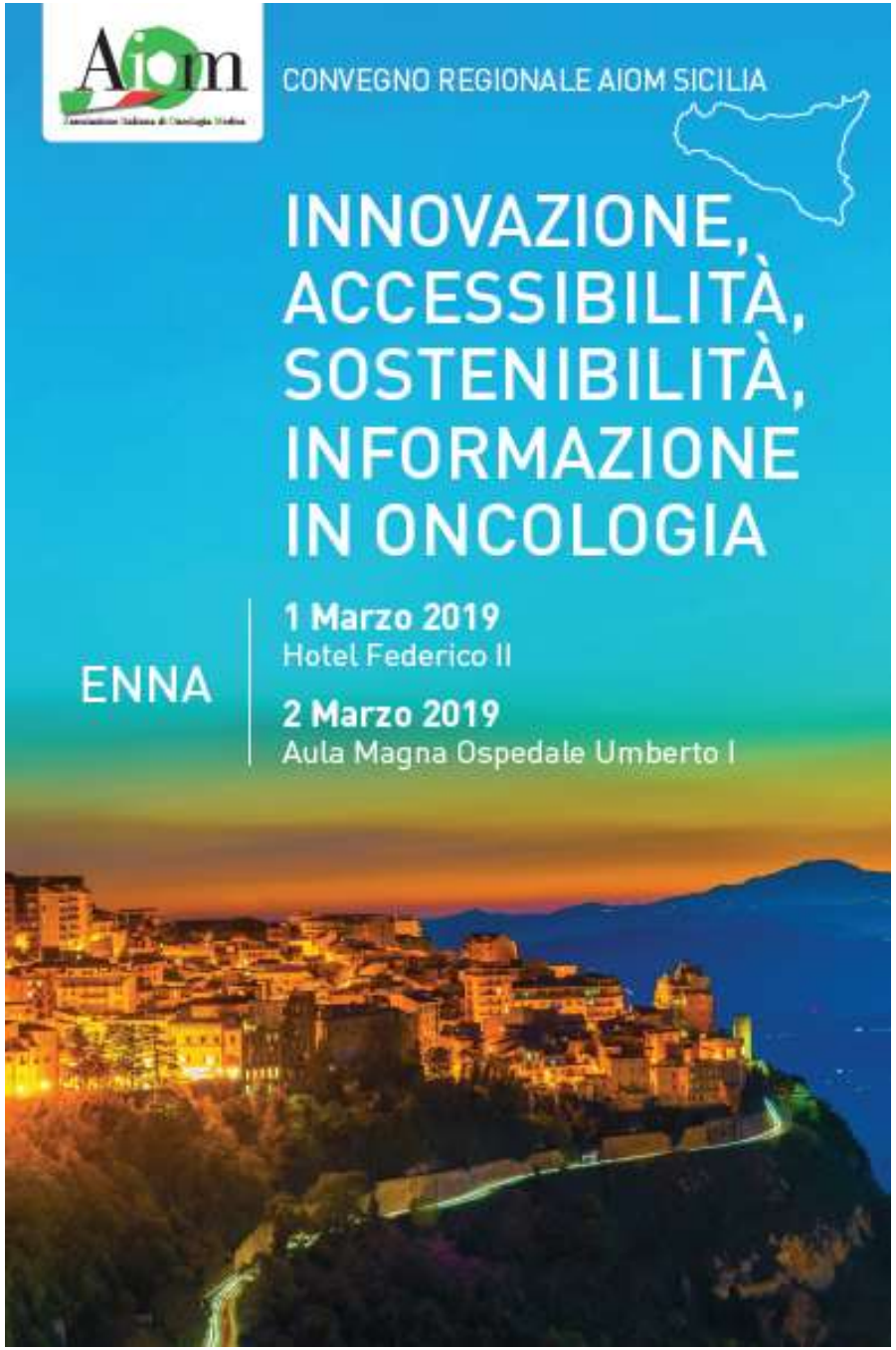


I PARP inibitori nella paziente con Carcinoma ovarico BRCA mutato e non mutato. Sono tutti uguali?

Giusy Scandurra

UOS Oncologia Medica

Dipartimento Materno Infantile

Ospedale Cannizzaro di Catania

Domande…

- Che cos’è un PARP inibitore? Perché funziona un PARP Inibitore?
- Quali sono i farmaci PARP inibitori?
- Indicazioni attuali e del nostro immediato futuro
- In che cosa si somigliano ed in che cosa si differenziano?
- Perché fallisce un PARP inibitore?
- …Qual è il futuro dei PARP inibitori?

What is a PARP Inhibitor?

How a PARP Inhibitor works?

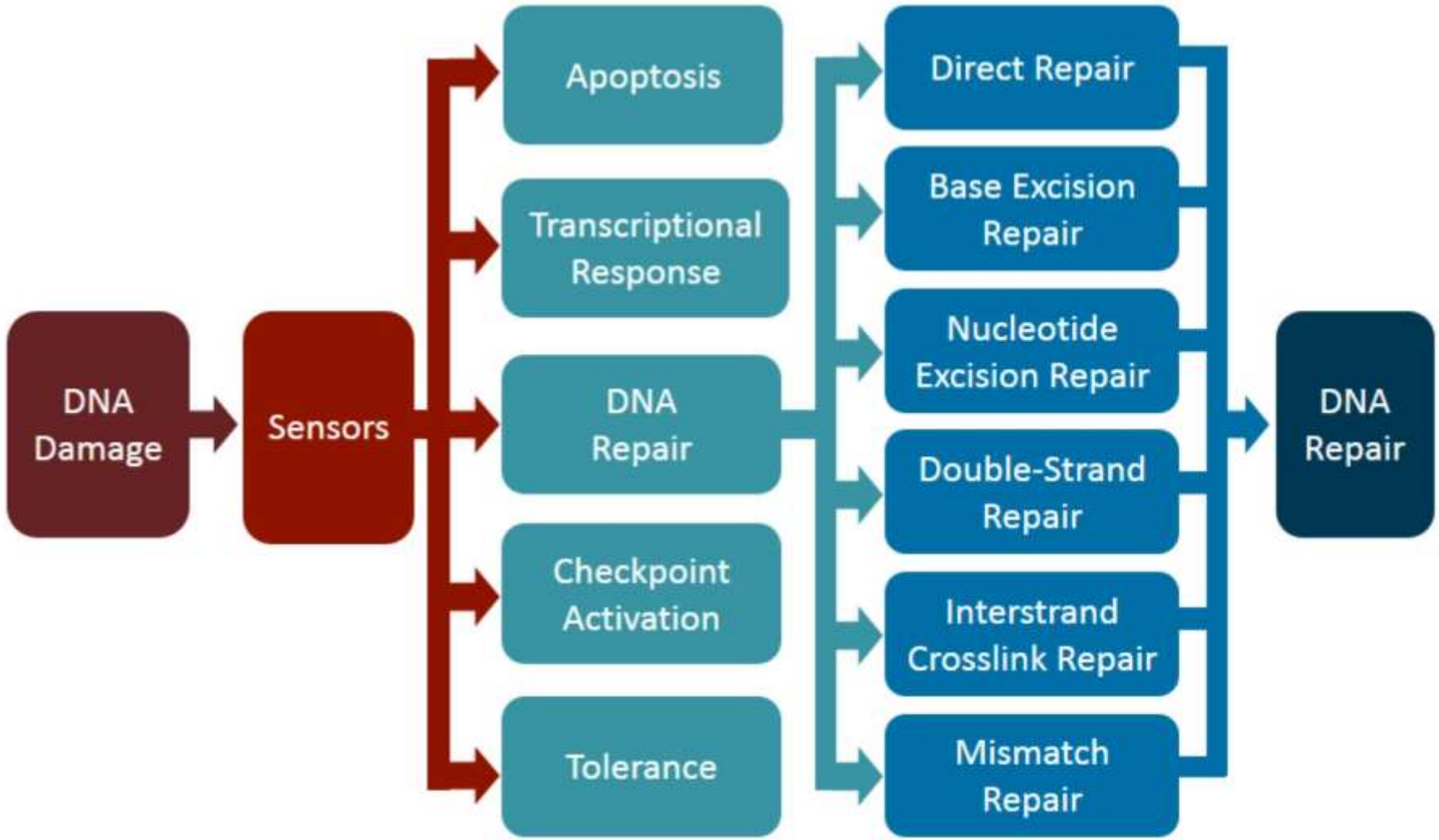
Scusate….
ma per parlare di questo concetto devo partire da Adamo ed Eva..

DNA Repair

- DNA is damaged daily
- DNA repair maintains DNA integrity
- Presence of 2 DNA strands supports high-fidelity repair
- Complex process involving very large number of genes
- Multiple DNA repair processes repair different types of damage
- Cancer occurs as a consequence of inadequate DNA repair

Mehta A, Haber JE. *Cold Spring Harb Perspect Biol.* 2014;6:a016428; Broustas CG, et al. *Radiat Res.* 2014;181:111-130.

ABCs of DNA Repair



Mehta A, Haber JE. *Cold Spring Harbor Perspect Biol.* 2014;6:a016428.

DNA Repair Defects in Cancer

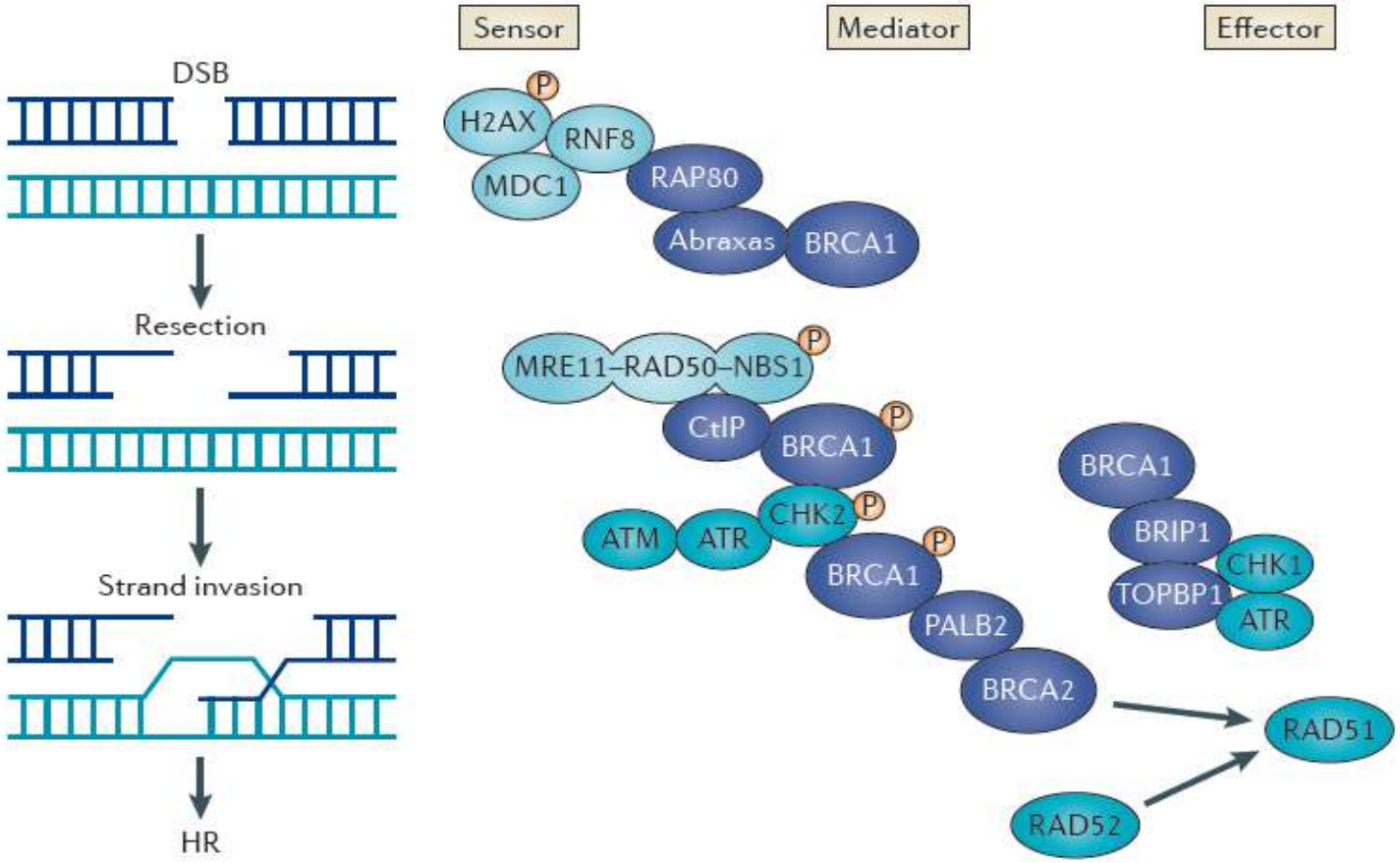
- Common in cancer
- Defects found in multiple repair processes
- Commonly mutations
  - Loss of function of *TP53* (guardian of the genome)
  - Loss of cell cycle inhibitors/checkpoints p15, p16, p21, p27, CHEK1, CHEK2
  - Mismatch repair defects: MSH2, MSH6, MLH1, PMS2, others
  - HR repair defects: *BRCA2, BRCA1, ATM, PALB2, RAD51,* others
  - Loss of DNA damage sensors

Mehta A, Haber JE. *Cold Spring Harb Perspect Biol.* 2014;6:a016428.
Cerrato A, et al. *J Exp Clin Cancer Res.* 2016;35:179.

What is the function of BRCA 1 and BRCA 2 ?

- ✓ Tumor suppressor genes involved in DNA repair
- ✓ Autosomally transmitted (chromosomes 17 and 13)
- ✓ When mutated: higher incidence of hereditary breast and ovarian cancer (HBOC syndrome)

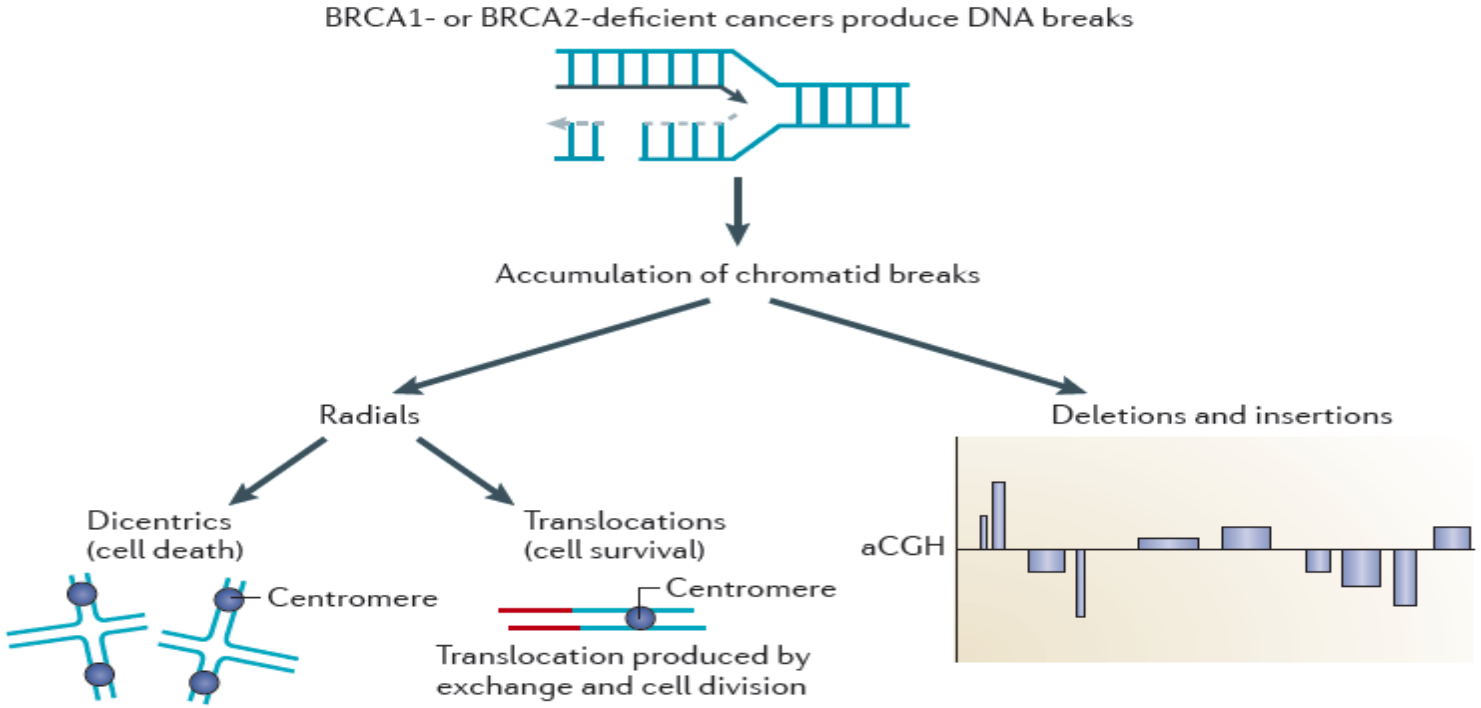
What is the function of BRCA 1 and BRCA 2 ?



HOMOLOGOUS RECOMBINATION

What is the function of BRCA 1 and BRCA 2 ?

Impairment of BRCA1 and BRCA2 function leads to DNA instability, telomere shortening and higher risk of endocrine related cancer (breast and ovary)



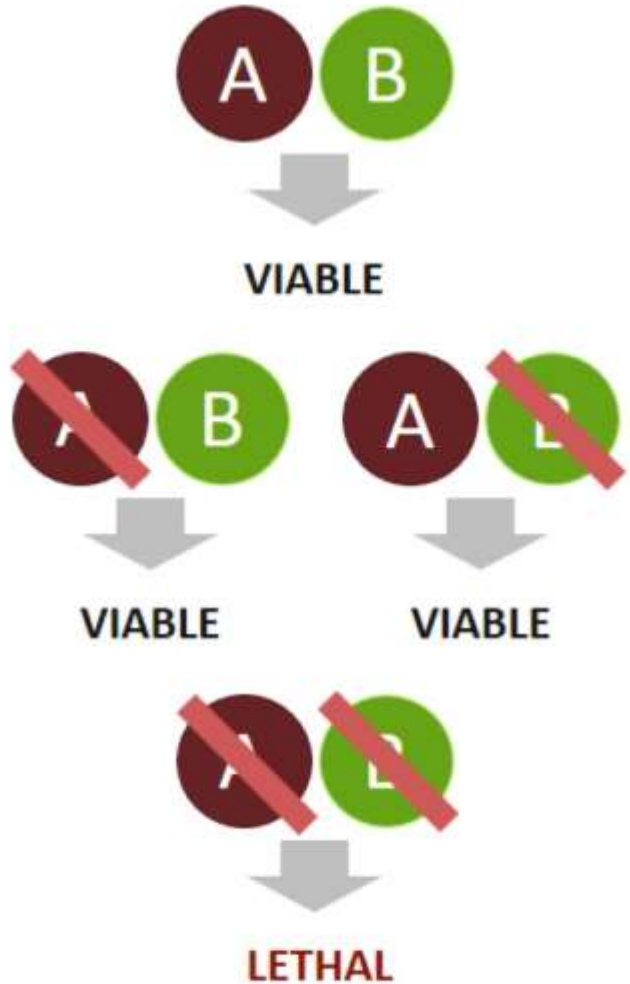
DNA Repair Defects: The Achilles' Heel in Cancer Cells

- Normal cells
  - Regular, complete repair processes
  - Easily repair minor defects
- Tumor cells
  - Highly defective repair
  - Minimal, but sufficient, repair capability
- Pharmacological inhibition of DNA repair is lethal to cancer cells, but spares normal cells

Cerrato A, et al. *J Exp Clin Cancer Res*. 2016;35:179.

