Maintenance therapy in newly diagnosed ovarian cancer

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There remains a significant unmet need for newly diagnosed ovarian cancer[1]

Platinum-based chemotherapy

Bevacizumab

10-18 months

Median progression-free survival[2,3,4]

~70%

of women relapse within 3 years of first line treatment[1]

38%

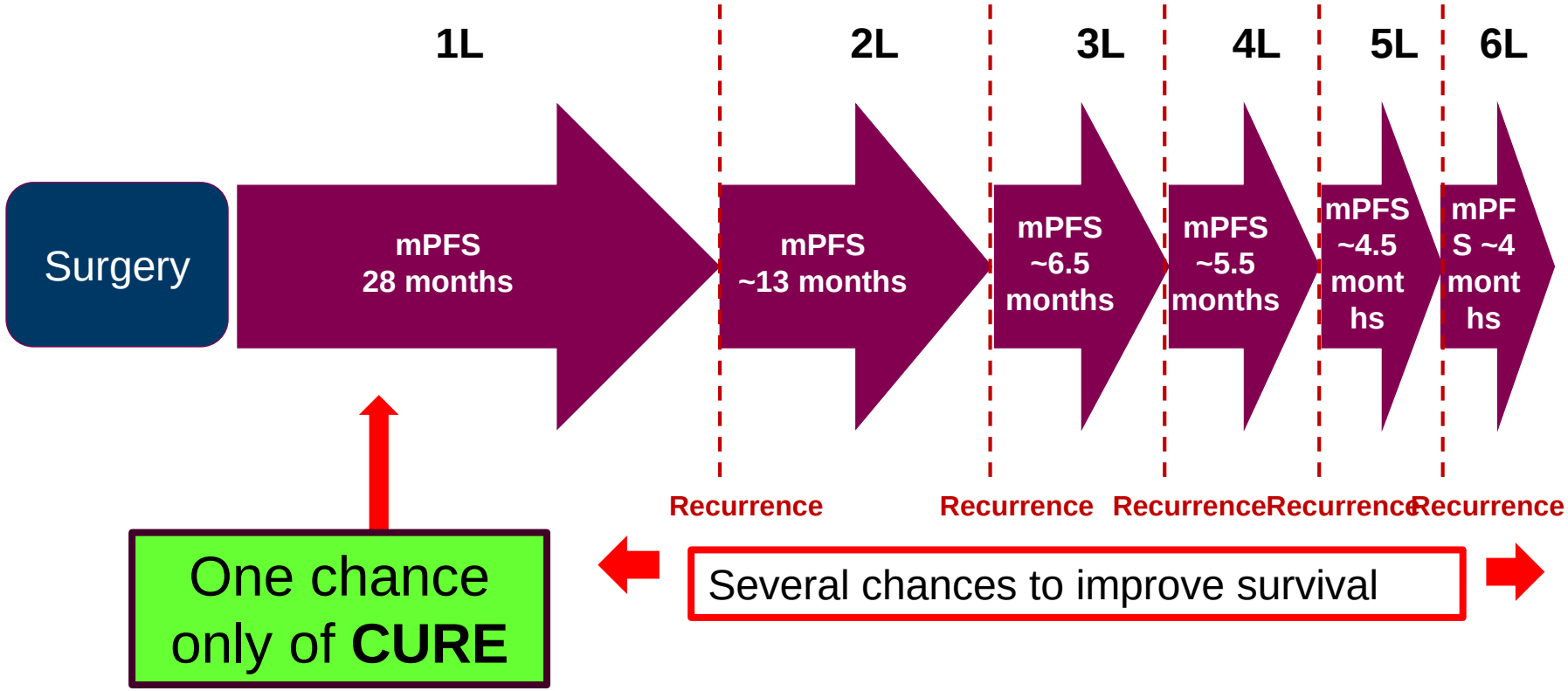
5-year survival rate[5]

There is a significant need for better frontline treatment to improve outcomes for women with ovarian cancer[1-5]

1. Ledermann, J. A. et al. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 24 Suppl 6, vi24-32 (2013) 2. Bookman, M. A. et al. J. Clin. Oncol. 27, 1419–1425 (2009); 3. Burger, R. A. et al. N. Engl. J. Med. 365, 2473–2483 (2011); 4. Perren, T. J. et al. N. Engl. J. Med. 365, 2484–2496 (2011); 5. de Angelis R et al. Lancet Oncol 2014;15:23-34.

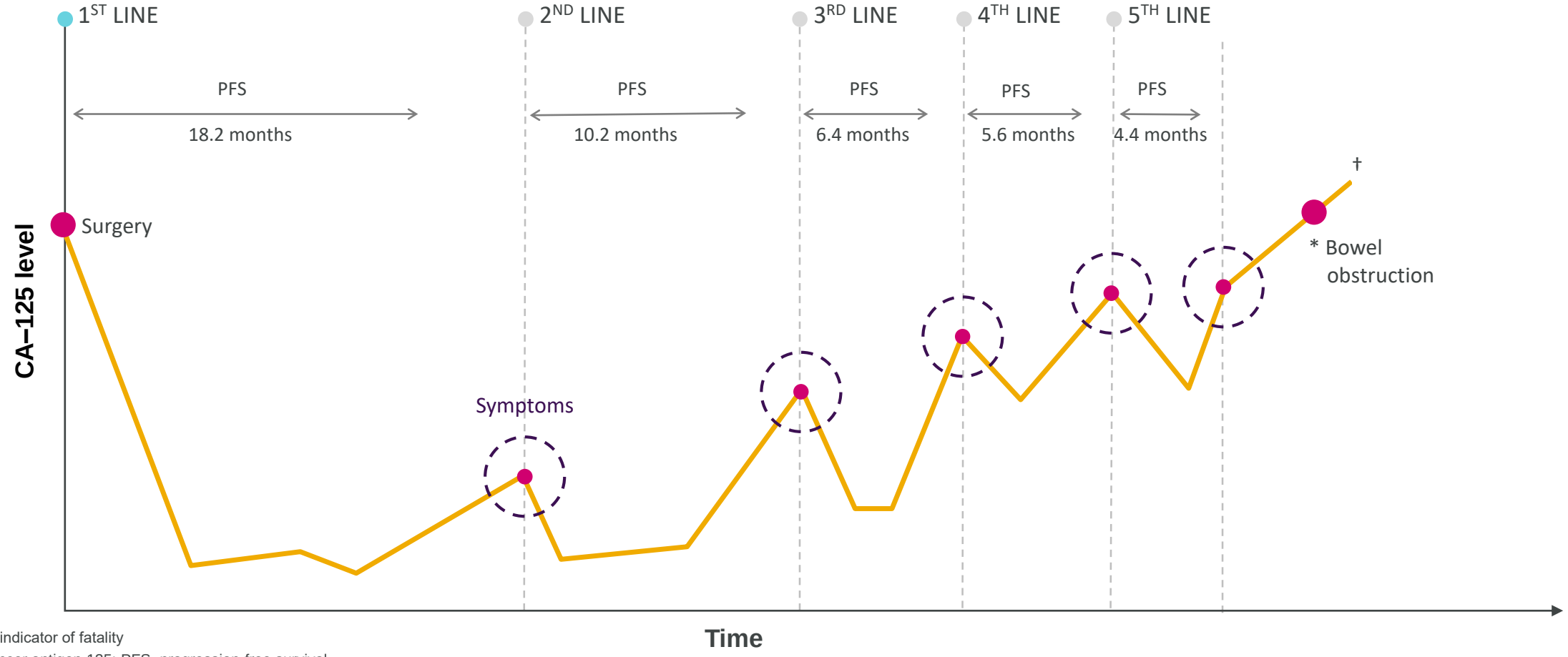
Ovarian Cancer: The Outlook

Once relapse has occurred, the treatment free interval reduces with each line of chemotherapy



Importance of maintenance treatment

Patients receive multiple lines of chemotherapy which is associated with cumulative toxicity & decreasing periods of remission[1-4]

