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CON IL PATROCINIO DI

SIOG

SIGO

PARP inhibitors in the treatment of advanced ovarian cancer: *literature analysis and comparative clinical studies*

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Disclosures

- Advisory Boards and Lecture Fees: AstraZeneca; Clovis Oncology; Tesaro Bio
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Understanding DNA repair as a target for precision cancer therapy

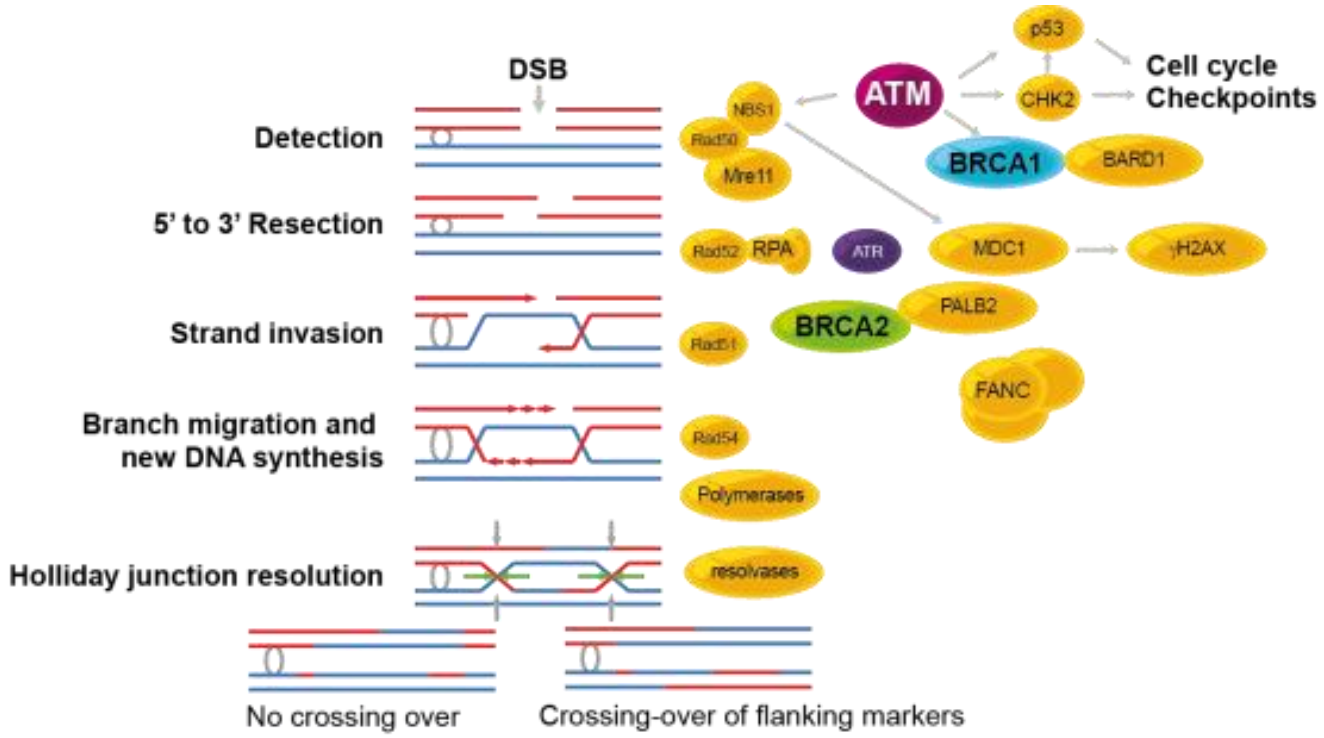
DNA damage response pathway drug targets

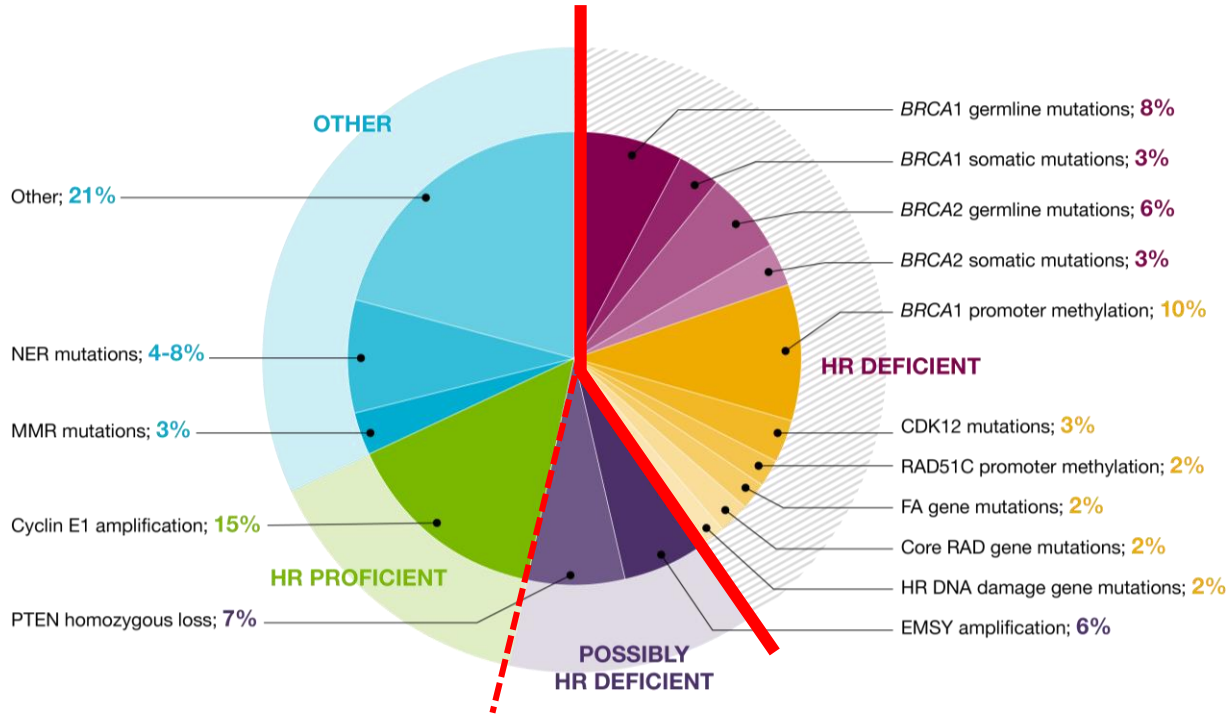
Type of damage:	Single-strand Breaks (SSBs)	Double-strand breaks (DSBs)		Bulky adducts e.g. from platinum and UV	Nucleotide mutations, substitutions, deletions, insertions
Repair targets:	**PARP** APE1	**ATR**	**ATM** **DNA-PK**	ERCC1 XP proteins Polymerases	MLH, MSH etc
Repair pathway:	Base Excision Repair	Homologous Recombination Repair	Non-Homologous End Joining	Nucleotide Excision Repair and TransLesion Synthesis	MisMatch Repair
Damaging agent(s):	RTx Alkylating agents	RTx Topo I inhibitors Nucleoside analogue	RTx Topo II inhibitors	UV light Platinum agents	Replication errors Alkylating agents
Rational for targeting:	The most common lesion	The most cytotoxic lesion		Platinum potentiation but safety concern over UV sensitization	Increased mutational load

Adapted from O'Connor M *et al. Mol Cell* 2015;60:547–560.

PARP Inhibitor Activity Extends beyond non-*BRCA* HRR Deficiencies (HRD)

Homologous recombination repair





ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; CHK2, checkpoint 2; DSB, double-strand break; HRD, homologous recombination repair deficient; HRR, homologous recombination repair.

McCabe N et al. *Cancer Res* 2016; 66: 8109-15.

Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5(11):1137–54.

PARP inhibitor development strategies

Bring along the pill……

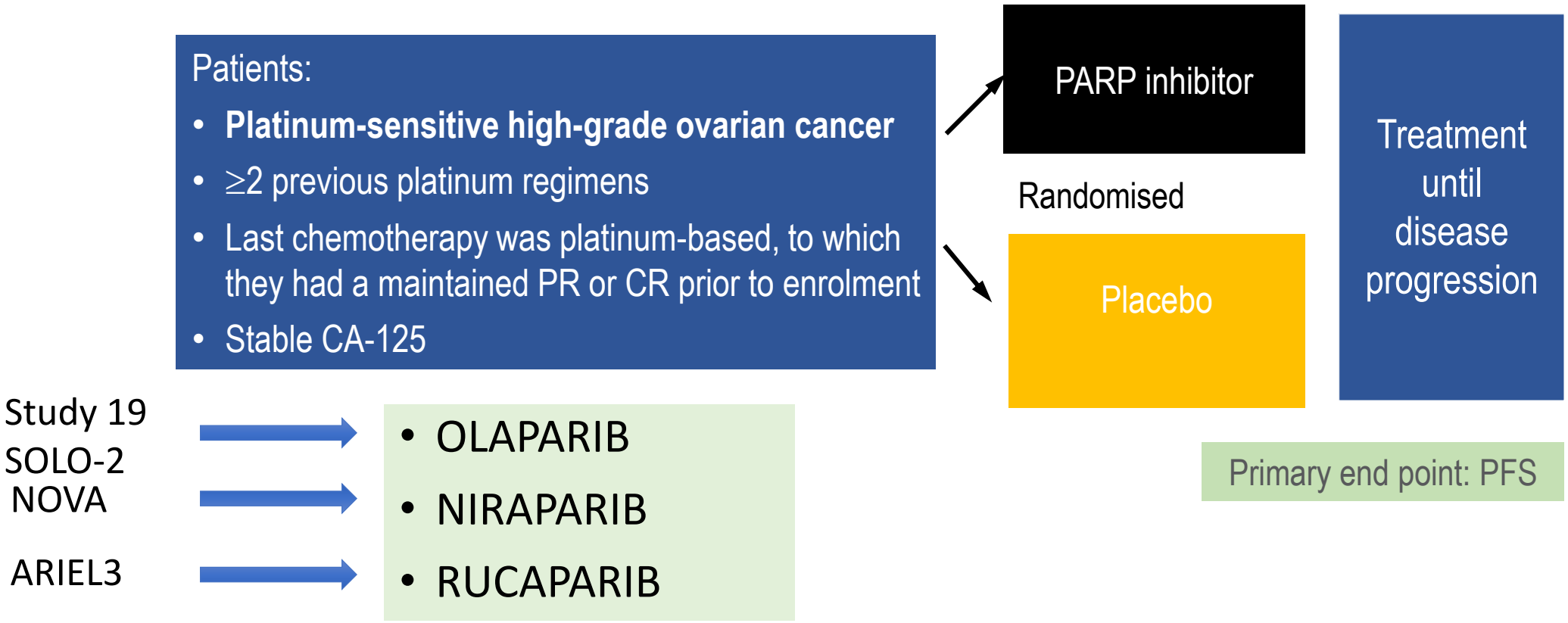
- **Chemotherapy combinations** - to enhance the activity of cytotoxic drugs
  - compounded toxicity and no clear evidence of synergy in ovarian cancer[1]
- **Maintenance therapy**
  - treatment beyond chemotherapy to build on and sustain response (Study 19[2]; SOLO2[3])
  - shifting treatment to first-line maintenance (SOLO1[4])

- **Single agent (monotherapy)** in place of chemotherapy (SOLO3[5])
- Combination therapies with other molecularly targeted drugs

1. Oza et al J Clin Oncol 2015; 2. Ledermann et al NEJM 2012; 3.Pujade-Lauraine et al Lancet Oncol 2017;
4. Moore et al NEJM 2018; 5. Penson et al ASCO 2019

Maintenance Trials: building on the benefit of chemotherapy

Randomised trials of PARP inhibitors in platinum-sensitive high-grade relapsed ovarian cancers



Ledermann J et al. N Engl J Med 2012; Mirza N Engl J Med 2016; Pujade-Lauraine et al Lancet Oncol 2017; Coleman et al Lancet 2017

PARP inhibitors maintenance post platinum-based chemotherapy

	Study 19 Olaparib	SOLO2 Olaparib	NOVA Niraparib	ARIEL 3 Rucaparib
N (pts)	265	295	533	564
Inclusion	• HGSOC	• BRCA1/2 mutated • HGSOC or high-grade endometrioid ovarian cancer	• HGSOC	• HGSOC or high-grade endometrioid ovarian cancer
Median PFS months	**All HGSOC** ▪ 4.8 v 8.4 mo ➢ HR 0.35 **BRCA mutation** ▪ 11.2 v 4.3 mo ➢ HR 0.18 **BRCA-wt** ▪ 7.4 v 5.5 mo ➢ HR 0.54	**BRCA mutation** ▪ 19.1 vs 5.5 mo ➢ HR 0.30	**gBRCA mutation** ▪ 21.0 vs 5.5 mo ➢ HR 0.27 **non gBRCA** ▪ 9.3 vs 3.9 mo ➢ HR 0.45	**tBRCA mutation** ▪ 16.6 vs 5.4 mo ➢ HR 0.23 **ITT (with or w/o BRCA mutation)** ▪ 10.8 vs 5.4 mo ➢ HR 0.36
Median OS	▪ 27.8 vs 29.8 months • HR 0.73	▪ 45 vs 27 months • HR 0.80 (immature)	• immature	• immature
Reference	Ledermann et al NEJM 2012; Lancet Oncol 2014	Pujade-Lauraine, E et al Lancet Oncol 2017	Mirza, M et al., NEJM 2016	Coleman, RL et al, Lancet 2017

HRD Testing to select PARP inhibitor benefit- NOVA (niraparib) ARIEL3 (rucaparib)

Myriad Assay

HRD +ve

***sBRCA* mut (n=47)**

	Niraparib (n=35)	Placebo (n=12)
PFS median (95% CI) (Months)	**20.9** (9.7–NR)	**11.0** (2.0–NR)
Hazard ratio (95% CI); *P* value	**0.27** (0.081–0.903); *P*=0.0248	
% of patients without progression or death at 12 mo	62%	19%

HRD +ve

***BRCA* wt (n=115)**

	Niraparib (n=71)	Placebo (n=44)
PFS median (95% CI) (Months)	**9.3** (5.8–15.4)	**3.7** (3.3–5.6)
Hazard ratio (95% CI); *P* value	**0.38** (0.231–0.628); *P*=0.0001	
% of patients without progression or death at 12 mo	45%	11%

HRD - ve

BRCA wt (n=134)

	Niraparib (n=92)	Placebo (n=42)
PFS median (95% CI) (Months)	**6.9** (5.6–9.6)	**3.8** (3.7–5.6)
Hazard ratio (95% CI); *P* value	**0.58** (0.361–0.922); *P*=0.0226	
% of patients without progression or death at 12 mo	27%	7%

