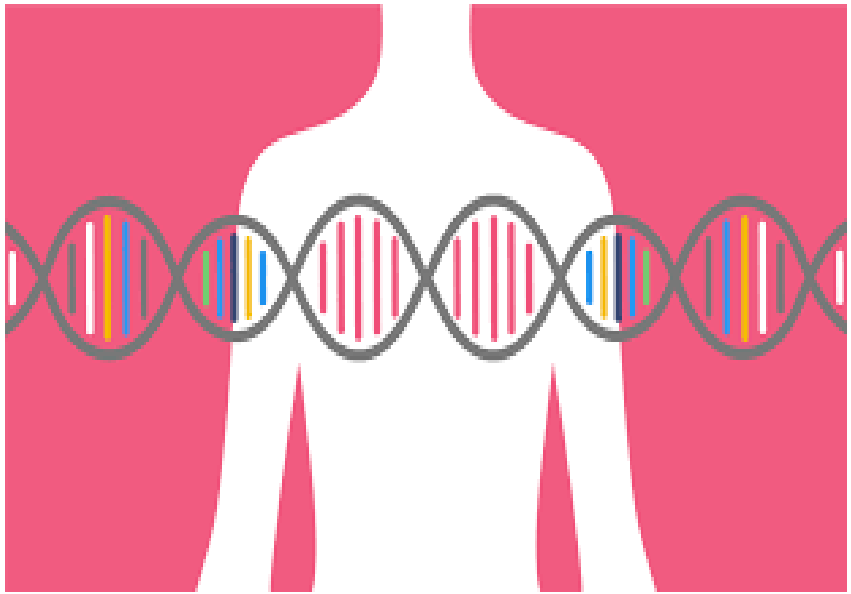
TUMORI FEMMINILI E BRCA: IL PRESENTE PER CAMBIARE IL FUTURO

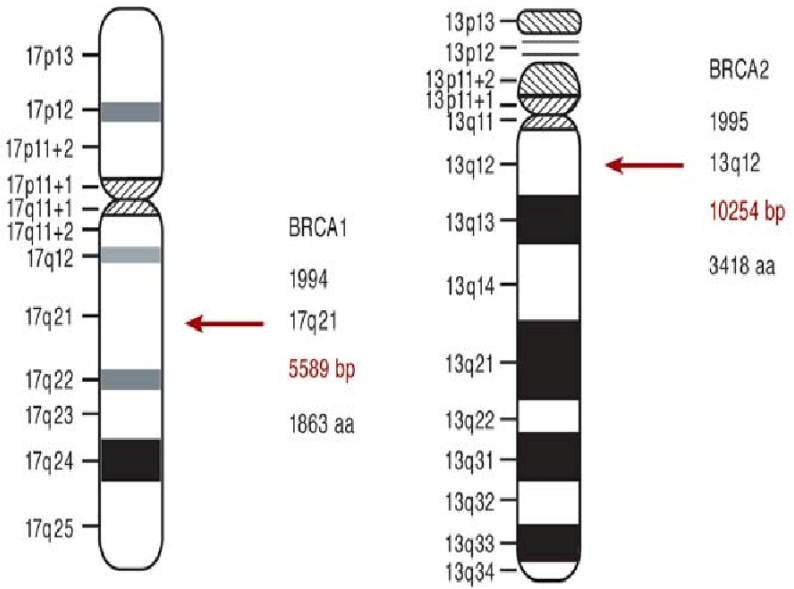


L’esito del test BRCA e le sue implicazioni cliniche nelle pazienti affette da tumori femminili

Udine, 20 settembre 2023

Dr.ssa Elena Poletto

BRCA1 and BRCA2



- BRCA 1 and 2 are proteins normally expressed in tissues → they help repair damaged DNA or destroy cells if DNA cannot be repaired
- If BRCA itself is damaged by a BRCA mutation → damaged DNA is not repaired properly → increased risk of developing cancer cells (mainly for loss of tumor suppressive function)
- BRCA1:
  - Absolute risk breast cancer > 60%
  - Absolute risk ovarian cancer 39-58%
- BRCA2
  - Absolute risk breast cancer > 60%
  - Absolute risk ovarian cancer 13-29 %

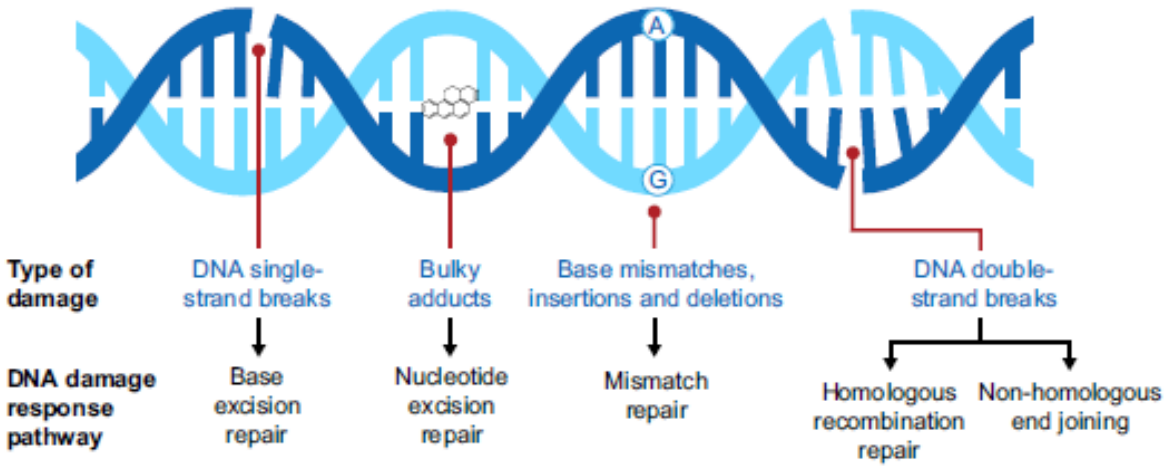
NCCN 2023

BRCA clinical implications

BRCA clinical implications: Achille's heel-> PARP inhibitors

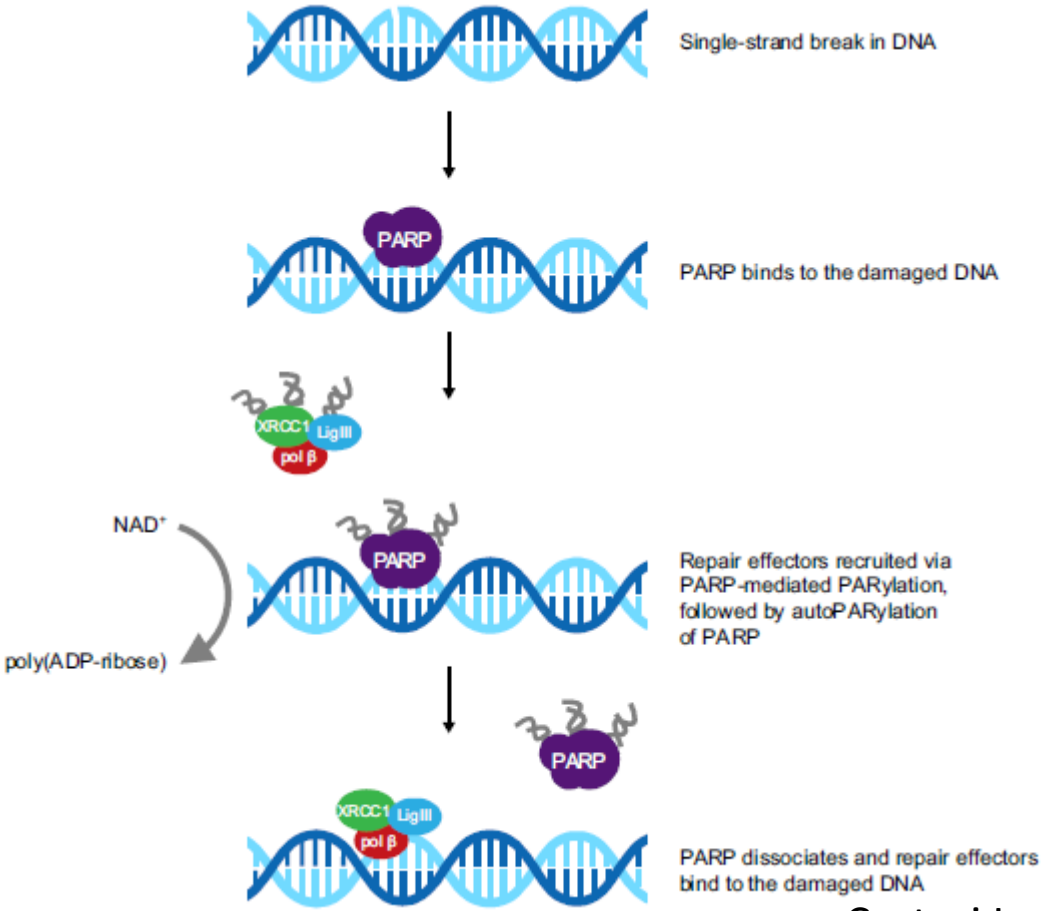
PARP-inhibitors: mechanism of action (1)

DNA damage response pathways



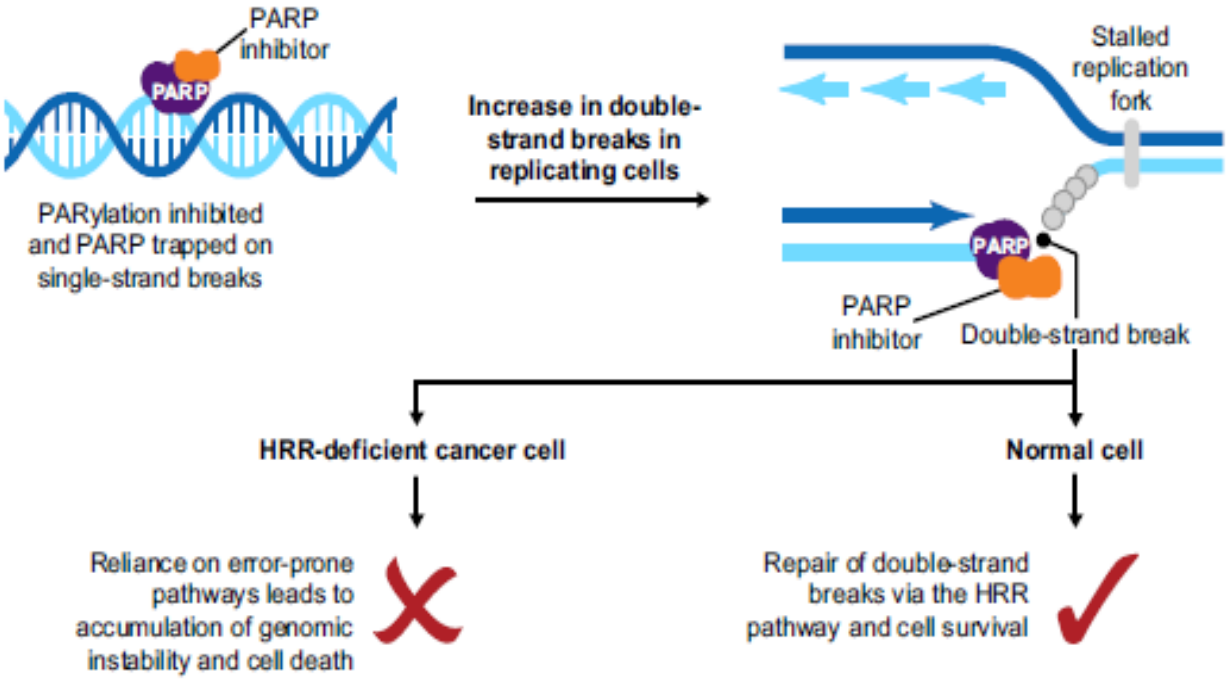
Cortesi L et al Targeted Oncology 2021

PARP-inhibitors: mechanism of action (2)



