Gemelli

7a Giornata Mondiale sul Tumore Ovarico
Torino 08/05/2019

Update sul ruolo dei Parp Inibitori nella pratica clinica e prospettive future: quali possibili cambiamenti nello scenario terapeutico?

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Disclosure

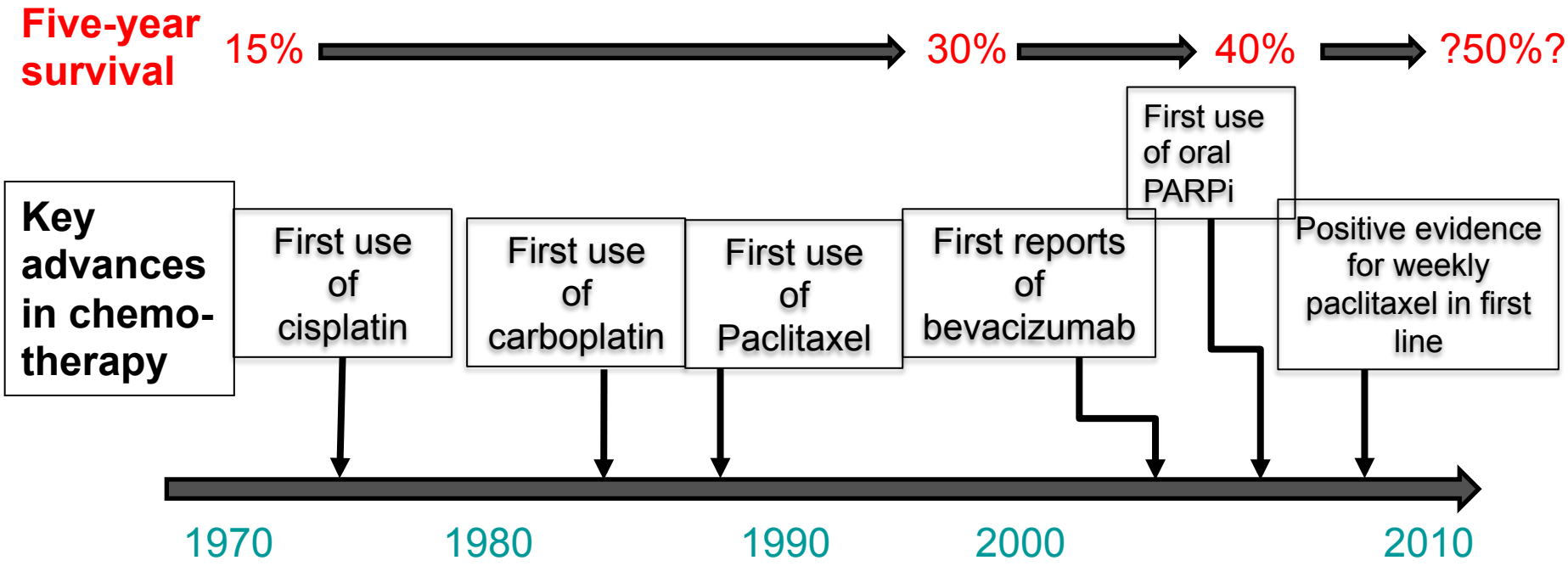
Advisory board for

- Roche
- Tesaro
- Merck
- Astra Zeneca
- Clovis Oncology

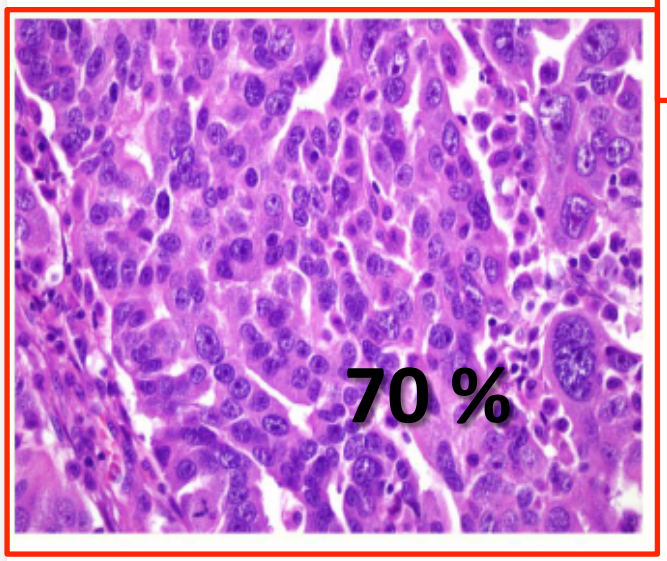
Institutional Research Support from

Pharma Mar, Clovis Oncology and Merck

Progress in the Management of Ovarian Cancer: Evolution Over 40 Years

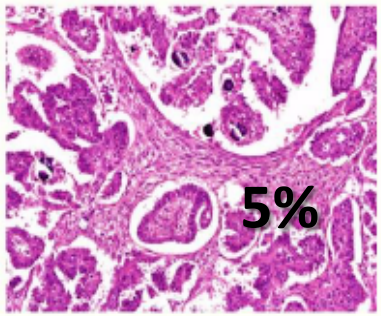


Ovarian cancer is not a single disease

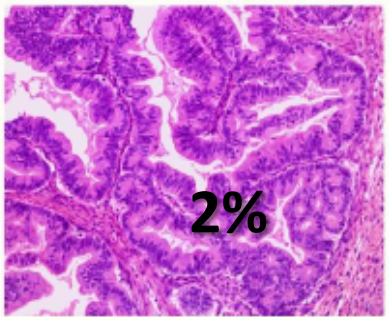


High-grade serous ovarian cancer

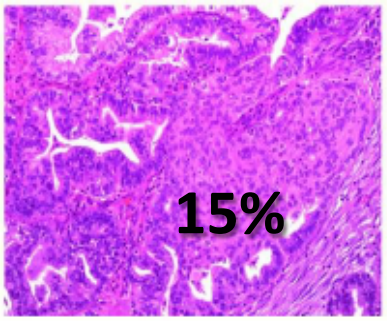
- *TP53*: encodes a protein that regulates the cell cycle
- *BRCA1* and *BRCA2*: encode proteins that are involved in genome protection



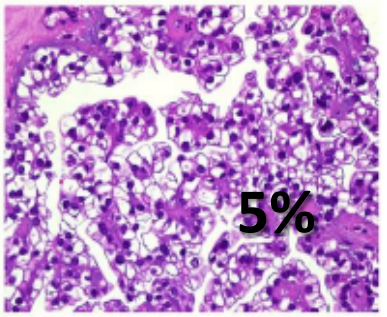
Low-grade serous
BRAF; KRAS



Mucinous carcinoma
KRAS



Endometrioid carcinoma
PTEN (low grade); *TP53*; *BRCA1/2*



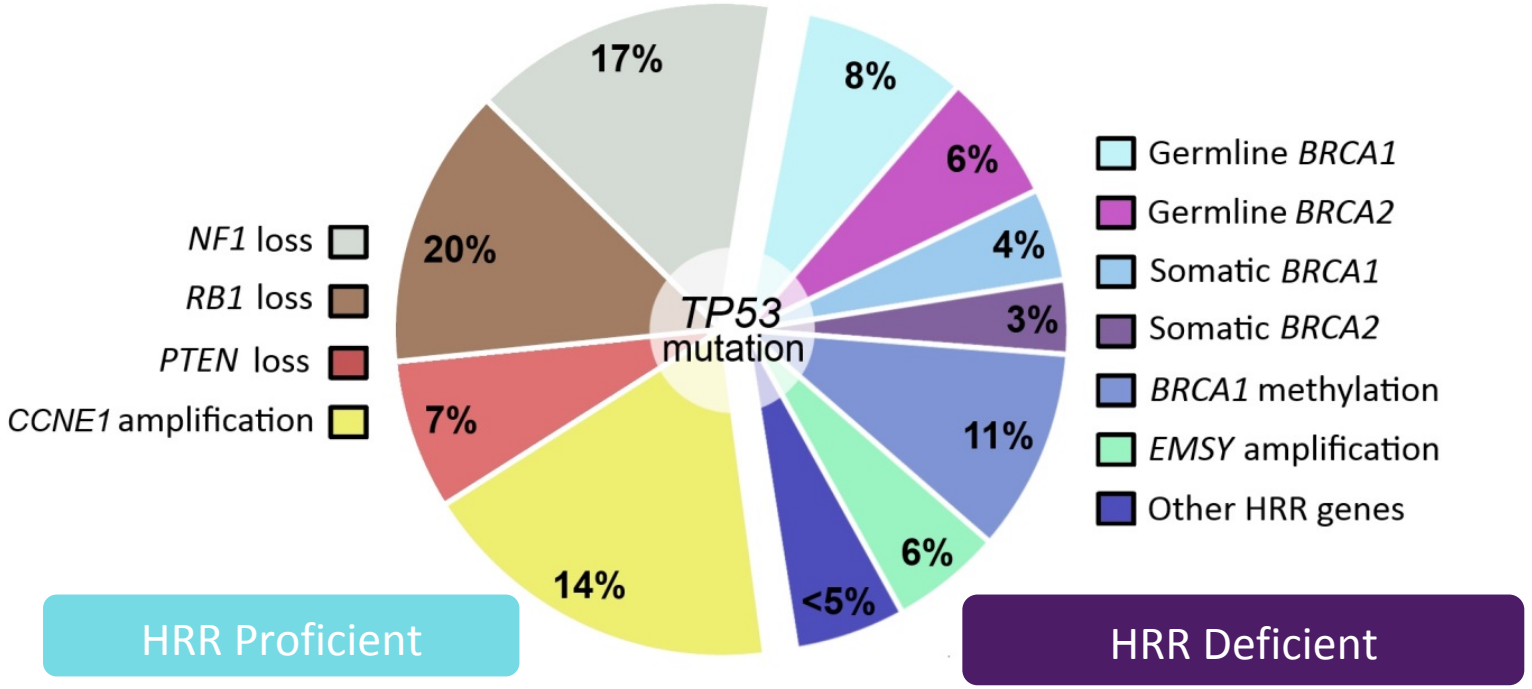
Clear cell carcinoma
PTEN; *PIK3CA*; *ARID1A*

Other subtypes

Tumour protein 53

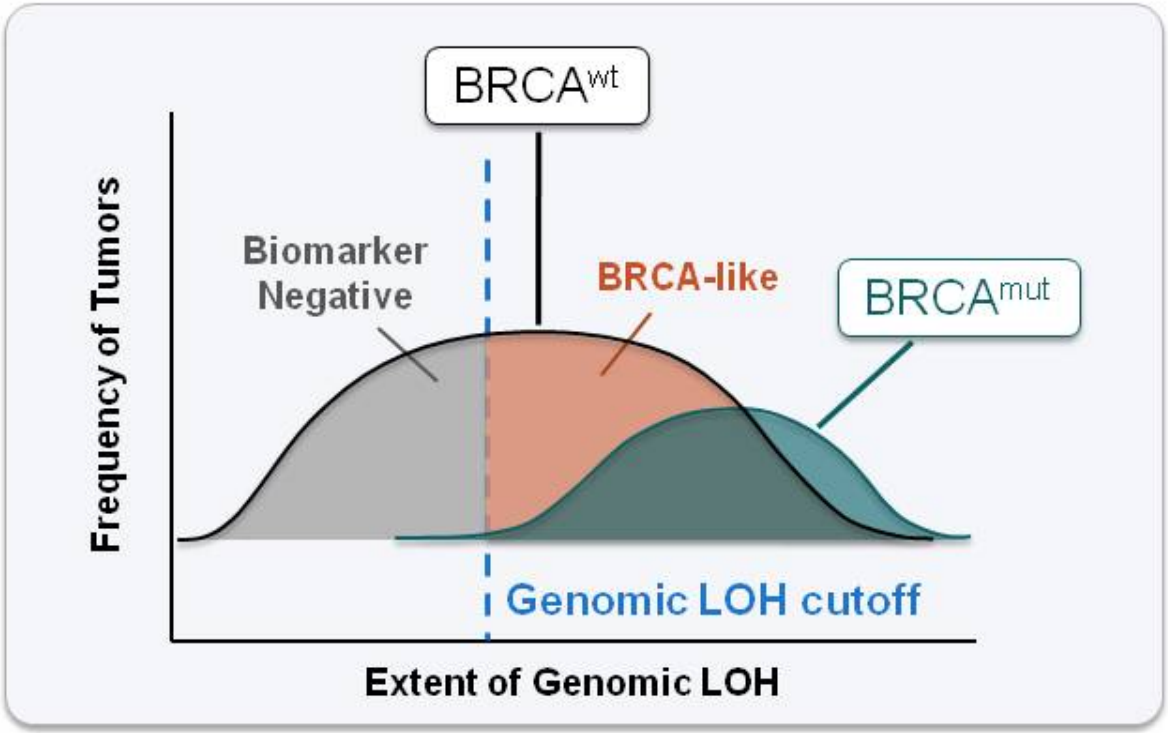
Romero I et al. Endocrinology 2012; 153: 1593-1602