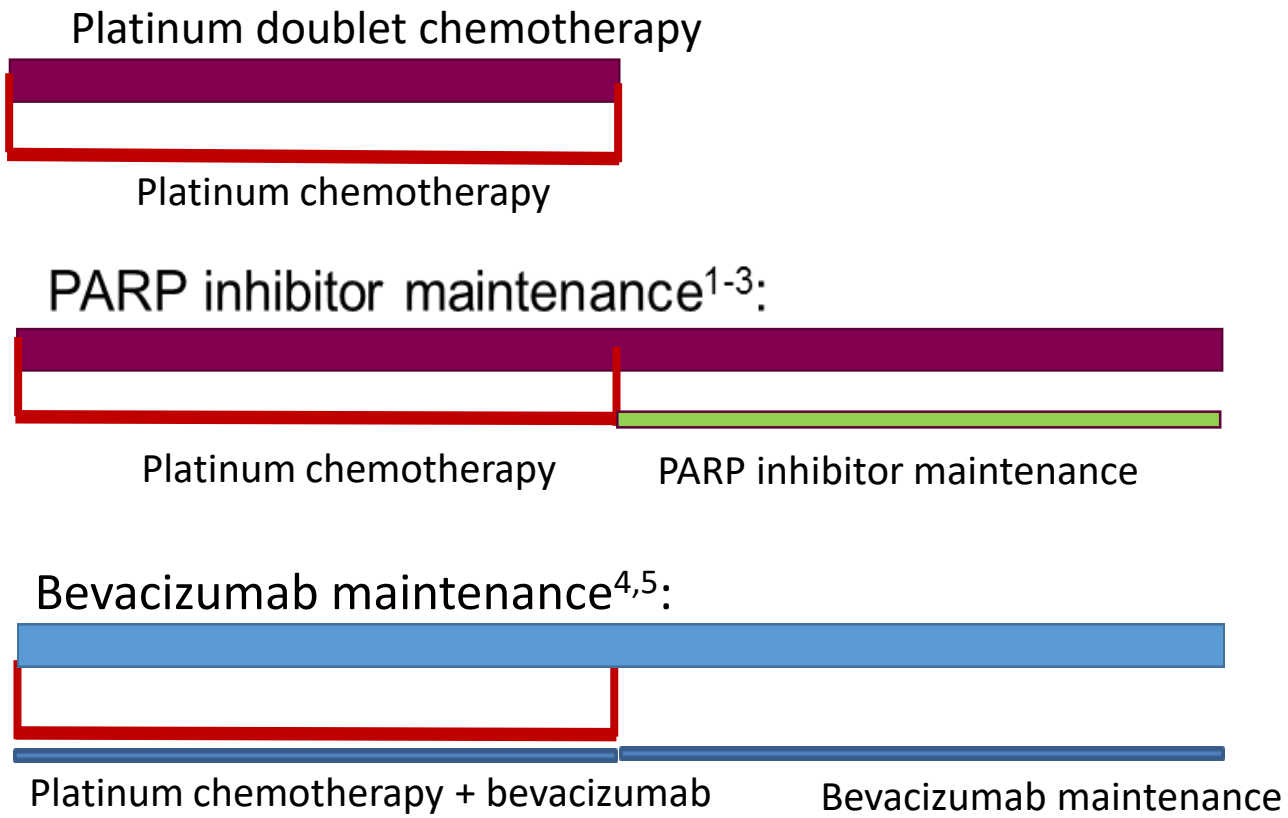


† Common indicator of fatality

CA-125=cancer antigen 125; PFS=progression-free survival

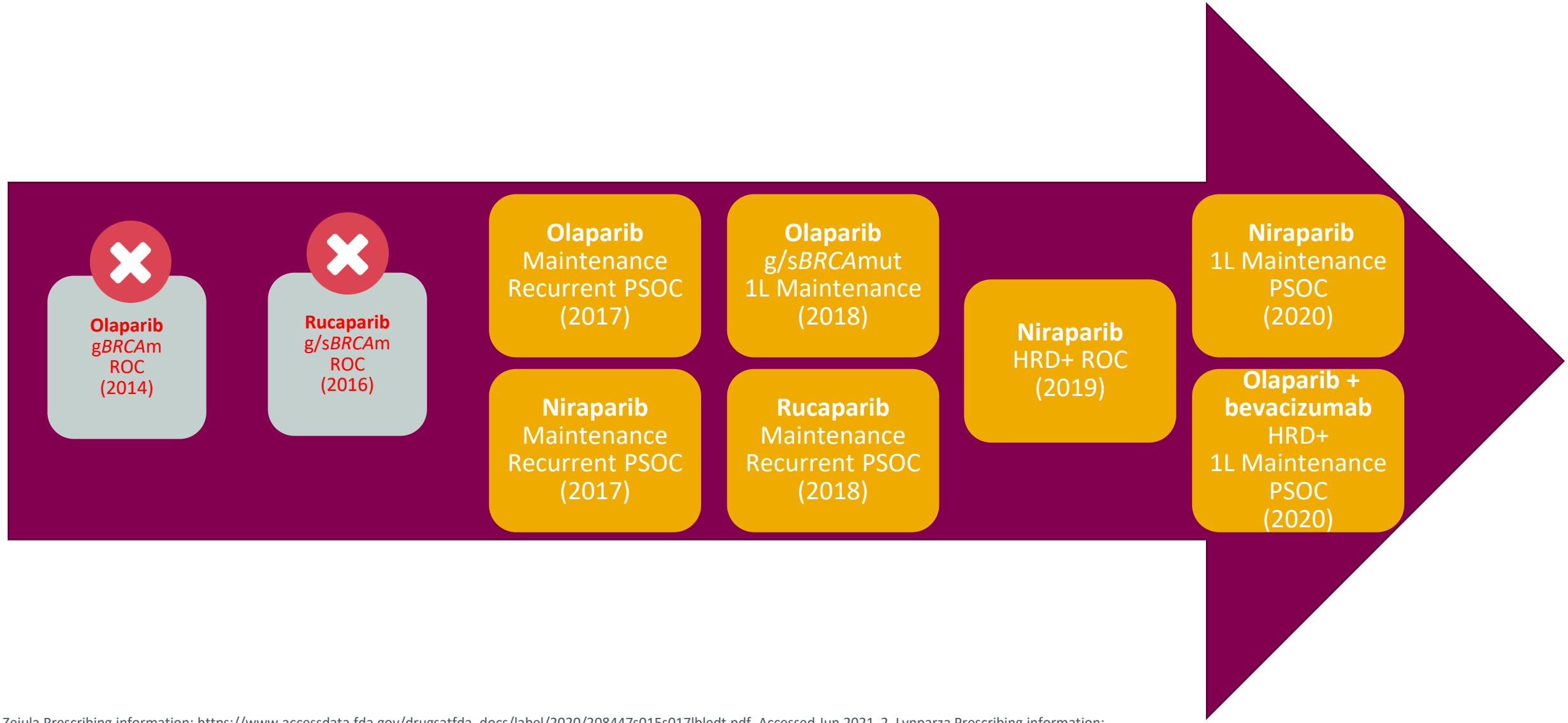
1. Markman M et al. *The Oncologist.* 2000;5:26–35; 2. Hanker LC, et al. *Ann Oncol.* 2012;23:2605–2612; 3. Armstrong DK. *The Oncologist.* 2002;7:20–28; 4.Fotopoulou C. *Eur J Cancer Suppl.* 2014;12:13–16.

Strategies for Platinum-Sensitive Ovarian Cancer



- Decision making needs to occur at the start of the platinum doublet and should include risks/benefits of these approaches

US FDA-Approved PARP Inhibitors in Ovarian Cancer[1,2,3]



1. Zejula Prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf, Accessed Jun 2021 2. Lynparza Prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf, Accessed Jun 2021 3.. Rubraca Prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s004lbl.pdf, Accessed Jun 2021

Olaparib has demonstrated PFS & OS benefit among PARPi's in 1st line OC maintenance BRCAm & HRD+ve

Study	**SOLO-1**[1] (Only BRCAm were enrolled)	**PAOLA-1**[2] (HRD positive group)	**PRIMA**[3] (HRD positive group)	**ATHENA-MONO**[4] (HRD positive group)
Agent/comparator	Olaparib vs placebo	Ola+Bev vs Placebo+Bev	Niraparib vs placebo	Rucaparib vs placebo
Median PFS, mos	56 vs 13.8 **Δ 42.2 mo**	37.2 vs 17.7 **Δ 19.5 mo** (combination therapy)	21.9 vs 10.4 **Δ 11.5 mo**	28.7 vs 11.3 **Δ 17.4 mo** **(monotherapy)**
PFS HR	0.33 (95% CI: 0.25-0.43)	0.33 (95% CI: 0.25-0.45)	0.43 (95% CI: 0.31-0.59)	0.47 (95% CI: 0.31-0.72)
OS HR	0.55 (95% CI: 0.40-0.76)	0.62 (95% CI: 0.45-0.85)	NA	NA

*No head to head trials available between PARPi in this setting.

Banerjee S, et al. Presented at ESMO Virtual Congress 2020. 19-21 September. Abstract #811MO.; DiSilvestro P, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; Ray-Coquard I, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France; Gonzalez-Martin. NEJM. 2019; 381:2391-402.; Monk BJ, Parkinson C, Lim MC, et al. J Clin Oncol. 2022 Jun 6; JCO2201003.

1.

SOLO 1 trial

SOLO 1: Trial design

- 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 bid (N=260)

2:1 randomisation

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

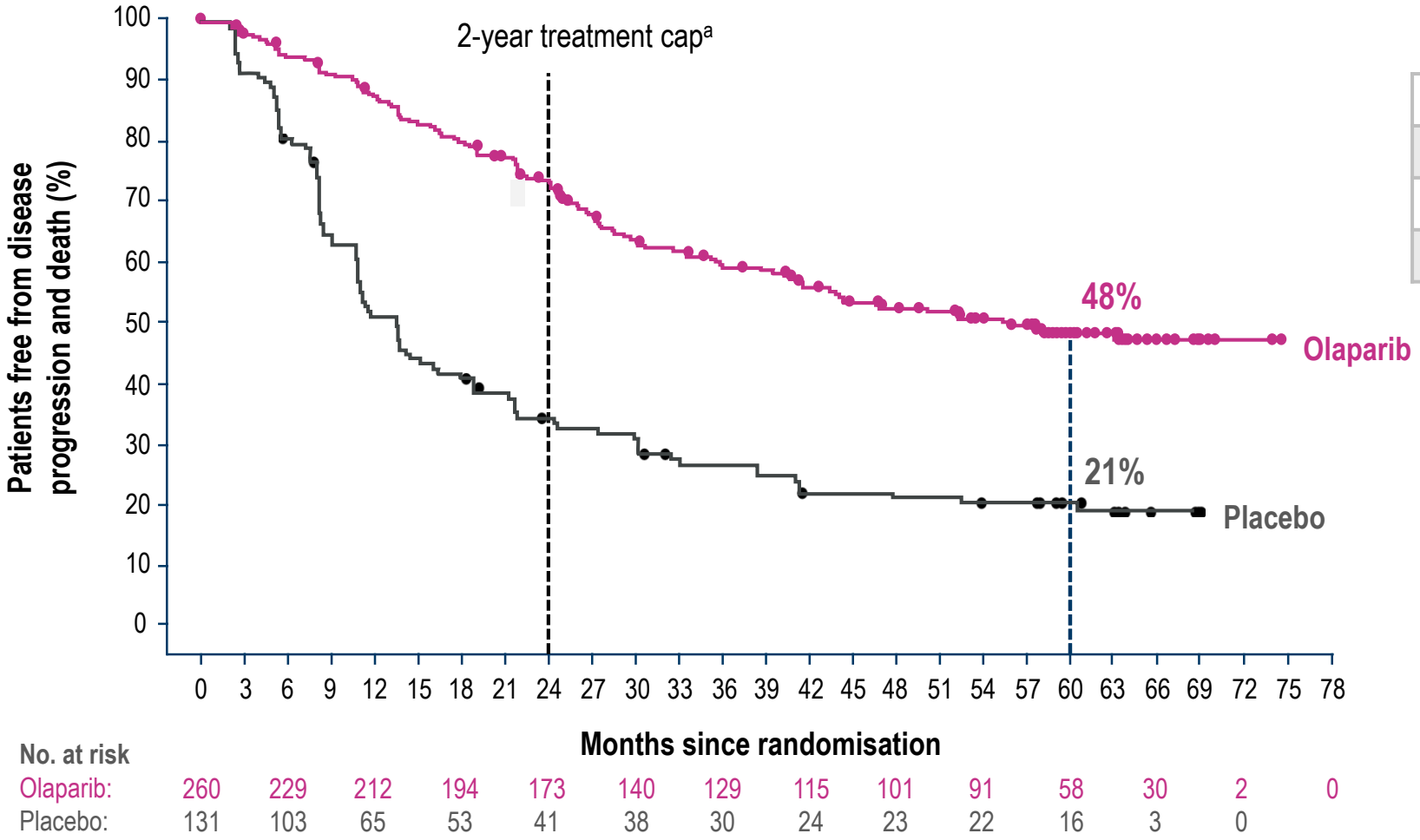
- PFS using BICR
- PFS2
- Overall survival
- Time from randomisation to first subsequent therapy or death
- Time from randomisation to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*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; PARP = poly (ADP-ribose) polymerase; *BRCA*m = *BRCA* gene mutation; Maintt: Maintenance