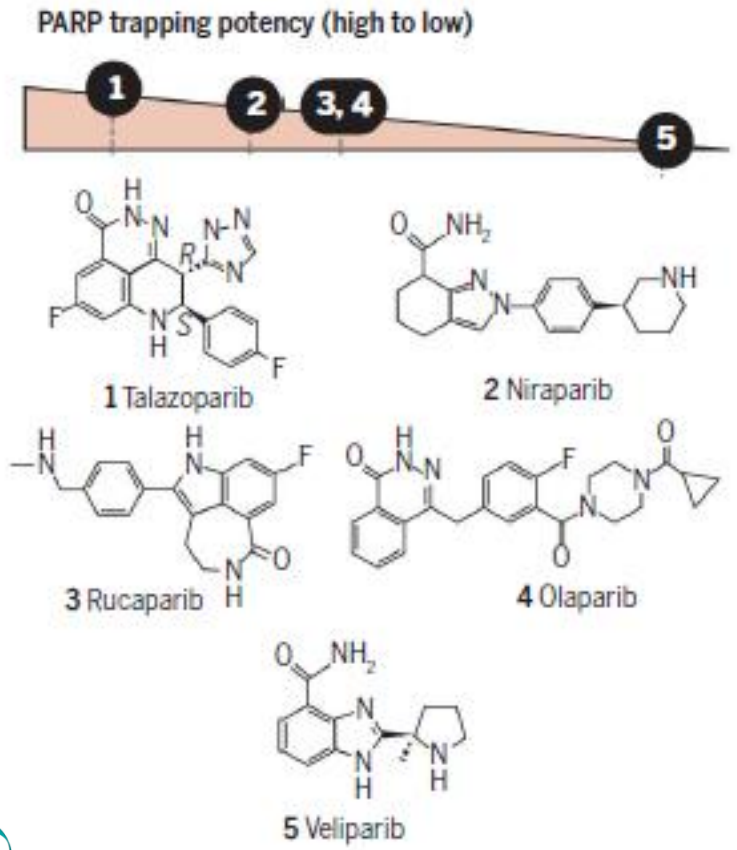
Cortesi L et al Targeted Oncology 2021

PARP-inhibitors: mechanism of action (3)



Cortesi L et al Targeted Oncology 2021

PARP-inhibitors



OVARIAN CANCER:

- Olaparib:
  - first line BRCAm maintenance/plus bevacizumab in HRD positive disease
  - Beyond first line-> BRCAm maintenance platinum sensitive disease
- Niraparib:
  - first line maintenance
  - Beyond first line -> maintenance platinum sensitive disease
- Rucaparib:
  - Beyond first line -> maintenance platinum sensitive disease

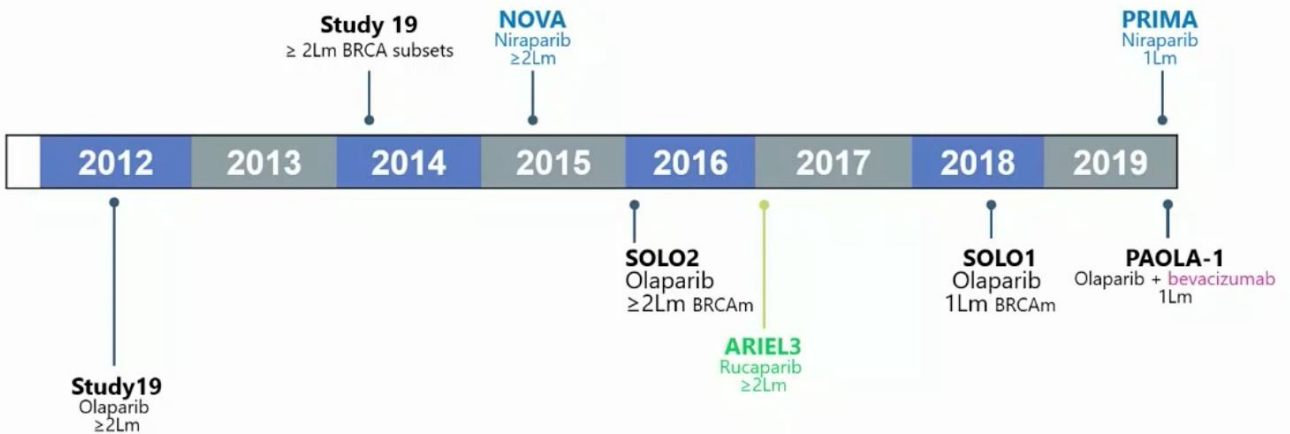
BREAST CANCER:

- Olaparib:
  - Adjuvant treatment high risk BRCA muated breast cancer
  - Metastatic BRCA mutated breast cancer
- Talazoparib:
  - Metastatic BRCA mutated breast cancer

PARP inhibitors in ovarian cancer

BRCA mutations open the door to biomarker directed therapy of ovarian cancer

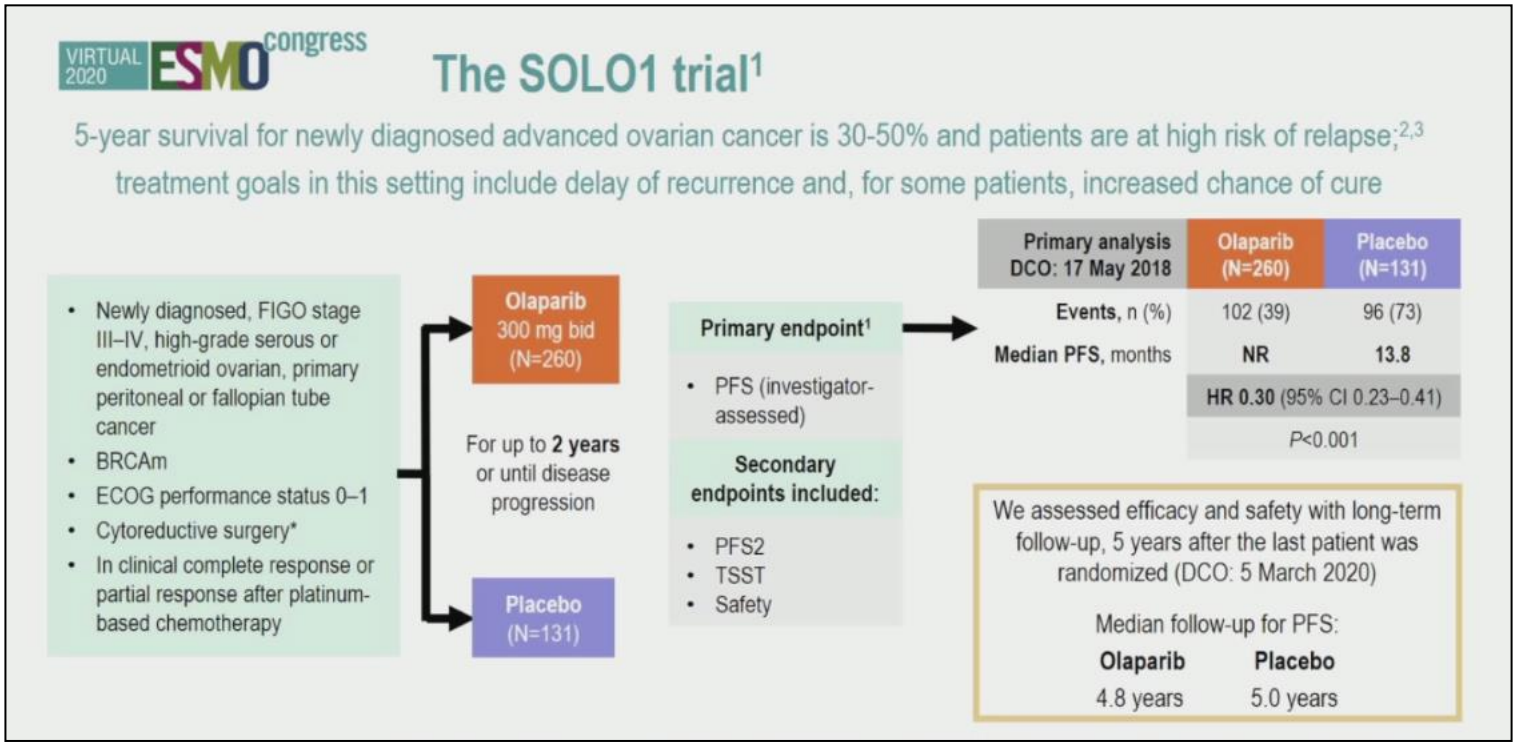
A decade of maintenance therapy in advanced ovarian cancer



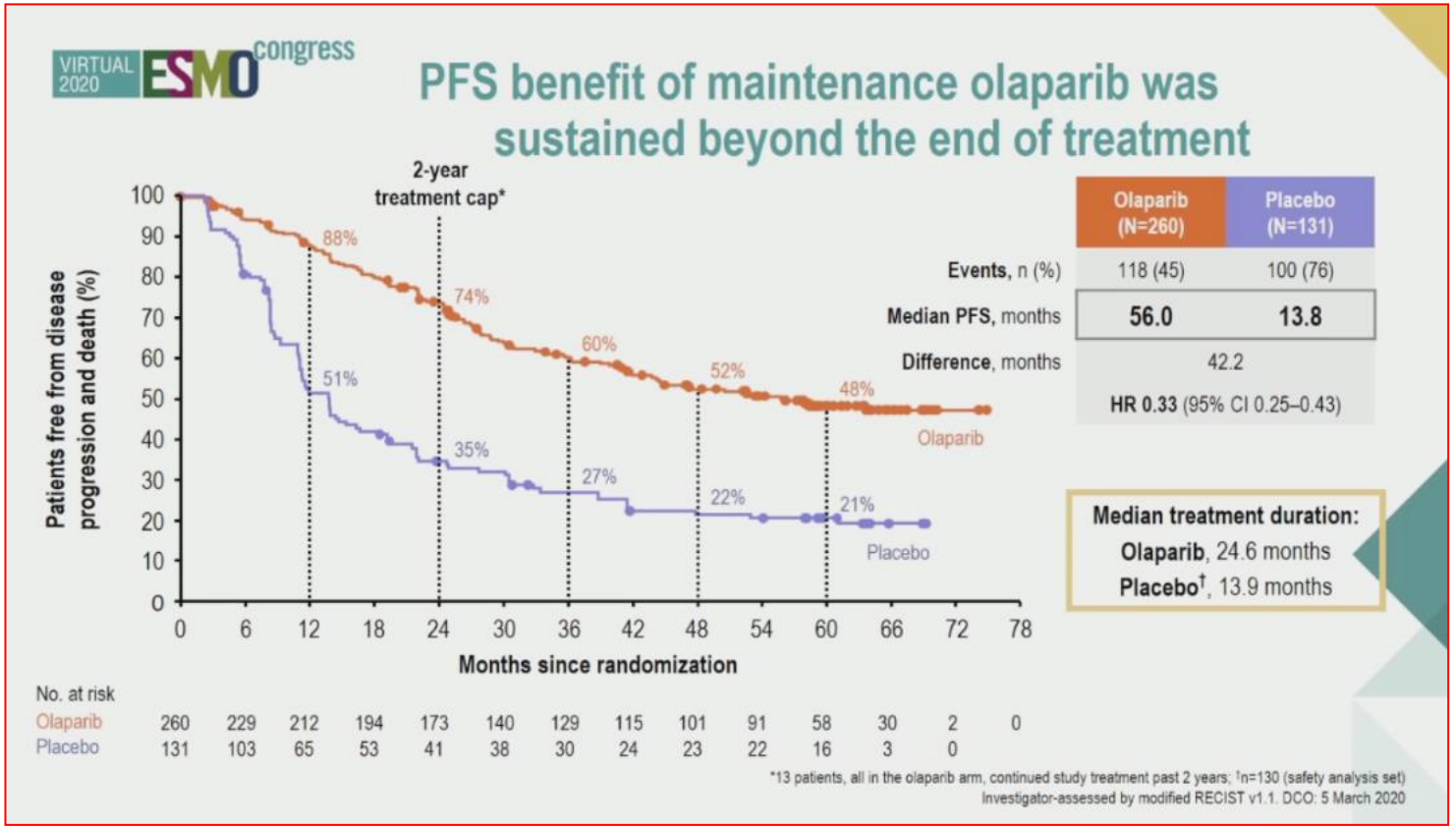
PARIS 2022 ESMO congress

1. Ledermann J, et al. N Engl J Med 2012;366:1382–92; 2.Ledermann et al Lancet Oncol 2014 15: 852-61.3. Mirza MR, et al. N Engl J Med 2016;375:2154–64;; 4. Pujade-Lauraine E, et al. Lancet Oncol 2017;18:1274–84; 5. Coleman R, et al. Lancet 2017;390:1949–61; 6. Moore K, et al. N Engl J Med 2018;379:2495–505; 7. González Martín A, et al. N Engl J Med 2019;381:2391–402; 8. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–28.

