Advanced Ovarian Cancer: Changing landscape

The end of the chemotherapy era and the beginning of the PARPi era?

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Faculty Disclosure

Nothing to disclose

Acknowledgements

- K Moore for sharing some of the slides presented at IGCS Rio 2019
- My wife Randa for her support

Major Changes Are Coming in the Medical Treatment of Advanced Epithelial Cancer

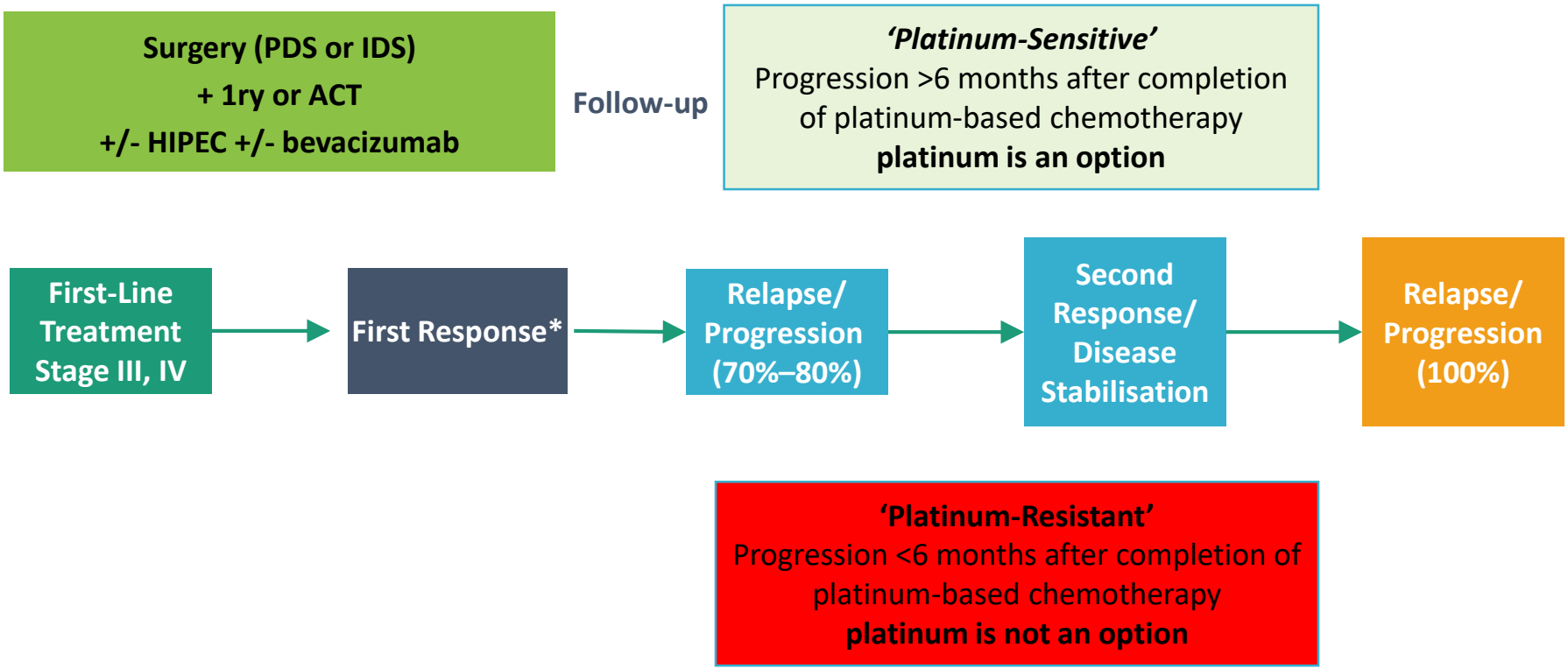
Updates from ASCO/IGCS/ESMO 2019

- ***Front Line treatment:***
  - Bevacizumab with and to follow chemotherapy (BRCAwt)
  - Olaparib to follow chemotherapy (BRCA+)
  - Niraparib +/- Bevacizumab with and to follow (BRCA+/-)
  - Rucaparib with and to follow chemotherapy (BRCA+/-)
  - Velaparib with and to follow chemotherapy (BRCA+/-)

- ***Platinum Sensitive Recurrence treatment***
  - PARPi to follow chemotherapy (BRCA+ preferred but all comers)
  - PARPi +/- Bevacizumab with and to follow chemotherapy (BRCAwt)

- ***What's Next?***
  - PARPi instead of chemo?
  - PARPi combinations?
  - PARPi and other targeted therapies?
  - PARPi after PARPi

The Typical Course of Stages IIIC and IV Ovarian Cancer



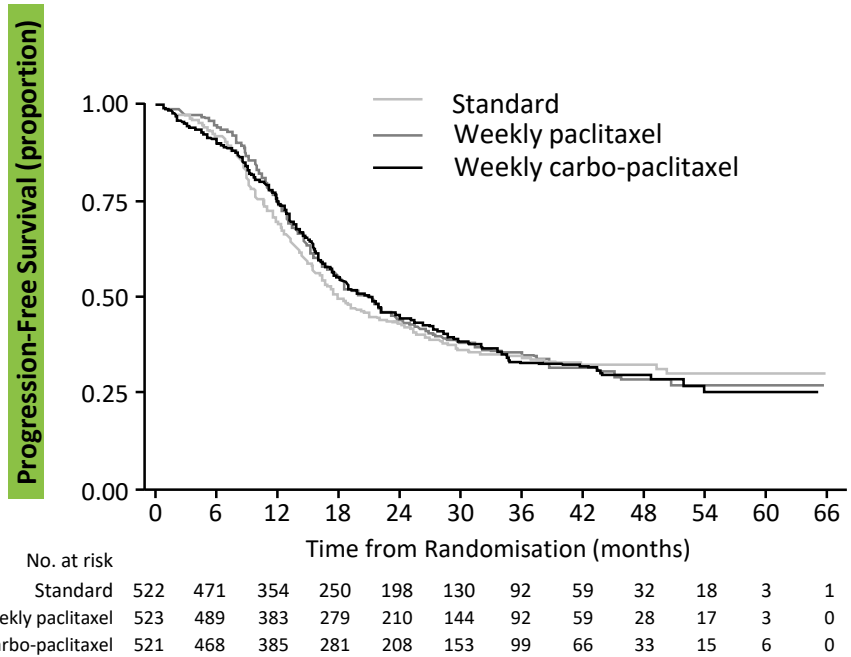
1. Ledermann JA et al. *Ann Oncol.* 2013;24(Suppl 6):vi24-vi32. 2. Giornelli GH. *Springerplus*. 2016;5(1):1197. 3. Pignata S et al. *Ann Oncol.* 2017;28(suppl_8):viii51-viii56. 4. du Bois A et al. *Cancer*. 2009;115(6):1234-1244. 5. Wilson MK et al *Ann Oncol*. 2017;28(4):727-732.

Changing Landscape in the ***Frontline*** Treatment of Advanced Epithelial Ovarian Cancer

Dose-dense weekly paclitaxel
JGOG3016

Study of Japanese ovarian cancer patients showed SS increased median PFS and OS in those treated with ***dose-dense weekly paclitaxel*** Vs. to the standard three-weekly schedule.

First-Line Chemotherapy Standard of Care (*BRCAwt*)
ICON 8 ***Carboplatin and Dose Dense Paclitaxel***



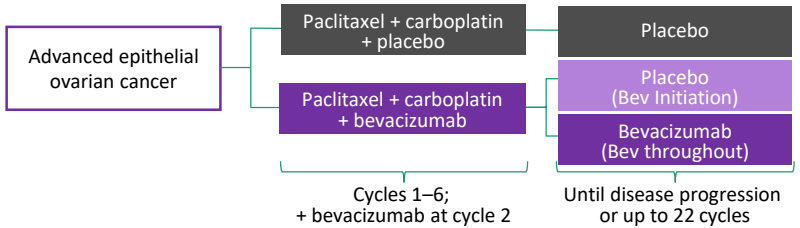
	Arm 1 3 weekly carbo-paclitaxel (n=522)	Arm 2 Weekly paclitaxel (n=523)	Arm 3 Weekly carbo-paclitaxel (n=521)
Progressions	**330 (63%)**	**335 (64%)**	**338 (65%)**
Median PFS, mo	**17.9**	**20.6**	**21.1**
Log rank (vs standard)		***P*=0.45**	***P*=0.56**
HR vs Standard (97.5% CI)		**0.92 (0.77–1.09)**	**0.94 (0.79–1.12)**
Restricted means	**24.4 months**	**24.9 months**	**25.3 months**

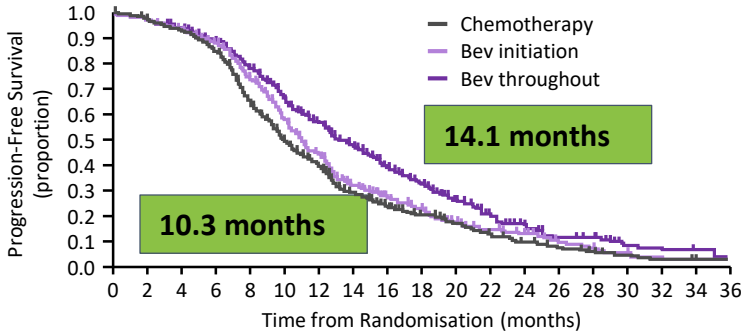
Weekly dose-dense chemoRx can be delivered successfully as first-line EOC Rx without substantial toxicity increase; it does not significantly improve PFS compared to standard 3-weekly chemotherapy

Clamp AR et al. Presented at: ESMO Annual Meeting; 2017.

1rst major change: 1rst-Line Chemotherapy Standard of Care (*BRCAwt*) Carboplatin, Paclitaxel & Bevacizumab + Maintenance

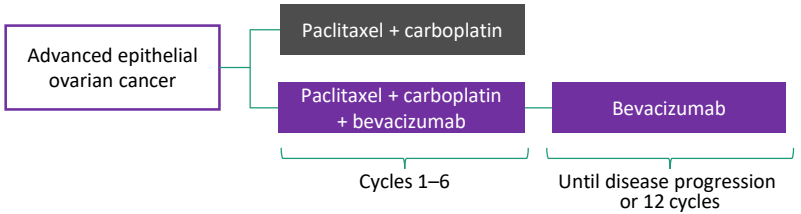
GOG 218[1]

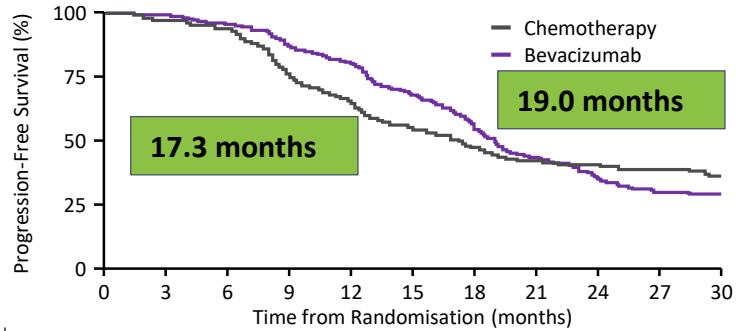




No. at risk				
Chemotherapy	625	199	33	8
Bev initiation	625	219	29	6
Bev throughout	623	254	38	8

ICON7[2]





No. at risk						
Chemotherapy	764	693	464	216	91	25
Bevacizumab	764	715	585	263	73	19

Bev=bevacizumab.

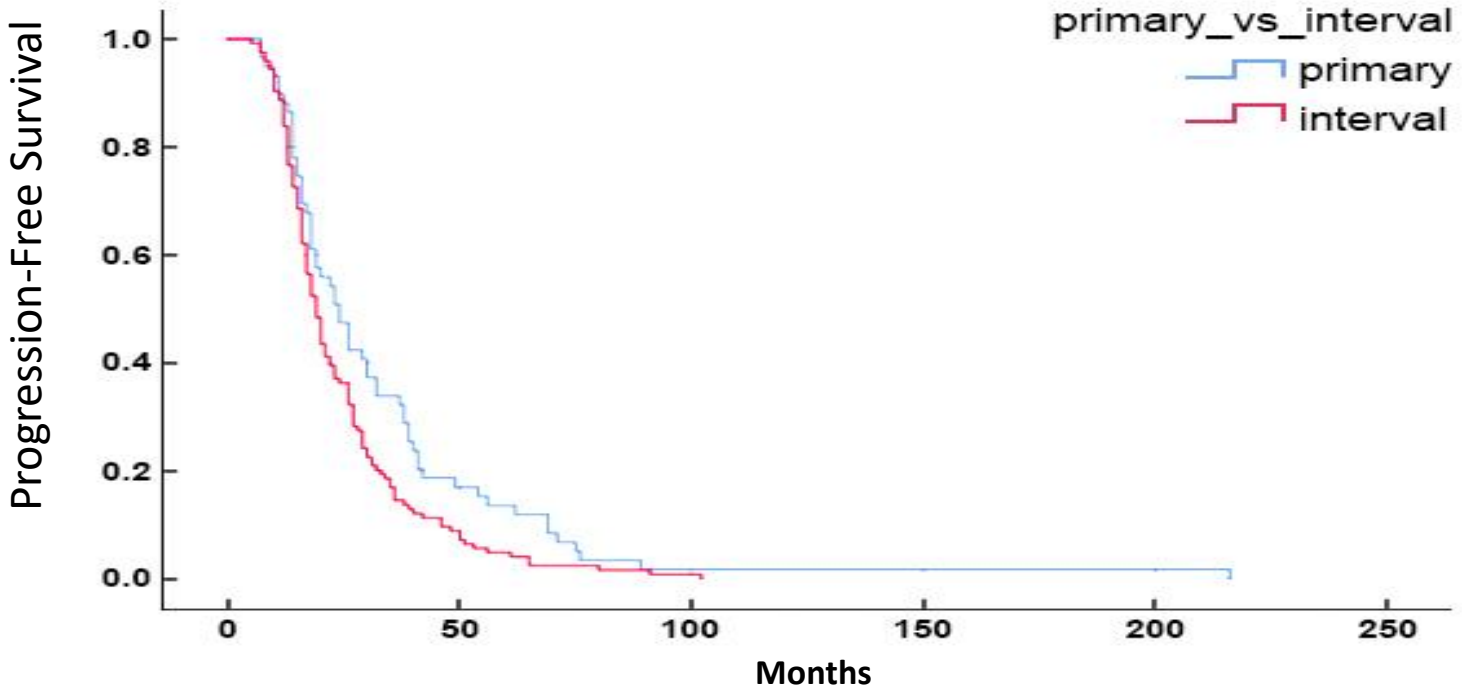
1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. 2. Perren TJ et al. *N Engl J Med.* 2011;365(26):2484-2496.

