Maintenance therapy with PARP inhibitors- an evolving strategy for the treatment of ovarian cancer

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Disclosures

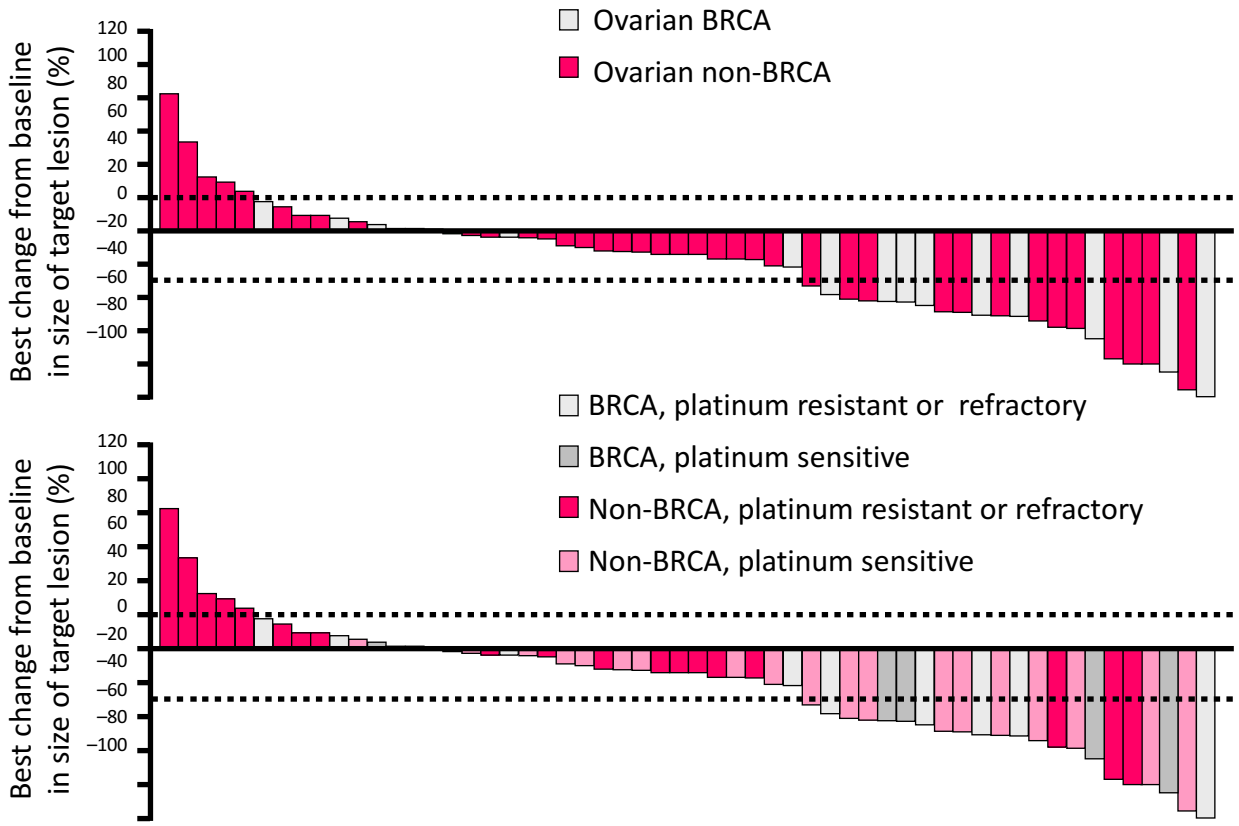
Advisory Committee	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Merck, Pfizer Inc, Roche Laboratories Inc
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Pfizer Inc

Current treatment: Platinum combinations for recurrent ovarian cancer

Trial	Regimen	Med PFS
ICON 4	Carboplatin/Paclitaxel	12.0
CALYPSO	Carboplatin /Paclitaxel	9.4
CALYPSO	Carboplatin/ PLD	11.3
OVAR 2.5	Carboplatin/Gemcitabine	8.6
OCEANS (control)	Carboplatin/Gemcitabine	7.4

- Gaps between successive lines of treatment become shorter
- Targeted - personalised treatment with markers predictive of a response are needed
- New treatments needed to extend chemotherapy-free periods and maintain QoL

Olaparib in BRCA and non-BRCA ovarian cancer



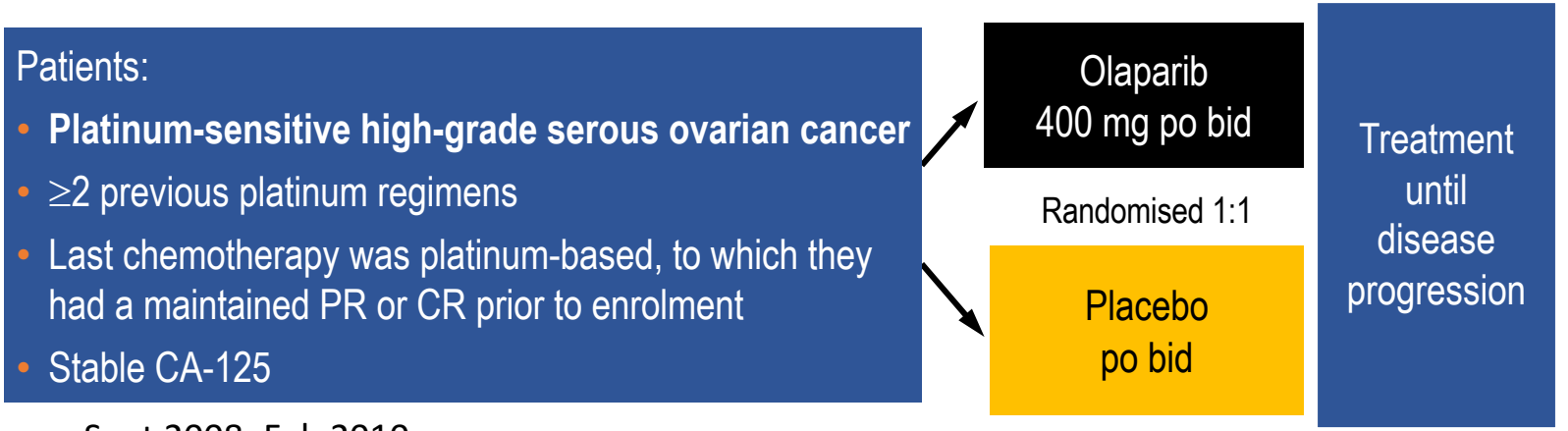
- Olaparib activity in $BRCA^{mut}$ and $BRCA^{wt}$
- Activity greater in 'platinum-sensitive' compared with 'platinum-resistant' relapse