Synthetic Lethality

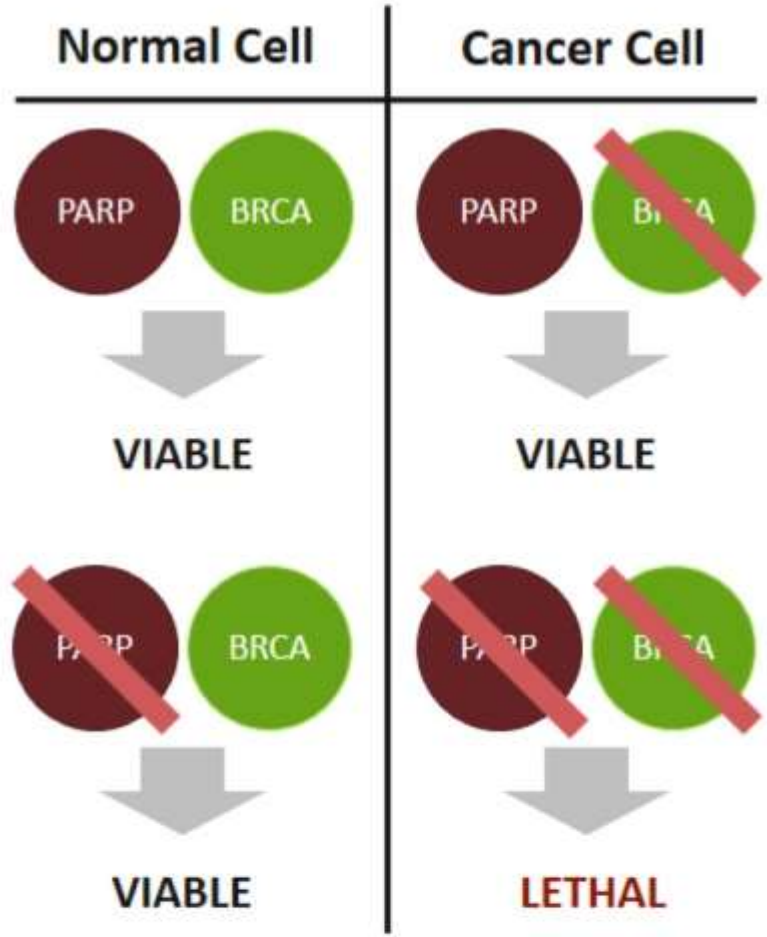
- Two genes are "synthetic lethal" if:
  - Mutation of either gene A or B alone is compatible with viability, but
  - Simultaneous mutation of both genes A and B causes death
- "Holy Grail" of cancer care: selective tumor cell kill, sparing normal cells



Dietlein F, et al. *Clin Cancer Res.* 2014;20:5882-5887; Lupo B, Trusolino L. *Biochim Biophys Acta.* 2014;1846:201-215.

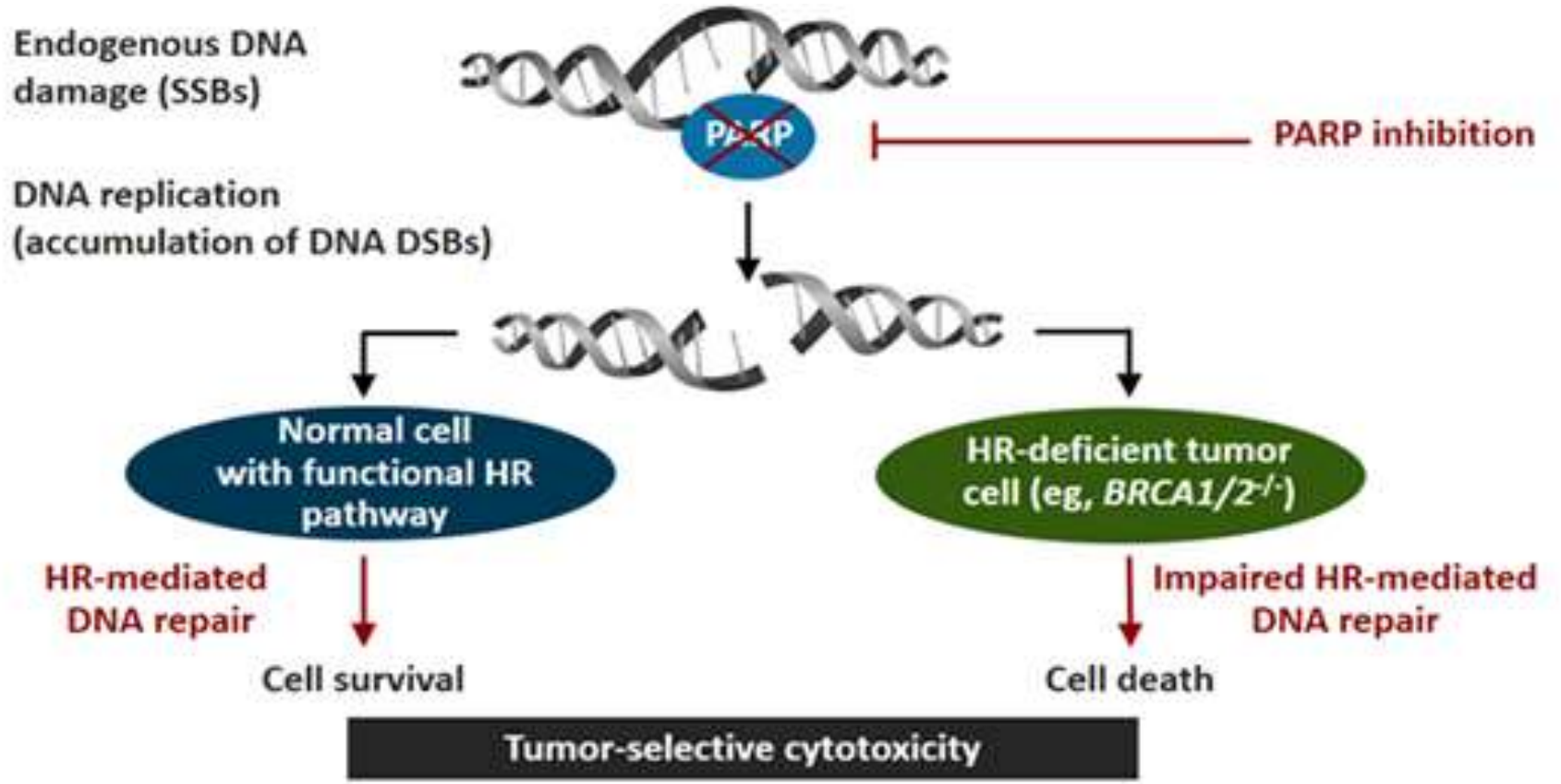
PARP and Synthetic Lethality

- PARP family[a]
  - 17 members
  - PARP1, PARP2 recruit proteins for DNA resection, single-strand formation, and initiation of HR
- PARP inhibitors have a synthetic lethal interaction with loss of HR DNA repair genes[a-c]
  - *BRCA1* and *BRCA2* involved in high-fidelity HR



a. Riffell JL, et al. *Nat Rev Drug Discov.* 2012;11:923-936; b. Dietlein F, et al. *Clin Cancer Res.* 2014;20:5882-5887; c. Lupo B, et al. *Biochim Biophys Acta.* 2014;1846:201-215.

PARP Inhibition May Result in Tumor Cell Death via Multiple Pathways, in HRD Deficient and Platinum Sensitive Tumors



DSB = double-strand break; HR = homologous recombination; SSB = single-strand break.

Iglehart JD, Silver DP. *N Engl J Med*. 2009;361:189-191[26]; Farmer H, et al. *Nature*. 2005;434:917-921[23]; Bryant HE, et al. *Nature*. 2005;434:913-917[24]; McCabe N, et al. *Cancer Res*. 2006;66:8109-8115.[25]

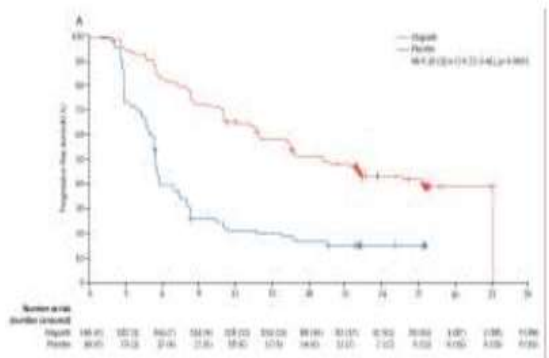
Quali sono i farmaci PARP inibitori?

OLAPARIB, NIRAPARIB AND RUCAPARIB HIGHLY EFFECTIVE IN BRCA MUT

Olaparib

gBRCA mut

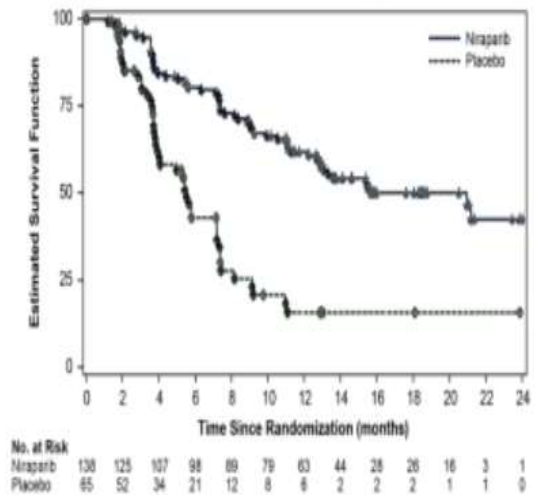
19.3 *vs* 5.5 months (HR 0.27)



Niraparib *

gBRCA mut

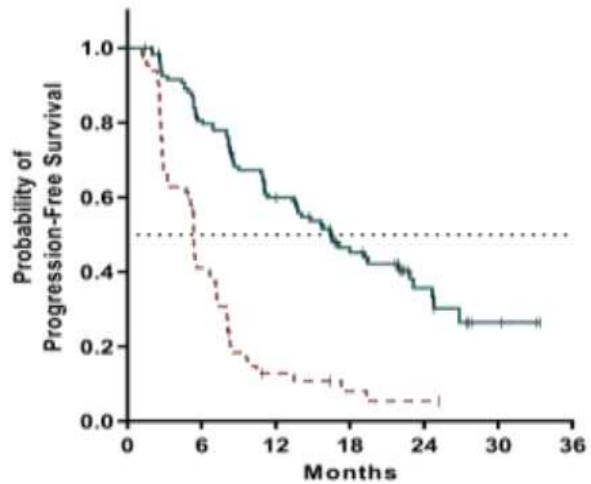
21 *vs* 5.5 months (HR 0.27)



Rucaparib

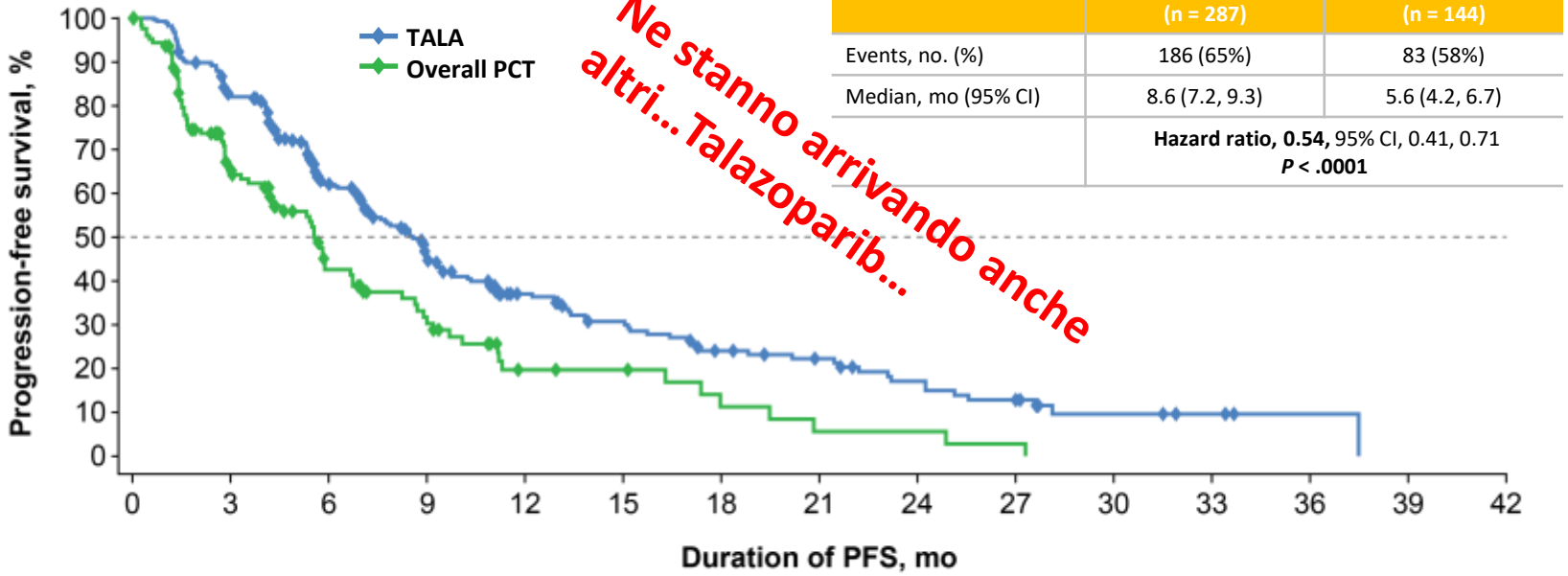
gBRCA mut

16.6*vs* 5.4 months (HR 0.27)



* Central radiological review

Study Design: EMBRACA
Primary Endpoint: PFS by Blinded Central Re



	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

Ne stanno arrivando anche altri… Talazoparib…

1-Year PFS 37% vs 20% Median follow-up time: 11.2 months

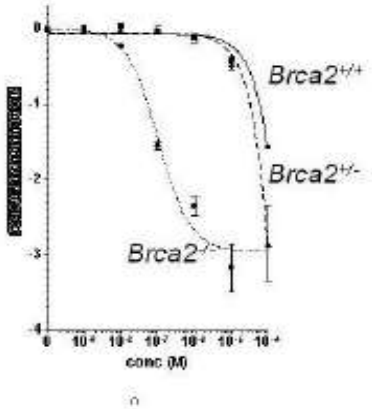
PARP Inhibitors

Based on "tumour synthetic lethality" targeting cells with homologous recombination deficiency (HRD) – is this a new treatment for BRCA mutation associated ovarian cancer?

Pre-clinical → Early Clinical Trials (Phase I, incl. IB) → Randomised Clinical Trials (Phase II and III)

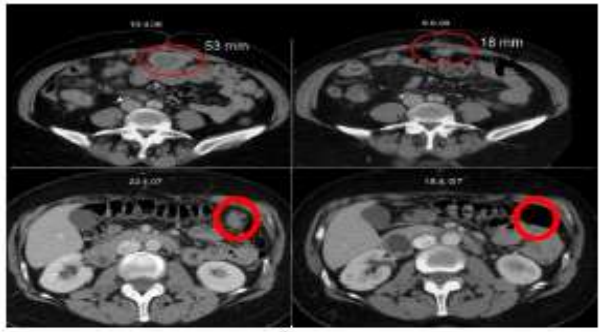
PARP : poly(ADP) ribose polymerase

Exquisite preclinical efficacy of PARPi



Farmer et al, Nature 2005

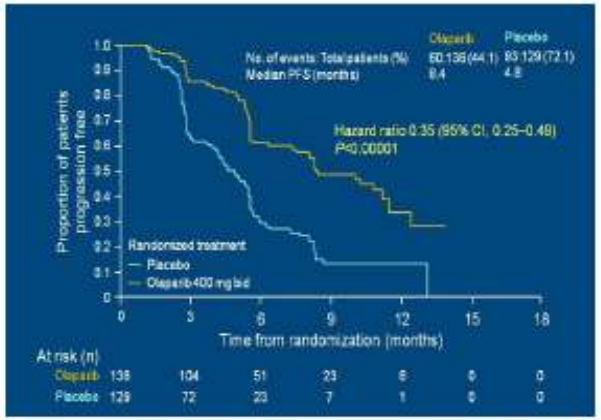
Phase I trial confirms excellent tolerance and expansion in 50 BRCA patients showed 46% response.



"this is nothing like chemotherapy

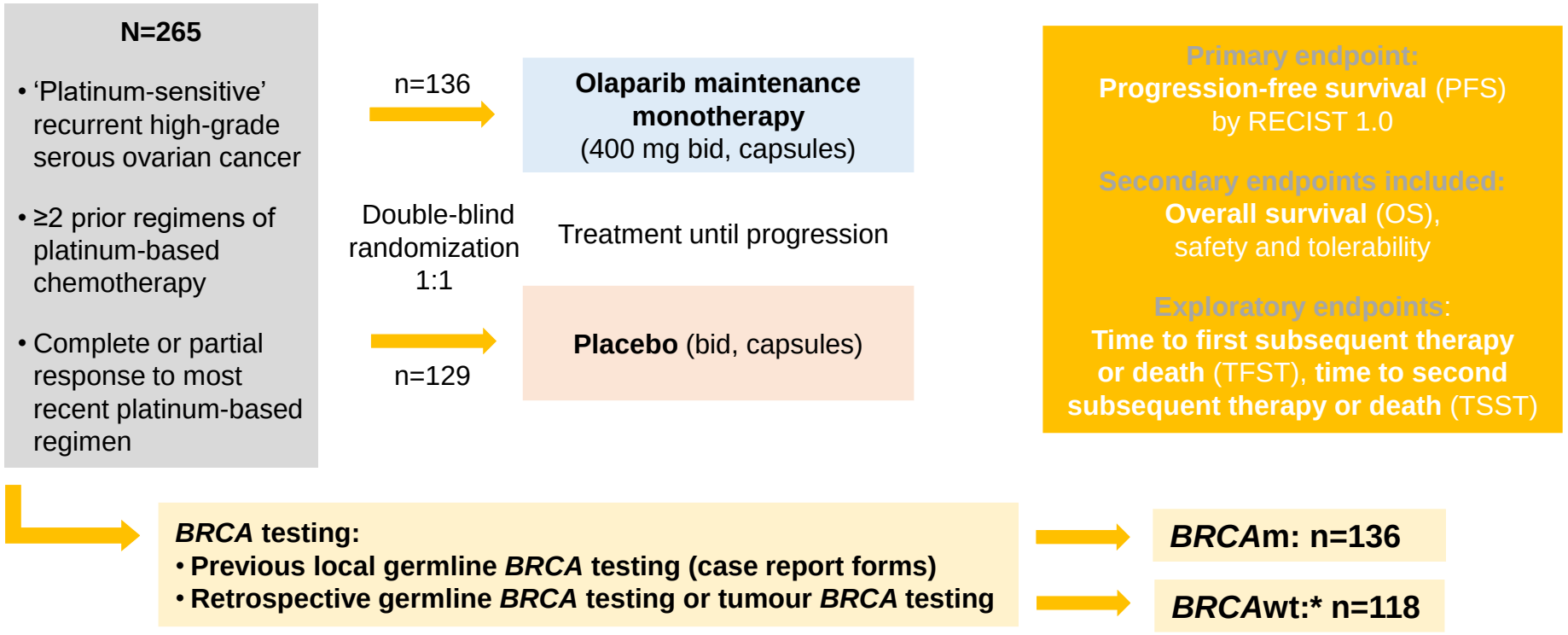
Fong P et al. N Engl J Med, 2009; **361**, 123-134;
Fong P et al. J Clin Oncol, 2010; **28**, 2512-2519

Randomised trial (maintenance therapy) showed marked PFS benefit



Ledermann et al, NEJM 2012 366 1382-92

Study 19: Phase II trial design, endpoints and *BRCA* testing



N=265

- 'Platinum-sensitive' recurrent high-grade serous ovarian cancer
- ≥2 prior regimens of platinum-based chemotherapy
- Complete or partial response to most recent platinum-based regimen

n=136 → **Olaparib maintenance monotherapy** (400 mg bid, capsules)

Double-blind randomization 1:1

Treatment until progression

n=129 → **Placebo** (bid, capsules)

Primary endpoint:
Progression-free survival (PFS) by RECIST 1.0

Secondary endpoints included:
Overall survival (OS), safety and tolerability

Exploratory endpoints:
Time to first subsequent therapy or death (TFST), **time to second subsequent therapy or death** (TSST)

***BRCA* testing:**
- **Previous local germline *BRCA* testing (case report forms)**
- **Retrospective germline *BRCA* testing or tumour *BRCA* testing**