Impact of *timing of cytoreductive surgery* (CRS) on the PFS, OS and extent of debulking in patients with advanced epithelial ovarian cancer (EOC), primary peritoneal carcinomatosis (PPC), and fallopian tube cancer (FTC) at American University of Beirut Medical Center (AUBMC)

Muhieddine Seoud, Alaa Husheimi, Iman Jaafar,
Karam Hamed, Faek Jamali, Ali Khalil and Reem Abdallah

IGCS 2019 Rio de Janeiro BRAZIL SEPTEMBER 19-21, 2019

Median PFS
EOC Stages IIIC and IV (no stage IIB-IIB)
No Bevacizumab



24 months
19 months

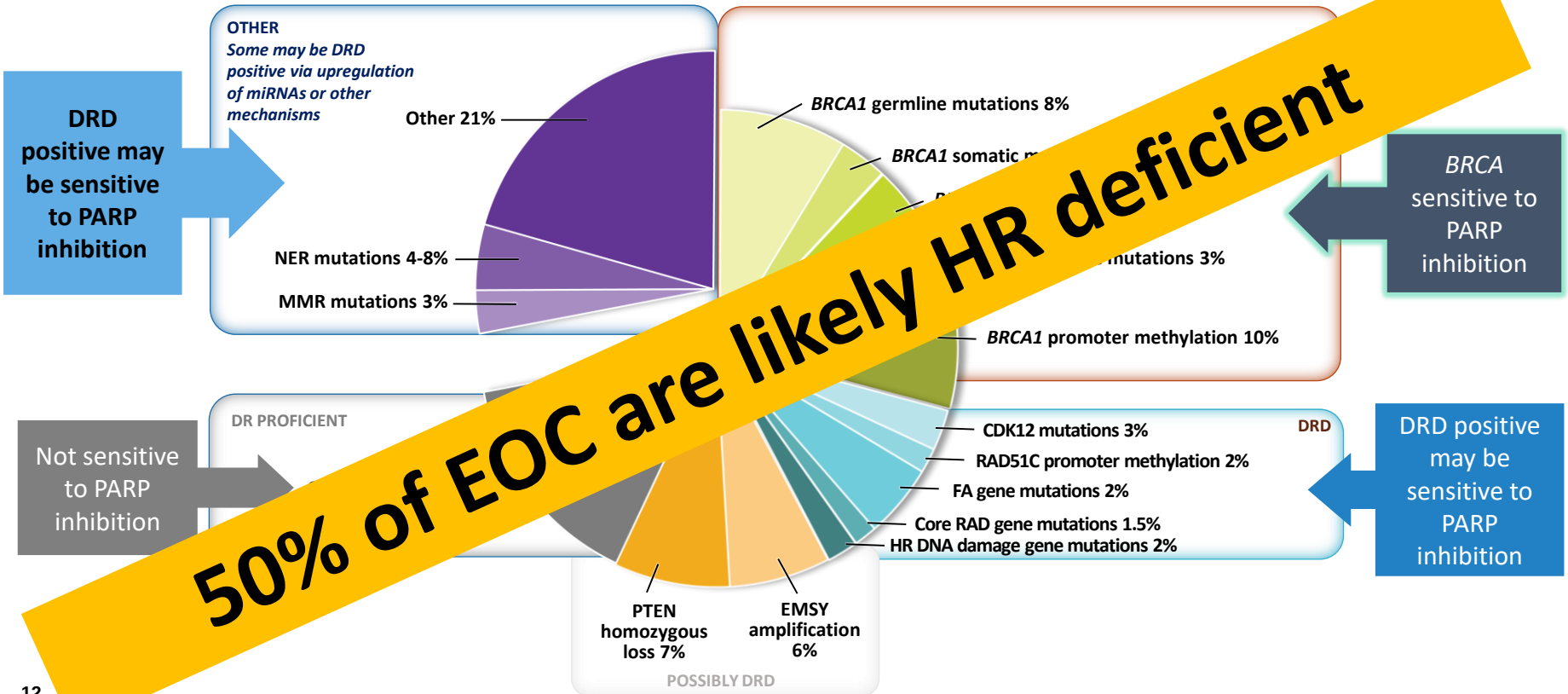
P-value: 0.025

Advanced Epithelial Ovarian Cancer

Looking Beyond Anti-angiogenesis

Genetic Alterations Responsible for Homologous Recombination Repair (HRR) Pathways in Ovarian cancer

A subset of ovarian tumors may exhibit DRD in the absence of *BRCA1/2* mutations- *"BRCA-ness"*



CDK12, cyc ident kinase 12; EMSY, BRCA2-interacting transcriptional repressor; FA, Fanconi anemia; MMR, mismatch repair; miRNA, micro messenger ribonucleic acid; NER, nucleotide excision repair; PTEN, phosphatase and tensin homolog.

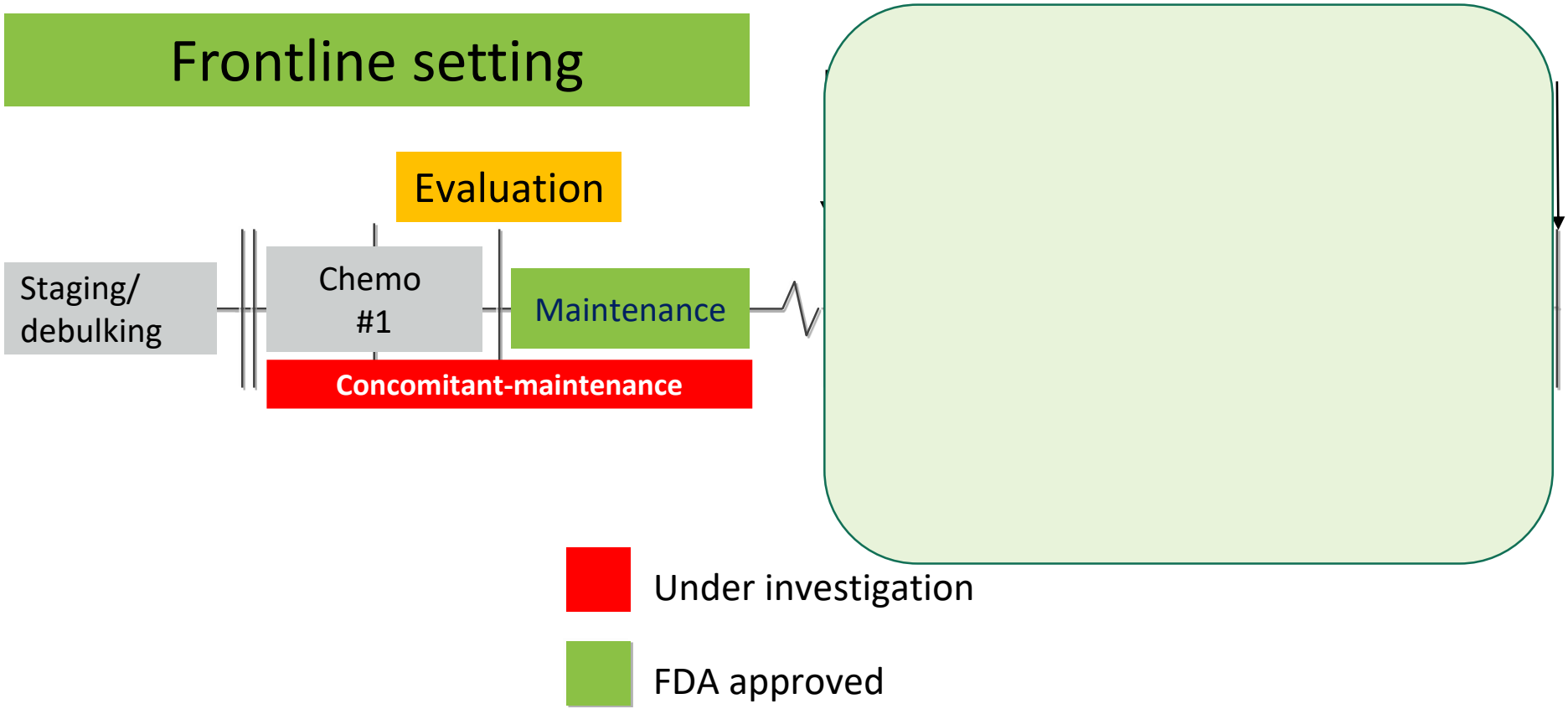
Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1137-1154.

Current Positioning of PARP inhibitors in Advanced EOC

Olaparib	Niraparib	Rucaparib
First-line maintenance therapy for BRCA-mut advanced ovarian cancer	***First-line treatment*** PRIMA ESMO 2019 AVANOVA	***First-line treatment*** VELIA ESMO 2019

Olaparib PI 2018; Rucaparib PI 2018; Niraparib PI 2019.

Current Treatment Landscape for PARPi in Ovarian Cancer



LaFargue. Lancet Oncol. 2019;20:e15.

2nd major change

Phase III SOLO1 Trial of ***Olaparib vs Placebo*** as ***First-line Maintenance Therapy*** in Ovarian Cancer With *BRCA* Mutation

Randomized, double-blind, placebo-controlled, multicenter phase III trial

Stratified by response to platinum-based CT

Newly diagnosed, Stage III/IV, HGS or endom OVCA, PPC, or FC, g*BRCA* or tBRCA mut; ECOG PS 0/1; CRS CR/PR to P-based CT (N = 391)

Randomized 2:1

Olaparib 300 mg BID (n = 260)

Placebo (n = 131)

2 yrs of treatment if no evidence of disease

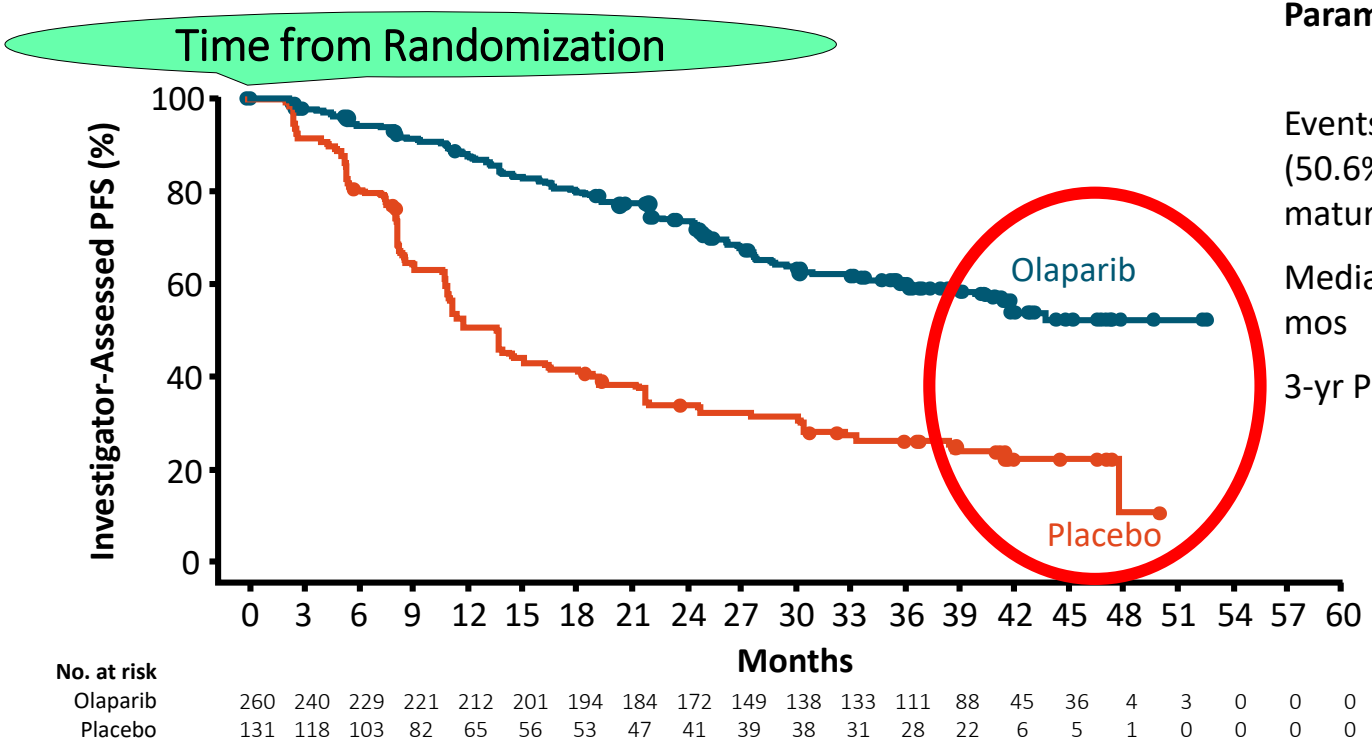
Treatment until PD or NED at 2 yrs; treatment continued beyond 2 yrs if PR

- ***1y endpoint:*** investigator-assessed PFS (RECIST 1.1)
- ***2ry endpoints:*** PFS by BICR, PFS2, OS, TSST or death, HRQoL (FACT-O TOI score)

Moore. NEJM. 2018;379:2495.