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

SOLO-1: PFS benefit of maintenance olaparib was sustained beyond the end of treatment



	Olaparib (n=260)	Placebo (n=131)
Median treatment duration, months	24.6	13.9
Events, n (%)	118 (45)	100 (76)
Median PFS, months	56.0	13.8
HR (95% CI)	0.33 (0.25, 0.43)	

Median PFS difference for olaparib vs placebo: 42.2 months

Median follow-up for PFS:

Olaparib	Placebo
4.8 years	5.0 years

•[a]Patients who had no evidence of disease at 2 years stopped receiving the trial intervention; patients who had a PR at 2 years were permitted to continue receiving the trial intervention in a blinded manner; 13 patients (all in the olaparib arm) continued study treatment past 2 years

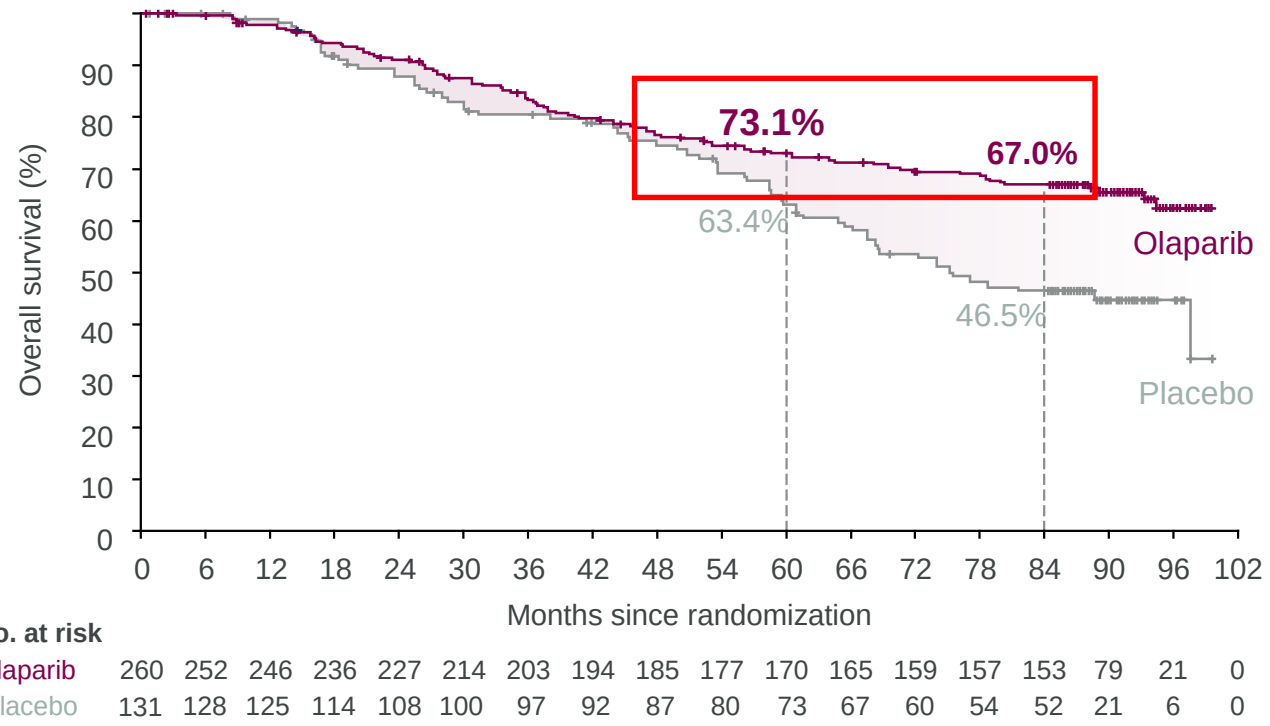
Investigator-assessed by modified RECIST v1.1

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours

Banerjee S, et al. Presented at ESMO Virtual Congress 2020; 19th–21st September 2020

SOLO-1: At the 7-year DCO, clinically meaningful OS benefit was observed with olaparib vs. placebo

***67% of olaparib** patients were alive at **7 years vs 46.5%** of placebo patients*



	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	NR	75.2

HR 0.55
(95% CI, 0.40–0.76)
P=0.0004*

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

- DCO for the 7-year descriptive OS analysis: 07 March 2022. Median follow-up of approximately 88 months.
- *P<0.0001 required to declare statistical significance

- DiSilvestro P, et al. Presented at ESMO Congress 2022, 9–13 September, Paris, France.

Lynparza® olaparib tablets 150 mg

SOLO-1: TAKEAWAY MESSAGES

Maintenance olaparib led to a substantial, unprecedented improvement in PFS in patients with newly diagnosed, advanced ovarian cancer and a BRCAm, with a difference in median PFS estimated to be in the region of 3 years[1,2]

A **70% reduction in risk of disease** progression or death was observed for olaparib vs. placebo-treated patients (**HR 0.33; p<0.001**)[1]

- After the landmark analysis, **median PFS was 56 months** on the olaparib arm vs. 13.8 months for placebo with PFS at 5 years: 48% vs. 21% for olaparib vs placebo[1]
- After **7 years of follow up**, **45% reduction in risk of death** was observed as compared to placebo (**HR 0.55; p=0.0004**) [2]

A **reduction in the risk of second progression or death** was observed demonstrating that **olaparib maintenance** does not diminish the benefit conferred by subsequent therapy[1]

After **7-years of follow-up**, the safety profile remained consistent with the primary analysis[2]
Most AEs being mild or moderate in severity, generally do not lead to dose reduction or permanent discontinuation[1]

PFS = progression-free survival; AE = adverse event; HRQoL = health-related quality of life; HR = hazard ratio; *BRCA*m = *BRCA* gene mutation

1. Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018) 2. DiSilvestro P, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France.

2.

PAOLA 1 trial

PAOLA-1: Trial design

Sponsored by ARCAGY research

- FIGO stage III–IV high-grade ovarian cancer (serous or endometrioid)* or non mucinous BRCAm
- Surgery (upfront or interval)
- Platinum taxane-based chemotherapy
- ≥3 cycles of bevacizumab†

NED/ CR/PR

Olaparib (300 mg BID) x 2 years
+ bevacizumab†

2:1 randomisation; **N=806**

Stratification by tBRCA status‡ and 1L treatment outcome

Placebo x 2 years
+ bevacizumab†

2 years' maintenance treatment

Primary endpoint

- Investigator-assessed PFS (RECIST 1.1)
  Sensitivity analysis by BICR

Secondary endpoints

- TFST
- PFS2
- TSST
- OS
- Safety
- PRO/HRQoL

Pre-specified exploratory endpoints

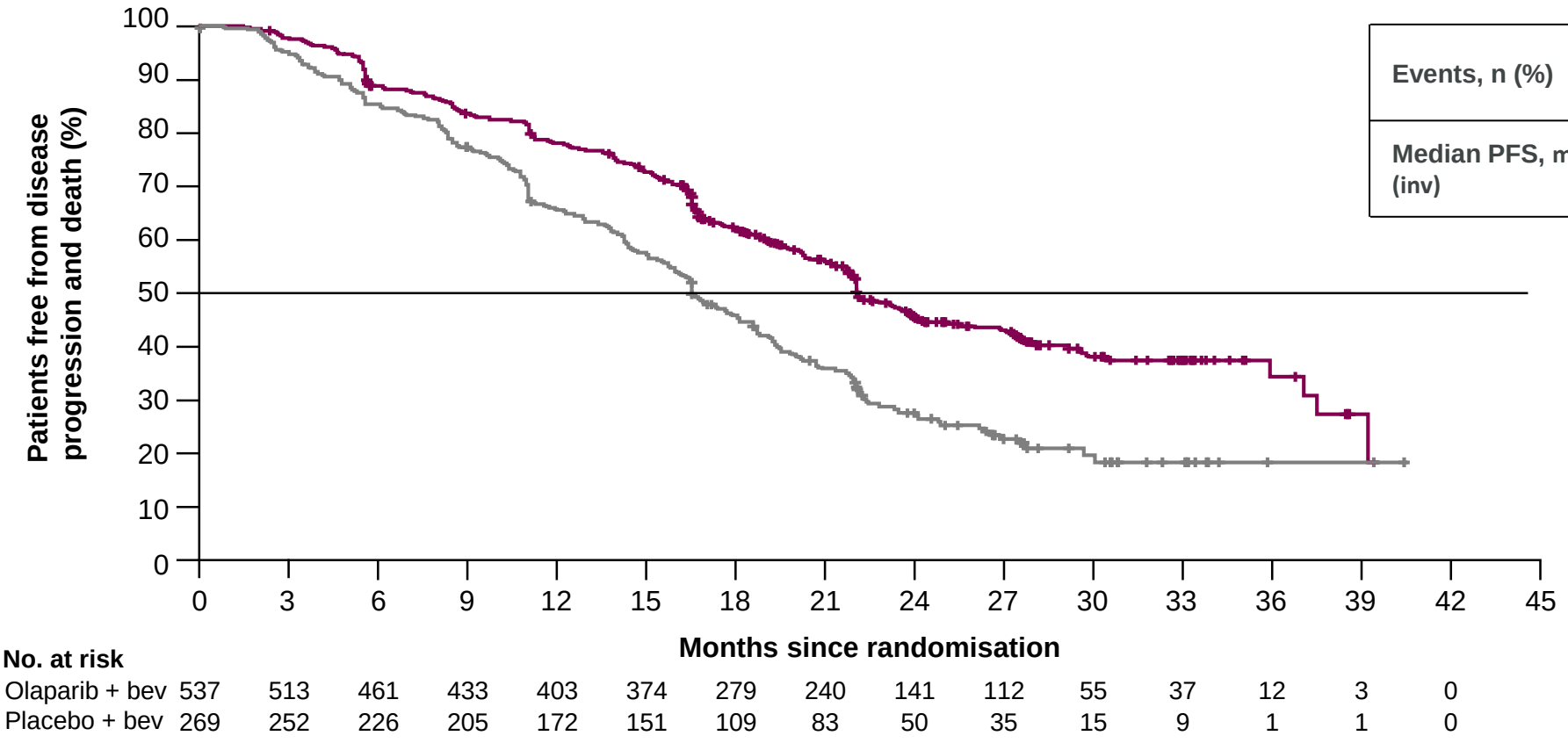
- PFS in pre-defined subgroups including tBRCAm and Myriad myChoice CDx

N=762 patients were planned to be randomised in the study so that maturity of the PFS data is ~60%. 458 events will give >80% power, at 5% alpha, to show HR 0.75, mPFS from 15.8 months (control) to 21.1 months (olaparib)
*Also includes fallopian tube and primary peritoneal cancer. †Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy. ‡By central labs
1L= first-line; BICR=blinded independent central review; BID=twice daily; BRCAm=mutation in BRCA; CDx=companion diagnostic test; CR=complete response; FIGO=Fédération Internationale de Gynécologie Obstétrique; 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; PRO=patient-reported outcomes; RECIST=Response Evaluation Criteria in Solid Tumours; tBRCA=tumour BRCA; tBRCAm=mutation in tumour BRCA; TFST=time to first subsequent therapy; CTx=Chemotherapy; Bev=Bevacizumab

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:Clinical Study Protocol; 2. Study NCT02477644. Available at: https://clinicaltrials.gov/ct2/show/NCT02477644. Last accessed December 2019.