Rationale for PARP inhibitors in ovarian cancer: high grade serous ovarian cancer biology



Hollis RL, et al. Cancer Biol Med. 2016; 13:236-247

HGOC patients can be classified into three molecular subgroups: BRCA^{mut}, BRCA-like, Biomarker Negative



PARP inhibitor maintenance therapy is changing clinical practice in ovarian cancer

In clinical studies, PARP inhibitors have demonstrated improved progression-free survival compared with placebo[1–3]

Current approval status of PARP inhibitors as maintenance therapy for recurrent ovarian cancer:

	Niraparib NOVA trial, 2016[1]	Olaparib Study 19, 2014[2]	Rucaparib ARIEL3 study, 2017[3]
Europe	Indicated as maintenance therapy[4]	Indicated as maintenance therapy for patients with *BRCA*mut disease[5]	Not indicated as maintenance therapy[7]
USA	Indicated as maintenance therapy[4]	Indicated as maintenance therapy[6]	Indicated as maintenance therapy[8]

BRCA, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutation; PARP, poly(ADP) ribose polymerase.

1. Mirza MR *et al. N Engl J Med* 2016; 375 (22): 2154–2164. 2. Ledermann J *et al. Lancet Oncol* 2014; 15 (8): 852–861.3. Coleman RL *et al. Lancet* 2017; 390 (10106): 1949–1961. 4. Tesaro, Inc. ZEJULA™ – package insert; 2017. 5. AstraZeneca Pharmaceuticals LP. Lynparza™ – package insert; AstraZeneca Pharmaceuticals LP, Wilmington, USA, 2017. 6. AstraZeneca UK Ltd. Lynparza™ – product information; AstraZeneca UK Ltd. Waltham, MA: TESARO, Inc; 2017. 7. Clovis Oncology UK Ltd. Rubraca® 200 mg / 250 mg / 300 mg film-coated tablets – summary of product characteristics. Clovis Oncology UK Ltd., Cambridge, May 2018. 8. Clovis Oncology, Inc. Rubraca® – prescribing information; April 2018.

Parp Inhibitor: active disease setting

	Rucaparib Pooled Analysis (103 pts) US and EMA label	**Olaparib US Label (137 pts)**
Potential Line of Therapy	≥3rd line treatment (regardless platinum sensitivity)	≥4th line treatment (regardless platinum sensitivity)
Dosing	600 mg BID	400 mg BID
Potential label Populations	Tumour BRCA^{mut} (includes germline and somatic mutations)	Germline BRCA^{mut}
Most common Grade ≥3 AEs in treatment setting	• Fatigue (11%) • Anaemia (23%) • ↑ALT/AST (11%)	• Fatigue (8%) • Anaemia (18%) • Abdominal pain (8%)
Dose interruptions/ reductions due to side effects	• 8% • 44.3%	• 36% • 42%
ORR (RECIST 1.1) by investigator	54%	34%
Progression free survival (median, months)	10.0	7.0

Platinum combination followed by iPARP

Olaparib study design and patient selection

Study-19 aim and design

265 patients

- **Platinum-sensitive high-grade serous ovarian cancer**
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

Olaparib 400 mg po bid

Randomized 1:1

Placebo po bid

Primary end point : PFS

Ledermann J, et al. N Engl J Med 2012;366:1382–92

SOLO-2 aim and design

295 patients

- *Germilne BRCA1/2* mutation
- Platinum-sensitive relapsed ovarian cancer
- At least 2 prior lines of platinum therapy
- CR or PR to most recent platinum therapy

Randomized 2:1

Olaparib 300 mg bid n=196

Placebo n=99

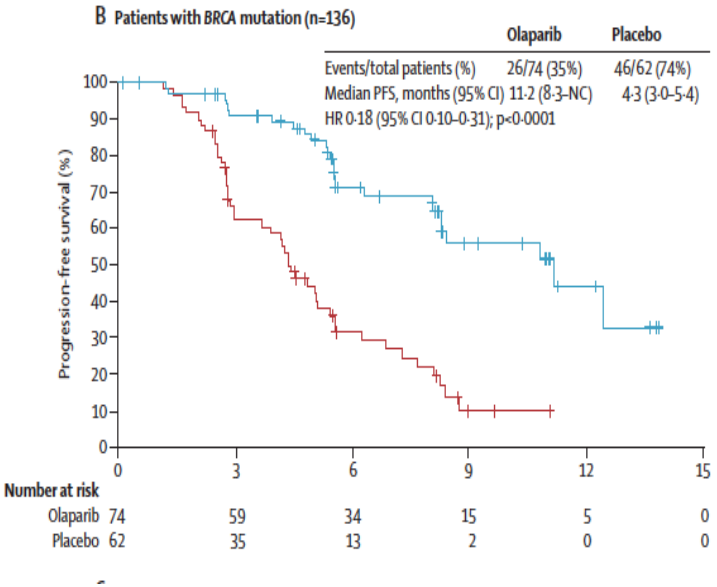
Primary endpoint: Investigator-assessed PFS

Pujade-Laurine et al. SGO 2017

Platinum combination followed by iPARP

Olaparib data on primary endpoint: BRCA mutated patients

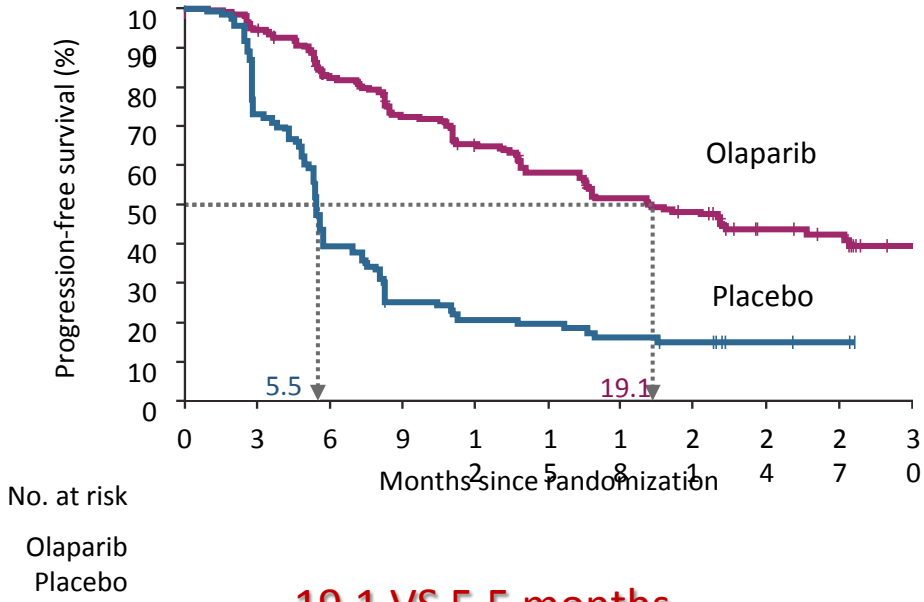
Study-19 PFS



11.2 vs 4.3 months
HR 0.18 (95% CI: 0.10-0.31)