2nd major change

SOLO1: Investigator-Assessed PFS Olaparib Maintenance (*BRCA+*)



Parameter	Olaparib (n = 260)	Placebo (n = 131)
Events (%) (50.6% maturity)	102 (39)	96 (73)
Median PFS, mos	NR	13.8
3-yr PFS (%)	60	27
	HR: 0.30	
	95% CI: 0.23-0.41; *P* < .0001	

Overview of Phase 3 1rst Line Maintenance Trials: Completed & Pending

Study Design		GOG-0218 (N=1873)[1-3]	SOLO-1 (N=451)[3]	Velia (N=1140)[4]	PRIMA (N=620)[3]	PAOLA-1 (N=612)[4]
Treatment arms vs placebo		Bevacizumab (n=625)	Olaparib (n=260)	Veliparib	Niraparib	Bevacizumab ± Olaparib
Key Patient Population		All comers	*BRCA* mutation	*All comers*	All comers	All comers
Undergo tumor testing		HRR (post-hoc)	*BRCA*	*BRCA*	HRD	*BRCA*
Stage	III	73.8%	84.6%	Eligible	Eligible: Attempt upfront debulking	Eligible
	IV	26.2%	15.4%	Eligible	Eligible: Any debulking attempts	Eligible
Surgery	Residual disease after surgery	Stage III incomplete • Macroscopic:32.8% • >1 cm: 41.0%	Macroscopic[a] • 1ry: 23.0% • Interval:19.1%	Primary or Interval	Required for Stage III	NR[b]
	Inoperable disease	0	1.5%		Eligible	NR[b]
Treatment Duration		15 months	24 months	24 months	Until PD	15 months for Bev 24 months for Olaparib

[a]Residual disease based on stage was not reported. [b]Stage III and IV eligible, but requirements for prior surgery not reported (NR) on clinicaltrials.gov

1. Burger RA, et al. *N Engl J Med.* 2011;365:2473-2483. 2. Norquist B, et al. *Clin Cancer Res.* 2018;24(4):777-783. 3. AVASTIN [prescribing information] South San Francisco, CA: Genentech, Inc; 2016. 4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02470585. Accessed 1 October 2018. 5. . Clinicaltrials.gov. NCT02655016. 6. Gonzalez-Martin A, et al. Presented at ASCO Annual Meeting 2016; June 3-7, 2016; Chicago, IL. Abstract TPS5606. 7. . Clinicaltrials.gov. NCT02477644

3 additional 1rst Line trials may change the landscape for BRCAwt +/- HRD+

ESMO 2019

Study Design		GOG-0218 (N=1873)[1-3]	SOLO-1 (N=451)[3]	Velia (N=1140)[4]	PRIMA (N=620)[3]	PAOLA-1 (N=612)[4]
Treatment arms vs placebo		Bevacizumab (n=625)	Olaparib (n=260)	Veliparib	Niraparib	Bevacizumab ± Olaparib
Key Patient Population		All comers	*BRCA* mutation	*All comers*	All comers	All comers
Undergo tumor testing		HRR (post-hoc)	*BRCA*	*BRCA*	HRD	*BRCA*
Stage	III	73.8%	84.6%	Eligible	Eligible: Attempt upfront debulking	Eligible
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PARPi in frontline treatment at ESMO

September 2019

LBA3 - ***VELIA/GOG-3005:*** Integration of ***Veliparib*** (V) with front-line chemotherapy and maintenance in women with HGSC, FTC, or PPC (HGSC) (ID 2772) ESMO Sept 2019

- Phase III RPL controlled MN trial evaluated whether Velaprib ***added to front-line CP*** and ***continued as maintenance*** increases PFS in Stage III-IV HGSC pts considering BRCA mutations (m), HRD, and NACT.

- 6 cycles (21-d interval) of CP using 3-weekly or weekly paclitaxel, following PDS or NACT + IDS
- Veliparib or PL was administered during CP (150 mg BID PO) and as maintenance (400 mg BID for 30 cycles).

- ***Randomization was 1:1:1, stratified by***
  1. Stage III vs IV
  2. RD and regimen
  3. Region
  4. gBRCA status

- ***The 3 arms of the study:***
  1. ***Arm 1: CP + PL then PL maintenance***
  2. Arm 2: CP + V then PL maintenance
  3. ***Arm 3: CP + V then V maintenance***

Clinical trial identification NCT02470585.

LBA3 - ***VELIA/GOG-3005:*** Integration of veliparib (V) with front-line chemotherapy and maintenance in women with HGSC, FTC, or PPC (HGSC) (ID 2772) ESMO Sept 2019

- ***1ry endpoints: PFS (KM)***
  - in Arm 3 vs 1 using hierarchical testing in BRCAm, HRD (incl. BRCAm)
  - whole populations by log-rank tests

- ***2ry endpoints:***
  - PFS (Arm 2 vs 1), OS, and disease related symptom scores

- Germline and tissue BRCAm and HRD were determined by central testing

- 1140 pts enrolled with 26% in BRCAm and 55% in HRD populations/Relative CP dose intensities were similar between arms

- ***Grade 3-4 adverse events*** (AE; Arm 3 vs 1)
  - During treatment: were similar during CP with the exception of ***thrombocytopenia*** (27% vs 8%)
  - During maintenance: any grade 3-4 AE was higher for V (45% vs 32%) but serious AEs were similar (17% vs 19%)

Clinical trial identification NCT02470585.

LBA3 - ***VELIA/GOG-3005***: Integration of ***Veliparib*** (V) with front-line chemotherapy and maintenance in women with HGSC, FTC, or PPC (HGSC) (ID 2772) ESMO Sept 2019

Arm 1: CP + PL then PL maintenance ***Arm 2:*** CP + V then PL maintenance ***Arm 3:*** CP + V then V maintenance

	BRCAm	HRD	Whole			
	Arm 3 n = 108	Arm 1 n = 92	Arm 3 n = 214	Arm 1 n = 207	Arm 3 n = 382	Arm 1 n = 375
Median PFS (months)	34.7	22.0	31.9	20.5	23.5	17.3
PFS HR (95% CI) P value	0.44 [0.28, 0.68] < 0.001	0.57 [0.43, 0.76] < 0.001	0.68 [0.56, 0.83] < 0.001			

BRCAm, BRCA mutated; HRD, homologous recombination deficient; HR, hazard ratio; P value by stratified log-rank test; PFS, progression-free survival

LBA3 - ***VELIA/GOG-3005:*** Integration of veliparib (V) with front-line chemotherapy and maintenance in women with HGSC, FTC, or PPC (HGSC) (ID 2772) ESMO Sept 2019

Conclusions

1. Velaparib added to front-line CP and continued as monotherapy maintenance significantly extended PFS in all women with newly diagnosed HGSC without selection according to BRCAm or HRD status, or response to CP

2. Observed toxicities were consistent with known Velaparib safety profile

Clinical trial identification NCT02470585.

LBA1 - ***Niraparib*** therapy in newly diagnosed advanced ovarian cancer ***(PRIMA/ENGOT-OV26/GOG-3012 study)*** (ID 4627) ESMO Sept 2019

- ***Background:***
  - Niraparib has shown PFS benefit in ROC after platinum-based chemotherapy (CT) regardless of BRCA status

- ***Aim:***
  - Efficacy of Niraparib in advanced OC ***after completion of 1rst-line*** (1L) CT regardless of BRCA status in DBPBOCT phase III trial

- ***Stratification factors:***
  1. Best response to the 1rst line CT regimen (CR/PR)
  2. NACT
  3. HRD status (positive/negative/unknown) per the Myriad myChoice HRD test

LBA1 - ***Niraparib*** therapy in newly diagnosed advanced ovarian cancer ***(PRIMA/ENGOT-OV26/GOG-3012 study)*** (ID 4627) ESMO Sept 2019

- ***1ry end point: PFS assessed by:***
  1. BICR using a stratified Cox proportional hazards model
  2. Hierarchically tested in HRD-positive (HRDpos) pts and then the overall population

- Of 733 randomized pts (niraparib, 487; PBO, 246)
  - 373 (51%) were HRDpos:
    - Niraparib: 247
    - PBO 126

- 35% had stage IV disease, 67% received NACT, and 31% had a PR to 1rst line CT.

BICR: Blinded independent central review

LBA1 - ***Niraparib*** therapy in newly diagnosed advanced ovarian cancer ***(PRIMA/ENGOT-OV26/GOG-3012 study)*** (ID 4627) ESMO Sept 2019

	Niraparib Median PFS (95% CI)	Placebo Median PFS (95% CI)	Hazard Ratio (95% CI) P Value
HRDpos subgroup	21.9 (19.3–NE)	10.4 (8.1–12.1)	0.43 (0.31–0.59) P<0.0001
Overall population	13.8 (11.5–14.9)	8.2 (7.3–8.5)	0.62 (0.5–0.75) P<0.0001

Niraparib-treated pts in the HRDpos subgroup and overall population had a ***SSR in the risk of disease recurrence or death with a substantial improvement in PFS***
All subgroups showed a sustained and durable treatment effect.

CI, confidence interval; mPFS, median progression-free survival; NE, not estimable.

LBA1 - ***Niraparib*** therapy in newly diagnosed advanced ovarian cancer ***(PRIMA/ENGOT-OV26/GOG-3012 study)*** (ID 4627) ESMO Sept 2019

Conclusions

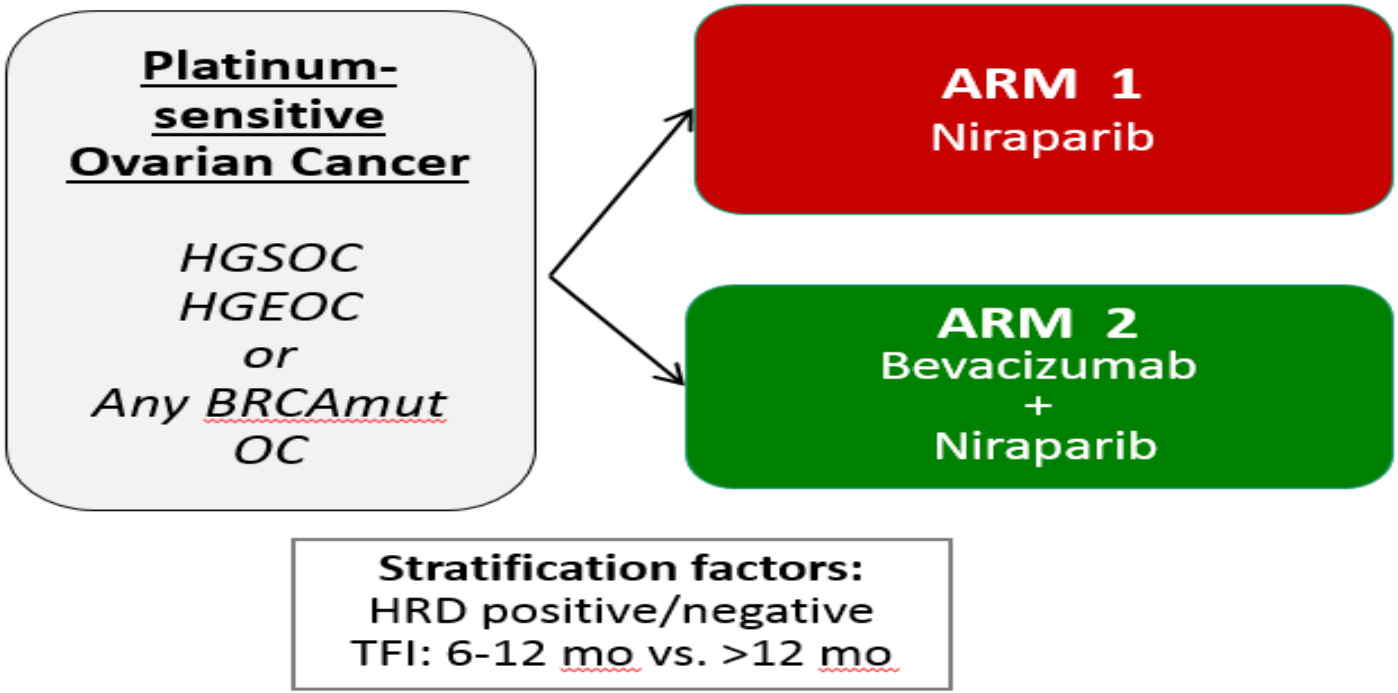
1. Niraparib significantly improved PFS in pts with newly diagnosed advanced OC, including pts at HR of PD in the HRDpos subgroup and overall population.

2. No new safety signals were identified.

3. Niraparib should be considered as a treatment option for pts with advanced OC after completion of 1rst line CT.

ENGOT-OV24-NSGO / **AVANOVA2**

Combination of Nariparib and Bevacizumab to upfront CT in Advanced OCA

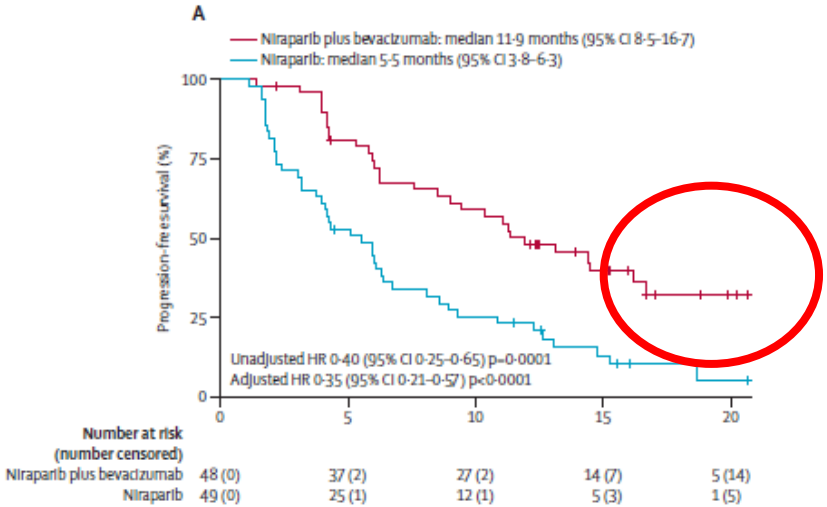


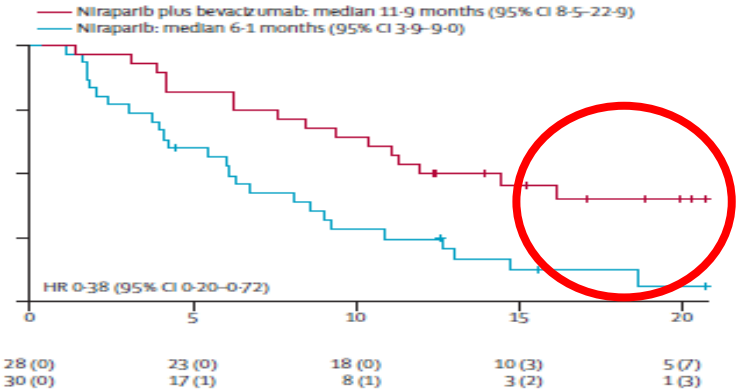
Mirza et al. Lancet Oncol (2019) ***Published Online August 29, 2019***

ENGOT-OV24-NSGO / AVANOVA2

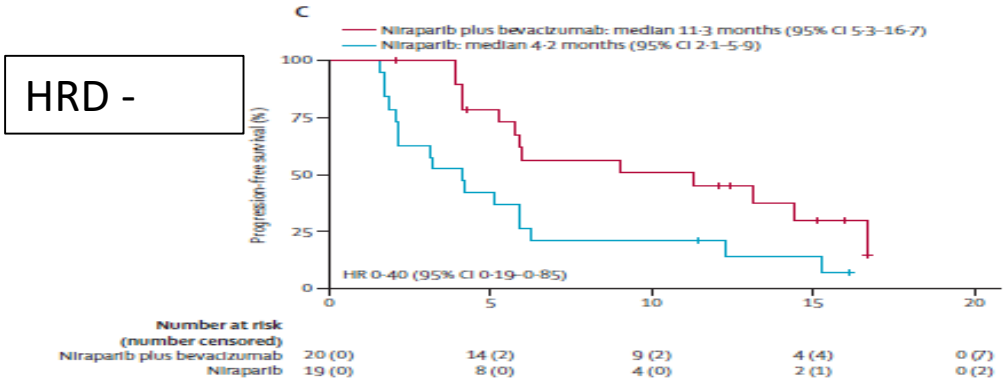
Combination of Nariparib and Bevacizumab to upfront CT in Advanced OCA