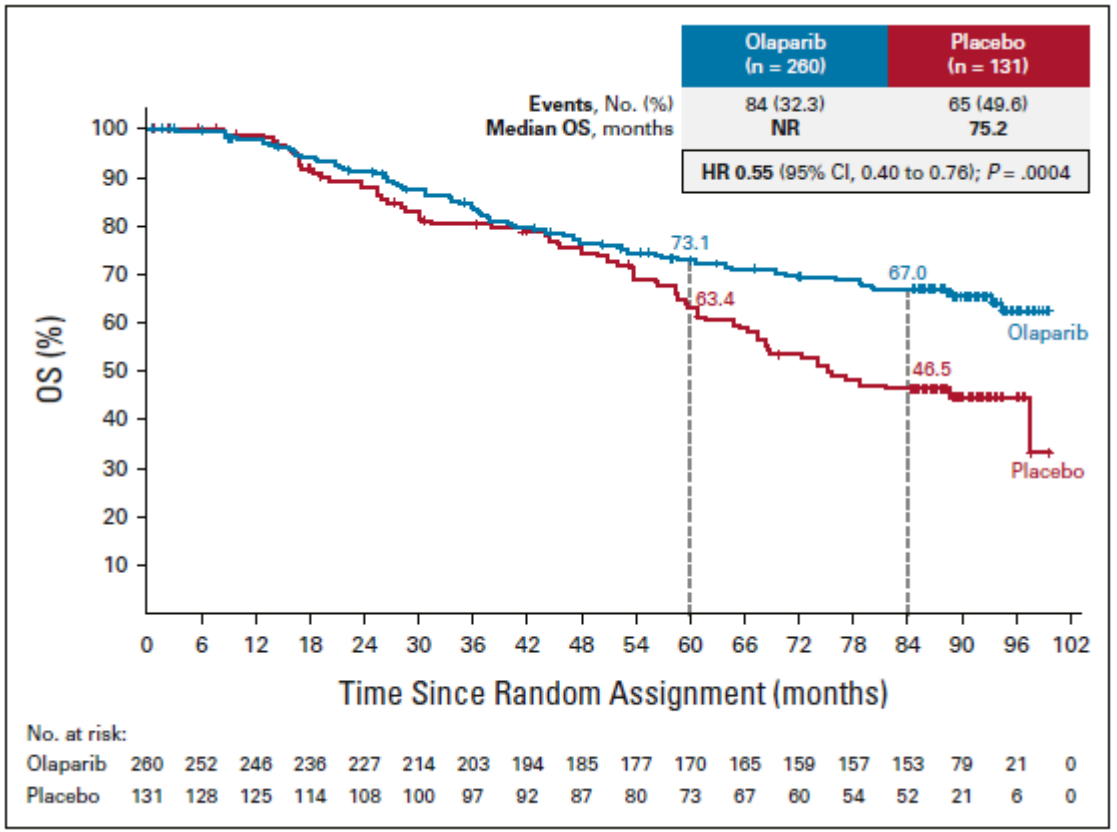
OLAPARIB 1° line ovarian cancer



OLAPARIB 1° line ovarian cancer: PFS

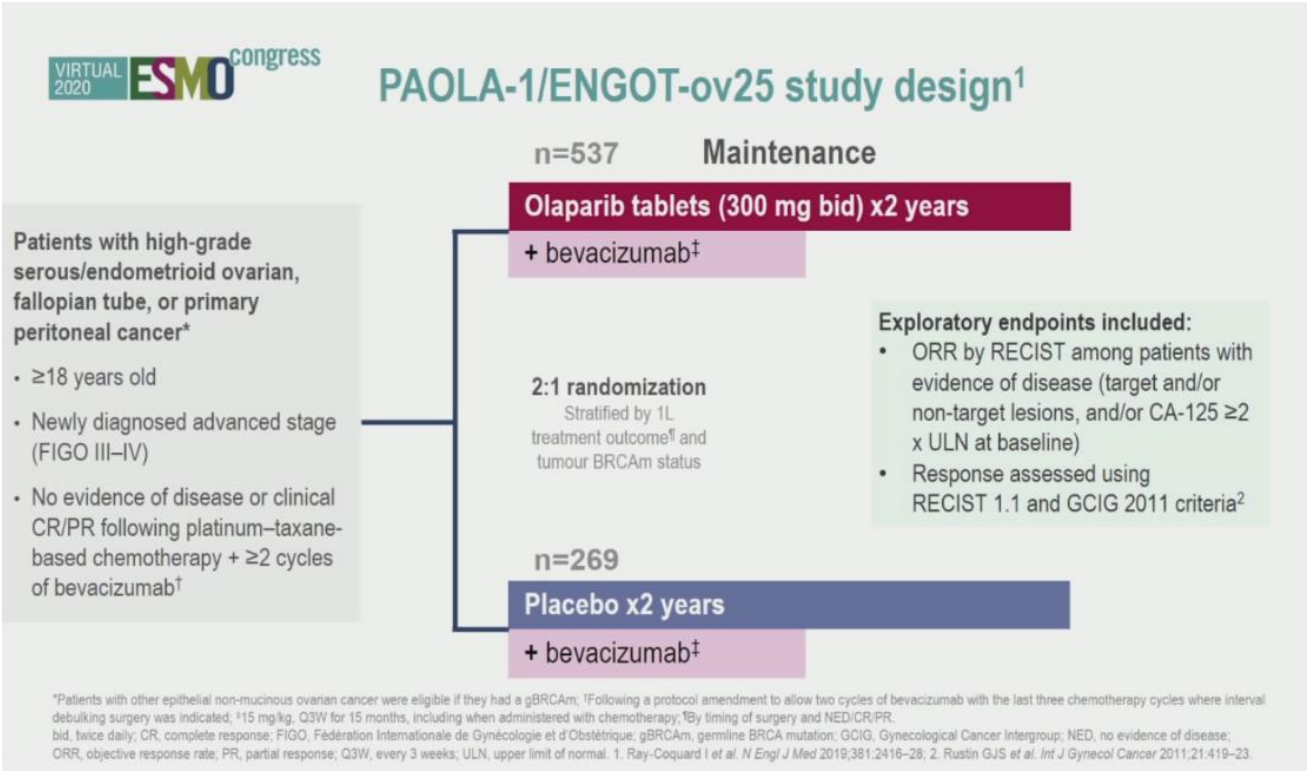


OLAPARIB 1° line ovarian cancer: OS



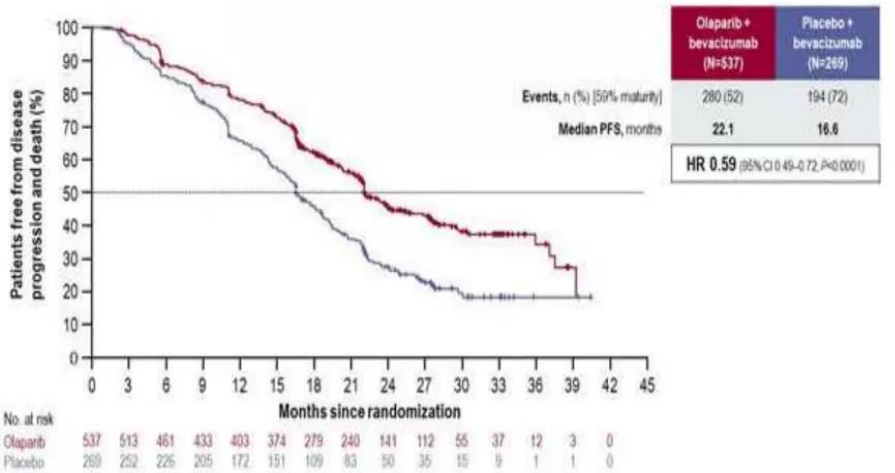
DiSilvestro P et al J Clin Oncol 2022

OLAPARIB 1° line ovarian cancer



OLAPARIB 1° line ovarian cancer: PFS

PFS by investigator assessment: ITT population

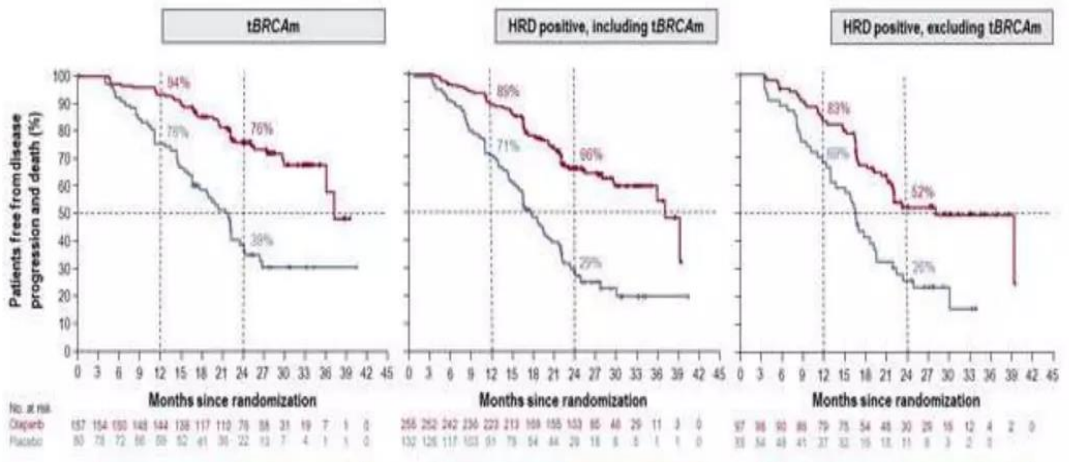


	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	22.1	16.6
HR 0.59 (95% CI 0.49–0.72; P<0.0001)		

Median time from first cycle of chemotherapy to randomization = 7 months

ITT, intention-to-treat population
Median follow up for PFS was 24.0 months in the olaparib + bevacizumab arm and 22.7 months in the placebo + bevacizumab arm

