PARPi a imunoterapie v léčbě ovariálního karcinomu

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PARPi

První linie léčby

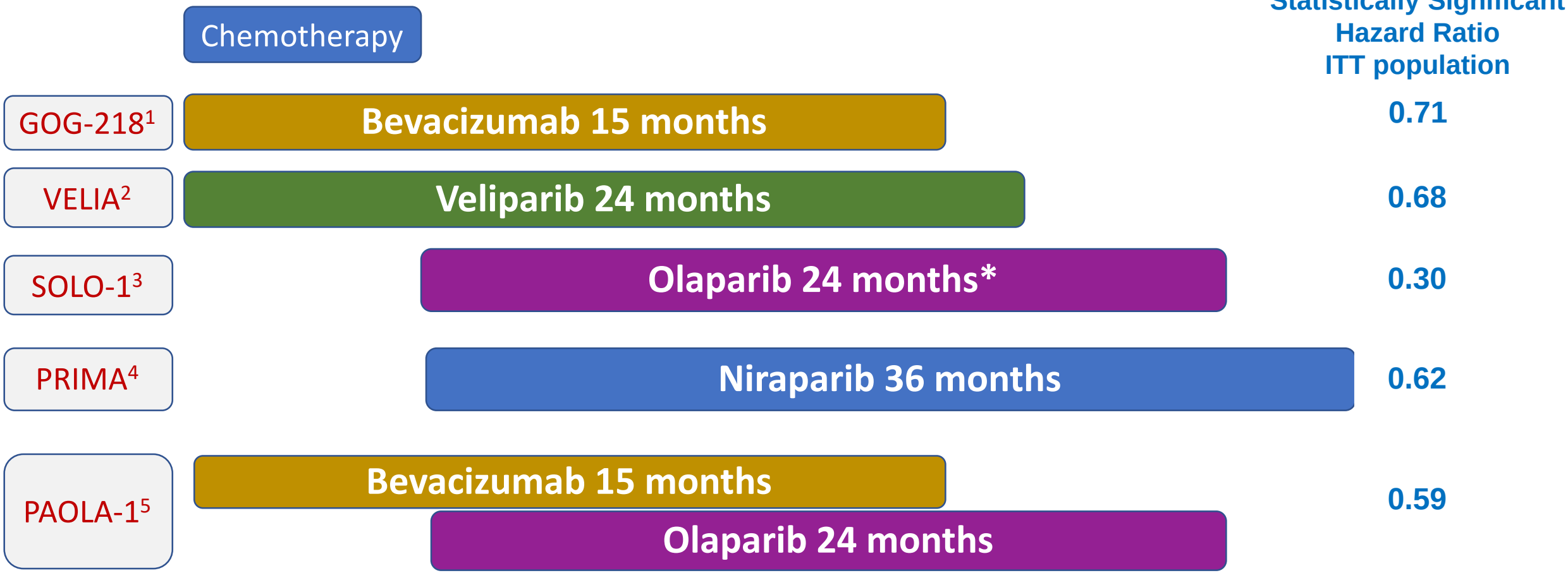
Recidivující OC

Toxicita

Imunoterapie

Současná doporučení

Phase III trials with maintenance in front line



* Only BRCA mut

1.Burger. NEJM 2011; 2 .Coleman. NEJM 2019; 3. Moore. NEJM 2018; 4. Gonzalez-Martin. NEJM 2019; 5. Ray-Coquard. NEJM 2019

SOLO-1 was the first Phase III trial to investigate maintenance PARP inhibitor treatment in newly diagnosed advanced ovarian cancer[1,2]

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

- Newly diagnosed, FIGO Stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic BRCAm
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical CR or PR after platinum-based chemotherapy

Olaparib 300 mg BID (n=260)

2:1 randomisation
Stratified by response to platinum-based chemotherapy

Placebo (n=131)

- Study treatment continued until disease progression
- Patients with NED at 2 years stopped treatment
- Patients with a PR at 2 years could continue treatment

2 years' treatment if NED

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

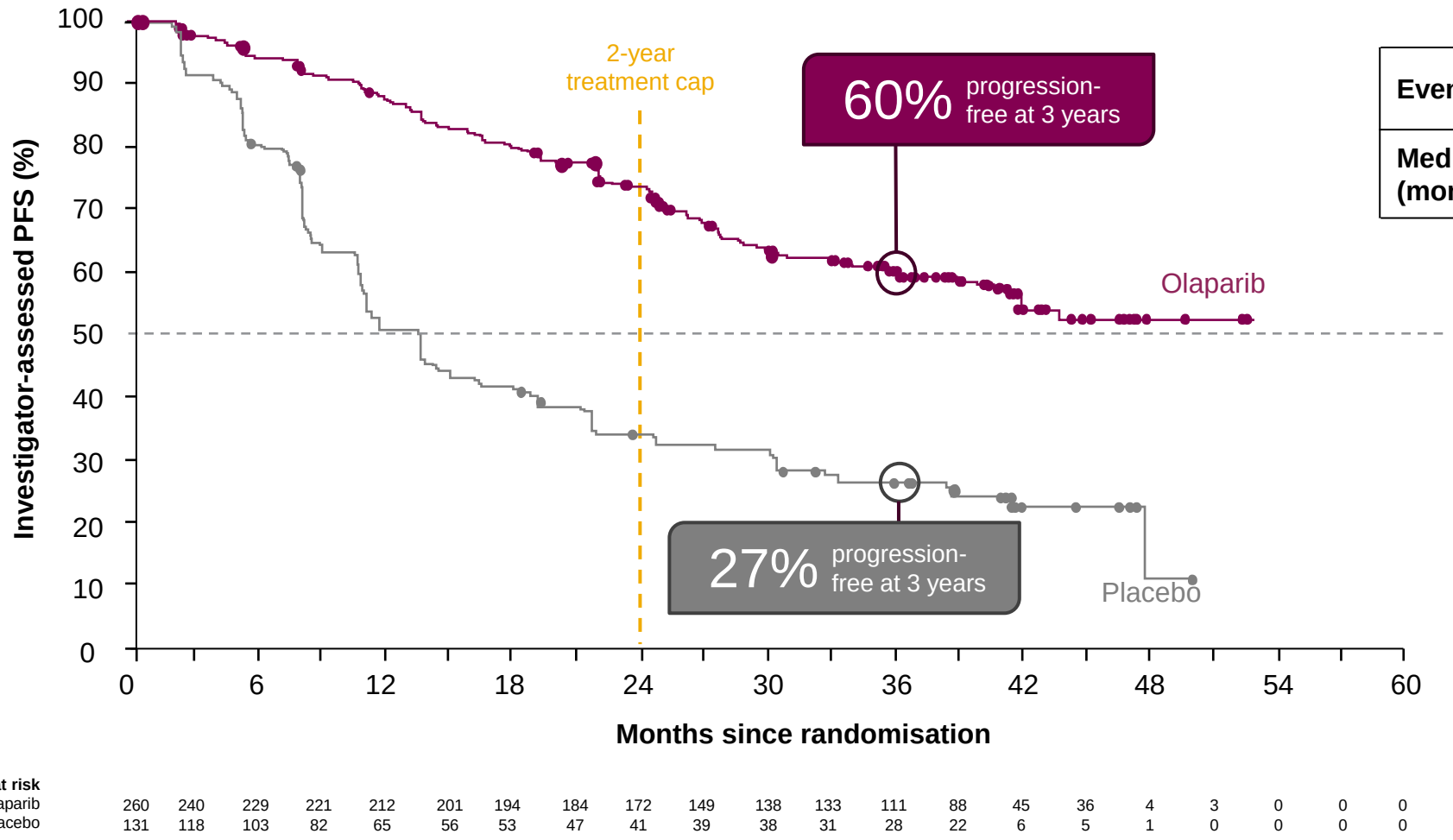
Secondary endpoints

- PFS using BICR
- PFS2
- OS
- TFST
- TSST
- 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; BID=twice daily; BRCAm=BRCA mutation; CR=complete response; 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; NED=no evidence of disease;
OS=overall survival; PFS=progression-free survival; PFS2=time to second progression or death; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours;
TFST=time from randomisation to first subsequent therapy or death; TSST=time from randomisation to second subsequent therapy or death; TOI=Trial Outcome Index

1. Moore K, et al. N Engl J Med. 2018;379:Clinical Study Protocol; 2. Moore K, et al. N Engl J Med. 2018;379:2495–2505

Olaparib reduced the risk of progression or death by 70% vs. watch and wait placebo



	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	102 (39)	96 (73)
Median PFS (months)	NR	13.8
	HR 0.30 95% CI 0.23–0.41 p<0.001	

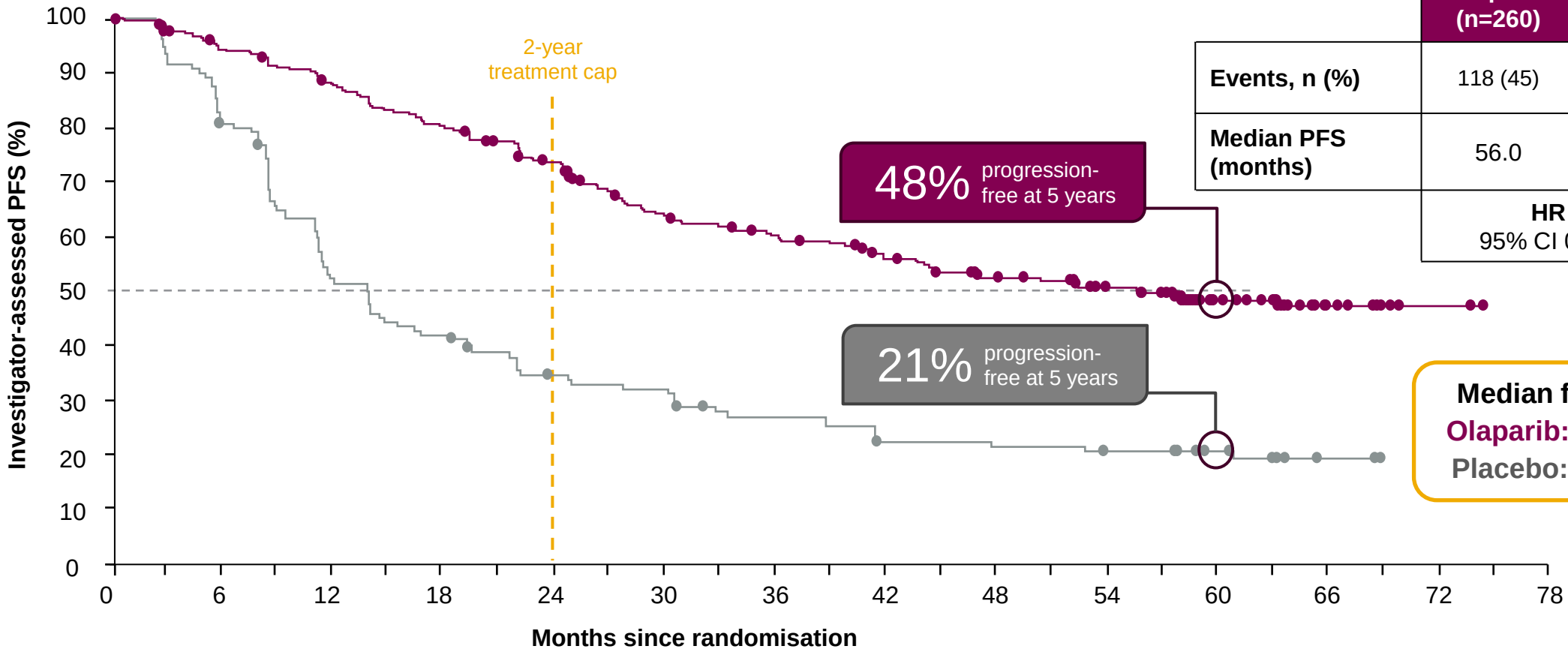
Primary endpoint:
investigator-assessed PFS

BICR analysis of PFS was consistent with the primary endpoint

Investigator-assessed PFS
DCO: May 2018; median follow-up: olaparib 40.7 months, placebo 41.2 months
Analysis was performed after 198 progression events had occurred (in 51% of patients)
BICR=blinded independent centralised review; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; NR=not reached; PFS=progression-free survival

Moore K, et al. N Engl J Med. 2018;379:2495–2505

After 5 years' follow-up, the PFS benefit derived from maintenance olaparib was sustained substantially beyond the end of treatment



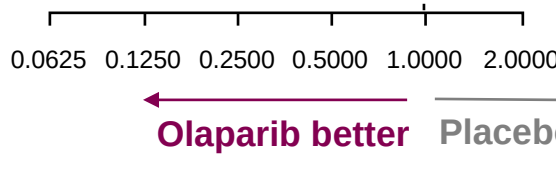
	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)
Median PFS (months)	56.0	13.8
	HR 0.33 95% CI 0.25–0.43	

Median follow-up
Olaparib: 4.8 years
Placebo: 5.0 years

Investigator-assessed PFS
DCO: March 2020; median follow-up: olaparib 4.8 years, placebo 5.0 years
CI=confidence interval; DCO=data cut-off; HR=hazard ratio; PFS=progression-free survival
Banerjee S, et al. Presented at ESMO Virtual Congress 2020. 19–21 September. Abstract #811MO

A consistent benefit was seen across all PFS subgroups

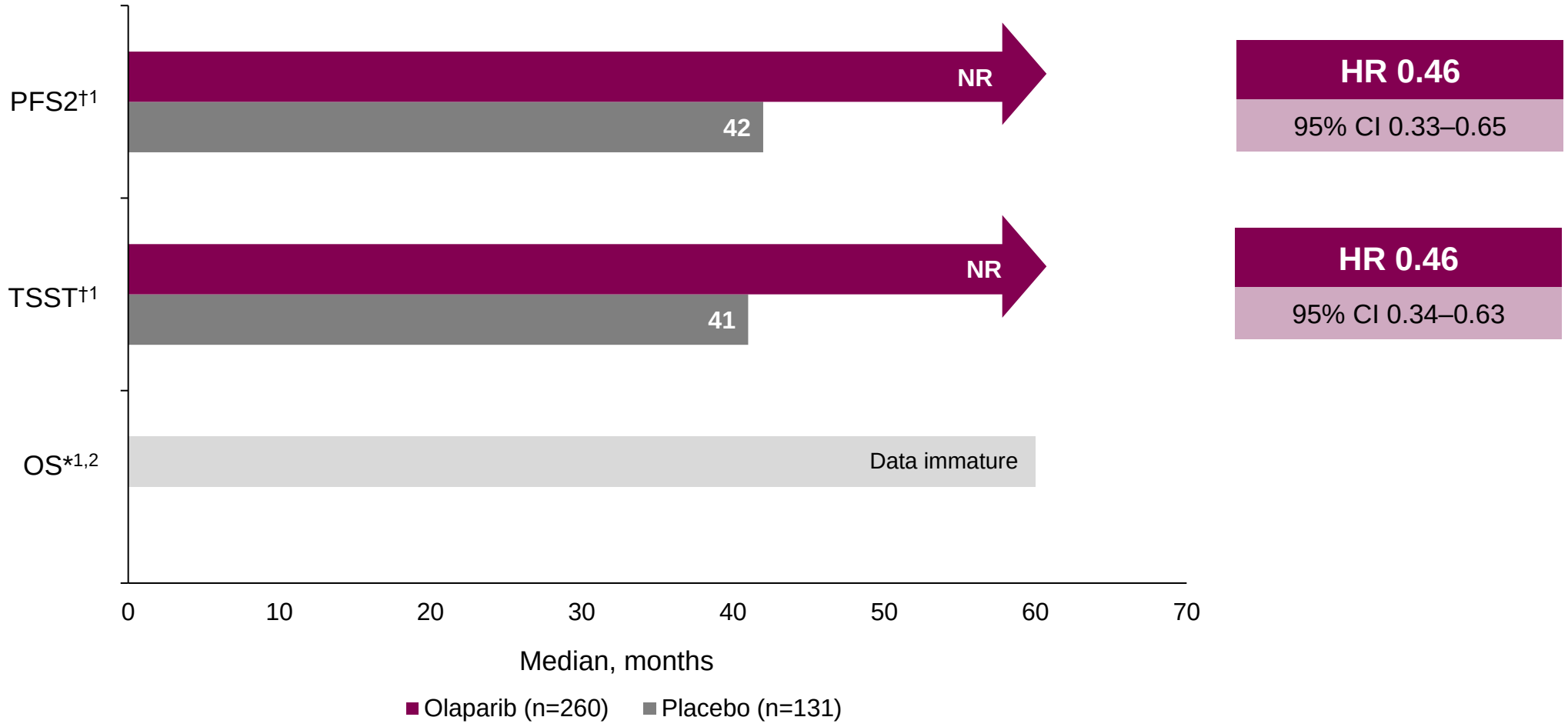
Subgroup	Olaparib	Placebo	HR (95% CI)
	Number of patients with events/total number of patients (%)		
All patients	102/260 (39)	96/131 (73)	0.30 (0.23–0.41)
Response to previous chemotherapy			
CR	73/213 (34)	73/107 (68)	0.35 (0.26–0.49)
PR	29/47 (62)	23/24 (96)	0.19 (0.11–0.34)
ECOG performance status at baseline			
Normal activity	75/200 (38)	76/105 (72)	0.33 (0.24–0.46)
Restricted activity	27/60 (45)	20/25 (80)	0.38 (0.21–0.68)
Baseline CA-125 value			
≤ULN	92/247 (37)	89/123 (72)	0.34 (0.25–0.46)
>ULN	10/13 (77)	7/7 (100)	NC
gBRCAm type by Myriad testing			
BRCA1	84/188 (45)	69/91 (76)	0.40 (0.29–0.56)
BRCA2	15/62 (24)	26/39 (67)	0.20 (0.10–0.38)
BRCA1/2 (both)	0/3 (0)	0/0 (0)	NC
Negative	3/7 (43)	1/1 (100)	NC
Age			
<65 years	85/225 (38)	82/112 (73)	0.33 (0.24–0.45)
≥65 years	17/35 (49)	14/19 (74)	0.45 (0.22–0.92)
Stage of disease at initial diagnosis			
Stage III	83/220 (38)	79/105 (75)	0.32 (0.24–0.44)
Stage IV	19/40 (48)	17/26 (65)	0.49 (0.25–0.94)
Following debulking surgery prior to study entry			
Residual macroscopic disease	29/55 (53)	23/29 (79)	0.44 (0.25–0.77)
No residual macroscopic disease	70/200 (35)	69/98 (70)	0.33 (0.23–0.46)