HRD +





HRD -

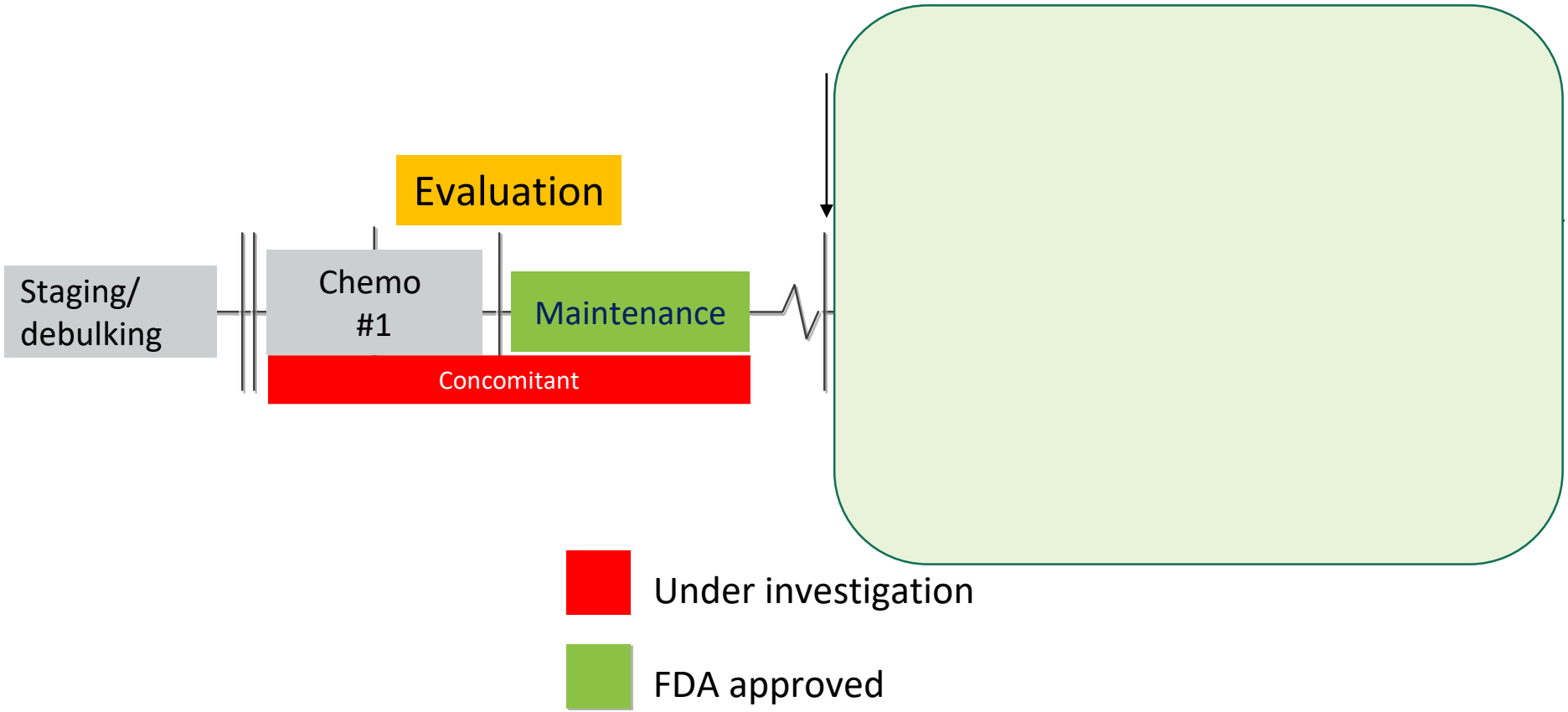


Mirza et al. Lancet Oncol (2019) Published Online August 29, 2019

Changing Landscape in the treatment of

Recurrent Epithelial Ovarian Cancer

Current Treatment Landscape for PARPi in Ovarian Cancer



LaFargue. Lancet Oncol. 2019;20:e15.

3rd major change: bevacizumab in combination with chemotherapy

Study	Randomization	N	Median PFS (mo)	HR, p-value	Median OS (mo)	HR, p-value
OCEANS[1-2]	C/gem + placebo	242	8.4	HR = 0.484 p<0.0001	32.9	HR = 0.952 p = 0.6479
	C/gem + bev until progression	242	12.4		33.6	
GOG-0213[3]	C/P	337	10.4	HR = 0.628 p<0.0001	37.3	HR = 0.829 p = 0.056
	C/P + bev	377	13.8		42.2	HR = 0.823* p = 0.0447*
AGO-OVAR 2.21[4]	C/gem + bev	337	11.7	HR=0.807 p=0.0128	NR	NR
	C/PLD + bev	345	13.3			
AURELIA[5]	Chemo	182	3.4	HR=0.48, P<0.001	13.3	HR=0.85, P<0.174
	Chemo + bev	179	6.7		16.6	

1. Aghajanian C et al. *J Clin Oncol* 2012;30(17):2039-45; 2. Aghajanian C et al. *Gynecol Oncol* 2015;139(1):10-6; 3. Coleman RL et al. *Lancet Oncol* 2017;18(6):779-91. 4. AGO OVAR 2.21 ESMO 2018 Munich, 5. Pujade-Lauraine E et al. JCO 2014;32:1302-1308

Current Positioning of PARP inhibitors in Advanced EOC

Olaparib	Niraparib	Rucaparib
First-line maintenance therapy for BRCA-mut advanced ovarian cancer	***First-line treatment*** PRIMA ESMO 2019 AVANOVA	***First-line treatment*** VELIA ESMO 2019
Maintenance therapy for recurrent ovarian cancer regardless of BRCA mut status	***Maintenance*** therapy for recurrent ovarian cancer regardless of BRCA mutation status	***Maintenance*** therapy for recurrent ovarian cancer regardless of BRCA mutation status
Fourth-line and beyond ***treatment*** for advanced ovarian cancer with germline BRCA mut		Third-line and beyond ***treatment*** for advanced ovarian cancer with BRCA mutations

Olaparib PI 2018; Rucaparib PI 2018; Niraparib PI 2019.

4th major change: ***PARPi maintenance– regardless of BRCA***

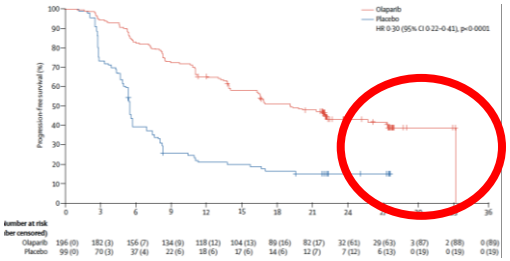
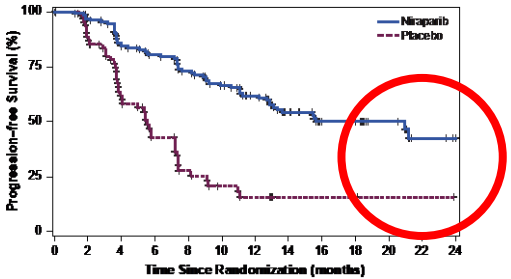
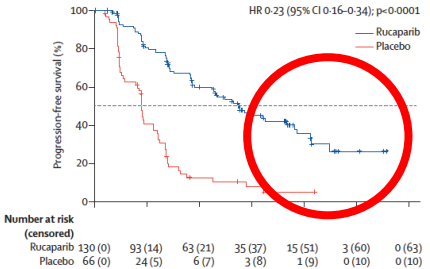
Pivotal studies of PARPi in ROC ***after response to platinum***

	Olaparib		Niraparib		Rucaparib	
Study	**Study 19[1]**	**SOLO-2[2] g*BRCA*m**	**NOVA[3] g*BRCA*m**	**NOVA[3] Non-g*BRCA*m**	**ARIEL-3[4] *BRCA*m**	**ARIEL-3[4] ITT**
Agent	**Olaparib**	**Olaparib**	**Niraparib**	**Niraparib**	**Rucaparib**	**Rucaparib**
Difference in PFS (months)	**8.4 vs 4.8**	**19.1 vs 5.5**	**21.0 vs 5.5**	**9.3 vs 3.9**	**16.6 vs 5.4**	**10.8 vs 5.4**
PFS HR (investigator assessed)	**0.35** (95% CI 0.25 - 0.49; p<0.001)	**0.30** (95% CI 0.22-0.41; p<0.0001)	**0.27** (95% CI 0.18-0.40)	**0.53** (95% CI 0.41, 0.68)	**0.23** (95% CI 0.16-0.34, p<0.0001)	**0.36** (95% CI 0.30-0.45; p<0.0001)
PFS HR (BICR)	**0.39** (95% CI 0.27-0.55; P<0.001)	**0.25** (95% CI 0.18-0.35; p<0·0001)	**0.27** (95% CI 0.17-0.41; p<0.0001)	**0.45** (95% CI 0.34-0.61; p<0.0001)	**0.20** (95% CI 0.13-0.32; p<0.0001)	**0.35** (95% CI 0.28-0.45; p<0.0001)

1. Ledermann J, et al. NEJM. 2012;366:1382-1392. 2. Pujade-Lauraine E et al. Lancet Oncol. 2017 Sep;18(9):1274-1284. 3. FDA NDA review ref 4074987, application no 208447. 4. Coleman RL et al. Lancet. 2017 Oct 28;390(10106):1949-1961.

PARPi use has been transformative in EOC, especially in certain molecular subgroups: *BRCA*m patients

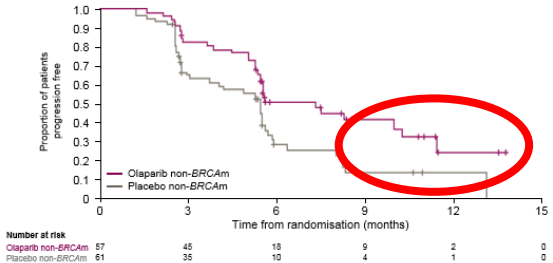
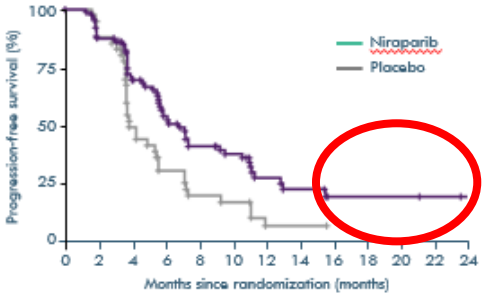
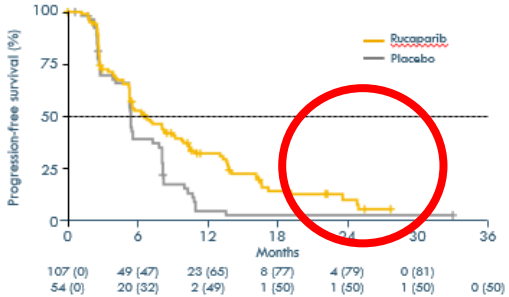
Primary endpoint: PFS

	SOLO-2 - g*BRCA*m[1]	NOVA – g*BRCA*m[2]	ARIEL-3 - t*BRCA*m[3]
			
INV REVIEW	**19.1 vs 5.5 months** **HR 0.30 (95% CI: 0.22-0.41)**	14.8 vs 5.5 months HR 0.27 (95% CI 0.18-0.40)	**16.6 vs 5.4 months** **HR 0.23 (0.16-0.34)**
BICR REVIEW	30.2 vs 5.5 months HR 0.25 (95% CI: 0.18–0.35)	**21.0 vs. 5.5 months** **HR 0.27 (95% CI: 0.17-0.41)**	26.8 vs 5.4 months HR 0.20 (0.13-0.32)

1. Pujade et al. Lancet Oncol 2017; 18: Mirza et al., 3. Coleman RL et al. Lancet. 2017 Oct 28;390(10106):1949-1961

Certain subgroups benefit less (? Not at all)
How do we improve efficacy for these patients?

Primary endpoint: PFS

	Study 19 (BRCA-)	NOVA – BRCA/HRD-[2]	ARIEL-3 – t*BRCA*/LOH-[3]
			
INV REVIEW	**7.4 vs. 5.5 months** **HR 0.54 (95% CI 0.34-0.85)**		**6.7 vs. 5.4 months** **HR 0.58 (95% CI 0.40-0.85)**
BICR REVIEW		**6.9 vs. 3.8 months** **HR 0.58 (95% CI 0.361-0.922)**	

1. Ledermann et al. 2. Mirza et al. 3. Coleman RL et al. Lancet. 2017 Oct 28;390(10106):1949-1961

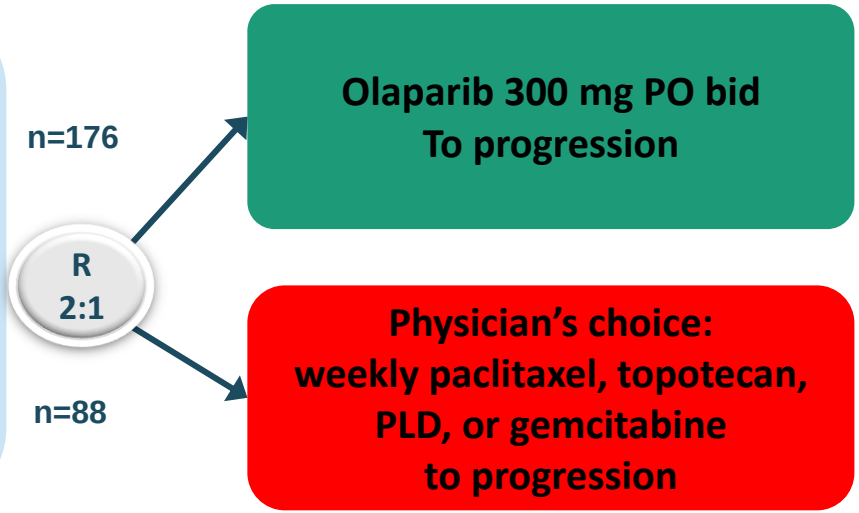
5th major change: PARP Inhibitors in Recurrent Ovarian Cancer
Instead of chemo

	Olaparib	Rucaparib		Niraparib	
Study	**Study 1[1]**	**ARIEL2/Study 10[2,3] BRCAm**	**ARIEL2/Study 102,[3,4] BRCAwt**	**QUADRA[5] gBRCAm**	**QUADRA[5] HRD+**
ORR	34% (95% CI, 26-42)	53.8% (95% CI, 44-64)	29% (LOH high) 10% (LOH low)	29%	27%
DOR	7.9 mo (95% CI, 5.6-9.6)	9.2 mo (95% CI, 6.6-11.6)	10.8 (5.7-NR) LOH-H 5.6 (4.6-8.5) LOH-L	8.3 (6.6-NR)	9.2 (5.9-15.2)
LOT	≥3	≥2	≥2	4th -5th line	4th -5th line

- 1. Domchek, et al. Gynecol Oncol. 2016;140(2):199-203. 2. Pujade-Lauraine E, et al. Lancet Oncol. 2017 Sep;18(9):1274-1284. 3. Oza et al. Gynecol Oncol 12(2): 267-275
  4. Swisher, et al. Lancet Oncol. 2017 (1):75-87. 5. Moore, et al. Lancet Oncol. in press.