Gelmon KA, et al. Lancet Oncol 2011;12:852–61

Randomised trial of maintenance olaparib in platinum-sensitive high-grade serous relapsed ovarian cancer – 'study 19'

- **Aim: to assess the efficacy and safety of olaparib as a maintenance treatment**
- **Design: randomized, double-blind, placebo-controlled phase II maintenance study**

265 patients in 82 investigational sites in 16 countries

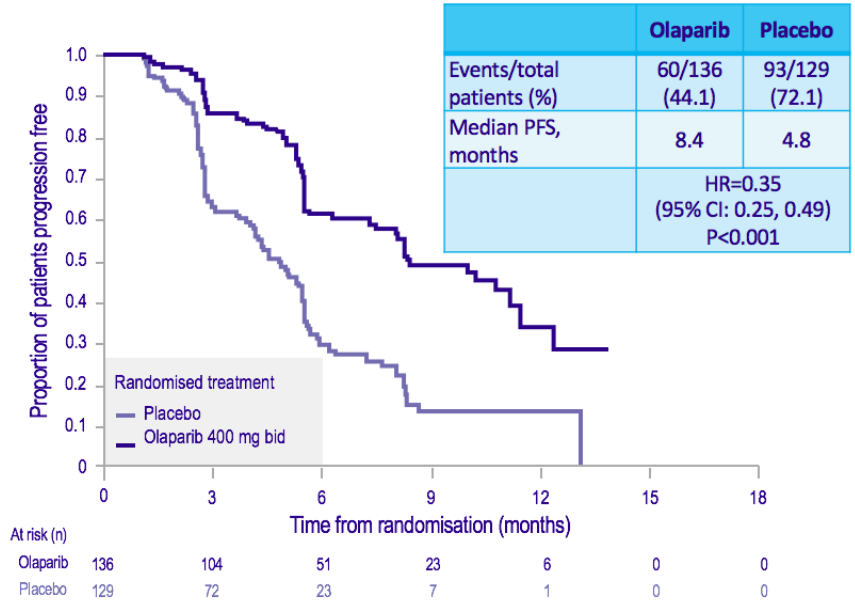


Sept 2008–Feb 2010
bid, twice daily; CA-125, Cancer Antigen 125;
CR, complete response; po, orally; PR, partial response.

Ledermann J et al. N Engl J Med 2012;366:1382–1392

Randomised trial of maintenance olaparib in platinum-sensitive high-grade serous relapsed ovarian cancer: Study 19

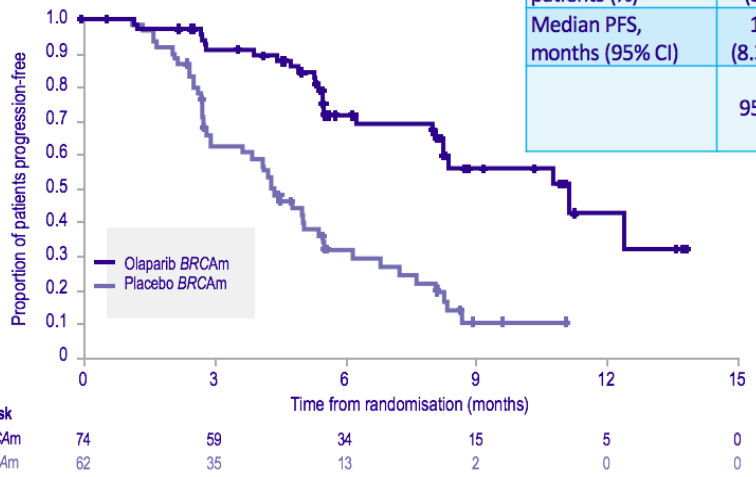
Whole population with HGSOC



	Olaparib	Placebo
Events/total patients (%)	60/136 (44.1)	93/129 (72.1)
Median PFS, months	8.4	4.8
	HR=0.35 (95% CI: 0.25, 0.49) P<0.001	

Ledermann J et al. N Engl J Med 2012

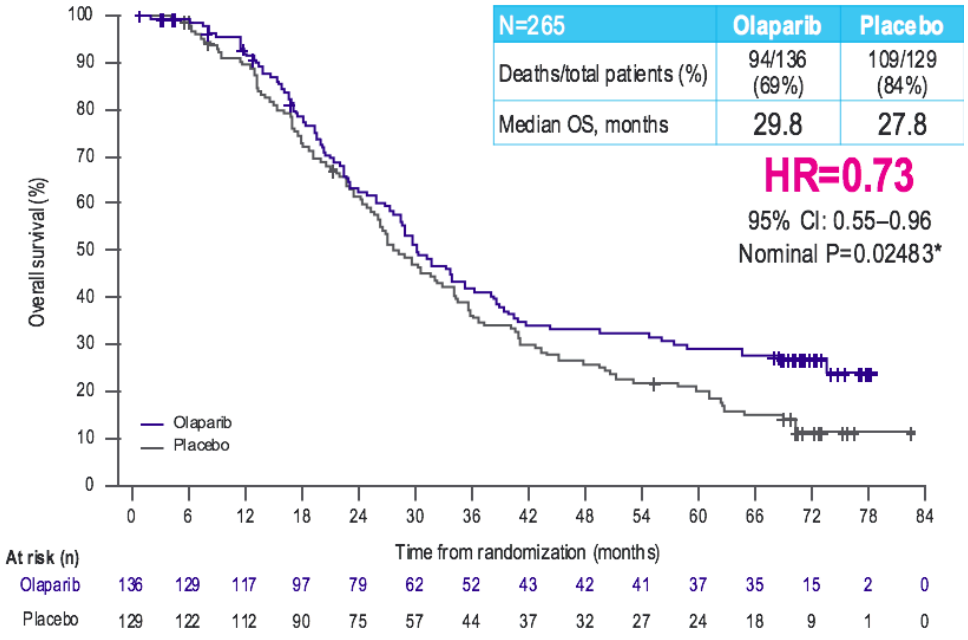
Subpopulation with a BRCA mutation



	BRCAm (n=136)	
	Olaparib	Placebo
Events/total patients (%)	26/74 (35%)	46/62 (74%)
Median PFS, months (95% CI)	11.2 (8.3, NC)	4.3 (3.0, 5.4)
	HR=0.18 95% CI: 0.10, 0.31; P<0.0001	