PAOLA1 TRIAL:
Olaparib + bev significantly improved PFS vs. placebo + bev in the ITT population

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



No. at risk

Olaparib + bev	537	513	461	433	403	374	279	240	141	112	55	37	12	3	0
Placebo + bev	269	252	226	205	172	151	109	83	50	35	15	9	1	1	0

	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		

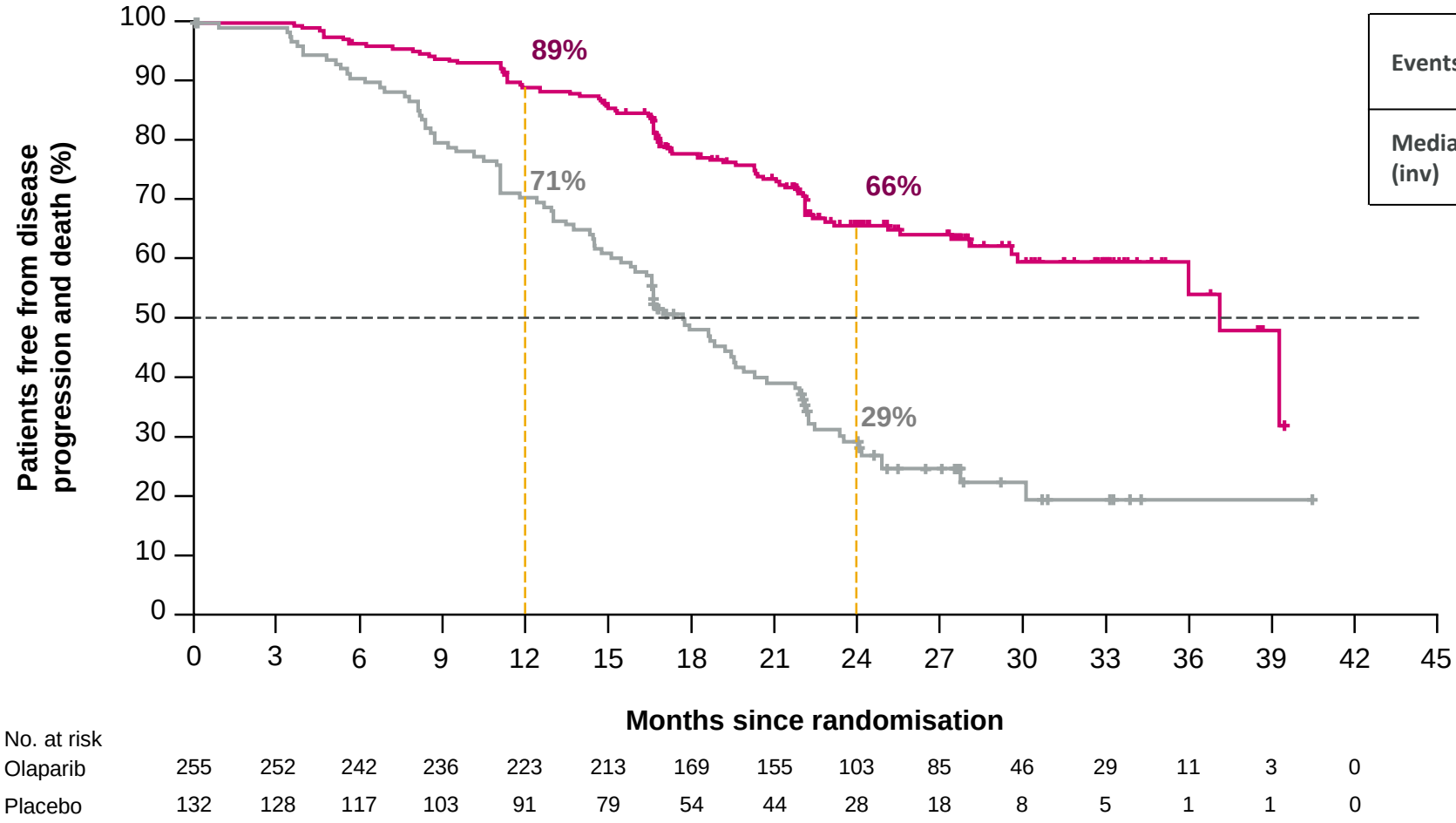
Primary endpoint:
investigator-assessed PFS

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

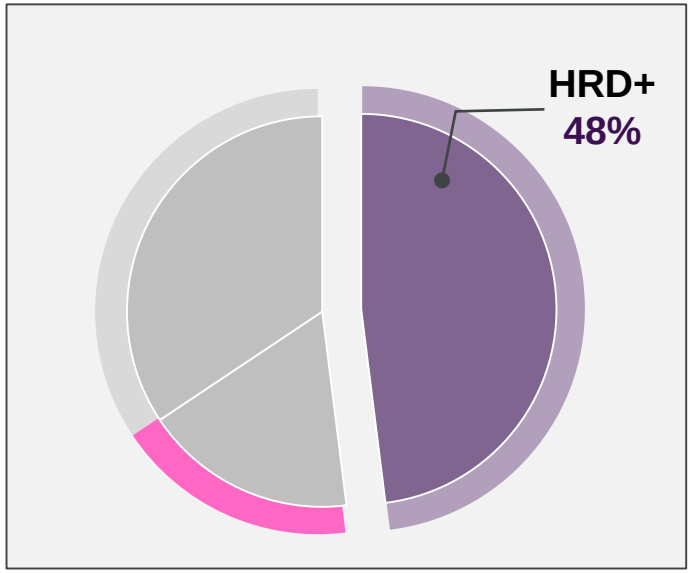
PFS by investigator assessment. Analysis per eCRF. Data maturity=59% | Median duration of follow-up for primary analysis: olaparib, 22.7 months; placebo, 24.0 months | Data cut-off: 22 March 2019
Bev=bevacizumab; CI=confidence interval; eCRF=electronic case report file; HR=hazard ratio; inv=investigator-assessed;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

PAOLA1 TRIAL: Pre-specified subgroup analysis showed substantial PFS benefit in HRD-positive* (including tBRCAm) patients



	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	

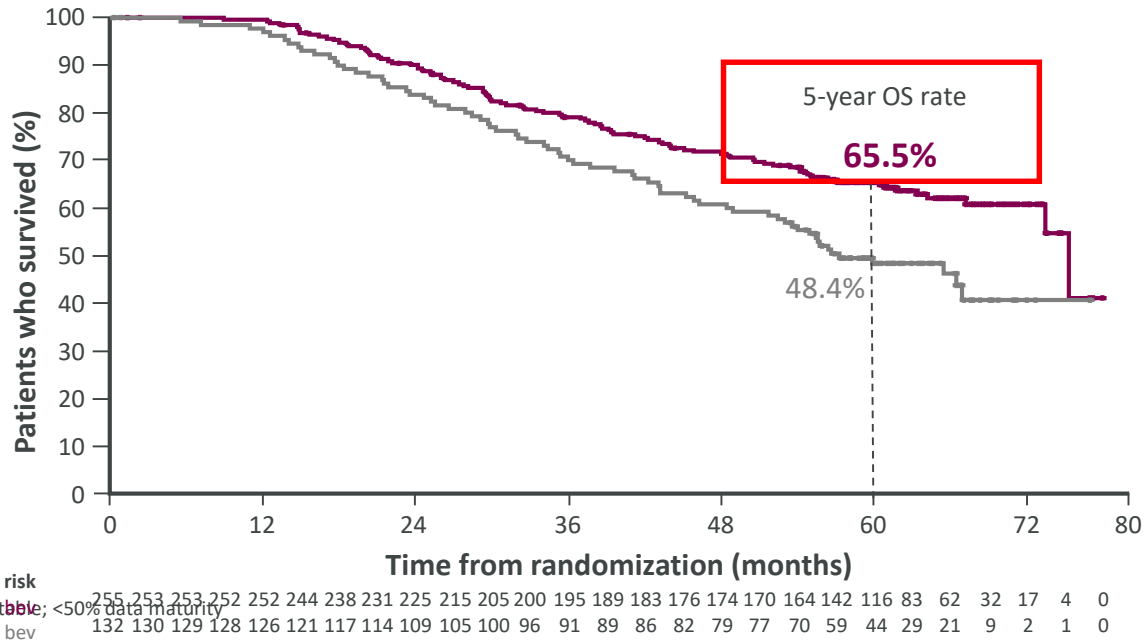


Data maturity=46%. The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates
*HRD-positive determined by tBRCAm or Myriad myChoice CDx genomic instability score ≥42. †This median is unstable due to a lack of events – less than 50% maturity.
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.

PAOLA1 TRIAL: Olaparib + bev provided a clinically meaningful improvement in OS in HRD-positive patients

*At **5 years, 65.5% of patients** receiving **Olaparib + bevacizumab** were still alive vs 48.4% who received bevacizumab alone*



*Median unstable; <50% data maturity

	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62
95% CI, 0.45-0.85

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone*

Patients receiving a PARP inhibitor during any subsequent treatment:
Olaparib + bev: **17.3%** (44/255)
Placebo + bev: **50.8%** (67/132)

Final OS DCO: 22 March 2022. Final OS analysis planned for 3 years after the primary PFS analysis or 60% data maturity.