Olaparib: SOLO-3 Phase 3 Trial: ASCO 2019

- Recurrent ovarian cancer after ≥2 lines of platinum therapy
- Serous or endometrioid high-grade histology
- Measurable disease
- No prior PARP inhibitor
- Documented deleterious *BRCA* mutation



Primary endpoint: PFS

Secondary endpoints: OS, time to earliest progression by RECIST or CA-125 or death, PFS2, best ORR, HRQoL by TOI of the FACT-O, TDT, TFST, TSST, and safety and tolerability

ClinicalTrials.gov. NCT02282020. Accessed May 31, 2016.

SOLO-3- patient Characterisctics

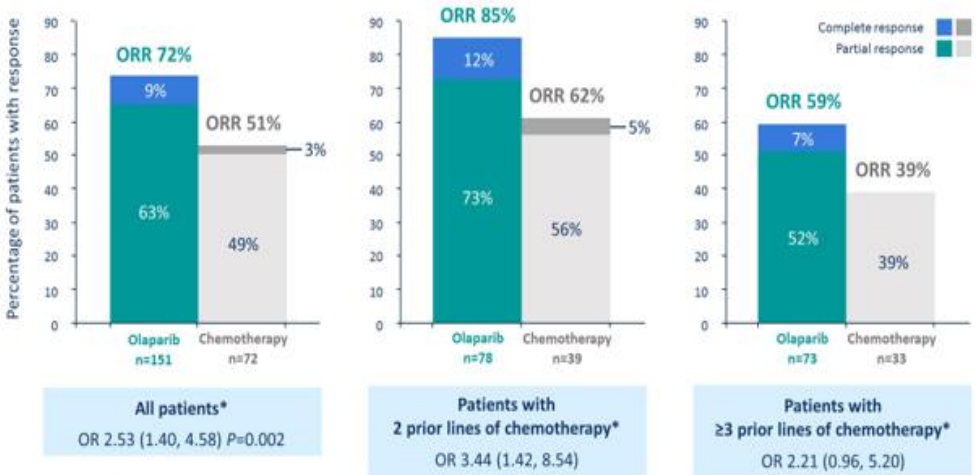
	Olaparib (n=178)	Chemotherapy (n=88)
Primary tumor location, n (%)		
Ovary	160 (90)	74 (84)
Fallopian tube	7 (4)	8 (9)
Primary peritoneal	10 (6)	3 (3)
Other*	1 (1)	3 (3)
gBRCAm by Myriad testing, n (%)		
BRCA1	120 (67)	52 (59)
BRCA2	50 (28)	32 (36)
Negative or missing†	8 (4)	4 (5)
Platinum sensitivity, n (%)		
Progressed ≤6 months after platinum	0	1 (1)
Progressed >6 to ≤12 months after platinum	114 (64)	50 (57)
Progressed >12 months after platinum	64 (36)	37 (42)
Number of previous chemotherapy regimens, n (%)		
2	92 (52)	47 (53)
3	41 (23)	24 (27)
≥4	45 (25)	17 (19)

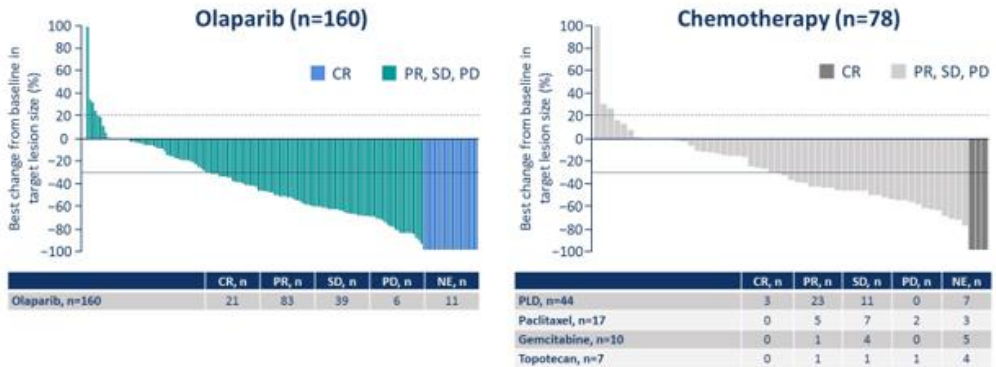
~50%
≥4th line

*Other primary tumor locations were "rectal wall" in the olaparib arm, and "uterus", "liver metastasis", and "pleura" in the chemotherapy arm;
†Central Myriad results were either unavailable or negative, but patients had been shown to have a gBRCAm by local testing

Presented By Richard Penson at 2019 ASCO Annual Meeting

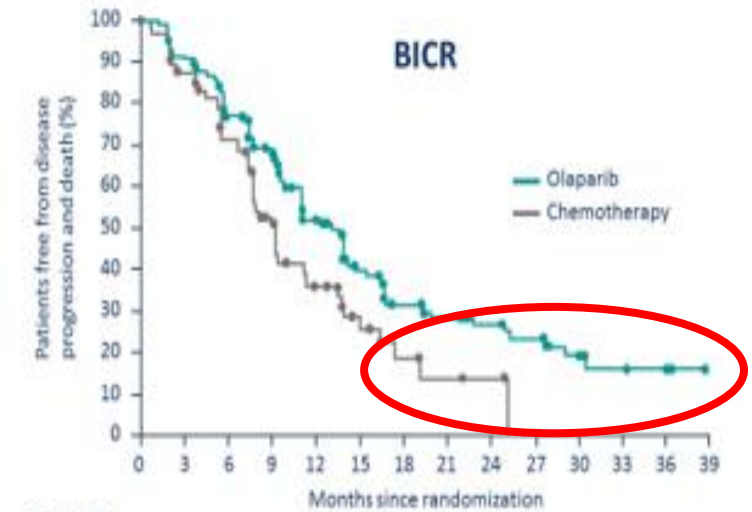
Efficacy Endpoints for SOLO 3: Primary Endpoint is ORR





	CR, n	PR, n	SD, n	PD, n	NE, n
Olaparib, n=160	21	83	39	6	11

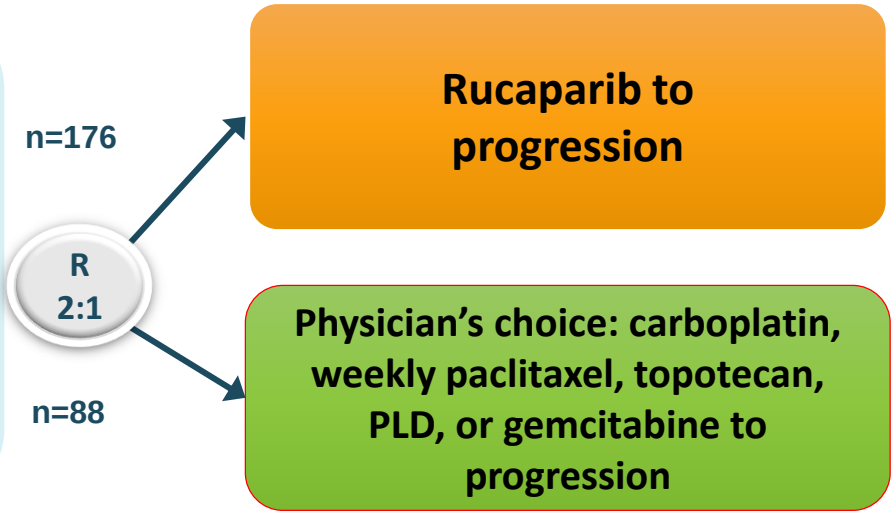
	CR, n	PR, n	SD, n	PD, n	NE, n
PLD, n=44	3	23	11	0	7
Paclitaxel, n=17	0	5	7	2	3
Gemcitabine, n=10	0	1	4	0	5
Topotecan, n=7	0	1	1	1	4



	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	110 (62)	49 (56)
Median PFS, months	13.4	9.2
HR (95% CI), P value	0.62 (0.43, 0.91); P=0.013	

Rucaparib: ARIEL-4 Phase 3 Trial

- Recurrent ovarian cancer after ≥2 lines of platinum therapy
- Serous or endometrioid high-grade histology
- Measurable disease
- No prior PARP inhibitor
- Documented deleterious *BRCA* mutation



Primary endpoint: PFS

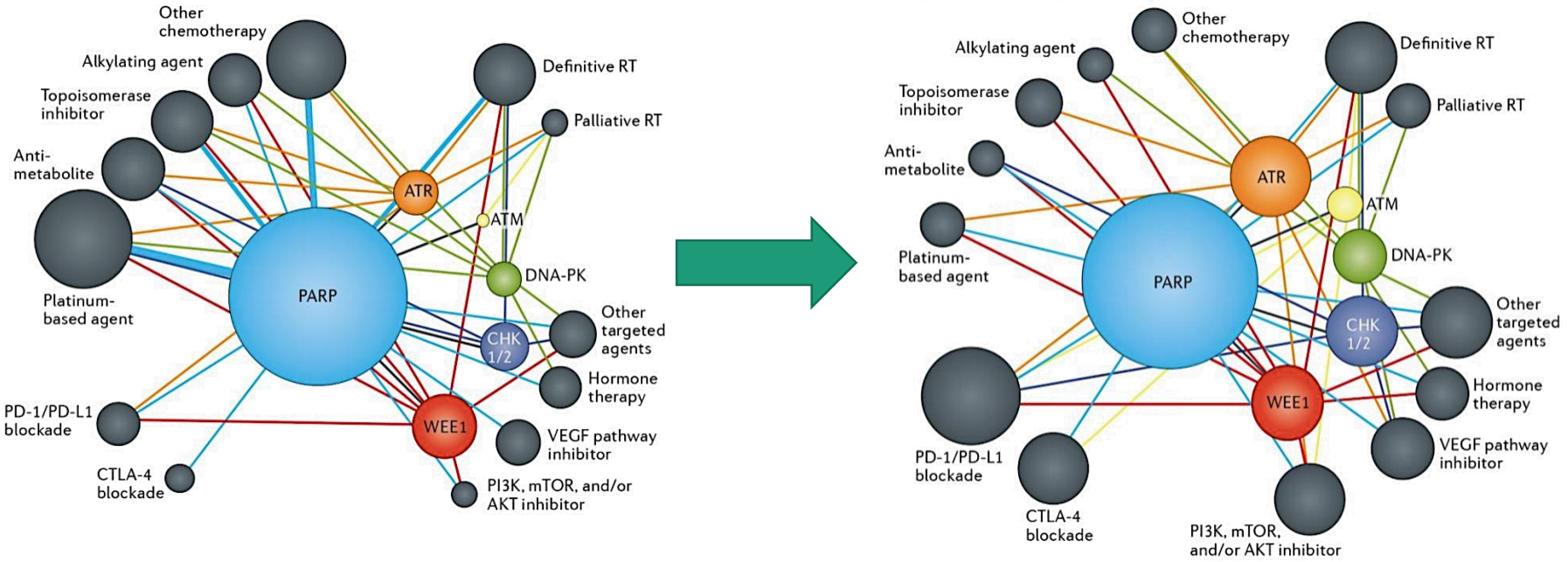
Secondary endpoints: OS, time to earliest progression by RECIST or CA-125 or death, PFS2, best ORR, health-related quality of life by TOI of the FACT-O, TDT, TFST, TSST, and safety and tolerability

ClinicalTrials.gov. NCT02282020. Accessed May 31, 2016.

Current Treatment Landscape for PARPi in Ovarian Cancer

What is our plan for treatment in a Post-PARPi world?

Current and Future Landscape of Ongoing DDR Inhibitor Clinical Trials



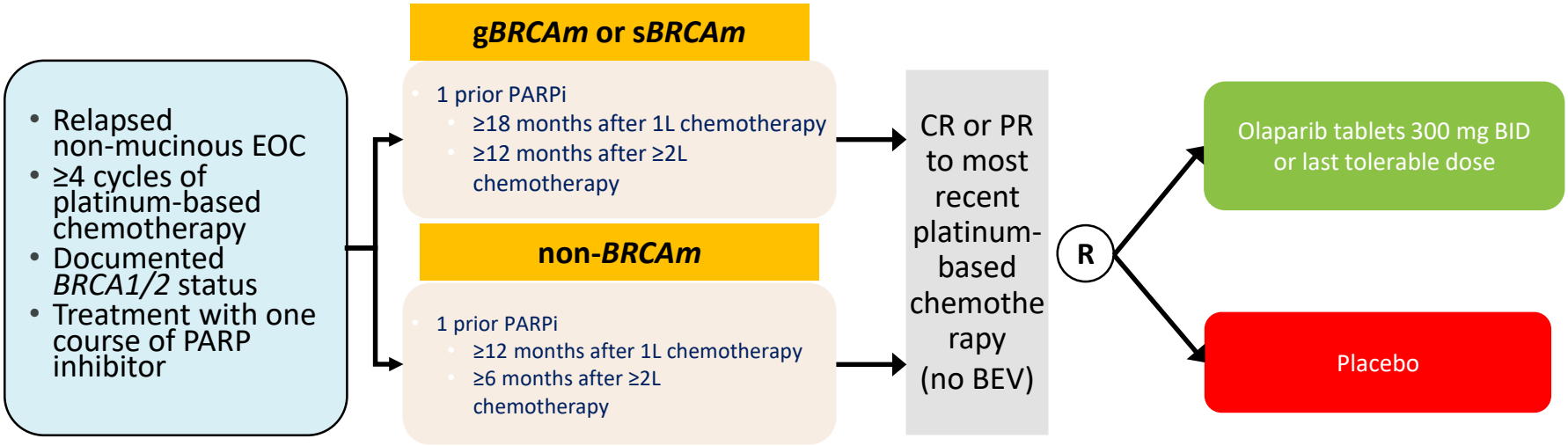
AKT, protein kinase B; CTLA, cytotoxic T-lymphocyte-associated protein;
PD-1, programmed death-1; PD-L1, programmed death-ligand 1; RT, radiation therapy.

Pilie PG, et al. *Nat Rev Clin Oncol*. 2019.

What's Next for PARP Inhibitors in Ovarian Cancer?

