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PARP monotherapy in advanced ovarian cancer

Ursula Matulonis, M.D.

Director and Program Leader
Gynecologic Oncology Program
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, MA

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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Cerulean Pharma Inc, Clovis Oncology, Genentech BioOncology, ImmunoGen Inc, Lilly
Consulting Agreement	AstraZeneca Pharmaceuticals LP

PARP inhibitor monotherapy: FDA approved and under review

PARP inhibitor	# of prior lines	Biomarker
Olaparib	3	g*BRCA*m
Rucaparib	2	g*BRCA*m and somatic (tumor) *BRCA*m
Niraparib	Post platinum maintenace	g*BRCA*m, somatic *BRCA*m and HRD test (under review by the FDA)

Examples of predictors of activity of single agent PARP inhibitor response

1) BRCA mutations: ~20% of high grade serous cancers have a BRCA mutation
2) Homologous recombination deficiency (HRD) testing
3) Level of platinum sensitivity
4) Number of prior lines of treatment
5) Histology: High grade serous

Stover et al. Clin Cancer Research 2016

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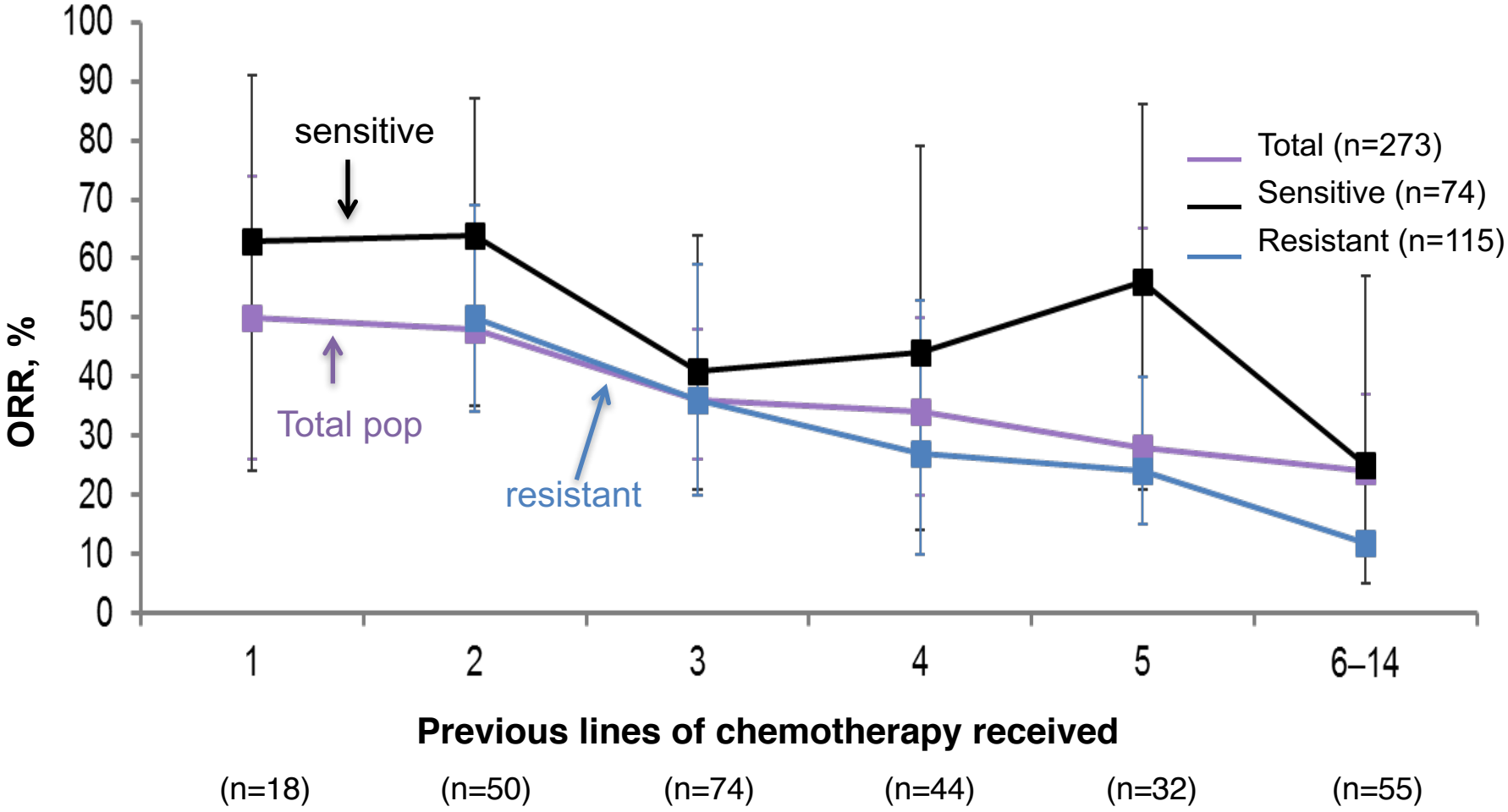
Comparison of patient populations and Activity in different data sets; **all *BRCA*m cancers**