PFS by *tBRCA* mutation status and HRD status

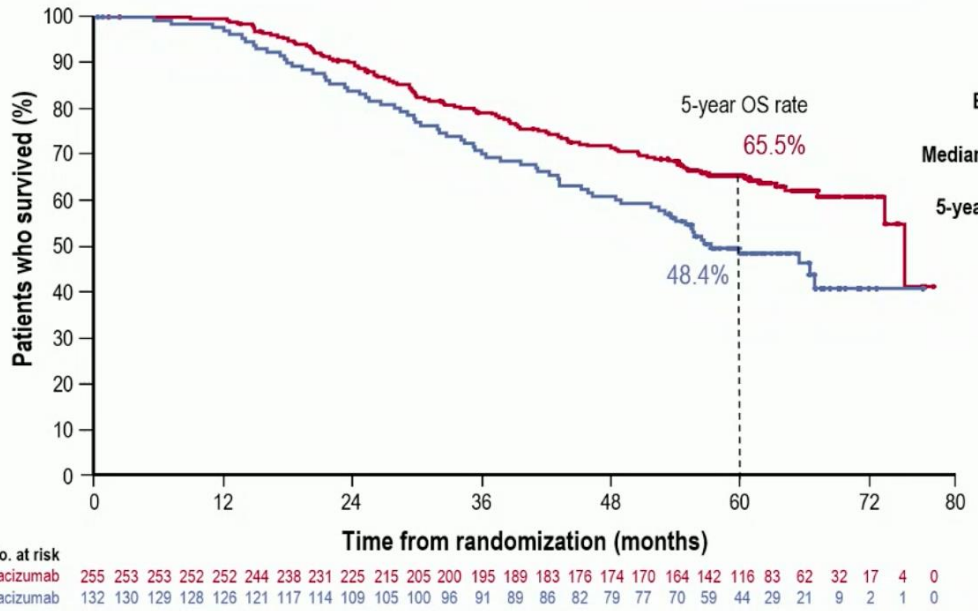


	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events, n (%)	41 (26)	46 (61)	87 (34)	92 (70)	43 (44)	40 (73)
Median PFS, months	37.2	21.7	37.2	17.7	28.1	16.6
	HR 0.31 (95% CI 0.20–0.47)		HR 0.33 (95% CI 0.25–0.45)		HR 0.43 (95% CI 0.28–0.66)	

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42

OLAPARIB 1° line ovarian cancer: OS

OS was prolonged in the HRD-positive subgroup



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62 (95% CI 0.45–0.85)

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

*Median unstable; <50% data maturity.
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

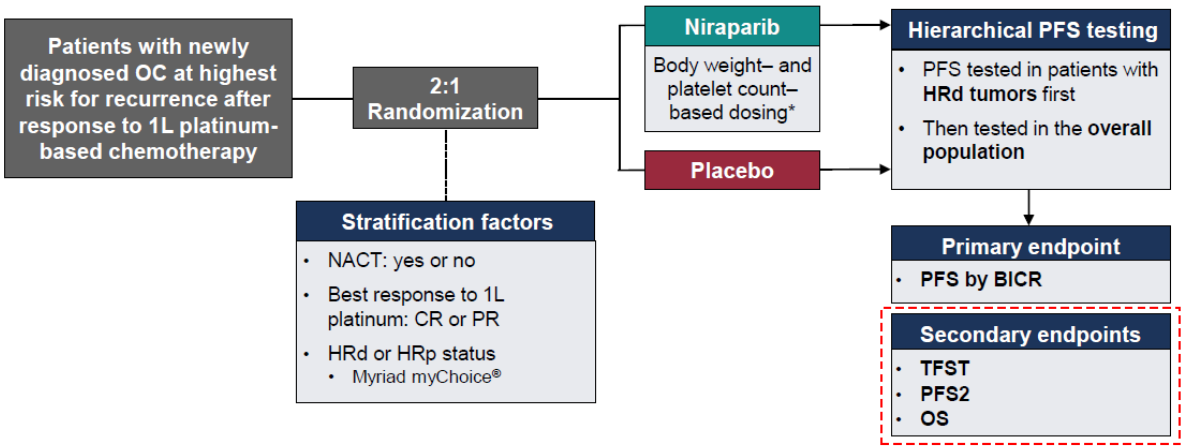
PARIS 2022 ESMO congress

Isabelle Ray-Coquard

NIRAPARIB 1° line ovarian cancer

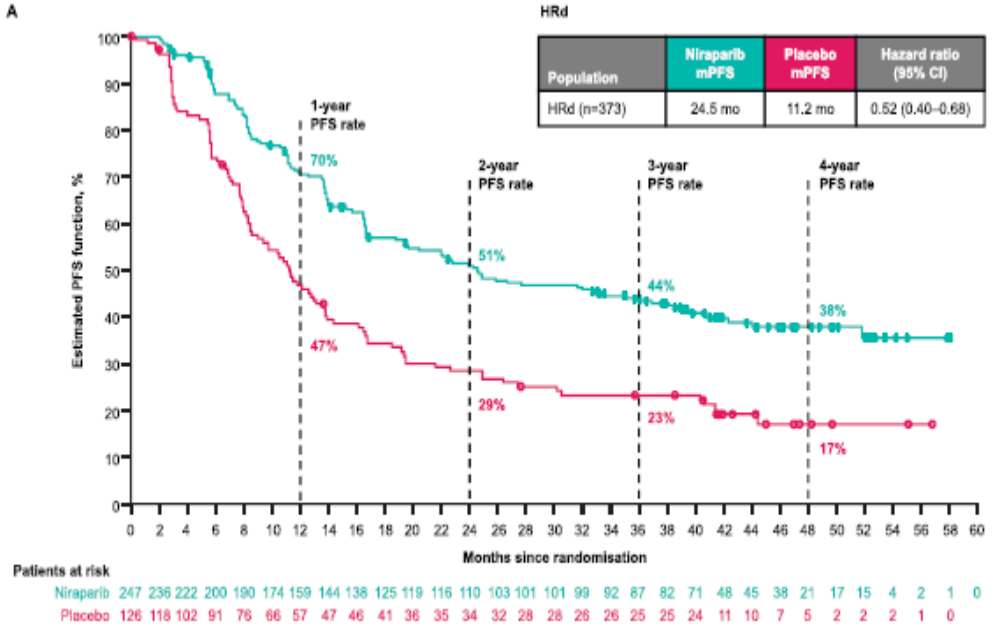
PRIMA Trial Design

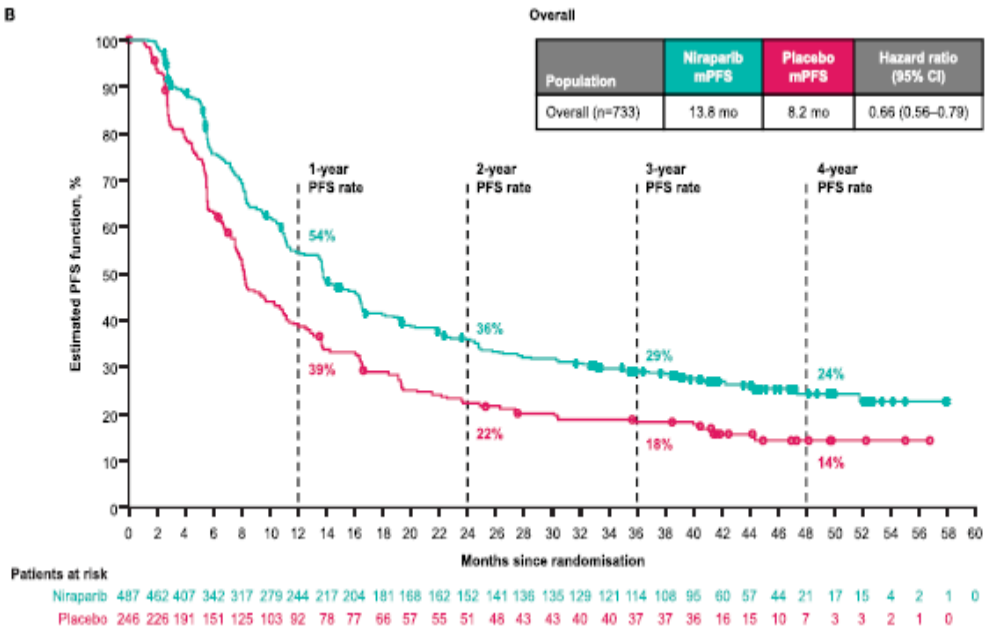
- PRIMA is a randomized, double-blind, placebo-controlled phase 3 trial of niraparib as 1L maintenance treatment after response to platinum-based chemotherapy
- OS was a key efficacy secondary endpoint
- PFS2 and TFST were additional efficacy secondary endpoints



Patients received treatment until disease progress or a maximum of 36 months.
*After November 27, 2017, patients with body weight <77 kg and/or platelet count <150,000/μL started at 200 mg QD; all other patients started at 300 mg QD.
1L, first-line; BICR, blinded independent central review; CR, complete response; HRd, homologous recombination deficient; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; QD, once daily; TFST, time to first subsequent therapy.

NIRAPARIB 1° line ovarian cancer: PFS





Gonzalez-Martin A Eur J Cancer 2023

OLAPARIB in relapsed ovarian cancer

SOLO2: study design

Eligible patients had:
- Relapsed, high-grade serous or endometrioid ovarian cancer*
- BRCAm
- Received ≥2 previous lines of platinum-based chemotherapy
- Responded to most recent platinum regimen

Olaparib 300 mg bid

2:1 randomization

Stratified by:
- Response to previous chemotherapy†
- Length of platinum-free interval‡

Placebo

Study treatment continued until disease progression§

Primary endpoint
- Investigator-assessed PFS

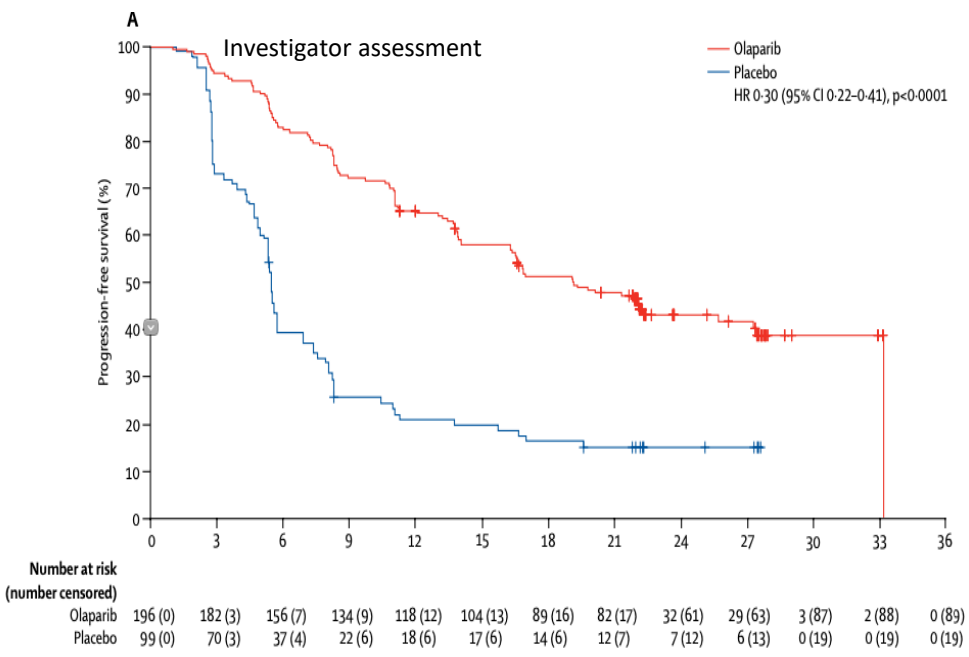
Time-dependent secondary endpoints
- Overall survival
- PFS2
- TFST
- TSST
- TDT
- HRQoL¶