→ ***BRCA*m: n=136**

→ ***BRCA*wt:* n=118**

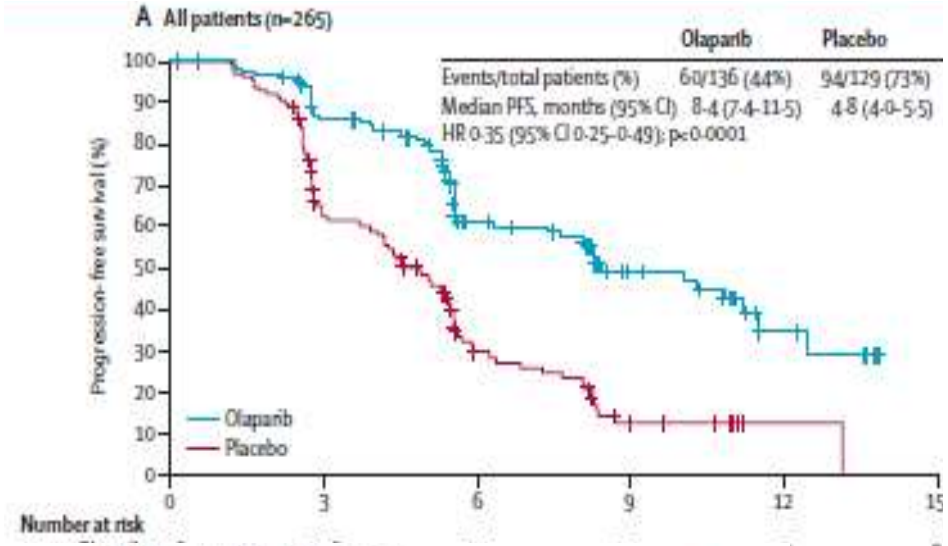
**BRCA*m*: n=136*

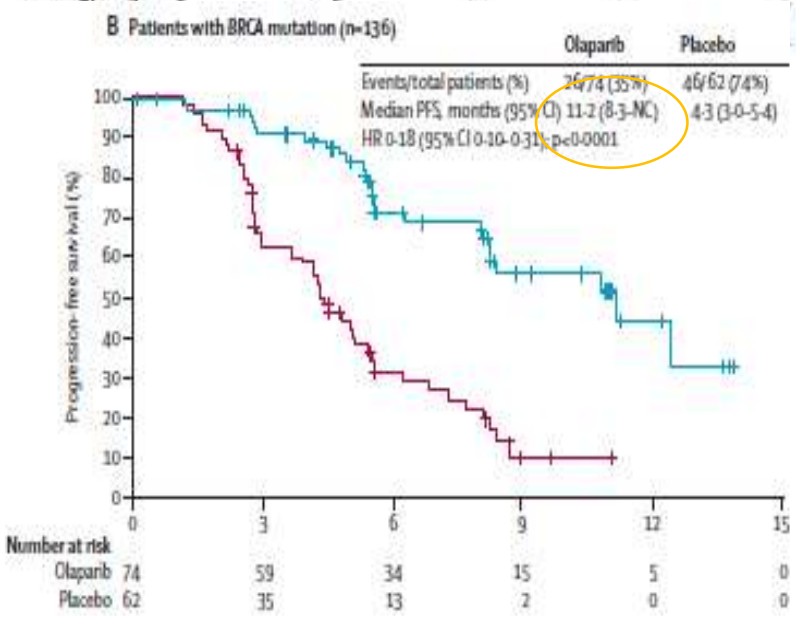
**BRCA*wt*:* n=118*

**BRCA*wt patients did not have a detected *BRCA*m or had a *BRCA*m of unknown significance*

bid, twice daily; *BRCA*wt, *BRCA1/2* wild type; RECIST, Response Evaluation Criteria in Solid Tumors

Study 19: Progression free survival results



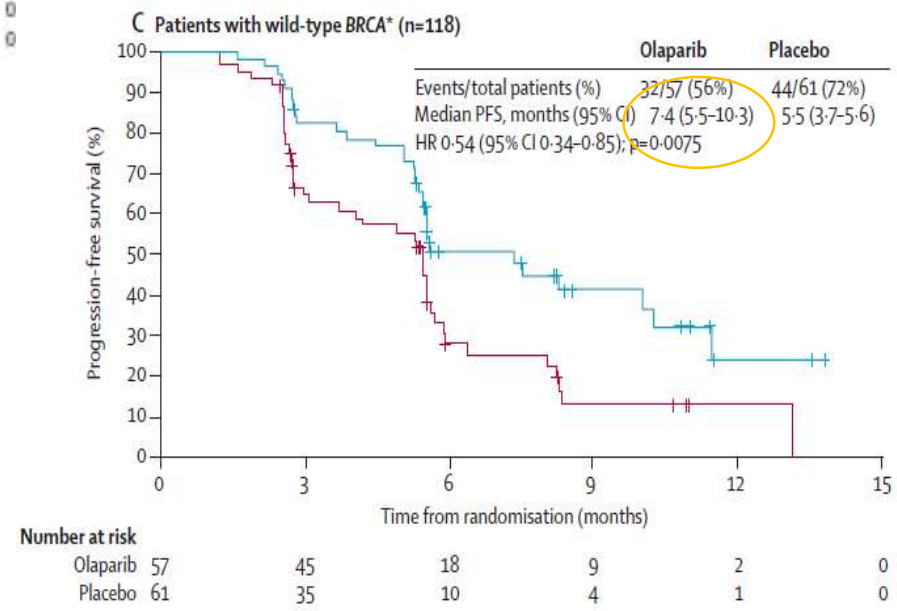


PFS ⇧

Statistically significant improvement in progression-free survival with olaparib[1,2]

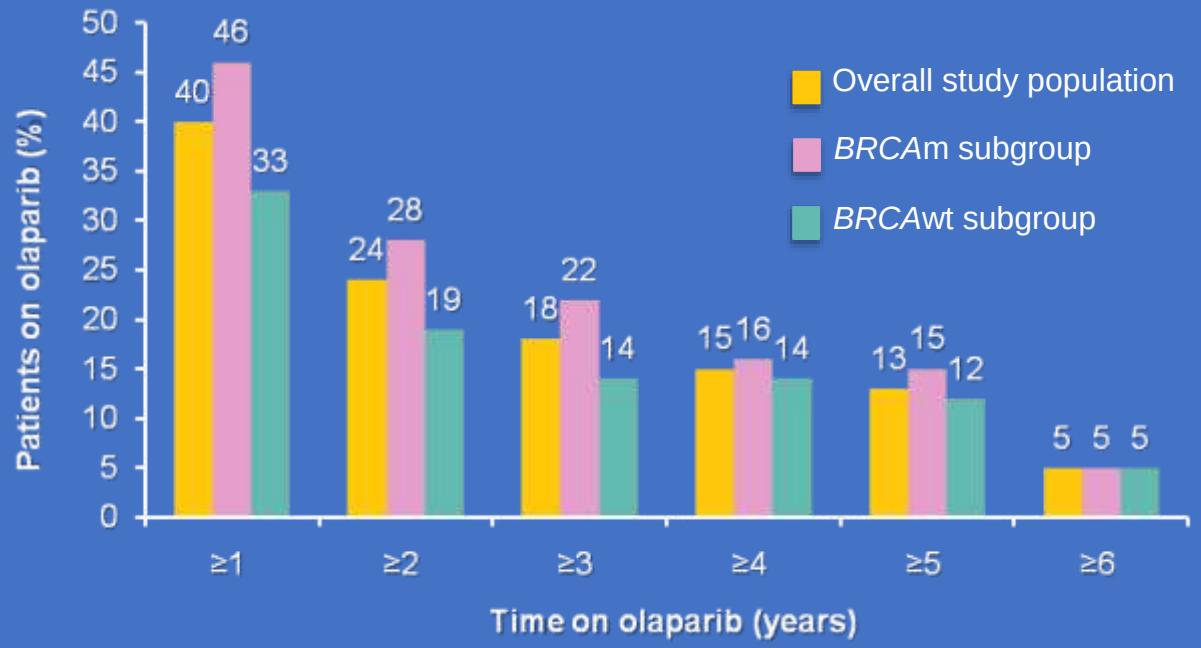
Overall population:
Median PFS (olaparib vs placebo): 8.4 months vs 4.8 months **HR=0.35**, *P*<0.0001

***BRCA*m subgroup:**
Median PFS (olaparib vs placebo): 11.2 months vs 4.3 months **HR=0.18**, *P*<0.0001

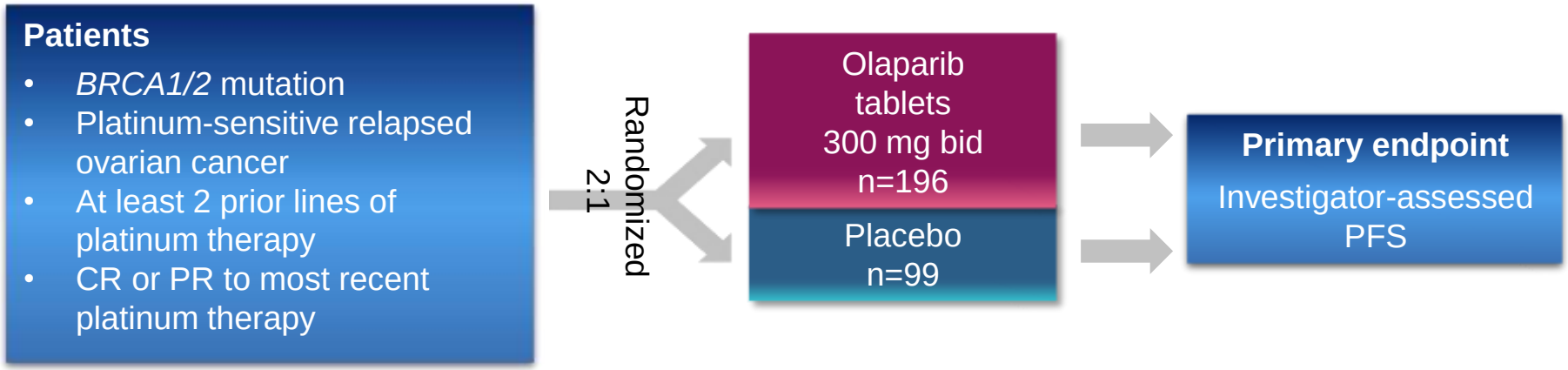


Long-term exposure to treatment

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



SOLO2/ENGOT-Ov21: study design



Sensitivity analysis: PFS by blinded independent central review (BICR)

- **Key secondary endpoints:**
  - Time to first subsequent therapy or death (TFST), time to second progression (PFS2), time to second subsequent therapy or death (TSST), overall survival (OS)
  - Safety, health-related quality of life (HRQoL*)

*Primary endpoint for HRQoL was trial outcome index (TOI) of the FACT-O (Functional Assessment of Cancer Therapy – Ovarian)

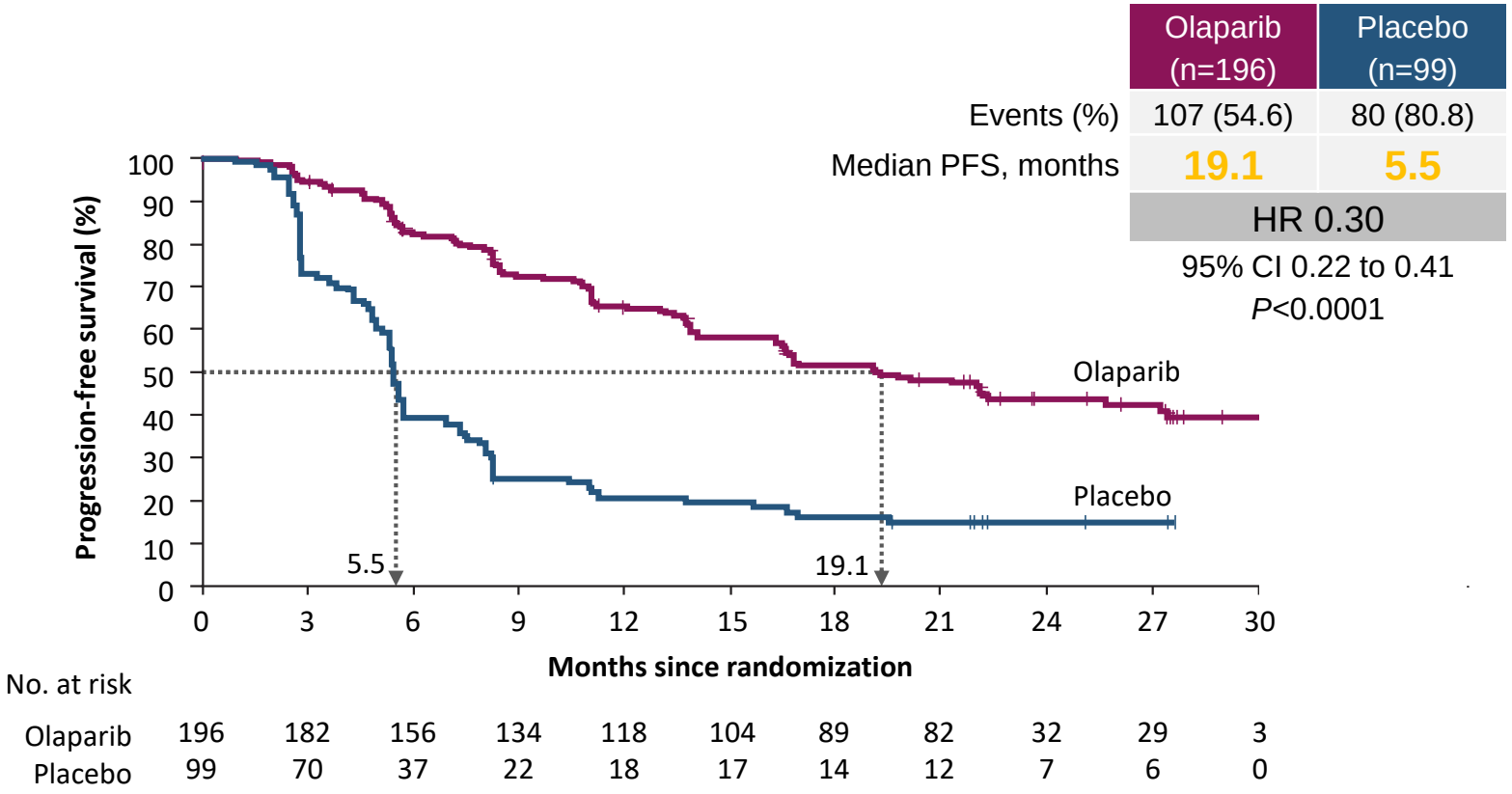
Presented by Pujade-Lauraine at SGO 2017 annual meeting

Demographic and baseline characteristics

Characteristic		Olaparib (n=196)	Placebo (n=99)
Age, median (range)		56 (28–83)	56 (39–78)
Primary tumor type, n (%)	Ovarian	162 (82.7)	86 (86.9)
	Fallopian tube or primary peritoneal	31 (15.8)	13 (13.1)
	Other/missing	3 (1.5)	0
Prior platinum regimens, n (%)	2 lines	110 (56.1)	62 (62.6)
	3 lines	60 (30.6)	20 (20.2)
	≥4 lines	25 (12.8)	17 (17.2)
Platinum-free interval, n (%)	6–12 months	79 (40.3)	40 (40.4)
	>12 months	117 (59.7)	59 (59.6)
Response to platinum therapy, n (%)	Complete response	91 (46.4)	47 (47.5)
	Partial response	105 (53.6)	52 (52.5)

Presented by Pujade-Lauraine at SGO 2017 annual meeting

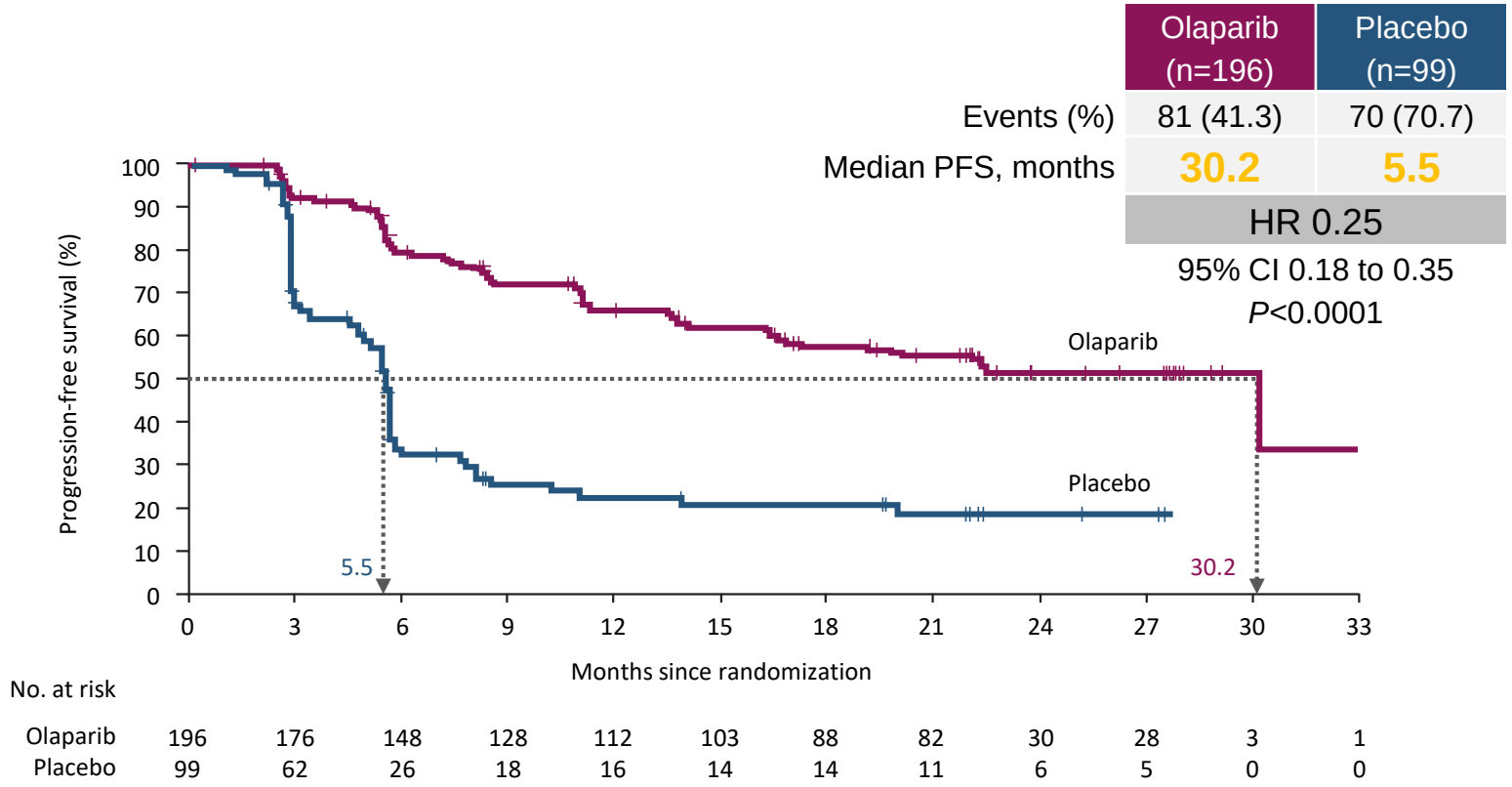
PFS by investigator assessment



Median follow-up was 22.1 months in the olaparib group and 22.2 months for placebo

Presented by Pujade-Lauraine at SGO 2017 annual meeting

PFS sensitivity analysis using BICR



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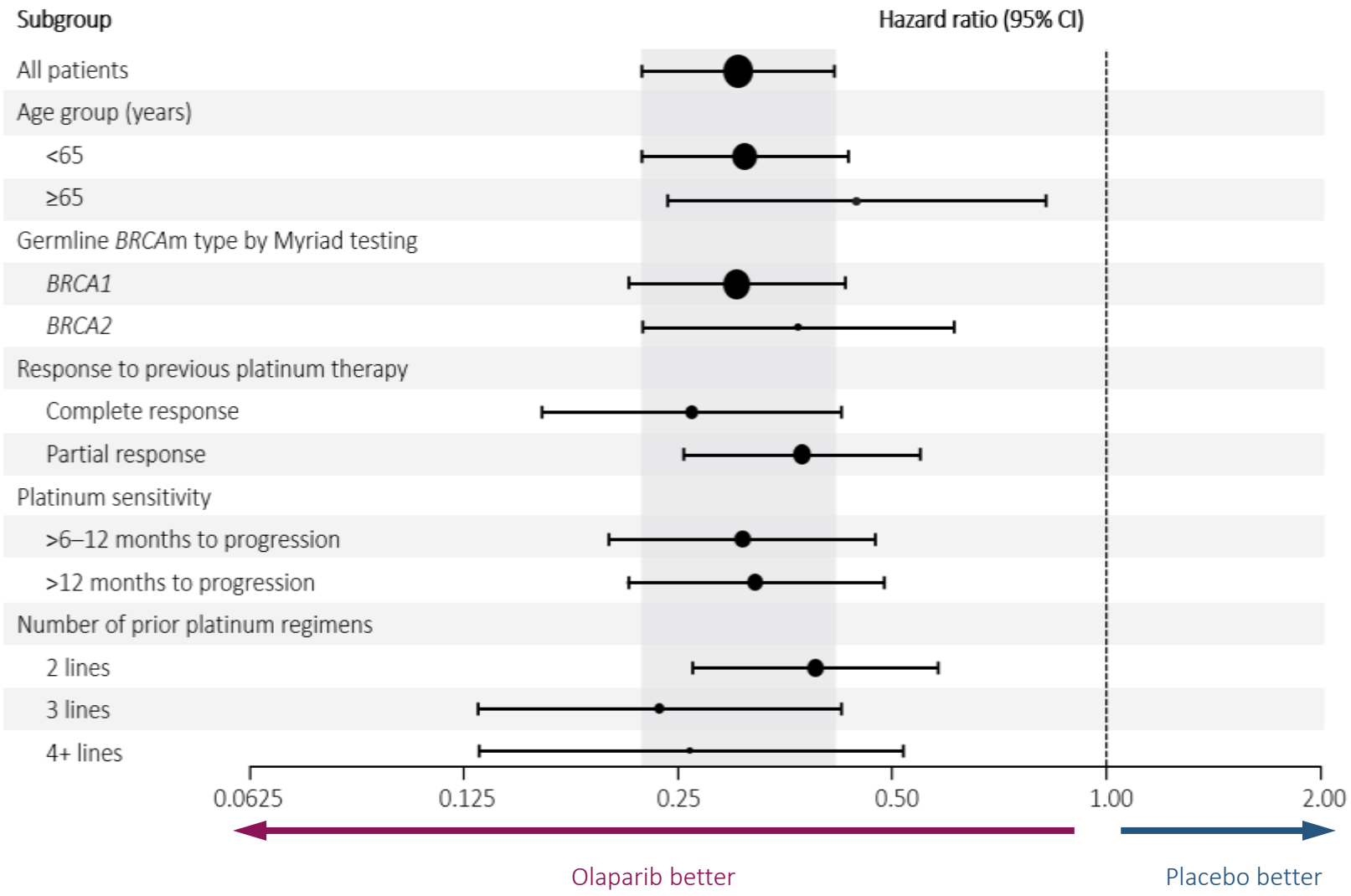
Subgroup analysis of PFS