Ledermann J et al. Lancet Oncol 2014

Updated survival of Study 19- maintenance olaparib



N=265	Olaparib	Placebo
Deaths/total patients (%)	94/136 (69%)	109/129 (84%)
Median OS, months	29.8	27.8

HR=0.73

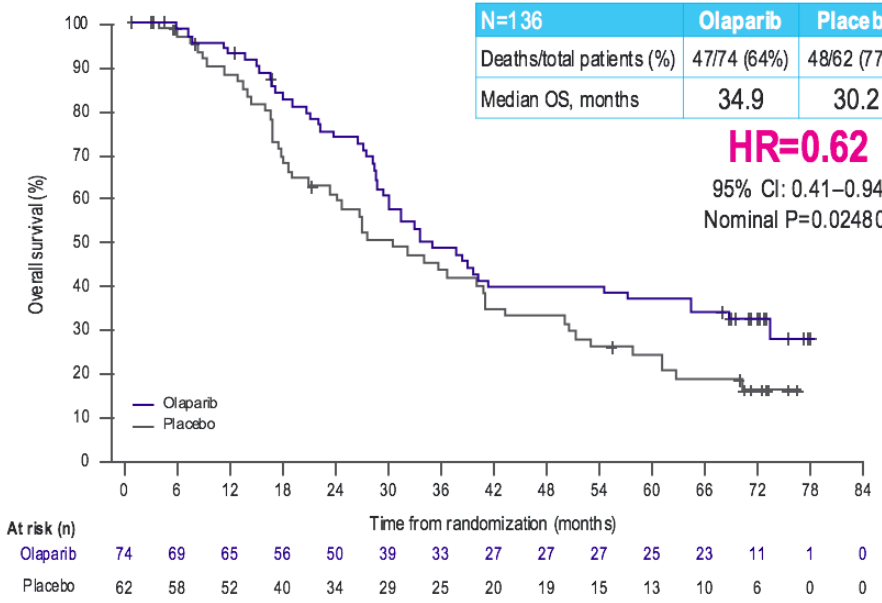
95% CI: 0.55–0.96

Nominal P=0.02483*

Maturity 77 %

Whole study population

BRCAm subgroup



N=136	Olaparib	Placebo
Deaths/total patients (%)	47/74 (64%)	48/62 (77%)
Median OS, months	34.9	30.2

HR=0.62

95% CI: 0.41–0.94

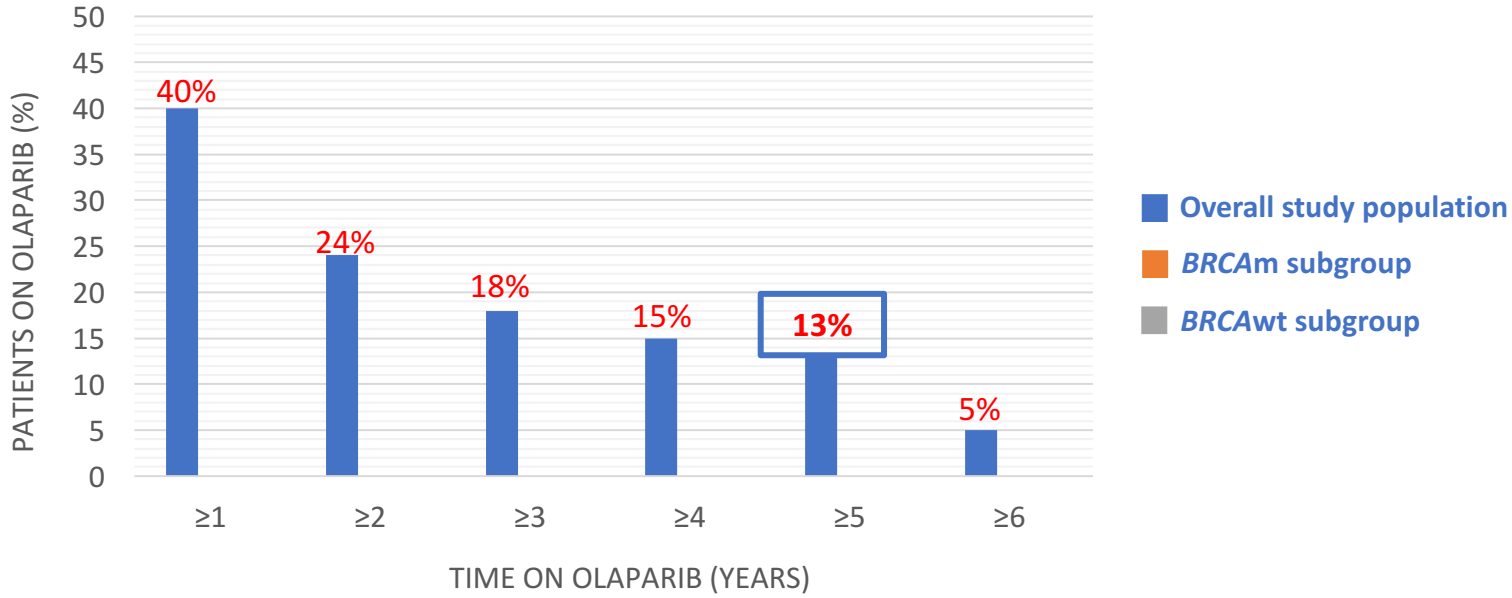
Nominal P=0.02480*

Maturity 70%

Ledermann et al ASCO 2016; Lancet Oncol 2016

Long-term exposure to olaparib in ‘study 19’ in BRCAm and BRCA^{wt}

Median follow-up of 5.9 years: **15 patients (11%)** still receiving **olaparib** (**8 *BRCA*m**, 7 *BRCA*wt); one patient (<1%) still receiving placebo (*BRCA*m)