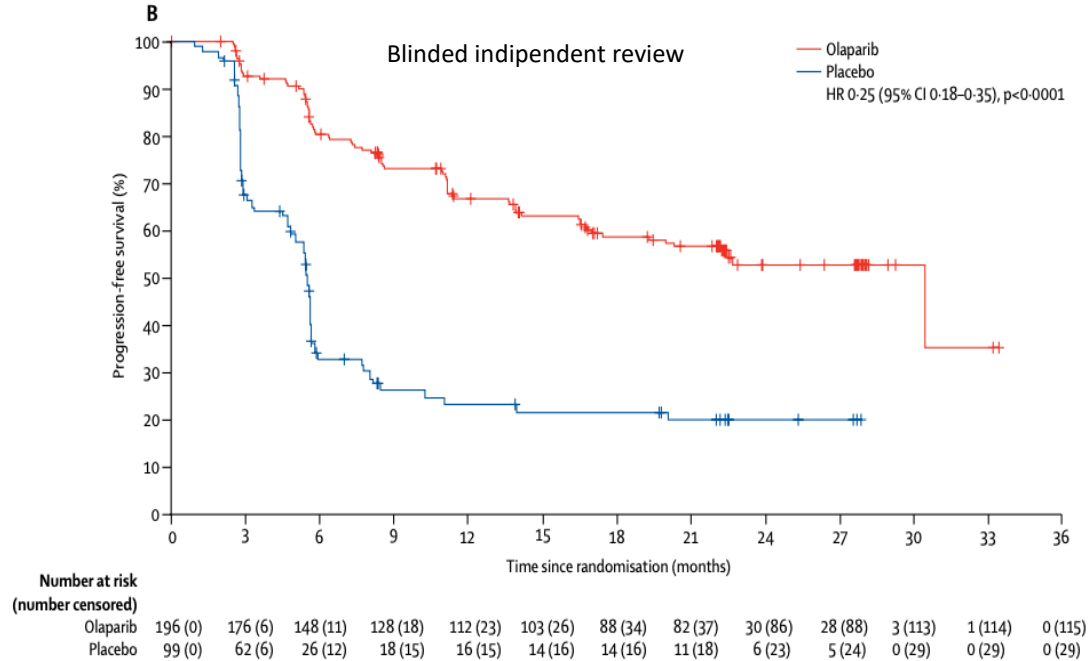
Final analysis
DCO: Feb 3, 2020
- Planned for **60% data maturity** (~177 events)
- **Prespecified adjusted OS analysis (RPSFT model, re-censored)**: to adjust for subsequent PARP inhibitor therapy in placebo group
- ***Post hoc* OS sensitivity analysis (eCRF)**: to correct for patients mis-stratified at randomization
- **Prespecified OS sensitivity analysis**: Myriad gBRCAm subgroup

*Includes primary peritoneal or fallopian tube cancer; †Complete or partial response; ‡>6–12 or >12 months; §Or until discontinuation criteria were met, and treatment could continue beyond progression if the investigator deemed the patient be experiencing benefit; ¶Assessed by the TOI of the FACT-O

eCRF, electronic case report form; gBRCAm, germline BRCA mutation; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; HRQoL, health-related quality of life; PFS2, time to second progression; RPSFT, rank preserving structural failure time model; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent therapy or death; TOI, trial outcome index; TSST, time to second subsequent therapy or death

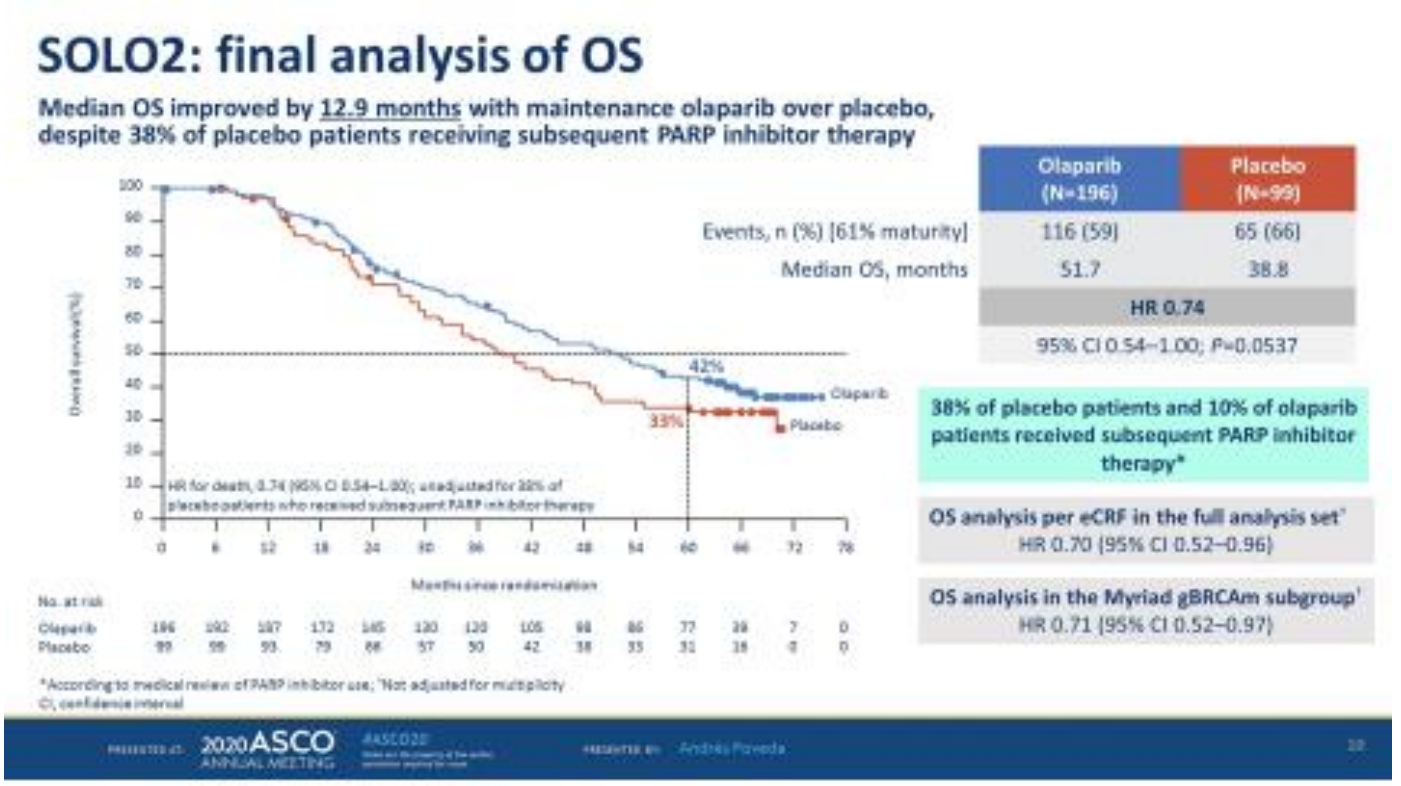
OLAPARIB in relapsed ovarian cancer:PFS





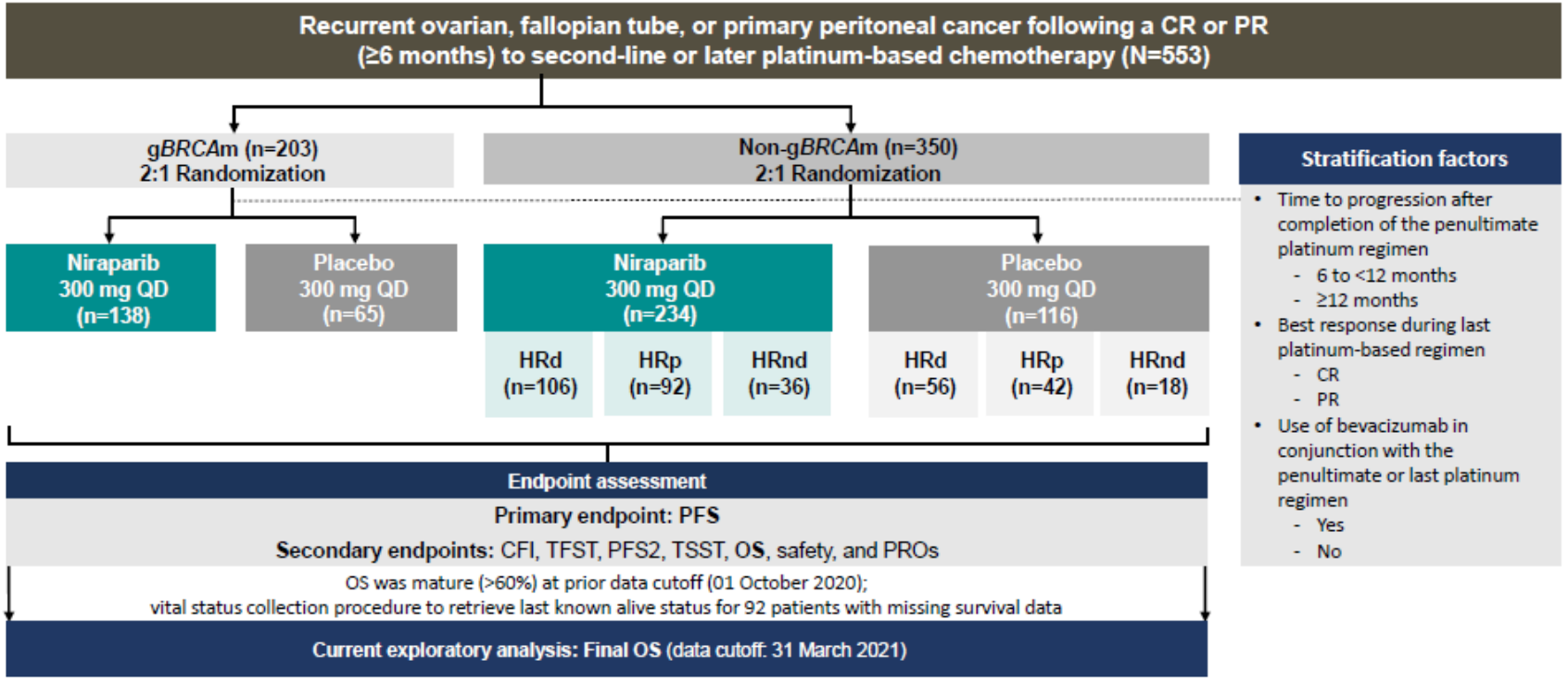
Pujade-Lauraine Lancet Oncol 2017

OLAPARIB in relapsed ovarian cancer: OS



Poveda A ASCO 2020

NIRAPARIB in relapsed ovarian cancer



CFI, chemotherapy-free interval; CR, complete response; g*BRCA*m, germline *BRCA*-mutated; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression or death; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

SGO ANNUAL MEETING ON WOMEN'S CANCER TAMPA, FL • 2023

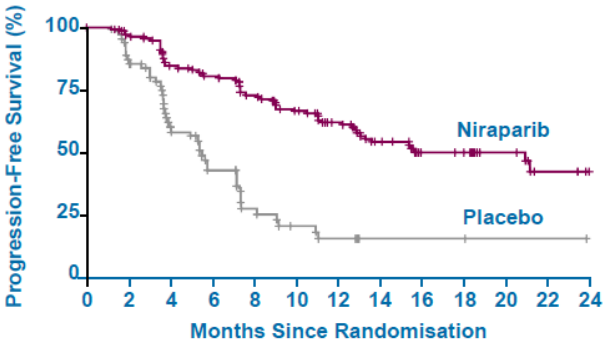
Presented by Dr. Ursula A. Matulonis

NSGO-CTU Nordic Society of Gynaecological Oncology - Clinical Trial Unit

ENGOT European Network of Gynaecological Oncological Trial groups

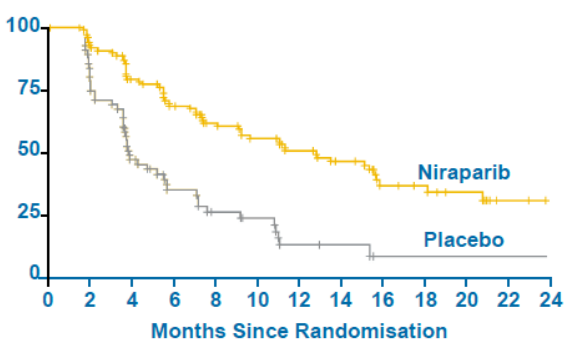
NIRAPARIB in relapsed ovarian cancer: PFS

g*BRCA*m



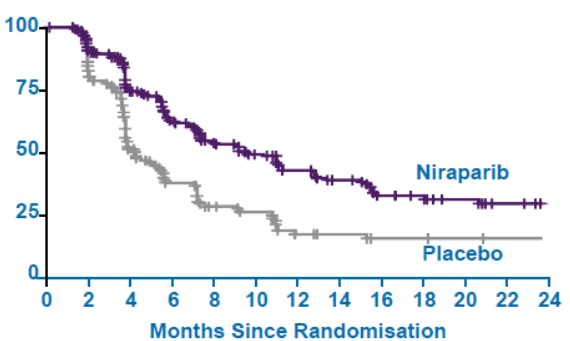
Treatment	BICR PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) *P* Value
Niraparib (N=138)	21.0 (12.9, NR)	0.27 (0.173, 0.410) *P*<.0001
Placebo (N=65)	5.5 (3.8, 7.2)	