	Olaparib[1]	Rucaparib[2]	Niraparib[3]	Veliparib[4]
No of pts	137	106	20	50
# of lines of prior therapy	At least 3 prior lines	At least 2 prior lines (43% had 3 or more)	NA	1 prior: 32% 2 or 3: 68%
Objective RECIST RR	34%	54% (IRR[5] 42%)	40%	26%
RR based on platinum sensitivity	NA for this population; other data available	Plat sens 66% Plat resis 25% Plat refrac 0%	Plat sens 50% Plat resis 33% Plat refrac 0%	Plat sens 35% Plat resis 20%
Median Duration of response	7.4 mos	9.2 mos (IRR[5] 6.7 months)	12.9 months	8.18 (reported as median PFS)

[1]olaparib FDA package insert, [2]rucaparib FDA package insert,
[3]Sandhu, Lancet Oncol 2013, [4]Coleman, Gyn Onc 2015, [5]IRR= independent radiology review

Pooled g*BRCA* pts treated with olaparib: Gradual decline in ORR with increasing lines of chemotherapy received



	(n=18)	(n=50)	(n=74)	(n=44)	(n=32)	(n=55)
ORR						
Veliparib	43%	22%	17%			

Matulonis/Coleman, Annals of Oncology 2016
Coleman et al Gyn Onc 2015

Do somatic or tumor *BRCA* mutations predict response to a PARP inhibitor like germline *BRCA* mutations do?

- Yes!
- ARIEL2 demonstrated similar ORR in somatic/tumor BRCA (tBRCA) and germline BRCA cancers
- NOVA and Study 19 data showed similar efficacy of niraparib and olaparib in both gBRCA and tBRCA ovarian cancers

	Confirmed objective responses by RECIST	Objective responses by combined RECIST and CA-125
BRCA mutant (n=40)	32 (80%, 64–91)	34 (85%, 70–94)
Germline mutation (n=20)	17 (85%, 62–97)	17 (85%, 62–97)
Somatic mutation (n=19)	14 (74%, 49–91)	16 (84%, 60–97)
Indeterminate (n=1)	1 (100%, 3–100)	1 (100%, 3–100)
BRCA1 mutation (n=29)	23 (79%, 60–92)	25 (86%, 68–96)
BRCA2 mutation (n=11)	9 (82%, 48–98)	9 (82%, 48–98)
PFI ≥6 to <12 months (n=23)	20 (87%, 66–97)	20 (87%, 66–97)
PFI ≥12 months (n=17)	12 (71%, 44–90)	14 (82%, 57–96)
BRCA wild-type and LOH high (n=82)	24 (29%, 20–40)	36 (44%, 33–55)
BRCA wild-type and LOH low (n=70)	7 (10%, 4–20)	14 (20%, 11–31)
BRCA wild-type and LOH not classified (n=12)	4 (33%, 10–65)	7 (58%, 28–85)

Data are n (%, 95% CI). Confidence intervals calculated using Clopper-Pearson method. CA-125=cancer antigen 125. LOH=loss of heterozygosity. PFI=progression-free interval following completion of platinum-based chemotherapy. RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

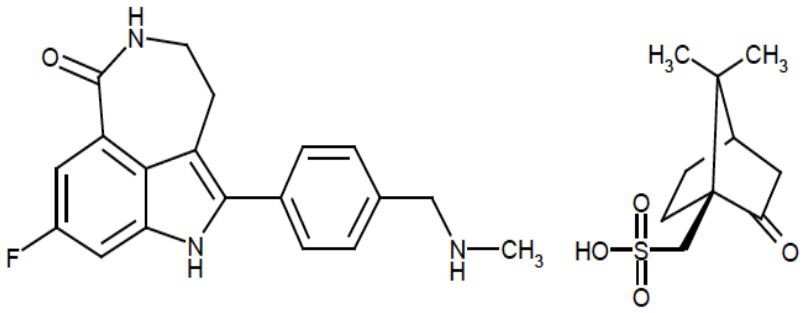
Table 2: **Objective response rates by homologous recombination deficiency subgroup**

Swisher et al, Lancet Oncology 2015, Rucaparib FDA insert
Study 19, NEJM 2014, NOVA, NEJM 2016

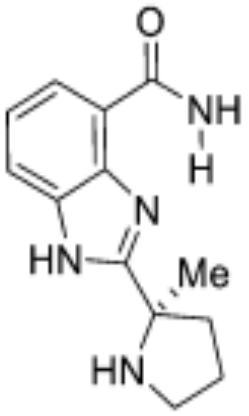
How do we decide which PARP inhibitors to use when?