Ledermann et al ASCO 2016

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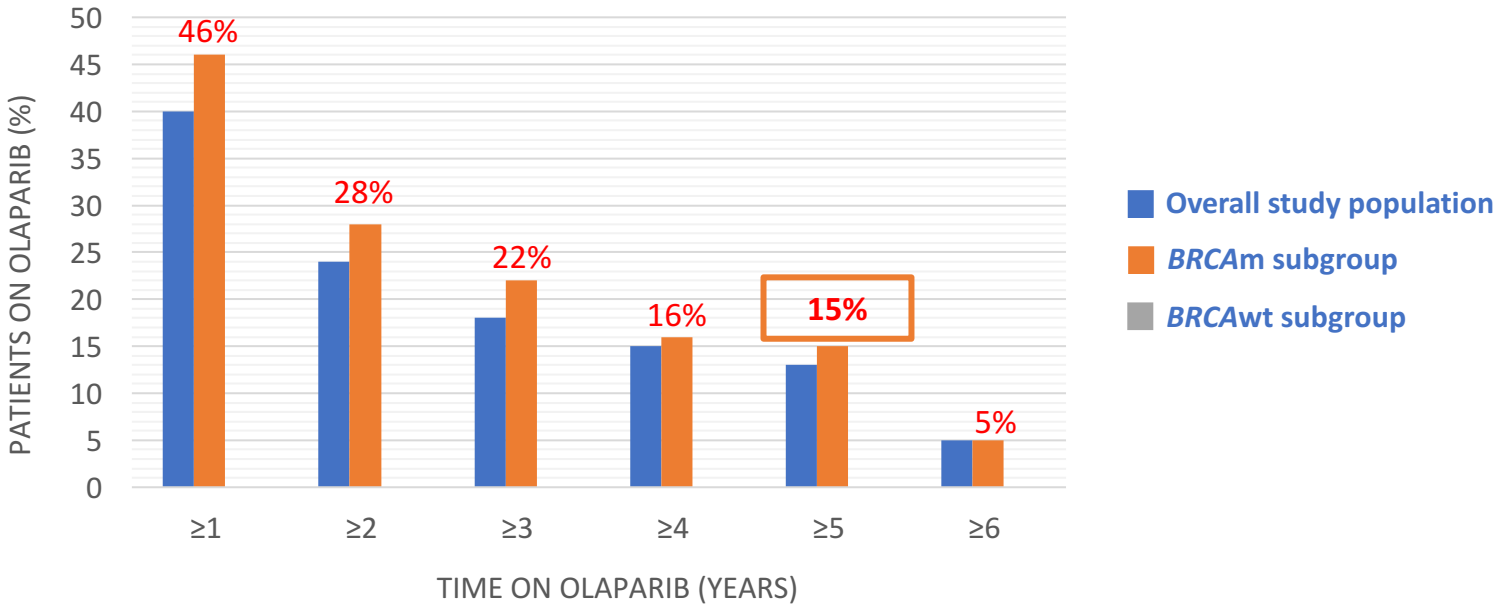

Ledermann et al ASCO 2016

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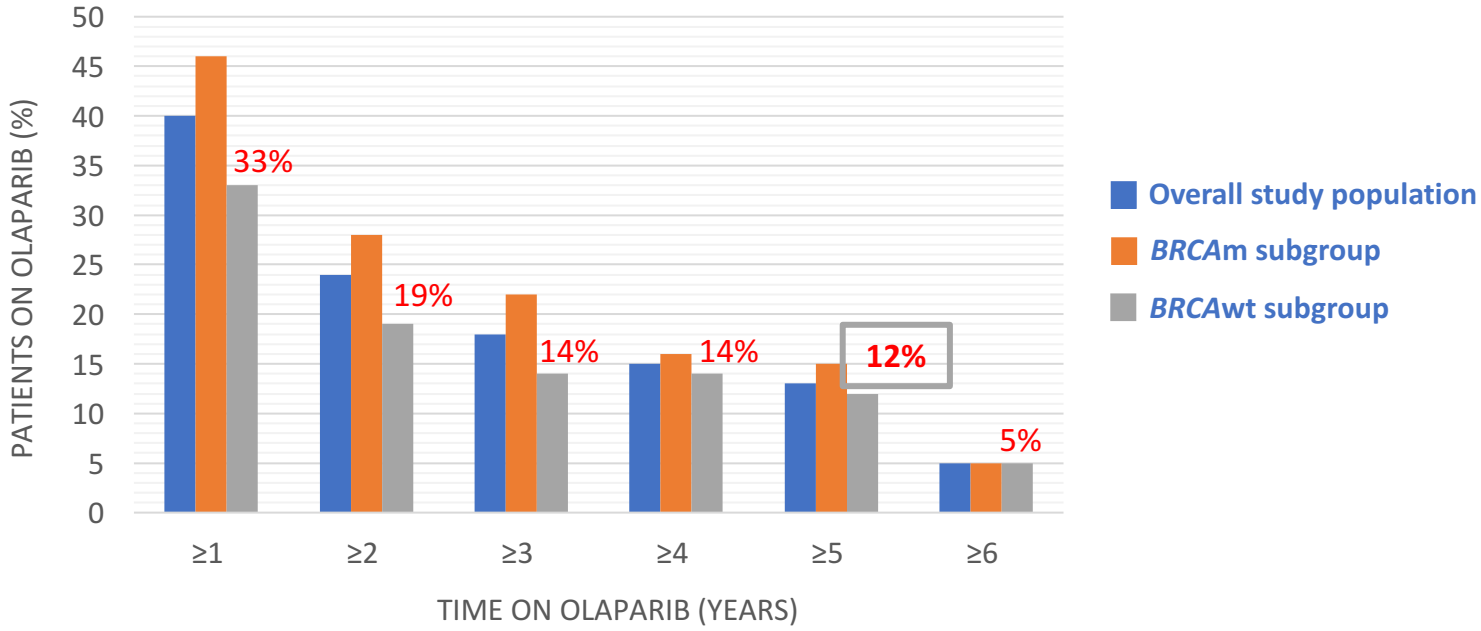
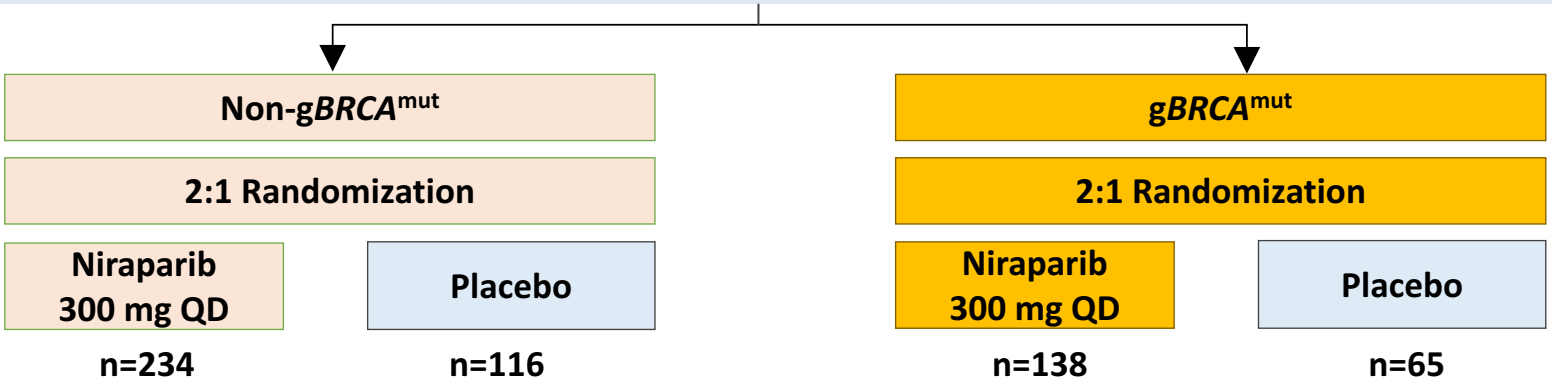