Investigator-assessed PFS
DCO: May 2018; median follow-up: olaparib 40.7 months, placebo 41.2 months
CA-125=cancer antigen 125; CI=confidence interval; CR=complete response; DCO=data cut-off; ECOG=Eastern Cooperative Oncology Group; gBRCAm=germline BRCA mutation; HR=hazard ratio; NC=not calculable; PFS=progression-free survival; PR=partial response; ULN=upper limit of normal

Moore K, et al. N Engl J Med. 2018;379:2495–2505

After 5 years' follow-up, patients continued to derive benefit from olaparib in a range of efficacy endpoints at long-term follow-up[1]

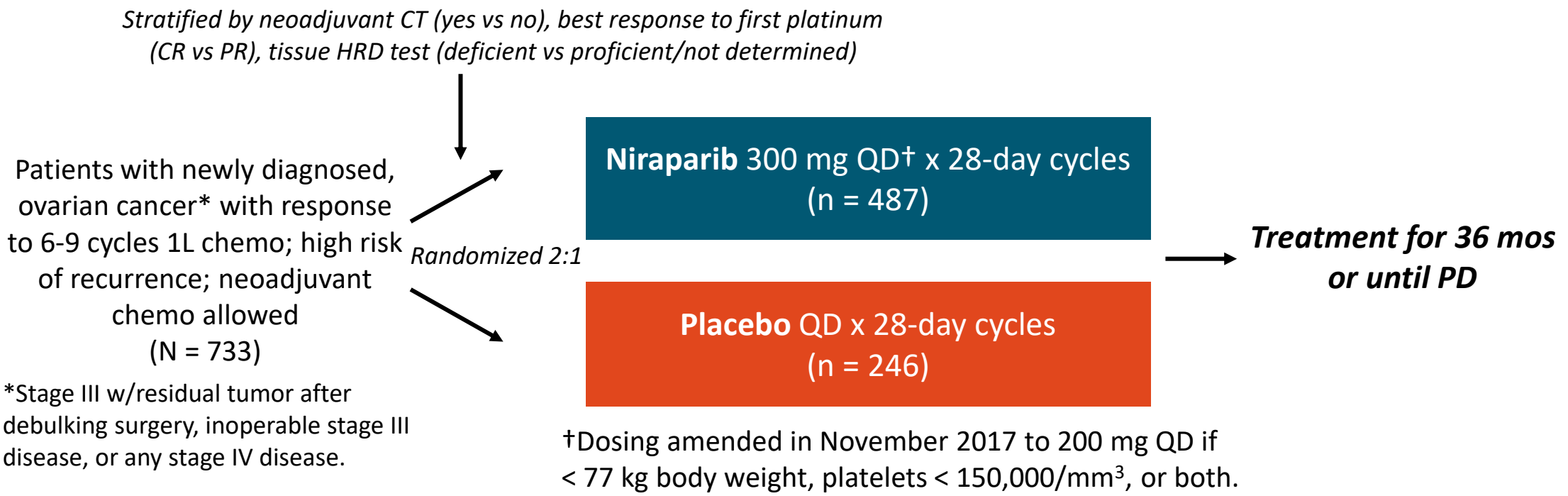


*TFST data from the primary DCO of May 2018. Median follow-up: olaparib 40.7 months, placebo 41.2 months
†Data are from the 5-year follow-up DCO of March 2020. Median follow-up: olaparib 4.8 years, placebo 5.0 years
CI=confidence interval; DCO=data cut-off; HR=hazard ratio; NR=not reached; OS=overall survival; PFS2=time to second progression or death; TFST=time to first subsequent treatment or death; TSST=time to second subsequent treatment or death

1. Banerjee S, et al. Presented at ESMO Virtual Congress 2020. 19–21 September. Abstract #811MO; 2. Moore K, et al. N Engl J Med. 2018;379:2495–2505

PRIMA: Maintenance Niraparib vs Placebo in Ovarian Cancer at High Risk of Recurrence After 1L Platinum

- Randomized, double-blind, placebo-controlled phase III trial (active, not recruiting, as of 10/2020)



- Primary endpoint: PFS (hierarchical HRD+ first and then overall population)
- Secondary endpoints: OS, PFS2, QoL PROs, safety

Gonzalez-Martin. NEJM. 2019;381:2391. Mirza. ASCO 2020. Abstr 6050.

Slide credit: clinicaloptions.com

PRIMA: Baseline Characteristics

Characteristic	Niraparib (n = 487)	Placebo (n = 246)
Median age, yrs (range)	62 (32-85)	62 (33-88)
ECOG PS 0/1, %	69.2/30.8	70.7/29.3
Stage at diagnosis, %		
▪ III	65.3	64.2
▪ IV	34.7	35.8
Prior adjuvant chemotherapy, %		
▪ Yes	66.1	67.9
▪ No	33.9	32.1
Best response to platinum chemotherapy, %		
▪ CR	69.2	70.0
▪ PR	30.8	30.0

- PRIMA included patients with a poor prognosis
  - Residual disease after primary debulking surgery: 85%
  - Stage IV disease: 35%
  - PR to first-line platinum chemotherapy: 31%

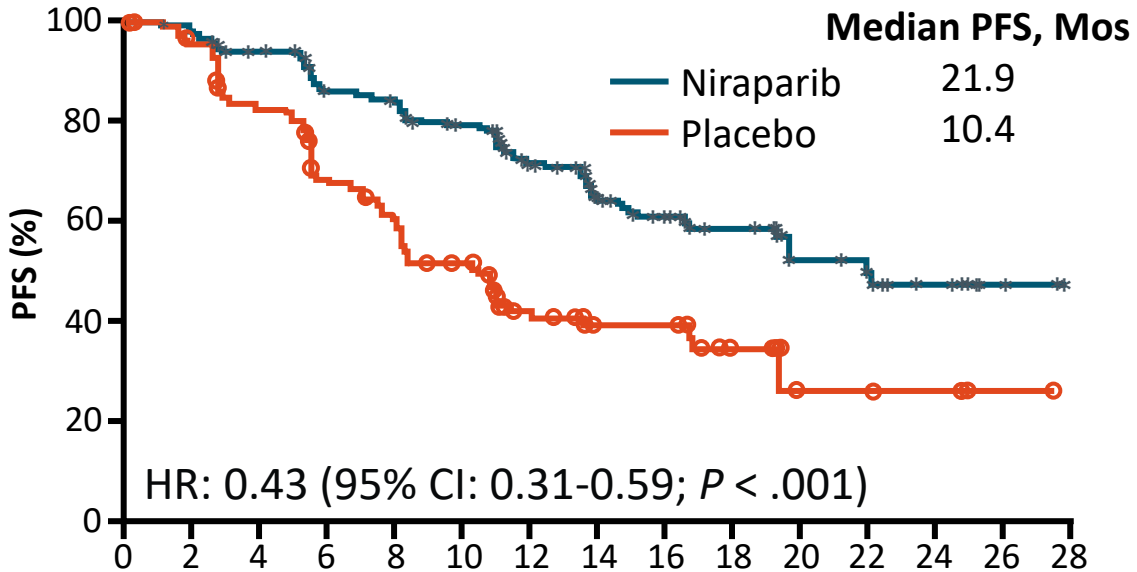
Gonzalez-Martin. NEJM. 2019;381:2391.

Slide credit: clinicaloptions.com

Phase III PRIMA Trial of Maintenance Niraparib After Initial Therapy for Ovarian Cancer

- Patients with newly diagnosed high-grade serous/endometrioid advanced ovarian cancer after CR/PR to first-line platinum-based CT (N = 730); Primary endpoint: PFS by BICR with hierarchical testing in patients with HRD (HR benefit: 0.43) followed by the overall patient population (HR benefit: 0.62)

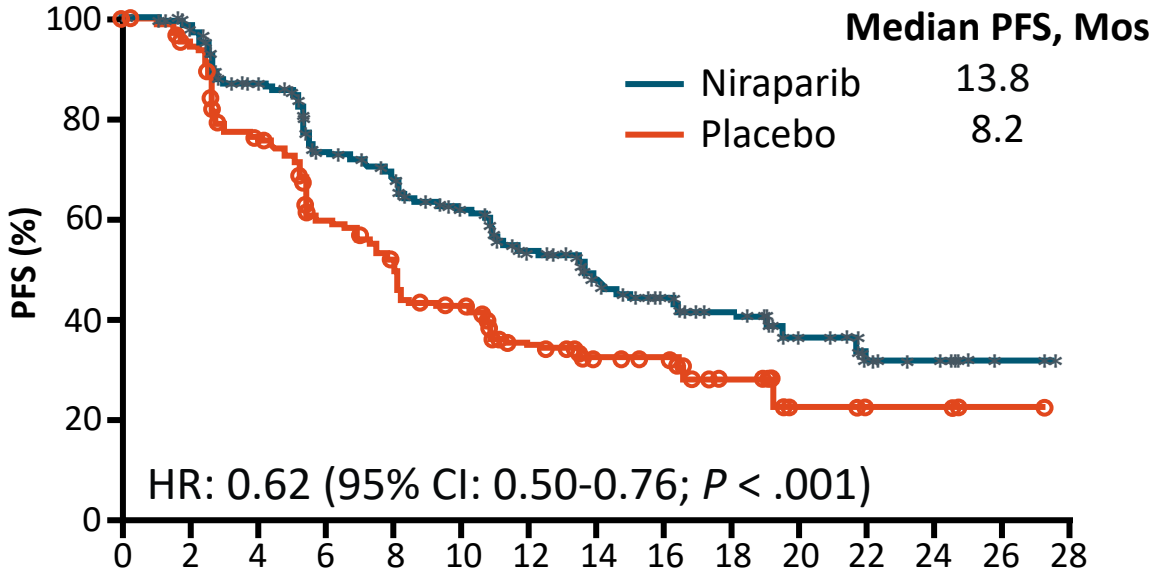
PFS in HRD Population



Pts at Risk, n

Niraparib	247	231	215	189	184	168	111	76	66	42	22	19	13	4	0
Placebo	126	117	99	79	70	57	34	21	21	11	5	5	4	1	0

PFS in Overall Patient Population



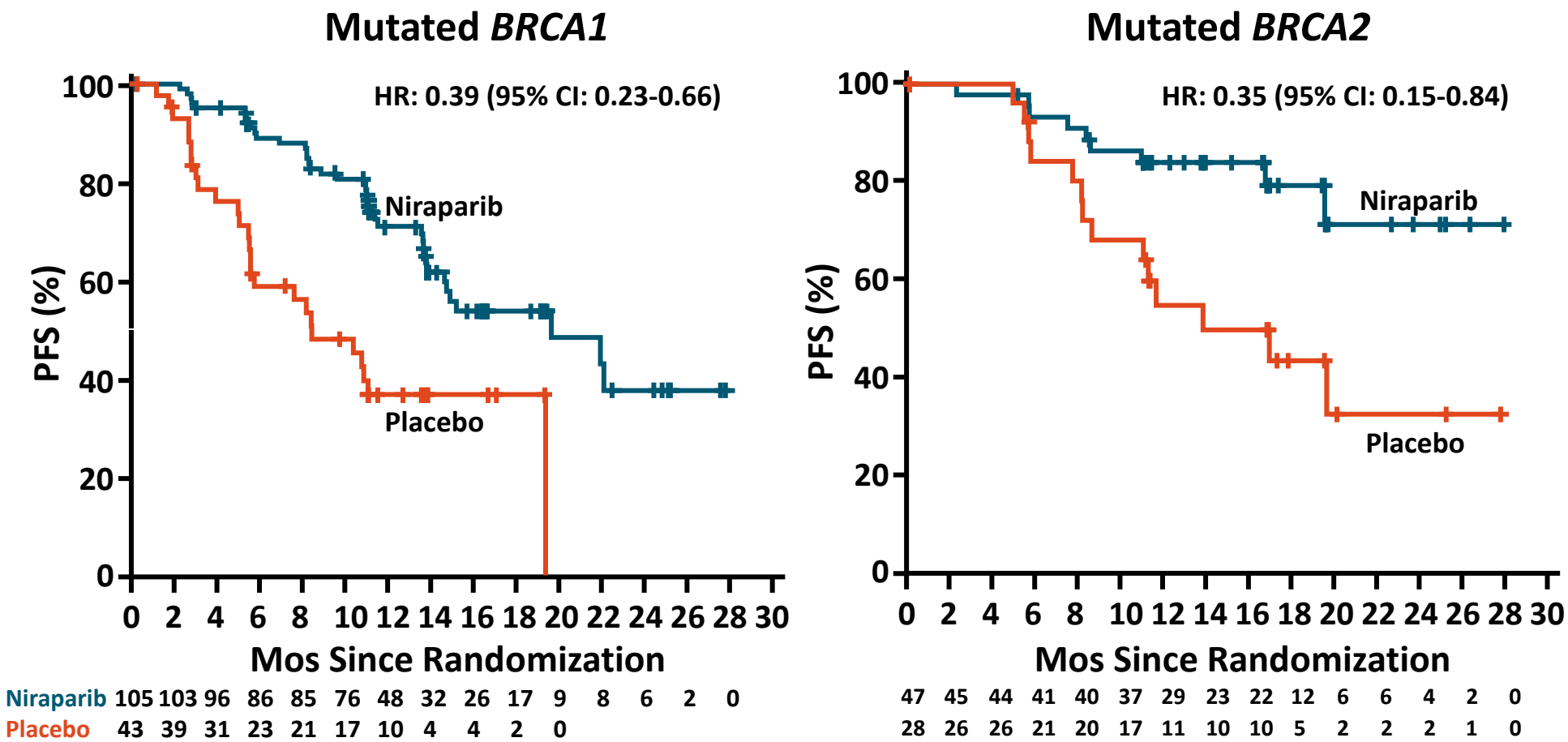
Pts at Risk, n

Niraparib	487	454	385	312	295	253	167	111	94	58	29	21	13	4	0
Placebo	246	226	177	133	117	90	60	32	29	17	6	6	4	1	0

González-Martin. NEJM. 2019;381:2391. González-Martin. ESMO 2019. Abstr LBA1.