HRD+



Treatment	BICR PFS Median (95% CI) (months)	Hazard Ratio (95% CI) *P* Value
Niraparib (N=106)	12.9 (8.1, 15.9)	0.38 (0.243, 0.586) *P*<.0001
Placebo (N=56)	3.8 (3.5, 5.7)	

Non-g*BRCA*m



Treatment	BICR PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) *P* Value
Niraparib (N=234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607) *P*<.0001
Placebo (N=116)	3.9 (3.7, 5.5)	

BICR, blinded independent central review; ENGOT, European Network for Gynaecological Oncological Trial Groups; HRD, homologous recombination deficiency; NR, not reached

1. Centre for Drug Evaluation and Research: Multidisciplinary review. www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf. Accessed 25 January 2019. 2. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-2164.

Mirza New Engl J Med 2016

NIRAPARIB in relapsed ovarian cancer: OS

TABLE 1: Median Overall Survival Final Analysis by Cohorts in NOVA

Cohort	Niraparib Maintenance	Placebo Maintenance	HR (95% CI)
Germline *BRCA*–mutated	40.9 months	38.1 months	0.85 (0.61–1.20)
Non–germline *BRCA*–mutated	31.0 months	34.8 months	1.06 (0.81–1.37)
Homologous repair–deficient	35.6 months	41.4 months	1.29 (0.85–1.95)
Homologous repair–proficient	27.9 months	27.9 months	0.93 (0.61–1.41)
Homologous repair not determined	29.8 months	20.2 months	0.62 (0.29–1.35)

CI = confidence interval; HR = hazard ratio.

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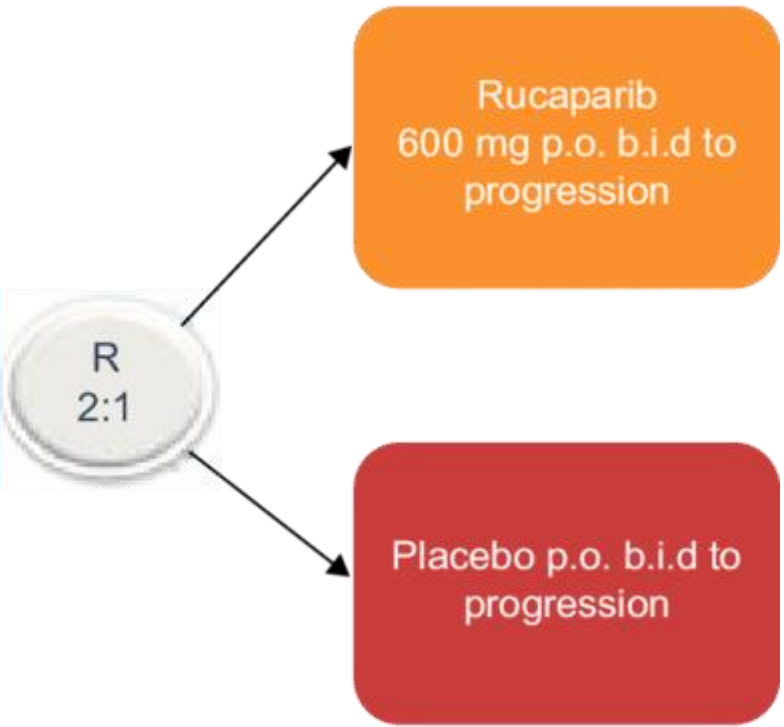
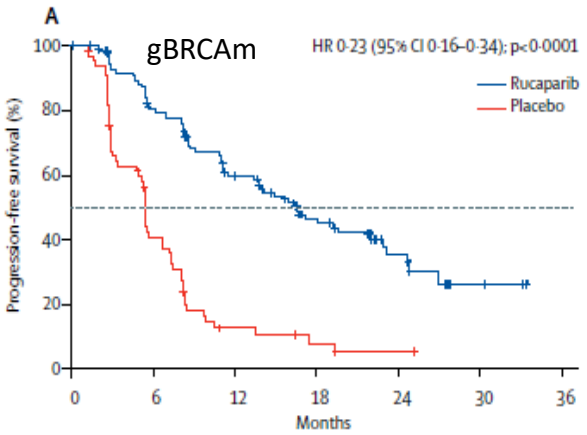
RUCAPARIB in relapsed ovarian cancer

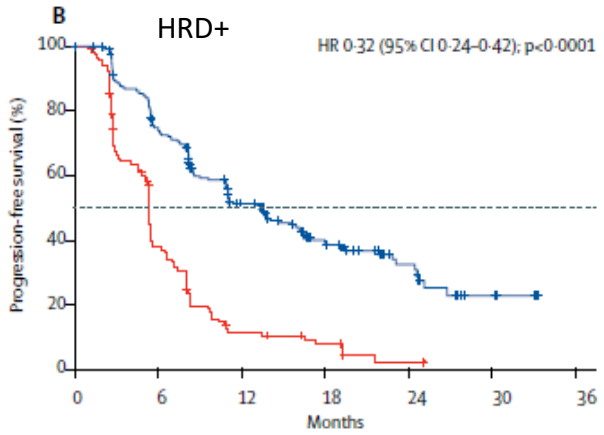
ARIEL3: phase III study design

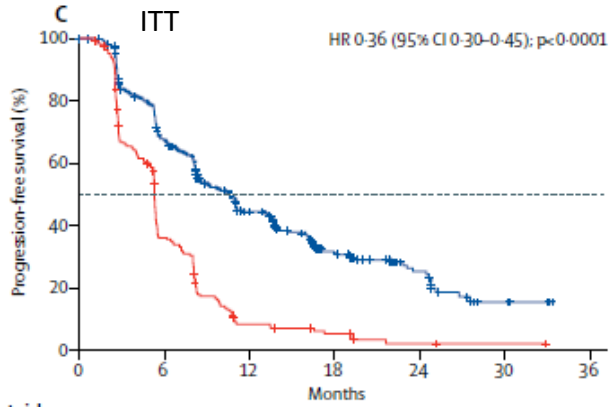
- Recurrent ovarian, primary peritoneal, or fallopian tube cancer
- High-grade serous or endometrioid histology
- One prior nonplatinum regimen
- Platinum sensitive
- In CR or PR at the end of just-completed platinum regimen
- No prior PARP in two prior platinum regimens
- No more than one nonplatinum chemotherapy regimen



RUCAPARIB in relapsed ovarian cancer:PFS







Treatment	Median PFS (95% IC) (Months)	HR (95% IC) P Value
Rucaparib (N=375)	16,6 (13,4-22,9)	0,23 (0,16-0,34) P<0,0001
Placebo (N=189)	5,4 (3,4-6,7)	

Treatment	Median PFS (95% IC) (Months)	HR (95% IC) P Value
Rucaparib (N=375)	13,6 (10,9-16,2)	0,32 (0,24-0,42) P<0,0001
Placebo (N=189)	5,4 (5,1-5,6)	

Treatment	Median PFS (95% IC) (Months)	HR (95% IC) P Value
Rucaparib (N=375)	10,8 (8,3-11,4)	0,36 (0,3-0,45) P<0,0001
Placebo (N=189)	5,4 (5,3-5,5)	

Coleman LR et al Lancet Oncol 2017

RUCAPARIB in relapsed ovarian cancer:OS

Abstract 2022-RA-249-ESGO Table 1

	PFS2 events, n (%)	Median PFS2, months (95% CI)	PFS2 HR (95% CI), *P* value	OS events, n (%)	Median OS, months (95% CI)	OS HR (95% CI), *P* value
BRCA						
Rucaparib (n=130)	98 (75.4)	26.1 (22.8–32.8)	0.672 (0.480–0.941) *P*=0.02	82 (63.1)	45.9 (37.7–59.6)	0.832 (0.581–1.192) *P*=0.32
Placebo (n=66)	54 (81.8)	18.4 (15.7–24.4)		48 (72.7)	47.8 (43.2–55.8)	
HRD						
Rucaparib (n=236)	183 (77.5)	24.7 (21.9–26.8)	0.718 (0.558–0.923) *P*=0.01	159 (67.4)	40.5 (36.6–48.4)	1.005 (0.766–1.320) *P*=0.97
Placebo (n=118)	99 (83.9)	18.4 (15.8–22.1)		85 (72.0)	47.8 (42.7–53.0)	
ITT						
Rucaparib (n=375)	302 (80.5)	20.6 (18.7–23.5)	0.703 (0.579–0.854) *P*<0.01	270 (72.0)	36.0 (32.8–39.4)	0.995 (0.809–1.223) *P*=0.96
Placebo (n=189)	162 (85.7)	16.3 (14.6–17.9)		140 (74.1)	43.2 (38.1–46.9)	

HRs and associated *P* values were calculated by using a stratified log-rank test and stratified Cox-proportional model.

P values are nominal with no adjustment for multiplicity.

BRCA, *BRCA1* and *BRCA2* genes; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficient; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

ESGO 2022

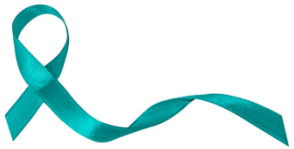
PARP inhibitors in gBRCA mutated breast cancer

OLAPARIB:

- adjuvant setting -> OlympiA trial
- metastatic setting -> OlympiAD trial

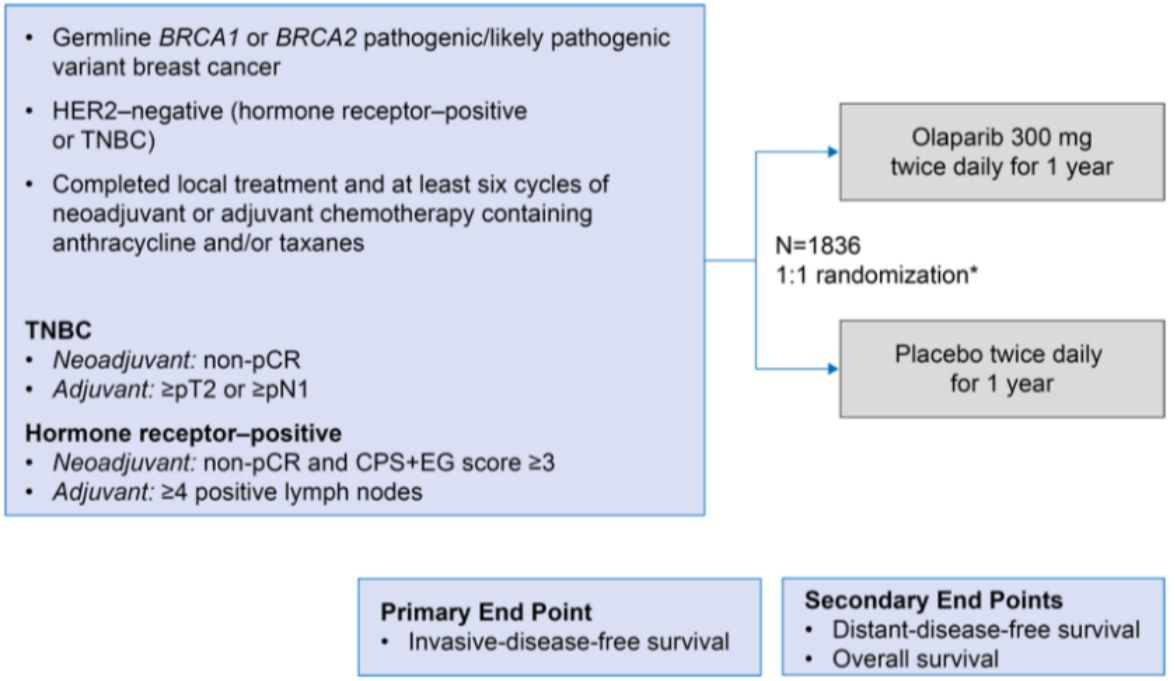
TALAZOPARIB:

- metastatic setting -> EMBRACA trial



Olaparib in adjuvant breast cancer treatment

OlympiA trial design



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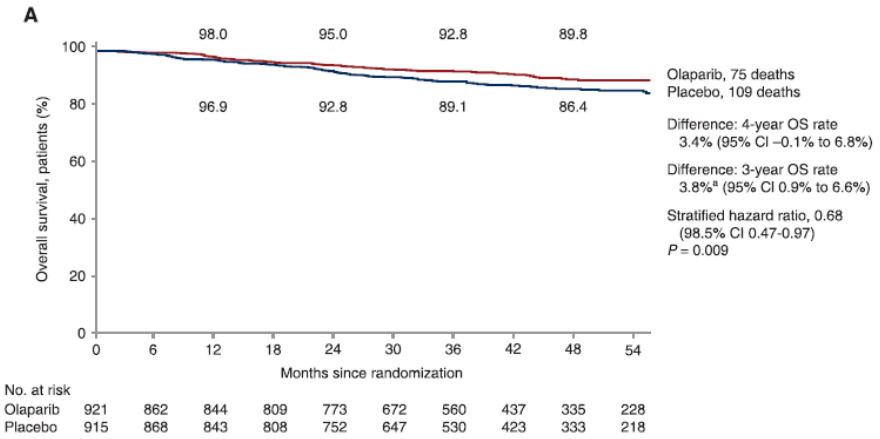
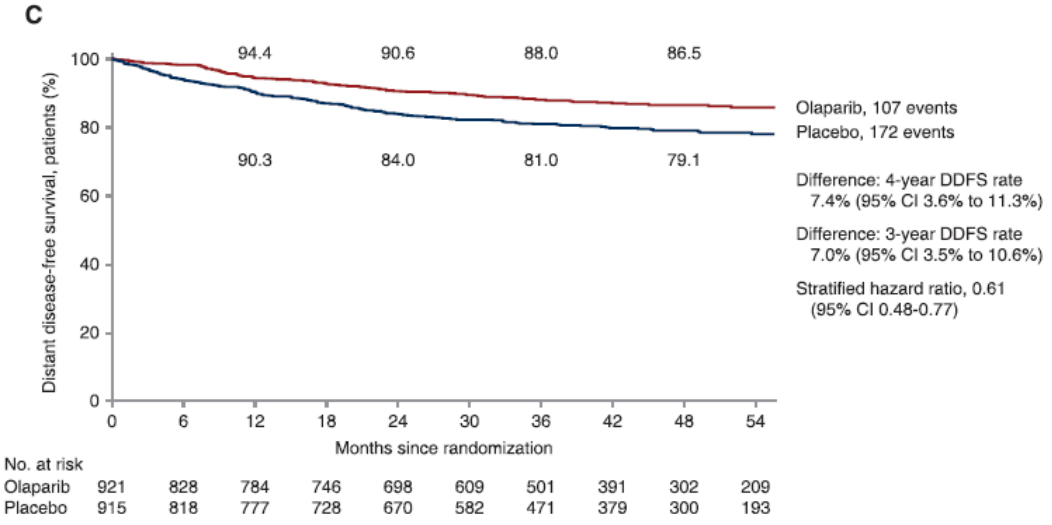
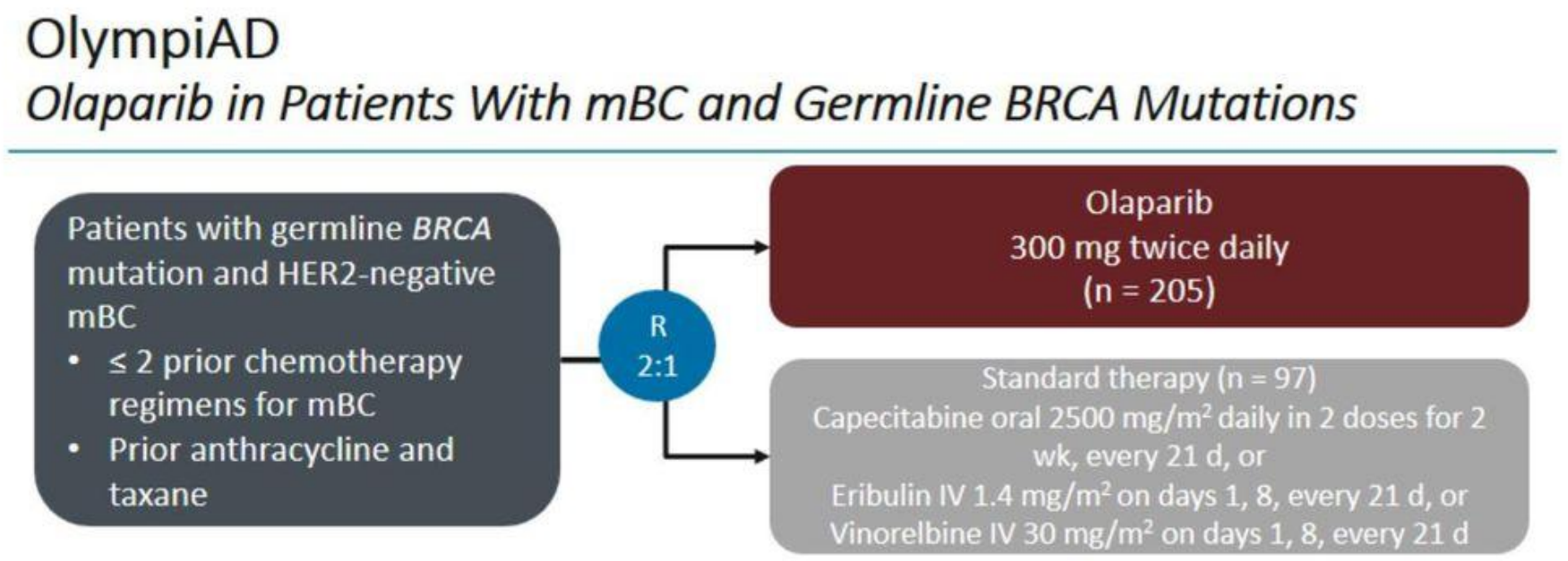
Olaparib in adjuvant breast cancer treatment



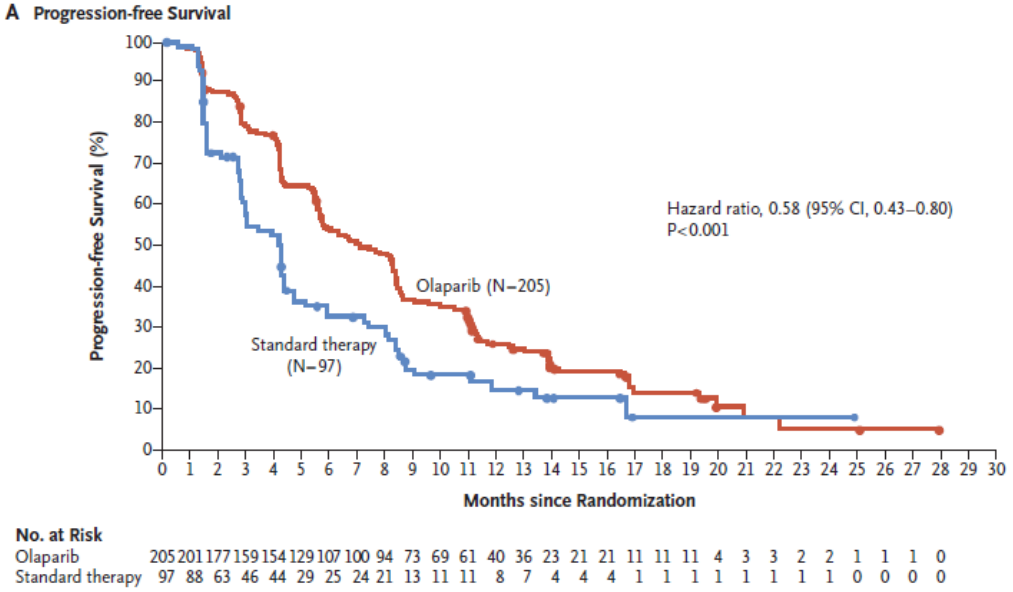


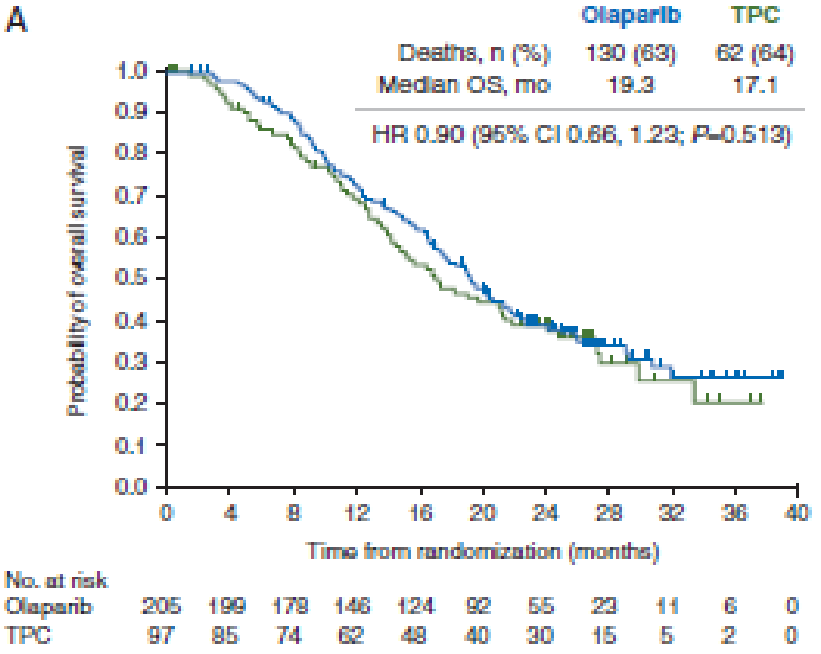
Geyer. Ann Oncol. 2022;33:1250.