Foundation Medicine

LOH high BRCA^{wt}

	Median (months)	95% CI
Rucaparib (n=106)	9.7	7.9–13.1
Placebo (n=52)	5.4	4.1–5.7

HR=0.44
95% CI, 0.29–0.66;
P<0.0001

LOH low BRCA^{wt}

	Median (months)	95% CI
Rucaparib (n=107)	6.7	5.4–9.1
Placebo (n=54)	5.4	5.3–7.4

HR=0.58
95% CI, 0.40–0.85;
P=0.0049

Mirza et al NEJM 2016; Coleman et al Lancet 2017

Summary of maintenance therapy with PARP inhibitors in recurrent high grade ovarian cancers

- PARP inhibitor maintenance significantly extends PFS
- Benefit seen in patients with or without BRCA mutation
- Magnitude of benefit greatest in patients with a BRCA mutation
- HRD testing (Myriad or Foundation Medicine) has not been able to exclude patients who may benefit from a PARP inhibitor

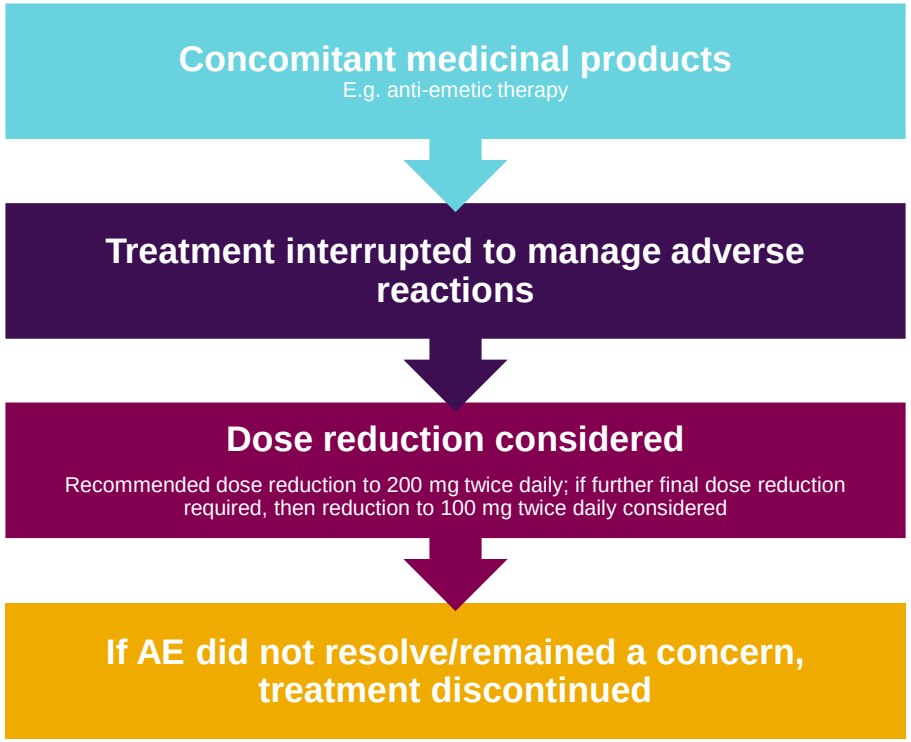
Maintenance therapy with PARP inhibitors a standard option for all patients with high grade ovarian cancer responding to platinum-based chemotherapy

How valuable is the clinical benefit and what are the side effects of PARP inhibitors?- *Toxicity and secondary endpoints*

Olaparib adverse events in Study 19

Olaparib monotherapy generally associated with mild or moderate severity adverse reactions (CTCAE 1 or 2) and patients generally did not require treatment discontinuation[1]

Study 19 general AE management flow*



- Most common AEs were nausea, fatigue and vomiting[2]
- Most common Grade 3 and 4 AEs: fatigue and anaemia[2]
- The majority of nausea, vomiting and fatigue were:
  - Grade 1
  - Reported early (within the first two months of treatment)
  - Suitably managed when required with dose modifications and supportive treatment such as anti-emetics for nausea/vomiting[3]
- AEs leading to permanent discontinuation of treatment was low (olaparib arm, 6%; placebo arm, 2%)[4]

*General flow – specific guidance was provide for some AEs

1. Lynparza 100mg and 150mg tablets Summary of Product Characteristics, May 2018; 2. Ledermann J et al. Lancet Oncol. 2014;15(8):85; 3. Matulonis U et al. J Clin Oncol 33, 2015 (poster associated to abstr 5550); 4. Ledermann J et al. Lancet Oncol. 2016 Nov;17(11):1579-1589

Safety profiles of the different PARP inhibitors

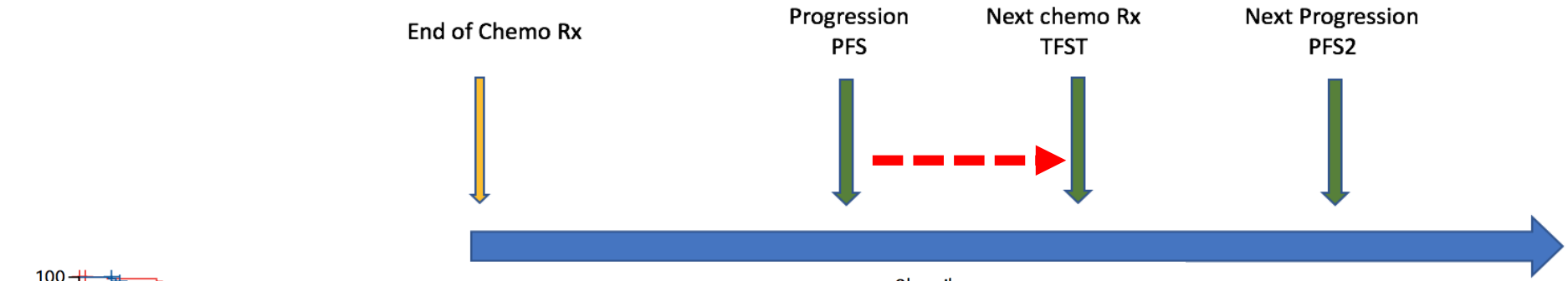
	Olaparib (SOLO-2)	Niraparib (NOVA)	Rucaparib (ARIEL 3)
Discontinuation	10.8%	14.7%	13%
Dose reduction	25.1%	66.5%	55%
Related SAE	18%	16.9%	21%
Nausea/vomiting, Grade ≥3	2.6%	3%	4%
Fatigue, Grade ≥3	4.1%	8.2%	7%
Anaemia, Grade ≥3	19.5%	25.3%	19%
Thrombocytopenia, Grade ≥3	1%	33.8%	5%
Neutropenia, Grade ≥3	5.1%	19.6%	7%
MDS	1 (0.5%)	5 (1.4%)	3 (1%)
GOT/GPT, Grade ≥3	-	-	10%

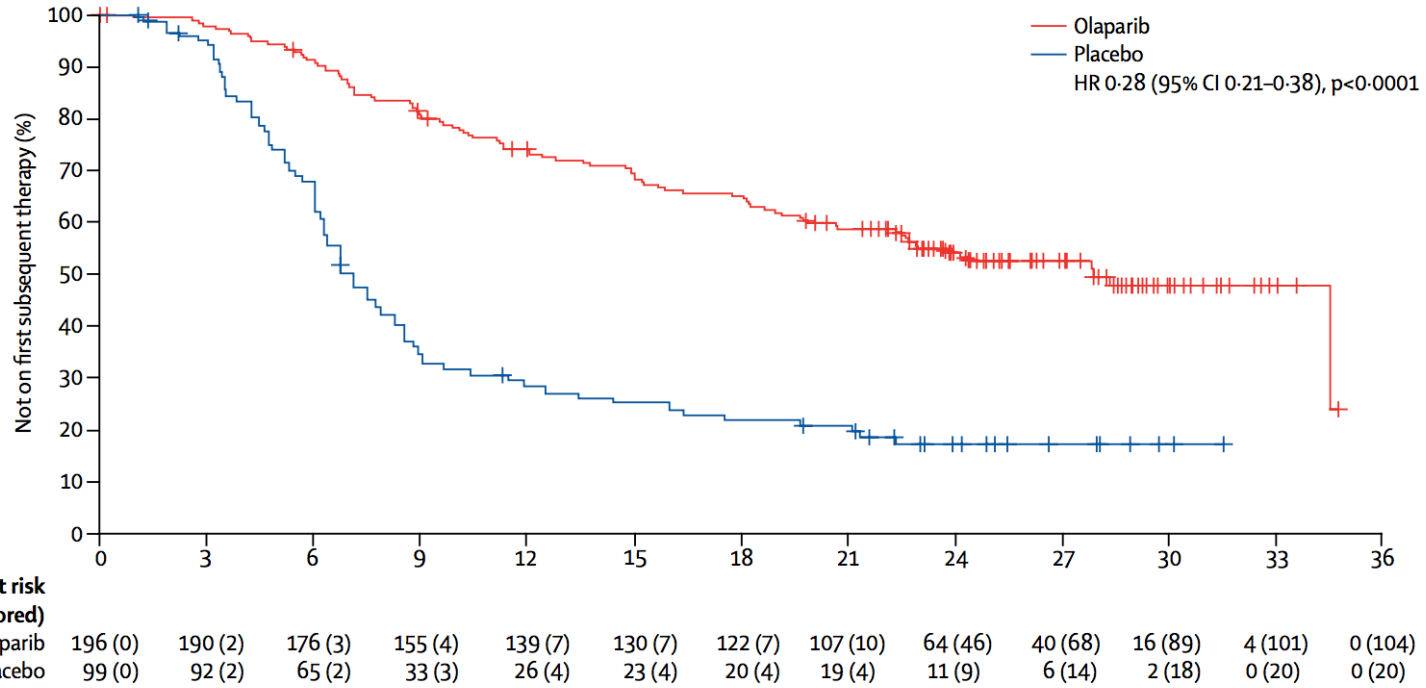
Note: In the absence of head to head data between PARPi efficacy and safety comparisons between PARPi are not to be made or communicated
MDS, myelodysplastic syndrome; SAE, serious adverse event

1. Pujade-Lauraine E, et al. Lancet Oncol. 2017;18(9):1274-1284. 2. Mirza MR, et al. N Engl J Med. 2016;375(22):2154-2164. 3. Coleman RL, et al. Lancet. 2017;390(10106):1949-1961.

Secondary endpoints

Secondary Endpoint: Time to First Subsequent Therapy (TFST) after progression: *SOLO2/ENGOT-Ov21 in BRCA-mutated ovarian cancer*





Med △ PFS-TFST:
13.6 to 20.8 months

Median (TFST)

27.9 months

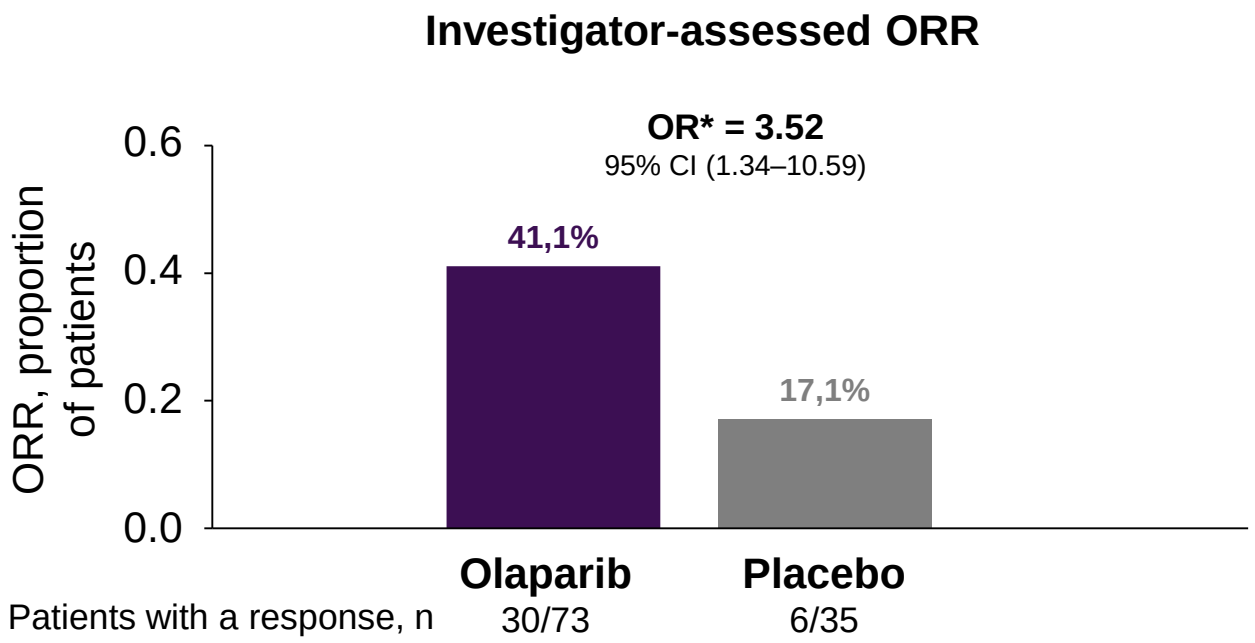
7.1 months

Pujade-Lauraine et al Lancet Oncol 2017

SOLO2- Response rate to olaparib in patients with measurable disease at baseline

ORR (investigator-assessed) was 41% for olaparib versus 17% for placebo[1]

- Median duration of response: 11.0 months (95% CI 8.3-13.8) with olaparib vs. 4.2 months (95% CI 2.8-NE) with placebo[1]



*Odds ratio is adjusted for response to previous platinum-based chemotherapy and time to disease progression following the penultimate platinum-based chemotherapy
ORR = objective response rate; BICR = blind independent centralised review; NE = not evaluable; OR = odds ratio

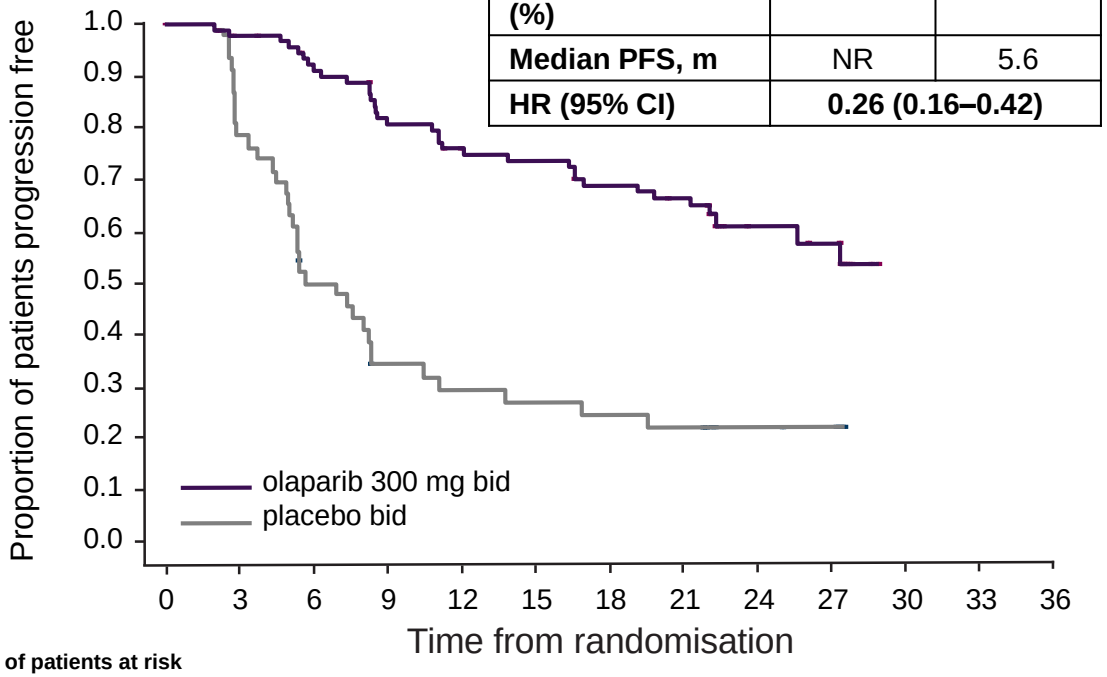
1. Oza et al. Poster 965P presented at ESMO 2017