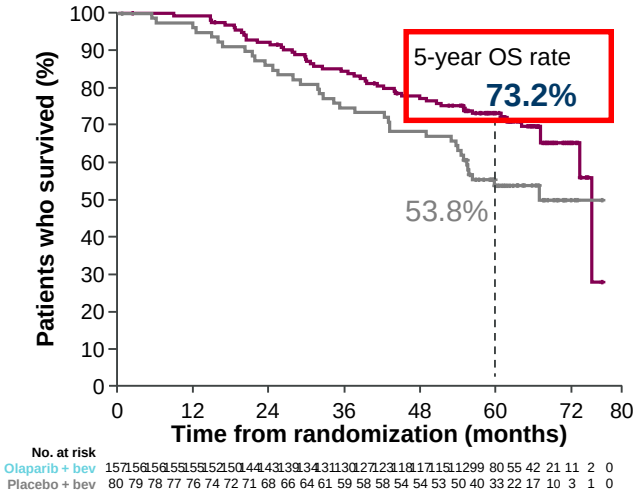
Median time from first cycle of chemotherapy to randomization = 6 months

*Descriptive analysis

Ray-Coquard I, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France

PAOLA1 TRIAL: The addition of olaparib to bevacizumab prolonged OS in HRD+ patients regardless of BRCA status

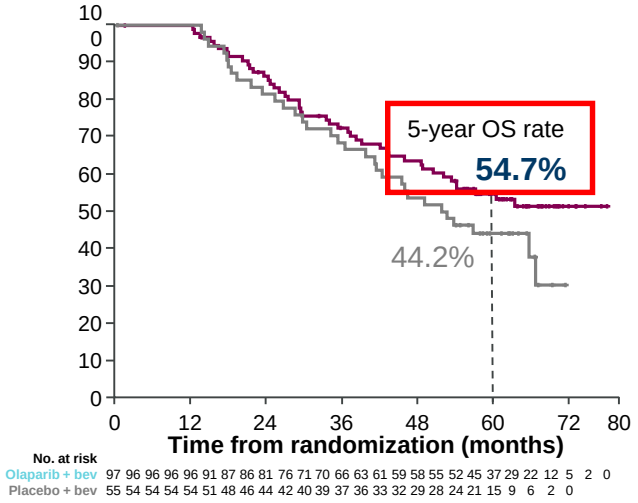
BRCAm*



	Olaparib + bevacizumab (n=157)	Placebo + bevacizumab (n=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	**75.2** (unstable) ‡	**66.9**
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent therapy, n (%)	38 (24.2)	44 (55.0)

HR 0.60 (95% CI, 0.39–0.93)

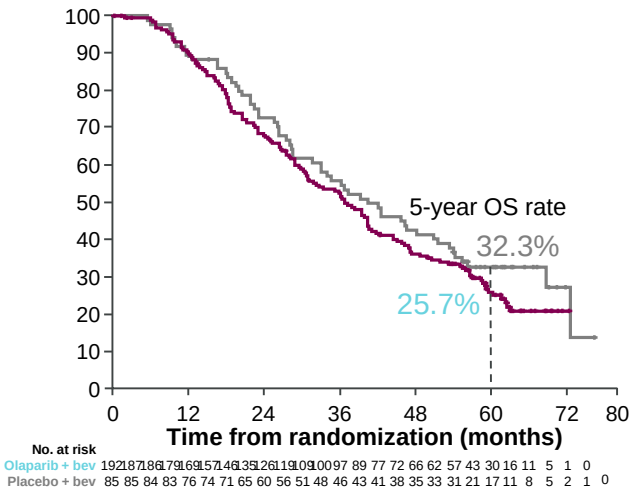
HRD-positive,† excluding tBRCAm



Olaparib + bevacizumab (n=97)	Placebo + bevacizumab (n=55)
44 (45.4)	32 (58.2)
NR	**52.0**
54.7	**44.2**
9 (9.3)	23.0 (41.8)

HR 0.71 (95% CI, 0.45–1.13)

HRD-negative†



Olaparib + bevacizumab (n=192)	Placebo + bevacizumab (n=85)
140 (72.9)	58 (68.2)
36.8	**40.4**
25.7	**32.3**
46 (24.0)	34 (40.0)

HR 1.19 (95% CI, 0.88–1.63)

*By central labs; †By Myriad myChoice® HRD Plus; ‡Unstable median; <50% data maturity; Final OS DCO: 22 March 2022. Final OS analysis planned for 3 years after the primary PFS analysis or 60% data maturity.; Ray-Coquard I, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France

PAOLA1 TRIAL: Take away messages

PAOLA-1 is the only Phase III randomised trial to investigate the addition of a PARP inhibitor (olaparib) to active treatment with bevacizumab in the newly diagnosed setting, with the intent of achieving maximum therapeutic benefit[1]

In a representative patient population, **unselected by biomarker status or surgical outcomes, olaparib added to bevacizumab significantly improved PFS vs. placebo plus bevacizumab[1]**

In **HRD-positive* patients, olaparib added to bevacizumab substantially improved PFS** vs. placebo plus bevacizumab (HR 0.33; 95% CI 0.25–0.45, median PFS 37.2 vs. 17.7 months)[1], demonstrating the importance of HRD testing in clinical decision making

The **significant improvement in PFS2 demonstrated** that olaparib added to bevacizumab was associated with continued benefit beyond first progression[2]

At **final 5yrs OS analysis**, **Olaparib added to bevacizumab substantially improved PFS** vs. bevacizumab alone with a median PFS of **almost 4 years (HR 0.41)[4]**

*HRD-positive determined by tBRCAm or Myriad myChoice CDx genomic instability score ≥42 CDx=companion diagnostic test; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; HRQoL=health-related quality of life; PFS=progression-free survival; PFS2=time to preogression on subsequent therapy; tBRCAm=mutation tumour BRCA

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Gonzalez-Martin A, et al. Presented at ESMO Virtual Congress 2020. 19-21 September. Abstract #LBA33;
3. Lynparza 150mg Film-Coated Tablets, SmPC, 2020.4. Ray-Coquard I, et al. Presented at ESMO Congress 2022. 9–13 September. Paris, France.

3.

PRIMA trial

PRIMA: Trial design

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

Stratified by neoadjuvant CT (yes vs no), best response to first platinum (CR vs PR), tissue HRD test (deficient vs proficient/not determined)

Patients with newly diagnosed, ovarian cancer* with response to 6-9 cycles 1L chemo; high risk of recurrence; neoadjuvant chemo allowed (N = 733)

Randomized 2:1

Niraparib 300 mg QD† x 28-day cycles (n = 487)

Placebo QD x 28-day cycles (n = 246)

Treatment for 36 mos or until PD

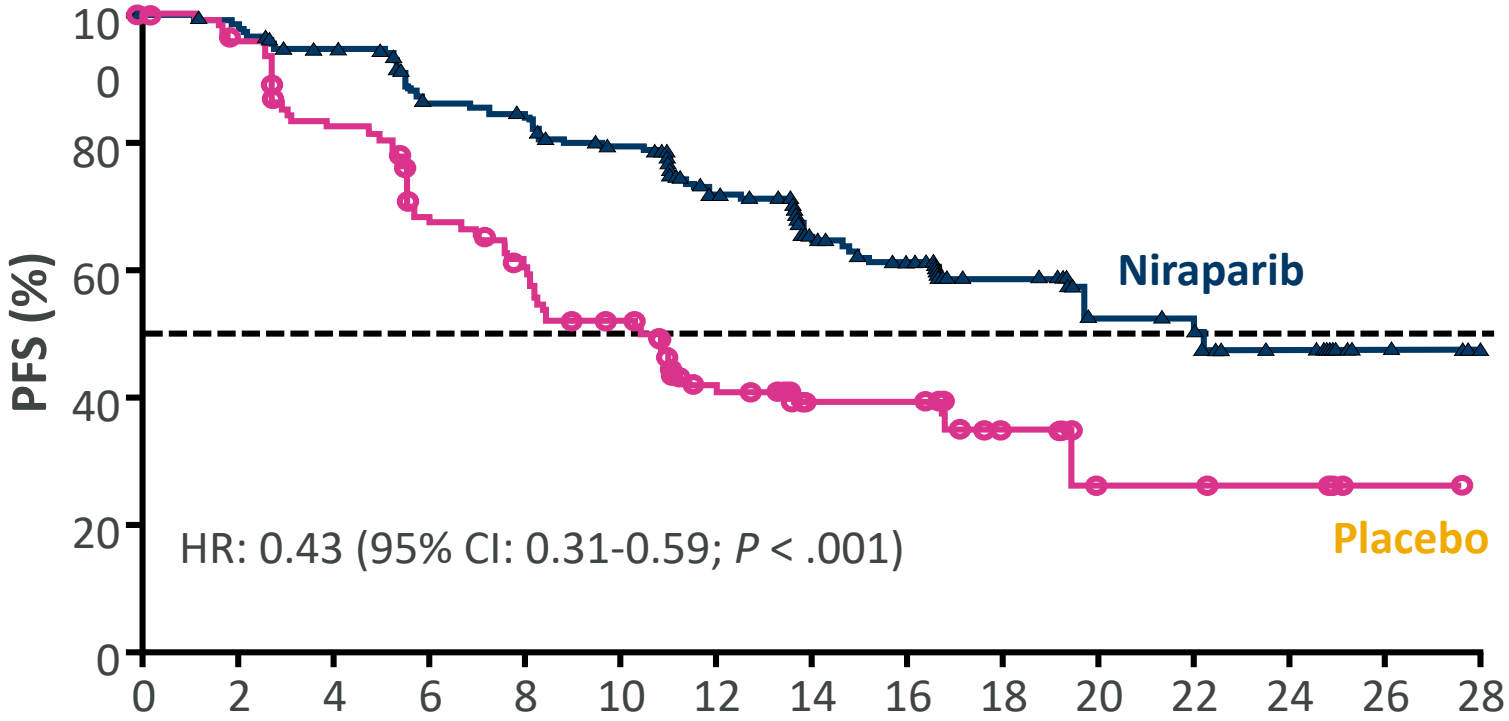
*Stage III w/residual tumor after debulking surgery, inoperable stage III disease, or any stage IV disease.

†Dosing amended in November 2017 to 200 mg QD if < 77 kg body weight, platelets < 150,000/mm^3, or both.