Slide credit: clinicaloptions.com

PRIMA: PFS in Patients With Mutated *BRCA1* vs *BRCA2*

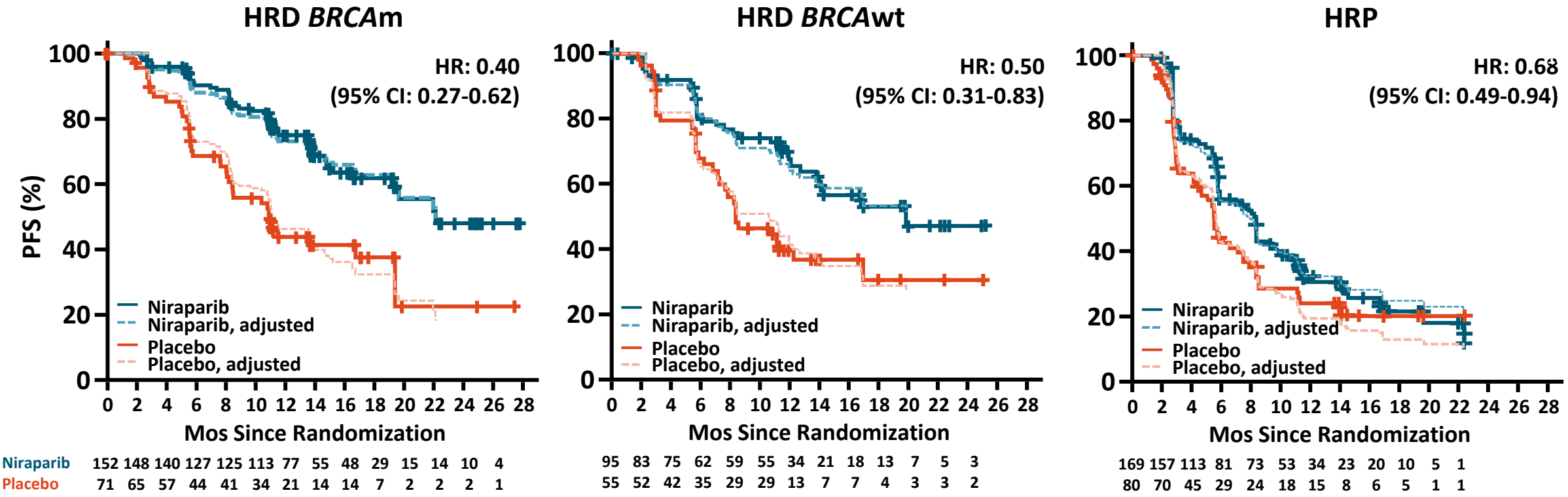


Niraparib efficacy was similar in mutated *BRCA1* and mutated *BRCA2*

Monk. SGO 2020. Webinar 2.

Slide credit: clinicaloptions.com

PRIMA: PFS in Patients With HRD and HRP (by BICR)



- Niraparib provided clinical benefit in the HRD (*BRCA*m and *BRCA*wt) and HRP subgroups
- All subgroups analyzed using adjusted Cox regression to account for stratification imbalances

Monk. SGO 2020. Webinar 2.

Slide credit: clinicaloptions.com

PAOLA-1/ENGOT-ov25 trial design

Patients:
- Newly diagnosed, FIGO stage III–IV high-grade serous or endometrioid ovarian, fallopian tube and/or primary peritoneal cancer*

First-line treatment:
- Upfront or interval surgery
- Platinum-taxane based chemotherapy plus ≥2 cycles of bevacizumab†

≤9 weeks

NED/CR/PR

2:1 randomization stratified by:
- Tumour BRCAm status
- First-line treatment outcome§

Maintenance therapy

Olaparib tablets 300 mg bid x 2 years
+ bevacizumab‡

Placebo x 2 years
+ bevacizumab‡

- Primary endpoint: investigator-assessed PFS (RECIST v1.1)
- In the primary analysis, a statistically significant PFS benefit was observed[1]

Primary PFS analysis (DCO 22 March 2019)

	Olaparib + bev (N=537)	Placebo + bev (N=269)
Median PFS, months	22.1	16.6
HR (95% CI); *P* value	0.59 (0.49–0.72) *P*<0.001	

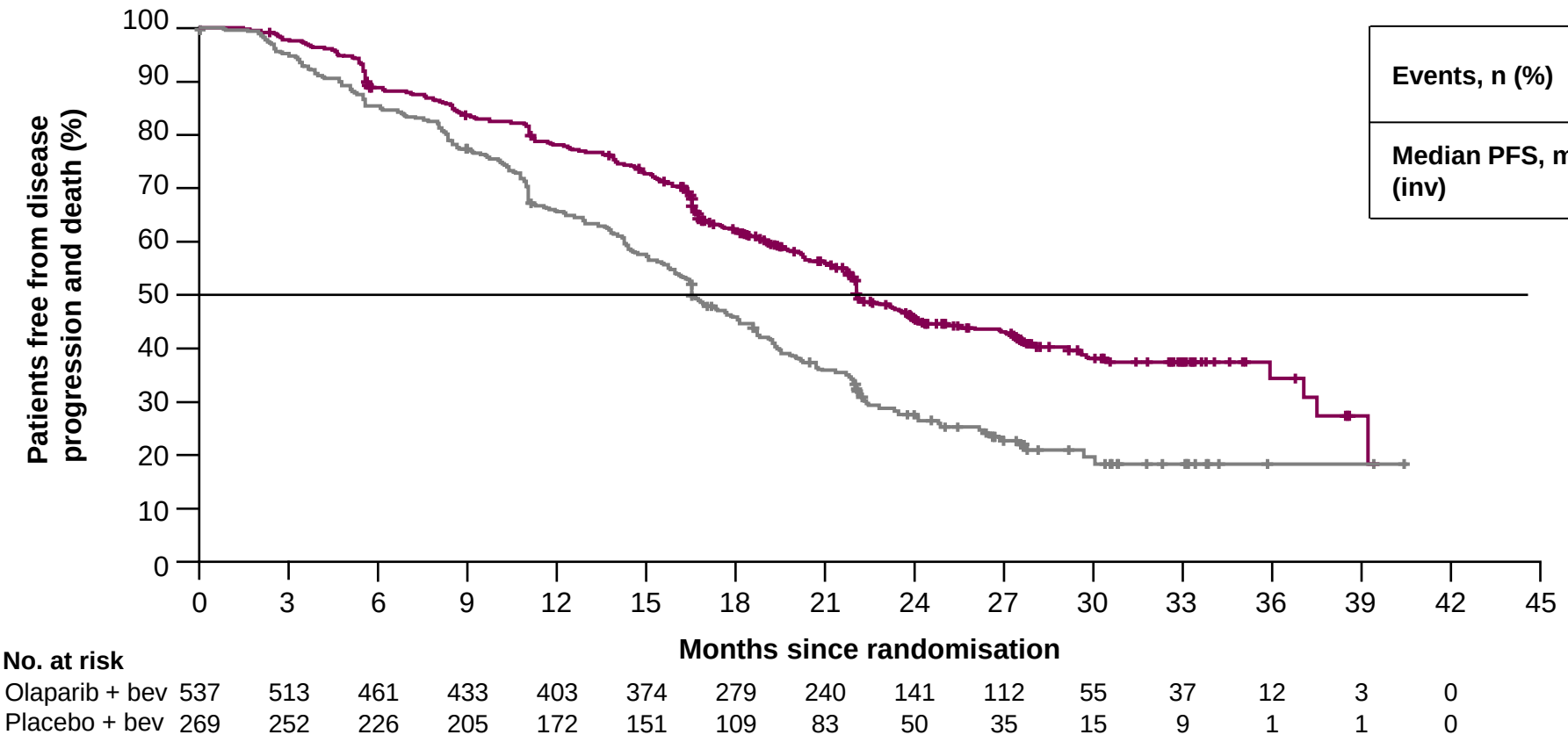
*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation; †Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; ‡Bevacizumab 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; §According to timing of surgery and NED/CR/PR

bid, twice daily; BRCAm, BRCA mutation; CI, confidence interval; CR, complete response; DCO, data cut-off; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NED, no evidence of disease; PFS; time from randomization to progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours;

1. Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28

Olaparib plus bevacizumab significantly improved PFS vs. placebo plus bevacizumab in the ITT population

PFS by BICR was consistent with investigator-assessed PFS, indicating robustness of the result



	Olaparib + bevacizumab n=537	Placebo + bevacizumab n=269
Events, n (%)	280 (52)	194 (72)
Median PFS, months (inv)	22.1	16.6
	HR 0.59 95% CI 0.49–0.72 p<0.001	

Primary endpoint:
investigator-assessed PFS

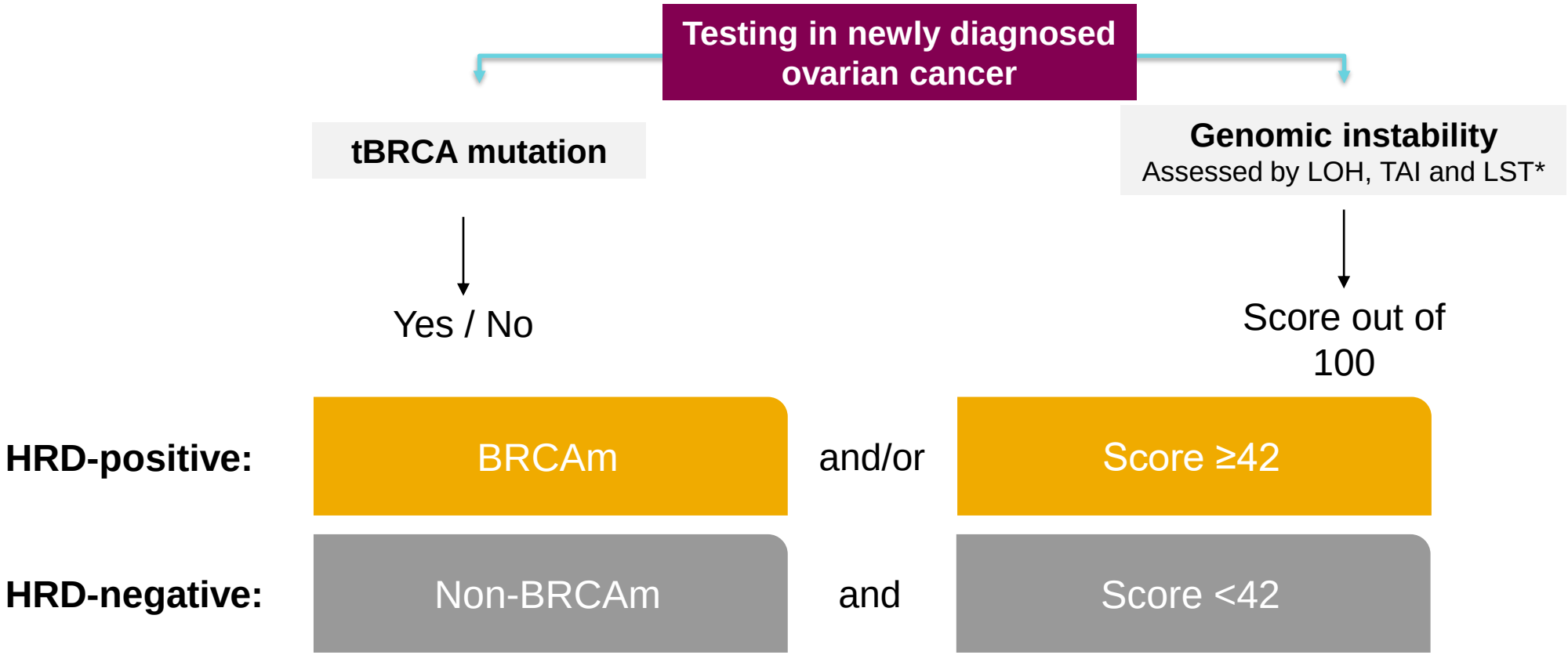
Median time from first cycle of chemotherapy to randomisation = **7 months**[2]

PFS by investigator assessment. Analysis per eCRF. Data maturity=59%
Median duration of follow-up for primary analysis: olaparib, 22.7 months; placebo, 24.0 months
Data cut-off: 22 March 2019
Bev=bevacizumab; CI=confidence interval; eCRF=electronic case report file; HR=hazard ratio; inv=investigator-assessed; ITT=intent to treat; PFS=progression-free survival

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain.

The Myriad myChoice® CDx test defines patients with a BRCAm and/or a genomic instability score ≥42 as HRD-positive[1,2]

HRD-negative is defined as absence of a BRCAm and a genomic instability score <42



* The genomic instability score is calculated from 3 components reflecting tumour genome rearrangements. LOH are regions of intermediate size (>15 Mb and <whole chromosome) in the tumour genome; LST are chromosome breaks (translocations, inversions or deletions) in adjacent segments of DNA ≥10 Mb; and TAI is defined as the number of regions with allelic imbalance which extend to the sub-telomere but do not cross the centromere

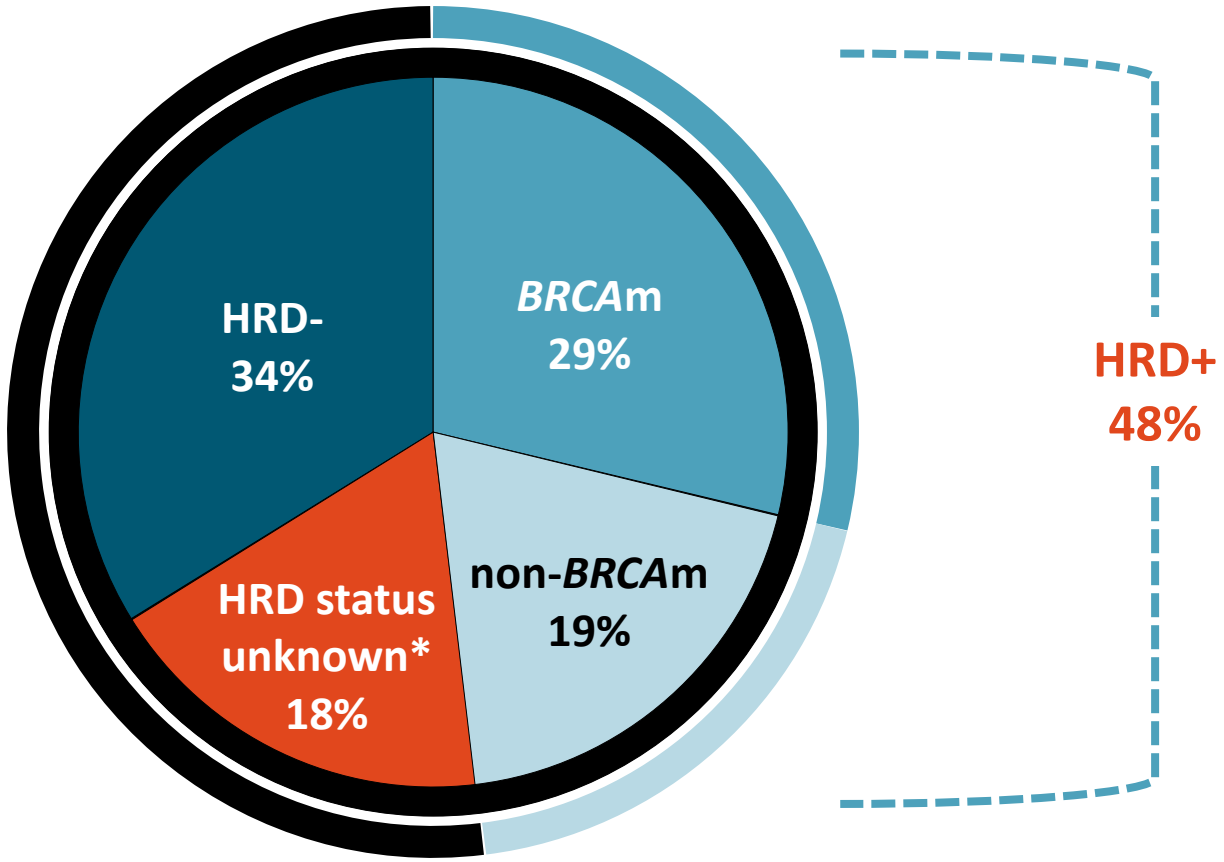
BRCAm=mutation in BRCA; CDx=companion diagnostic; HRD=homologous recombination deficiency; LOH=loss of heterozygosity; LST=large-scale state transitions; TAI=telomeric allelic imbalance; tBRCA=tumour BRCA

1. Myriad myChoice HRD Technical Specifications. Available at: https://myriad-web.s3.amazonaws.com/myChoice/downloads/myChoiceHRDTechSpecs.pdf (accessed September 2020);
2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428

PAOLA-1: Approximately 50% of Patients Were HRD+

- **All trial participants evaluated for HRD using the Myriad myChoice test**

Prevalence of HRD in the PAOLA-1 overall study population consistent with HRD prevalence in the general ovarian cancer population



Based on PAOLA-1, olaparib plus bevacizumab was FDA approved for first-line maintenance therapy in advanced ovarian cancer with HRD