SOLO2 : PFS advantage for olaparib vs. placebo depending on prior response to platinum-based chemotherapy[1]

A numerical increase in olaparib efficacy seen in patients entering the study with a prior complete response[1]

PFS for patients in CR at time of study entry

	Olaparib (N=91)	Placebo (N=47)
PFS events, n (%)	34 (37)	35 (75)
Median PFS, m	NR	5.6
HR (95% CI)	**0.26 (0.16–0.42)**	

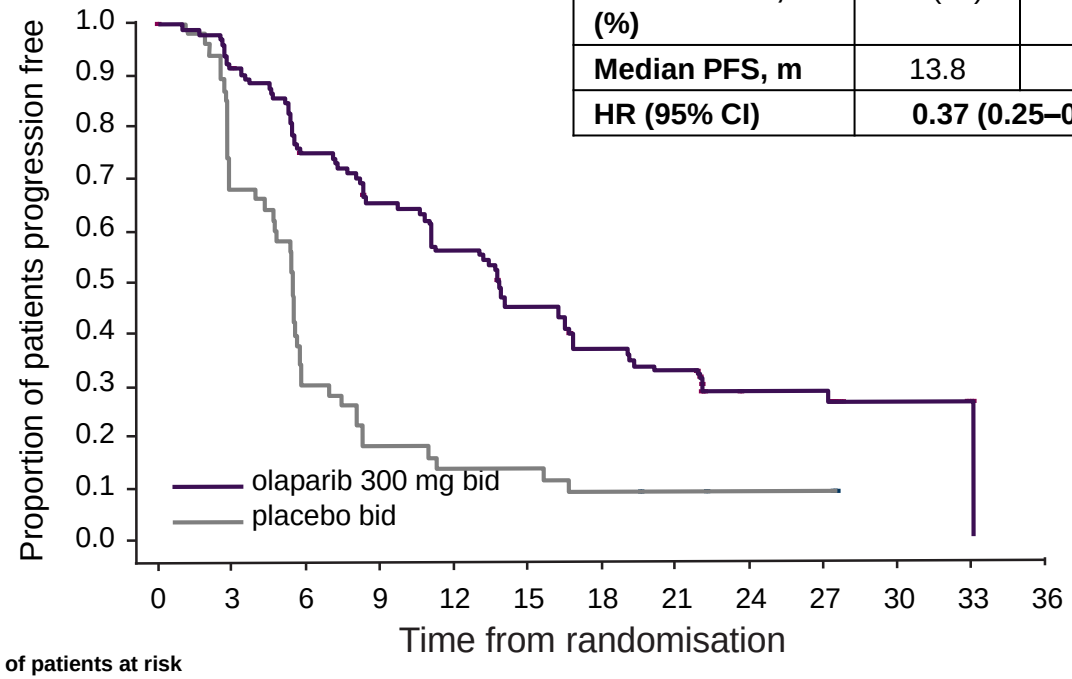


Number of patients at risk

Olaparib 300 mg bid	91	87	80	69	62	60	54	51	19	16	0	0	0
Placebo bid	47	36	22	14	12	11	10	9	5	4	0	0	0

PFS for patients in PR at time of study entry

	Olaparib (N=105)	Placebo (N=52)
PFS events, n (%)	73 (70)	45 (87)
Median PFS, m	13.8	5.5
HR (95% CI)	**0.37 (0.25–0.54)**	



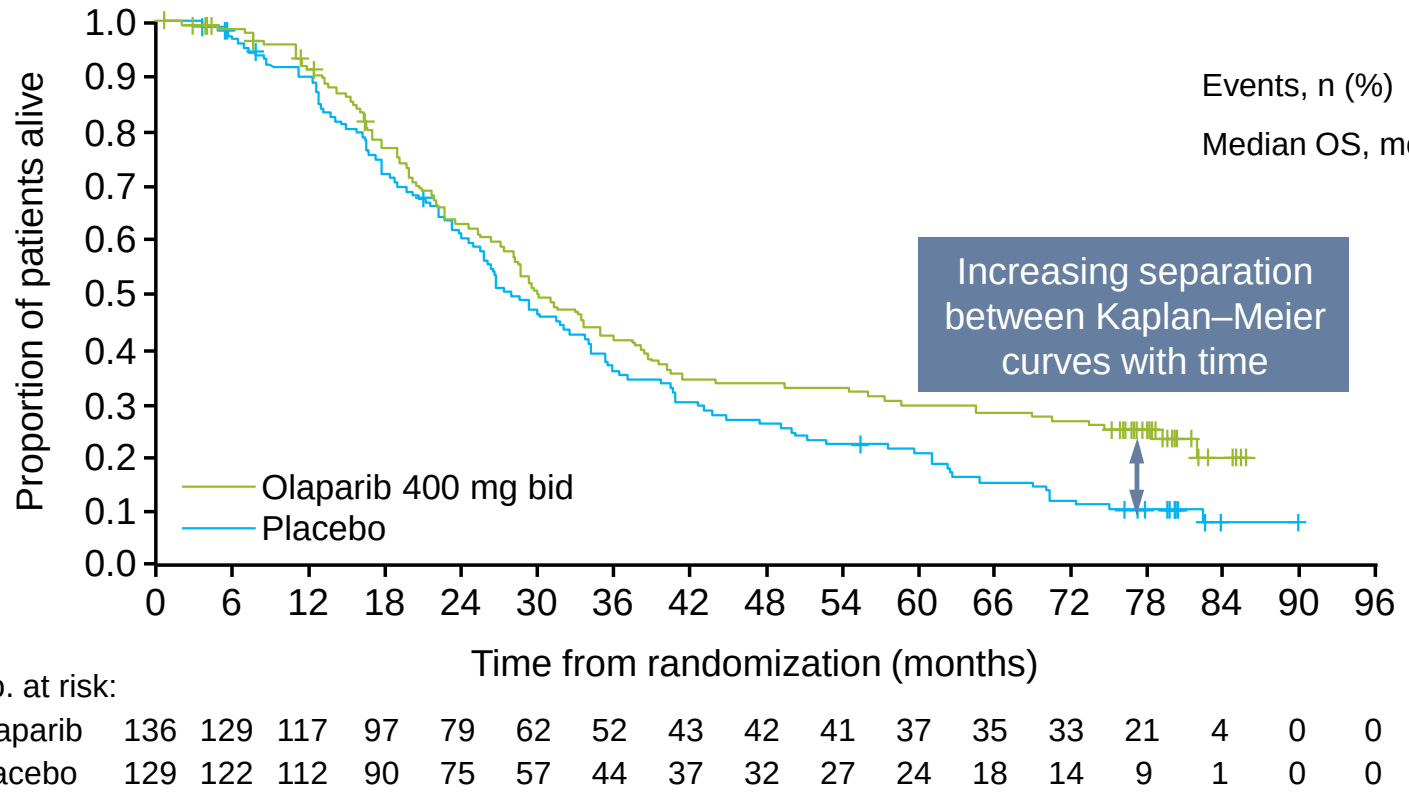
Number of patients at risk

Olaparib 300 mg bid	105	95	76	65	56	44	35	31	13	13	3	2	0
Placebo bid	52	34	15	8	6	6	4	3	2	2	0	0	0

Investigator-assessed progression or death by modified RECIST v1.1
PFS = progression free survival; NR = not reached

1. Oza et al. Poster 965P presented at ESMO 2017

Final OS analysis: Study 19 showed an OS advantage for olaparib-treated patients



No. at risk:

Olaparib	136	129	117	97	79	62	52	43	42	41	37	35	33	21	4	0	0
Placebo	129	122	112	90	75	57	44	37	32	27	24	18	14	9	1	0	0

Overall study population (N=265)

	Olaparib (n=136)	Placebo (n=129)
Events, n (%)	98 (72.1)	112 (86.8)
Median OS, months	29.8	27.8

HR=0.73
95% CI 0.55–0.95
Nominal *P*=0.02138

Median OS follow-up: 78.0 months
OS data maturity: 79%

Criterion for statistical significance (*P*<0.0095) not met

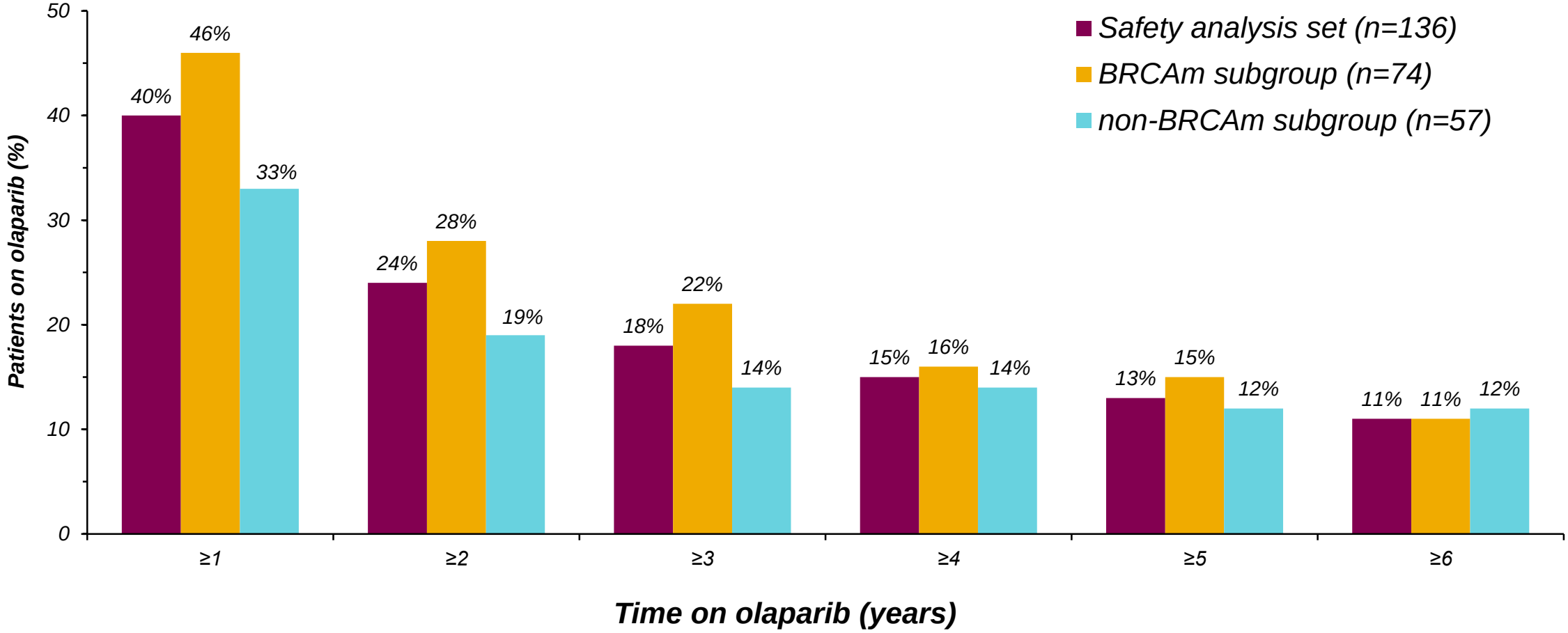
13% of placebo-receiving patients received post-discontinuation PARP inhibitor treatment in other studies

Data cut-off: 9 May 2016

Friedlander et al Br J Cancer 2018

Study 19: Long term survival shows there are patients responding to olaparib for ≥6 years[1]

11% of patients remained on treatment for ≥6 years[1]

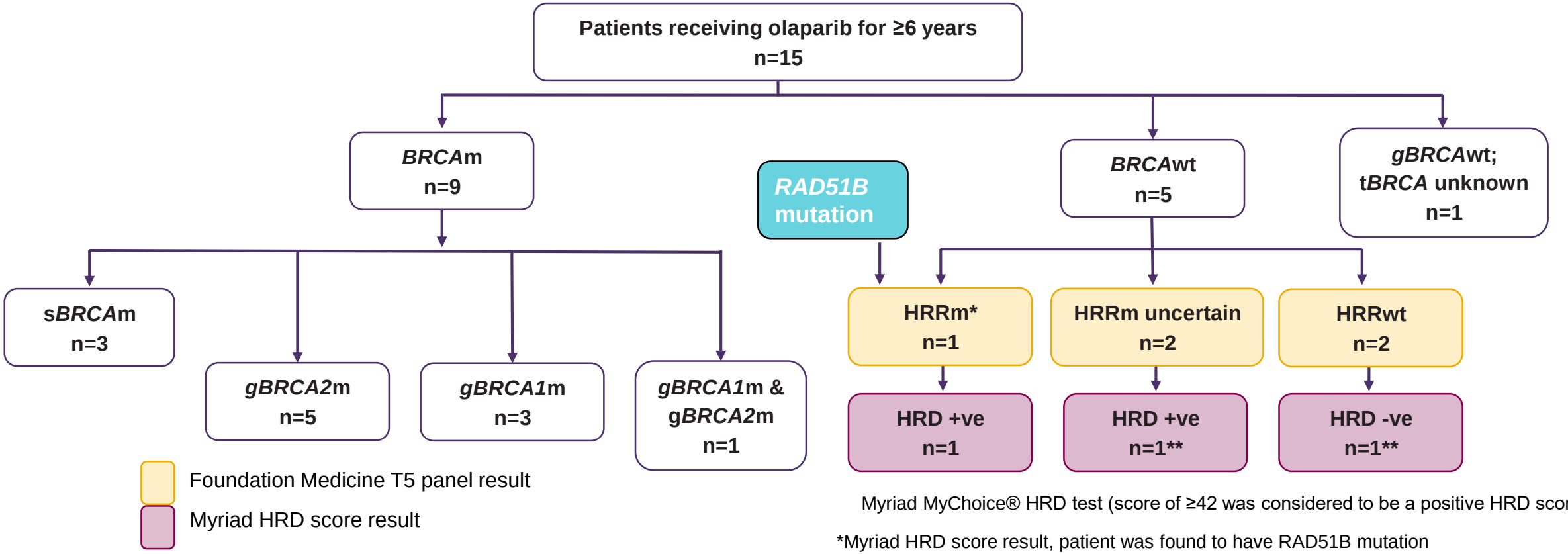


Subgroups were defined prior to exploratory biomarker analyses being performed; patients with no known *BRCA*m or a variant of unknown significance were classified as *BRCA*wt, and one patient with no known *BRCA*m who received olaparib treatment for ≥6 years was found to have a s*BRCA*m in subsequent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