- ***Enhancement therapy***
  - Chemotherapy (DNA-damaging agents); GOG-3005
  - Immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1)
  - Radiation therapy
- ***Resistance therapy***
  - P53 targeted agents (AZD-1775, COTI-2, selinexor)
  - CDK inhibitors (ribociclib, palbociclib, roniciclib)
  - HDAC
  - HSP90
  - MEK
- ***Contextual synthetic lethality (inducing HRD in HR compliant tumors)***
  - Hypoxia inducement (antiangiogenesis, EZH2); PAOLA-1
  - PI3K pathway inhibitors
  - ATR/ATM, CHK inhibitors, BRD4/BETi

OReO:
Olaparib *re-treatment* in PS ROC

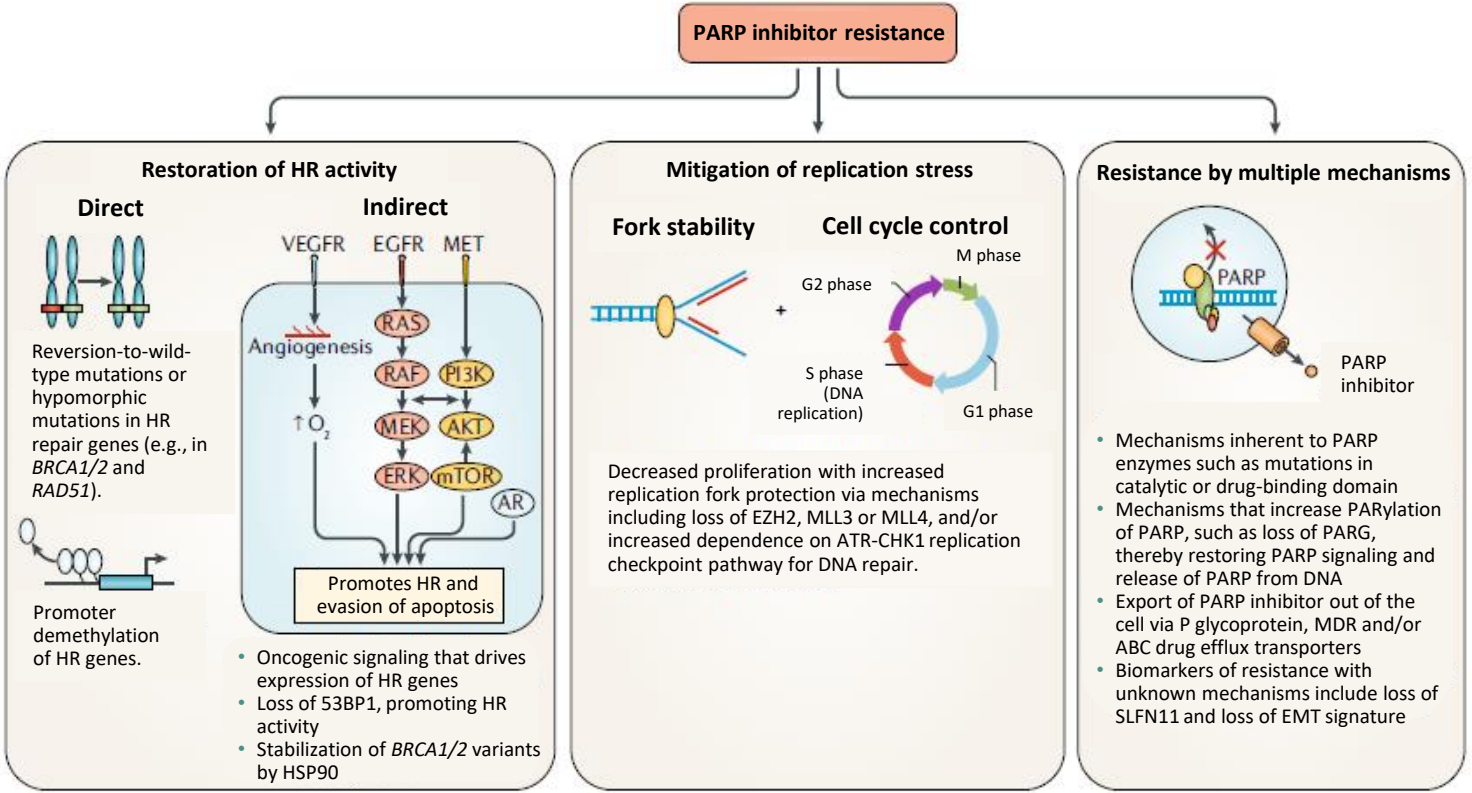


Primary endpoint: **Investigator-assessed PFS**

Secondary endpoints:

- OS
- TTP per GCIG
- TFST and TSST
- TDT
- HRQoL (FACT-O)
- Safety

Overcoming PARPi Resistance

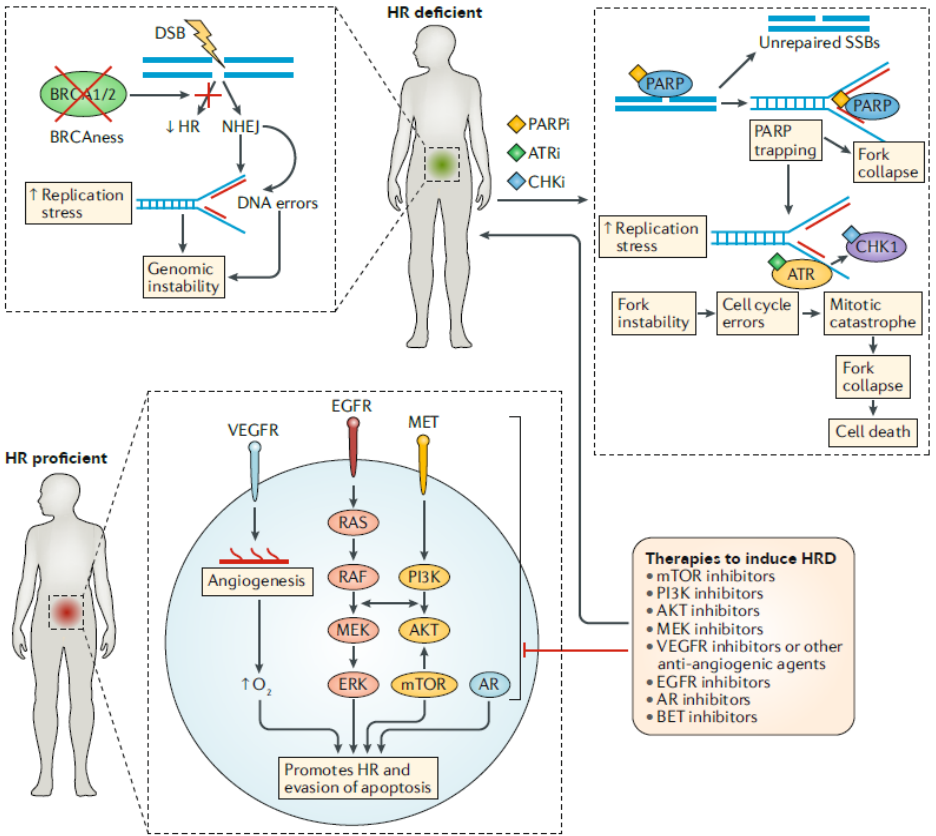


EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; MDR, multi-drug resistance; VEGF, vascular endothelial growth factor.

Pilie PG, et al. *Nat Rev Clin Oncol*. 2019.

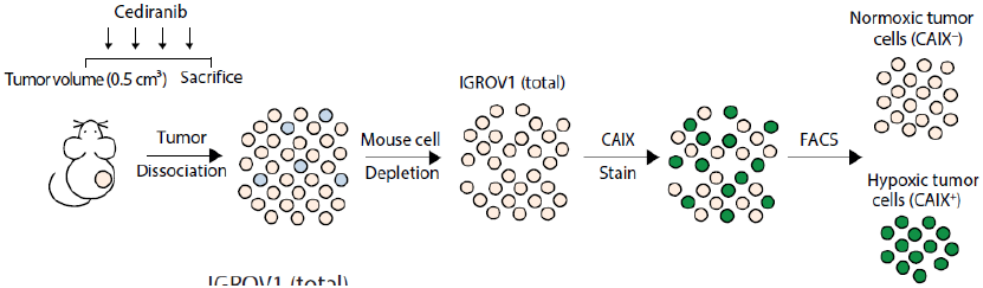
Induction of HRD in HR Proficient Cells

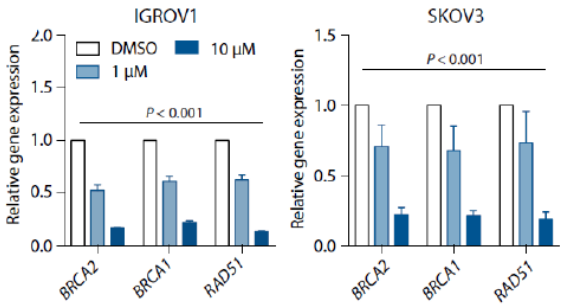
- ***Anti-angiogenesis:***
  - Cediranib + olaparib
  - Niraparib + bevacizumab vs niraparib in PSR (AVANOVA)
- ***Molecularly Targeted Strategies***
  - Olaparib + HSP90 I
  - Olaparib + BYL719 (PI3K)
  - Olaparib + MEK (phase I)
- ***Immune combinations***
  - TOPACIO
  - MEDIOLA

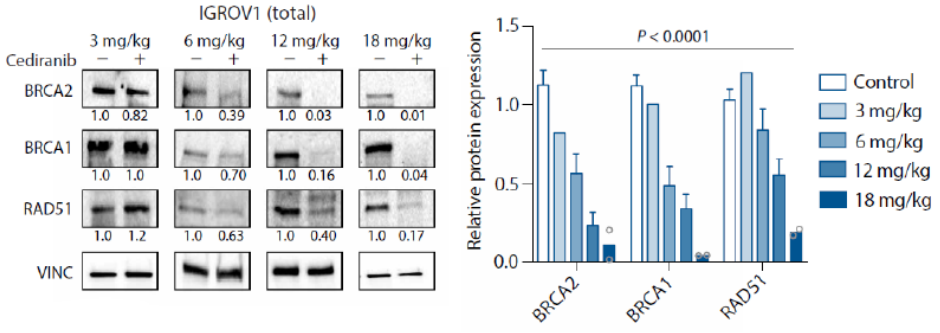


Pilie PG, et al. *Nat Rev Clin Oncol*. 2019; ClinicalTrials.gov; Westin SN, et al. *ASCO*. 2018. Abstract 5504; Matulonis U, et al. *ASCO*. 2014. Abstract 2510; Wilson AJ, et al. *Gynecol Oncol*. 2018.

VEGF inhibition downregulates hypoxia induces HR repair in ovarian cancer cells



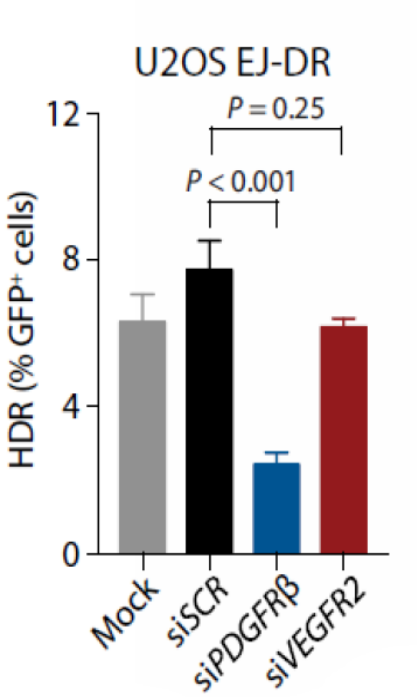


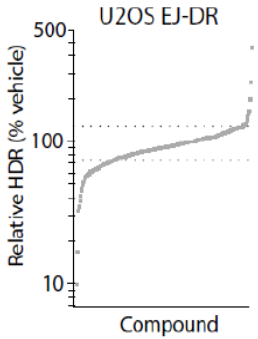


- Hypoxic conditions stimulate VEGF and upregulate the HR DNA repair pathway
- Cediranib, a potent VEGF inhibition abrogated Homologous Recombinant DNA repair across various Breast Cancer cell lines

Kaplan et al. Sci Trans. Med. 2019 Slide Courtesy of Tim Yap, MD

PDGFRβ not VEG2 inhibits HR Repair via Cediranib inhibition





U2OS EJ-DR

Compound	Targets	HDR (% vehicle)	Viability (% vehicle)
Fingolimod	S1PR, Bcr-Abl, PKC	9.90	81.44
Crenolanib	PDGFR	16.79	106.02
NVP-ADW742	IGF-1R	32.67	53.73
Dovitinib	c-Kit, FGFR, VEGFR, PDGFR	34.53	102.16
JNK-IN-8	JNK	34.95	61.98
WYE-125132	mTOR	38.19	90.41
Cabozantinib	VEGFR, c-Kit, PDGFR	41.55	122.96
AZ20	ATM/ATR	45.20	71.02
WP1066	JAK	46.10	76.76

- Cediranib inhibits PDGFRβ as well as VEGFR-1, VEGFR-2, VEGFR-3.
- Regulation of HR repair by Cediranib is due to PDGFRβ inhibition.
- VEGF inhibition alone had no effect on HR repair

Slide courtesy of Tim Yap, MD

Cediranib + Olaparib

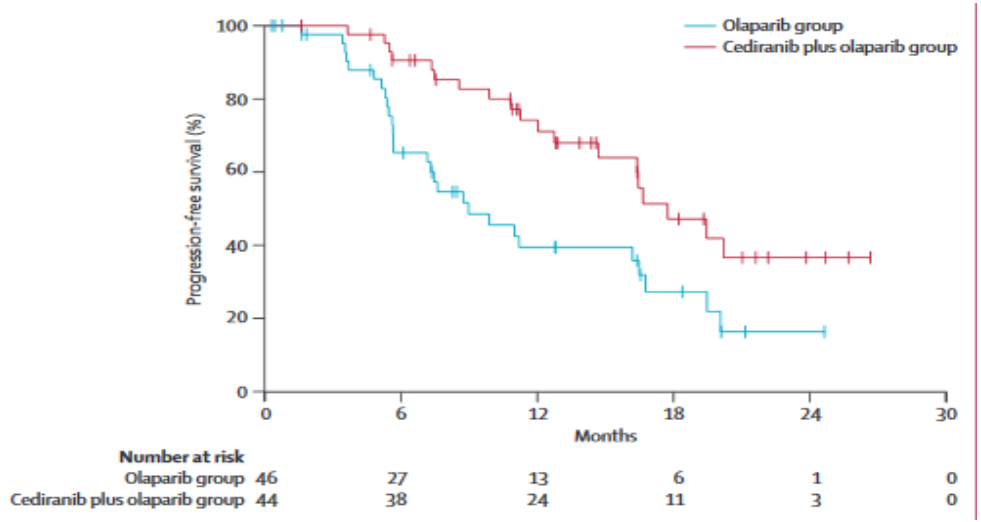
Platinum-sensitive Ovarian Cancer

HGSOC
HGEOC
or
Any BRCAmut OC

ARM 1
Olaparib 400mg po BID

ARM 2
Olaparib 200mg po BID
and Cediranib 30mg QD

Stratification factors:
BRCA positive/negative
Prior Anti-Angiogenic Agent yes/no