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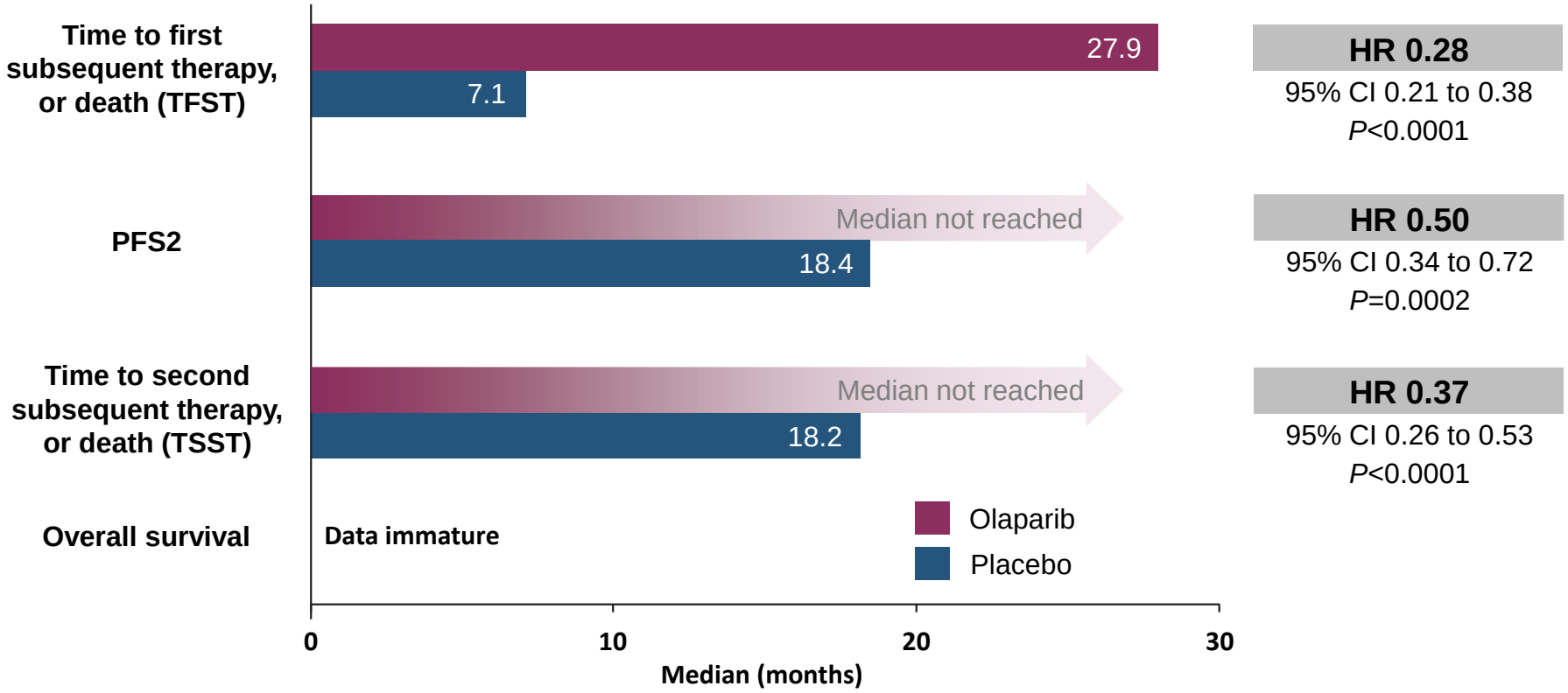
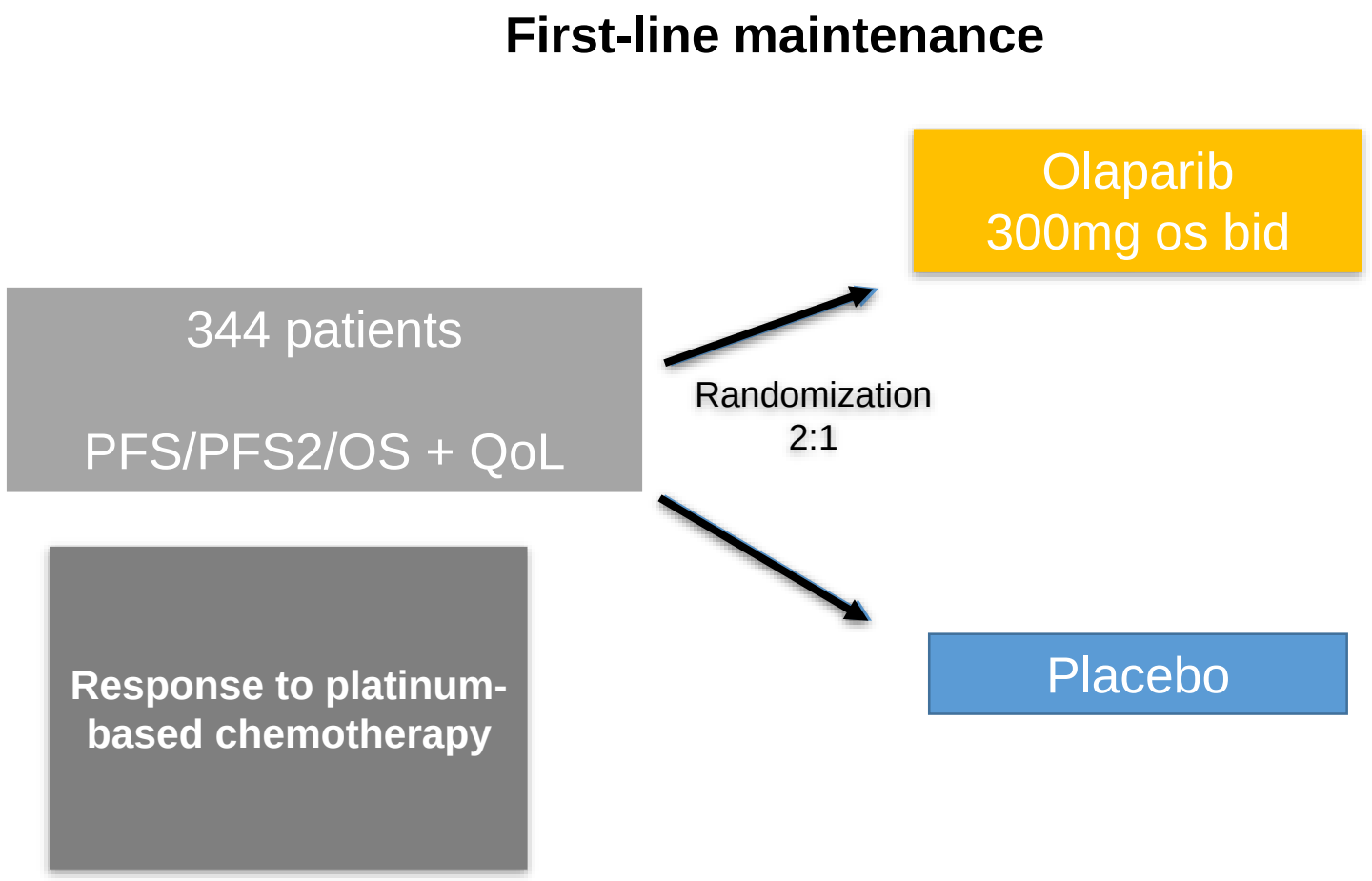
Secondary efficacy endpoints



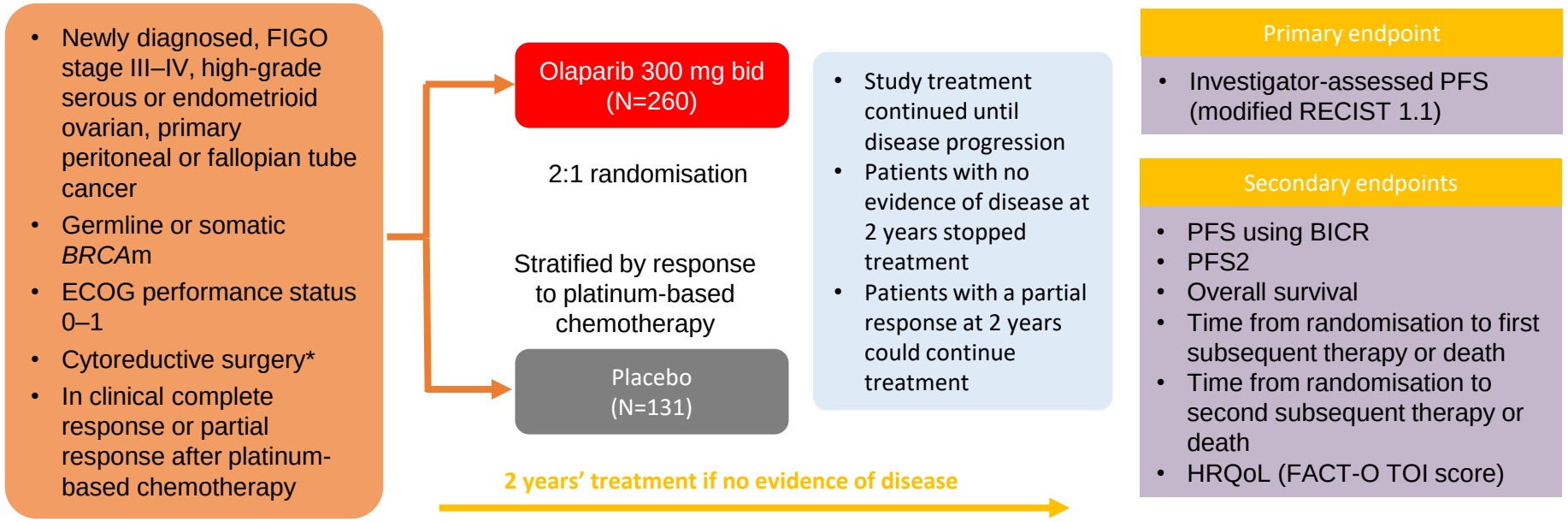
Presented by Pujade-Lauraine at SGO 2017 annual meeting

Olaparib in first line:
SOLO-1 Phase III trial- BRCAm population only



SOLO-1 is the first Phase III trial to investigate maintenance therapy with a PARP inhibitor in newly diagnosed ovarian cancer

SOLO-1 is a global randomised multicentre placebo controlled Phase III study



- *Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease
- BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; FACT-O = Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO = International Federation of Gynecology and Obstetrics; HRQoL = health-related quality of life; PFS = progression-free survival; PFS2 = time to second progression or death; RECIST = Response Evaluation Criteria in Solid Tumours; TOI = Trial Outcome Index; PARP = poly (ADP-ribose) polymerase; *BRCA*m = *BRCA* gene mutation
- https://clinicaltrials.gov/ct2/show/NCT01844986 (accessed October 2018)

Baseline characteristics were well balanced between treatment groups

Characteristic	Olaparib (N=260)	Placebo (N=131)
Median age, years (range)	53.0 (29–82)	53.0 (31–84)
Response after platinum-based chemotherapy, N (%)		
Clinical complete response*	213 (81.9)	107 (81.7)
Partial response†	47 (18.1)	24 (18.3)
ECOG performance status, N (%)		
0	200 (76.9)	105 (80.2)
1	60 (23.1)	25 (19.1)
Missing	0	1 (0.8)
Primary tumour location, N (%)		
Ovary	220 (84.6)	113 (86.3)
Fallopian tubes	22 (8.5)	11 (8.4)
Primary peritoneal	15 (5.8)	7 (5.3)
Other‡	3 (1.2)	0
FIGO stage, N (%)		
III	220 (84.6)	105 (80.2)
IV	40 (15.4)	26 (19.8)

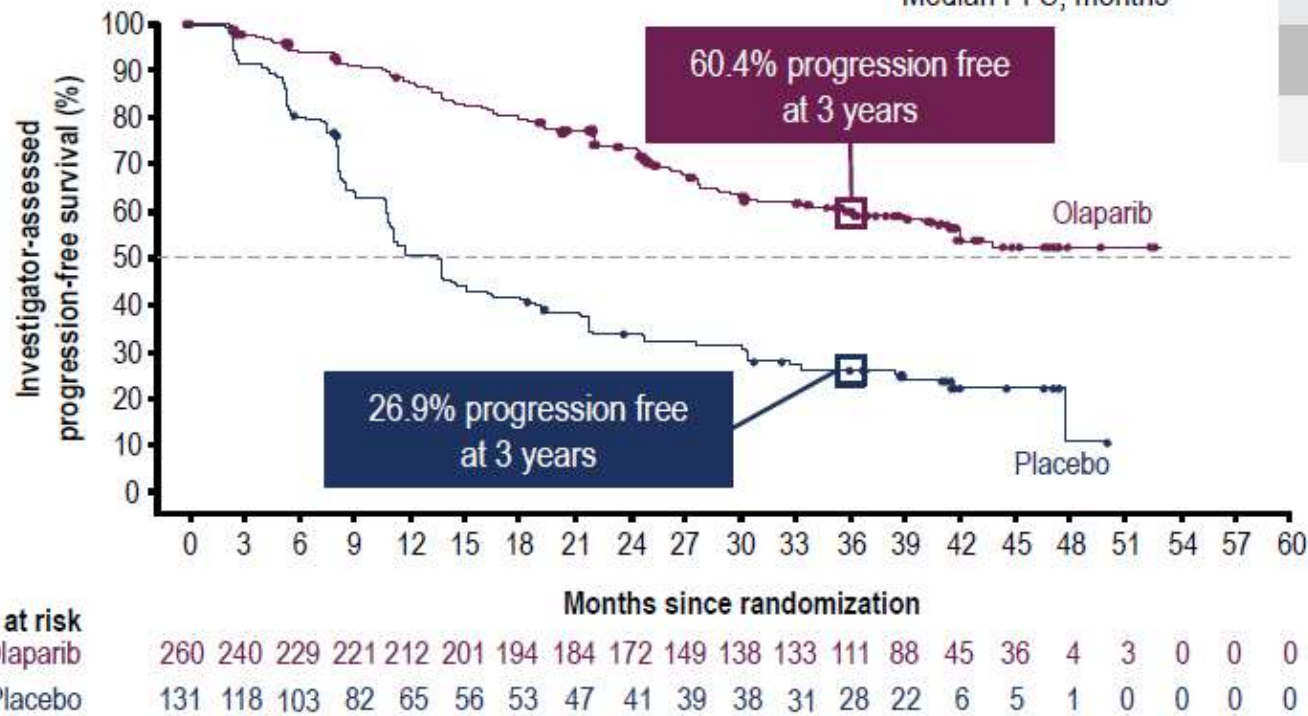
- *Clinical complete response was defined as no evidence of (RECIST) measurable or non-measurable disease on the post-treatment scan and a normal CA-125 level.
- †Partial response was defined as a ≥30% reduction in tumour volume from the start to the end of chemotherapy or no evidence of disease on the post-treatment scan, but with a CA-125 level which had not decreased to within the normal range
- ‡Other includes ovary, fallopian tube, peritoneum, and omentum (N=1), ovary and peritoneum (N=1) and tubo-ovary (N=1)
- ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics
- Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print

Baseline characteristics were well balanced between treatment groups

Characteristic	Olaparib (N=260)	Placebo (N=131)
Baseline CA-125 level, N (%)		
≤ULN	247 (95.0)	123 (93.9)
>ULN	13 (5.0)	7 (5.3)
Missing	0	1 (0.8)
Histology, N (%)		
Serous	246 (94.6)	130 (99.2)
Endometrioid	9 (3.5)	0
Mixed serous/endometrioid	5 (1.9)	1 (0.8)
***BRCA* mutation,[§] N (%)**		
BRCA1	191 (73.5)	91 (69.5)
BRCA2	66 (25.4)	40 (30.5)
Both *BRCA1* and *BRCA2*	3 (1.2)	0

- [§]Myriad/BGI or locally reported; the five patients from China had germline *BRCA* mutation testing performed within China, using the BGI test. Central germline testing confirmed that 388/391 patients had a *BRCA1/2* mutation, 1 patient had a *BRCA* variant of uncertain significance, and 2 patients were *BRCA* wild-type. Foundation Medicine testing confirmed that the two germline *BRCA* wild-type patients had *somatic* BRCA mutations
- ULN = upper limit of normal per institutional standard.
- Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print

PFS by investigator assessment

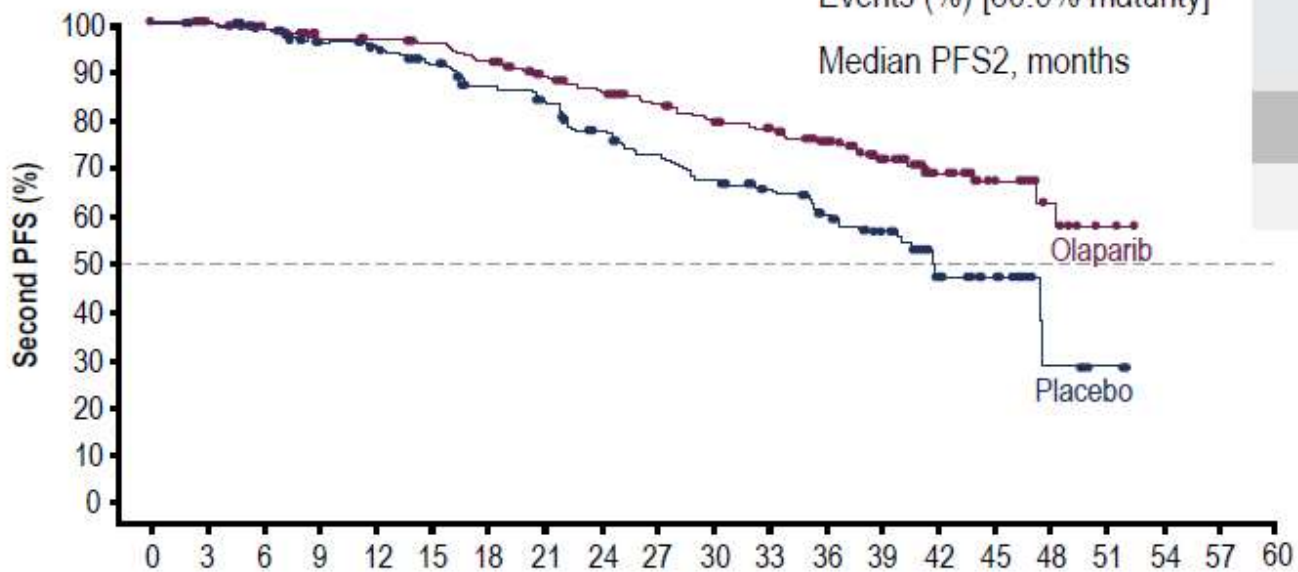


	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		

MUNICH 2018 ESMO congress

CI, confidence interval; NR, not reached

PFS2*



	Olaparib (N=260)	Placebo (N=131)
Events (%) [30.9% maturity]	69 (26.5)	52 (39.7)
Median PFS2, months	NR	41.9
HR 0.50		
95% CI 0.35, 0.72; *P*=0.0002		

No. at risk																					
Olaparib	260	246	239	231	229	225	216	204	194	177	168	163	140	111	61	48	13	5	0	0	0
Placebo	131	126	122	113	108	100	92	88	79	73	68	63	55	44	18	11	3	1	0	0	0

In second line, a PARP inhibitor was used in 33/94 (35%) patients in the placebo arm and 10/91 (11%) patients in the olaparib arm

