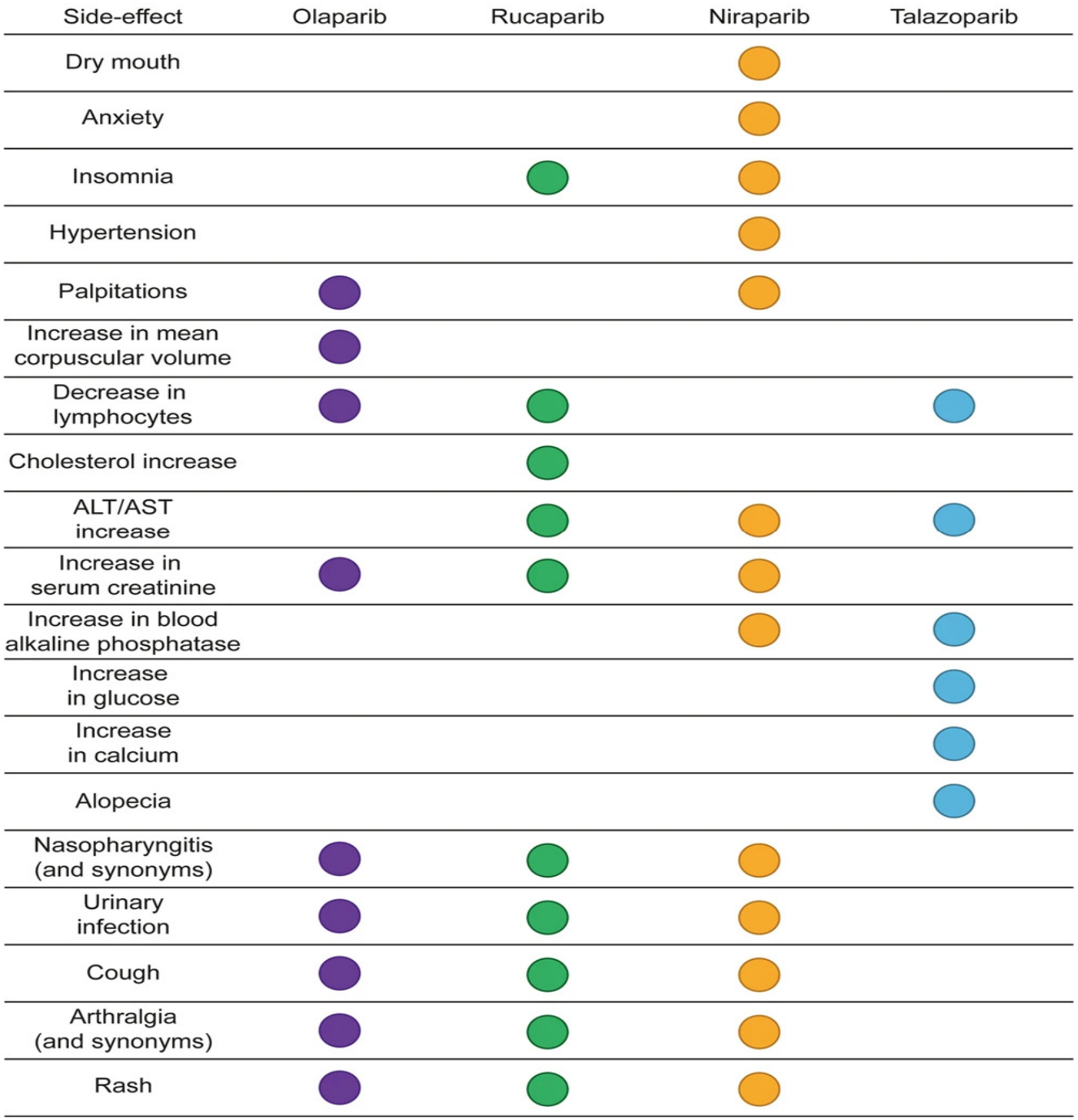
ls active as of January 2024. *Recruiting. †Not yet recruiting.

Phase III

Early phase

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
g	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)
o take	With/without food (taking at bedtime or 30-60 min after meal may help with nausea)			
ment ne)	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 m qd
ctions	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
or dose ions for ctions	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

rgue. 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

raterone 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.

Thank you for listening