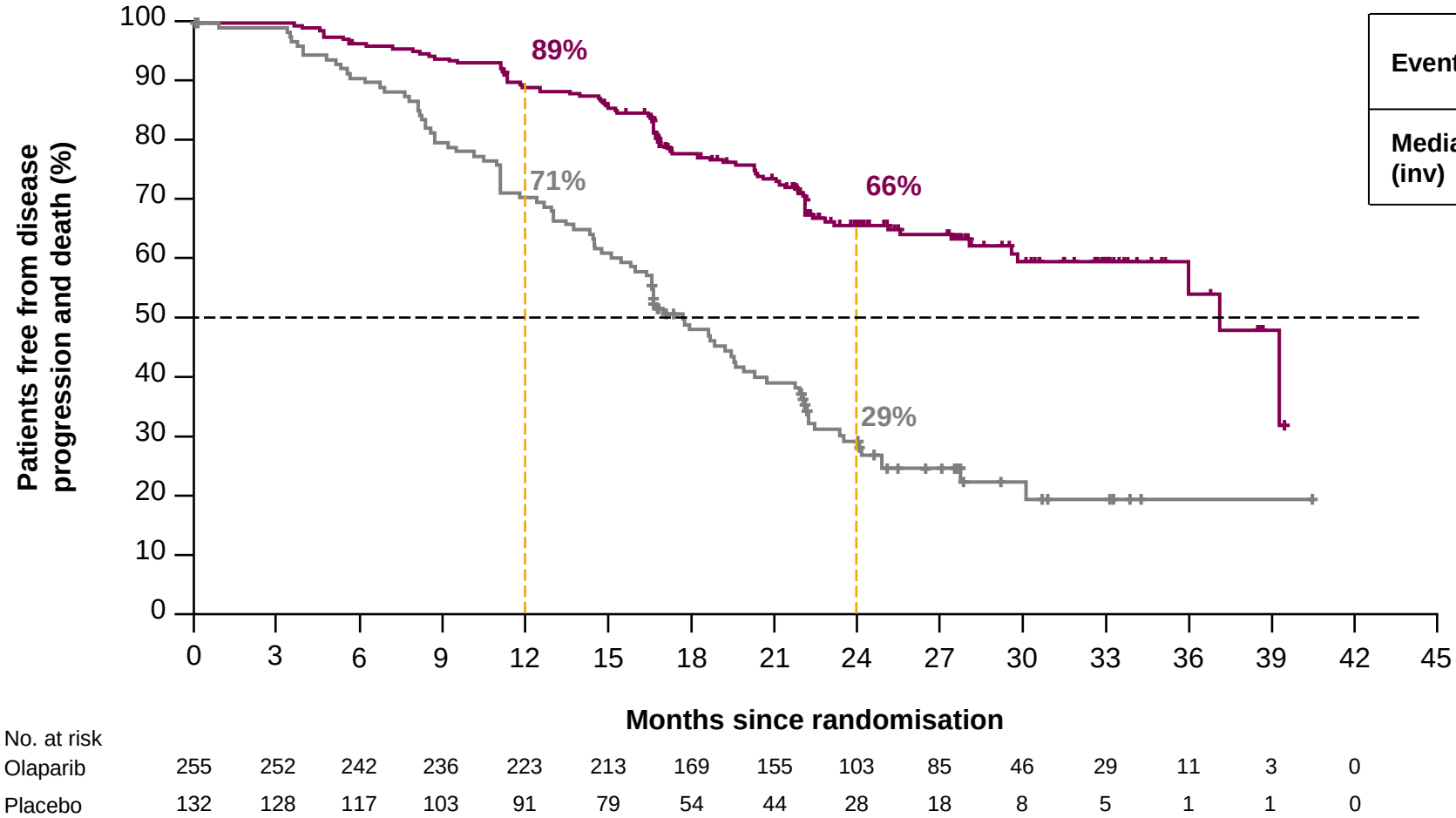
***4.2% missing; 2.1% fail; 11.3% inconclusive.**

Ray-Coquard. ESMO 2019. Abstr. LBA2.

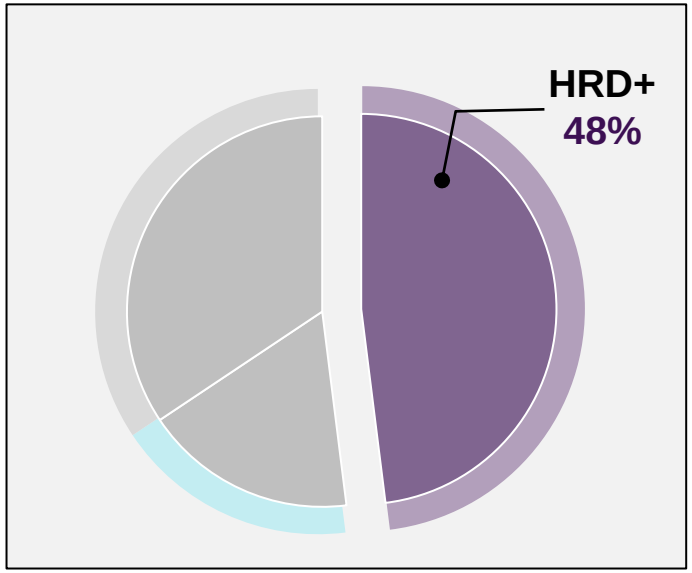
Slide credit: clinicaloptions.com

Pre-specified subgroup analysis showed substantial PFS benefit in HRD-positive* (including tBRCAm) patients

The clinically meaningful improvement in mPFS (20 months) may increase with longer follow-up



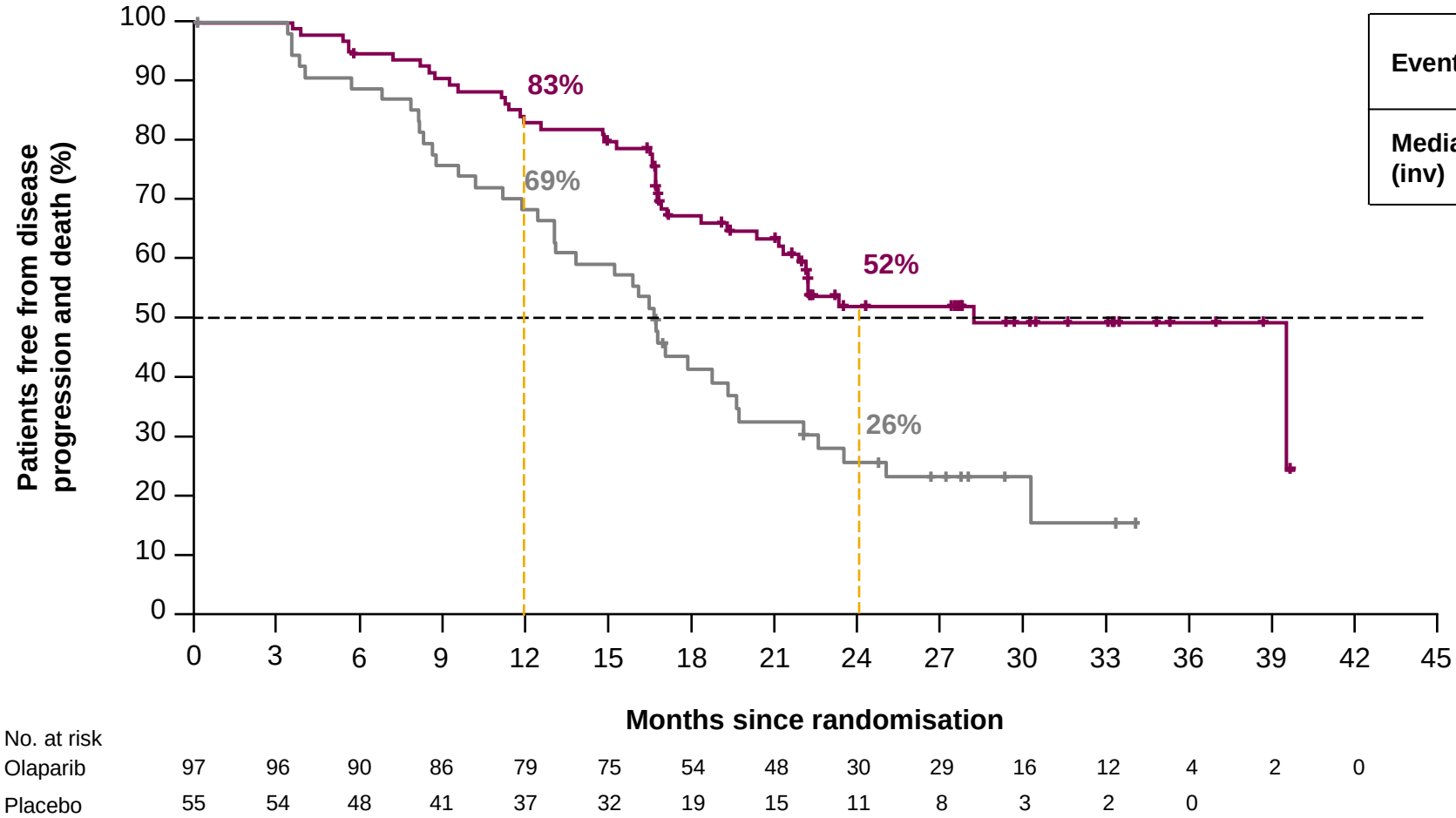
	Olaparib + bevacizumab n=255	Placebo + bevacizumab n=132
Events, n (%)	87 (34)	92 (70)
Median PFS, months (inv)	37.2†	17.7
	HR 0.33 95% CI 0.25–0.45	



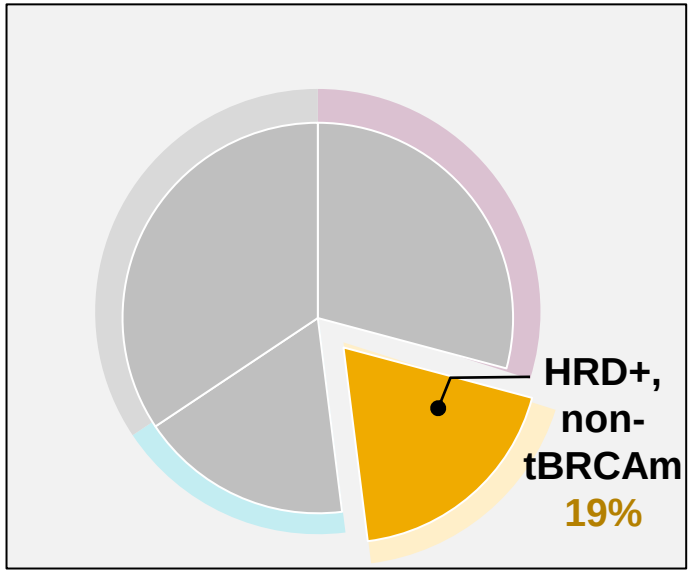
Data maturity=46%. The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates
*HRD-positive determined by tBRCAm or Myriad myChoice CDx genomic instability score ≥42. †This median is unstable due to a lack of events – less than 50% maturity.
CDx=companion diagnostic test; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; inv=investigator-assessed; (m)PFS=(median) progression-free survival; tBRCAm=mutation in tumour BRCA

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain.

Pre-specified subgroup analysis showed PFS benefit in HRD-positive*, non-tBRCAm patients



	Olaparib + bevacizumab n=97	Placebo + bevacizumab n=55
Events, n (%)	43 (44)	40 (73)
Median PFS, months (inv)	28.1†	16.6
	HR 0.43 95% CI 0.28–0.66	

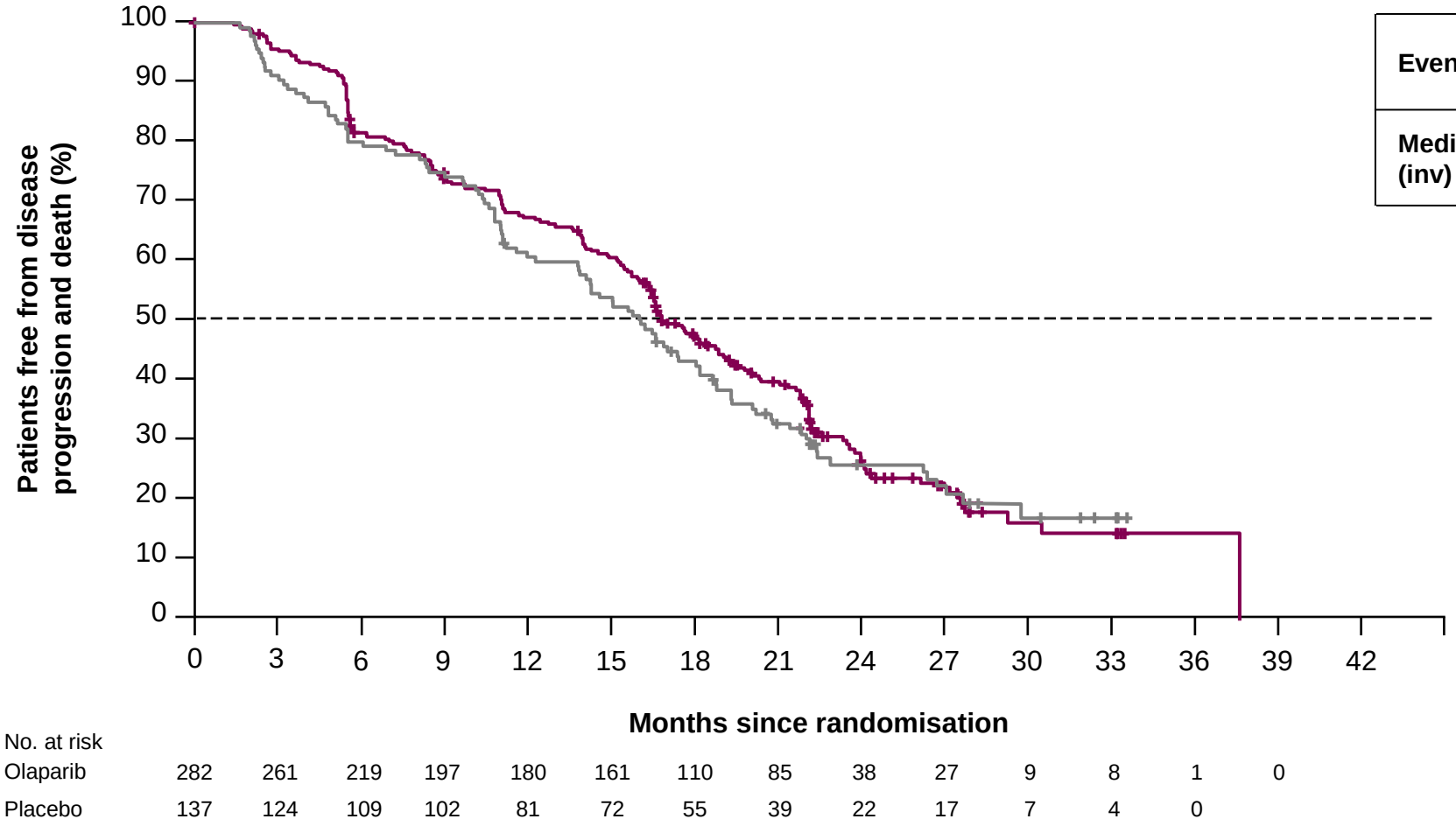


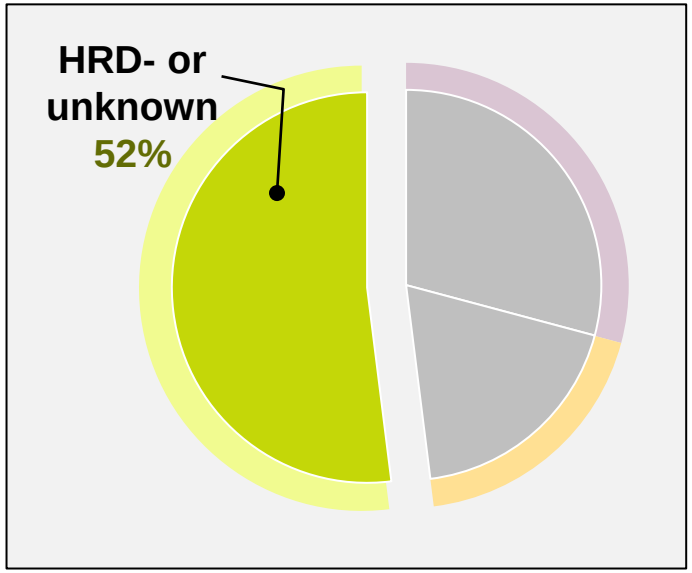
Data maturity=55%. The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates
*HRD-positive determined by Myriad myChoice CDx genomic instability score ≥42. †This median is unstable due to a lack of events – less than 50% maturity.
CDx=companion diagnostic test; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; inv=investigator-assessed; PFS=progression-free survival; tBRCAm= mutation in tumour BRCA

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain.