Ledermann et al. Lancet Oncol. 2014;15(8):852–861

SOLO-2 PFS

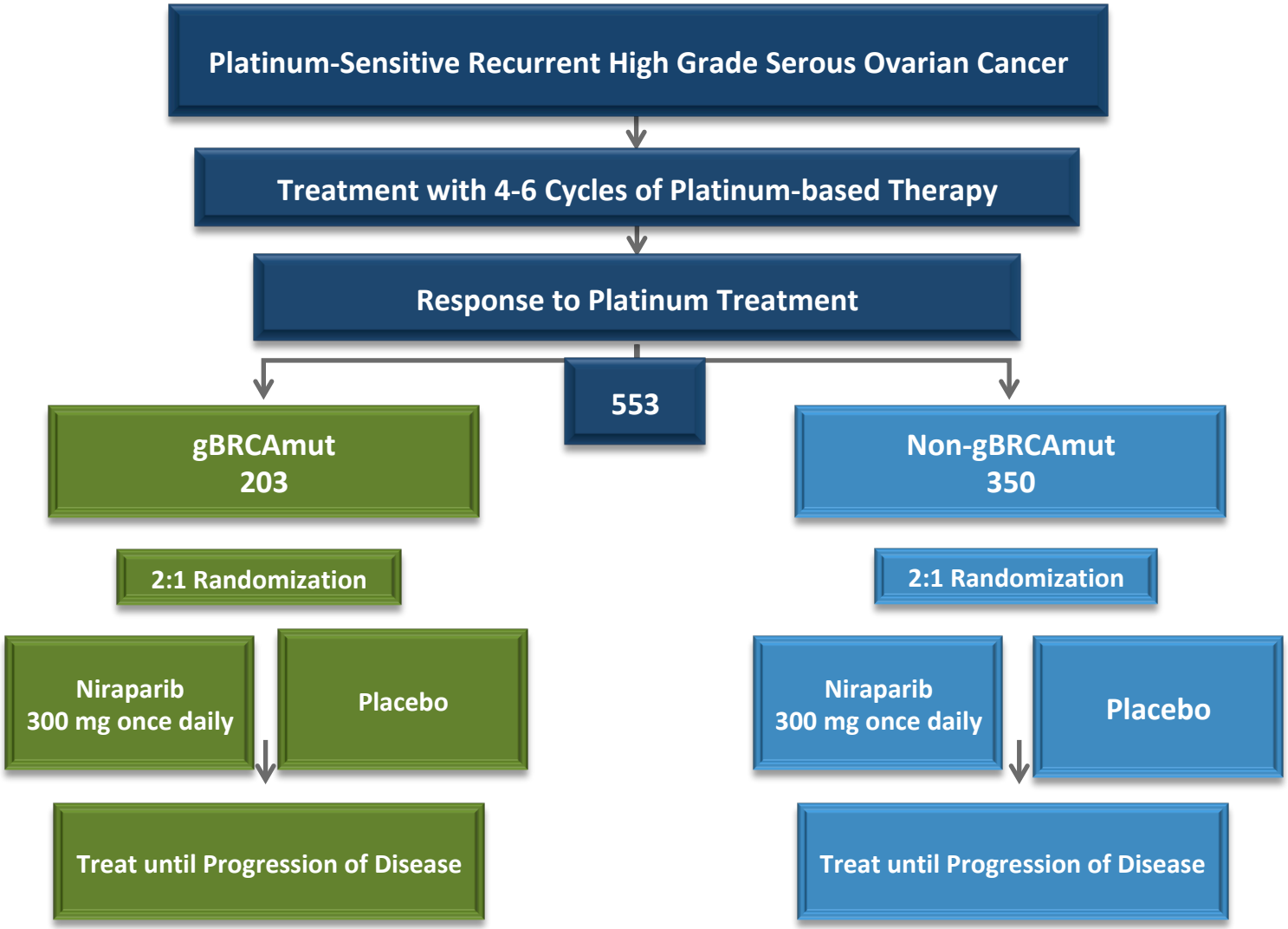


19.1 VS 5.5 months
HR 0.3 (95% CI: 0.22-0.41)

Pujade-Laurine et al. SGO 2017

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA study design



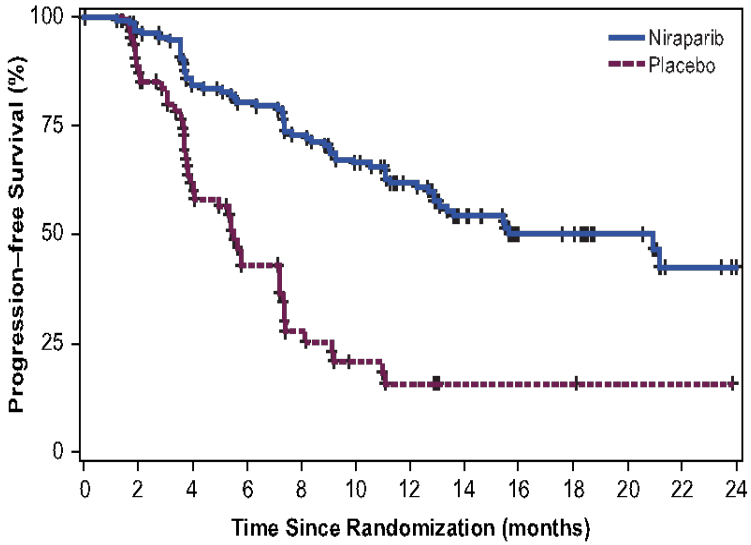
Mirza MR et al. N Engl J Med 2016

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA primary end-point

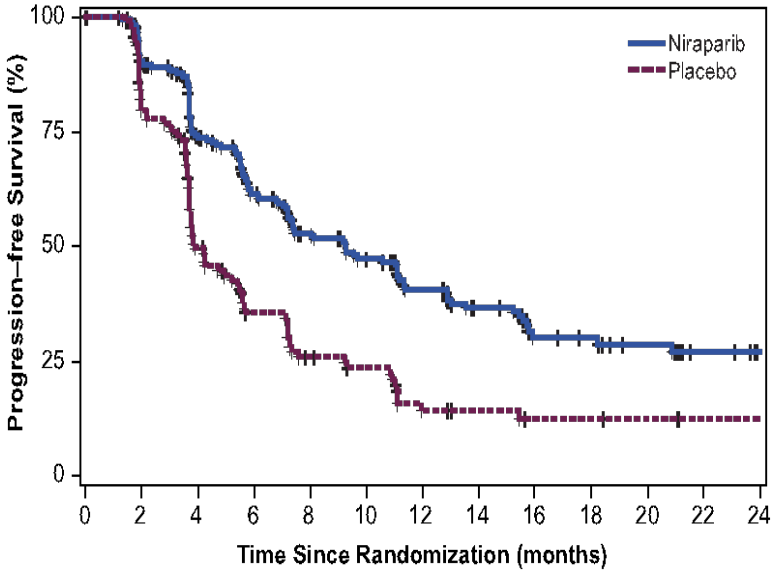
MADRID 2017 ESMO congress

PFS: gBRCAmut



Treatment	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<0.0001
Placebo (N=65)	**5.5** (3.8, 7.2)	

PFS: non-gBRCAmut



Treatment	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<0.0001
Placebo (N=116)	**3.9** (3.7, 5.5)	

Mirza MR et al. N Engl J Med 2016

Platinum combination followed by iPARP

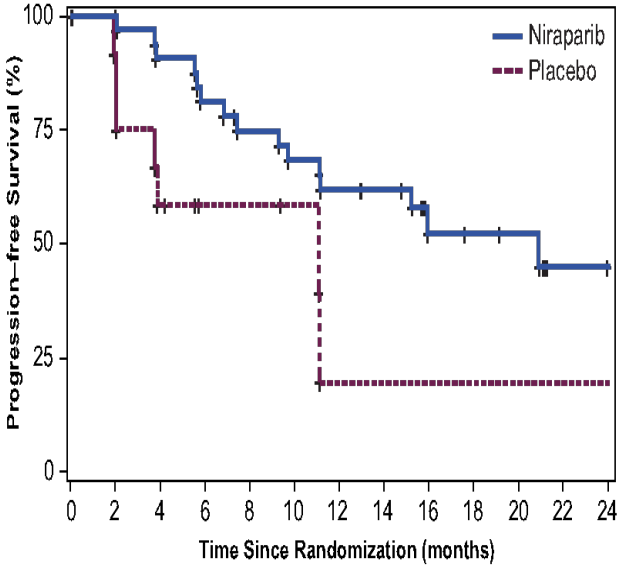
Niraparib: ENGOT ov16-NOVA exploratory analyses