Ledermann et al ASCO 2016

NOVA: Maintenance Niraparib in Recurrent Platinum-Sensitive High-Grade Serous Ovarian Cancer

- **Phase III, multicenter, randomized, double-blind, placebo-controlled study**
- Relapsed high-grade serous histology or known g*BRCA*^{mut}
- ≥2 prior regimens of platinum-based chemotherapy
- **Responded to last platinum regimen; remains in response and enrolled within 8 weeks of completion of last platinum regimen**
- **No measurable lesion ≥2cm**

N=553

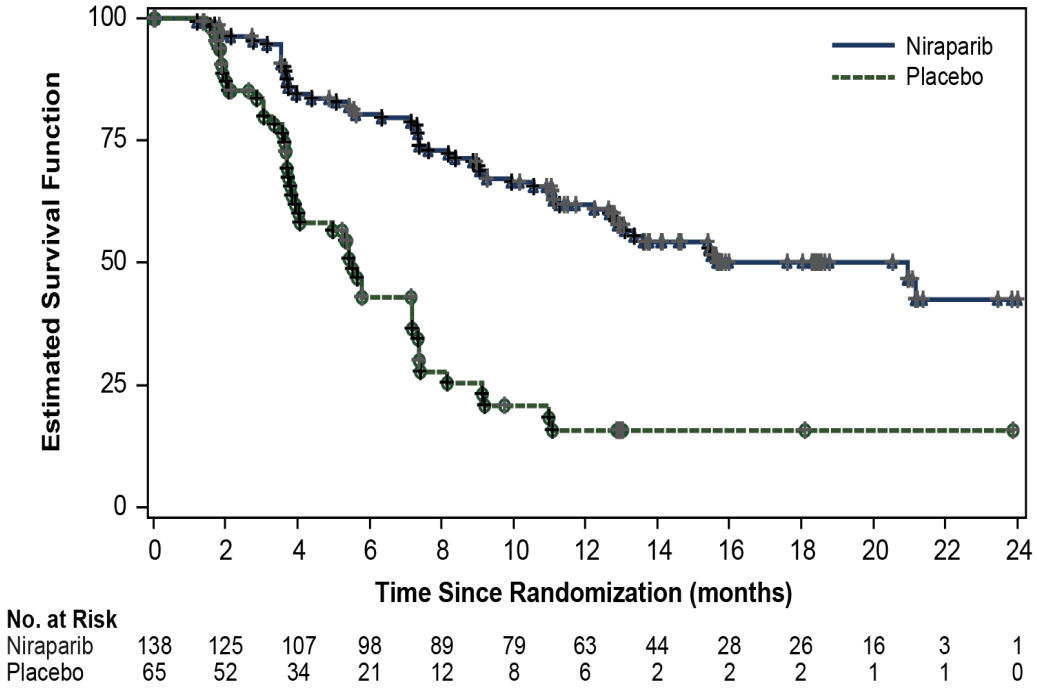


Primary Endpoint

- PFS; >90% power to detect 4.8-month improvement (HR 0.50)
- Non-g*BRCA*^{mut} cohort endpoint assessed hierarchically to control type 1 error: HRD+ population first, followed by entire population