Subgroup analysis in HRD-negative* or unknown patients

	Olaparib + bevacizumab n=282	Placebo + bevacizumab n=137
Events, n (%)	193 (68)	102 (74)
Median PFS, months (inv)	16.9	16.0
	HR 0.92 95% CI 0.72–1.17	



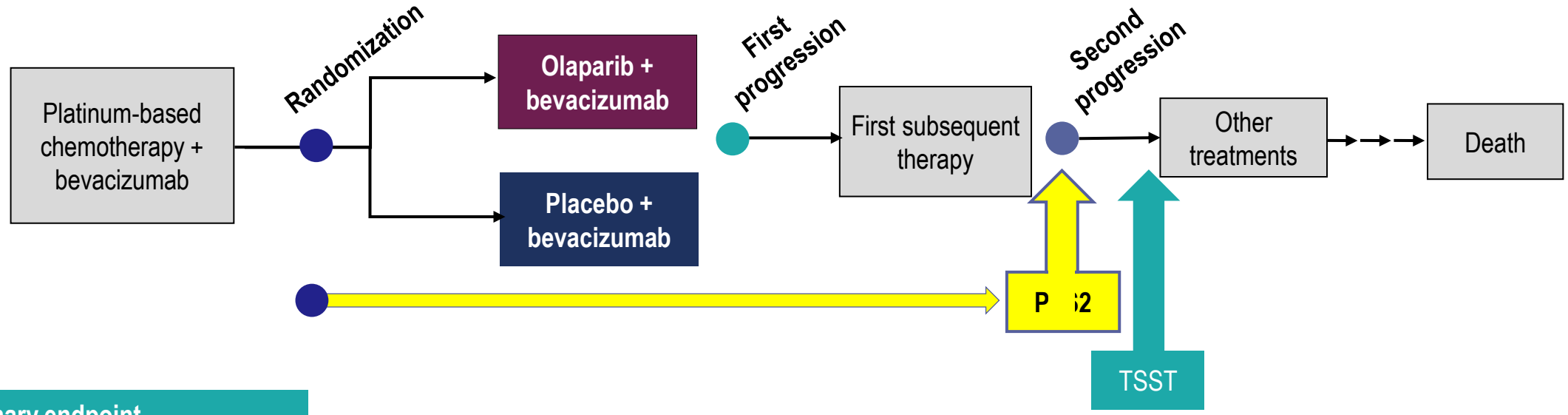


Data maturity=70%. *HRD-negative determined by non-BRCAm and Myriad myChoice CDx genomic instability score <42
CDx=companion diagnostic test; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; inv=investigator-assessed; PFS=progression-free survival

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:Supplementary appendix;
3. Ray-Coquard I, et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain.

PAOLA-1/ENGOT-ov25 PFS2 analysis

PFS2 is measured from the time of randomization to second progression or death and evaluates the effect of maintenance therapy with olaparib plus bevacizumab beyond first progression



Primary endpoint
- Investigator-assessed PFS

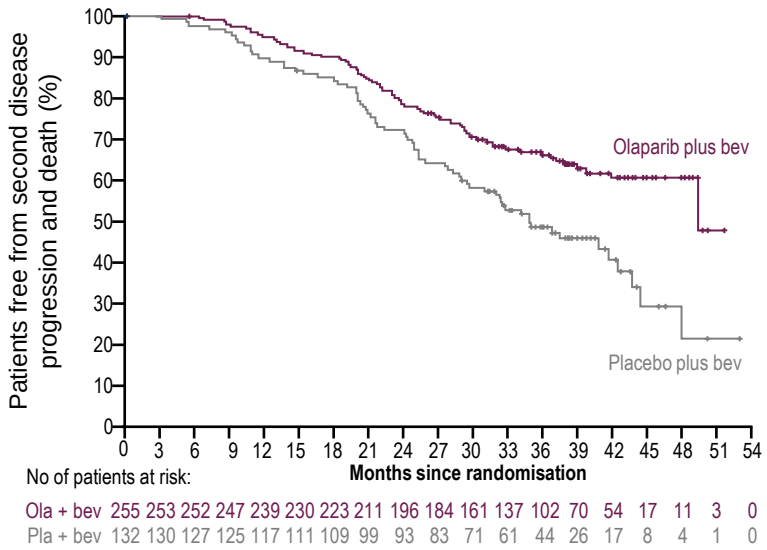
Secondary endpoints
- TFST
- **PFS2**
- TSST
- OS
- HRQoL
- Safety and tolerability

- PFS2 was immature at the time of primary PFS analysis (DCO 22 March 2019)
- We present the **prespecified final PFS2 analysis** planned for ≈53% data maturity or 1 year after primary analysis (DCO 22 March 2020)
- We also present post hoc analyses of PFS2 by biomarker status

DCO, data cut-off; HRQoL, health-related quality of life; OS, overall survival; PFS2, time from randomization to second progression or death; TFST, time from randomization to first subsequent therapy or death; TSST, time from randomization to second subsequent therapy or death

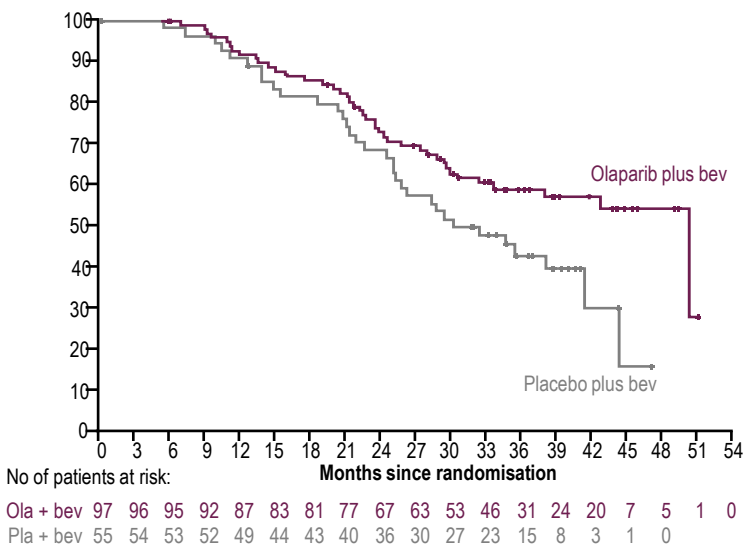
A substantial PFS2 benefit was also seen in HRD-positive* patients regardless of BRCAm status

HRD-positive,* including tBRCAm



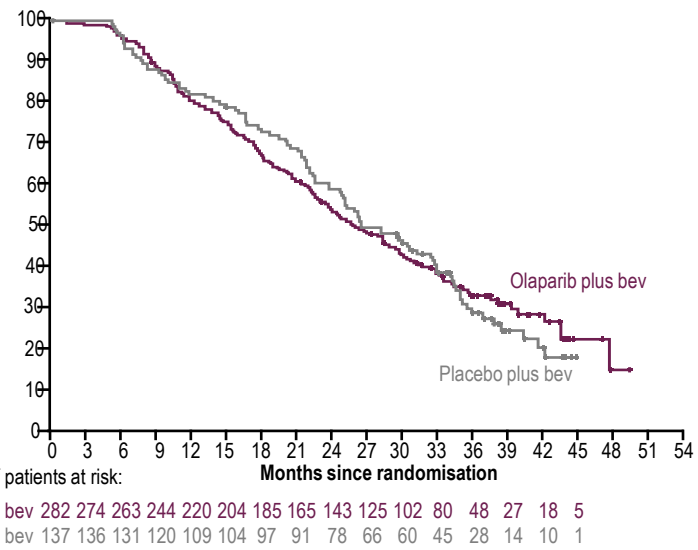
	Olaparib + bevacizumab n=255	Placebo + bevacizumab n=132
Events, n (%)	85 (33)	70 (53)
Median PFS2, months	**50.3‡**	**35.3**
	HR 0.56 95% CI 0.41–0.77	

HRD-positive,* excluding tBRCAm



Olaparib + bevacizumab n=97	Placebo + bevacizumab n=55
41 (42)	33 (60)
50.3‡	**30.1**
HR 0.60 95% CI 0.38–0.96	

HRD-negative†/unknown



Olaparib + bevacizumab n=282	Placebo + bevacizumab n=137
175 (62)	94 (69)
26.3	**28.1**
HR 0.98 95% CI 0.77–1.27	

*HRD-positive determined by tBRCAm or Myriad myChoice CDx genomic instability score ≥42; †HRD-negative determined by non-BRCAm and Myriad myChoice CDx genomic instability score <42; ‡This median is unstable due to a lack of events – less than 50% maturity

Bev=bevacizumab; BRCAm=mutation in BRCA; CDx=companion diagnostic; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; PFS2=time to progression on subsequent therapy; tBRCAm=tumour BRCA mutation

Gonzalez-Martin A, et al. Presented at ESMO Virtual Congress 2020. 19-21 September. Abstract #LBA33

PARPi

- První linie léčby
- **Recidivující OC**
- Toxicita

Imunoterapie

Současná doporučení

Recurrent Ovarian Cancer Population Characteristics

Time to re-challenge	Response Rate
< 1 year	17 %
1-2 years	27%
> 2 years	57%

Gore ME, et al. *Gynecol Oncol* 1990;

Platinum-free Interval (months)	Response
5-12	27 %
13-24	33 %
> 24	59 %

Markman.M, et al. *J Clin Oncol* 1991

Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 10, No 4 **April 1992**

EDITORIAL

Responses to Salvage Chemotherapy in Ovarian Cancer: A Critical Need for Precise Definitions of the Treated Population

- Primary Resistant
  - Progressing on primary treatment
- Secondary resistant
  - progressing on re-challenge
- **Potentially** sensitive
  - Sub-classified
    - < 6 months TFI
    - 6-12 months TFI
    - > 12 months TFI

Markman and Hoskins J Clin Oncol 1992

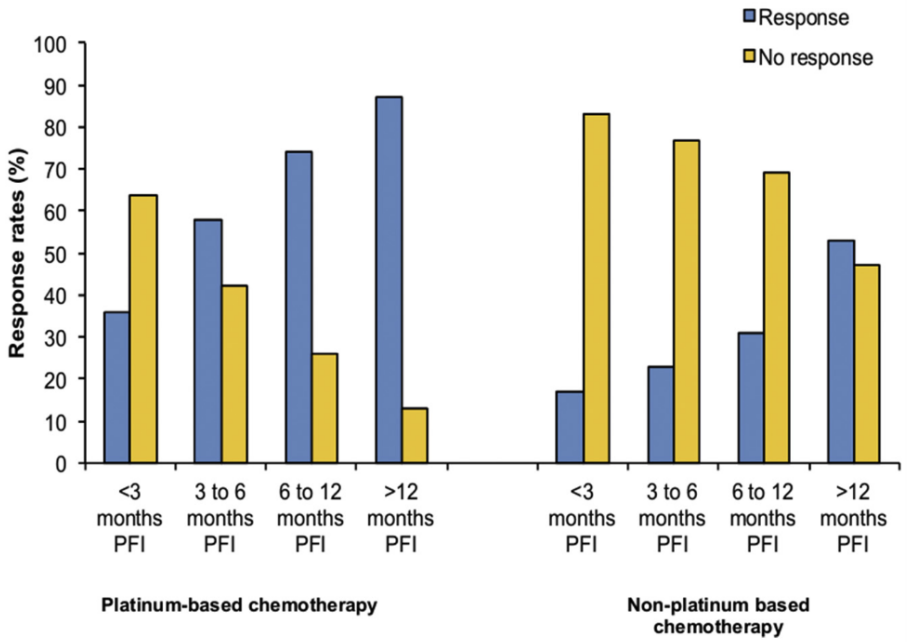
Activity of platinum combinations in "platinum-resistant" ovarian cancers

ESGO
European Society of Gynaecological Oncology

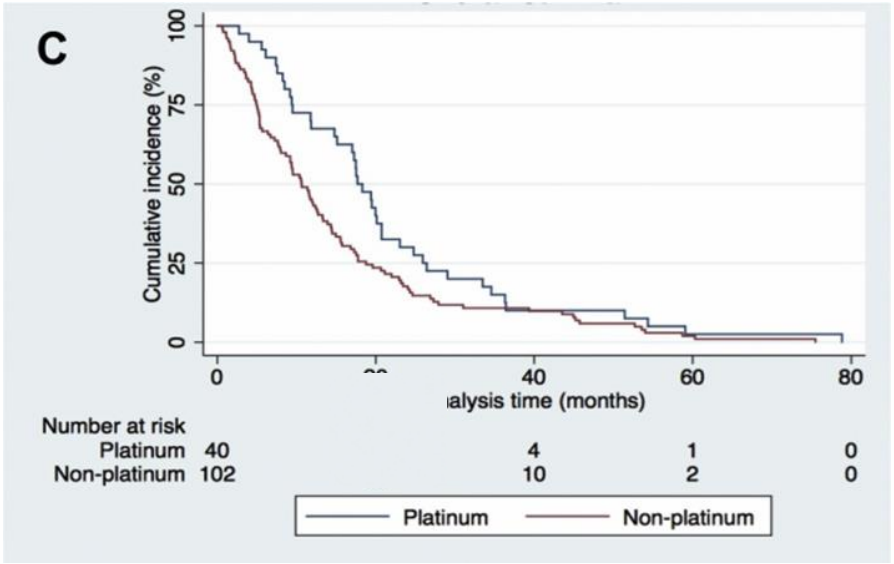
Response Rates

	<4 months PFI	<6 months PFI
Cisplatin/Paclitaxel (*de Jong et al 2002*)	62% [5 patients]	
Carboplatin/weekly paclitaxel induction then 3 weekly *(van der Burg 2012)*		51-58% [43 patients]
Cisplatin/Etoposide (*van der Burg et al 2002)*	46 % [28 patients]	
Cisplatin/ Gemcitabine *(Rose et al 2002)*		42 % [35 patients]
Cisplatin/Gemcitabine *(Nagourney et al 2002)*		57 % [14 patients]
Cisplatin/gemcitabine *(Brewer et al 2006)*		16% [57 patients]
Carboplatin/Gemcitabine *(Ledermann et al 2010)*		29% [40 patients]
Carbo/paclitaxel *(Cadron et al 2007)*		62% [8 patients]
Carboplatin/weekly paclitaxel *(Lortholarly et al 2010)*		39% [51 patients]

Platinum and non-platinum therapy in patients in first relapse with a ≤ 6 month platinum-free interval



PFI > 3-≤6 months



Median OS from treatment:
Platinum: 17.67 months (95% CI: 14.79–20.75)
Non-platinum: 10.62 months (95% CI: 8.02–12.72) [P = 0.022]

Lindemann et al Gynecol Oncol 2018

Definition of platinum-resistance

- Tumours that do not respond to platinum rechallenge, or progress while on platinum therapy

- Patients who have a symptomatic progression soon after completing treatment with platinum-based therapy

PARP inhibitor maintenance following platinum-based chemotherapy

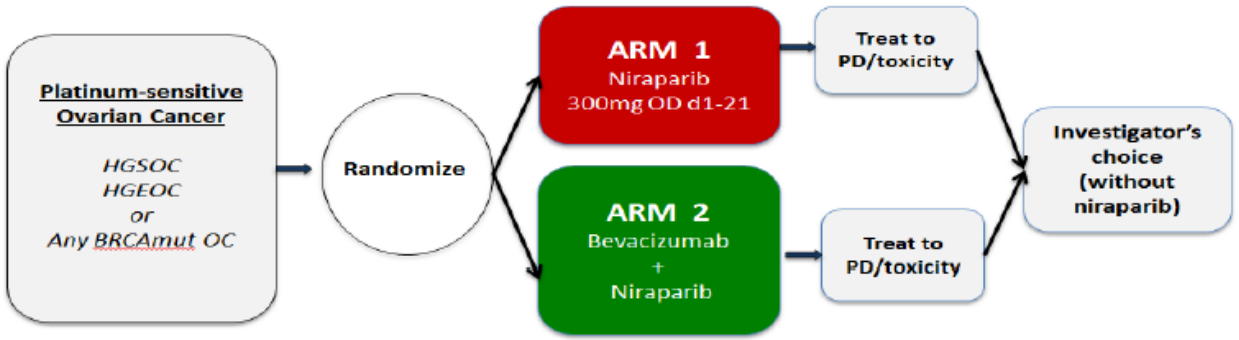
	Med PFS months Control	Med PFS months BRCA	Med PFS months Overall	PARP i
Study 19	4.8	11.2	8.4	Olaparib
SOLO2	5.5	19.1	-	Olaparib
NOVA	5.5	21.0	9.3 (excludes gBRCA)	Nirabarib
ARIEL3	5.4	16.6	10.8	Rucaparib

Note: these median PFS values are during maintenance which starts approximately 6 months after chemotherapy

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

ENGOT-OV24/NSGO-AVANOVA2

A two-arm, open-label, phase II randomized study to evaluate the efficacy of niraparib versus niraparib-bevacizumab combination in Women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.