MADRID 2017 ESMO congress

HRD-positive

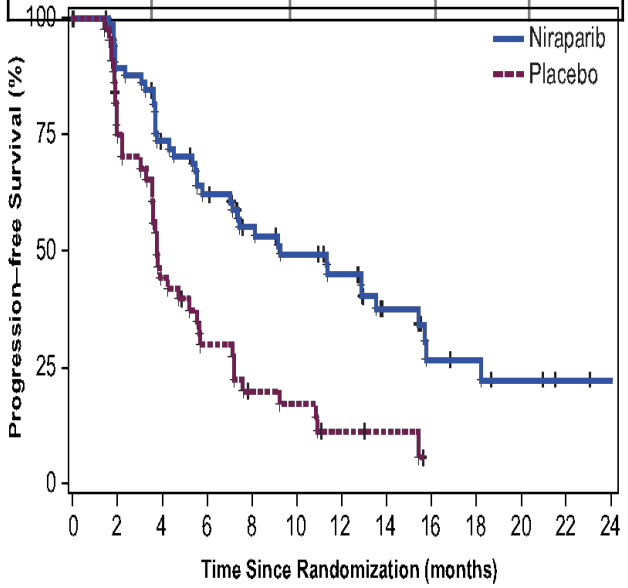
sBRCAmut

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%



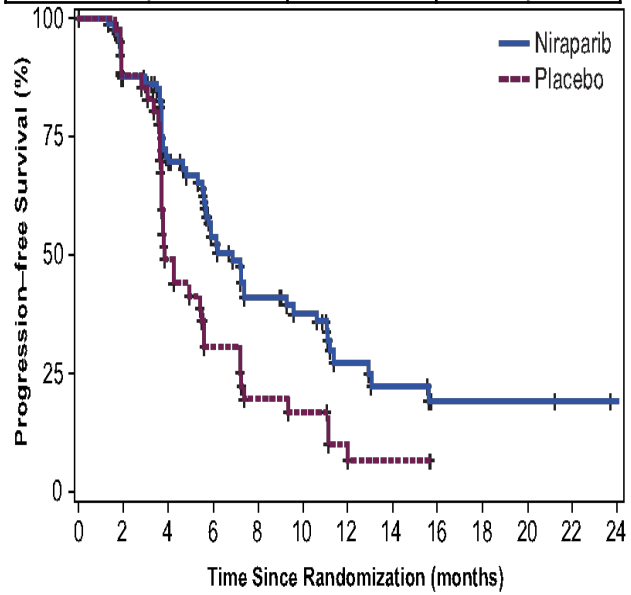
BRCAwt

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%

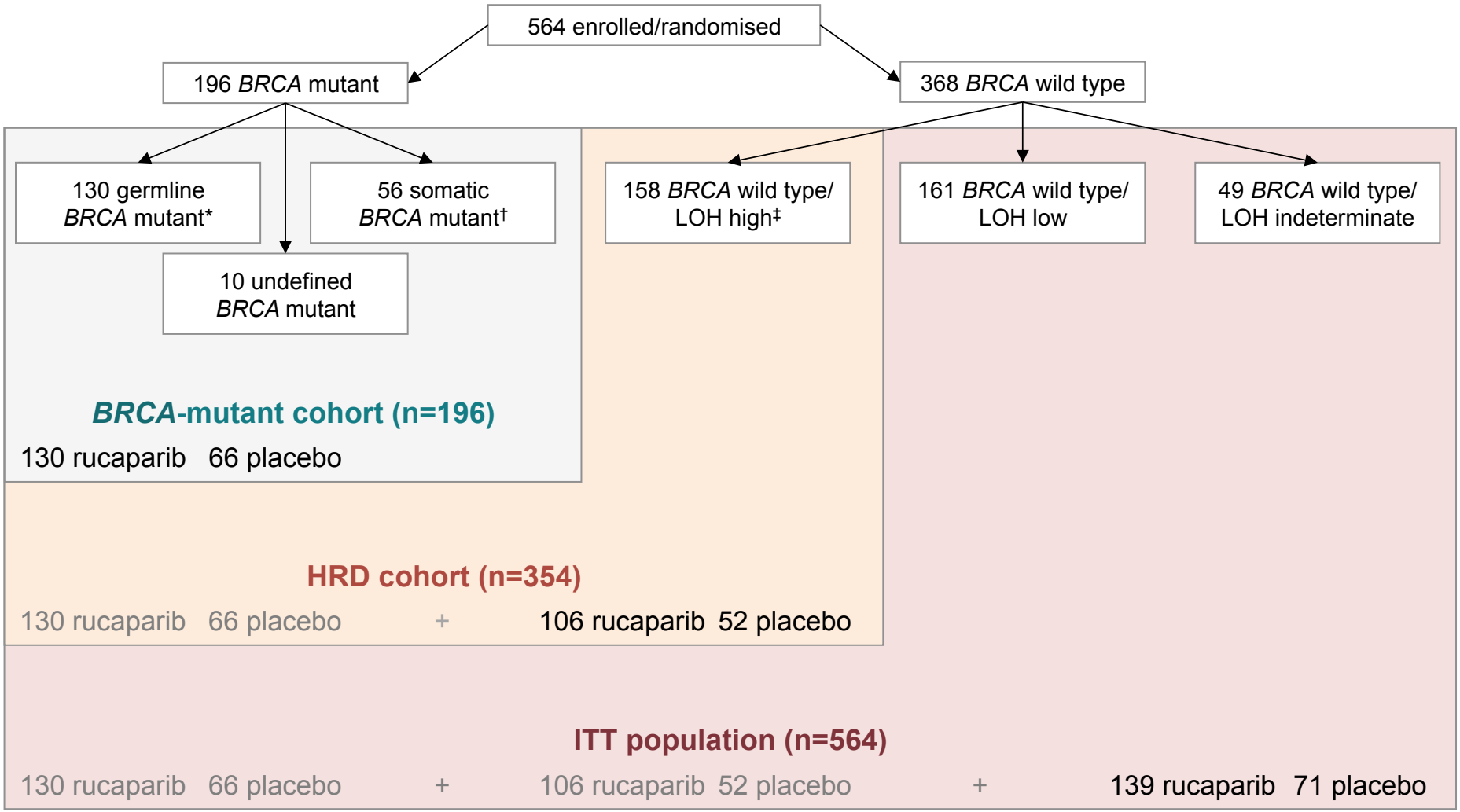


HRD-negative

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%

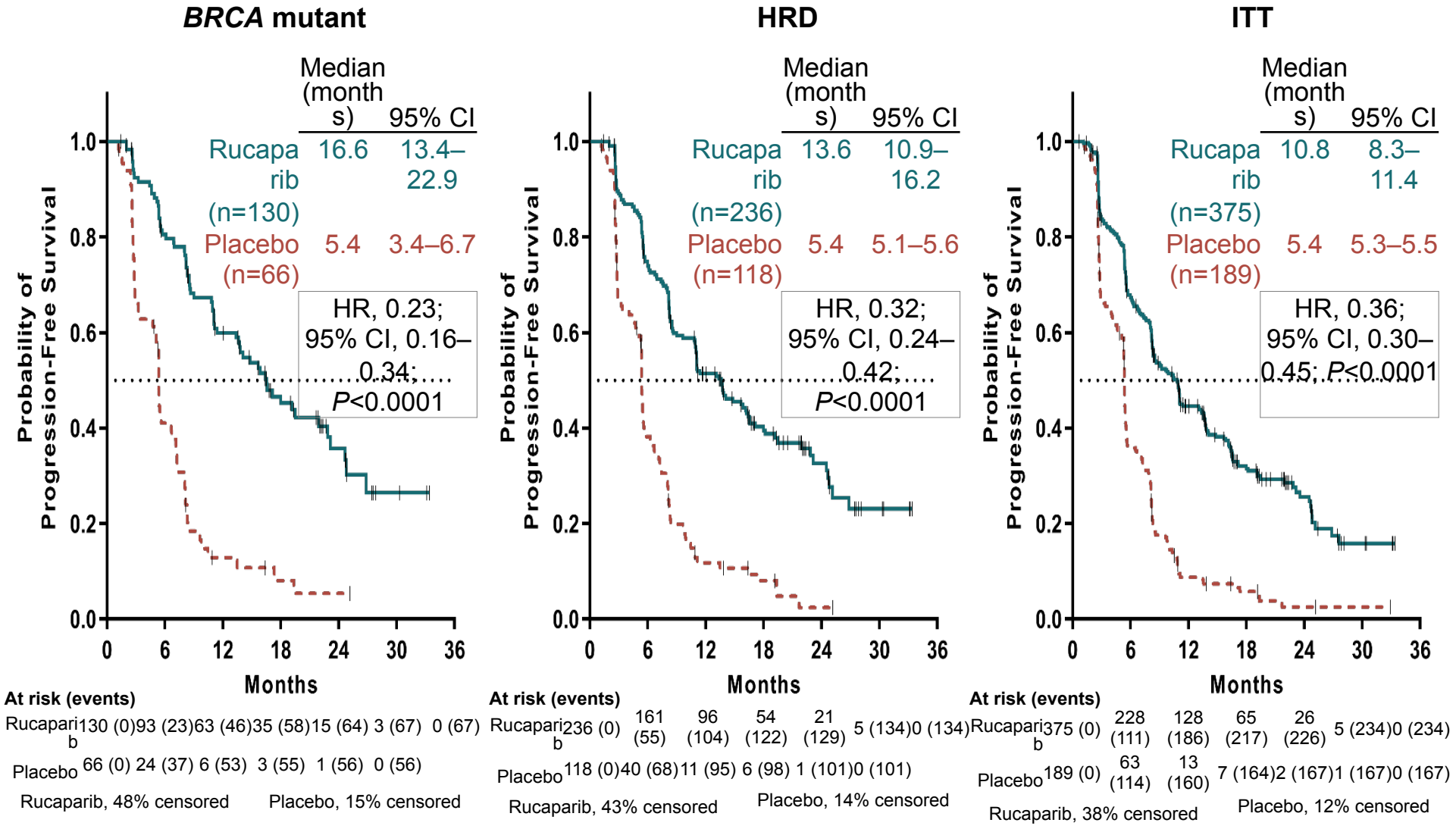


ARIEL3: Diagram of Analysis Cohorts



*No more than 150 patients with a known deleterious germline *BRCA* mutation were to be enrolled to ensure enough patients with carcinomas associated with a somatic *BRCA* mutation or wild-type *BRCA* were enrolled to determine statistical significance between rucaparib and placebo in the HRD cohort and the ITT population. †Deleterious *BRCA* mutation detected by next-generation sequencing of tumour tissue but not by central germline blood test. ‡For LOH high, a cutoff of ≥16% genomic LOH was prespecified for ARIEL3.

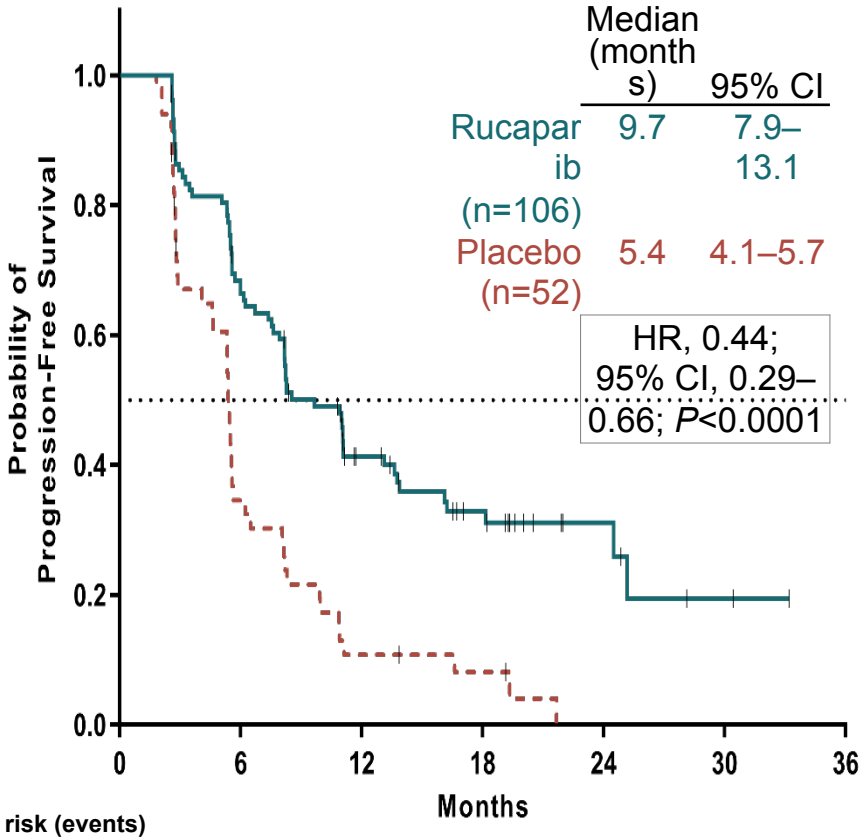
ARIEL3: Investigator-Assessed Progression-Free Survival



Visit cutoff date: 15 April 2017.

ARIEL3: Investigator-Assessed Progression-Free Survival: Patients with *BRCA* Wild-Type OC (Exploratoy Analysis)

LOH high



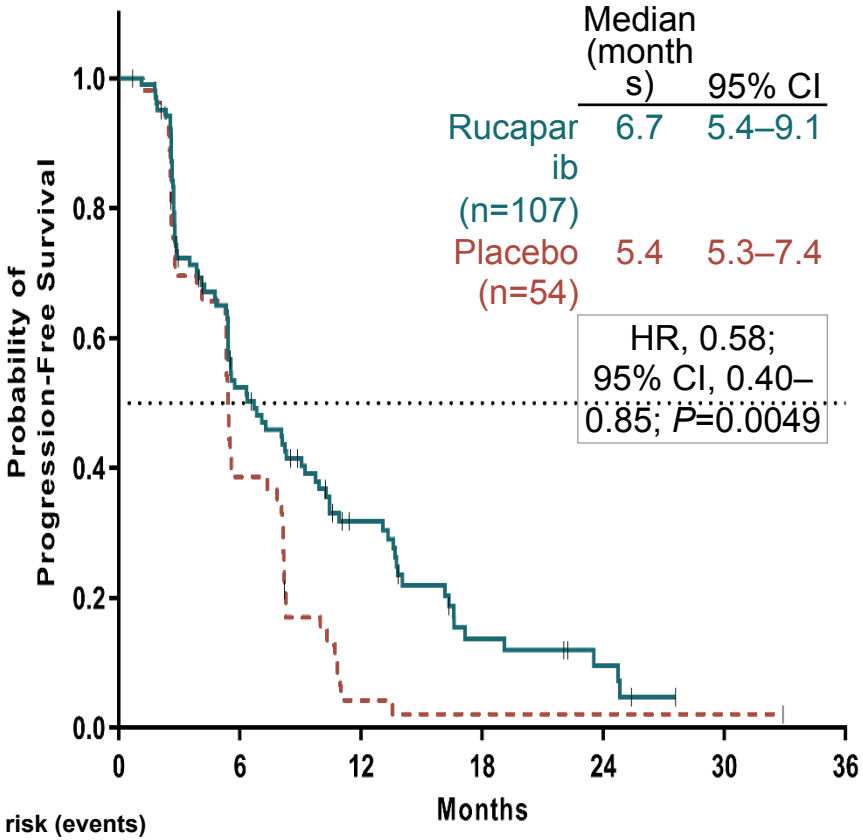
At risk (events)

Rucaparib	106 (0)	68 (32)	33 (58)	19 (64)	6 (65)	2 (67)	0 (67)
Placebo	52 (0)	16 (31)	5 (42)	3 (43)	0 (45)		

Rucaparib, 37% censored

Placebo, 13% censored

LOH low



At risk (events)

Rucaparib	107 (0)	49 (47)	23 (65)	8 (77)	4 (79)	0 (81)	
Placebo	54 (0)	20 (32)	2 (49)	1 (50)	1 (50)	1 (50)	0 (50)

Rucaparib, 24% censored

Placebo, 7% censored

Visit cutoff date: 15 April 2017.

SOME CONSIDERATIONS…….

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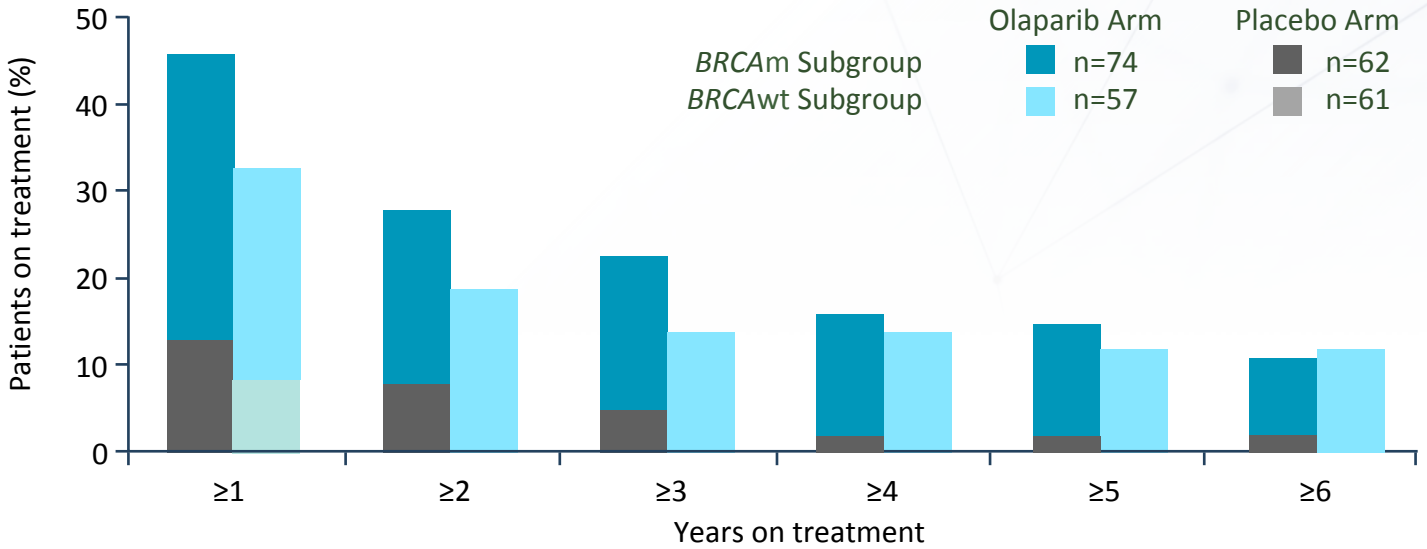
Study 19: Olaparib Treatment for ≥6 Years

- 11% of patients remained on treatment for ≥6 years with similar numbers of both *BRCA*m and non-*BRCA* patients receiving long-term olaparib (capsules) treatment[1,2]



Subgroups were defined prior to exploratory biomarker analyses being performed; patients with no known *BRCA*m or a variant of unknown significance were classified as non-*BRCA*, and one patient with no known *BRCA*m who received olaparib treatment for ≥ 6 years was found to have a s*BRCA*m in subsequent Myriad tumour testing DCO: May 2016.

*BRCA*m=*BRCA* mutated; *BRCA*wt=*BRCA* wild type; DCO=data cutoff.