- Published clinical trials and their results
- FDA guidance and package inserts
- Understanding drug metabolism and drug-drug interaction differences
- Toxicities

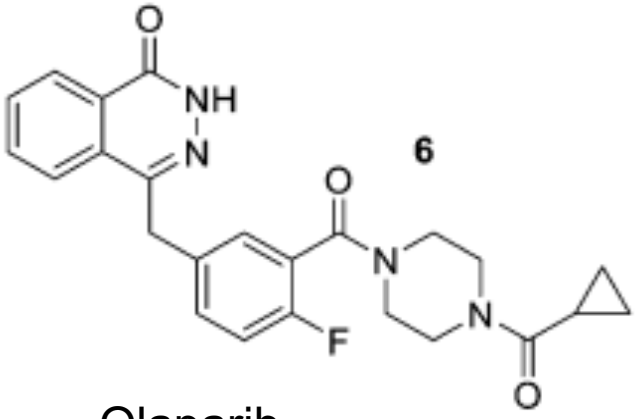
Chemical structure of PARP inhibitors



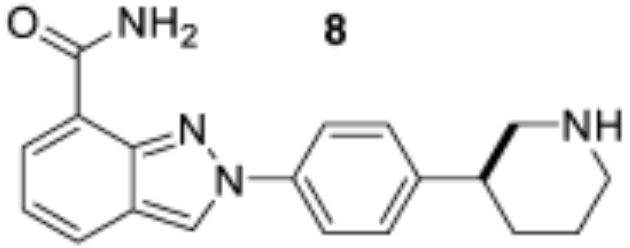
Rucaparib



Veliparib



Olaparib



Niraparib

Jones et al, J of Medicinal Chemistry 2015

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Differences in metabolism and DDI exist amongst PARP inhibitors

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Each drug is metabolized differently

Other drugs patients are taking may influence the PARP Inhibitor levels

Drug Drug interactions can occur based on CYP inhibition or induction

Effect on renal transporter proteins MATE1 and MATE2-K can increase serum creatinine

PARP inhibitor	CYP enzymes used for metabolism	Drug Drug Interactions	Effect on cell transporters
Rucaparib[1]	CYP2D6 (predominant) CYP1A2 and CYP3A4 (lesser extent)	Reversibly inhibits CYP1A2, CYP2C19, CYP2C9, CYP3A Induces CYP1A2	inhibits MATE1 and MATE2-K (potent), OCT1 (moderate) substrate of P-glycoporotein
Olaparib[1]	CYP3A4*	Inhibits CYP3A4 and induces CYP2B6	Inhibits OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K substrate of P-glycoprotein
Niraparib[2]	CYP3A4/5 and CYP1A2 CYP2D6 (lesser extent) Carboxylesterases (non-CYP)	Can induce CYP1A2 (weak)	No interaction with the major hepatic or renal uptake transporters substrate of P-glycoprotein

*Reduce dose if strong or moderate CYP3A inhibitors are co-administered

[1]FDA package inserts
[2]NEJM 2016

Beyond single agent strategies: Combinations

- Increase anti-cancer activity in non-BRCA cancers and possibly BRCAm cancers that might not respond well to single agent PARP inhibitors
- PARP inhibitor combinations
  - Anti-angiogenics
  - DNA repair inhibitors (ex. ATR inhibitors)
  - Immunotherapy agents

Combination studies: Phase III NCI-sponsored olaparib and cediranib studies in recurrent ovarian cancer

- **NRG-GY004 (platinum sensitive)**
  olaparib vs olaparib/cediranib vs platinum doublet (NCT02446600)
  Nearing accrual completion 4thQ 2017

- **NRG-GY005 (platinum resistant)**
  olaparib (or cediranib) vs olaparib/cediranib vs single agent chemotherapy (NCT02502266)

Conclusions

- Metabolism, DDI, toxicities, and results of studies differ amongst the PARP inhibitors
- Clinicians will need to know and understand these differences when faced with treatment decisions.
- Direct comparisons of RR and DOR amongst PARP inhibitors are difficult to make because of lack of comparable data