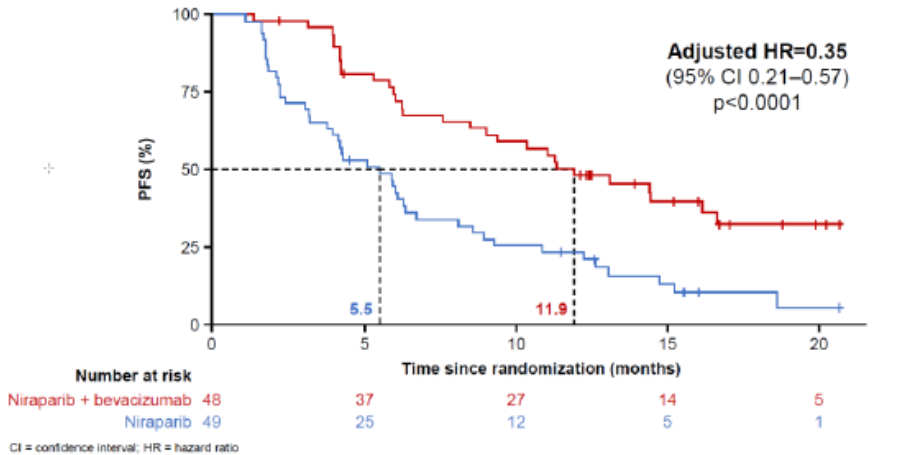
Stratification factors:
HRD positive/negative
TFI: 6-12 mo vs. >12 mo

Randomization: 1:1
n=94

Arm 1: niraparib median PFS 8mdr
Arm2: Nir + Bev median PFS 14mdr
inclusion 18 months
Drop outs: 10%

HR 0.57
Power 80%
alpha 0.1

Primary endpoint: PFS in the ITT population



Mirza MR et al. Lancet Oncol 2019; 20: 1409-1419

ENGOT model: A
Status: Randomization closed
Last patient randomized: 20-12-17
Sponsor: NSGO-CTU
NSGO-CTU lead PI: Mansoor Mirza
NSGO-CTU PM: Nicole Buchner Vinum

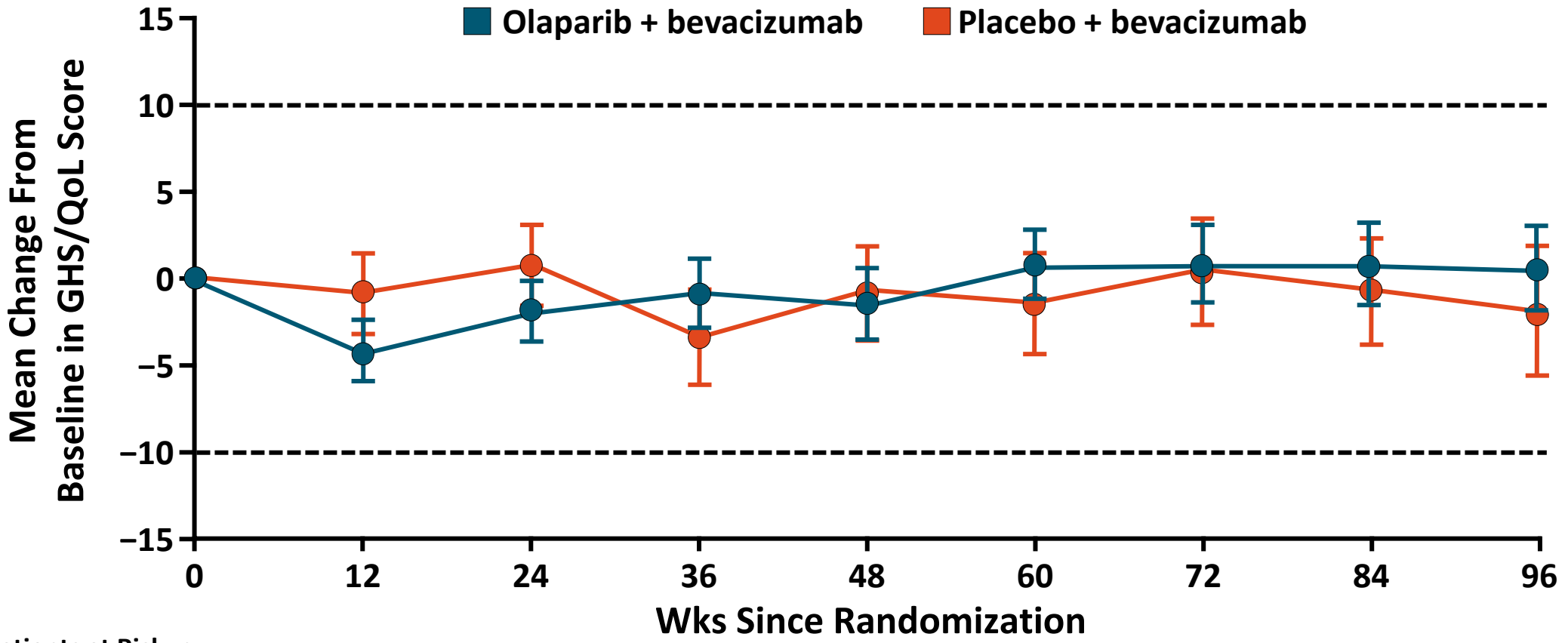
PARPi

- První linie léčby
- Recidivující OC
- **Toxicita**

Imunoterapie

Současná doporučení

PAOLA-1: Patient-Reported Quality of Life

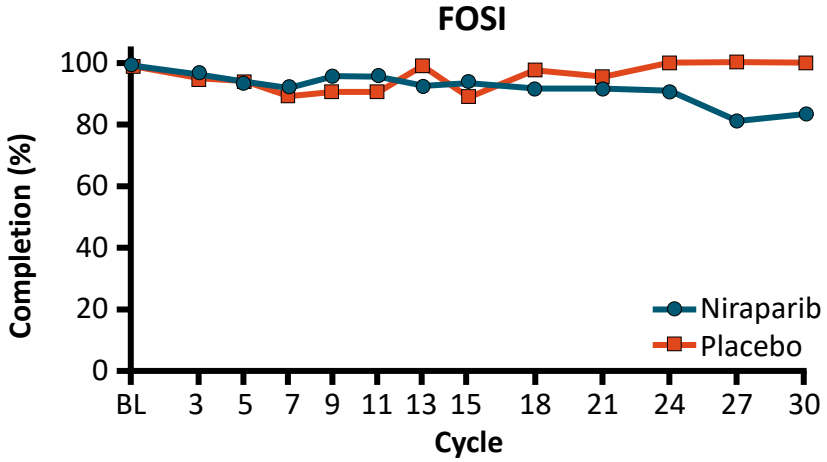


Patients at Risk, n								
Olaparib	508	458	432	396	393	352	342	308	252
Placebo	249	228	207	199	185	171	166	151	123

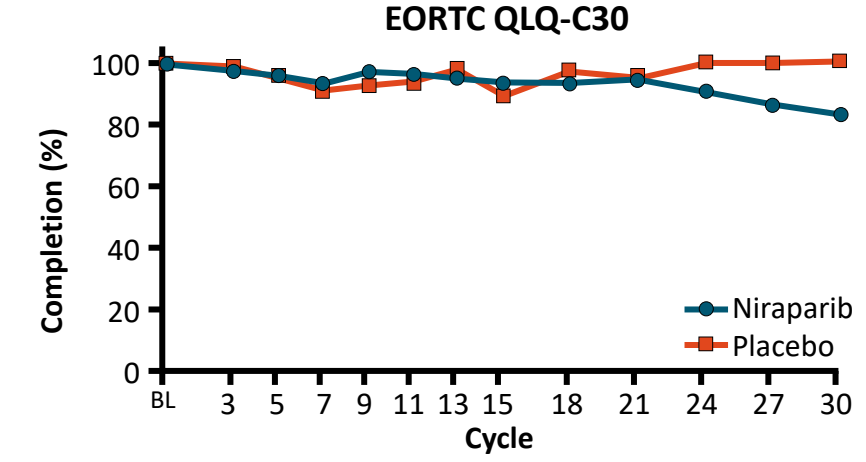
Ray-Coquard. NEJM. 2019;381:2416.

Slide credit: clinicaloptions.com

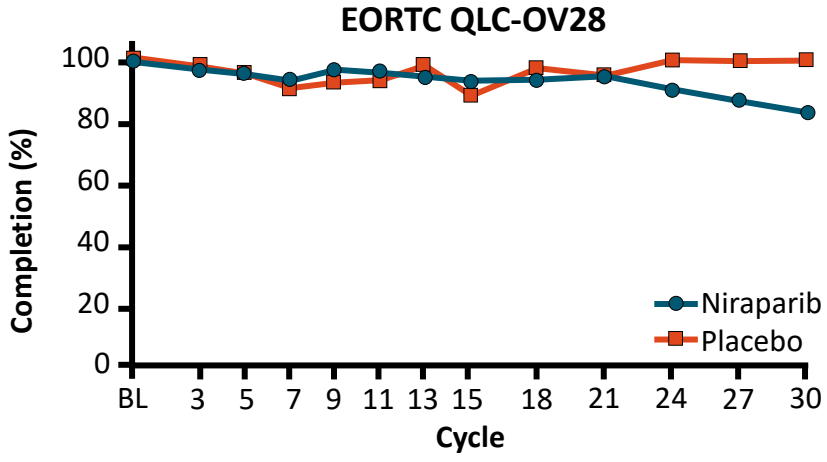
PRIMA PRO: Patient Compliance Rates Across All PRO Instruments remained high



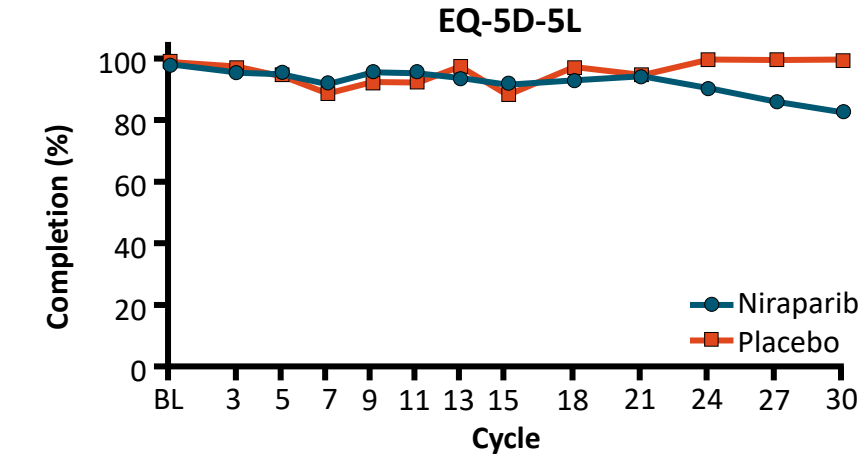
Niraparib	483	425	352	316	286	254	231	185	100	56	30	13	5
Placebo	242	221	185	158	125	99	97	74	38	21	8	5	4



Niraparib	484	430	359	322	290	256	236	185	10	58	30	13	5
Placebo	246	229	188	161	128	102	95	74	38	21	8	5	4



Niraparib	485	428	359	322	290	256	236	185	102	58	30	13	5
Placebo	246	228	188	161	128	102	96	74	38	21	8	5	4



Niraparib	481	424	358	319	287	255	235	183	102	58	30	13	5
Placebo	245	227	186	158	128	101	96	74	38	21	8	5	4

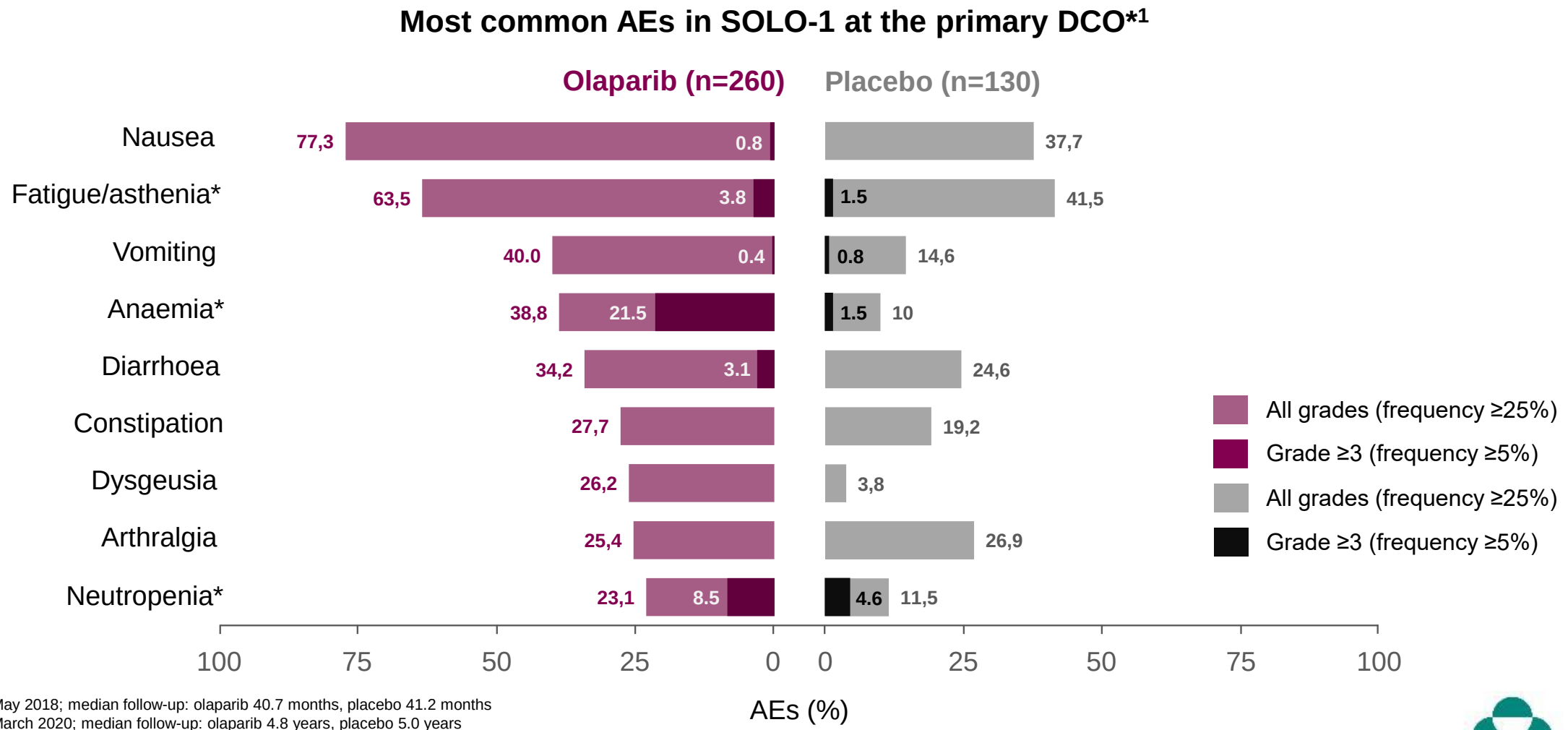
- Patient compliance rates remained consistently high (> 80%) throughout the trial

Pothuri. ESMO 2020. Abstr 810MO.