1. Gourley C et al. Presented at: ESGO Annual Meeting; 2017. 2. Gourley C et al. *J Clin Oncol 2017*:35(suppl):5533.

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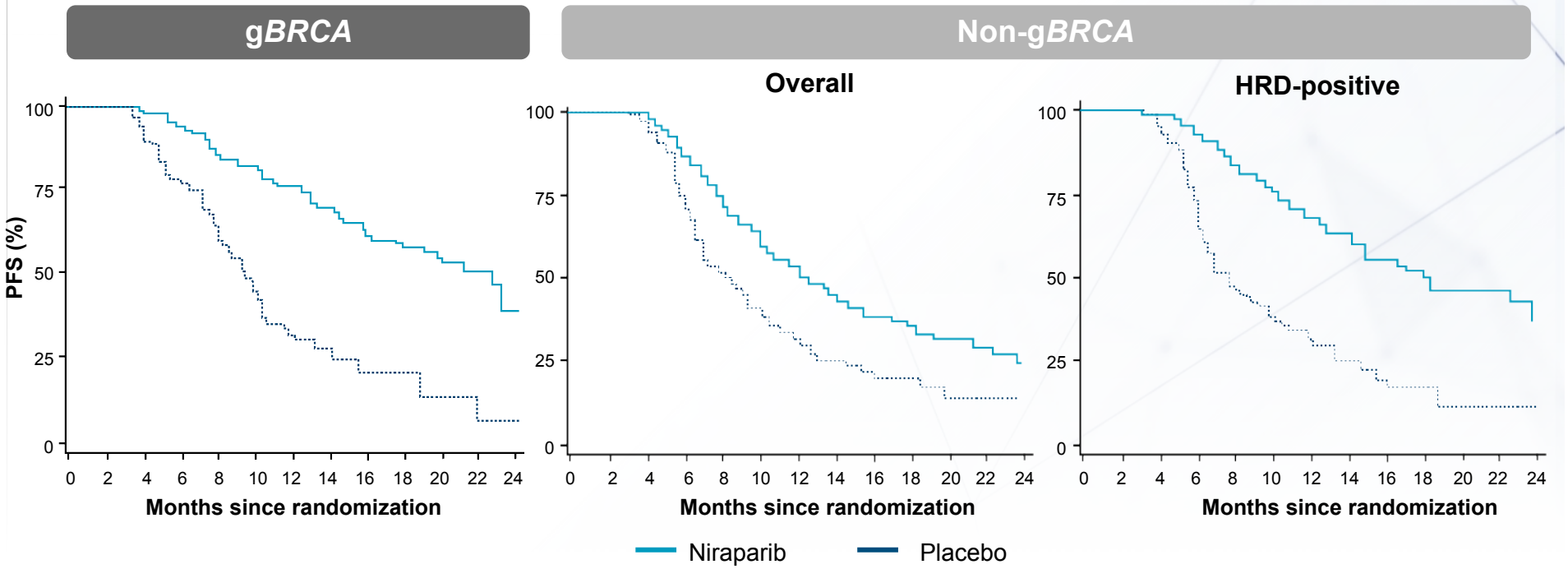
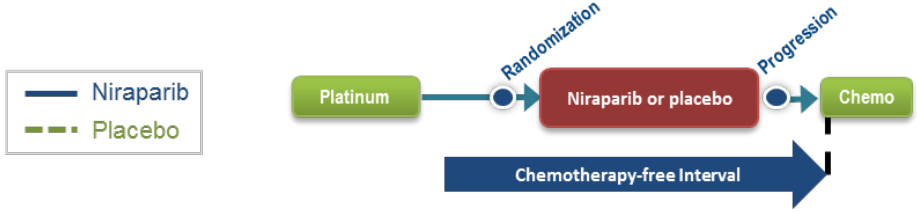
Niraparib significantly improved the chemotherapy-free interval in each cohort



Median CFI (months)
Niraparib 22.8
Placebo 9.4
HR 0.26, *P*<0.0001

Median CFI (months)
Niraparib 12.7
Placebo 8.6
HR 0.50, *P*<0.0001

Median CFI (months)
Niraparib 18.2
Placebo 7.7
HR 0.31, *P*<0.0001



BRCA, breast cancer susceptibility gene; CFI, chemotherapy-free interval; g*BRCA*, germline *BRCA* mutation; HR, hazard ratio; HRD, homologous recombination deficiency; non-g*BRCA*, no germline *BRCA* mutation; PFS, progression-free survival.
Mahner S *et al*. Oral presentation at SGO 2017; National Harbor, MD, USA, March 12–15, 2017.

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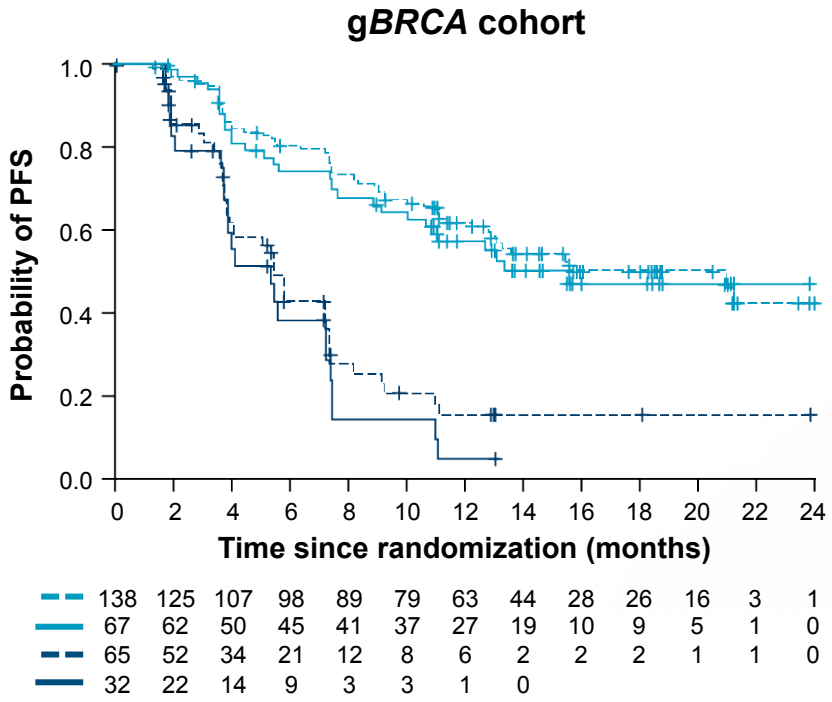
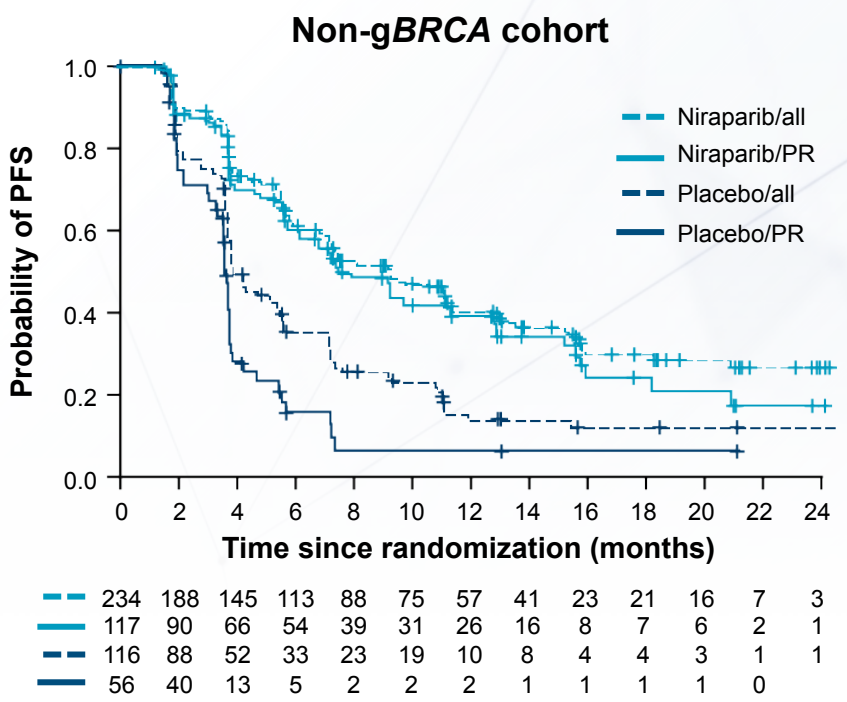
Improvement in PFS vs. placebo in patients with PR to their last platinum-based therapy was similar to that in the overall cohort





	gBRCA (n=203)		non-gBRCA (n=350)	
	PR to last platinum (n=99)	Overall (n=203)	PR to last platinum (n=173)	Overall (n=350)
PFS, HR (95% CI)*	0.24 (0.131–0.441)	0.27 (0.173–0.410)	0.35 (0.230–0.532)	0.45 (0.338–0.607)

*Niraparib compared with placebo.

BRCA, breast cancer susceptibility gene; CI, confidence interval; CR, complete response; g*BRCA*, germline *BRCA* mutation; HR, hazard ratio; non-g*BRCA*, no germline *BRCA* mutation; PFS, progression-free survival; PR, partial response.

Mirza MR *et al*. Poster 5517 presented at ASCO 2017; Chicago, IL, USA, June 2–6, 2017.

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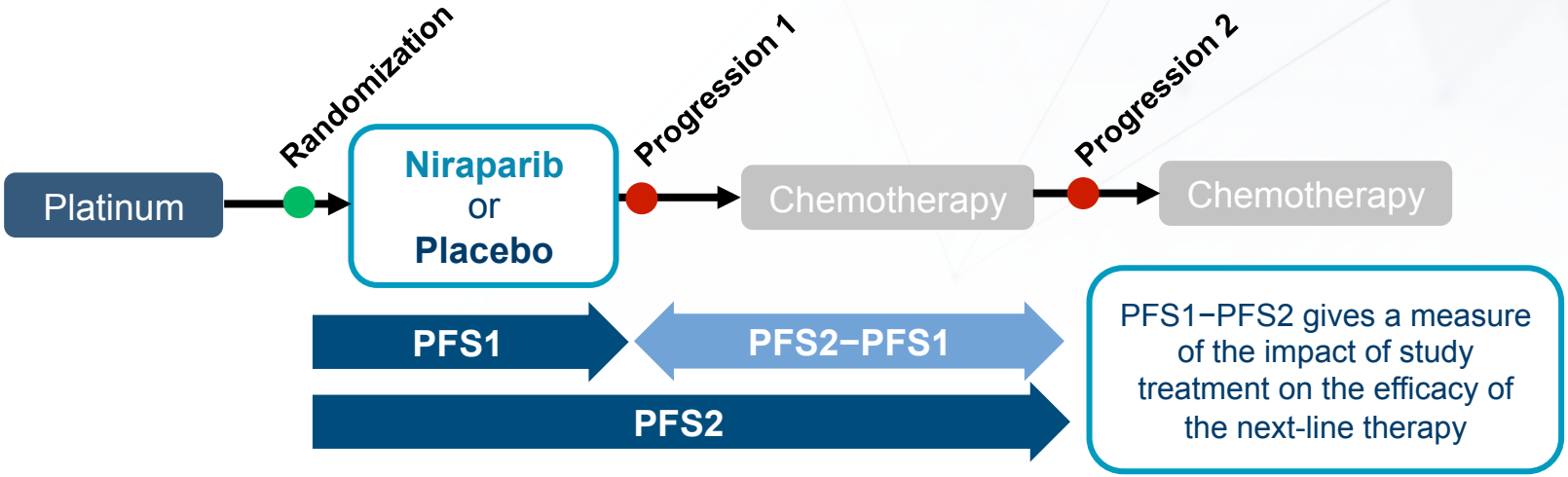
Niraparib had no impact on the efficacy of next-line therapy vs. placebo

- The impact of a treatment on the efficacy of the next-line therapy can be estimated by measuring the time difference between first and second progressions after study treatment
  - PFS1 is the time to the first disease progression after randomization to study treatment (niraparib or placebo)[1]
  - PFS2 is the time to the next disease progression after subsequent treatment[1]



PFS1−PFS2 did not differ significantly between niraparib and placebo (HR 1.02; 95% CI: 0.765–1.349)[2]

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

1. Mirza MR *et al. N Engl J Med* 2016; 375 (22): 2154–2164. 2. Mahner S *et al*. Oral presentation at SGO 2017; National Harbor, MD, USA, March 12–15, 2017.