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

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

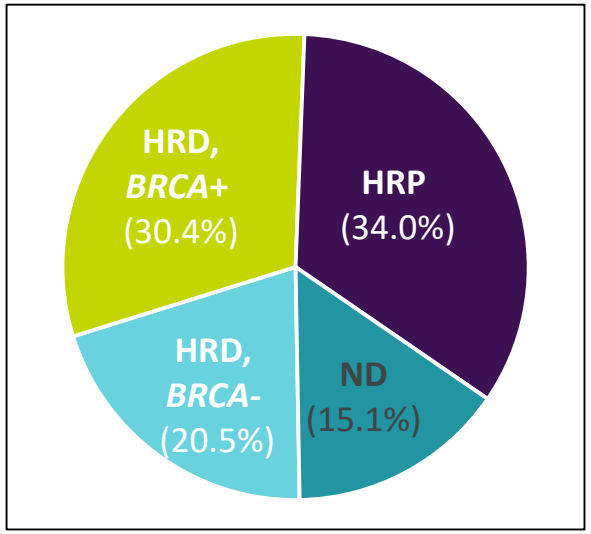
PRIMA: PFS in HRD Patients



Patients 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

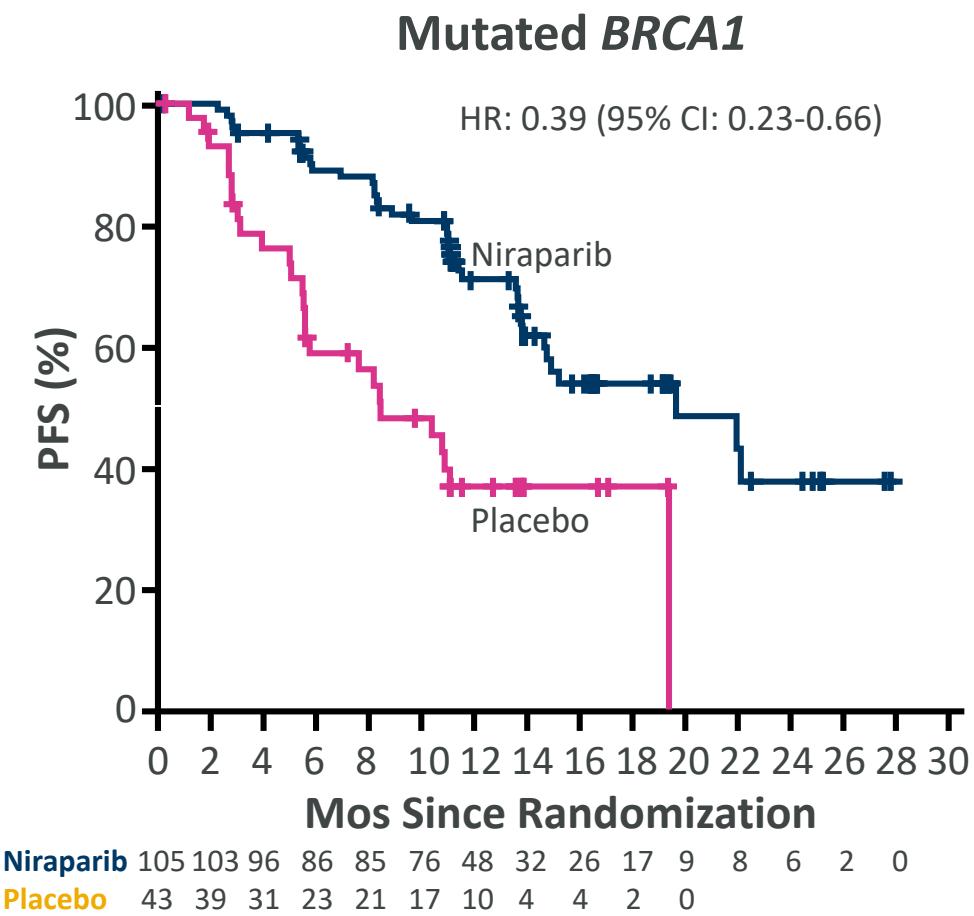
57% reduction in risk of relapse or death with niraparib vs placebo

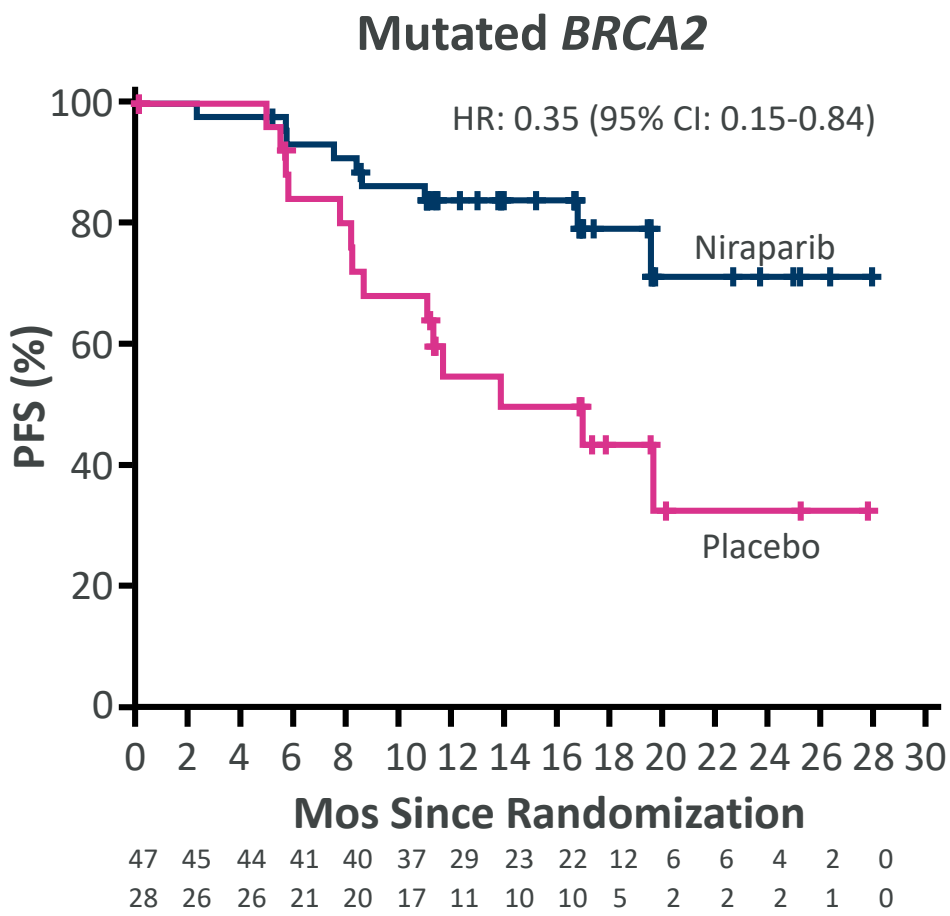
	Niraparib (n = 247)	Placebo (n = 126)
Median PFS, mos (95% CI)	21.9 (19.3-NE)	10.4 (8.1-12.1)
No PD or death, %		
• 6 mos	86	68
• 12 mos	72	42
• 18 mos	59	35



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

PRIMA: PFS in Patients With Mutated BRCA1 vs BRCA2

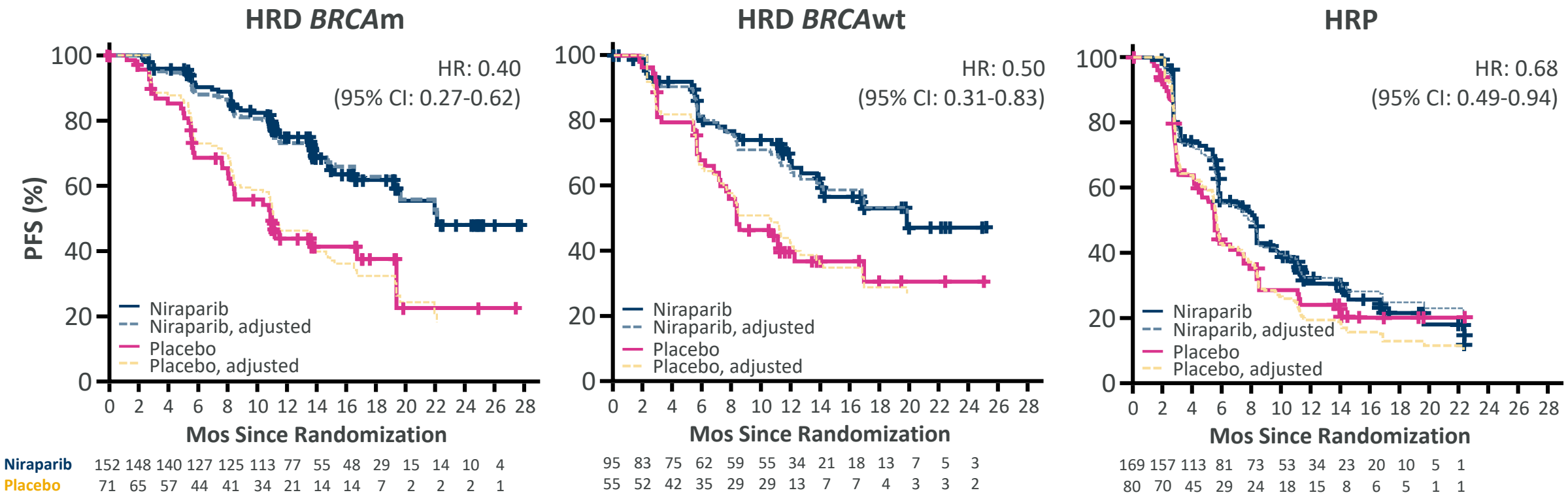




Niraparib efficacy was similar in mutated *BRCA1* and mutated *BRCA2*

Monk. SGO 2020. Webinar 2.

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.

4.

ATHENA- MONO

ATHENA* (GOG 3020/ENGOT-ov45) trial: Study schema and analysis plan

Key Patient Eligibility

- Newly diagnosed, stage III/IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR without disease progression or rise in CA-125 at any time during frontline platinum-doublet chemotherapy
  - Received cytoreductive surgery (R0 permitted), either prior to chemotherapy or following neoadjuvant chemotherapy, with sufficient tissue available for analysis
- ECOG PS 0 or 1
- No prior treatment for ovarian cancer, including any maintenance treatment, other than frontline platinum regimen

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib PO + nivolumab IV

Arm B (n≈400)
rucaparib PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab IV

Arm D (n≈100)
placebo PO + placebo IV

Treatment for 24 months, or until radiographic progression, unacceptable toxicity, or other reason for discontinuation

Stratification Factors

- Centrally assessed tumor status (BRCA mutation, BRCA wild-type/high LOH, BRCA wild-type/low LOH, BRCA wild-type/LOH indeterminate)
- Response to frontline platinum doublet (no residual disease vs residual disease)
- Timing of surgery (primary vs interval debulking)

Study Analyses

ATHENA–MONO
(Arm B vs Arm D)

Arm B (n≈400)
rucaparib PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO
(Arm A vs Arm B)

Arm A (n≈400)
rucaparib PO + nivolumab IV

Arm B (n≈400)
rucaparib PO + placebo IV

Primary Endpoint

Investigator-assessed PFS per RECIST v1.