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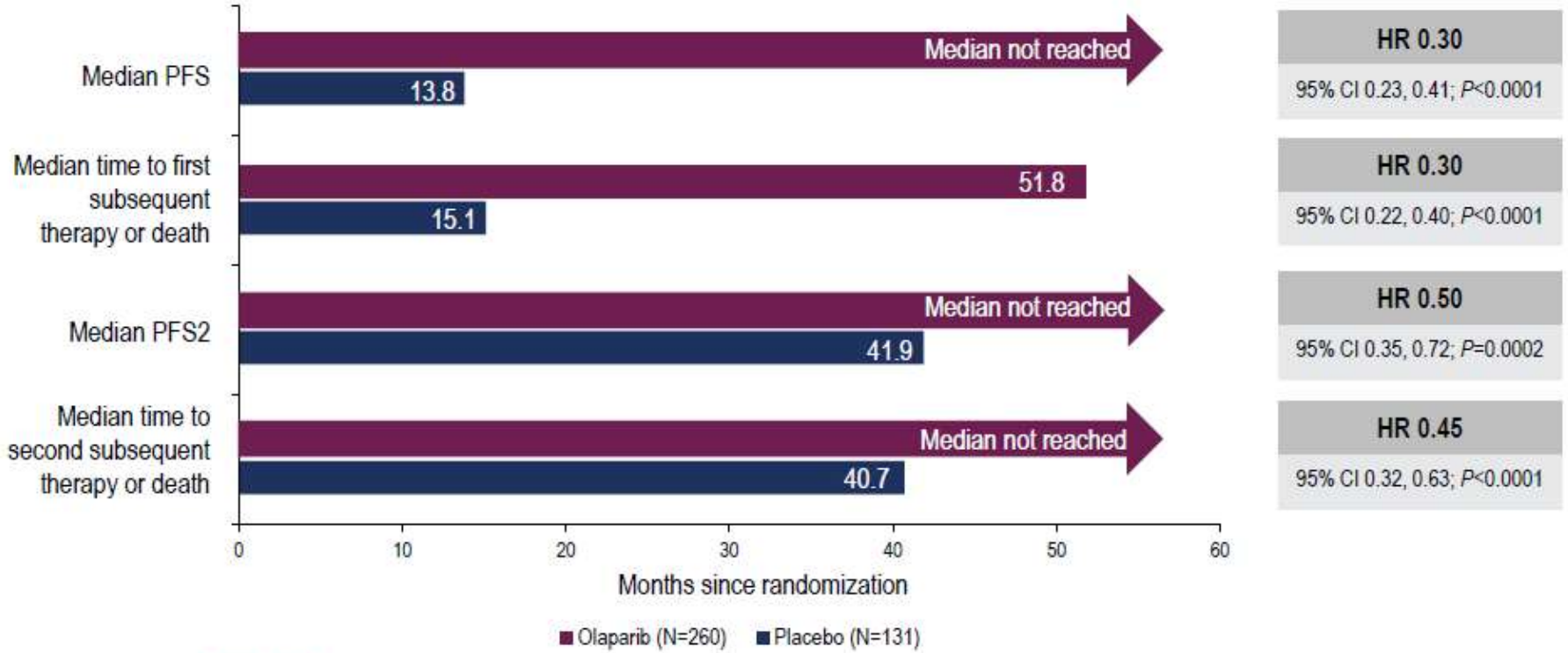
*Time from randomization to second progression or death

Summary of efficacy endpoints



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

MUNICH 2018 ESMO congress

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*

ENGOT-OV16/NOVA TRIAL

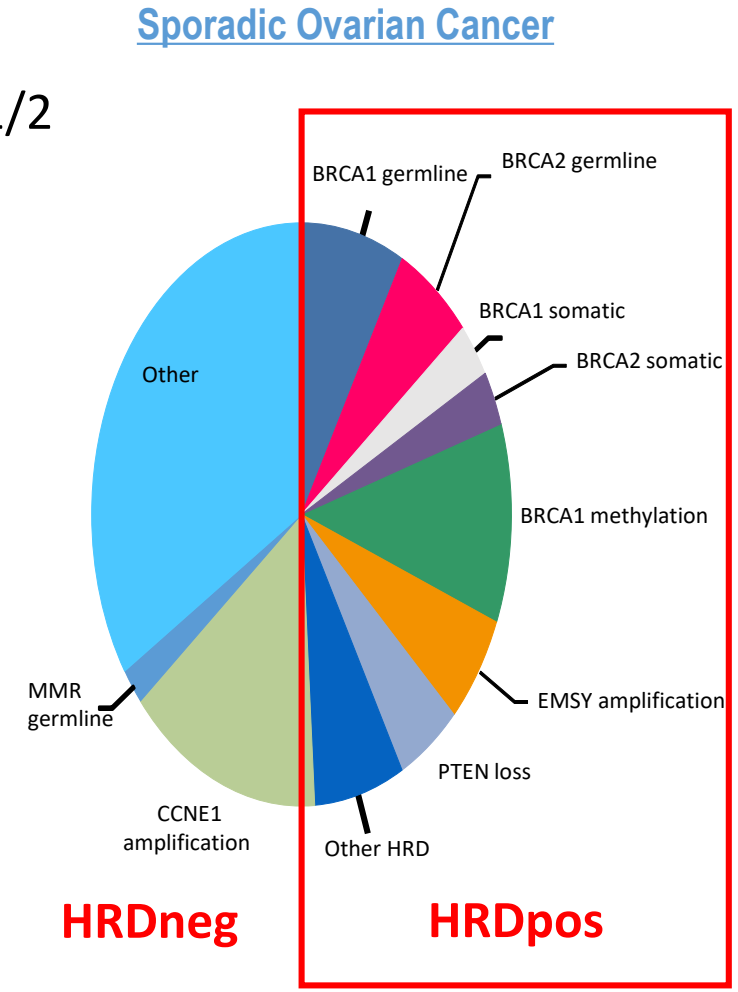
Nova Trial and HRD

- OC is a genetically heterogeneous disease; *BRCA*1/2 deleterious mutations or chromosomal damage result in similar biology

- The myChoice® HRD test measures DNA damage
  - Telomeric allelic imbalance (TAI)
  - Large-scale state transitions (LST)
  - Loss of heterozygosity (LOH)

  - PARP inhibitors block DNA repair pathways in homologous recombination repair deficient (HRD) cells[1]

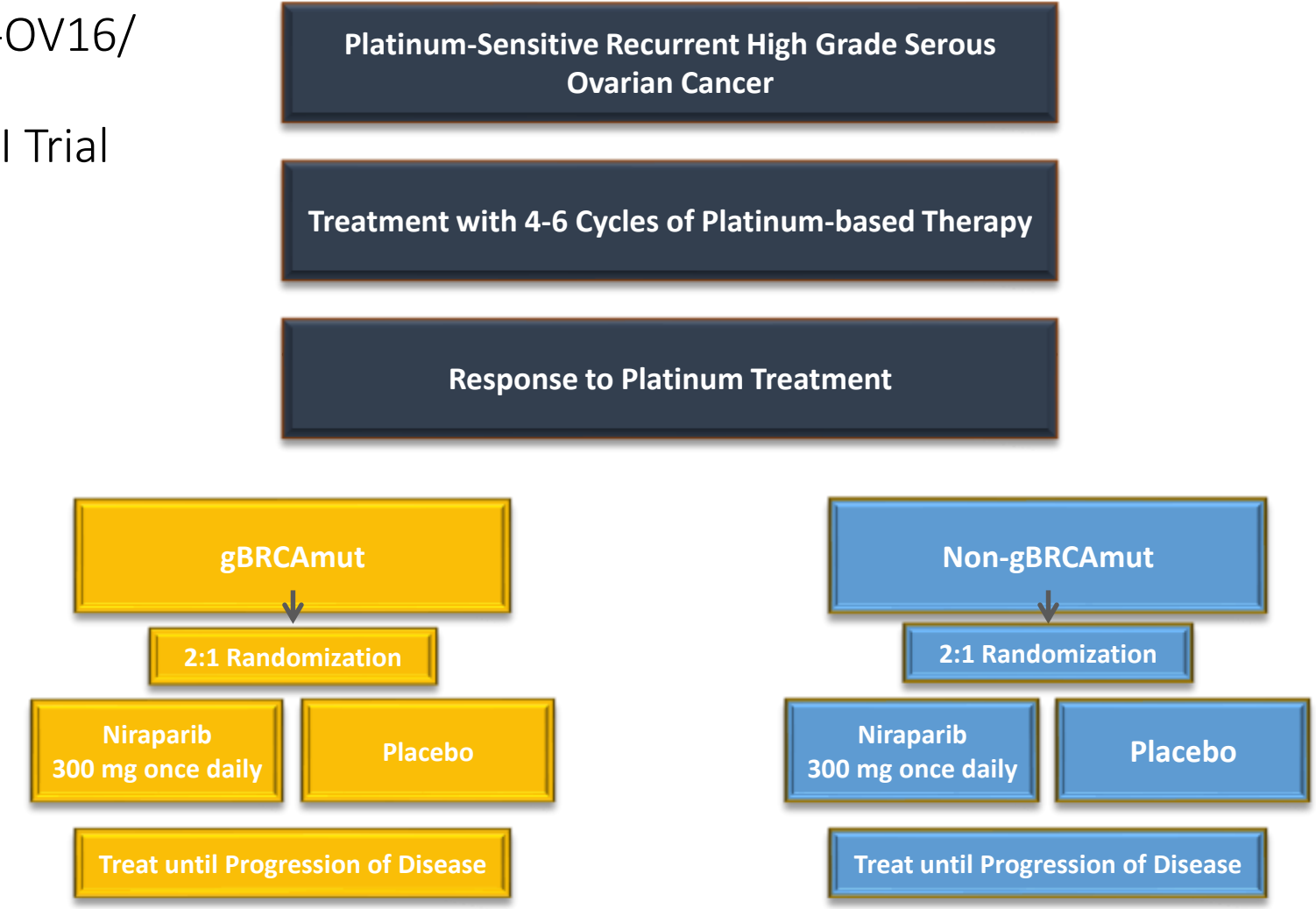
  - Platinum sensitivity correlates with HRD, and platinum-sensitive tumors are more responsive to PARP-inhibitors than platinum-resistant tumors[2-4]



Levine D. The Cancer Genome Atlas, 2011

1. Fong PC et al. J Clin Oncol 2010; 8(15):2512-9; 2. Matulonis UA et al. Ann Oncol. 2016 Jun;27(6):1013-9; 3. Liu JF et al. Gynecol Oncol. 2014 May;133(2):362-9 ; 4. Murai J et al. Cancer Res 2012;72:5588–5599.

ENGOT-OV16/ NOVA Phase III Trial

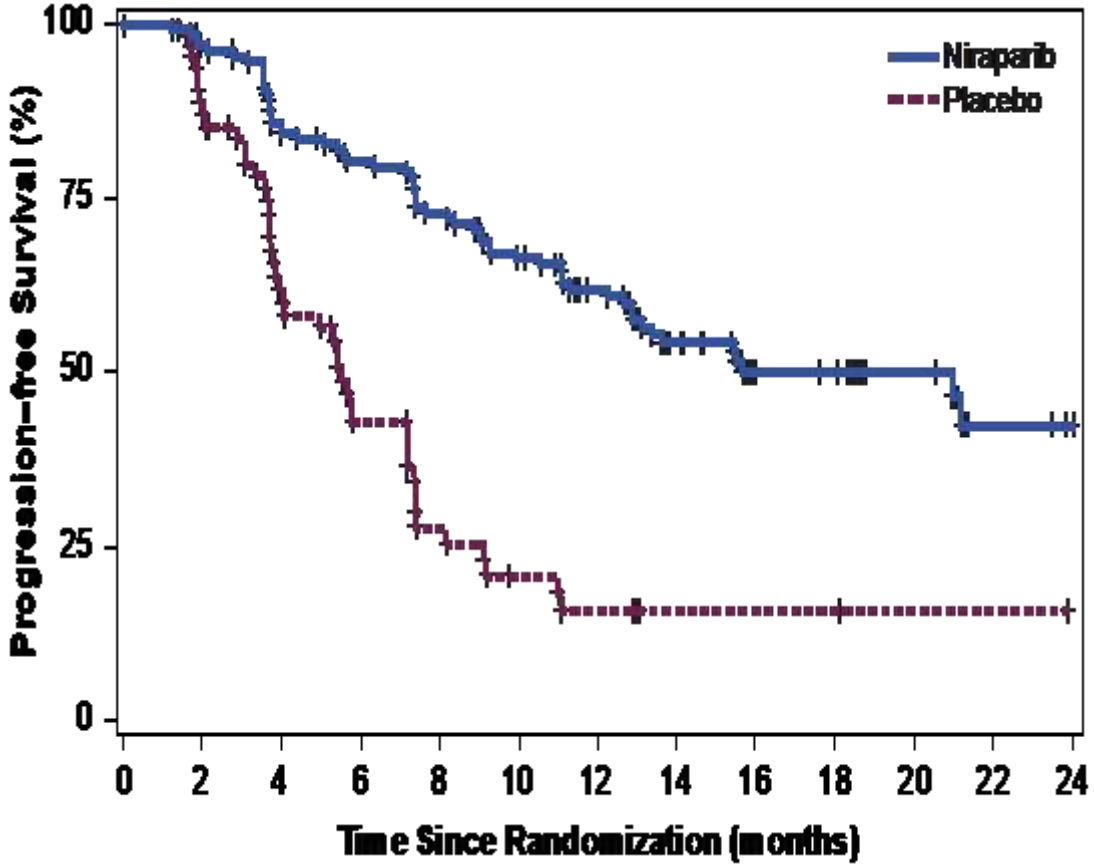


Patient Demographics & Baseline Characteristics

Characteristic	gBRCAmut		Non-gBRCAmut	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Age - years				
Median (min, max)	57.0 (36, 83)	58.0 (38, 73)	63.0 (33, 84)	60.5 (34, 82)
Region – n (%)				
USA and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
ECOG performance status – n (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Primary tumor site – n (%)				
Ovarian	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneal	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Lines of previous chemotherapy – n (%)				
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)

*One patient received one line of prior therapy.

Progression-free Survival: gBRCAmut

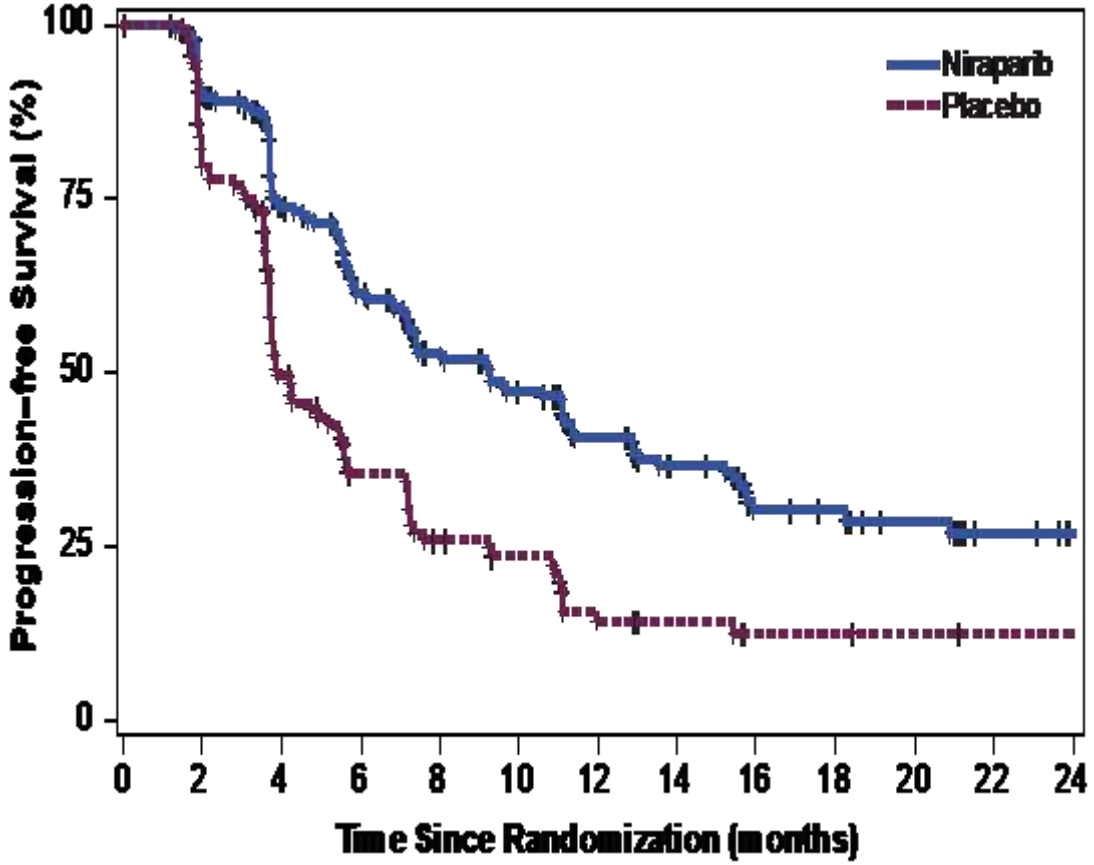


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	**21.0** (12.9, NR)	**0.27** (0.173, 0.410) p<0.0001	62%	**50%**
Placebo (N=65)	**5.5** (3.8, 7.2)		16%	16%

PFS was analyzed using a 2-sided log-rank test using randomization stratification factors, and summarized using the Kaplan-Meier methodology. Hazard ratios with 2-sided 95% confidence intervals were estimated using a stratified Cox proportional hazards model, with the stratification factors used in randomization.

NR=not reached

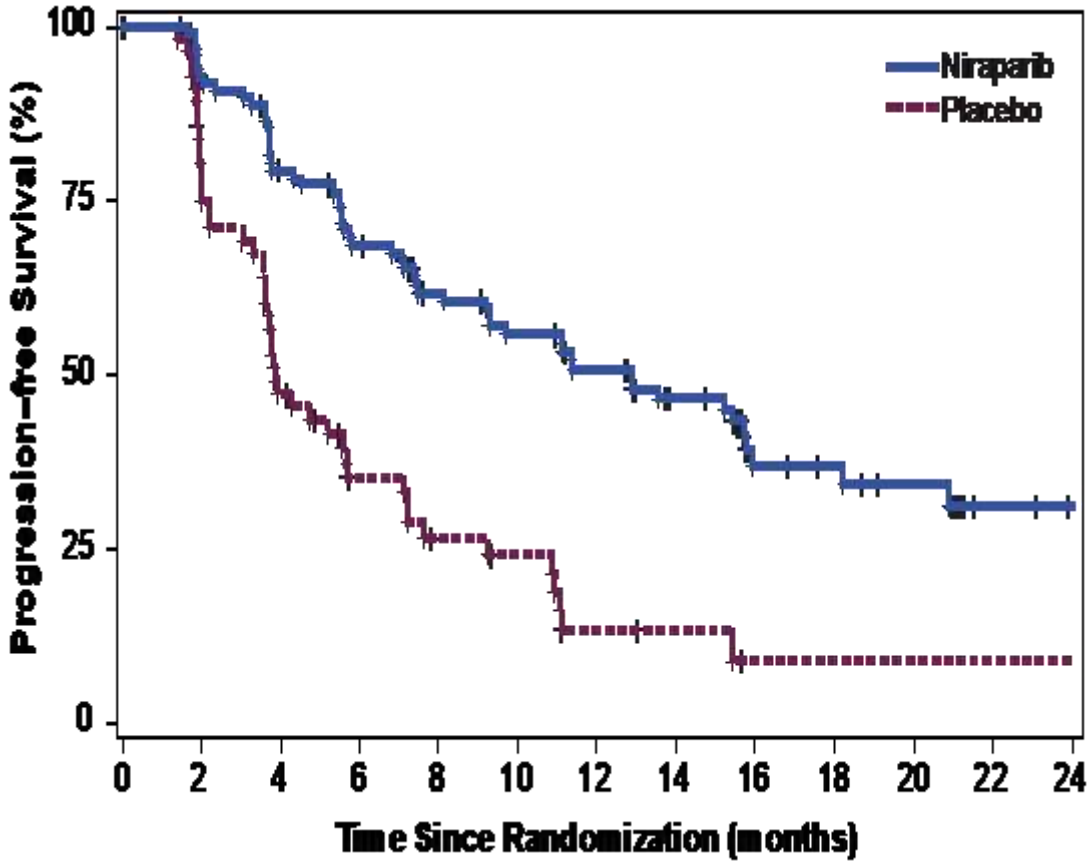
Progression-free Survival: Non-gBRCAmut



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%

PFS was analyzed using a 2-sided log-rank test using randomization stratification factors, and summarized using the Kaplan-Meier methodology. Hazard ratios with 2-sided 95% confidence intervals were estimated using a stratified Cox proportional hazards model, with the stratification factors used in randomization.

Progression-free Survival: Non-gBRCAmut HRDpos



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=106)	**12.9** (8.1, 15.9)	**0.38** (0.243, 0.586) p<0.0001	51%	**37%**
Placebo (N=56)	**3.8** (3.5, 5.7)		13%	9%

PFS was analyzed using a 2-sided log-rank test using randomization stratification factors, and summarized using the Kaplan-Meier methodology. Hazard ratios with 2-sided 95% confidence intervals were estimated using a stratified Cox proportional hazards model, with the stratification factors used in randomization.