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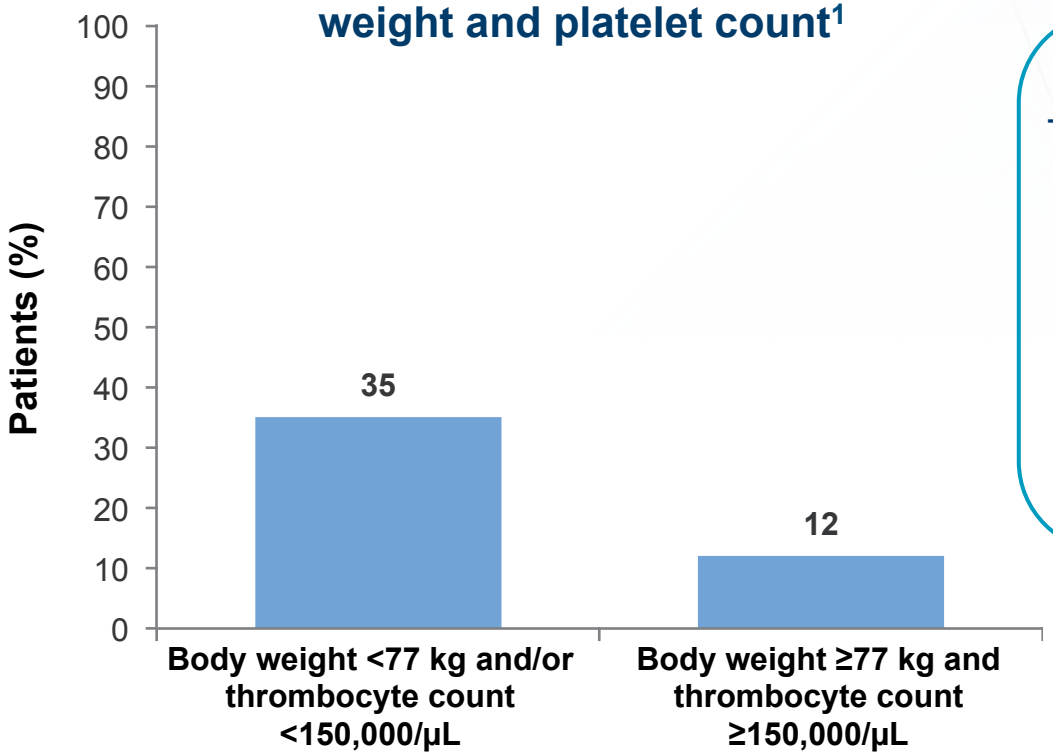
Tolerance (CTCAE grade 3/4)

	Olaparib (SOLO2) (n=195)	Niraparib (NOVA) (n=367)	Rucaparib (ARIEL 3) (n=561)
Dose reductions due to AEs, (%)	25	**66.5**	54.6
Treatment discontinuation due to AEs, (%)	10.8	**14.7**	13.4
Hematologic toxicity (Gr 3/4)			
- Anemia	19.5	**25**	18.8
- Neutropenia	5	**20**	6.7
- Thrombocytopenia	0	**34**	5.1
Hypertension	NR	**8**	NR
ASAT/ALAT	2	NR	**10.5**
Nausea	3	3	3.8
Fatigue	4	8	6.7

Rapid Adjustment of Dose to reduce Adverse Reactions: RADAR analysis

- RADAR was an exploratory analysis of data from the NOVA trial that examined predictive factors for the development of Grade 3/4 thrombocytopenia

Grade 3/4 thrombocytopenia within 30 days of first dose integrated analysis of baseline weight and platelet count[1]



The patients deemed to be most likely to develop thrombocytopenia had:

Baseline body weight lower than 77 kg

and/or

Baseline thrombocyte count lower than 150,000/µL[1,2]

1. Berek JS *et al. Ann Oncol* 2018; Epub ahead of print. DOI: 10.1093/annonc/mdy255. 2. Berek JS *et al. Ann Oncol* 2018; Epub ahead of print. DOI: 10.1093/annonc/mdy255 – supplementary material.

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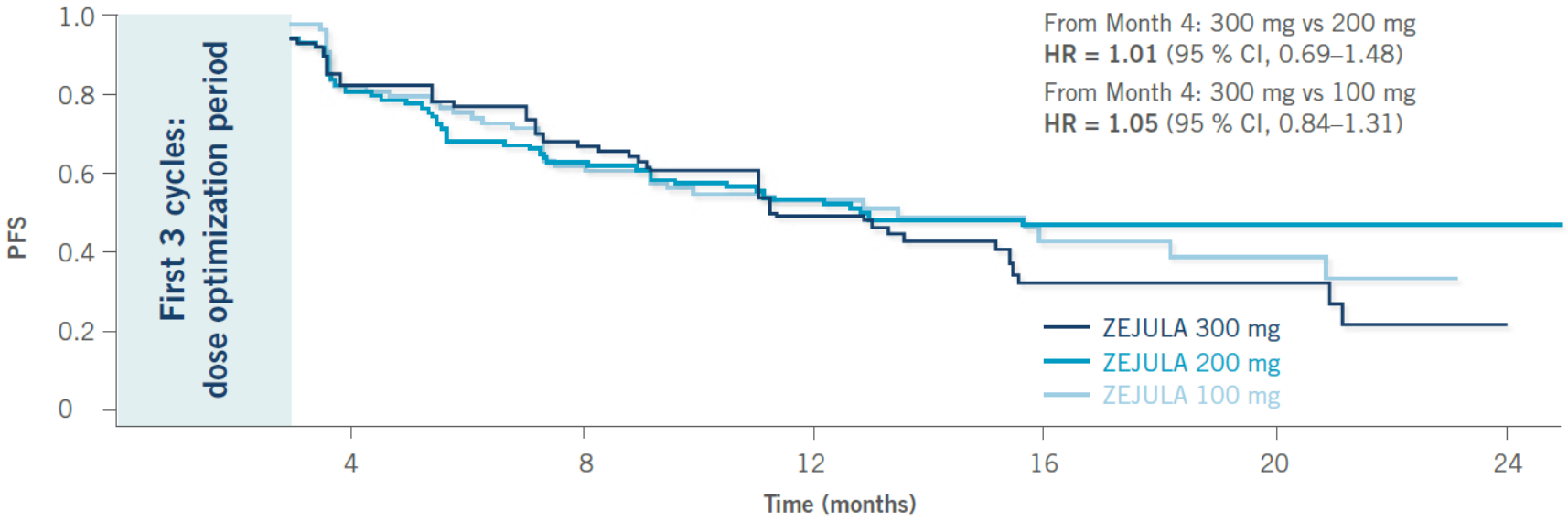
Dose reductions did not compromise efficacy

- PFS after cycle 3 was comparable for patients receiving 100 mg, 200 mg and 300 mg niraparib

Kaplan–Meier estimated probability of PFS by dose beyond cycle 3



BRCA, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutation; *BRCA*wt, *BRCA* wild-type; PFS, progression-free survival.
Figure adapted from Lord L *et al.* Presented at SGO 2018; New Orleans, LA, USA, March 24–27, 2018.

BRCA1/2 Mutations in Ovarian Cancer

- Who should be tested?

Leading oncology societies recommend testing all women with ovarian cancer[1-4]

NCCN	SGO	ASCO	ESMO
Genetic counseling and testing should be considered in women with a history of ovarian carcinoma, fallopian tube cancer, or primary peritoneal cancer[1]	Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of family history[2]	Genetic counseling and testing should be considered in women with epithelial ovarian, fallopian tube, or primary peritoneal cancer even in the absence of family history[3]	Patients with high-grade tumours should be tested for a germline *BRCA* mutation. Consideration should be given to testing tumours for a somatic *BRCA* mutation[4]

ASCO=American Society of Clinical Oncology; ESMO=European Society for Medical Oncology; NCCN=National Comprehensive Cancer Network; SGO=Society of Gynecologic Oncology.

1. NCCN Guidelines. https://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed 24 September 2018. 2. SGO. https://www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer/. Accessed 24 September 2018. 3. ASCO. https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/assessing-your-patient%E2%80%99s-hereditary. Accessed 24 September 2018. 4. Ledermann JA et al. https://www.esmo.org/Guidelines/Gynaecological-Cancers/Newly-Diagnosed-and-Relapsed-Epithelial-Ovarian-Carcinoma/eUpdate-Treatment-Recommendations. Accessed 24 September 2018.

The Evolving Role of *BRCA* Mutation Testing

- Why are patients with ovarian cancer being tested for *BRCA*?

Risk assessment	• Women who harbour a *BRCA* mutation are more likely to suffer from breast cancer or ovarian cancer in their lifetime, than those without a mutation • Allows patients to take preventive action
Prognostic factor	• Important prognostic factor, other than stage and extent of surgical debulking • Estimate PFS and OS according to *BRCA* status
Predictive factor	• Identification of patients who may be more sensitive to different treatment options

PFS=progression-free survival; OS=overall survival.
Neff RT et al. *Ther Adv Med Oncol.* 2017;9(8):519-531.

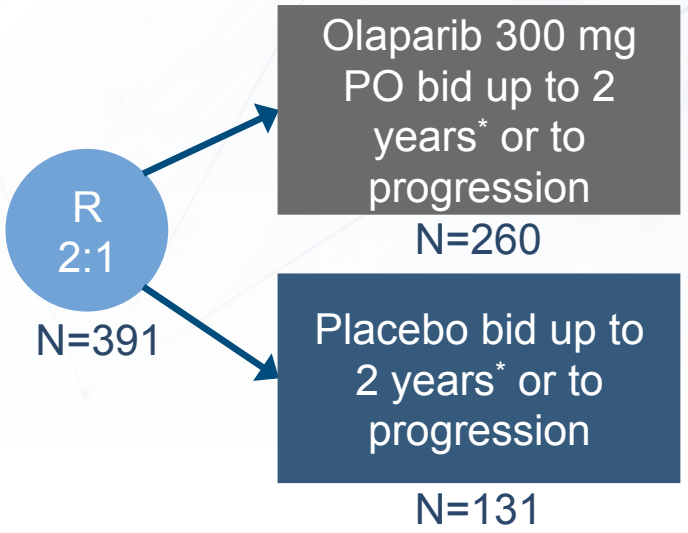
Unmet Clinical Need: Future Research Into PARP Inhibitor Use

- Resistance to PARP inhibitors
- Retreatment with PARP inhibitors: Overcoming or compounding the resistance problem?
- PARP inhibitors in the front-line setting
- Combinations with other agents
  - Anti-angiogenic agents
  - Immuno-oncology agents

PARP, poly(ADP-ribose) polymerase

PARP inhibitor maintenance therapy has proven to be effective in the first-line setting in the SOLO-1 trial

- Newly diagnosed stage III–IV ovarian, primary peritoneal or fallopian tube cancer
- High grade serous or endometriod history
- **Only patients with documented deleterious *BRCA* mutation**
- Stage III: 1 optimal debulking attempt
- Stage IV: biopsy and/or 1 upfront or interval debulking
- In CR or PR at the end of frontline platinum-based chemotherapy



- **Primary endpoint:** Investigator-assessed **PFS by RECIST v1.1**
- **Secondary endpoints:**
  - OS, PFS2, best ORR, health-related quality of life by TOI of the FACT-O, TFST, TSST and safety and tolerability

*At investigators' discretion

bid, twice daily; *BRCA*mut, breast cancer gene mutation; CR, complete response; FACT-O, functional assessment of cancer therapy; HR, hazard ratio; NR, non-responder; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response; R, randomized; TOI, trial outcome index; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