Data Published, Not yet approved anywhere in the globe

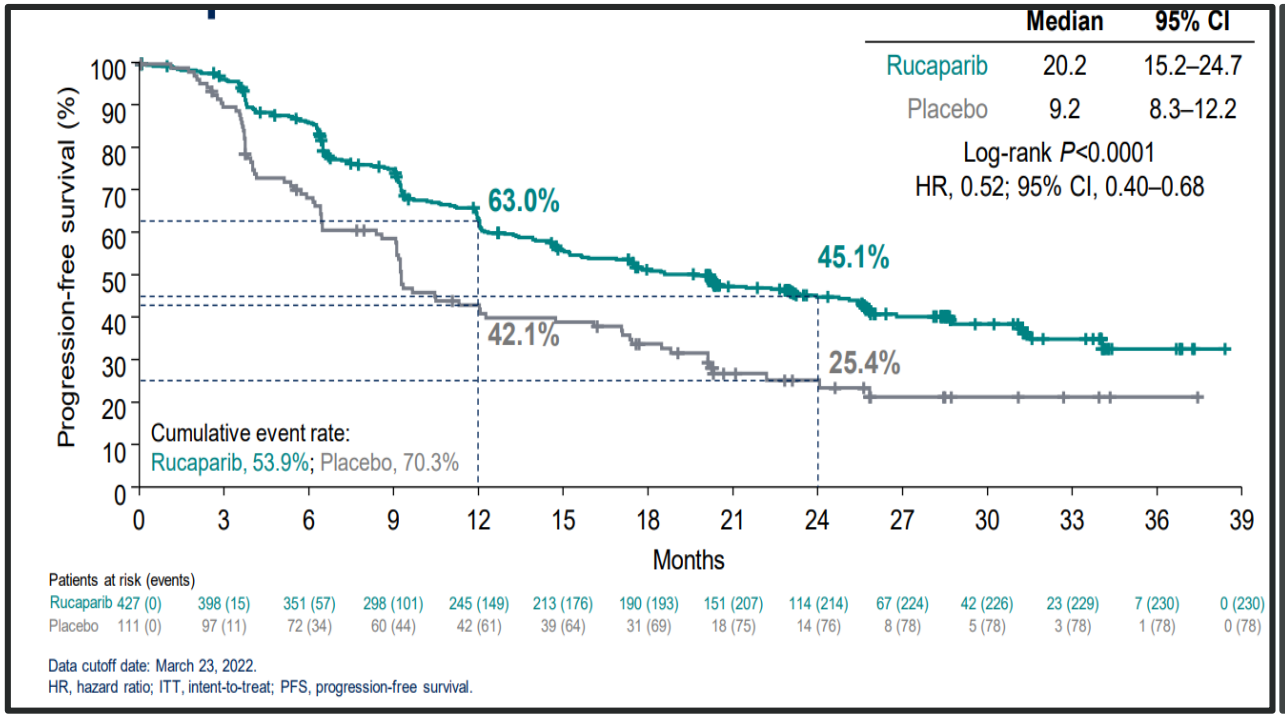
Study Ongoing

***ATHENA-MONO indication is not approved anywhere in the world**

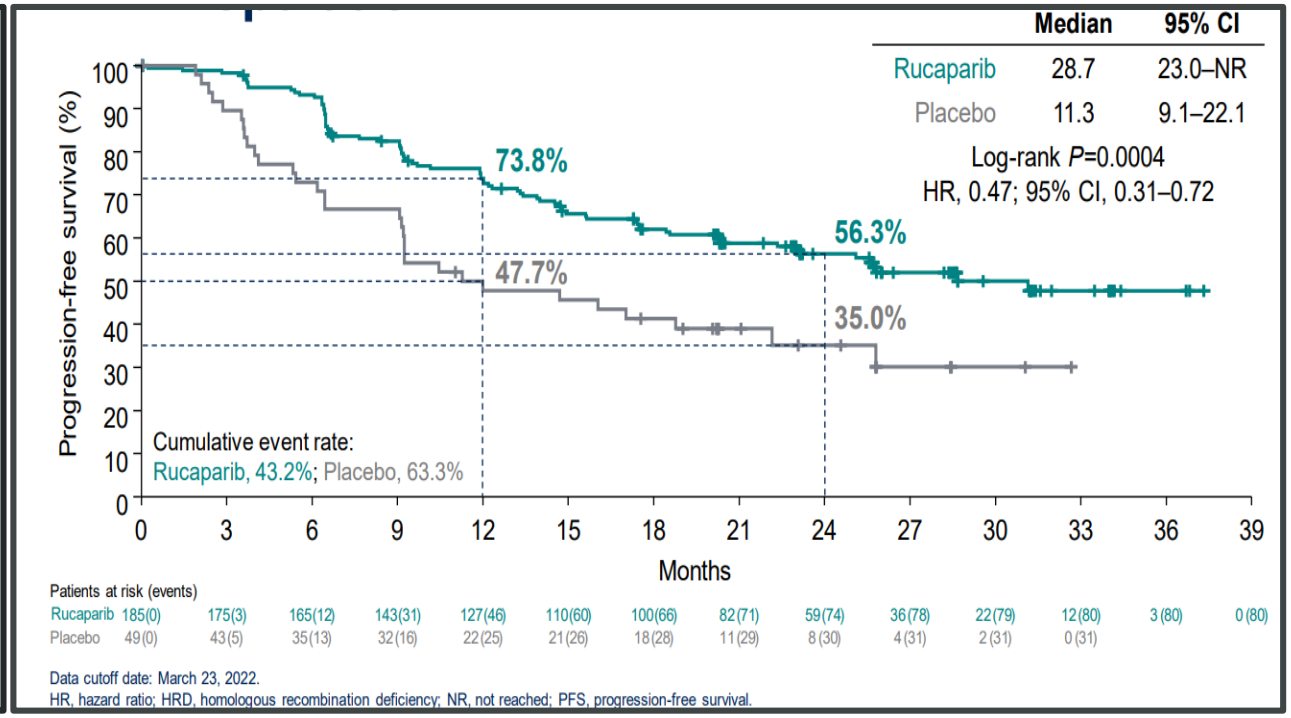
Monk BJ, Parkinson CN, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45) [published online ahead of print, 2022 Jun 6]. J Clin Oncol. 2022;JCO2201003. doi:10.1200/JCO.22.01003

Athena* MONO: Median PFS

In All Commers/ITT



In HRD positive



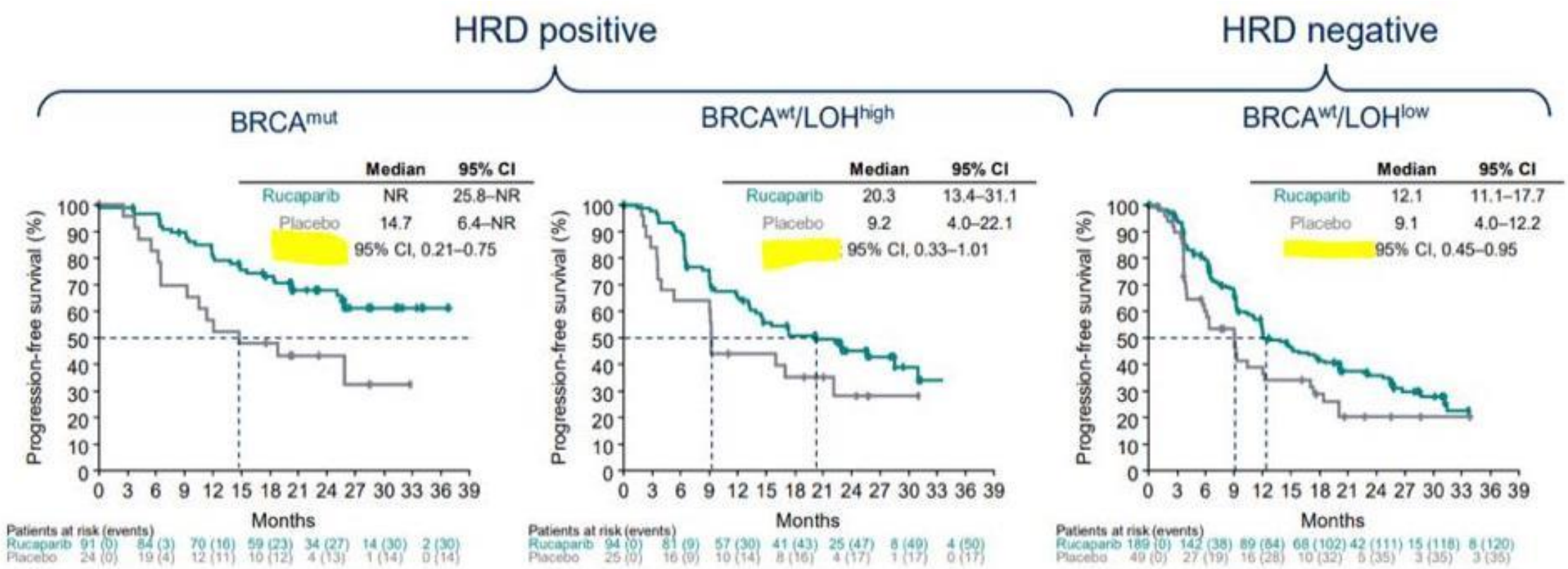
HR 0.52

HR 0.47

***ATHENA-MONO indication is not approved anywhere in the world**

Monk BJ, Parkinson CN, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45) [published online ahead of print, 2022 Jun 6]. J Clin Oncol. 2022;JCO2201003. doi:10.1200/JCO.22.01003

Investigator-Assessed PFS: Exploratory Subgroups



- Rucaparib demonstrated treatment benefit vs placebo regardless of BRCA mutation and HRD status