PARP Inhibitors in Monotherapy in Advanced Ovarian Cancer: Study 10 and ARIEL2 (Rucaparib)

Safety Population (n = 377)

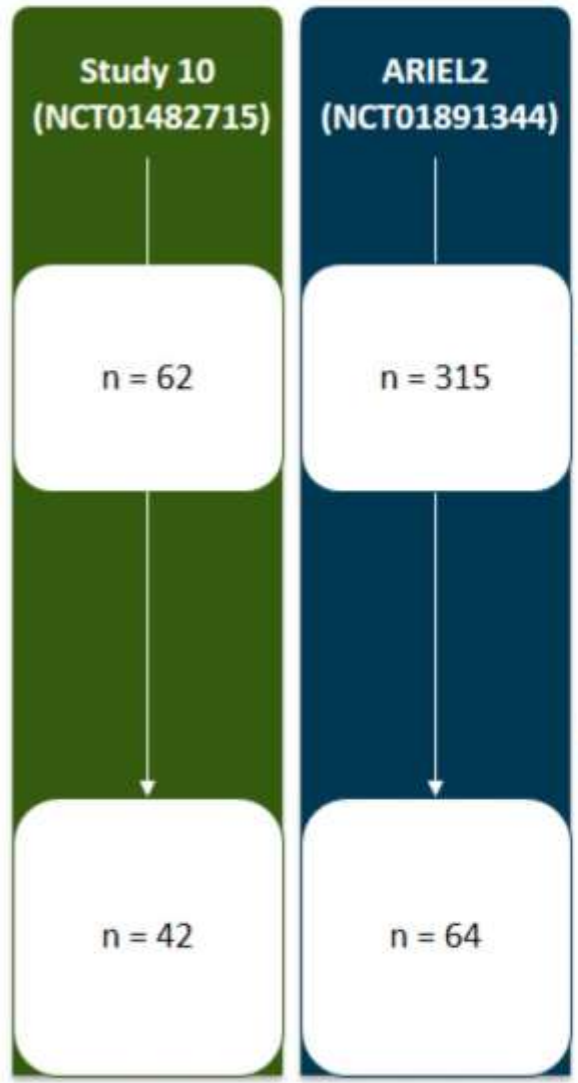
Criteria

- Diagnosis of ovarian cancer (inclusive of primary peritoneal and fallopian tube cancer)
- Enrolled at 600-mg twice daily dosing level and received ≥ 1 dose of rucaparib 600 mg

Efficacy Population (n = 106)

Criteria

- Received ≥ 2 prior chemotherapies, including ≥ 2 platinum-based regimens
- Had a deleterious g*BRCA* or somatic BRCA mutation
- Enrolled at 600-mg twice daily dosing level and received ≥ 1 dose of rucaparib 600 mg

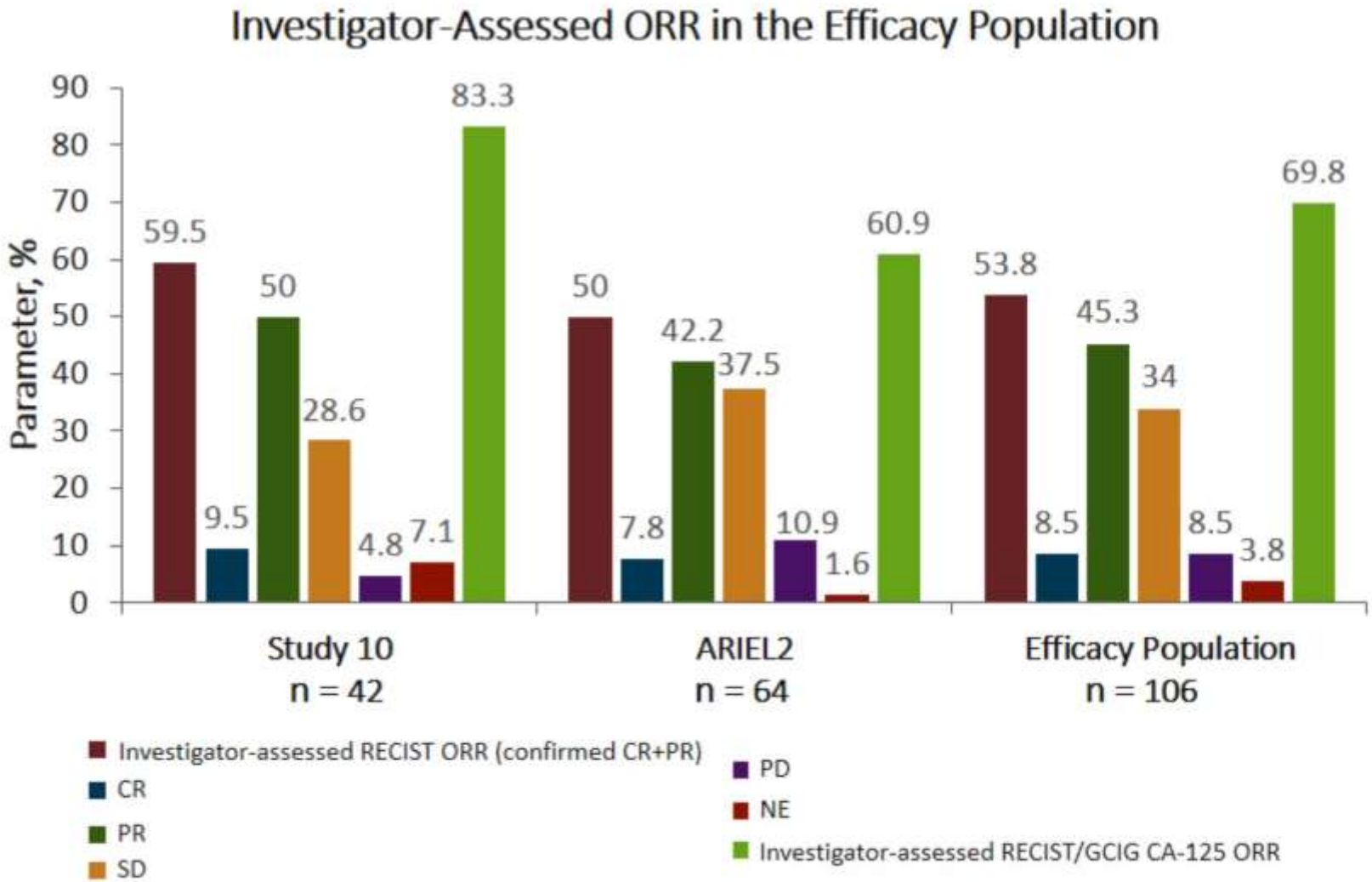


Efficacy Analysis Endpoints:

- **Primary outcome**: investigator-assessed ORR per RECIST v. 1.1
- **Secondary efficacy analyses:**
  - ✓ DOR
  - ✓ PFS

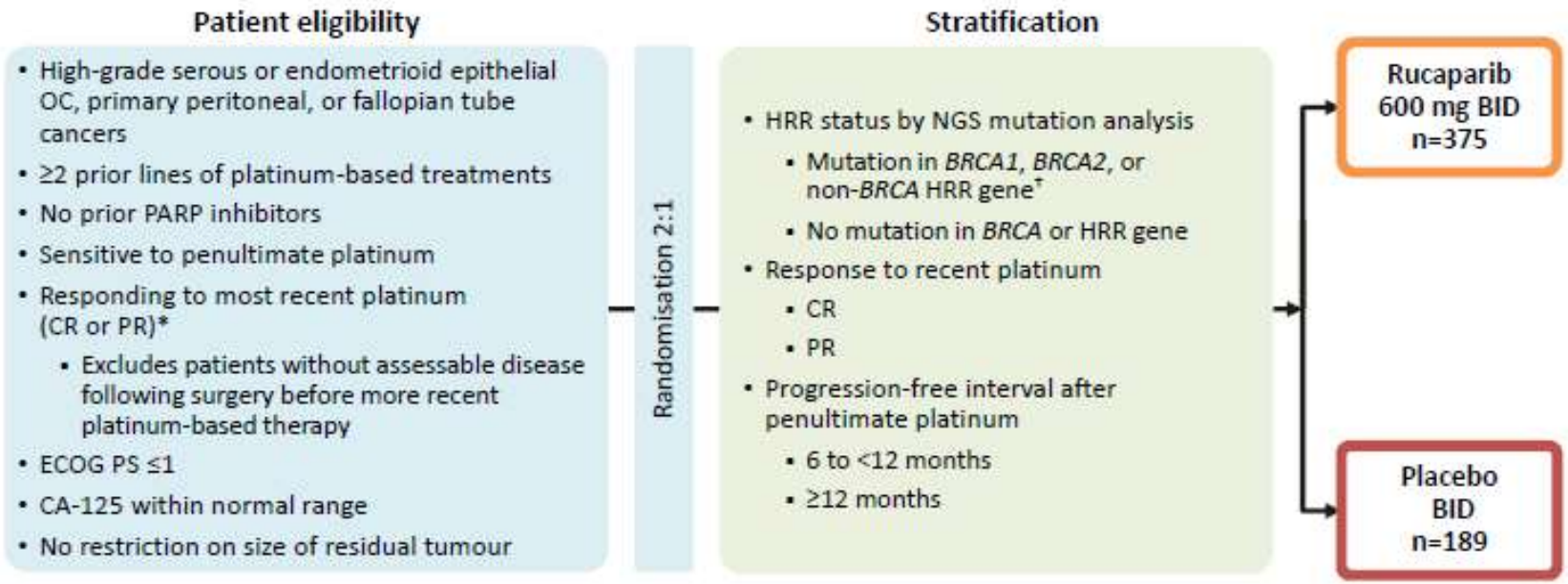
Oza AM, et al. *Gynecol Oncol*. 2017;147:267-275.

PARP Inhibitors in Monotherapy:
ORR in the Efficacy Population



Oza AM, et al. *Gynecol Oncol.* 2017;147:267-275.

ARIEL3: Study Design

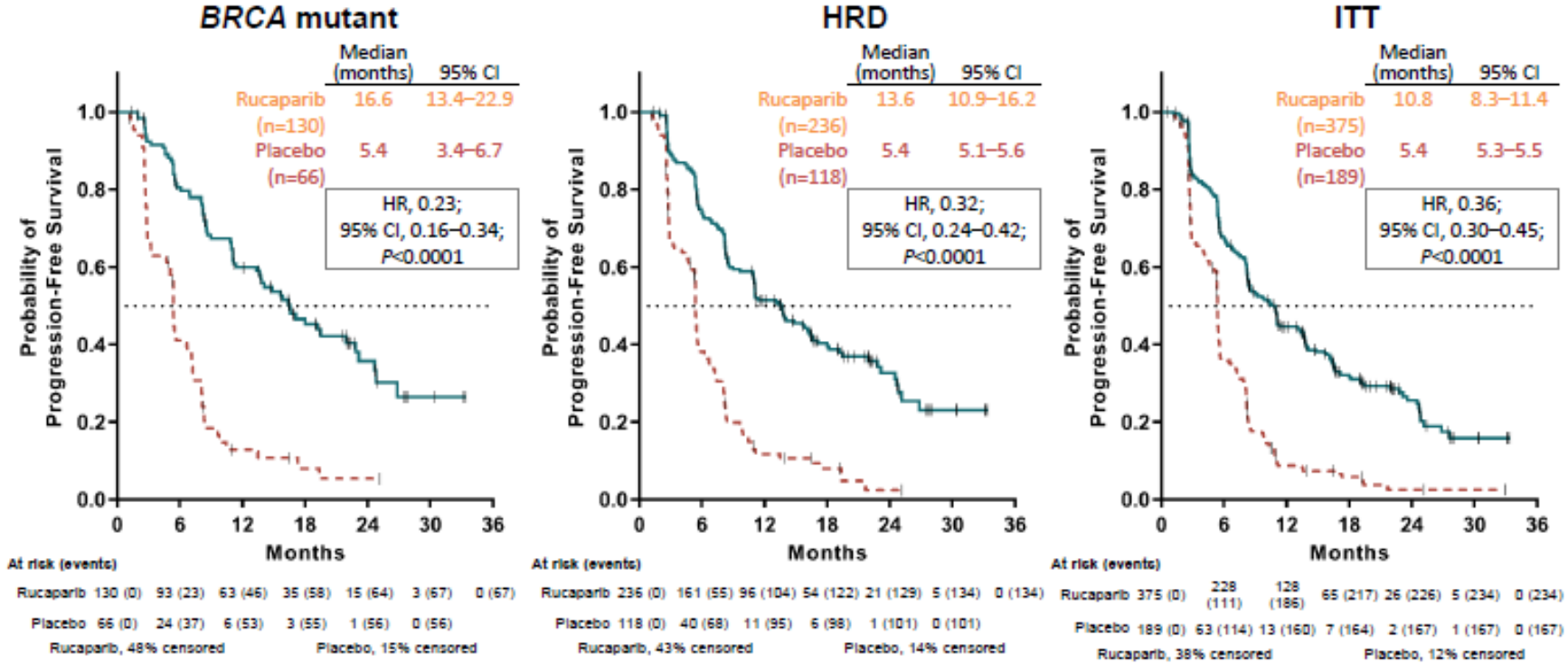


Primary endpoint: Investigator-assessed PFS (per RECIST)

*CR (defined by RECIST v1.1) or PR (defined by RECIST v1.1 and/or a GCIG CA-125 response [CA-125 within normal range]) maintained until entry to ARIEL3 (≤8 weeks of last dose of chemotherapy). †*ATM, ATR, ATRX, BARD1, BLM, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RPA1.* HRR, homologous recombination repair; NGS, next-generation sequencing.

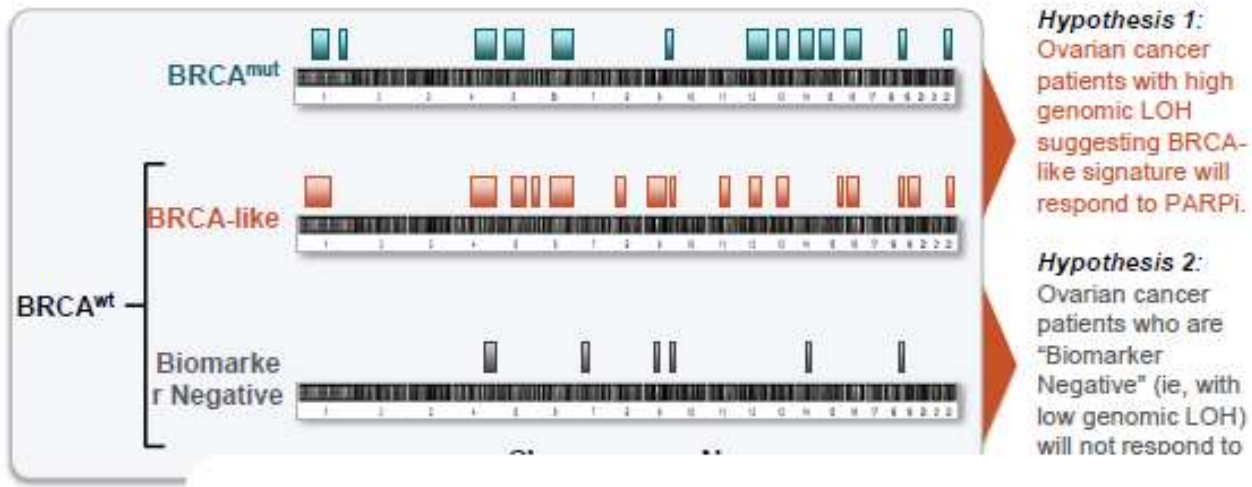
Ledermann et al.[6], ESMO 2016

ARIEL3: Investigator-Assessed Progression-Free Survival



Visit cutoff date: 15 April 2017.

HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling based on NGS



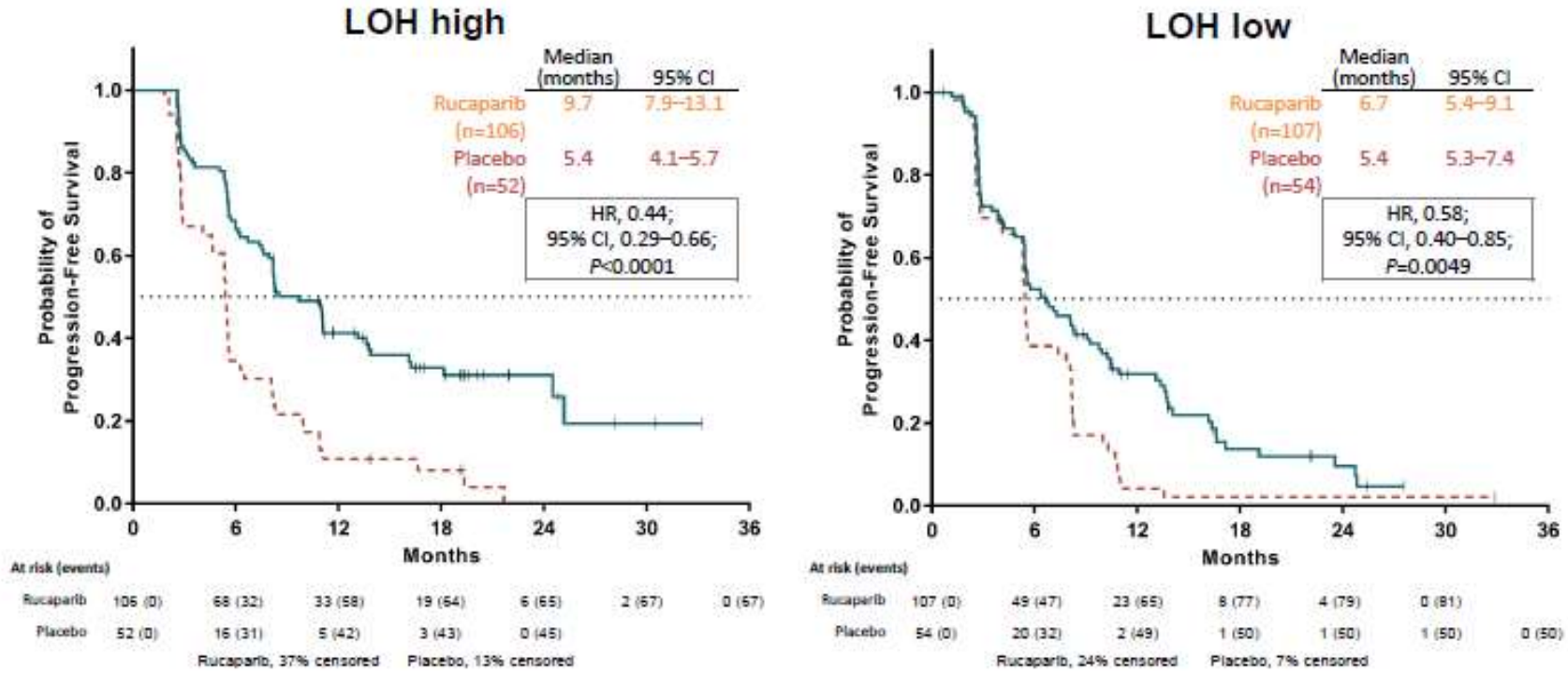
Hypothesis 1: Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to PARPi.

Hypothesis 2: Ovarian cancer patients who are "Biomarker Negative" (ie, with low genomic LOH) will not respond to

- Foundation Medicine's NGS-based comprehensive cancer genomic profiling assay sequences *BRCA1/2* genes in tumor-derived DNA
- The assay also sequences single-nucleotide polymorphisms (SNPs)
- SNP analysis identifies and quantifies genomic LOH

NGS=next-generation sequencing; mut=mutation; wt=wild type.

ARIEL3 Exploratory Analysis: Investigator-Assessed Progression-Free Survival in Patients with *BRCA* Wild-Type OC



Visit cutoff date: 15 April 2017.