1. ClinicalTrials.gov. NCT01844986. 2. Moore K. *et al. NEJM* 2018; Epub ahead of print. DOI: 10.1056/NEJMmo18/0858.

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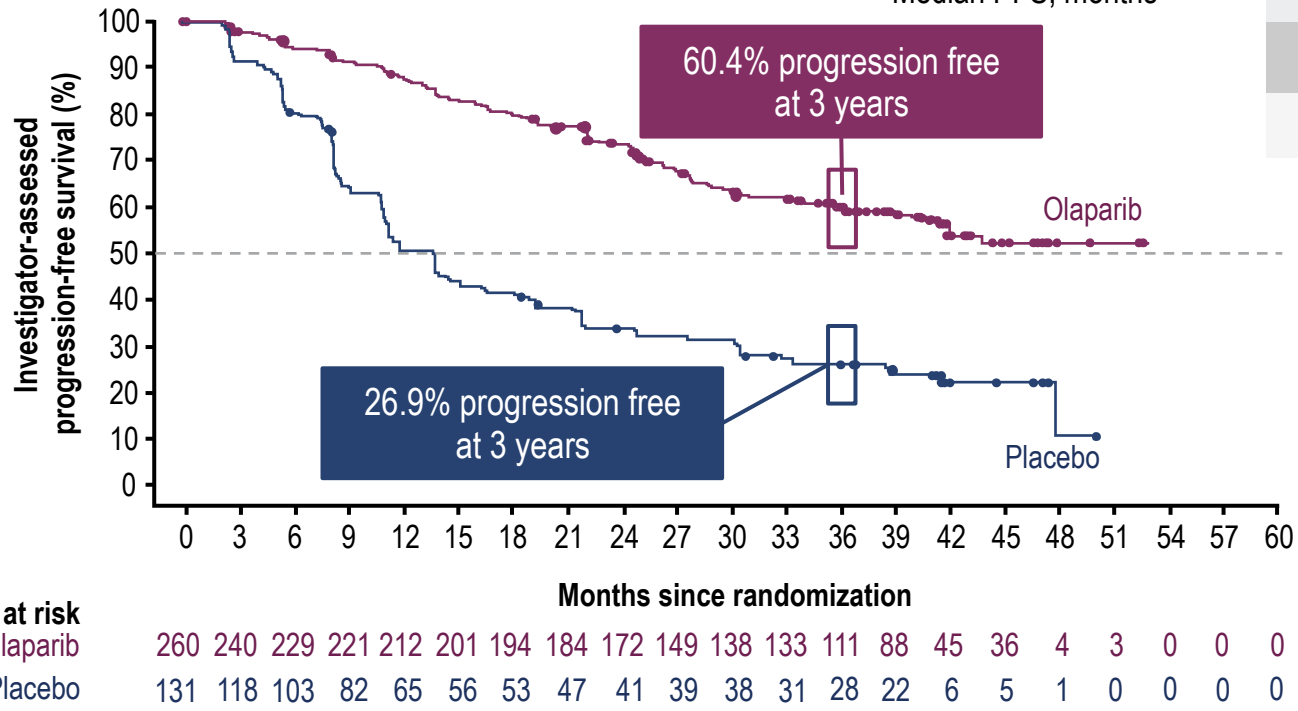
PFS by investigator assessment

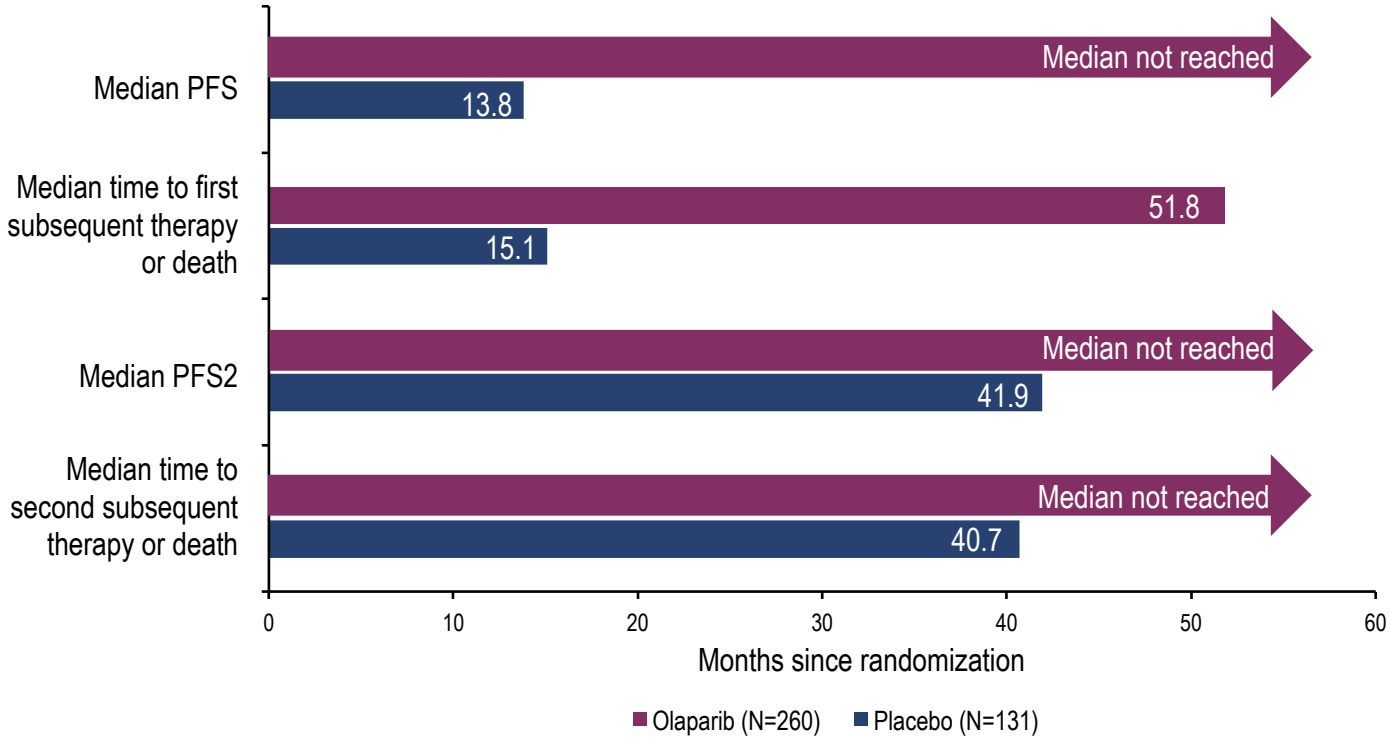


	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		

CI, confidence interval; NR, not reached

MUNICH 2018 ESMO congress

Summary of efficacy endpoints



HR 0.30
95% CI 0.23, 0.41; *P*<0.0001
HR 0.30
95% CI 0.22, 0.40; *P*<0.0001
HR 0.50
95% CI 0.35, 0.72; *P*=0.0002
HR 0.45
95% CI 0.32, 0.63; *P*<0.0001

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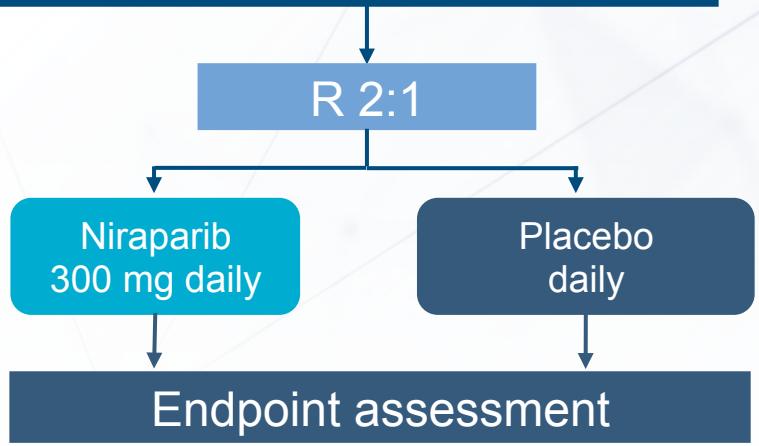
Niraparib is being assessed for maintenance therapy in the first-line setting in the PRIMA study

High-grade Stage III or IV ovarian cancer (all comers) and achieved a CR or PR following front-line platinum-based chemotherapy

Stratification factors

- Neoadjuvant chemotherapy administered: Yes or No
- Best response to 1st platinum therapy: CR or PR
- HRD status: positive or negative/not determined



Enrolment completed June 2018 (N=733)
Results expected end 2019

Primary endpoint	Hierarchical testing for PFS (radiologic, central review) • PFS in HRD positive population (HR 0.5) • PFS in ITT population (HR 0.65)
Key secondary endpoints	Overall survival | Patient-reported outcomes (FOSI, EQ-5D-5L, EORTC-QLQ-30, EORTC-QLQ-OV28) | Safety & tolerability | Time to CA-125 progression

Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Please consult the summary of product characteristics.

CR, complete response; EORTC-QLQ-30, European Organisation for Research and Treatment of Cancer; EORTC-QLQ-OV28, EORTC–Ovarian Cancer Module; EQ-5D-5L, European QoL five-dimension five-level questionnaire; FOSI, FACIT ovarian cancer symptom index; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat; PFS, progression free survival; PK, pharmacokinetic; PR, partial response; QoL, quality of life; R, randomized. ClinicalTrials.gov. PRIMA. Available at: https://clinicaltrials.gov/ct2/show/NCT02655016. Accessed October 2018.

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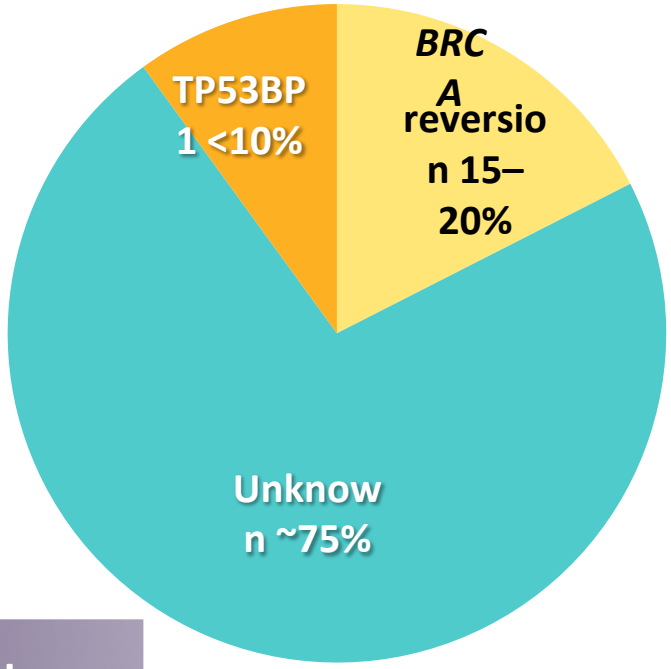
Understanding Mechanisms of Resistance

Clinical observations: Acquired resistance

- *BRCA* reversion responsible for 15–20% of resistance to PARP inhibitors
- TP53BP1 has opposing activity to *BRCA1* in preventing DNA resection and promoting NHEJ
  - Mutations in *TP53BP1* responsible for ~10% of resistance to PARP inhibitors
- ~75% of resistance is due to unknown mechanisms



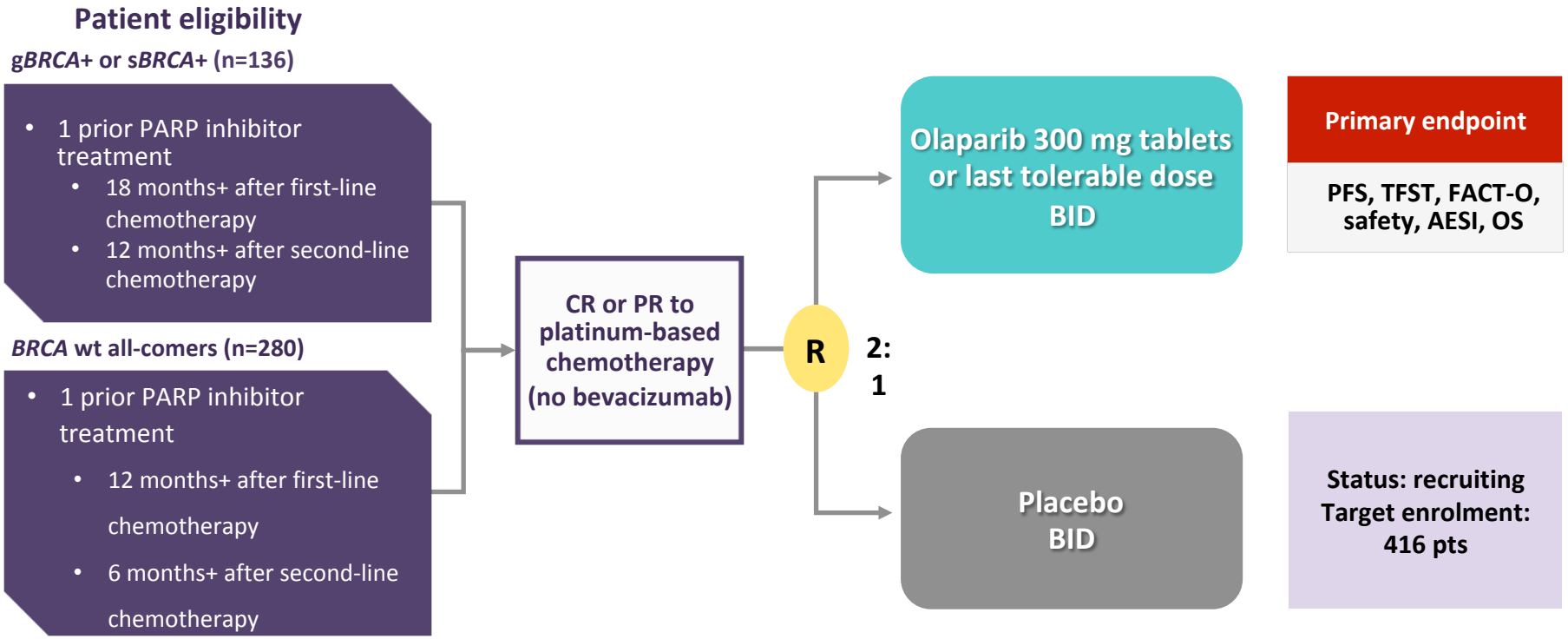
How can we overcome or avoid further development of resistance?