DCO: May 2016

1. Gourley C et al. J Clin Oncol 35, 2017 (suppl; poster related to abstr 5533)

Biomarker characterisation of the 15 patients who received olaparib for ≥6 years[1]



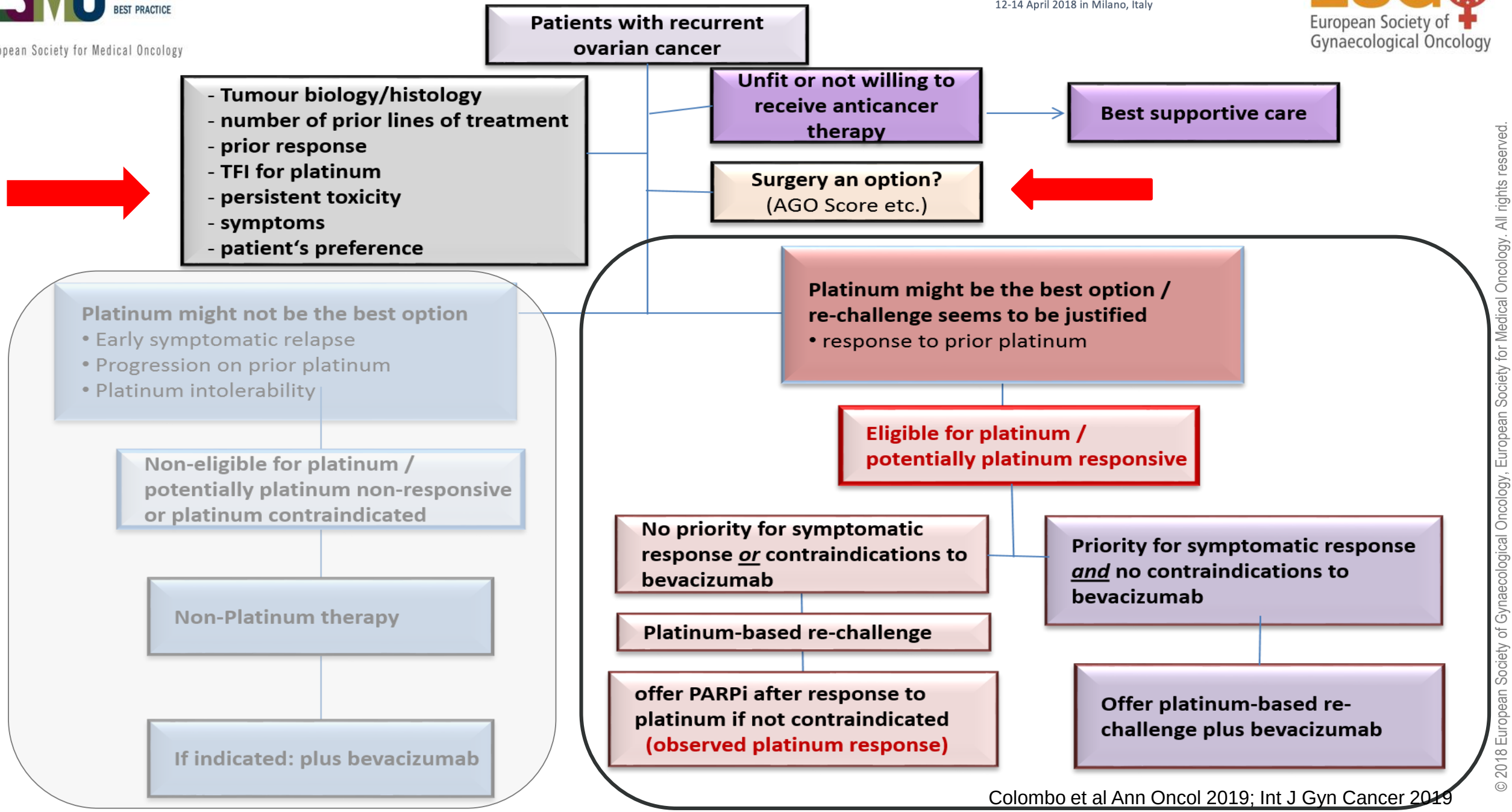
Myriad MyChoice® HRD test (score of ≥42 was considered to be a positive HRD score)

*Myriad HRD score result, patient was found to have RAD51B mutation

**2 of BRCAwt patients had unavailable Myriad HRD score result

†Biomarker identification was carried out using the following: g*BRCA*m: case report forms after local testing or Integrated BRACAnalysis® assay (Myriad Genetics); t*BRCA*m: Foundation Medicine T5 panel and Myriad MyChoice® HRD test; mutations in other HRR-associated genes: Foundation Medicine T5 panel; HRD scores:; *BRCA*1/2m, *BRCA*1/2 mutation; g*BRCA*wt, germline *BRCA* wild type; HRR, homologous recombination repair; HRD, homologous recombination deficiency; HRRm, HRR mutation; HRRwt, HRR wild type; s*BRCA*1/2m, somatic *BRCA*1/2 mutation; t*BRCA*, tumour *BRCA*. DCO: May 2016

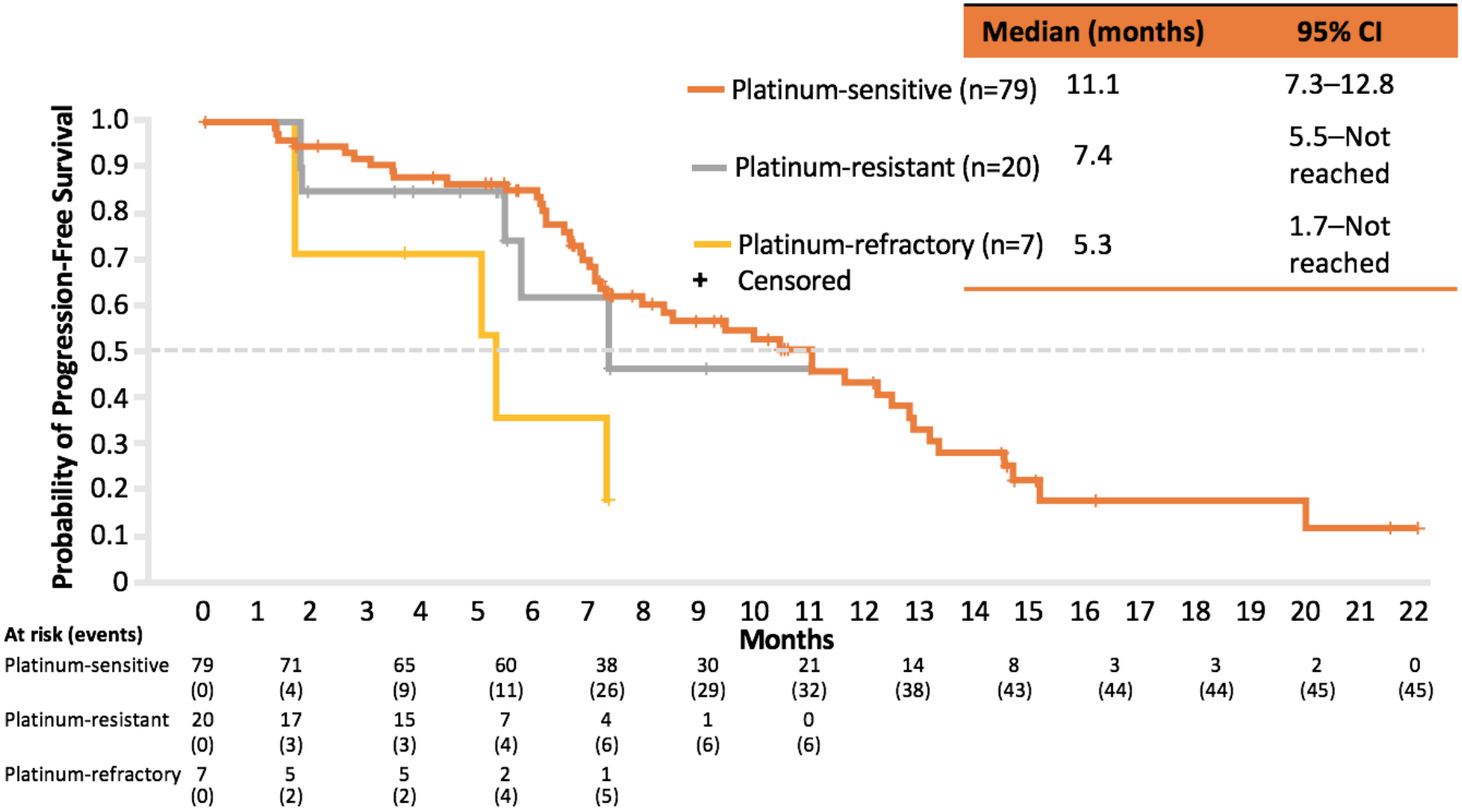
Gourley C et al. J Clin Oncol 35, 2017 (suppl; poster related to abstr 5533)



Colombo et al Ann Oncol 2019; Int J Gyn Cancer 2019

Monotherapy

Integrated Efficacy Results: Rucaparib monotherapy PFS in Specified Groups According to Platinum Sensitivity



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

Olaparib Monotherapy versus Chemotherapy for Germline BRCA-Mutated Platinum-Sensitive Relapsed Ovarian Cancer Patients: Phase III SOLO3 Trial

- Relapsed, high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer
- Germline BRCAm
- ECOG performance status 0–2
- ≥2 previous lines of platinum-based chemotherapy*
- Platinum sensitive†

Open-label

Study treatment administered until disease progression

Olaparib tablets 300 mg bid (n=178)

2:1 randomization

Stratified by:
- Selected chemotherapy‡
- Number of prior lines of chemotherapy
- Time to progression after previous platinum-based chemotherapy

Non-platinum chemotherapy§ (n=88)
- **PLD (n=47)**
- **Paclitaxel (n=20)**
- **Gemcitabine (n=13)**
- **Topotecan (n=8)**

Primary endpoint
- ORR by BICR (RECIST v1.1)

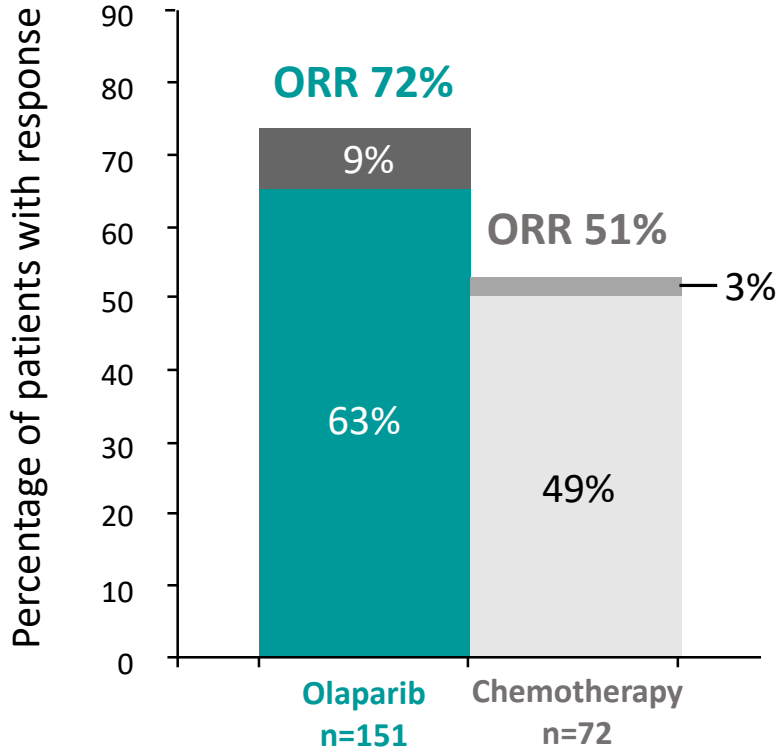
Secondary endpoints
- PFS
- PFS2
- OS
- TFST
- TSST
- HRQoL
- Safety

*Prior treatment with a PARP inhibitor was not permitted;
†Fully platinum sensitive: progression >12 months after platinum-based chemotherapy; partially platinum sensitive: progression 6–12 months after platinum-based chemotherapy;
‡For each patient, the investigator declared their choice of non-platinum chemotherapy before randomization;
§PLD, 50 mg/m^2 on day 1 q4w; paclitaxel, 80 mg/m^2 on days 1, 8, 15, and 22 q4w; gemcitabine, 1000 mg/m^2 on days 1, 8, and 15 q4w; topotecan, 4 mg/m^2 on days 1, 8, and 15 q4w

BICR, blinded independent central review; BRCAm, *BRCA1* or *BRCA2* mutation; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; PLD, pegylated liposomal doxorubicin; q4w, every 4 weeks; RECIST, response evaluation criteria in solid tumors; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Penson et al ASCO 2019

Primary Endpoint: ORR by BICR



All patients*

OR 2.53 (1.40, 4.58) *P*=0.002

*Patients with measurable disease at baseline

Patients with
2 prior lines of chemotherapy*

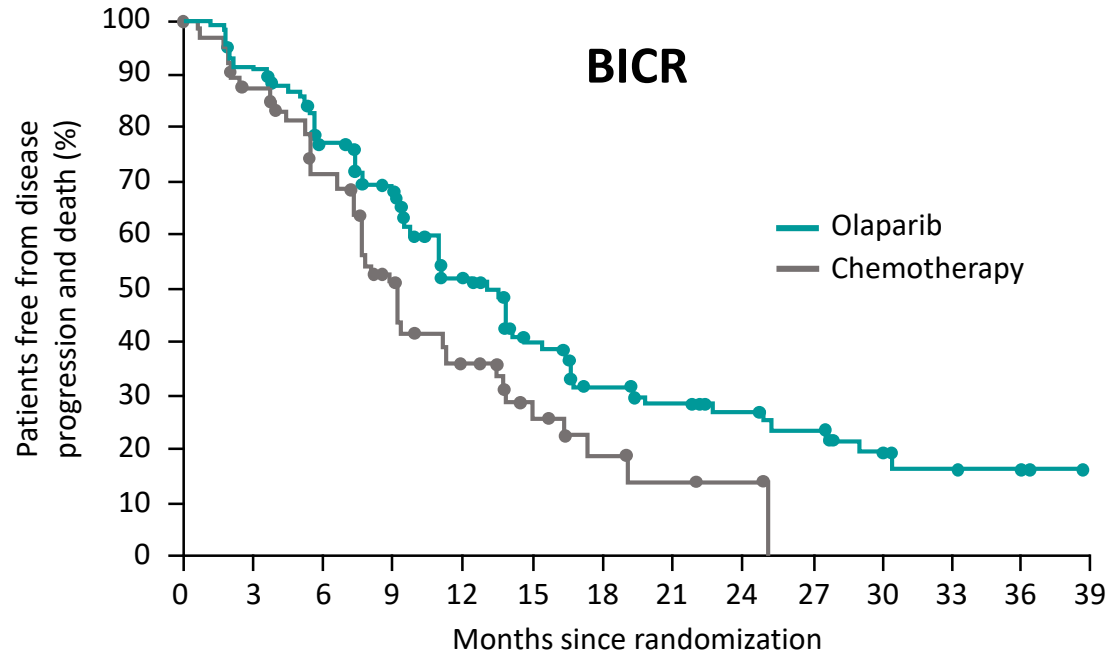
OR 3.44 (1.42, 8.54)