Comparing the toxicity of PARP inhibitors

Adverse events of special interest – MDS/AML

Study 19 – 3 cases in 265 patients

- Two in the olaparib arm
- One in the placebo arm

NOVA – 7 cases in 367 patients

- Five in the niraparib arm
- Two in the placebo arm

ARIEL3 – 3 cases in 564 patients

- Three in the rucaparib arm
- Zero in the placebo arm

GI toxicities are common with all PARP inhibitors (% pts)

Toxicities	Grade of Tox	Olaparib [1]	Rucaparib[2]	Niraparib[3]
Nausea	All Grades	64	77	73.6
	Grade 3 and 4	3	5	3.0
Constipation	All	20.6[5]	40	39.8
	Grades 3 and 4	0	2	0.5
Vomiting	All	43	46	34.3
	Grades 3 and 4	4	4	1.9
Decreased appetite	All	22	39	25.3
	Grades 3 and 4	1	3	0.3
Abdominal pain	All	43	32	22.6
	Grades 3 and 4	8	3	1.1
Diarrhea	All	31	34	19.1
	Grades 3 and 4	1	2	0.3
Dyspepsia	All	25	10[4]	11.4
	Grades 3 and 4	0	<1%	0
Dysgeusia	All	21[5]	39	10.1
	Grades 3 and 4	0	0.3	0

Slide courtesy of Ursula Matulonis MD

[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016, [4]Swisher Lancet Onc 2016, [5]Ledermann Lancet Oncology 2014

Presented By Kathleen Moore at 2017 ASCO Annual Meeting

Hematologic toxicities

(% of pts)

Toxicities	Grade of Tox	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Decrease in hemoglobin	All Grades	90	67	50.1
	Grade 3 and 4	15	23	25.3
Decrease in platelets	All	30	39	61.3
	Grades 3 and 4	3	6	33.8
Decrease in neutrophil count	All	25	35	30.2
	Grades 3 and 4	7	10	19.6

Slide courtesy of Ursula Matulonis MD

[1]FDA package insert, [2]FDA package insert, [3]NOVA NEJM 2016

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Presented By Kathleen Moore at 2017 ASCO Annual Meeting

Additional toxicities that appear to differ between agents

(% of pts)

Toxicities	Grade of Tox	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Increased Creatinine	All	30	92%	NR
	Grades 3 and 4	2	1	NR
Elevated ALT	All	NR	74%	NR
	Grades 3 and 4	NR	13%	NR
Elevated AST	All	NR	73%	NR
	Grades 3 and 4	NR	5%	NR
Hypertension	All	NR	NR	19.3%
	Grades 3 and 4	NR	NR	8.2%
Nasopharyngitis/URI	All	26	10[4]	11.2
	Grades 3 and 4	0	0[4]	0
Dypsnea	All	NR	21	19.3
	Grades 3 and 4	NR	0.5	1.1
Palpitations	All	NR	NR	10.4
	Grades 3 and 4	NR	NR	0

Slide courtesy of Ursula Matulonis MD

[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016, [4]Swisher Lancet Onc 2016
[5]Ledermann Lancet Oncology 2014

ing

Dose Modifications

	Olaparib (%)	Placebo (%)	Niraparib (%)	Placebo (%)	Rucaparib (%)	Placebo (%)
Interruption rate	45	18	69	5.0	64	10
Dose reduction rate	25	3	66	14.5	55	4
Discontinuation rate	11	2	15	2.2	13	2
Anaemia*			1.4	0		
Neutropenia*			1.9	0		
Thrombocytopenia*			3.3	0.6		

*Cause of discontinuation not reported specifically for rucaparib or olaparib

Pujade-Lauraine E, et al. *Lancet Oncol.* 2017;18(9):1274-1284. Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-2164.
Coleman RL, et al. *Lancet.* 2017 Sep 12. [Epub ahead of print].

SIDE EFFECT MANAGEMENT

- Most severe toxicity within first 3 cycles
  - Non-haematological symptoms often subsequently abate
- Management of AE common to all PARPi:
  - Symptomatic management
    - Fatigue – rest
    - Nausea, vomiting – regular antiemetics, take tablets with food
    - Bowel disturbance – laxatives or anti-diarrhea meds, dietary
    - Anaemia – blood transfusion, dietary
  - Dose interruption
    - If cumulative toxicity not responding adequately to supportive meds
    - Rechallenge at same dose
  - Dose reduction
    - If on rechallenge. further intolerable toxicity
- Management of PARPi-specific AE:
  - Rucaparib-related increase in transaminases – usually transient and resolves on maintained dose
  - Niraparib-related hypertension – be aware and monitor, treat as required
  - Niraparib-related myelosuppression – thrombocytopenia risk most marked in first month

TREATMENT MONITORING

- In general:
  - Baseline bloods, fortnightly for 2 months, every 4 weeks for 3-4 months extending to every 2 months, if stable
  - Baseline CT TAP, around 3 months for first assessment, then ad hoc if Ca125 remains controlled
  - Niraparib is different during cycle 1, requiring weekly bloods to monitor platelets
- Indicators for dose reduction in clinical practice:
  - Most commonly anaemia or multifactorial abnormal lab results
  - Fatigue, nausea, bowel disturbance (if drug) tend to settle with time or symptomatic management; rarely lead to dose reduction
  - Raised transaminases (rucaparib), creatinine changes (rucaparib and olaparib) and hypertension (niraparib) rarely need dose reduction
- Long-term considerations:
  - Myelodysplasia, haematological malignancy
  - Evidence so far is that risks in treatment vs placebo arms are no different for all three PARPi

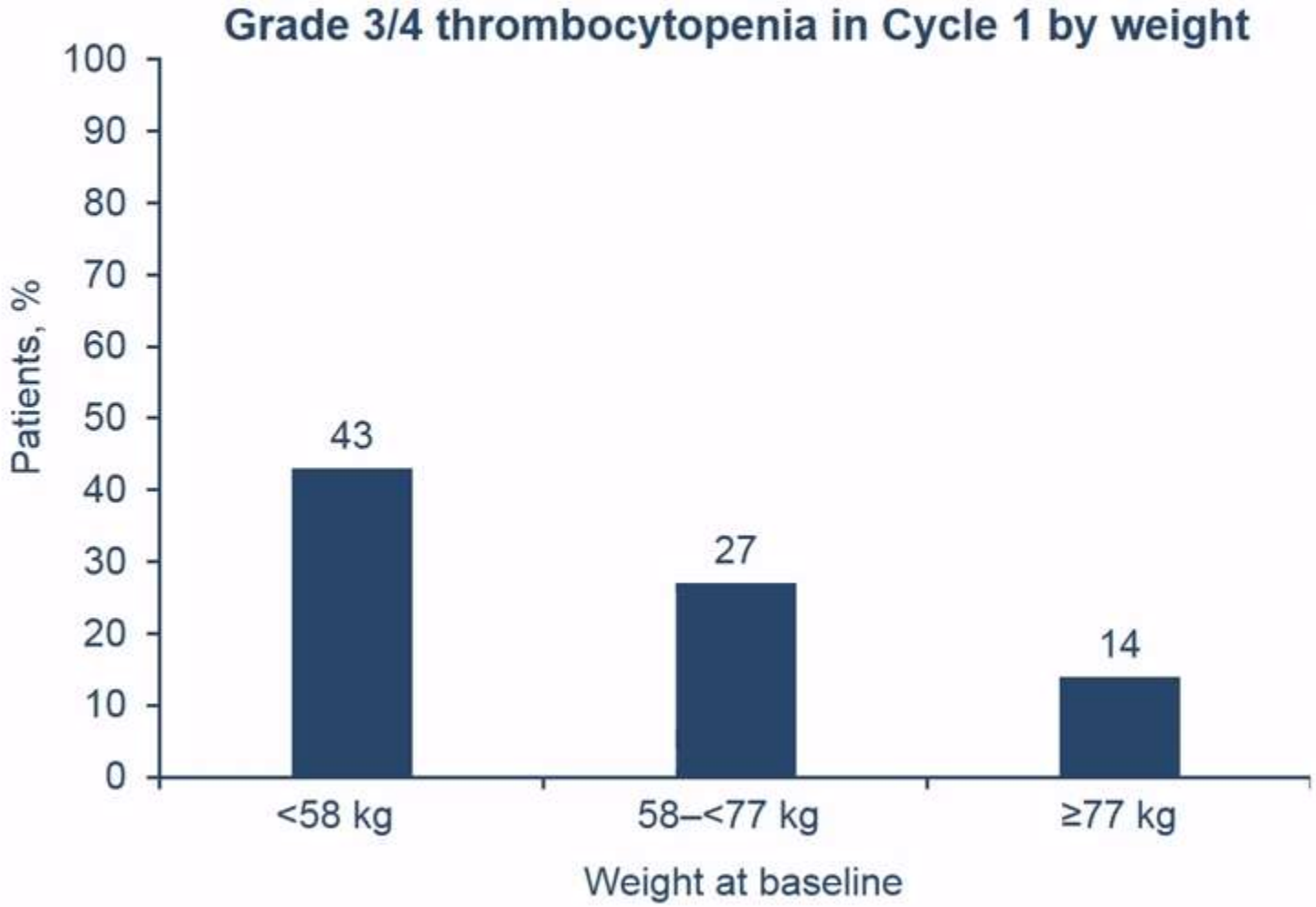
Evaluation of Predictors for Early Dose Modification

- A retrospective exploratory multivariate analysis of the ENGOT-OV16 / NOVA trial **identified a subset of patients who will require rapid dose modifications**
- **Body weight and baseline platelet counts** were identified as the two most significant predictors of early dose modification
- No other factors appeared to be significant predictors of early dose modification

TEAE=treatment-emergent adverse events; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ALP=alkaline phosphatase; LDH=lactate dehydrogenase
TESARO Inc., Data on File.

Weight at baseline is a predictive factor

TESARO
ESGO 2017
SATELLITE SYMPOSIUM



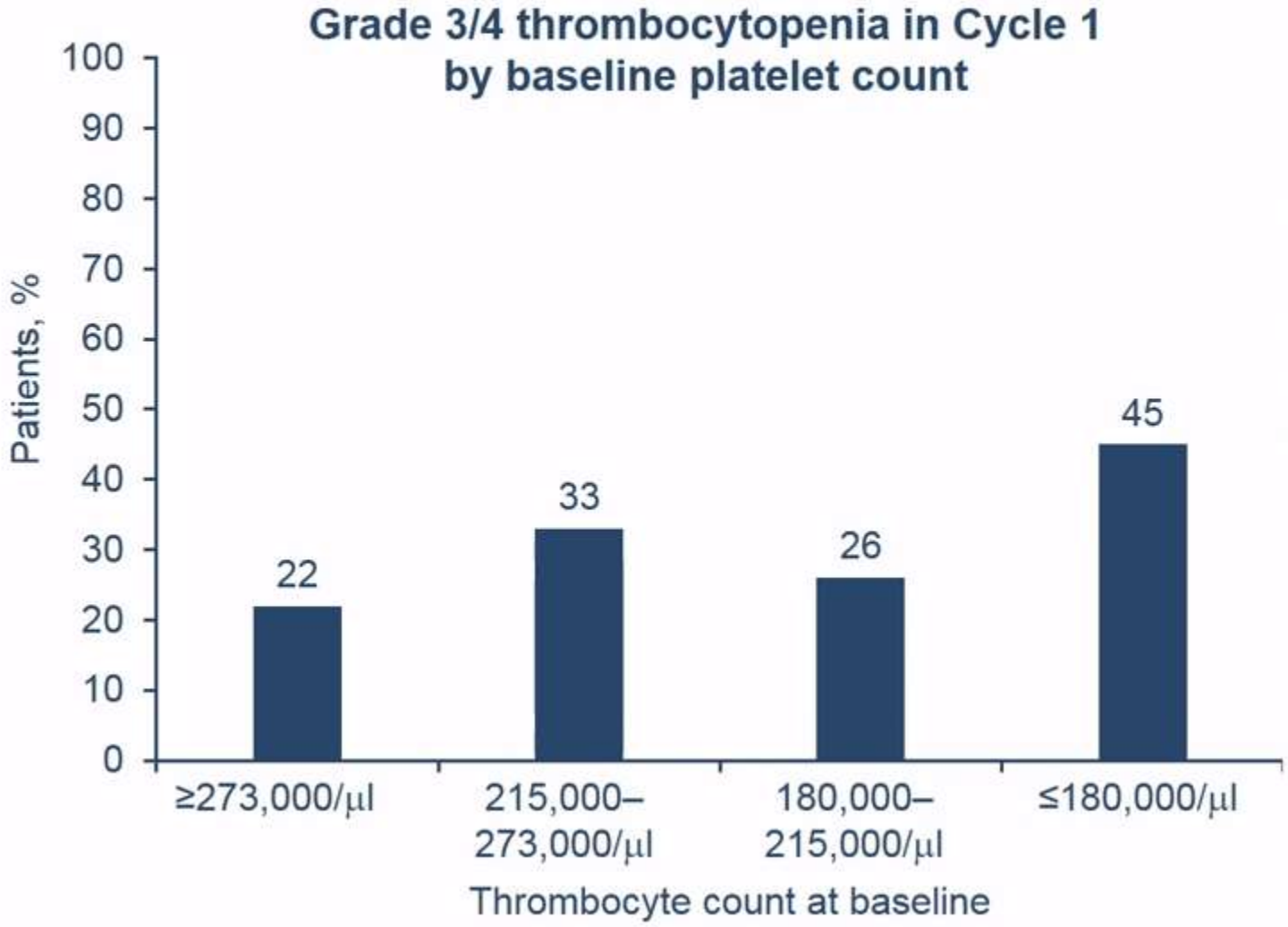
Weight groups were defined by quartiles with 25% of patients being <58 kg and 25% of patients having a weight at baseline of ≥77 kg

TESARO Inc., Data on File.

TESARO

Baseline thrombocyte count is a second predictive factor

TESARO
ESGO 2017
SATELLITE SYMPOSIUM



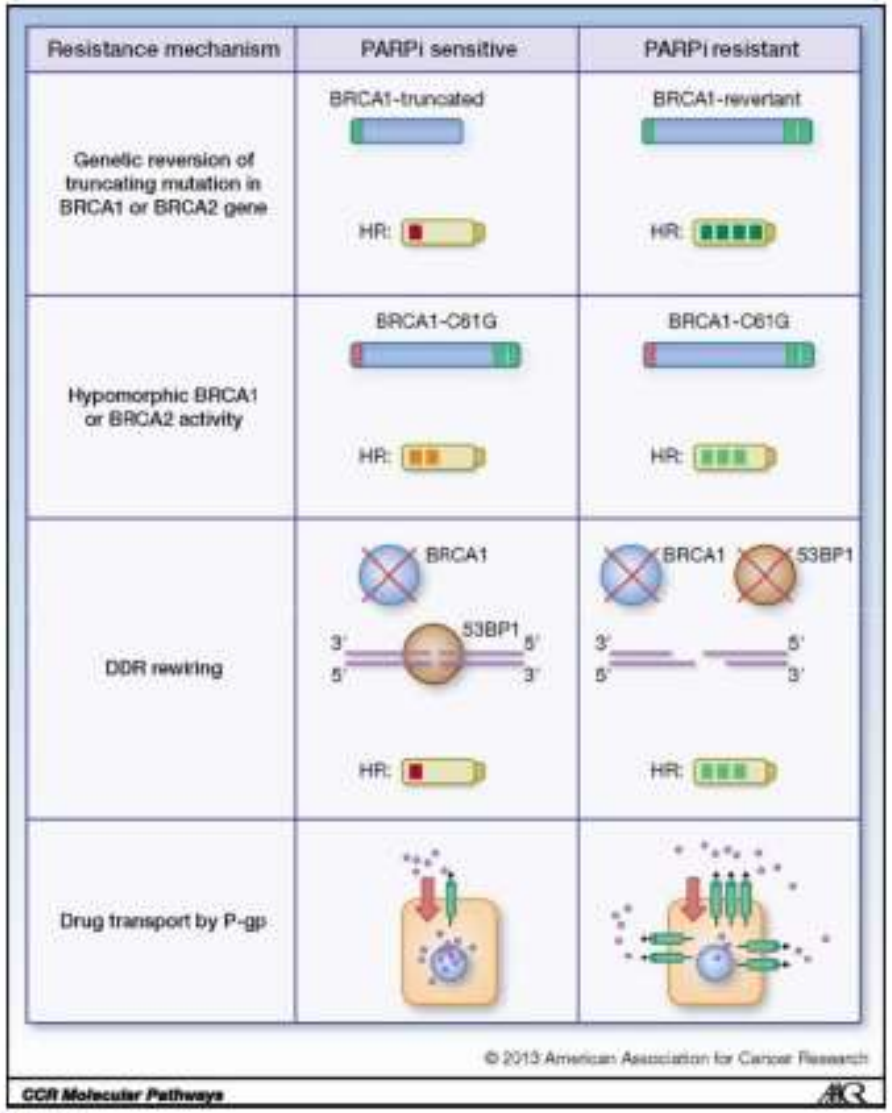
Groups were defined by quartiles, indicating that patients with lowest thrombocyte count at baseline have the highest risk to develop thrombocytopenia during Cycle 1

TESARO Inc., Data on File.

TESARO

Resistence to PARP inhibitors

Mechanisms of Resistance to PARP Inhibitors



Bouwman P, et al. *Clin Cancer Res*. 2014;20(3):540-547.

Mechanisms of PARPi resistance

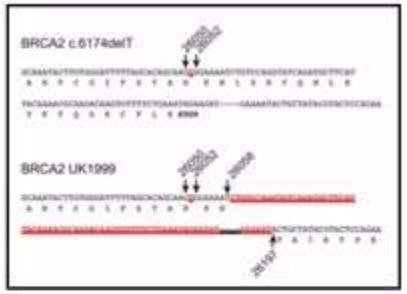
Primary/Acquired PARP inhibitor resistance

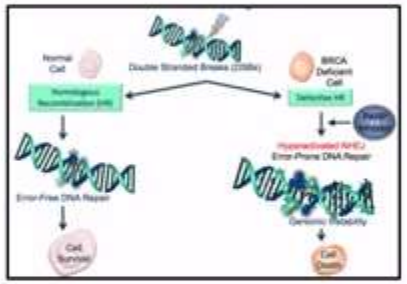
Intrinsic resistance

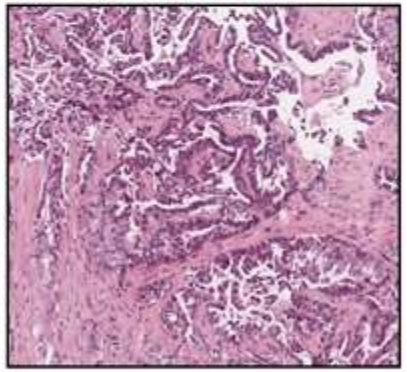
- DNA repair defect reversion
  - Mutation reversion – *BRCA1*, *RAD51C/D*
  - Methylation reversion – *BRCA1*, *RAD51C*
  - DNA repair pathway reversion - NHEJ loss
  - Structural reversion – *BRCA1* 5095C>T R1699 destabilizes the BRCT fold
- Oncogene-driven
  - CCNE1/CYCLIN E over-expression

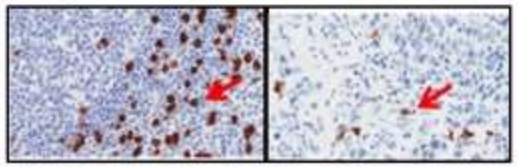
Extrinsic resistance

- Neo-angiogenesis
- Stromal reversion
- Immune reversion
  - Immune “switch”, improve cytotoxic T: Treg ratio