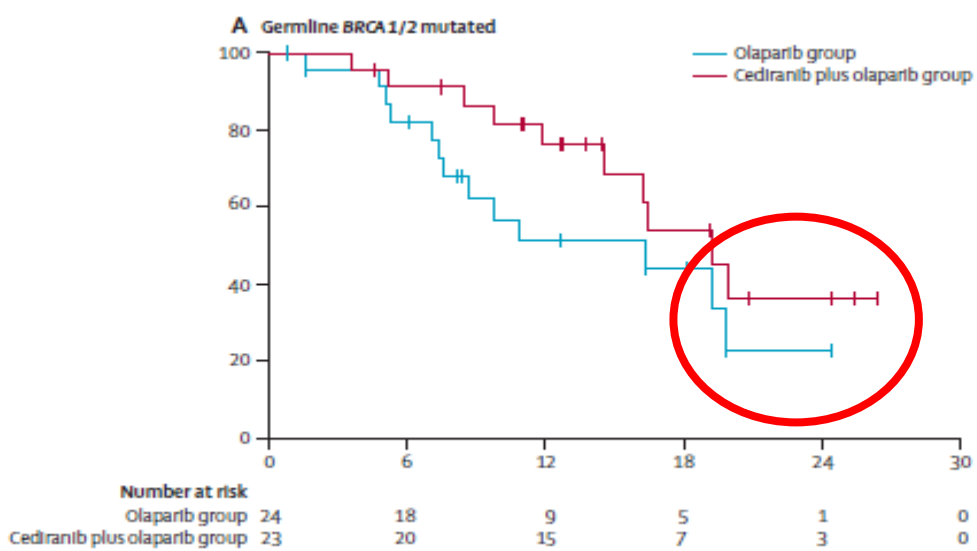


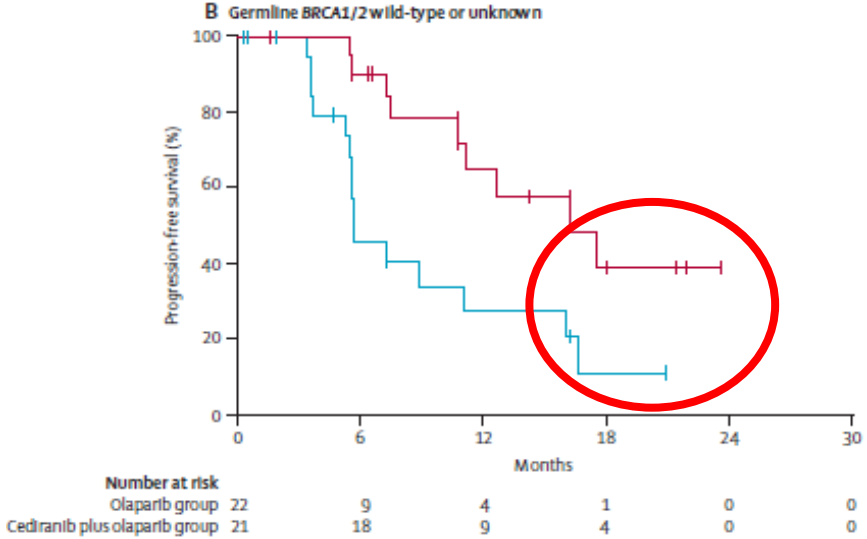
ITT

mPFS 9.0 vs. 17.7 mos (HR 0.42, 95% CI 0.23-0.76)

Liu et al. Lancet Oncology (2014): 15: 1207

Liu et al. Olap +/- Cediranib





mPFS 19.4 vs. 16.5 (HR 0.55)

mPFS 16.5 vs. 5.7 (HR 0.32)

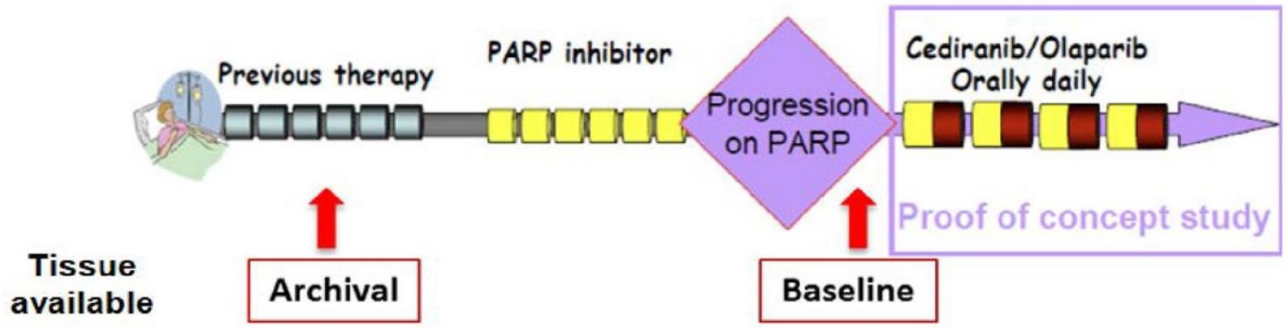
LBA at ESMO September 2019

- ***LBA 58: Randomized trial phase II BAROCCO***

- Weekly Taxol Vs Cediranib-Olaparib as continuous or intermittent in pt with PRROC; negative PFS, non superiority (continuous is better), ***none reached 1ry end point.***

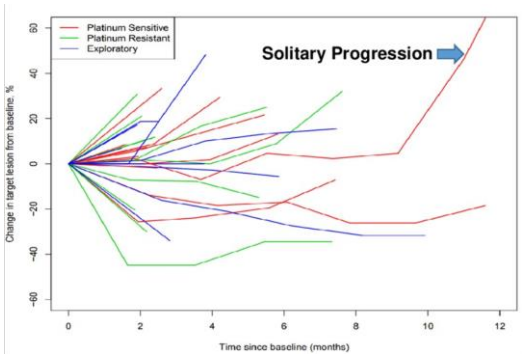
- 2 trials of this Combination are on going

EVOLVE: Cediranib/Olaparib after PARPi



Cohort	Platinum Sensitive	Platinum Resistant	Exploratory
Sample Size	11	10	13
Median age, Years (Range)	56 [50-65]	57 [51-63]	59 [55-70]
Race (White, Asian, East Asian)	7,4,0	8, 1, 1	13,0,0
ECOG PS (0:1)	7:27		
Prior Regimens for Recurrent Disease (2-9)	21 patients received between 2- 5 prior lines		
	13 patients received between 6-9 prior lines		

Best response	Platinum Sensitive	Platinum resistance	Exploratory
PR	0	2	2
PD	2	4	2
SD	9	4	6

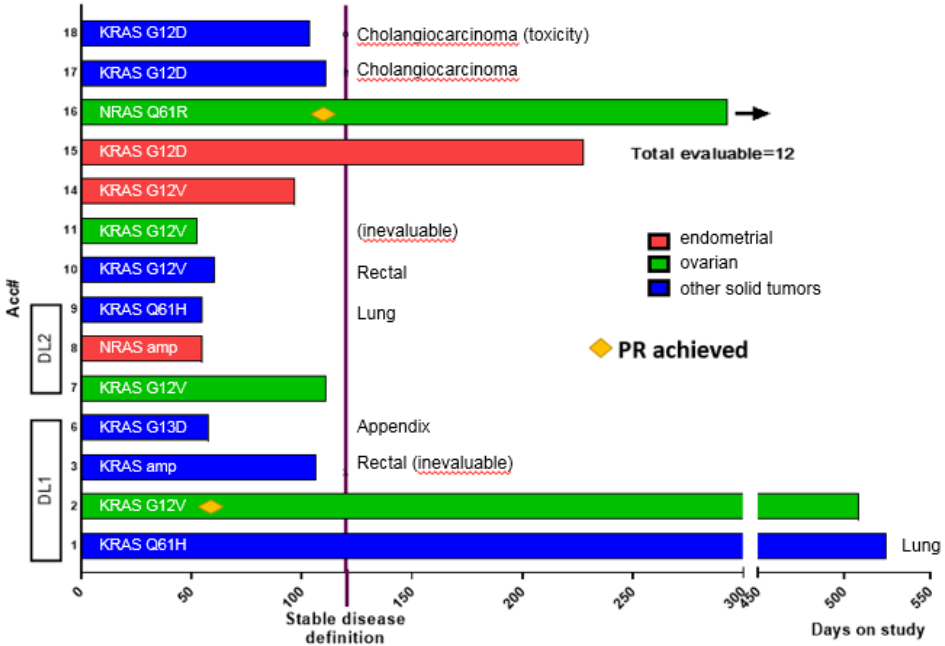


L' heureux et al. ASCO 2019 Abs 5521

SOLAR Trial: Phase I evaluation of Selumetinib and Olaparib

Dose Level	Selumetinib (PO BID)	Olaparib (PO BID)
-1	50 mg on d1-5 (5 days on, 2 days off)	150 mg
1	50 mg	150 mg
2	50 mg	300 mg
3	75 mg	300 mg

RPh2



Study Population for expansion cohorts:
Ovarian Cancer with ***RAS Pathway Alterations***
Endometrial Cancer with RPA
Other Solid Tumors with RPA
PARP resistant ovarian cancer

Toxicity	Any grade n (%)	Grade 3/4 n (%)
Abdominal pain	2 (14%)	2 (14%)
Acneiform rash	71%	1 (7%)
Anemia	79%	
Anorexia	29%	
Constipation	29%	
Decreased ejection fraction	14%	1 (7%)
Decreased white blood cell count	36%	1 (7%)
Diarrhea	50%	
Dizziness	29%	
Dry mouth	43%	
Dry skin	29%	
Dysgeusia	36%	
Edema	29%	
Elevated aspartate aminotransferase	50%	1 (7%)
Elevated bilirubin	7%	1 (7%)
Elevated CPK	36%	1 (7%)
Elevated creatinine	29%	
Fatigue	64%	1 (7%)
Hypophosphatemia	79%	
Nausea	57%	
Neutropenia	21%	1 (7%)
Oral mucositis	50%	
Other skin effects	36%	
Thromboembolic event	7%	1 (7%)

*No grade 4 events occurred

Kurnit et al. AACR 2019

992O - ***FORWARD I (GOG 3011):*** Phase III study of ***mirvetuximab soravtansine***, a folate receptor alpha (FRa)-targeting antibody-drug conjugate (ADC) Vs. chemotherapy in PROC (ID 4093) ESMO Sept 2019

- Mirvetuximab soravtansine (MIRV) is an ADC comprising:
  - ***Cleavable linker:*** FRα-binding antibody
  - ***Potent tubulin-targeting agent:*** Maytansinoid DM4

- FORWARD I, a phase III study: to evaluate safety and efficacy of MIRV Vs. chemotherapy in pts with PROC

- Pts with PROC, 1-3 prior lines of therapy, and FRα positivity by immunohistochemistry (stratified by predefined medium or high expression) were enrolled

- ***Randomized 2:1 to:***
  1. MIRV (6 mg/kg, adjusted ideal body weight) once every 21 days
  2. Or investigators' choice chemotherapy (paclitaxel, PLD, or topotecan)

- ***1ry endpoint:*** PFS by blinded independent review committee, in both the ITT population (medium and high FRα expression) and, separately, in pts with high FRα
- ***2ry endpoints:*** ORR and OS- Median follow-up time was 12.5 months

Clinical trial identification, NCT02631876/ Kathleen N. Moore (Oklahoma City, Oklahoma, United States of America)

992O - ***FORWARD I (GOG 3011):*** Phase III study of ***mirvetuximab soravtansine***, a folate receptor alpha (FRa)-targeting antibody-drug conjugate (ADC) Vs. chemotherapy in PROC (ID 4093) ESMO Sept 2019

- 366 pts randomized: 248 received MIRV and 118 chemotherapy / Baseline characteristics were well balanced
- ***ITT population:***
  - Median PFS : 4.1 vs 4.4 months for MIRV and chemotherapy: HR 0.981
  - For the high FRα pt subset (n = 218), additional outcomes favored MIRV over chemotherapy:
    - ***PFS: 4.8 vs 3.3 months HR: 0.693 (; p = 0.049***, not significant by Hochberg procedure)
    - ORR (24% vs 10%)
    - Interim OS (83/213 events (34%); median not reached vs 11.8 months; HR, 0.618).
    - AEs: Nausea (54%), diarrhea (44%), and blurred vision (43%). Fewer high grade (≥ 3) events, dose modifications, and discontinuations due to AEs were seen with MIRV.

- ***Did not meet the 1ry endpoint:*** promising and consistent efficacy measures in the subset of high FRα PROC

- Along with favorable tolerability and differentiated safety, these findings suggest a favorable benefit-risk profile for MIRV in this biomarker-defined and difficult-to-treat population.