Patients with
≥3 prior lines of chemotherapy*

OR 2.21 (0.96, 5.20)

Penson et al ASCO 2019

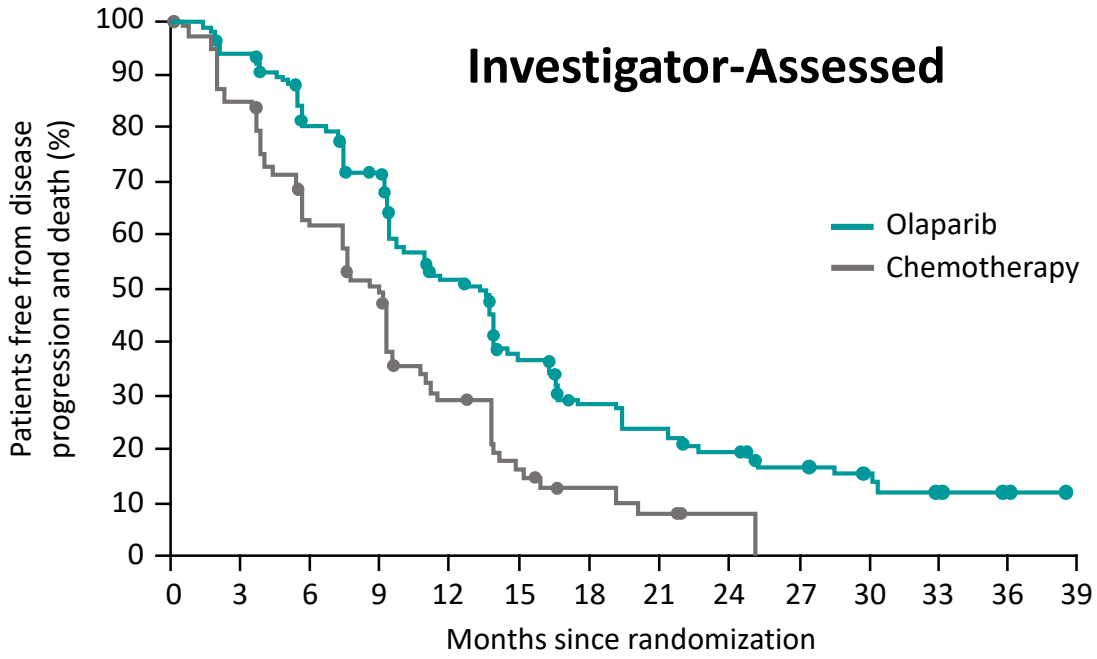
SOLO3: PFS (Intention-To-Treat Population)



No. at risk

Olaparib	178	156	126	108	71	47	30	25	18	14	8	5	2	0
Chemotherapy	88	63	47	31	18	9	5	3	2	0	0	0	0	0

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



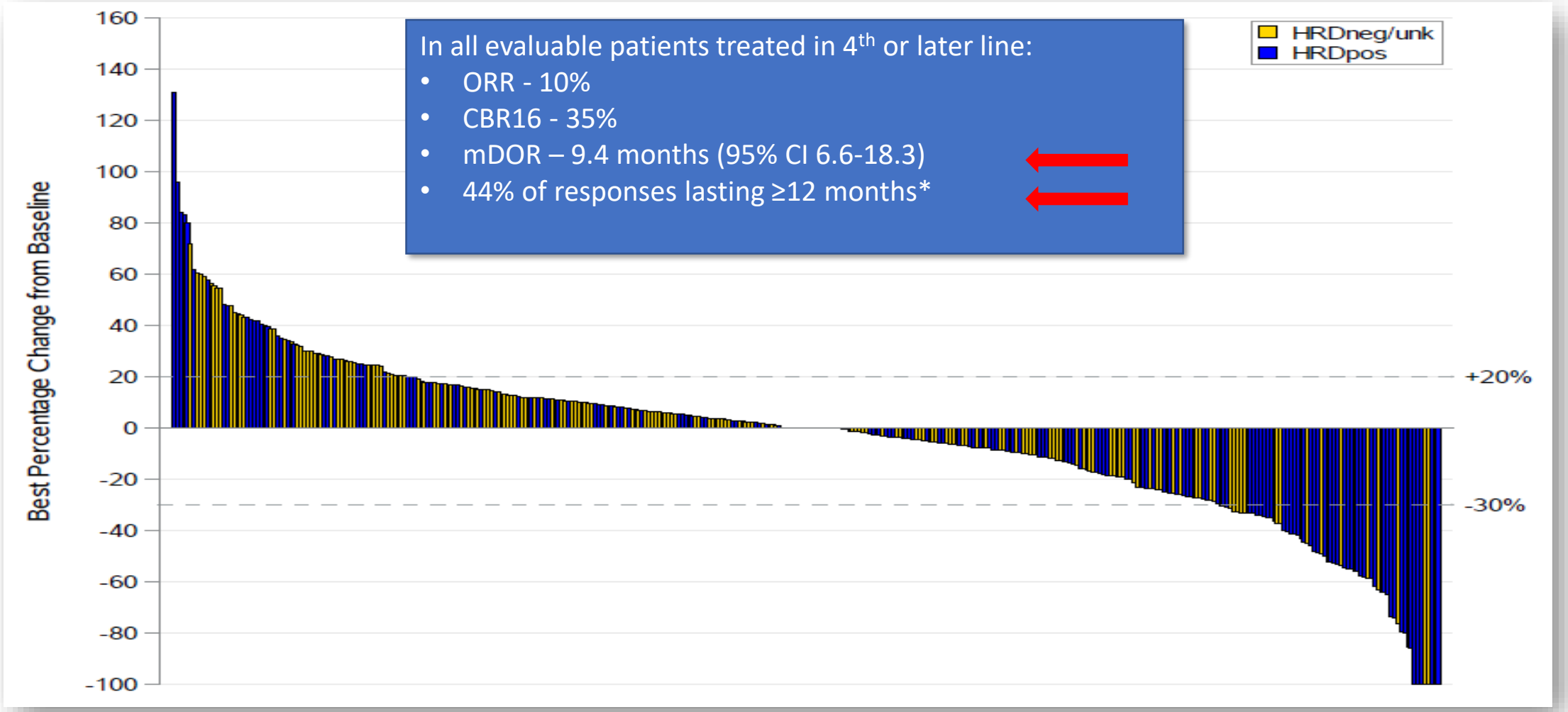
No. at risk

Olaparib	178	155	126	110	72	48	31	26	19	12	8	6	2	0
Chemotherapy	88	62	43	34	18	9	5	3	1	0	0	0	0	0

	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	123 (69)	63 (72)
Median PFS, months	**13.2**	**8.5**
HR (95% CI), *P* value	**0.49 (0.35, 0.70); *P*<0.001**	

Penson et al ASCO 2019

QUADRA- Benefit of niraparib across all population



Patients with at least one follow-up scan with an evaluable target lesion treated in 4th or later line (n=379) included on the waterfall plot
Patients previously treated with PARP inhibitors are included
* Based on KM estimate

ORR – objective response rate
CBR16 – clinical benefit rate (CR+PR+SD for at least 16 weeks)

Moore et al ASCO 2018; Lancet Oncol 2019

First Line Treatment of Ovarian Cancer

First line therapy

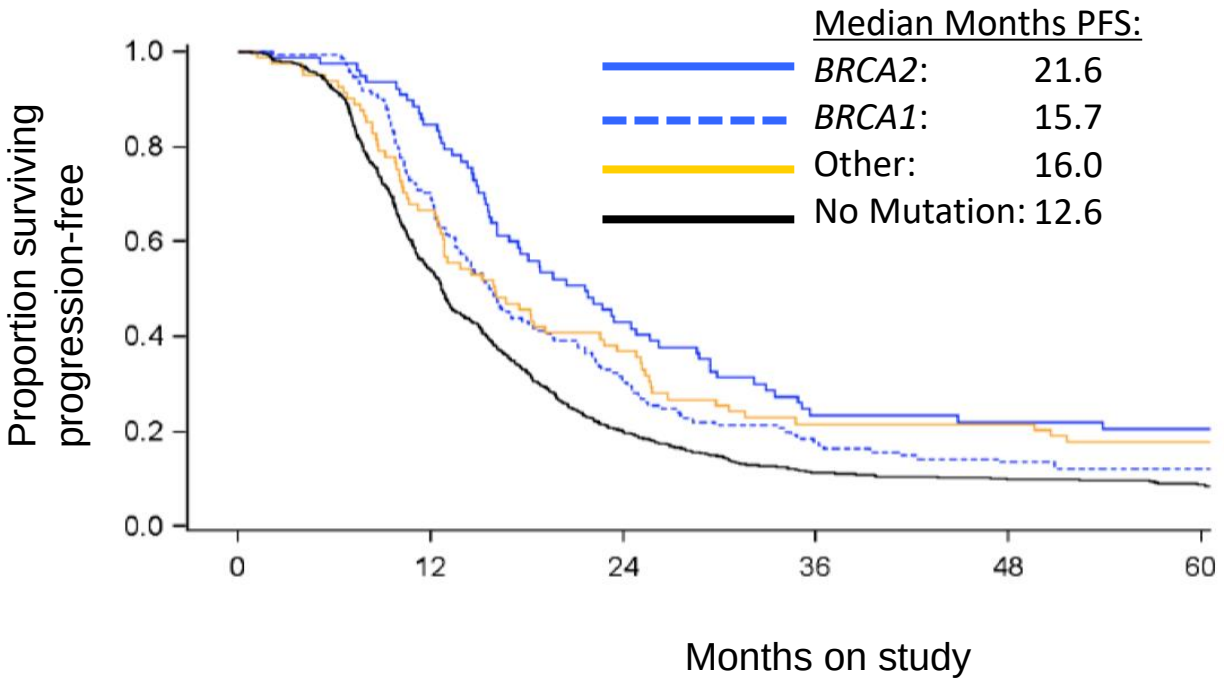
Where are we now…… ?

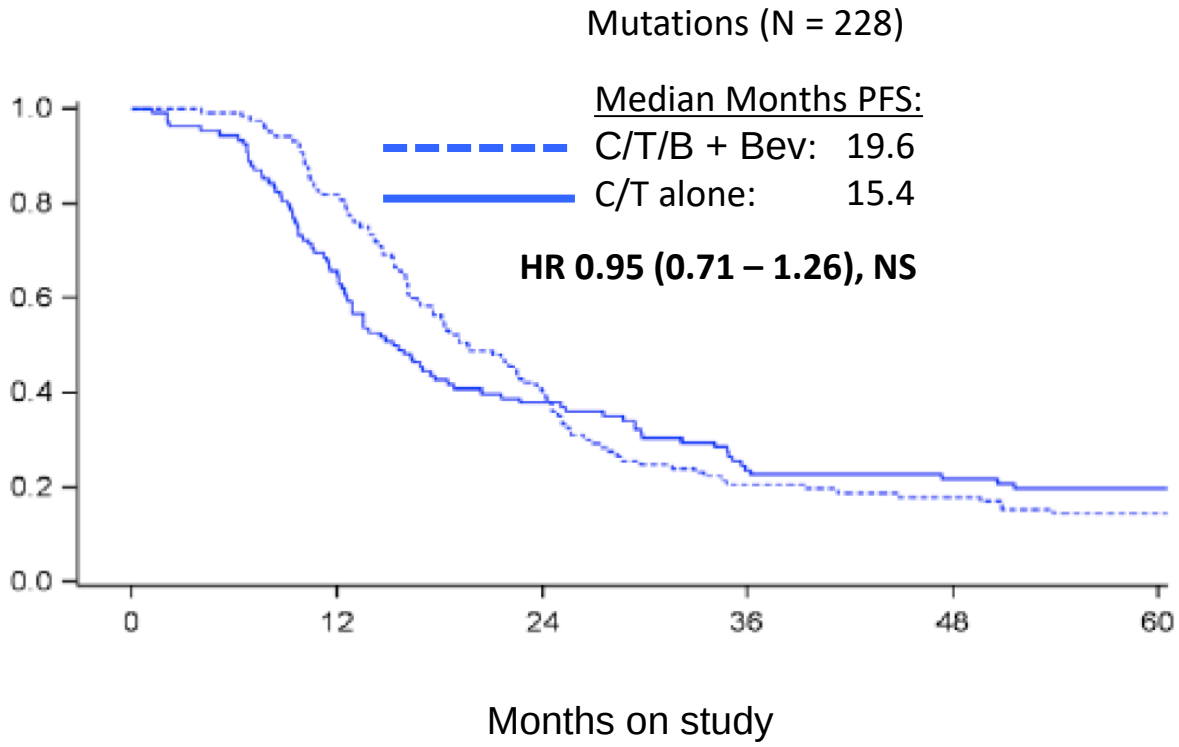
- Carboplatin/paclitaxel are the mainstay of treatment.
- Addition of bevacizumab to chemotherapy followed by maintenance has extended median PFS by around 4 months
- But overall, PFS following first line therapy has changed little in the last 20 years
- PFS is affected by
  - FIGO stage
  - Amount of residual disease
  - BRCA status

BRCA mutations confer a better prognosis – what is the outcome of these patients with 'standard of care' chemotherapy and bevacizumab?

GOG 218 :

Carboplatin/paclitaxel versus carboplatin/paclitaxel+ bevacizumab with bevacizumab maintenance





Norquist et al SGO 2016; Clin Cancer Res 2017

- Patients with BRCA mutation have a longer PFS than BRCA wild type
- Relapse still occurs in most patients of these patients within 3 years of diagnosis
- Current chemotherapy with bevacizumab leads to a high first failure rate

Can olaparib maintenance therapy following front-line therapy significantly extend PFS, and will this lead to an increase in overall survival ?