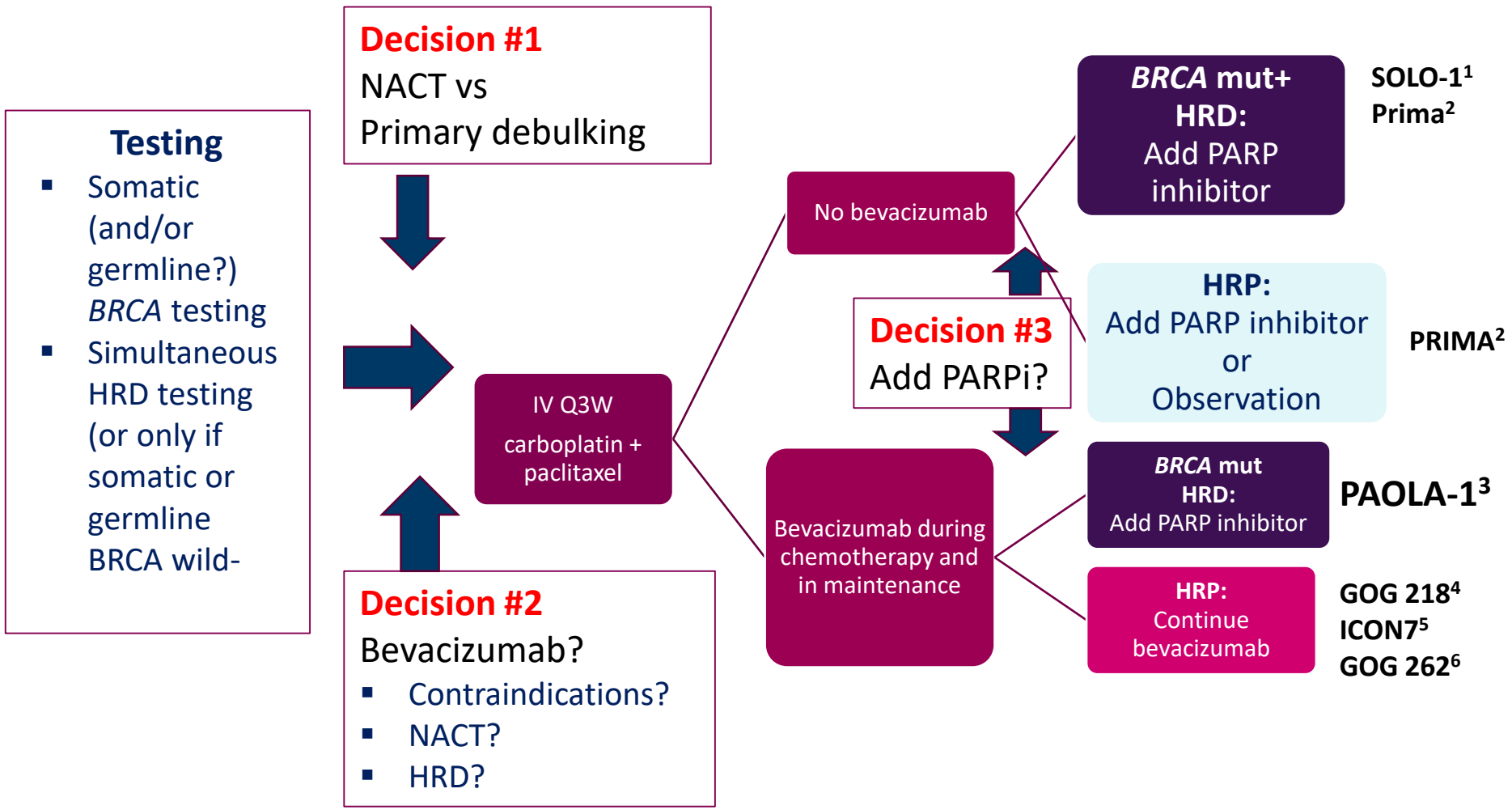
Data cutoff date: March 23, 2022.

BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; mut, mutant; NR, not reached; PFS, progression-free survival; wt, wild type.

***ATHENA-MONO indication is not approved anywhere in the world**

Monk BJ, Parkinson CN, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45) [published online ahead of print, 2022 Jun 6]. J Clin Oncol. 2022;JCO2201003. doi:10.1200/JCO.22.01003

Integrated Maintenance Treatment Paradigm for First-line Ovarian Cancer (2022)



Athena-Mono : Data Published, *indication is not approved anywhere in the world*

Abbreviated Prescribing information

For the use of registered oncologist only

Olaparib Tablets

LYNPARZA® 100 mg and 150 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION: Each 150 mg film-coated tablet contains 150 mg of olaparib.| Each 100 mg film-coated tablet contains 100 mg of olaparib.

INDICATIONS

LYNPARZA is indicated in: **Ovarian Cancer:**for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy; for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy; for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy (**This treatment indication is voluntarily withdrawn and is under regulatory review**); Lynparza in combination with bevacizumab is indicated for the: maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy with bevacizumab

Breast Cancer: In patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment; as monotherapy for the adjuvant treatment of adult patients with *BRCA*-mutated HER2-negative high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy

Prostate cancer: Lynparza is indicated as monotherapy for the: treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent

Adenocarcinoma of the pancreas: Lynparza is indicated as monotherapy for the: maintenance treatment of adult patients with germline *BRCA*-mutated metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy

DOSAGE & ADMINISTRATION: The recommended dose of LYNPARZA is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

Duration of treatment: Maintenance treatment of newly diagnosed advanced ovarian cancer: can continue treatment for 2 years or until disease progression. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.**Advanced gBRCA-mutated Ovarian Cancer**: Continue treatment until disease progression or unacceptable toxicity. (**This treatment indication is voluntarily withdrawn and is under regulatory review**)

Platinum-sensitive relapsed ovarian cancer: it is recommended that treatment be continued until progression of the underlying disease

Maintenance treatment of newly diagnosed advanced ovarian cancer in combination with bevacizumab: patients can continue treatment for 2 years or until disease progression. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years **Metastatic HER2-negative breast cancer:** it is recommended that treatment be continued until progression of the underlying disease.

Adjuvant treatment of BRCA-mutated HER2-negative high risk early breast cancer: it is recommended that patients are treated for a total of 1 year, or until disease recurrence, whichever occurs first. Patients with hormone receptor-positive breast cancer should continue concurrent treatment with endocrine therapy as per local guidelines.

HRR-gene mutated metastatic castration-resistant prostate cancer: it is recommended that treatment be continued until progression of the underlying disease

Maintenance following first-line treatment of metastatic adenocarcinoma of the pancreas: It is recommended that treatment be continued until progression of the underlying disease

Abbreviated Prescribing information

CONTRAINDICATIONS:
None.

WARNINGS & PRECAUTIONS: Haematological toxicity: Haematological toxicity has been reported in patients treated with LYNPARZA including generally mild or moderate anaemia, neutropenia, thrombocytopenia and lymphopenia. If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted.**Myelodysplastic Syndrome/Acute Myeloid Leukaemia**: The incidence of MDS/AML in patients treated in clinical trials with Lynparza monotherapy, including long-term survival follow up, was <1.5%, with higher incidence in patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years. The majority of events had a fatal outcome. The duration of therapy with Lynparza in patients who developed MDS/AML varied from < 6 months to > 4 years If MDS and/or AML are confirmed while on treatment with LYNPARZA, it is recommended that LYNPARZA should be discontinued and the patient be treated appropriately. **Venous Thromboembolic Events** Venous thromboembolic events, including pulmonary embolism, have occurred in patients treated with Lynparza and had no consistent clinical pattern. A higher incidence was observed in patients with metastatic castration-resistant prostate cancer, who also received androgen deprivation therapy, compared with other approved indications. It is recommended to monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.**Pneumonitis**: Pneumonitis has been reported in <1.0% patients treated with LYNPARZA monotherapy in clinical studies. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately. **Embryofoetal toxicity**: Based on its mechanism of action (PARP inhibition), LYNPARZA could cause foetal harm when administered to a pregnant woman. LYNPARZA should not be taken during pregnancy.**Breast-feeding**: The excretion of olaparib in milk has not been studied in animals or in breast-feeding mothers.**Interactions with other medicinal products: Co-administration of LYNPARZA with strong or moderate CYP3A inhibitors is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced.** Co-administration of LYNPARZA with strong or moderate CYP3A inducers is not recommended.
Undesirable effects: The most commonly reported adverse drug reactions (ADRs), reported in more than 10% of the patients and greater than placebo/ active comparator were: Anemia, Neutropenia and/or Leukopenia, Decreased apetite, Dizzyness, Headache, Cough, Dysguesia, Vomiting, Nausea and Diarrhoea, Fatigue.
INTERACTIONS: Concomitant use of itraconazole as well as other strong CYP3A inhibitors is not recommended with LYNPARZA due to an increase in Cmax and AUC. CYP3A inducers could substantially diminish the clinical efficacy of LYNPARZA and concomitant use of strong inducers is not recommended.
PHARMACOLOGICAL PROPERTIES:
Mechanism of action: Olaparib is a potent inhibitor of human poly (ADP ribose) polymerase enzymes (PARP 1, PARP 2, and PARP 3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies
Pharmacokinetic properties: The pharmacokinetics of olaparib at the 300 mg tablet dose is characterized by an apparent plasma clearance of ~7 L/h, an apparent volume of distribution of ~158 L and a terminal half-life of 15 hours. The *in vitro* plasma protein binding is approximately 82% at 10 µg/mL. CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib. Post administration, ~86% of the dose was recovered within a 7-day collection period, ~44% via the urine and ~42% via the faeces. Majority of the material was excreted as metabolites.
PHARMACEUTICAL PARTICULARS
PRESENTATION & STORAGE: LYNPARZA 150 mg tablet is a green to green/grey, oval, bi-convex tablet debossed with 'OP150' on one side and plain on the reverse.LYNPARZA 100 mg tablet is a yellow to dark yellow, oval, bi-convex tablet debossed with 'OP100' on one side and plain on the reverse.
This medicinal product does not require any special temperature storage conditions.
SHELF LIFE: Please refer outer carton.
LYNPARZA® is a trademark of AstraZeneca group of companies.
For Further information contact: AstraZeneca Pharma India Ltd., Block N1, 12th Floor, Manyata Embassy Business Park, Rachenahalli, Outer Ring Road, Bengaluru – 560 045 | www.astrazenecaindia.com
For more information, refer full prescribing information Version 10, dated 16th Aug 2022.API Version 6 Dated 22nd Aug 2022.