NHEJ, non-homologous end joining; PARP, poly(ADP-ribose) polymerase

1. Edwards SL et al. *Nature.* 2008;451:1111–1115;
2. Lord CJ, Ashworth A. *Nat Med.* 2013;19:1381–1388

OReO: Study Design

Phase III, trial of olaparib retreatment following receipt of prior PARP inhibitor and complete or partial response to platinum-based chemotherapy in patients with epithelial ovarian cancer



Olaparib no está autorizado en España por este tratamiento. Olaparib is not approved in Spain for this treatment setting.

AESI, adverse events of special interest; BID, twice daily; CR, complete response; FACT-O, functional assessment of cancer therapy – ovarian; g, germline; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PR, partial response; s, somatic; TFST, time to first subsequent therapy; wt, wild type

ClinicalTrials.gov. NCT03106987. https://clinicaltrials.gov. Accessed 1 August 2017

Unmet Clinical Need: Future Research Into PARP Inhibitor Use

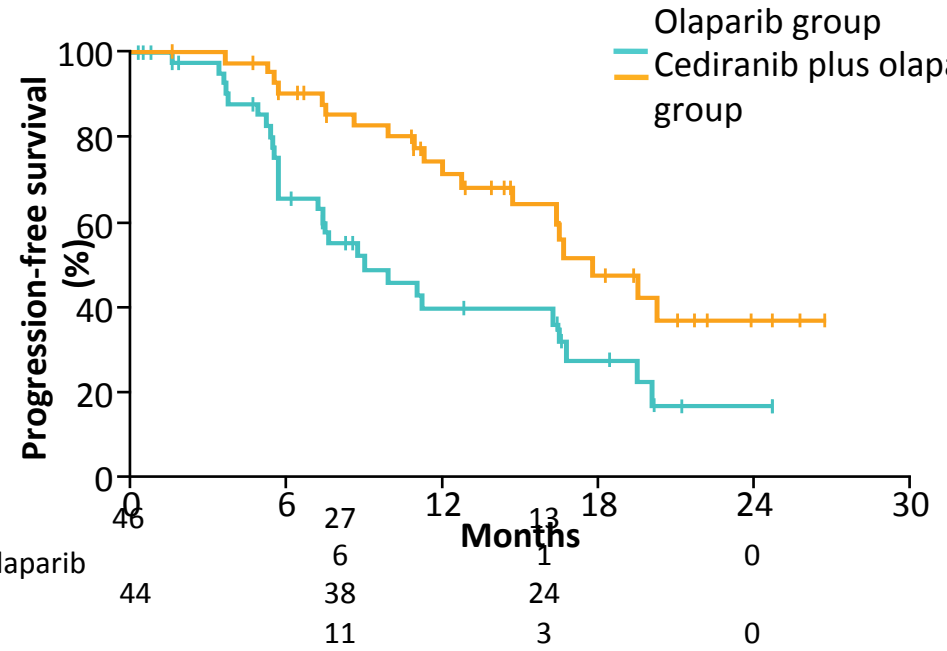
- Resistance to PARP inhibitors
- Retreatment with PARP inhibitors: Overcoming or compounding the resistance problem?
- PARP inhibitors in the front-line setting
- Combinations with other agents
  - Anti-angiogenic agents
  - Immuno-oncology agents

PARP, poly(ADP-ribose) polymerase

PARP Inhibitors in Combination with Anti-Angiogenic Agents: Scientific Support for Synergistic Effects

- Preclinical studies demonstrated that HR can be suppressed by hypoxia through downregulation of HR repair proteins such as *BRCA*1 and *RAD51*[1,2]
- Further studies showed sensitivity to PARP inhibitors enhanced in hypoxic states[3,4]
- Hypothesis: PARP-inhibitors and anti-angiogenics may have synergistic effects

- Phase I and II clinical studies show improved outcomes with the combination of olaparib and cediranib[5,6]



- 1. Bindra RS et al. *Cancer Res*. 2005;65:11597–11604; 2. Bindra RS et al. *Mol Cell Biol.* 2004;24:8504–8518;
- 3. Chan N, Bristow RG. *Clin Cancer Res.* 2010;16:4553–4560; 4. Hegan DC et al. *Proc Natl Acad Sci U S A.* 2010;107:2201–2206;
5. Liu JF et al. *Eur J Cancer.* 2013;49:2972–2978; 6. Liu JF et al. *Lancet Oncol.* 2014;11:1207–1214

PAOLA-1: Study Design

Phase III trial of olaparib in combination with bevacizumab as first-line maintenance therapy in patients with advanced ovarian cancer

Patient eligibility

- FIGO stage IIIb–IV high-grade serous/ endometrioid or non-mucinous *BRCA* mutation ovarian, fallopian tube or primary peritoneal cancer
- First line
  - Surgery (primary or interval)
  - Platinum–taxane based chemotherapy
  - ≥3 cycles of bevacizumab[†]
- CR/PR NED

2:1

R

Maintenance

Bevacizumab 15 mg/kg Q3W 15 months + olaparib 300 mg BID 2 years

Bevacizumab 15 mg/kg Q3W 15 months + placebo 2 years

PD[†]

Primary endpoint

PFS

Status: recruiting
Target enrolment: 612

Stratification factors

- Tumour *BRCA* status
- First-line outcome

La combinación de olaparib y bevacizumab no está autorizado en España. The combination of olaparib and bevacizumab is not approved in Spain.

[†]Tumour sample taken to provide tumour *BRCA* status

BID, twice daily; CR/PR NED, complete response/partial response no evidence of disease; FIGO, International Federation of Gynecology and Obstetrics; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks

ClinicalTrials.gov. NCT02477644. https://clinicaltrials.gov/. Accessed 1 August 2017

MITO-25: Study Design[1,2]

Phase II trial of rucaparib in combination with bevacizumab as first-line maintenance therapy in patients with advanced ovarian cancer

Patient eligibility

- FIGO stage IIIb–IV high-grade serous or endometrioid or clear-cell ovarian cancer, primary peritoneal and/or fallopian tube cancer, or other *BRCA*-mutated histotypes

1:1:1

R

Treatment (6 cycles)	Maintenance
Carboplatin AUC 5 + paclitaxel 175 mg/mq + bevacizumab 15 mg/kg	Bevacizumab 15 mg/kg 16 cycles
Carboplatin AUC 5 + paclitaxel 175 mg/mq + bevacizumab 15 mg/kg	Bevacizumab 15 mg/kg 16 cycles + rucaparib 600 mg BID 24 cycles
Carboplatin AUC 5 + paclitaxel 175 mg/mq	Rucaparib 600 mg BID 24 cycles

Primary endpoint

PFS

Status: due to start enrolling end 2017

Stratification factors

- Residual tumour at primary surgery
- Stage of disease
- HRD status (*BRCA* mutated *vs* HRD positive *vs* biomarker negative)

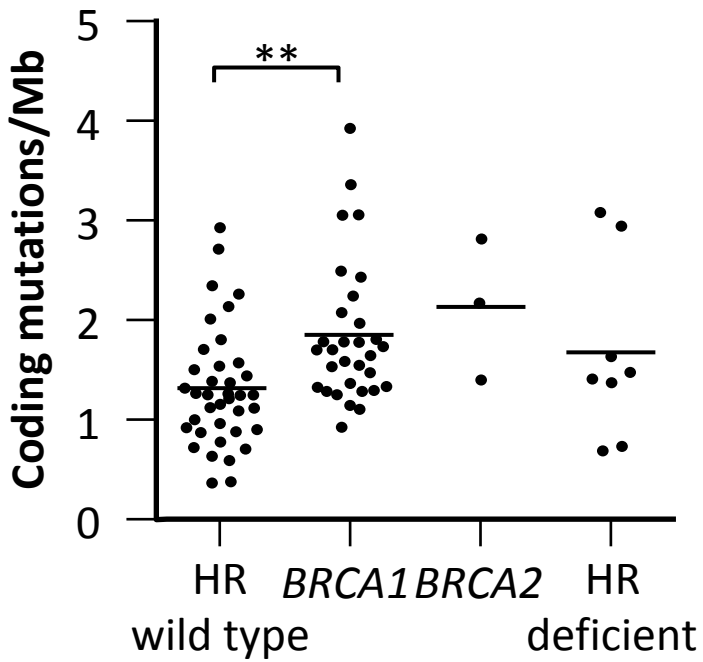
Rucaparib no está autorizado en España; solo está autorizado en los Estados Unid
Rucaparib is not approved in Spain; it is only approved for use in the United States of America.

AUC, area under the curve; BID, twice daily; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency

1. Adis Insight. 70028211. http://adisinsight.springer.com. Accessed 1 August 2017;
2. Adapted with input from the Principle Investigator from MITO Group. MITO 25. http://www.mito-group.it/en/xxix-riunione-mito-milano/diapositive/category/164-relazioni-mito-21-giugno-2017?download=745:12-lorusso. Accessed 1 August 2017

PARP Inhibitors in Combination with Immuno-Oncology Agents: Rationale

- Tumours with deleterious mutations in DNA repair genes (including *BRCA1/2*) have a high mutational load and a higher number of protein-coding mutations (neoepitopes) due to the inability of the cancer cell to repair DNA damage effectively[1]
- *BRCA1/2* mutant and HR-deficient tumours are correlated with higher PD-L1 expression and CD8 T-cell infiltration that predict PD-(L)1 mAb response[2]



1. Patch AM et al. *Nature.* 2015;521:489–494;
2. Strickland K et al. ASCO 2015; Abstract 5512

	PRIMA	Imagyn050 ENGOT OV39	Athena	First	ENGOT OV43	Duo-O	Total
Sponsor	Tesaro	Roche	Clovis	Tessaro	Merck	Astra Zeneca	
Group leader	GEICO(GOG)	GOG(MITO)	GOG(NCRI)	GINECO (GOG??)	BGOG(leading) – unsure whether GOG will join as supporting groups	AGO(GOG)	
ENGOT Model	**C**	C	C		C	C	
Randomisation	After CT	Upfront	Maintenance	Upfront	Upfront	Upfront	
Bev in Standardarm	No	Yes	No	Optional	Optional	Yes	
Exp. Arm	Nira	- TC-Bev-Atezo	- Ruca-Nivolu - Ruca - Nivolu	- Nira - Nira + O42	BRCA+: Ola + Pembro BRCA-: Pembro Pembro+Ola	- Durva - Durva+Ola	
NACT allowed	Yes	Yes	Yes	Yes	Yes	Yes	
RT=0	**NO after PDS** **YES after IDS**	No but Under discussion	CR/NED after CT	No	Yes	Yes	
Endpoint	PFS	PFS + OS	PFS	PFS	PFS+OS	PFS	
MITO	X 9	X 12	6	A 8	C 10	B 10	

Ovarian cancer: conclusions

- Treatment according to histotype is the future!

- Parp inhibitors are changing the natual history of ovarian cancer disease in a group of patients.

- Learning curve on toxicity management is necessary

- The most appopriate setting and combinatons will be addressed into the ongoing trials