Olaparib in metastatic breast cancer treatment



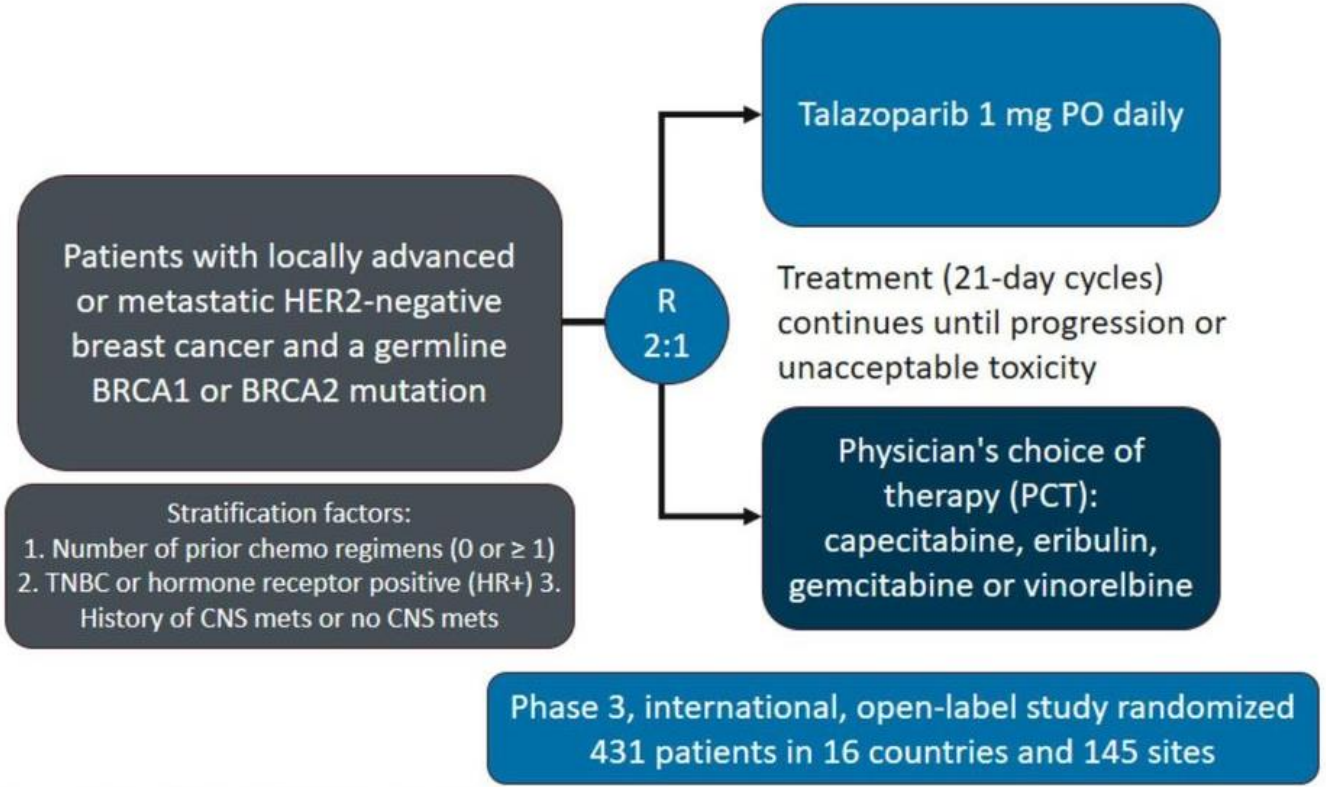
Olaparib in metastatic breast cancer treatment





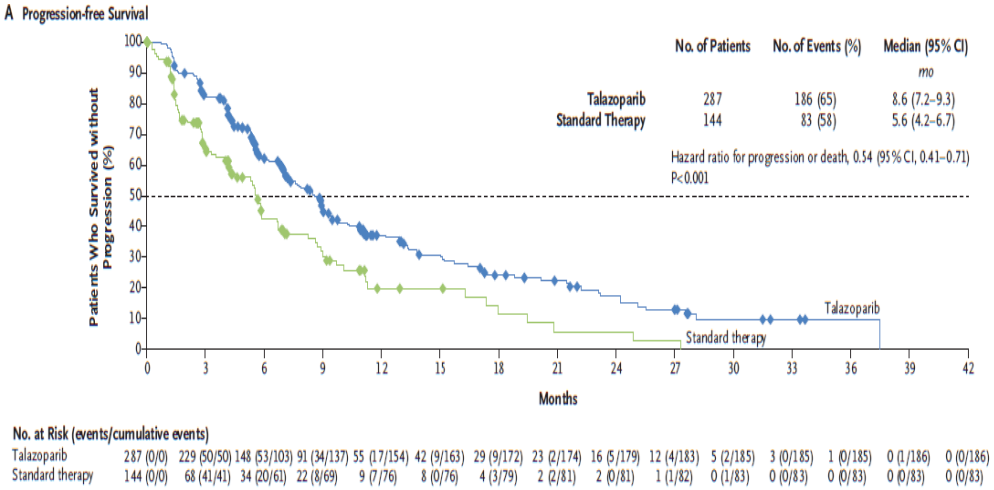
Robson M et al NEJM 2017; Robson M et al Ann Oncol 2019

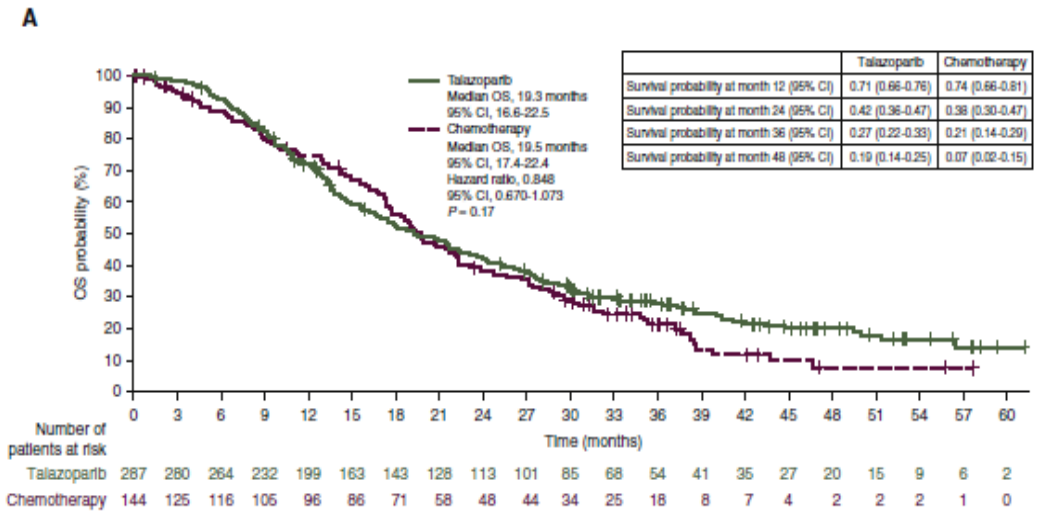
Talazoparib in metastatic breast cancer treatment



Litton JK, et al. *N Engl J Med.* 2018;379:753-763.

Talazoparib in metastatic breast cancer treatment

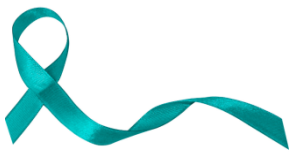




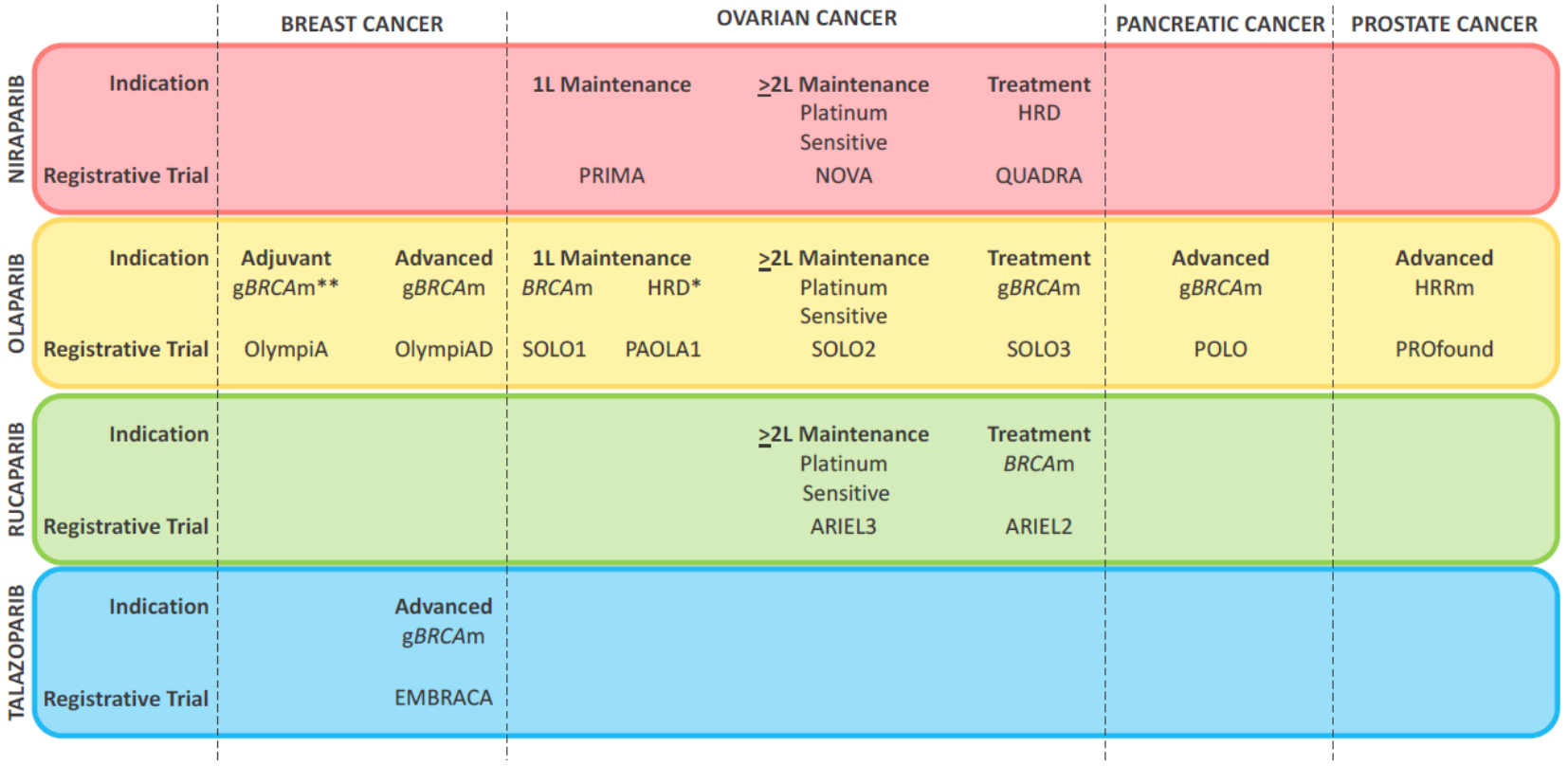
Litton JK et al NEJM 2018; Litton JK et al Ann Oncol 2020

PARP inhibitors: main adverse events

Toxicity Type	Implicated PARPi and Specific Toxicities
Cardiovascular	**Niraparib**: hypertension, tachycardia, palpitations
Dermatologic	**Rucaparib > olaparib ≅ niraparib**: rash **Rucaparib**: photosensitivity
Gastrointestinal	**All agents**: nausea, constipation, diarrhea, decreased appetite, dysgeusia, dyspepsia
Hematologic	**All agents**: anemia (**olaparib, talazoparib**), neutropenia, thrombocytopenia (**niraparib talazoparib**) MDS/AML - increased risk associated with treatment of recurrent disease, *BRCA*m, and duration of therapy >2 yr
Hepatic	**Rucaparib** increased AST/ALT
Musculoskeletal	**All agents**: arthralgia, back pain
Neurologic	**All agents**: fatigue, headache, dizziness **Niraparib** insomnia
Renal	**Olaparib and rucaparib**: increased creatinine
Respiratory	**All agents**: dyspnea/cough, pharyngitis **Olaparib**: pneumonitis



PARP inhibitors: summary



Martorana F et al Cancer 2022