SOLO1: Olaparib maintenance therapy after front-line treatment in women with BRCA^{mut} ovarian cancer

- **Newly diagnosed**, FIGO **stage III–IV**, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- **Cytoreductive surgery***
- In **clinical complete response or partial response** after platinum-based chemotherapy

Olaparib 300 mg bd (N=260)

2:1 randomization

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*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

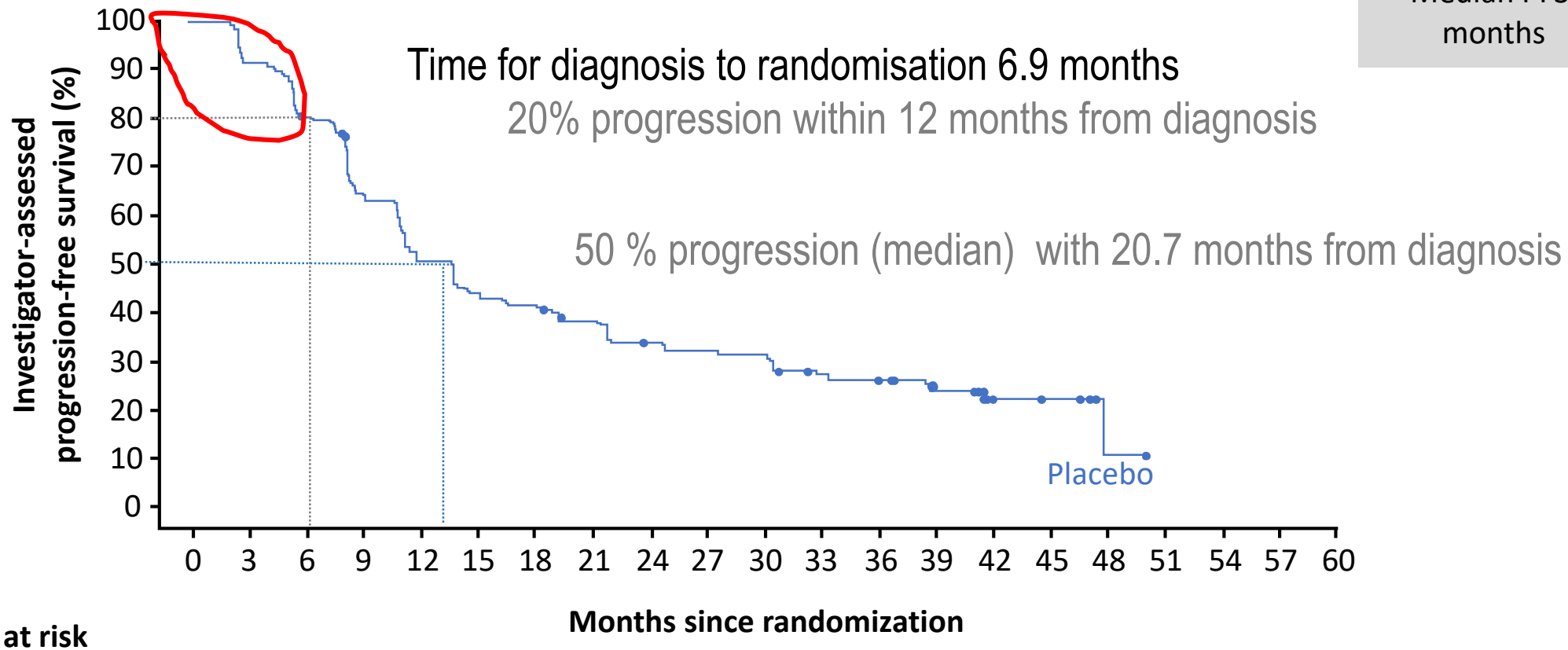
Moore et al ESMO 2018; NEJM 2018

SOLO1 Clinical Features

- 17% Stage IV
- 23% Residual disease after primary surgery
- 18 % Residual disease after IDS
- 82% Complete clinical response at end of treatment
- 18 % Partial Response

SOLO1 PFS by investigator assessment

	Placebo (N=131)
Events (%) [50.6% maturity]	96 (73.3)
Median PFS, months	**13.8**



No. at risk

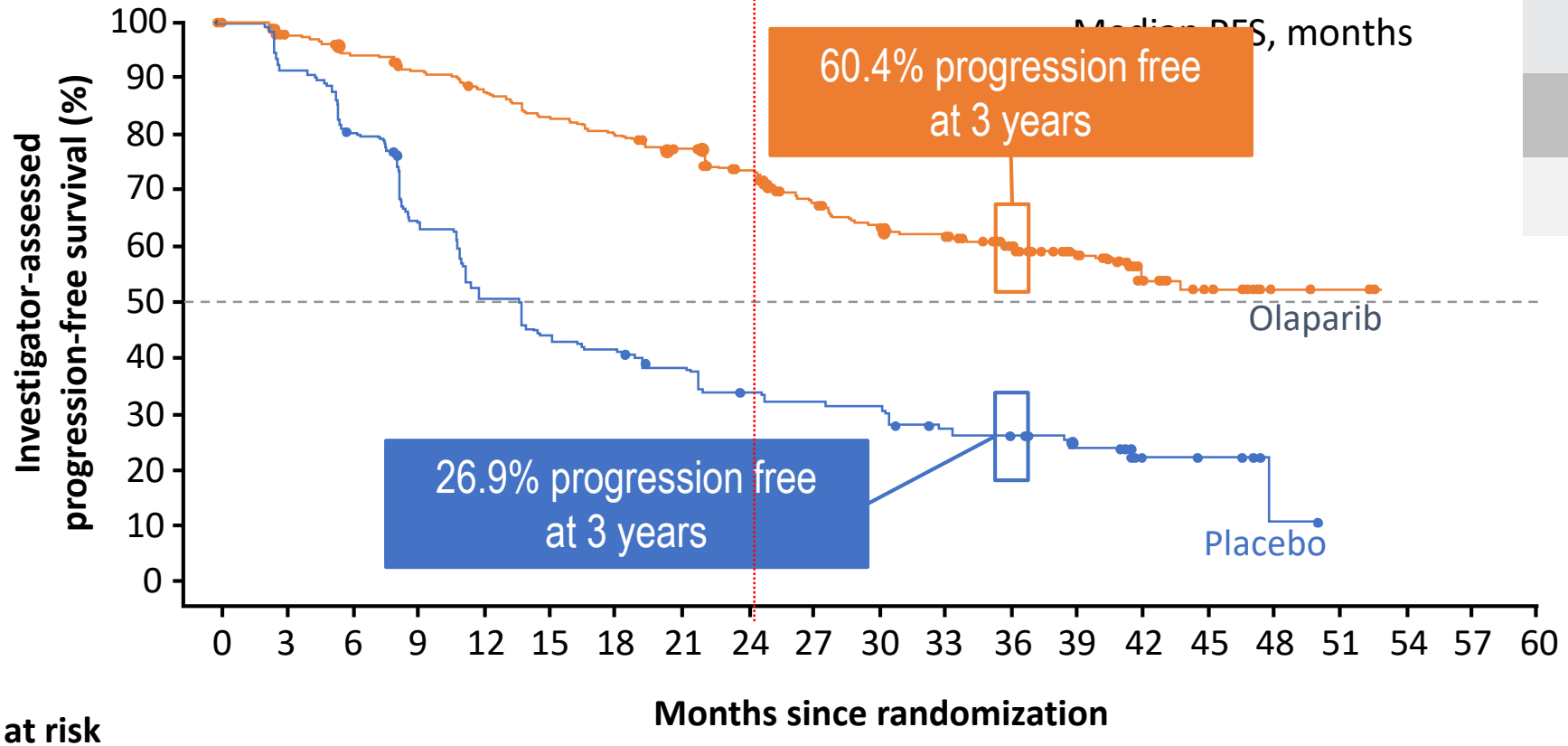
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

CI, confidence interval; NR, not reached

Moore et al ESMO 2018; NEJM 2018

SOLO1 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		



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CI, confidence interval; NR, not reached

Moore et al ESMO 2018; NEJM 2018

Interpretation of adding olaparib maintenance to first line therapy in patients with a *BRCA^{mut}*

Significant prolongation of Progression-Free survival

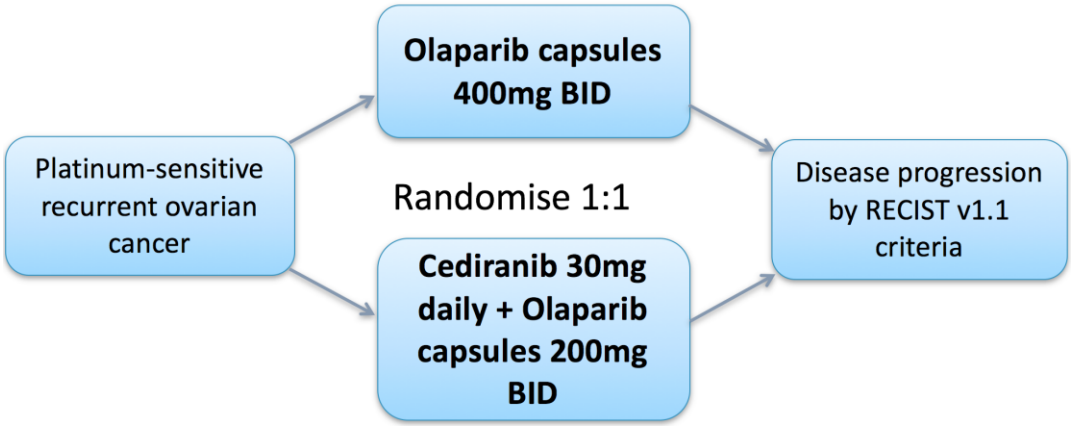
- Median PFS not reached in olaparib arm
- All patients followed for at least 3 years - 60.4 % remain progression-free
- Olaparib compared with placebo led to a 36.7 month difference in the median time to Time First Subsequent Therapy (TFST) - the next line of therapy

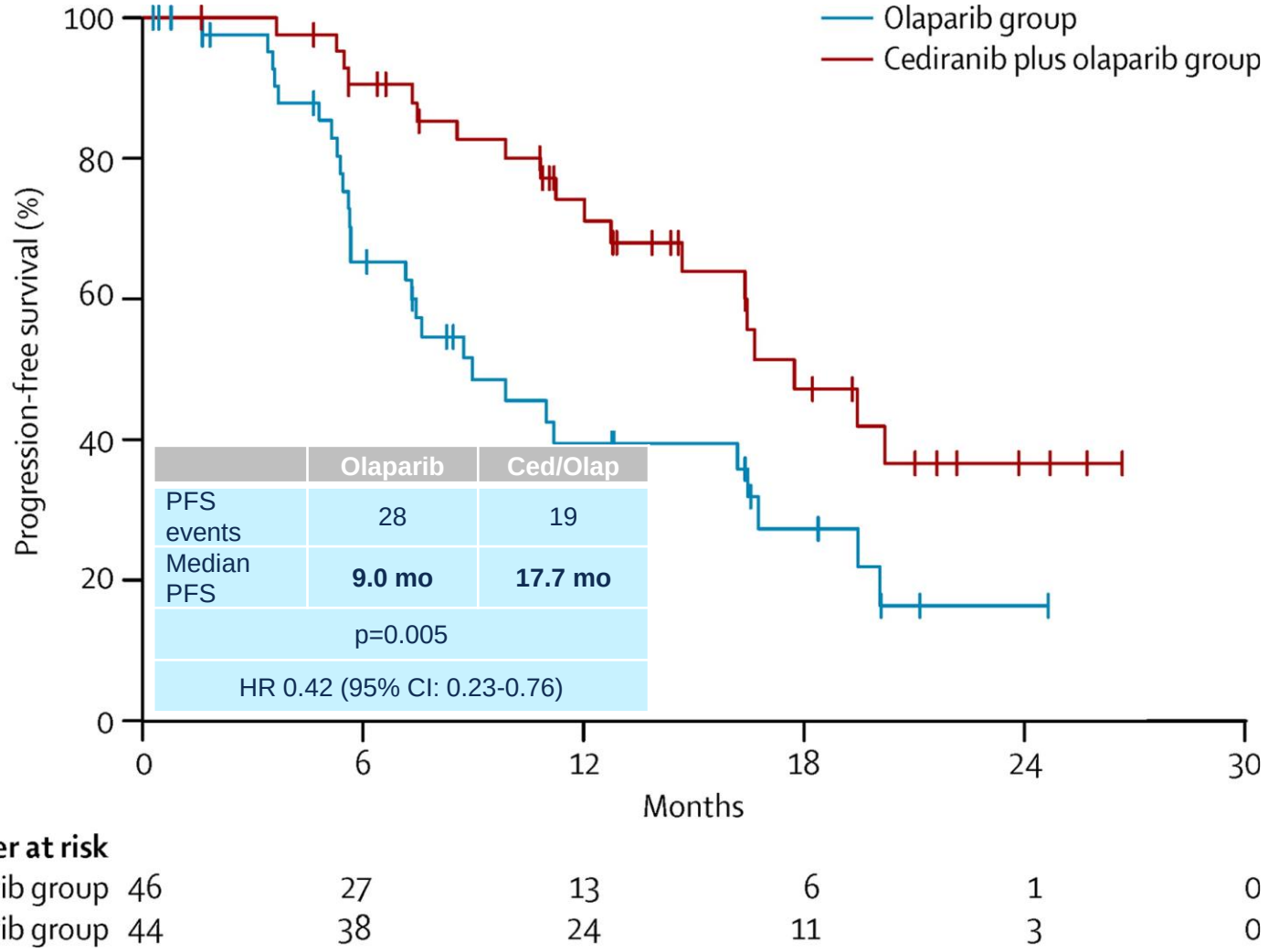
Results of SOLO1 underscore the importance of early checking for a BRCA mutation so that choices can be made between bevacizumab or olaparib maintenance

PARP inhibitor combination strategies

Combination therapy with anti-angiogenic agents

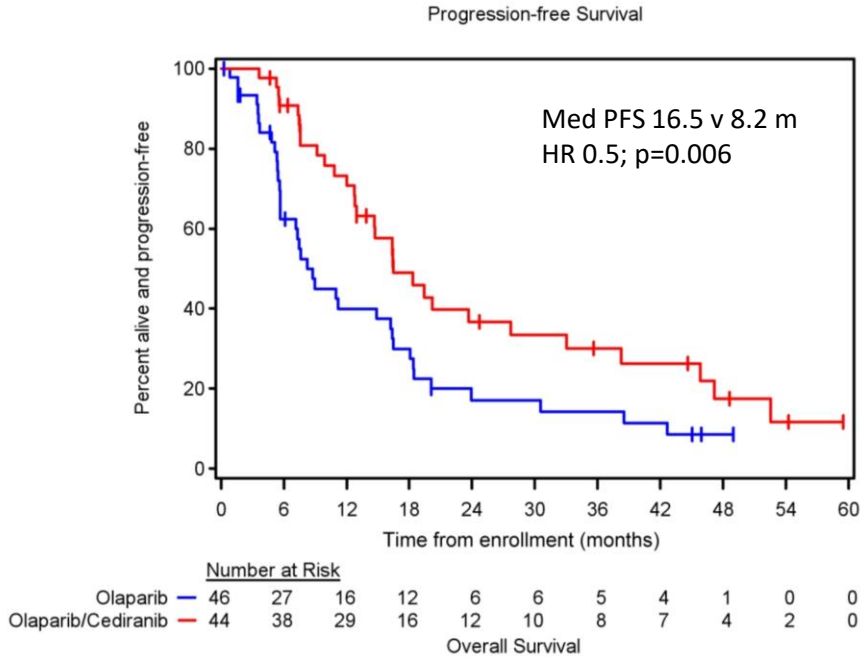
Phase II randomised trials of cediranib/olaparib *versus* olaparib