Slide credit: clinicaloptions.com

The most common AEs reported in patients on olaparib in SOLO-1 were gastrointestinal disturbances, fatigue and anaemia[1]

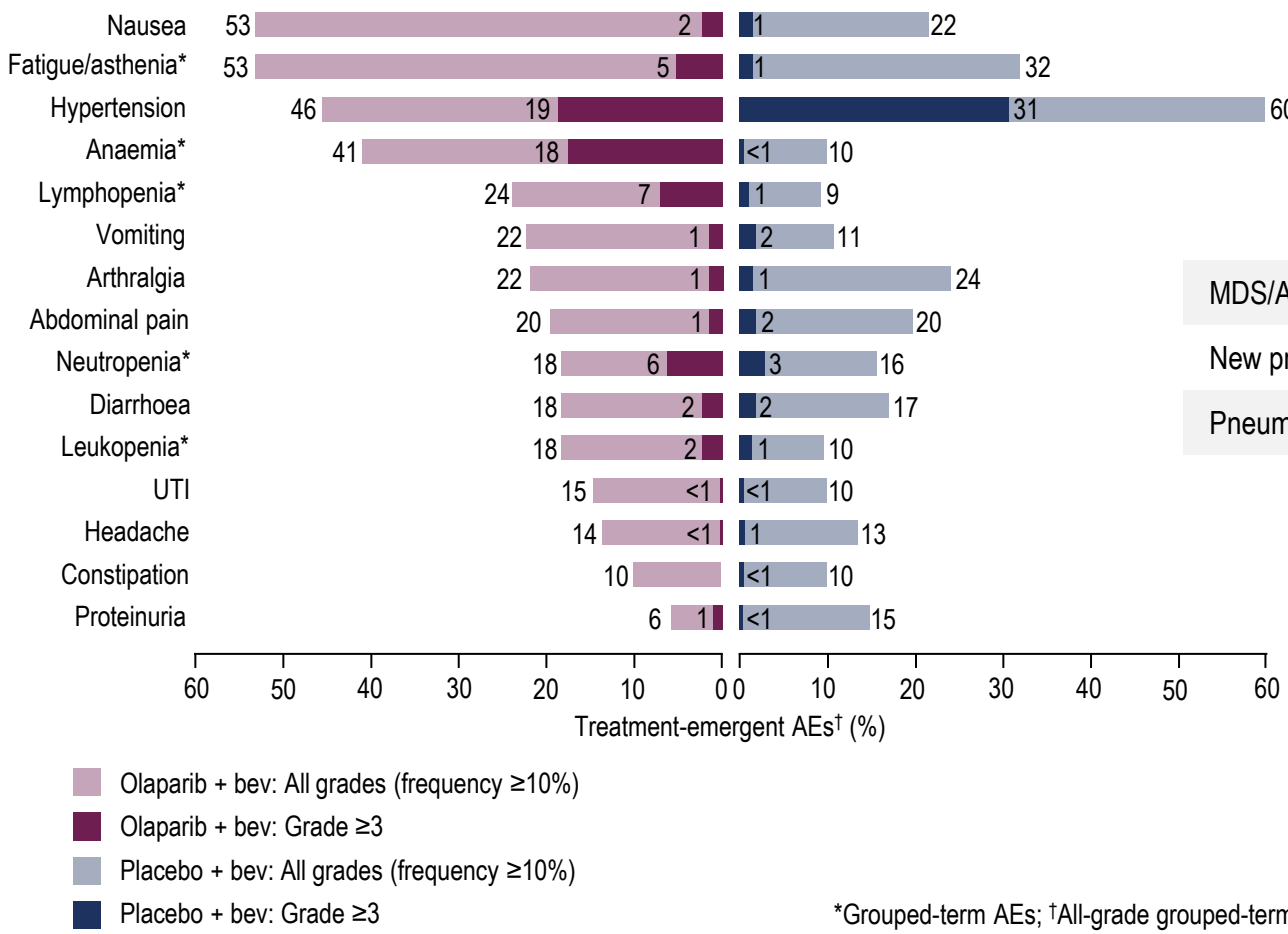
After 5-years' follow-up, the safety profile remained consistent with the primary analysis[2]



Primary DCO: May 2018; median follow-up: olaparib 40.7 months, placebo 41.2 months
Second DCO: March 2020; median follow-up: olaparib 4.8 years, placebo 5.0 years
*Grouped term
AE=adverse event; DCO=data cut-off

1. Moore K, et al. N Engl J Med. 2018;379:2495–2505; 2. Banerjee S, et al. Presented at ESMO Virtual Congress 2020. 19–21 September. Abstract #811MO

PAOLA 1 - Safety analyses



AEs of special interest

	Primary PFS analysis (DCO 22 March 2019)		Final PFS2 analysis (DCO 22 March 2020)	
	Olaparib + bev (n=535)	Placebo + bev (n=267)	Olaparib + bev (n=535)	Placebo + bev (n=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	6 (1.1)	4 (1.5)‡
New primary malignancies,§ n (%)	7 (1.3)	3 (1.1)	14 (2.6)	5 (1.9)
Pneumonitis/ILD/bronchiolitis, n (%)	6 (1.1)	0	6 (1.1)	0

	Olaparib + bev (n=535)	Placebo + bev (n=267)
Median duration of olaparib/placebo treatment, months	17.3	15.6
Median duration of bev treatment, months	11.0	10.6
Discontinuation due to AEs, n (%)	112 (21)	15 (6)

*Grouped-term AEs; †All-grade grouped-term thrombocytopenia occurred in 8% of olaparib plus bevacizumab patients and 3% of placebo plus bevacizumab patients; grade ≥3 grouped-term thrombocytopenia occurred in 2% of olaparib plus bevacizumab patients and <1% of placebo plus bevacizumab patients; ‡3 of the 4 patients in the placebo plus bevacizumab group who developed MDS/AML/AA received a PARP inhibitor as first subsequent treatment before onset of AML.
§At primary PFS analysis, new primary malignancies in the olaparib plus bevacizumab group were acute lymphocytic leukaemia (n=1), breast cancer (n=2), lung cancer (n=1), myeloma (n=1), squamous skin cancer (n=1), and pancreatic cancer (n=1), and in the placebo group were breast cancer (n=2) and thyroid cancer (n=1). Additional new primary malignancies reported at final PFS2 analysis in the olaparib plus bevacizumab group were breast cancer (n=5), squamous skin cancer (n=1), and colon cancer (n=1), and in the placebo group were breast cancer (n=1) and malignant neoplasm (n=1)
AA, aplastic anaemia; AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome; UTI, urinary tract infection

PRIMA: Safety

Adverse Event, n (%)	Niraparib (n = 484)	Placebo (n = 244)
Any TEAE	478 (98.8)	224 (91.8)
▪ Grade ≥3	341 (70.5)	46 (18.9)
Led to treatment discontinuation	58 (12.0)	6 (2.5)
Led to dose reduction	343 (70.9)	20 (8.2)
Led to dose interruption	385 (79.5)	44 (18.0)
TEAEs leading to death	2 (0.4)	1 (0.4)

- Dose interruptions similar incidence as prior niraparib trials
- Treatment discontinuation due to thrombocytopenia: 4.3%
- TEAS leading to death determined to not be related to treatment

- Most frequent grade ≥ 3 AEs:
  - anemia (31.0%),
  - thrombocytopenia (28.7%),
  - platelet count decrease (13.0%),
  - neutropenia (12.8%)
- TEAEs manageable, consistent with PARP inhibitor class

Gonzalez-Martin. NEJM. 2019;381:2391.

Slide credit: clinicaloptions.com

PARPi

- První linie léčby
- Recidivující OC
- Toxicita

Imunoterapie

Současná doporučení

ENGOT OV 39

VIRTUAL 2020 ESMO congress

IMagyn050 trial design

- Previously untreated epithelial ovarian, primary peritoneal or fallopian tube cancer
- Post-operative stage III with macroscopic residual disease or stage IV or neoadjuvant candidate with planned interval surgery
- ECOG PS 0–2

R

Cycles 1–6 / Cycles 7–22

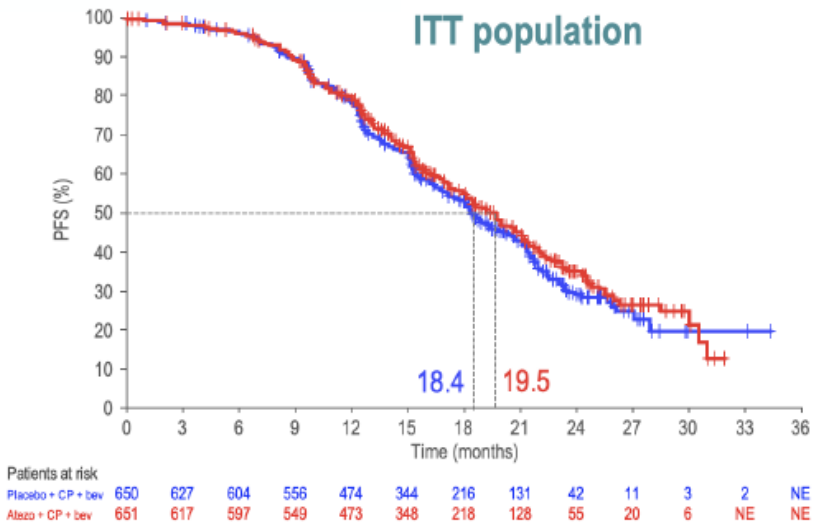
- Carboplatin AUC6 + paclitaxel 175 mg/m² q3w → Bev 15 mg/kg q3w (peri-operative cycles omitted) → Placebo q3w
- Carboplatin AUC6 + paclitaxel 175 mg/m² q3w → Bev 15 mg/kg q3w (peri-operative cycles omitted) → Atezo 1200 mg q3w

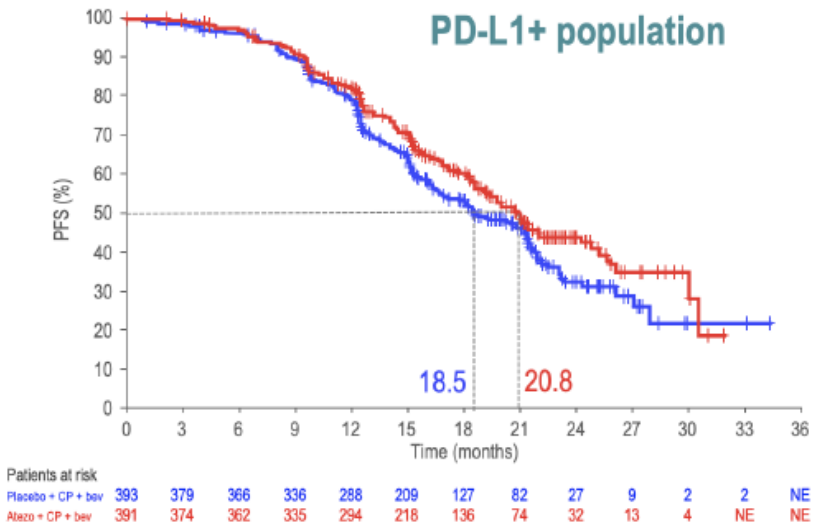
Co-primary endpoints

- **PFS** (per RECIST v1.1) (PD-L1+ and ITT populations tested simultaneously; p≤0.002 considered positive)
- **OS** (hierarchical testing, PD-L1+ then ITT)

Stratification factors

- Stage (III vs IV)
- ECOG PS (0 vs 1/2)
- Treatment approach (adjuvant vs neoadjuvant)
- PD-L1 status (IC <1% vs ≥1%; VENTANA SP142 assay)





PFS	ITT population		PD-L1+ population	
	Placebo + CP + bev (n=650)	Atezo + CP + bev (n=651)	Placebo + CP + bev (n=393)	Atezo + CP + bev (n=391)
Patients with events, n (%)	341 (52.5)	323 (49.6)	199 (50.6)	167 (42.7)
Median PFS, months (95% CI)	18.4 (17.2–19.8)	19.5 (18.1–20.8)	18.5 (16.6–21.4)	20.8 (19.1–24.2)
Stratified HR (95% CI)	0.92 (0.79–1.07)		0.80 (0.65–0.99)	
Stratified log-rank p-value	0.2785		0.0376	
2-year event-free rate (95% CI)	29.1 (23.9–34.3)	35.1 (30.0–40.3)	32.2 (25.4–39.0)	43.9 (37.2–50.5)

NINJA trial - STUDY DESIGN

Key inclusion criteria

- Platinum-resistant advanced or recurrent ovarian cancer
- ≥20 years of age
- Received ≤1 regimen after diagnosis of platinum resistance
- ECOG PS ≤1

Key exclusion criteria

- Current or previous severe hypersensitivity reactions to antibody products
- Current, recurrent, or chronic autoimmune disease
- Multiple primary cancers and/or CNS metastases
- Pregnant or breastfeeding

Randomization (1:1)

Nivolumab[a] (N=157)
- Nivolumab 240 mg IV every 2 weeks

Chemotherapy[a] (N=159)
- GEM 1000 mg/m^2 IV for 30 minutes on Days 1, 8, and 15, then every 28 days, OR
- PLD 50 mg/m^2 IV every 4 weeks

Stratification factors

- CCC vs other
- 0 vs 1 regimen after platinum resistance diagnosis

Planned sample size

- 316 patients (158 per group)

- Tumor was assessed every 8 weeks through Week 48, then every 12 weeks thereafter
- Patients were followed up for 28 days after end of treatment administration

Primary efficacy endpoint:

- **OS**

Secondary efficacy endpoints[b]:

- PFS
- ORR
- BOR
- DoR (RECIST v1.1), etc.

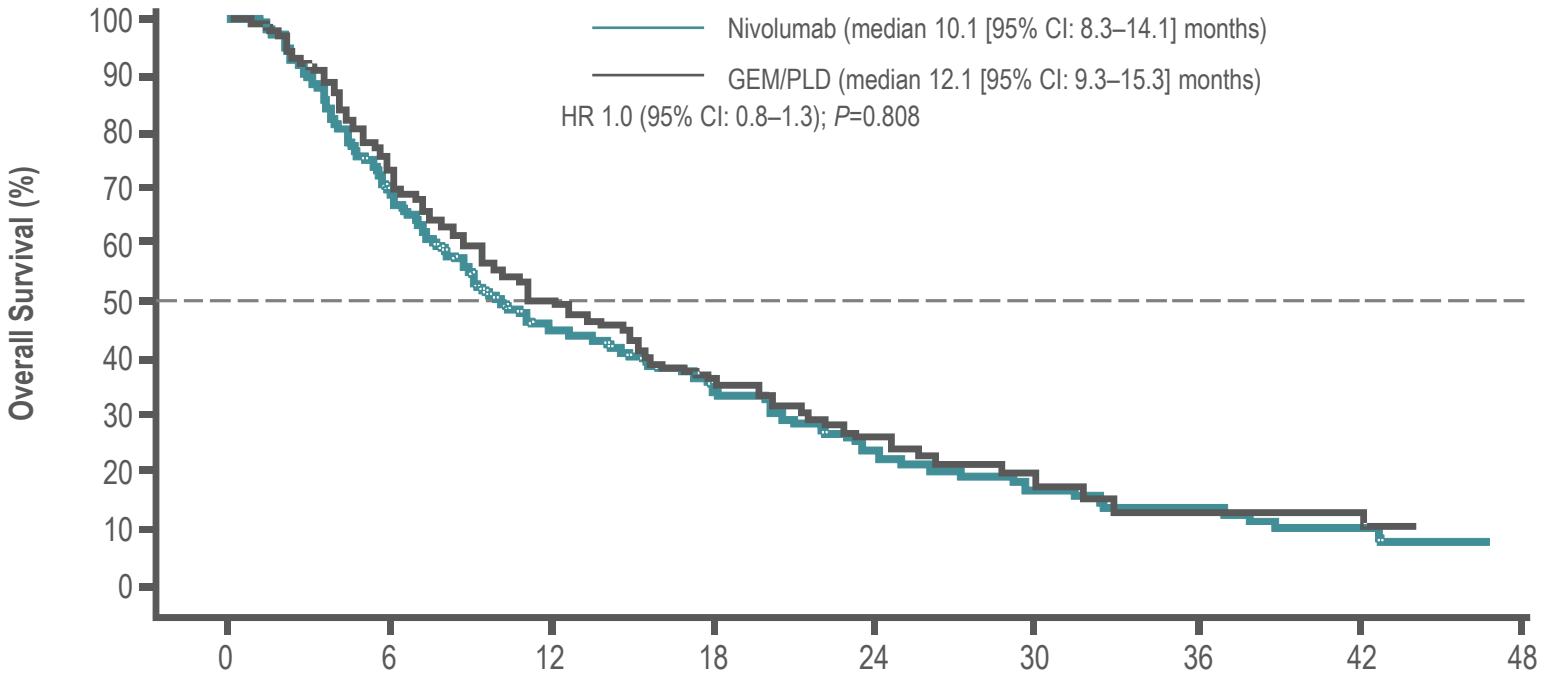
Safety

- TEAEs
- Treatment-related AEs, etc.

[a]Treatment continued until disease progression or unacceptable toxicity.
[b]Investigator assessed.
AE, adverse event; BOR, best overall response; CCC, clear cell carcinoma; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEM, gemcitabine; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAE, treatment-emergent adverse event.

OVERALL SURVIVAL

- Nivolumab showed no superiority over GEM/PLD in OS



Number at risk									
Nivolumab	157	108	71	52	30	15	12	6	0
GEM/PLD	159	115	79	57	28	8	6	5	0

CI, confidence interval; GEM, gemcitabine; HR, hazard ratio; OS, overall survival; PLD, pegylated liposomal doxorubicin.