NOVA Trial- Niraparib maintenance in high-grade serous ovarian cancer

Progression-free Survival: gBRCAmut

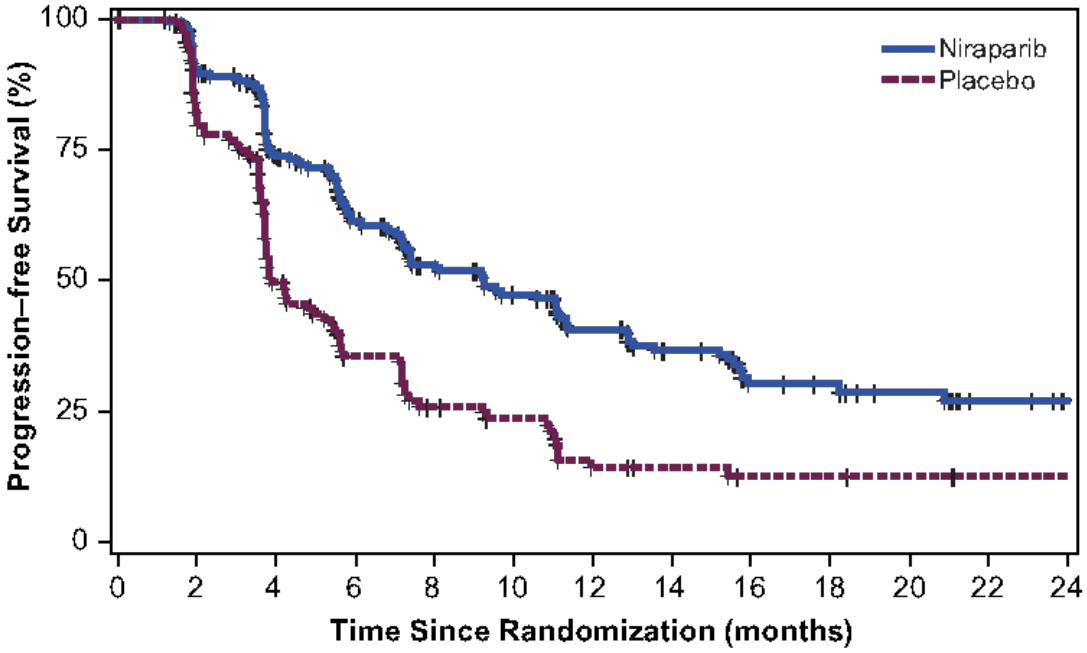


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	**21.0** (12.9, NE)	**0.27** (0.173, 0.410) p<0.0001	62%	**50%**
Placebo (N=65)	**5.5** (3.8, 7.2)		16%	16%

Mirza et al ESMO 2016; NEJM 2016

NOVA Trial- Niraparib maintenance in high-grade serous ovarian cancer

Progression-free Survival: Non-gBRCAmut



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=234)	**9.3** (7.2, 11.2)	**0.45** (0.338, 0.607) p<0.0001	41%	**30%**
Placebo (N=116)	**3.9** (3.7, 5.5)		14%	12%

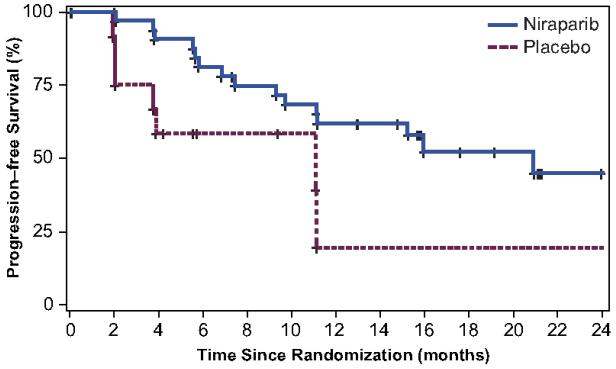
Mirza et al ESMO 2016; NEJM 2016

NOVA: Exploratory Analysis: PFS in non-gBRCAmut Subgroups

HRD-positive

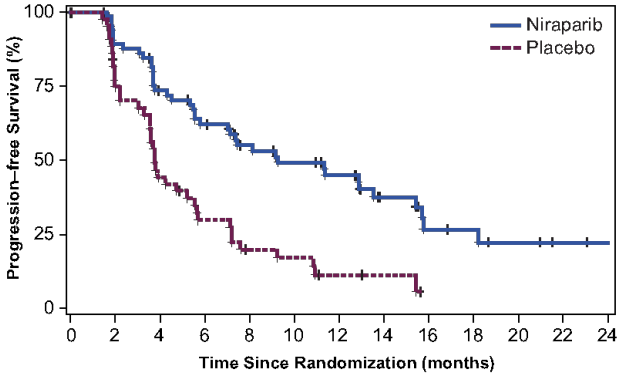
sBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=35)	**20.9** (9.7, NR)	**0.27** (0.081, 0.903) p=0.0248	62%	**52%**
Placebo (N=12)	**11.0** (2.0, NR)		19%	19%



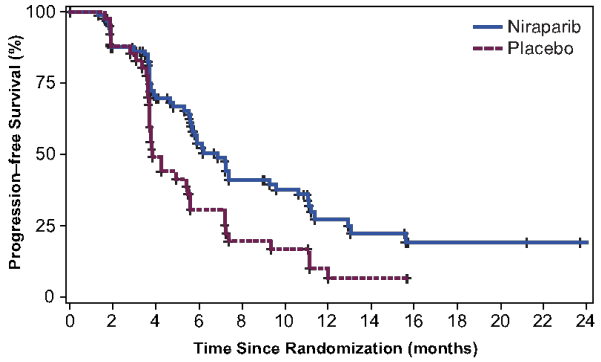
BRCAwt

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=71)	**9.3** (5.8, 15.4)	**0.38** (0.231, 0.628) p=0.0001	45%	**27%**
Placebo (N=44)	**3.7** (3.3, 5.6)		11%	6%