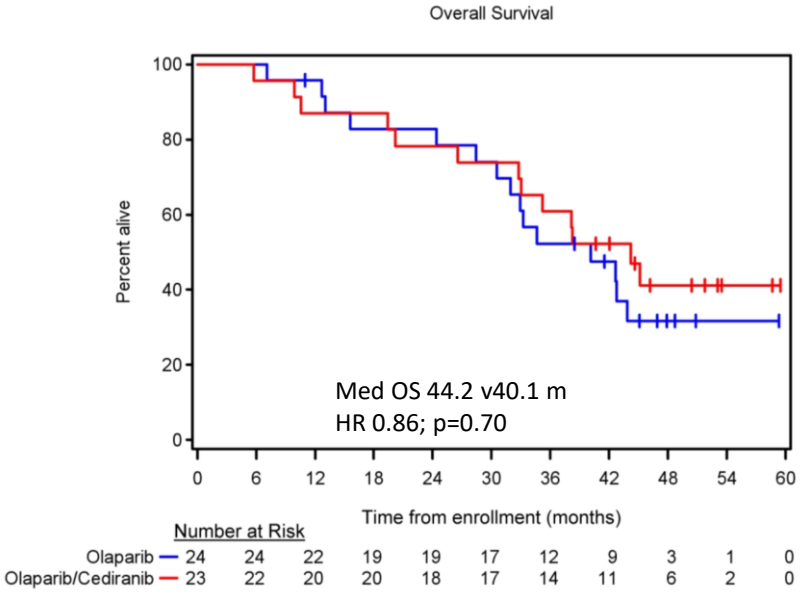


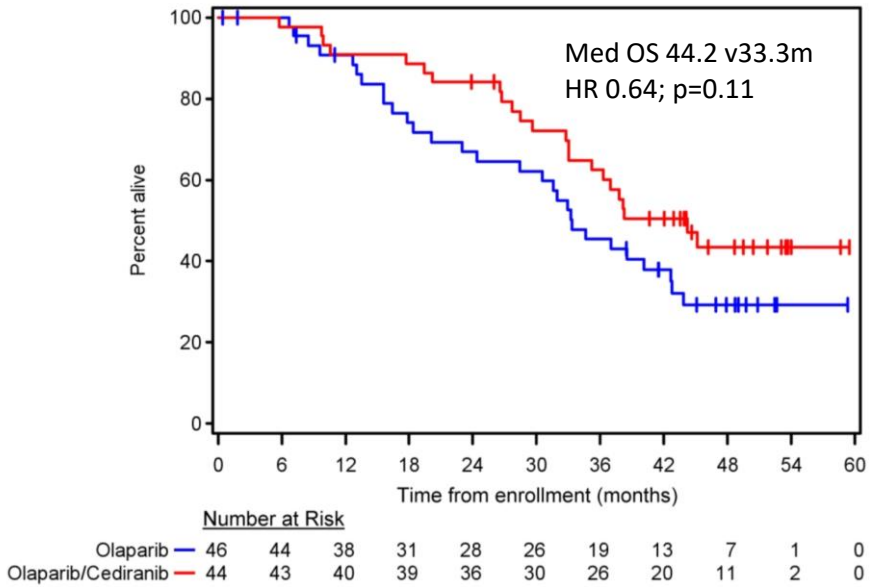
Liu et al Lancet Oncol 2014

Randomised phase II trial of cediranib and olaparib versus olaparib in 'platinum-sensitive' relapsed ovarian cancer

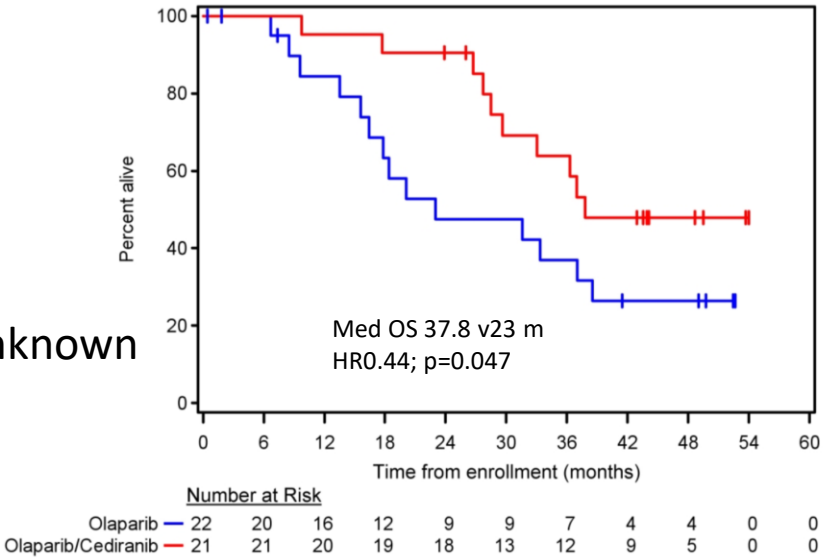


BRCA^{mut}





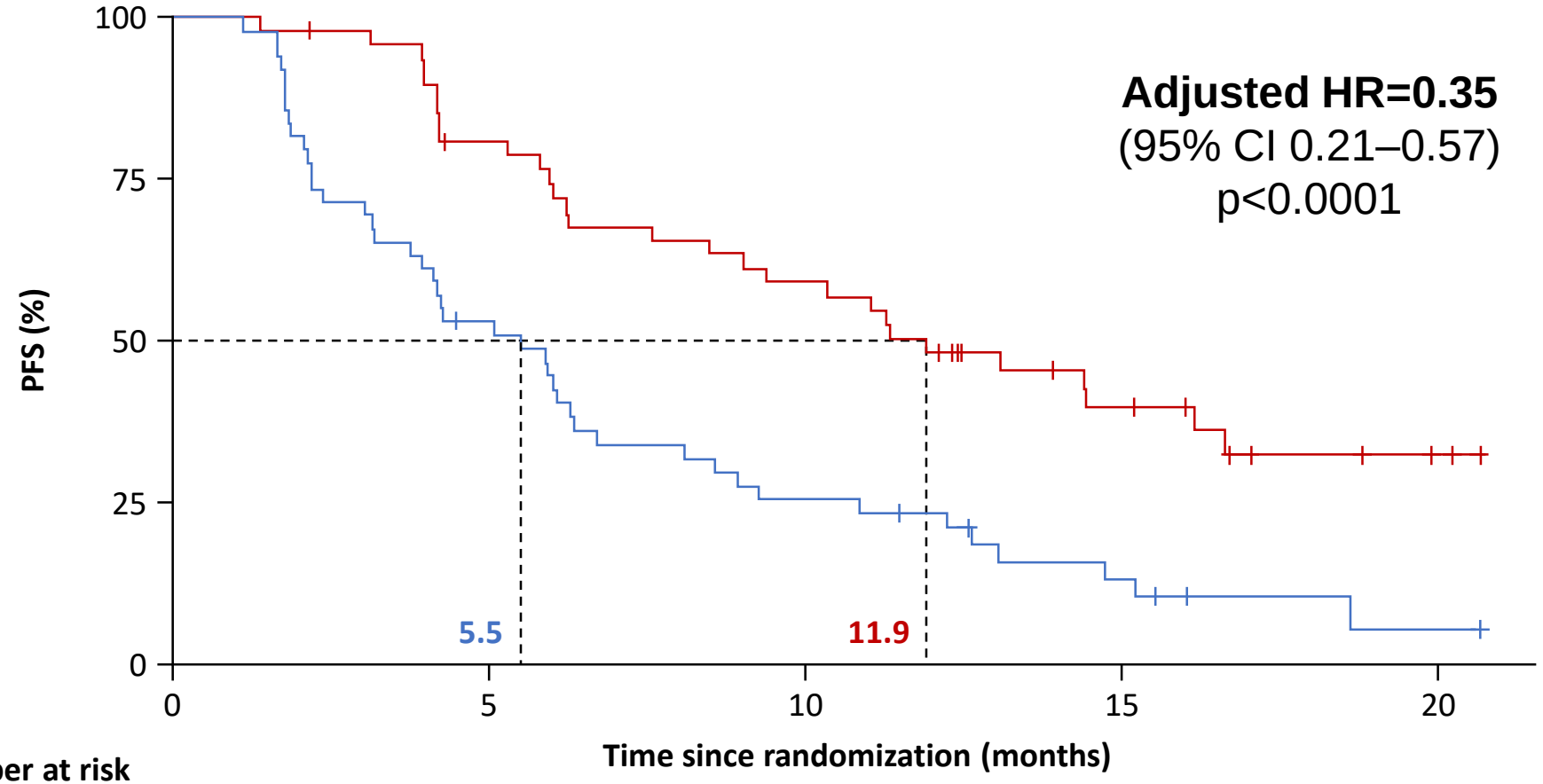
BRCA^{wt}/unknown



Liu et al Ann Oncol 2019

AVANOVA2: Niraparib + bevacizumab versus niraparib in ‘platinum-sensitive’ relapsed ovarian cancer

Primary endpoint: PFS in the ITT population



Number at risk					
Niraparib + bevacizumab	48	37	27	14	5
Niraparib	49	25	12	5	1

CI = confidence interval; HR = hazard ratio

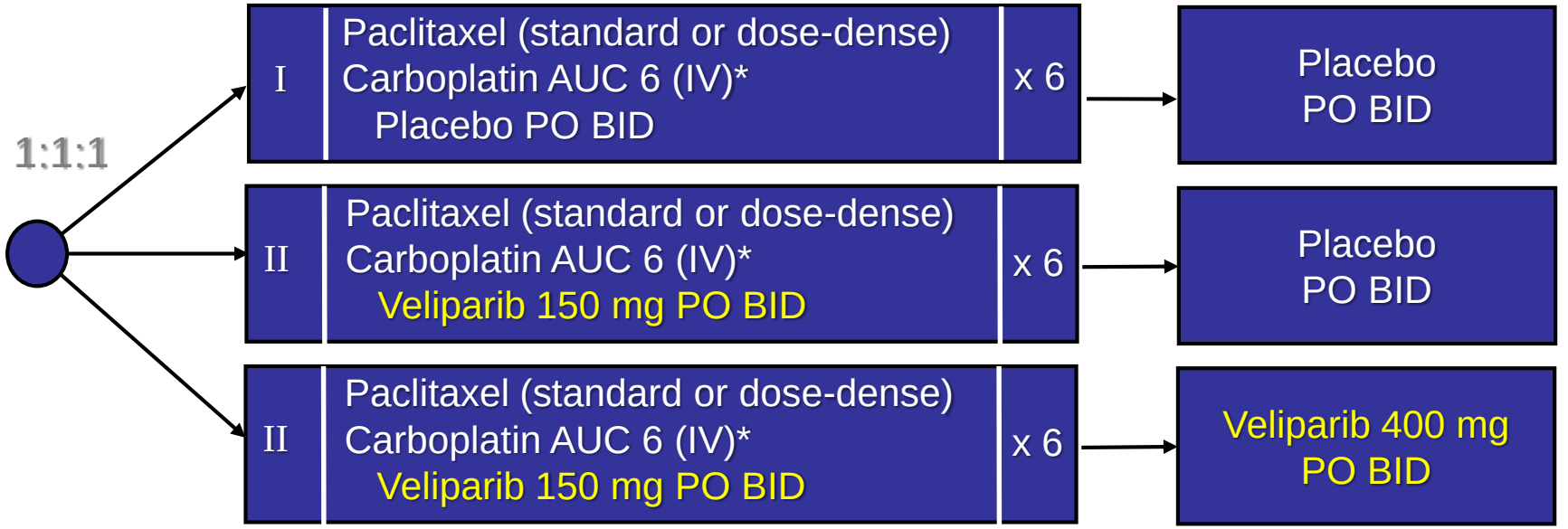
Mizra et al ASCO 2019

What’s coming…..?

PARP inhibitor- Veliparib: GOG3005 'Velia'

In combination with Primary Therapy & Maintenance

- High-grade extrauterine serous tumors, Stage I-C, II, III, IV
- Election for NACT-ICS and scheduling of paclitaxel (no IP therapy)
- Primary endpoint PFS: (1) Entire Population, (2) BRCA1/2 Population
- Stratifications: Stage, Residual Disease, NACT-ICS, Region, gBRCA status



Collaborative development with AbbVie (M13-694) including international participation, seeking EMA and FDA regulatory approval

Open: JUL 2015 (856 as of 07FEB2017)
Closed:
Target Accrual: ~1100 pts (264 BRCA1/2 +)

Coleman R, for GOG Foundation

First-Line Maintenance in Ovarian Cancer

SOLO-1- in *BRCA*^{mut}

- St III-IV Ov
- BRCA mutation
- HG serous or endometrioid
- PR/CR & ≥ 6 cycles

R 2:1

- Olaparib (PO) 300 mg tablet BID
- Placebo

Primary endpoint:
- PFS

Secondary:
- OS
- PFS2
- QoL

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

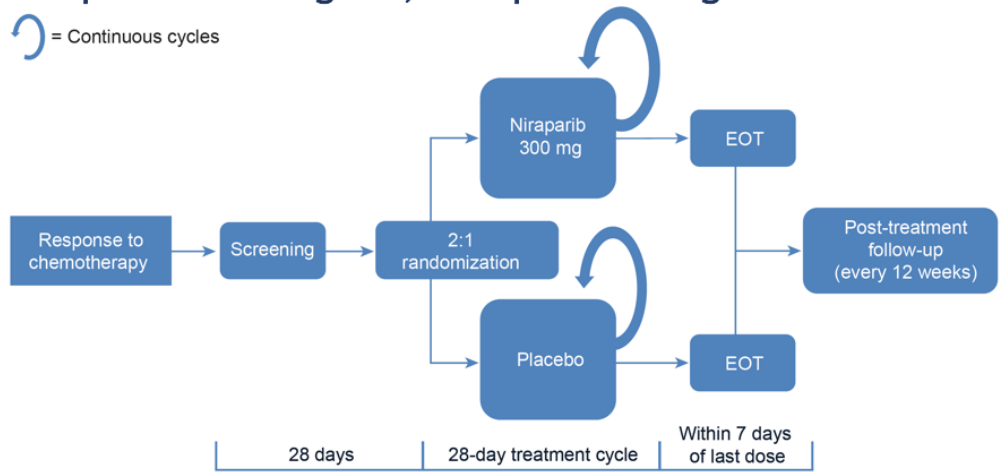
- Patients with sBRCA or tBRCAmut will be stratified as HRDpos
- Patients with unknown or wild type BRCA will be stratified based on HRD test results

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

PRIMA: Niraparib in ovarian cancer

High Risk patients: Stage IV; suboptimal Stage III



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

GY004 assesses olaparib +/- cediranib versus standard platinum-based chemotherapy in patients with platinum-sensitive relapsed ovarian cancer

Phase III, randomised, open-label study

- Platinum-sensitive high-grade ovarian cancer* (serous or endometrioid)
- PR or CR with prior line of platinum therapy
- Up to 1 non-platinum-based line of therapy in the recurrent setting
- Evaluable disease
- No prior anti-angiogenic agent in the recurrent setting; exposure in front-line setting permitted
- ECOG PS 0–2