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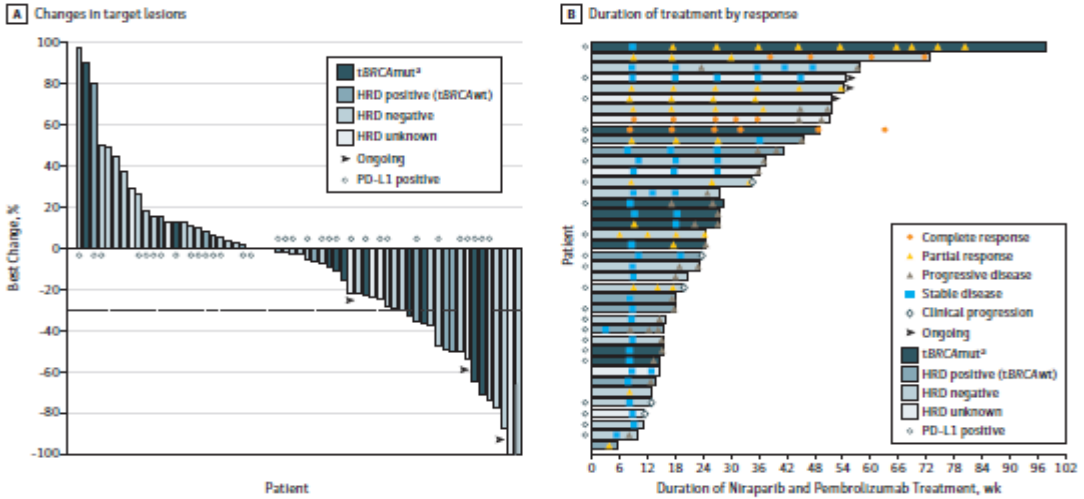
Immune Combinations: TOPACIO: Niraparib + Pembrolizumab

Table 1. Patient Characteristics at Baseline

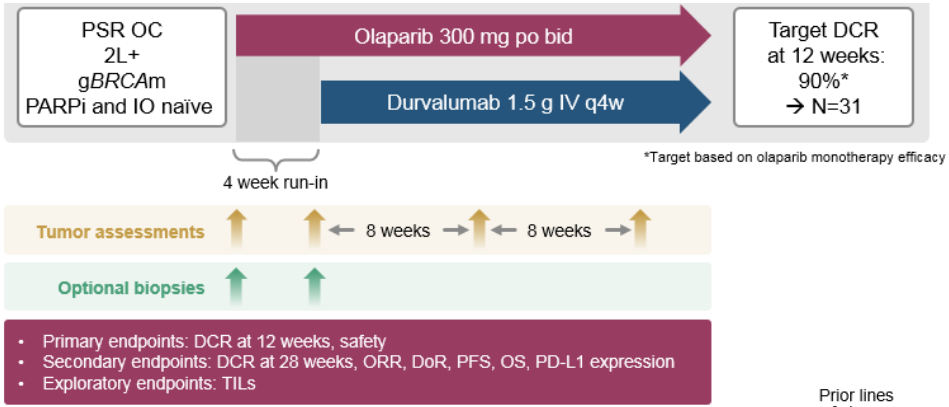
Characteristic	Combined Phases 1 and 2 Patients With Ovarian Carcinoma (n = 62)
Age, median (range), y	60 (46-83)
ECOG performance status, No. (%)[a]	
0	44 (71)
1	18 (29)
Prior lines of therapy, median (range)	3 (1-5)
Prior bevacizumab, No. (%)	39 (63)
Prior chemotherapy, No. (%)[b]	
Anthracycline	40 (65)
Cyclophosphamide	5 (8)
Gemcitabine hydrochloride	29 (47)
Paclitaxel	61 (98)
Platinum	62 (100)
Topotecan hydrochloride	3 (5)
Platinum status, No. (%)	
Resistant	30 (48)
Refractory	17 (27)
Not applicable[c]	15 (24)
tBRCA status, No. (%)	
BRCA1 mutation	9 (15)
BRCA2 mutation	2 (3)
BRCA wild type	49 (79)
Unknown	2 (3)
HRD status, No. (%)	
HRD positive	22 (35)
HRD negative	33 (53)
HRD unknown	7 (11)
PD-L1 status, No. (%)[d]	
Positive	35 (56)
Negative	21 (34)
Unknown	6 (10)

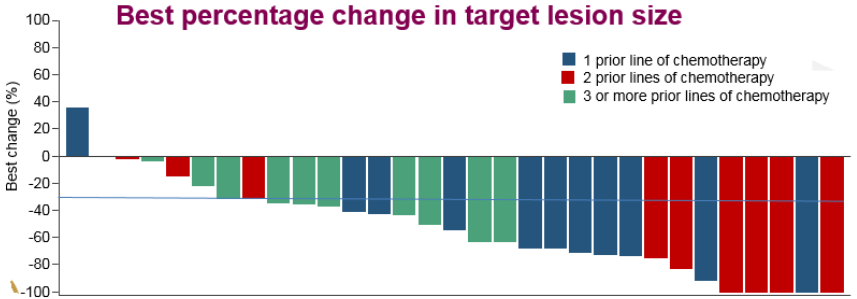


Best Overall Response	Response Data (n = 60)
Complete response, No. (%)	3 (5)
Partial response, No. (%)	8 (13)
Stable disease, No. (%)[a]	28 (47)
Progressive disease, No. (%)	20 (33)
Inconclusive, No. (%)[b]	1 (2)
ORR, % (90% CI)[c]	18 (11-29)
DCR, % (90% CI)[d]	65 (54-75)

Konstantinopoulos et al. JAMA Oncol. 2019; 5(8):1141

MEDIOLA: Olaparib and Durvalumab (BRCA+)/Platinum sensitive





N=32

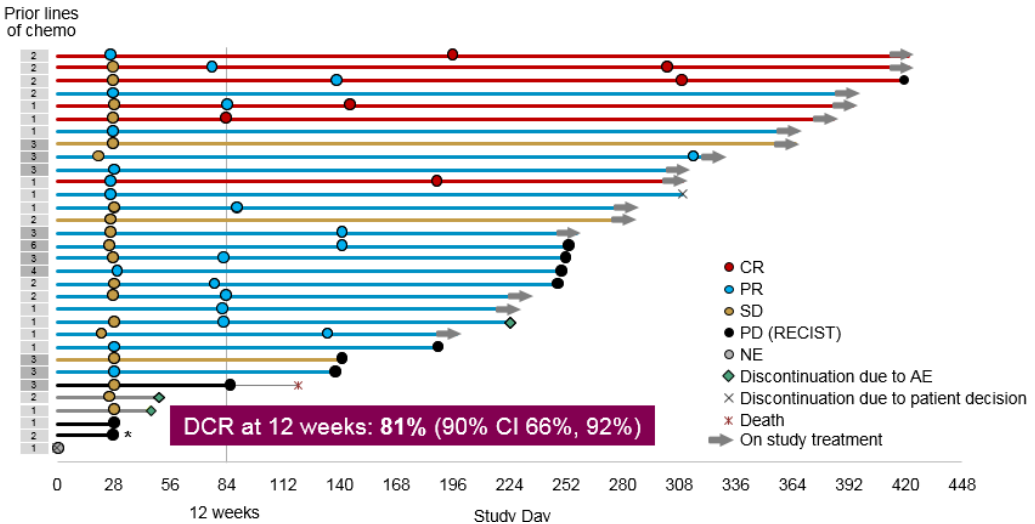
44% with 1 prior regimen

25% with 2

ORR 72% (23/32)

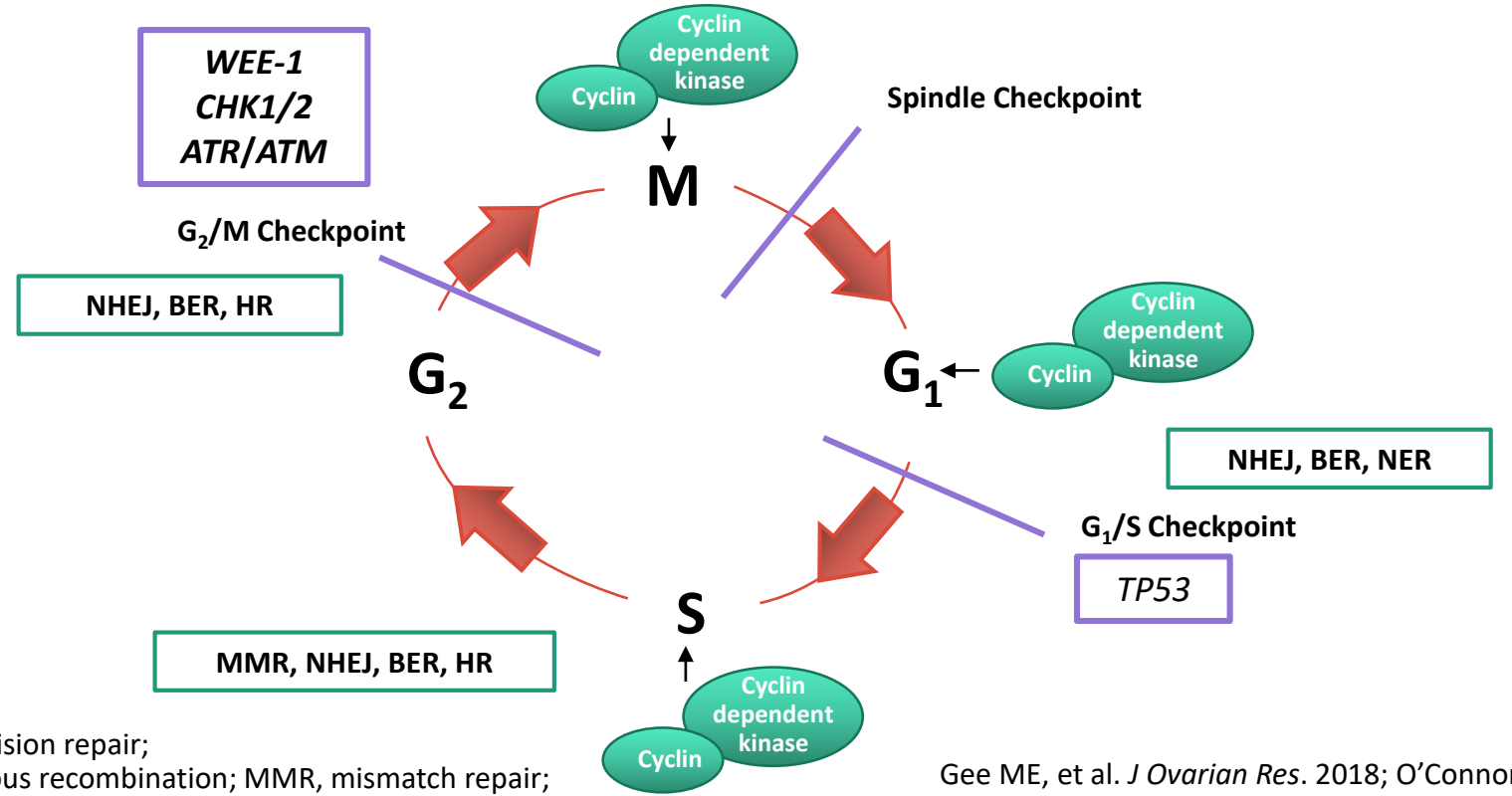
CR 19%

PR 53%



Drew et al. SGO Annual Meeting,2019 Oahu, HI

Detection of DNA Damage Results in Activation of Checkpoints That Enforce Cell Cycle Arrest



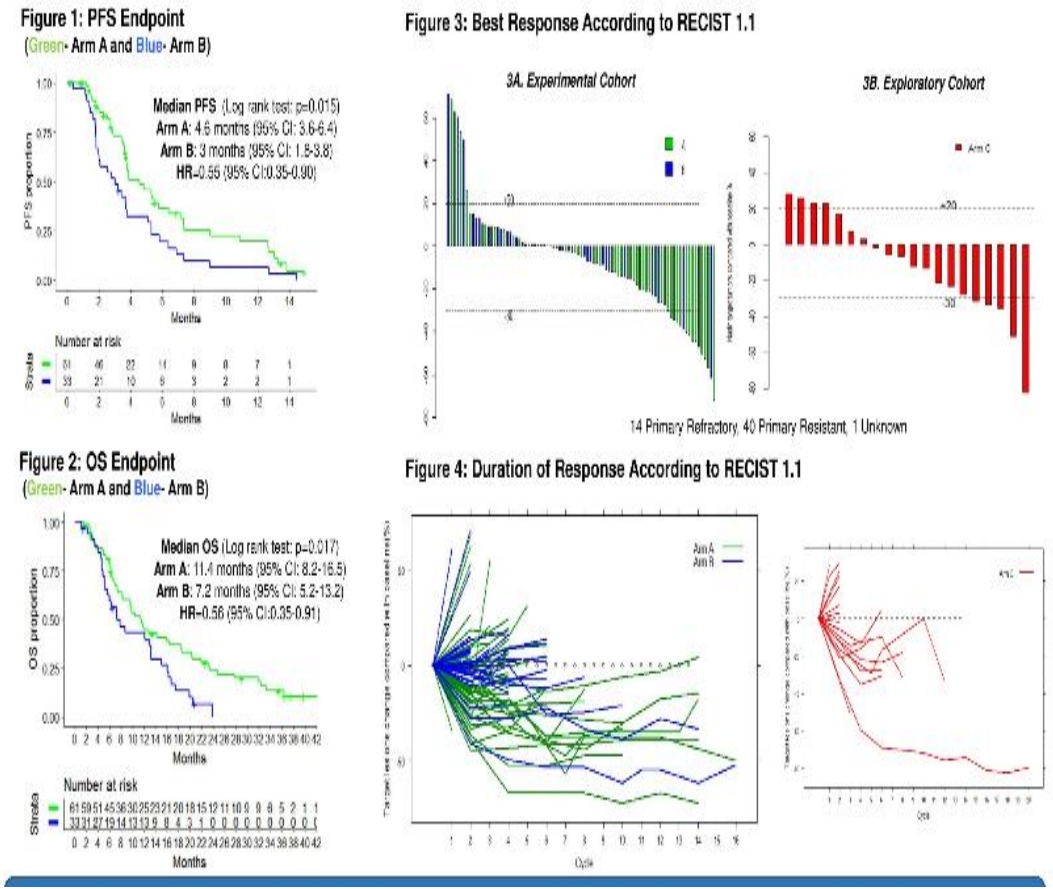
BER, base-excision repair;
HR, homologous recombination; MMR, mismatch repair;
NHEJ, non-homologous end joining; NER, nucleotide-excision repair.

Gee ME, et al. *J Ovarian Res*. 2018; O'Connor MJ. *Mol Cell*. 2015; Weber AM, Ryan AJ. *Pharmacol Ther*. 2015.

Adavosertib (wee-1 kinase inhibitor) in EOC

Most promising combinations:

- Olaparib + Wee-1 – results pending
- Carboplatin + Adavosertib
  ORR: 43-67%[1,2]
- ATRi/Wee-1 – results pending
- Adavosertib + gemcitabine



1. Moore et al. ASCO 2019 2. Leijen et al. JCO 2016; 34(36):4354 3. Lheureux et al. ASCO 2019

3 new trials presented as LBA at ESMO September 2019

- ***LBA 9930:*** ***OCTOPUS***; Multicentric Rand umbrella trial of weekly Taxol +/- Novel agents ***vistusertib MTOR ½ inhibitor*** (PI3K pathways synergy with Taxol:) in PRROC, ***no # in PFS***. PTEN loss better (only 6% of OCA are PTEN pos

- ***LBA 59: Phase IB/2 Study of AVB500 (high affinity inhibitor of GAS6/AXL path)*** B Monk; in combination with PAC and PLD in PRROC: promising. ***RR 40% merits better evaluation***

- ***LBA 60:*** Randomized phase 2 RP2 by Konstantinopolis study of ***ATR inhibitor M6620 in combination with Gemzar Vs Gemzar alone*** in PRRHGOC- DDR check point may work enough cases- dependent on the remaining working pathway- gemzar enhances the response to ATRi- ***PFS is better but not OS-*** enriched of replicative stress biomarker in highly resistant cases

Major Changes Are Coming
in the Medical Treatment of Advanced Epithelial Cancer

Chemotherapy is dead, Long live PARPis