HRD-negative

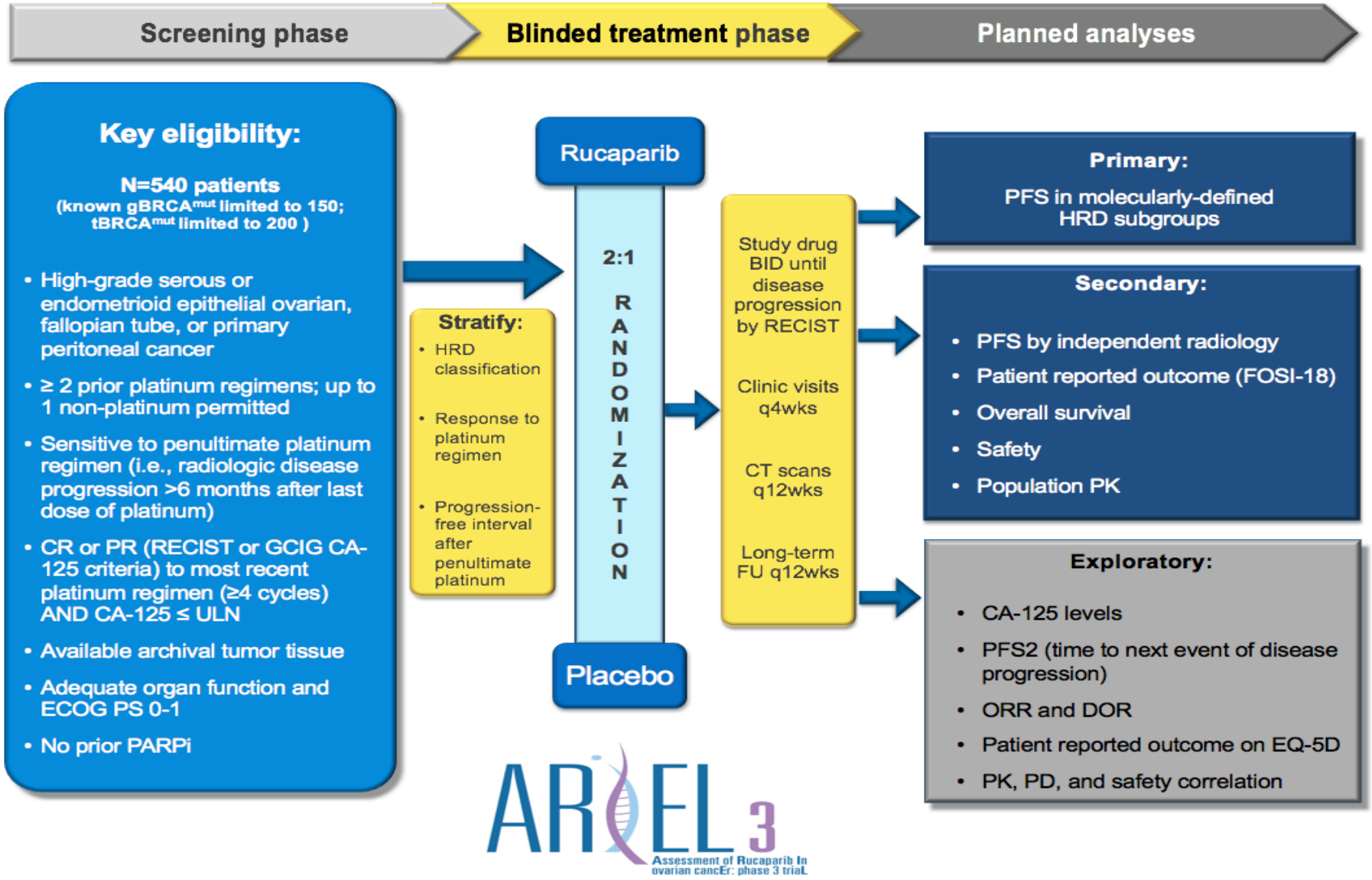
Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=92)	**6.9** (5.6, 9.6)	**0.58** (0.361, 0.922) p=0.0226	27%	**19%**
Placebo (N=42)	**3.8** (3.7, 5.6)		7%	7%



NR=Not reached

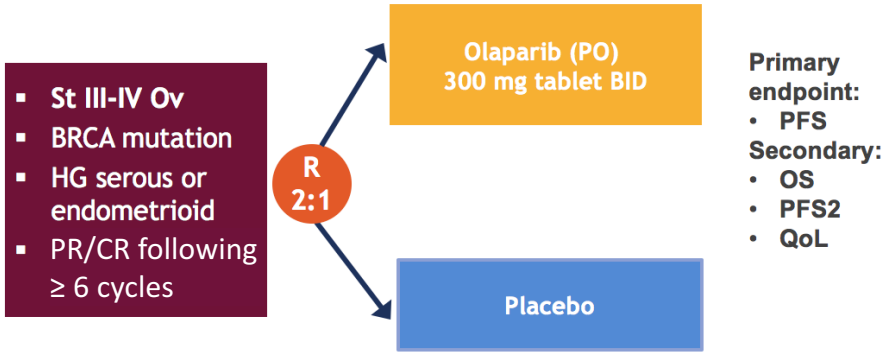
Mirza et al ESMO 2016

ARIEL 3- Rucaparib Maintenance Trial



SOLO studies- Maintenance in BRCA mutated Ovarian Cancer

SOLO-1- First line



Estimated Enrollment: 397
Study Start Date: Aug 2013
Estimated Study Completion Date: Jan 2022
Estimated enroll Completion: Jul 2016 (Final data)

ClinicalTrials.gov Id NCT01844986

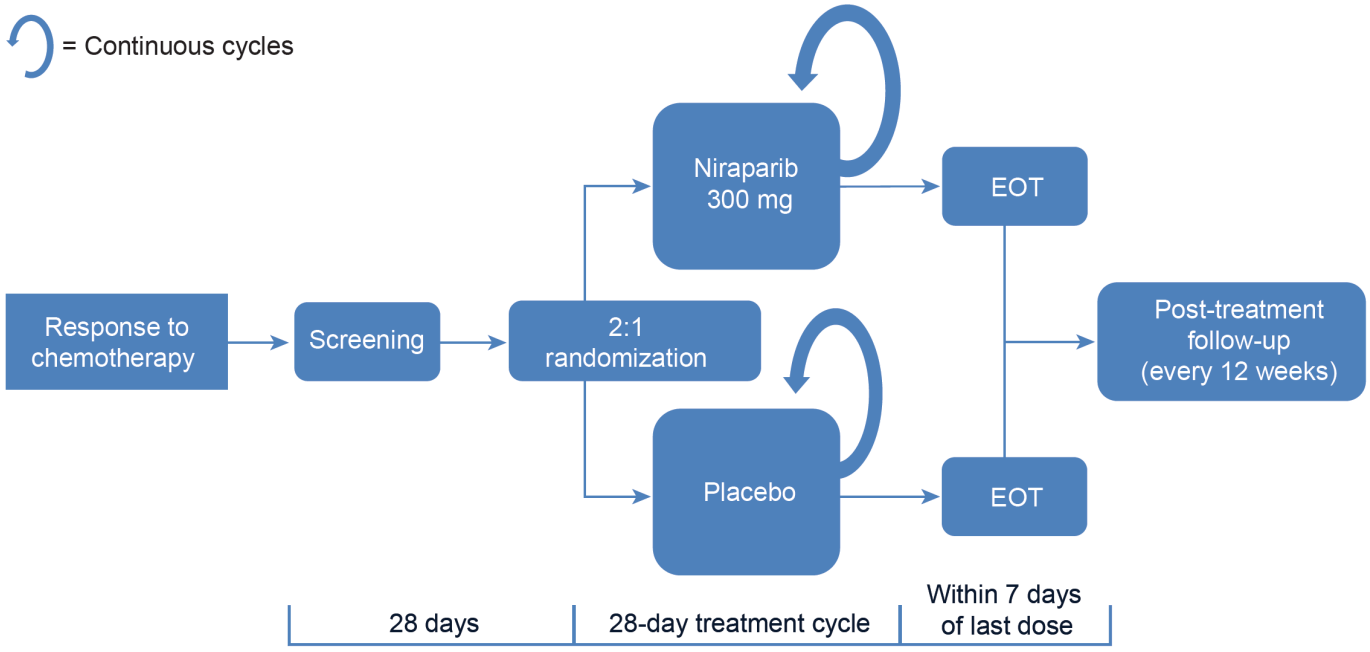
ENGOT-ov 26 (PRIMA study)