Randomise 1:1:1
N=565
+ 12 C+O Japanese patients

Stratification:

gBRCA mutation (yes vs no)

Prior anti-angiogenic therapy (yes vs no)

Platinum-free interval on last line of treatment (6–12 vs >12 months)

Olaparib
300mg *po* bid

Cediranib
30mg *po* qd
+
Olaparib
200mg *po* bid

Treatment of Physician's Choice[†]

Primary endpoint
- PFS (RECIST 1.1)

Secondary endpoints
- OS
- Safety
- HRQoL
- Patient-reported scores of disease-related symptoms

Other outcome measures
- PFS2

359 sites in US, Canada and Japan
Study start date: June 2015
*Status: Suspended***
Primary readout: 4Q 2019

*Includes patients with primary peritoneal and/or fallopian tube cancer.
Other specified histologies permitted if patients have a known or suspected deleterious g*BRCA*m
[†]Of Platinum-based chemotherapy
**Suspended for the evaluation of the six accrued Japanese patients
PR=partial response; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; C=cediranib; O=olaparib; po=by mouth; bid=twice daily; qd=once daily; PFS=progression free survival; RECIST=response evaluation criteria in solid tumours; OS=overall survival; HRQoL=health-related quality of life; PFS2=time to second progression
https://clinicaltrials.gov/ct2/show/NCT02446600

ENGOT ov 35

A phase III randomised study evaluating **maintenance** olaparib and cediranib or olaparib alone in relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy

Relapsed platinum sensitive ovarian, fallopian tube, primary peritoneal cancer (1st relapse)

→

Following completion of 6 cycles (min 4 cycles) of chemotherapy, if CT/MRI show 'CR' or 'PR' and patients are eligible they will be randomised

→

Arm 1

Olaparib
+
Cediranib

Arm 2

Olaparib

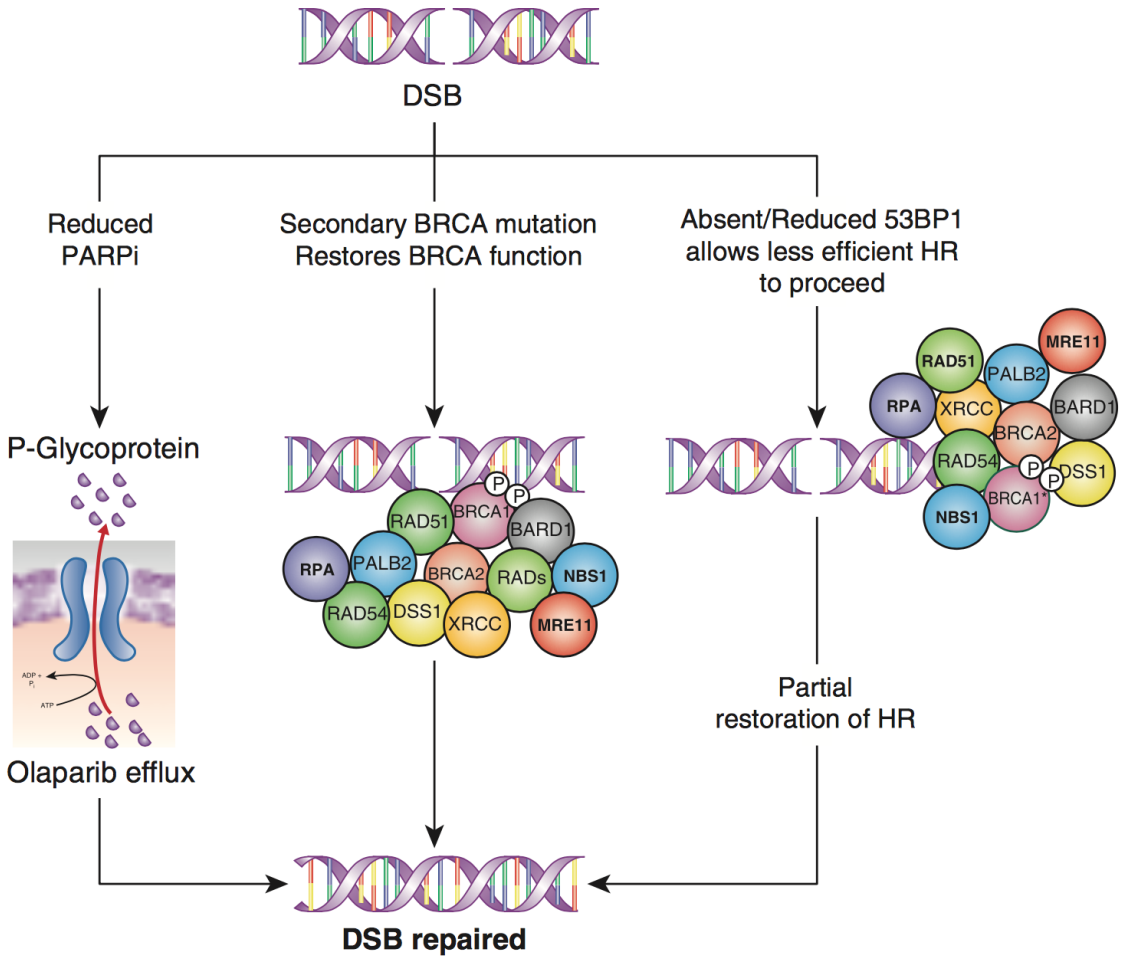
Patient Number: 618 (max 250 BRCA mutant)
Stratified by 6-12 vs >12 month progression free interval; surgery vs no surgery at relapse prior to chemotherapy; prior bevacizumab therapy; BRCA status; country

Olaparib: 300 mg tablets BD
Cediranib: 20 mg tablets OD

Conclusions

- PARP inhibitors – a new class of drug targeting DNA repair pathways
- Deficiency of (HRD) Homologous recombination repair of DNA is the phenotypic marker of activity
- Platinum sensitivity (response) is the best identifier of activity in recurrent disease. Highest level of activity seen in *BRCA* mutation carriers
- Significant benefit in PFS seen with olaparib maintenance in first-line treatment of *BRCA*^{mut} high grade cancers
- Increasing use in first-line will affect subsequent use at relapse. Understanding the mechanisms underlying resistance is key to optimum use and re-use of PARP inhibitors

Resistance to PARP Inhibitors

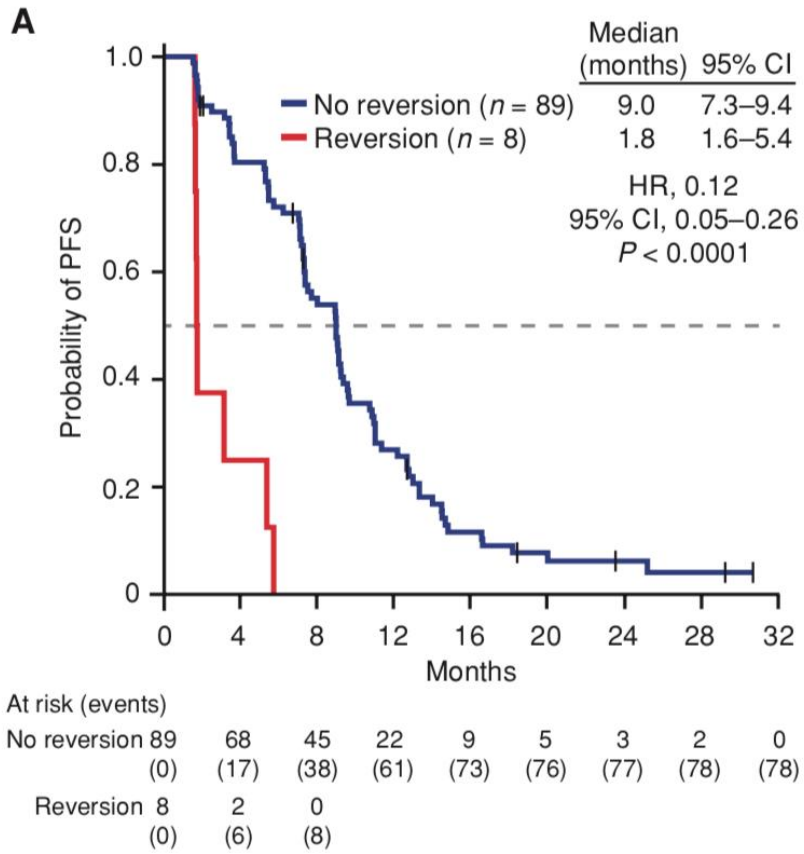


- Trend for shorter response time in patients without a *BRCA* mutation, or partial response to platinum-based chemotherapy
- Reversion of *BRCA* mutations detected in tumour and cfDNA
- Increase P-Glycoprotein efflux pump
- Increased expression of RAD51
- Loss of 53BP1 restores HR
- Increased miR-622 supresses NHEJ and leads to increased DSB repair

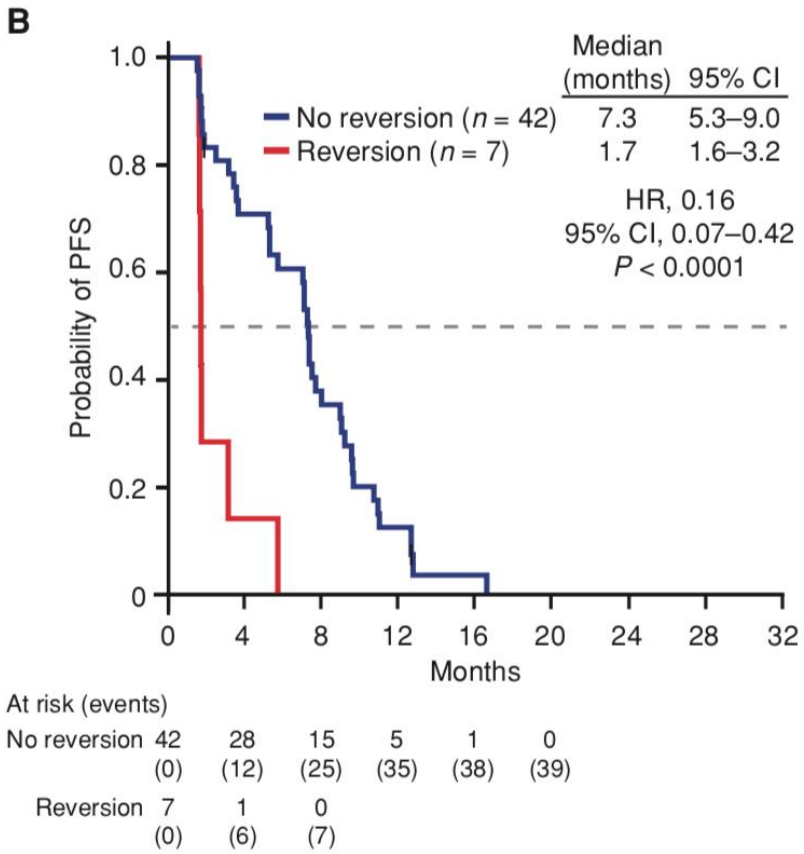
Fojo & Bates Cancer Disc 2013

BRCA reversion mutations in cfDNA and response to rucaparib

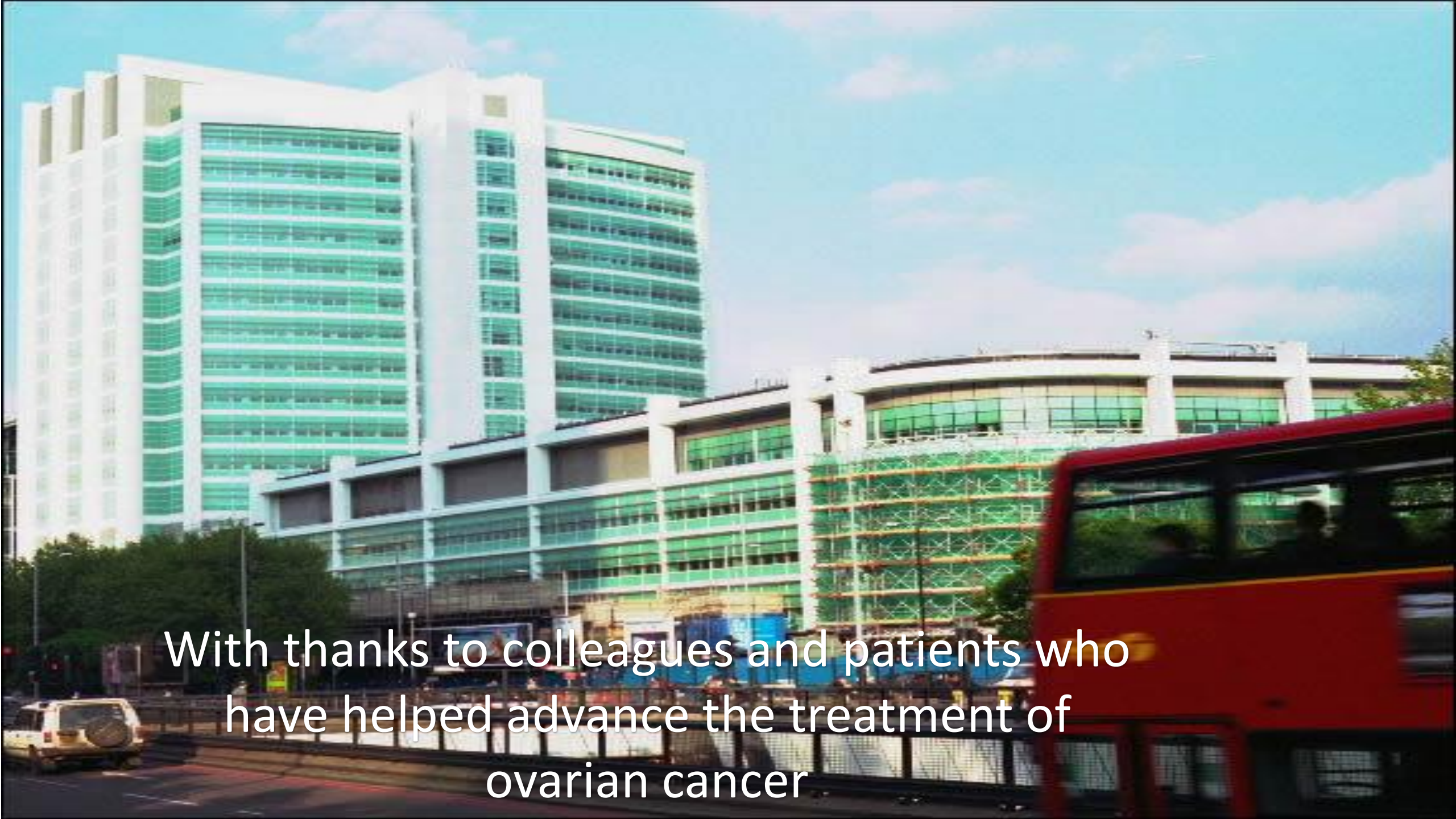
All patients with *BRCA*^{mut}



Platinum 'resistant/refractory' disease



Lin et al Cancer Disc 2019


With thanks to colleagues and patients who have helped advance the treatment of ovarian cancer