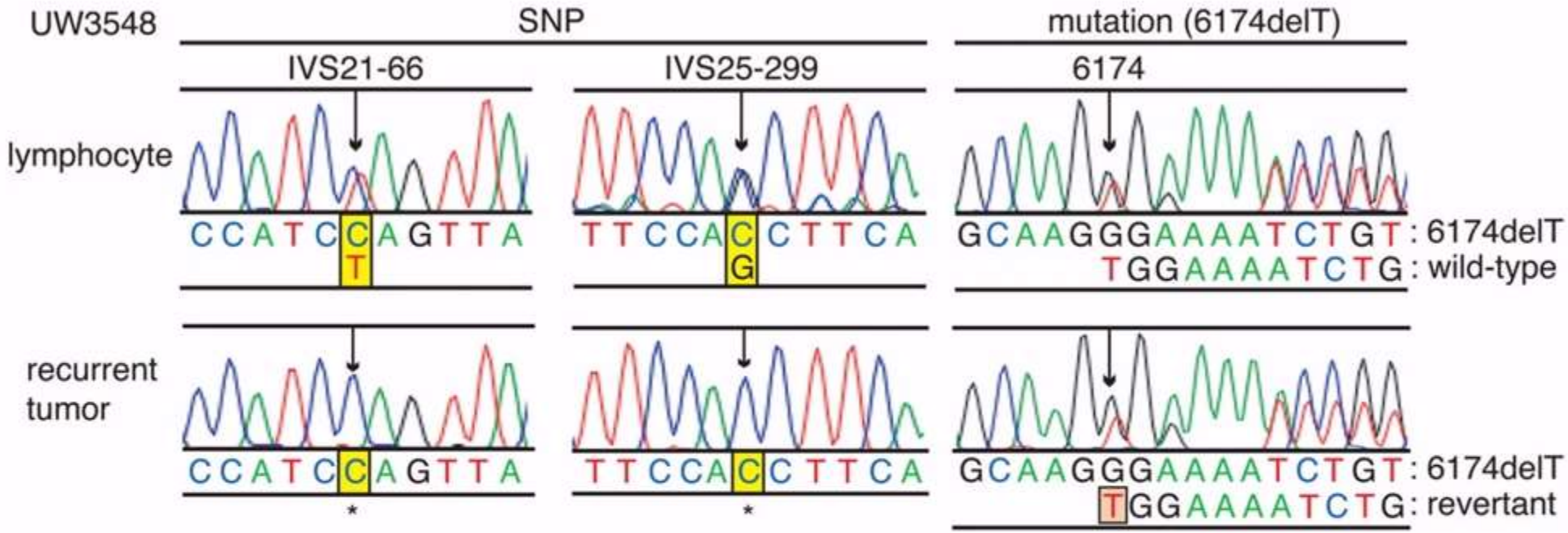








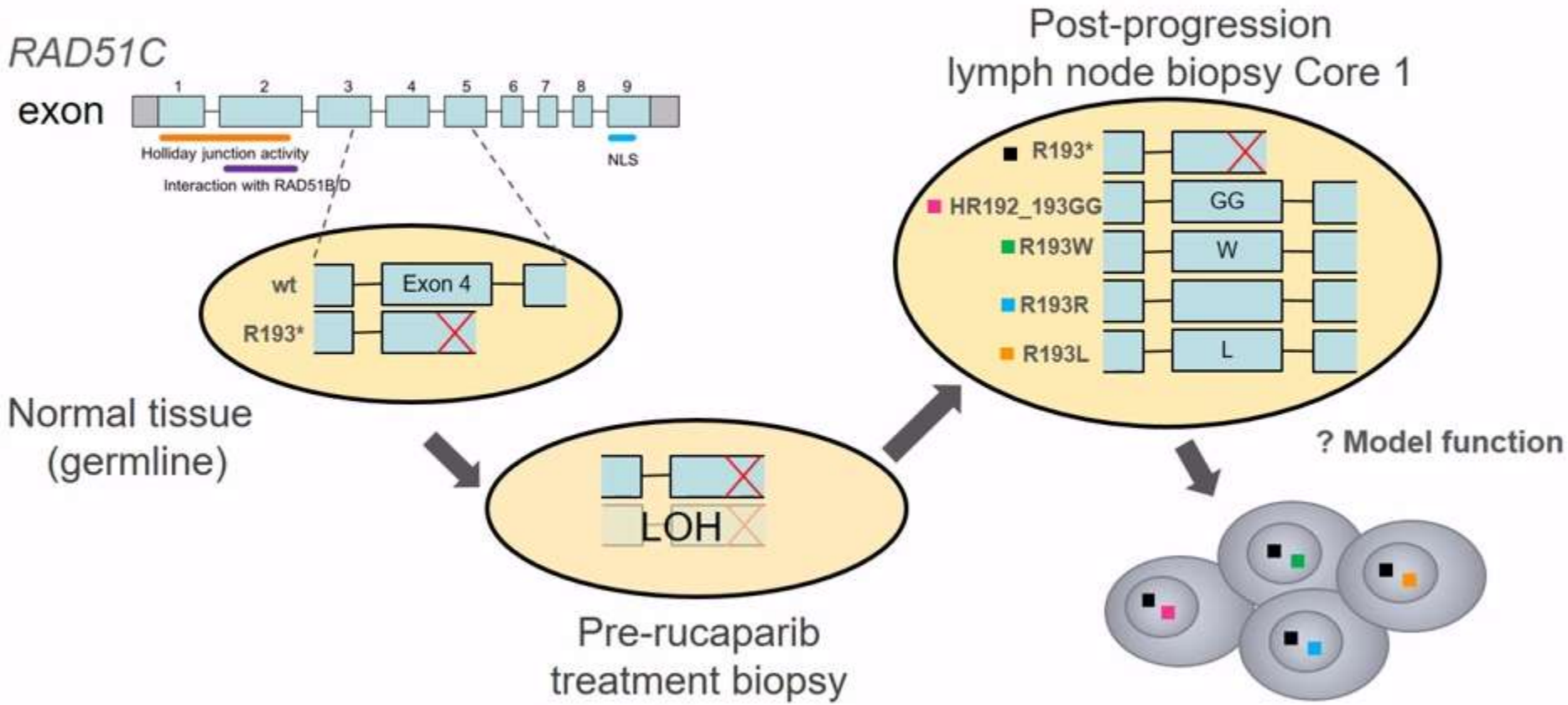
Mutation “reversion”: secondary mutations



Secondary mutations were found in cell lines and tumor samples in *BRCA1* or *BRCA2*
Rare event at diagnosis of OC, only found with prior treatment for breast cancer
Platinum or PARPi pressure: drives genomic instability post-treatment

Sakai et al Nature 2008; Edwards et al., Nature 2008; Norquist et al., JCO, 2011

Multiple secondary mutations indicate tumour heterogeneity?



Stromal impact on PARPi response

- Stromal factors: CTGF antagonism enhances chemotherapy response

Neesse A, Proc Natl Acad Sci USA 2013;

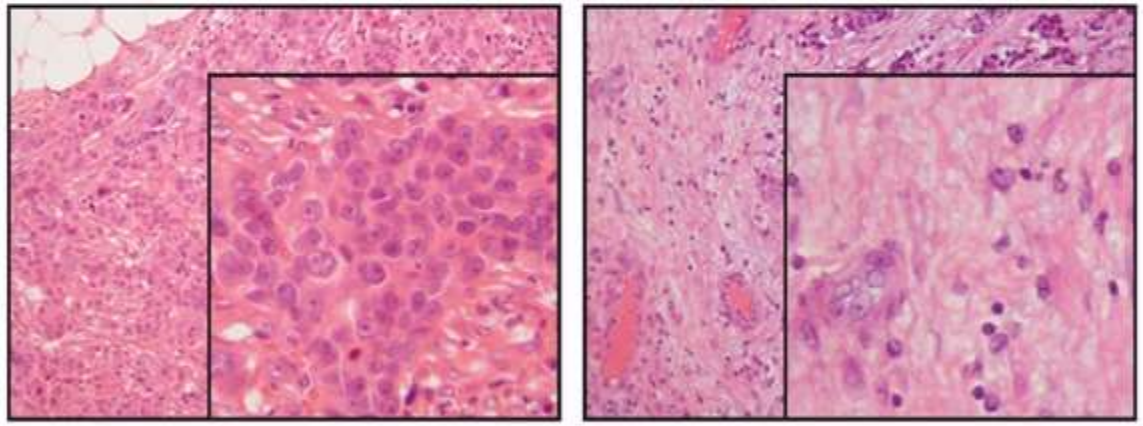
Mesenchymal C1
Immunoreactive C2
Differentiated C4
Proliferative C5

Tothill C1 stromal/desmoplastic/mesenchymal type
"High levels of reactive tumor stroma"

Stroma:
The cause of a
"C1 switch"

Anti-immunogenic

AOCS-139



Primary - omentum

"C2" immune high
Good prognosis

Autopsy - omentum

"C1" stromal
Poor prognosis

David Bowtell, Petermac; **Tothill et al Clin Ca Res 2008; Patch et al, Nature May 2015**

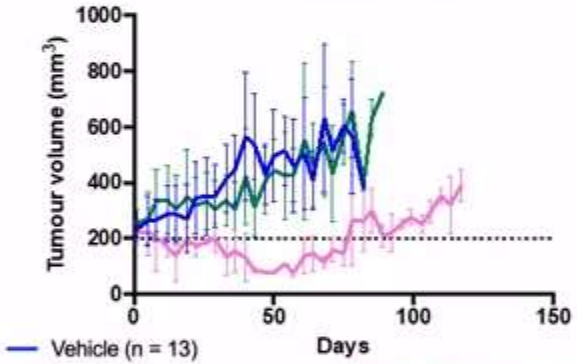
Stromal impact on PARPi response

Mesenchymal C1
Immunoreactive C2
Differentiated C4
Proliferative C5

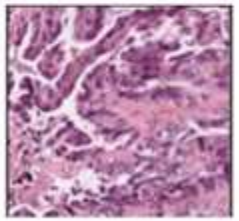
Tothill C1 stromal/desmoplastic/mesenchymal type
"High levels of reactive tumor stroma"

Time to PDX relapse: shorter

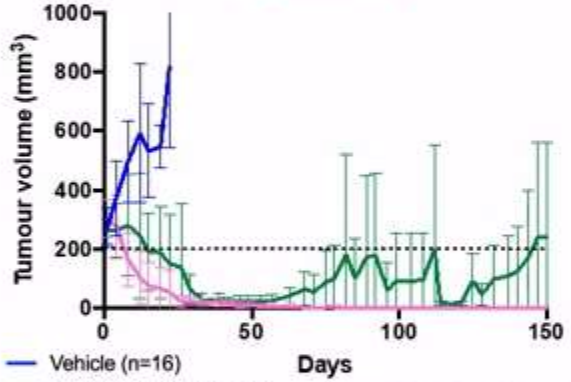
PDX #13



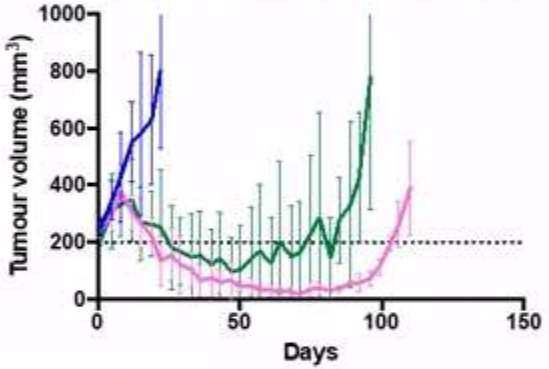
C1 subtype
CTGF high



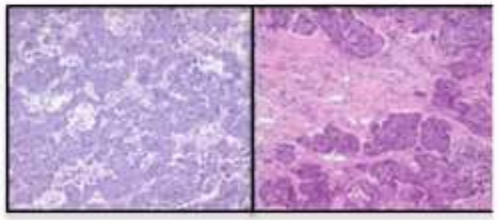
PDX #19



PDX #19B 1st relapse in Pt



C1 subtype
CTGF low



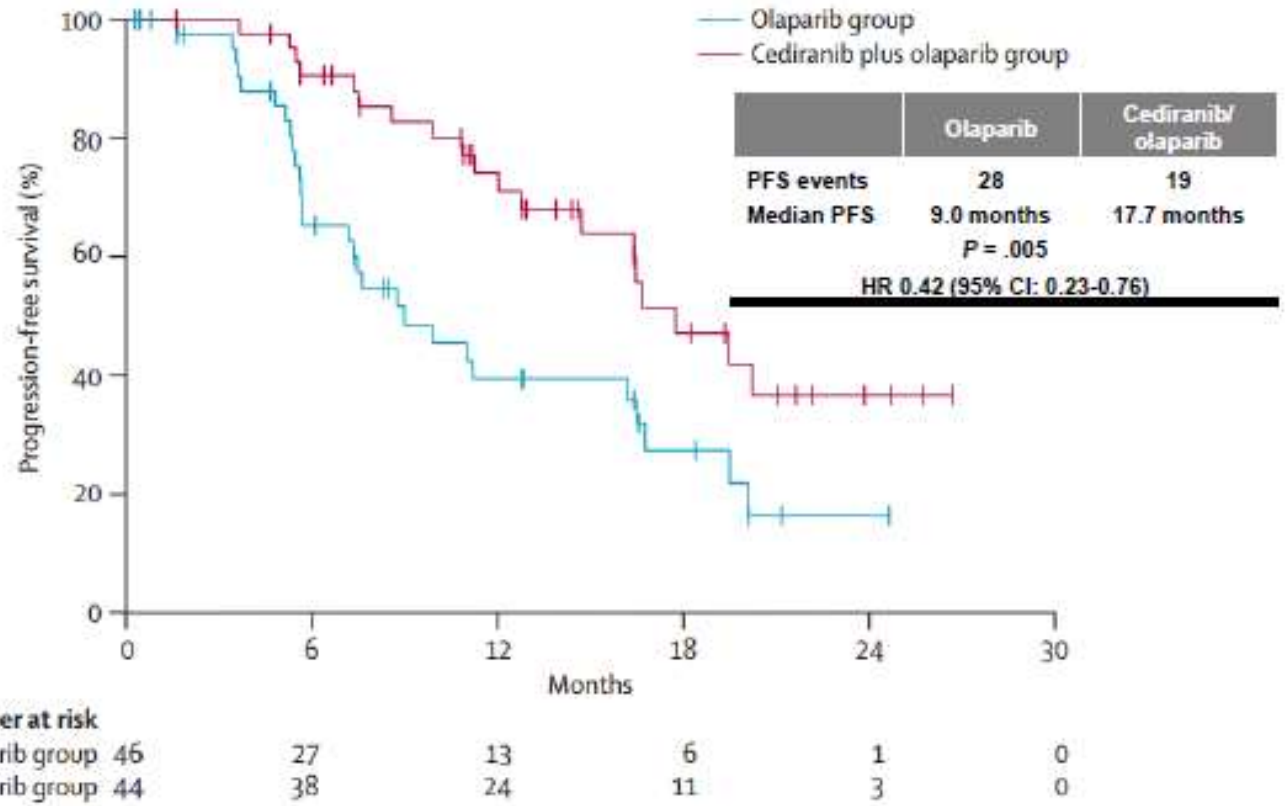
Desmoplasia more obvious upon relapse

THE FUTURE OF PARP INHIBITOR

Antiangiogenesis and PARP Inhibition: Rationale

- **Chronic hypoxia induces down-regulation of *BRCA1* and *RAD51*, and decreases homologous recombination in cancer cells**
- **Anti-VEGF induces hypoxia in the tumor microenvironment, which contributes to genomic instability and increased sensitivity of cells to PARP inhibition**

Cediranib/Olaparib Significantly Increased PFS Compared to Olaparib Alone in Platinum-Sensitive Recurrent Ovarian Cancer

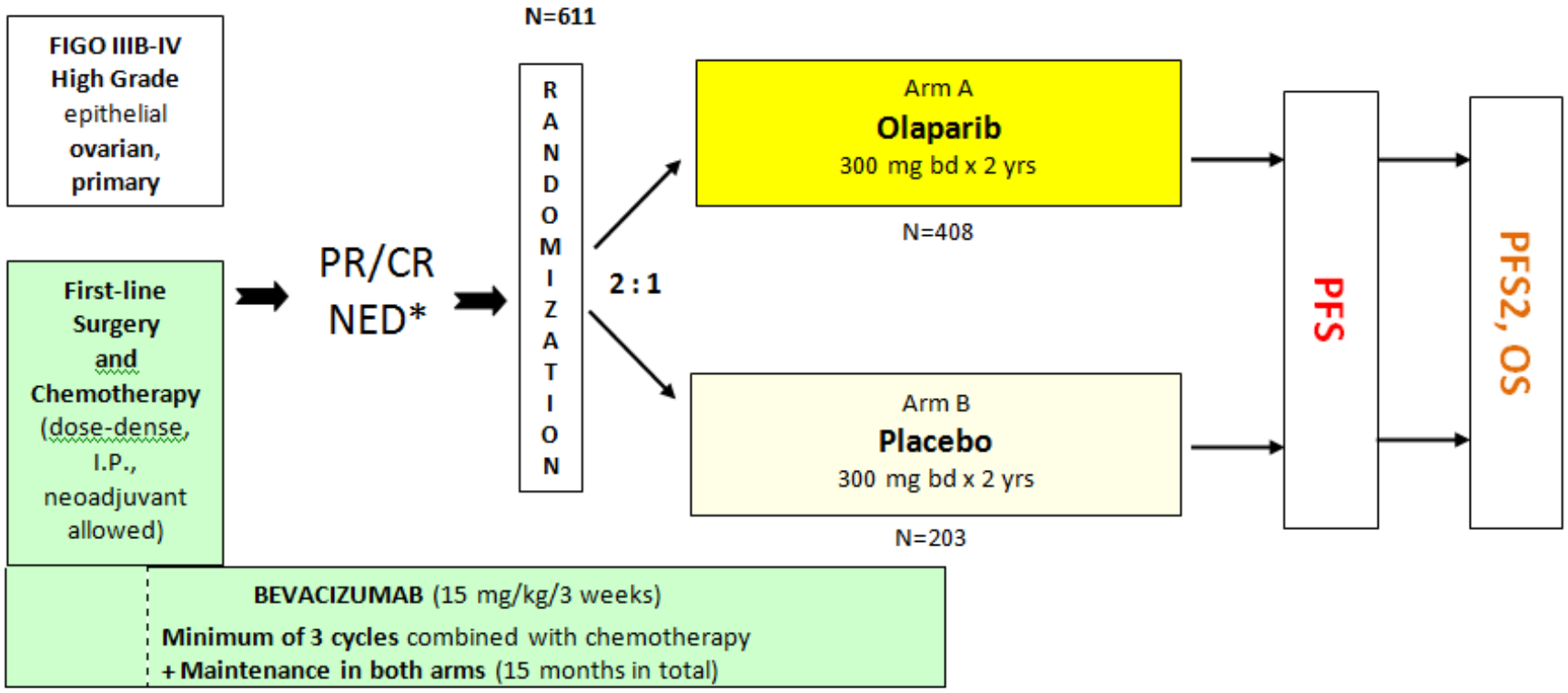


	Olaparib	Cediranib/ olaparib
PFS events	28	19
Median PFS	9.0 months	17.7 months
	P = .005	
	HR 0.42 (95% CI: 0.23-0.76)	

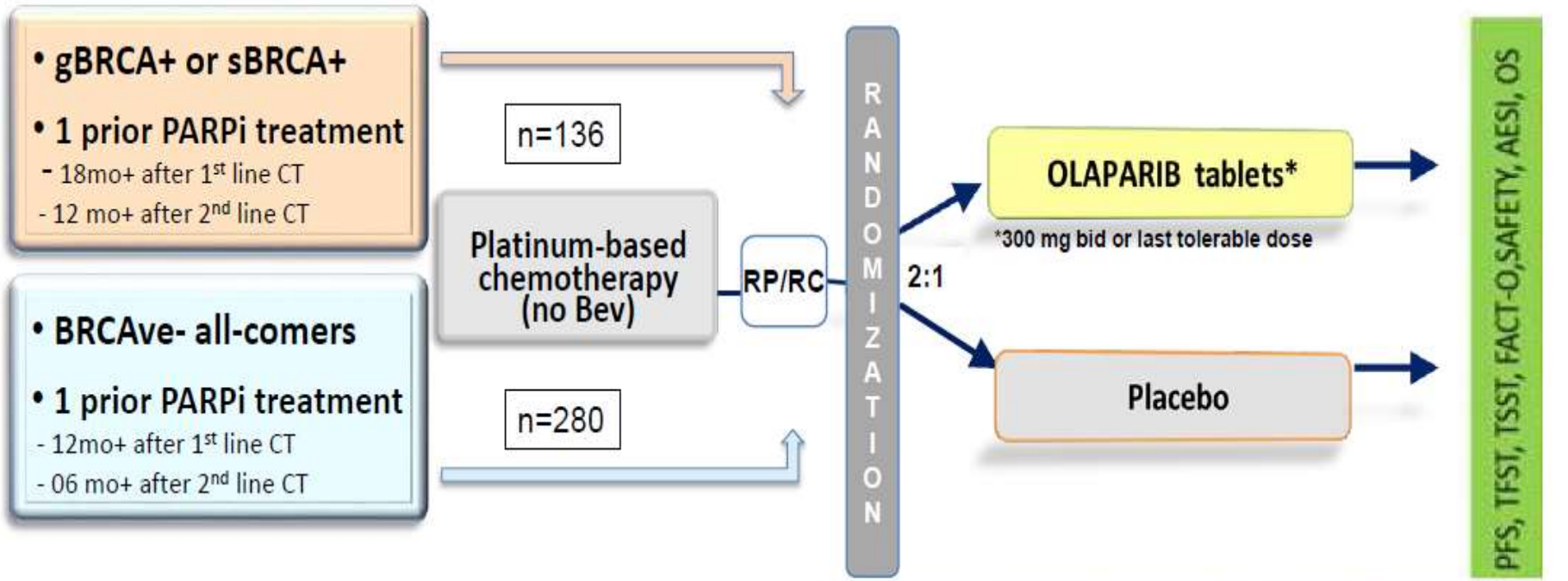
Tentori L, et al. *Eur J Cancer.* 2007;43(14):2124-2133.

Liu J, et al. *Lancet Oncol.* 2014;15(11):1207-1214.

Olaparib in first line: PAOLA 1 study design



OReO Study: Olaparib Retreatment in Platinum-Sensitive Ovarian Cancer



Stratification factors

- Prior bevacizumab
- <3 vs ≥3 chemo lines

Powered 80% for PFS primary endpoint. BRCA+ HR=0.5, 74 events. BRCA- HR=0.65, 191 events. Patients followed to OS for long term safety

Rationale for PARPi With Immune Checkpoint Inhibitors

- Hypermutable states
  - *BRCA*-mutant (somatic/germline) have high intrinsic LOH
  - High-grade serous ovarian cancer has a hypermutable genotype in a proportion of patients
  - PARPi can induce a hypermutable state
- All increase potential for neoantigens potentially amenable to PD-1/L1 targeting
- PARPi synergy may vary by PARPi and checkpoint inhibitor

PARPi Therapy +immune checkpoint inhibitors in Recurrent OC

Treatment	Study	Condition	Primary Outcome
Niraparib + pembrolizumab	NCT02657889	Adv TNBC or recurrent EOC	DLT RR
Durvalumab + cediranib or olaparib	NCT02484404	Adv solid tumors or recurrent EOC	Recommended dose ORR
Olaparib + tremelimumab	NCT02571725	Recurrent *BRCA*m EOC	Recommended dose, ORR
Tremelimumab ± olaparib	NCT02485990	Recurrent/ persistent EOC	Safety

Conclusions

- PARP Inibitors are a great opportunity for our patients
- The information about BRCA mutation is very important for the patients and their family
- We have many things to learn about the Parp Inhibitors…