Niraparib maintenance in First-line therapy

High Risk patients: Stage IV; suboptimal Stage III

Stratification factors:
- Use of NACT: yes or no
- Best tumor response: CR or PR
- HRD status: pos or neg/nd

- Patients with sBRCA or tBRCAmut will be stratified as HRDpos
- Patients with unknown or wild type BRCA will be stratified based on HRD test results



Primary Endpoint
PFS in HRDpos patients; hierarchical analysis for all patients regardless of HRD status

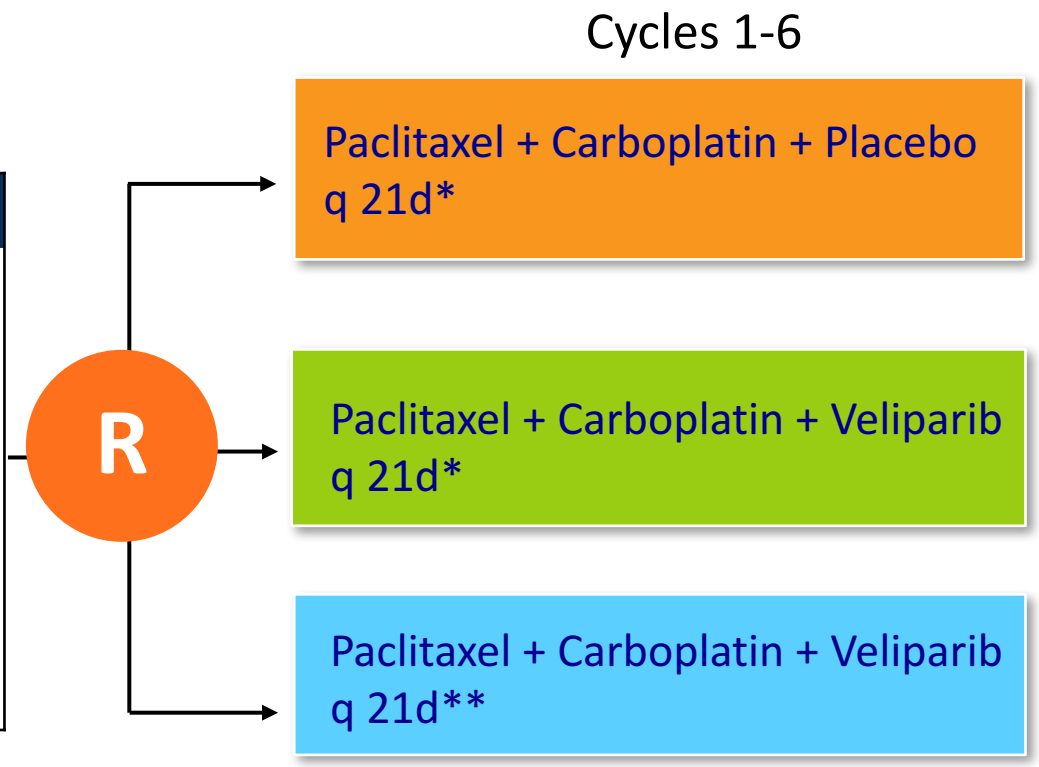
Secondary:
OS, Patient Reported Outcomes (PRO's), tTme to First Subsequent Treatment, PFS2, safety and tolerability of study therapy

Phase III GOG-3005

Trial Identifier: NCT02470585
Enrollment: 1,100 (recruiting)

Eligibility

- High-grade serous epithelial, ovarian, fallopian tube or primary peritoneal carcinoma
- Stage III-IV
- ECOG PS 0-2
- Archived diagnostic FFPE tumor tissue or tumor tissue biopsy collected prior to Cycle 1 Day 1



Primary endpoint:
Progression-free survival

* Cycles 7-30: placebo maintenance
** Cycles 7-30: veliparib maintenance

www.clinicaltrials.gov. Accessed March 2017.

PARP inhibitors – represent a change in practice for treating recurrent ovarian cancer

- Olaparib is the first licensed PARP inhibitor directed at a genotypically defined predictive marker (BRCA mutation) in recurrent ovarian cancer
- Significant improvement in PFS with maintenance therapy in platinum-sensitive high-grade serous carcinoma
- 15% patients with a $BRCA^{mut}$ remain on olaparib for > 5 years
- Well-tolerated oral medication, with low drop-out rate due to side effects
- Olaparib and niraparib maintenance therapy in platinum-sensitive recurrent BRCAm tumours- similar benefit
- Testing for BRCA ^{mut} (approximately 15-20 % HGSOC) should now become part of routine practice
- Both niraparib and olaparib demonstrate activity in BRCA wt patients. Platinum-sensitivity and HRD testing help to define patients that benefit

The future……..

- Assessing strategy of single agent therapy compared to maintenance- equivalent clinical benefit?-
- Combining anti-angiogenic drugs with PARP inhibitors
  - Platinum-sensitive disease- therapy and maintenance (cediranib/olaparib)
  - First-line maintenance (bevacizumab/olaparib)
- Combinations with checkpoint inhibitors
  - Niraparib/atezolizumab
  - Olaparib/durvalumab