ENGOT-ov43:
Pembro and Olaparib in first-line OC

STUDY DESIGN

Trial setting: **Ovary/newly diagnosed**
Sponsor(s): **MSD**
No. of patients: **811/1086**
FPI: **EU - Jan 2019**
Co-primary Endpoints: **PFS (by PI) and OS**

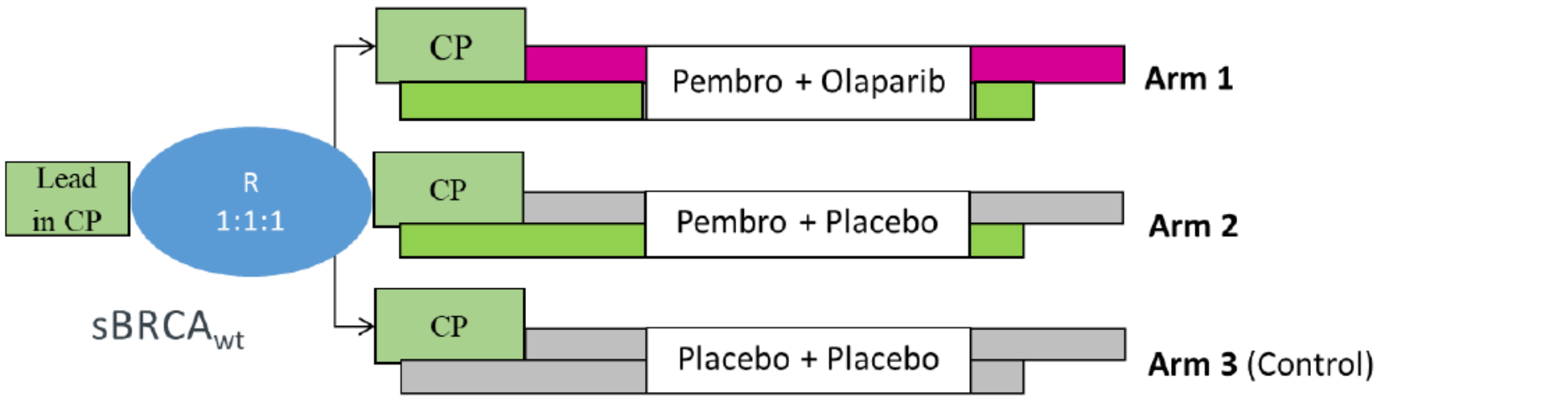
First biopsy for somatic BRCA testing (taken at PDS or laparoscopy or core,...)

Randomization before 2nd chemo cycle if not somatic mutated in BRCA

Stratification: 1. Bev use 2. PDS R0; PDS R>0; NACT->IDS
3. PD-L1 status (CPS < or >= 10)

Primary debulking | **Interval debulking**

Phase II in sBRCAm expected Q2 2019



CP: Carboplatin / Paclitaxel

Pembro 200mg iv q 3wk 2y
Start at 2nd chemo cycle

Olaparib 300 mg BID, till PD (2Y is NED after CP)

Placebo

Bevacizumab allowed; to be specified in advance; randomization to be stratified by use of bev or not

FIRST CLINICAL TRIAL

TESARO 3000-03-005/ENGOT OV-44

FIRST Trial : First-line ovarian cancer treatment with Niraparib plus TSR-042

A randomized, Double-Blind, Phase 3 comparison of platinum-based therapy with TSR-042 and niraparib versus standard of care platinum-based therapy as First-line treatment of stage III IV nonmucinous Epithelial ovarian cancer

GINECO

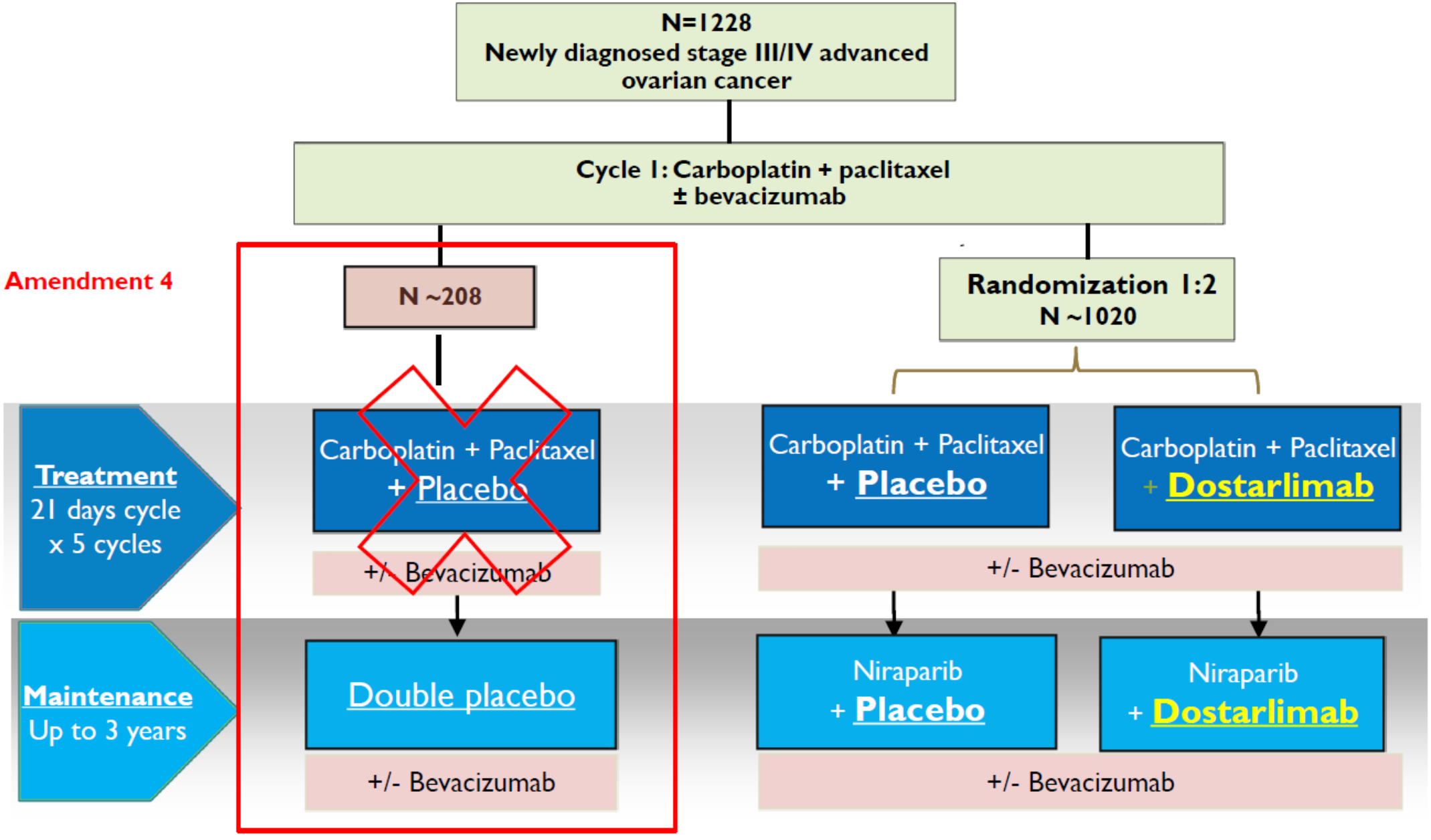
GCIG GYNECOLOGIC CANCER INTERGROUP

ENGOT European Network of Gynaecological Oncological Trial groups

TESARO

ENGOT model C: ENGOT ov-
Sponsor: TESARO 1L OvCaStudy (3000-01-0005)
ENGOT group leader: GINECO

Study design



ENGOT-ov45/NCRI/ATHENA

Study design:

Patient Eligibility

- Newly diagnosed Stage III/IV ovarian cancer
- Response of CR or PR to first-line platinum doublet
- Cytoreductive surgery
  - Sufficient tissue
- ECOG PS ≤1
- No maintenance treatment

R

4:4:1:1

Stratification

- HRR status by NGS mutation analysis
- Disease Status Post-Chemo
- Timing of Surgery

Treatment

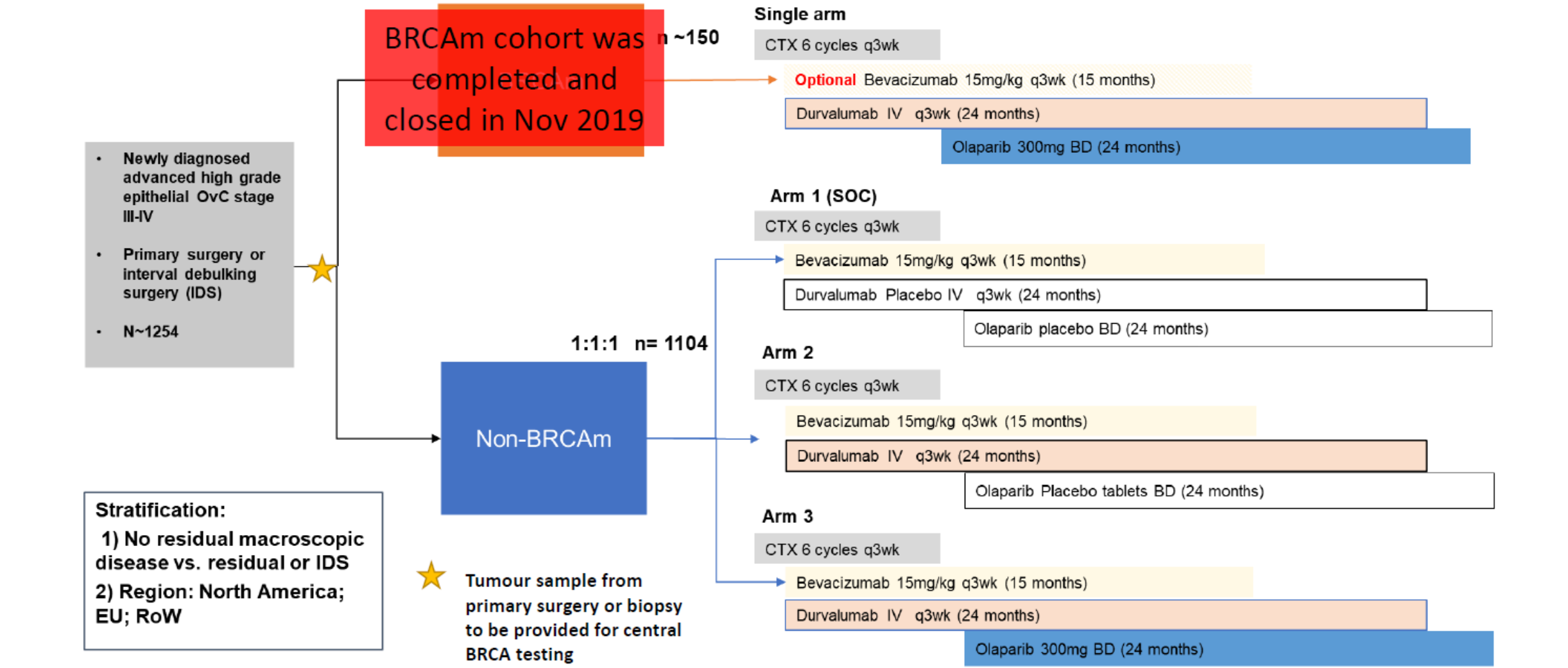
Arm A	Rucaparib + Nivolumab n=400
Arm B	Rucaparib + IV Placebo n=400
Arm C	Oral Placebo + Nivolumab n=100
Arm D	Oral Placebo + IV Placebo n=100

Primary Endpoint

- PFS by Investigator in molecularly-defined HRD subgroups

AGO-OVAR 23 / ENGOT-ov46
DUO-O

Olaparib and Durvalumab in addition to SoC in newly diagnosed, advanced, ovarian cancer patients



PARPi

- První linie léčby
- Recidivující OC
- Toxicita

Imunoterapie

Současná doporučení

ESMO-ESGO Recurrent Ovarian Cancer Consensus

- Tumour biology/histology
- Prior exposure
- prior response
- TFI platinum
- persistent toxicity
- Patient symptoms/preference

Pat not fit enough or not willing to receive anticancer therapy → **Best supportive care**

Surgery an option?
(AGO Score etc.)

Platinum might not be the best option
- Early symptomatic relapse/Progression on prior platinum
- Platinum intolerability

Platinum might be the best option
- response to prior platinum
- assumed sensitive

Potentially platinum non-responsive or platinum contraindicated

Non-Platinum therapy

If indicated: + bevacizumab

Potentially platinum responsive

No priority for symptomatic response *or* contraindications to bevacizumab

Platinum re-challenge

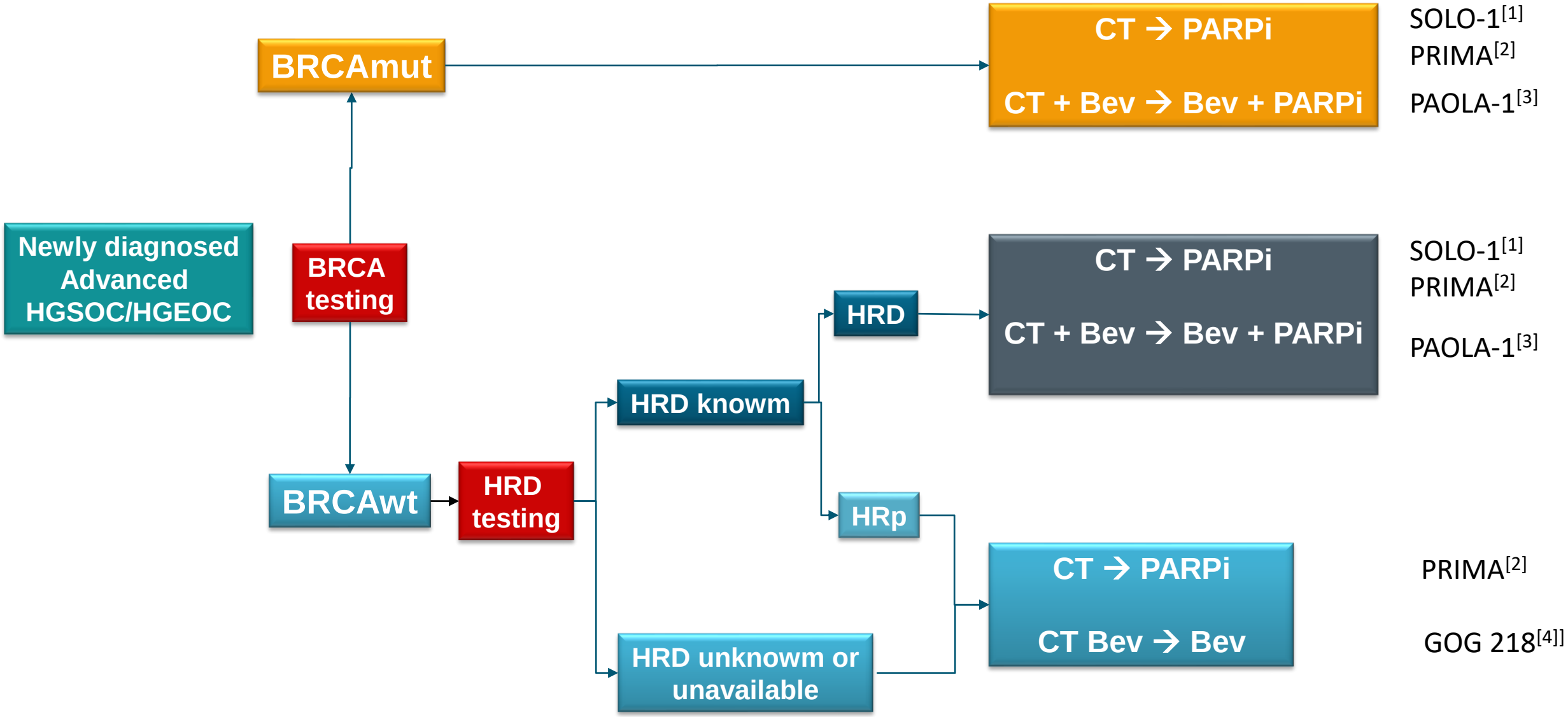
Offer PARPi after response to platinum if not contraindicated
(Proven platinum response)

Priority for symptomatic response or contraindications to bevacizumab

Offer platinum-based re-challenge plus bevacizumab

Colombo et al Ann Oncol 2019; IJGC 2019

What Is the Standard Systemic Treatment for Newly Diagnosed Advanced EOC in 2020?



1. Moore. NEJM. 2018;379:2495. 2. González-Martin. NEJM. 2019;381:2391. 3. Ray-Coquard. NEJM. 2019;381:2416. 4. Burger. NEJM. 2011;365:2473.