Controversies in the Management of Ovarian Cancer: A Focus on First-Line Treatment

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Discussion Outline

- Review ovarian treatment landscape
- Review recently studied/approved agents
- Review treatment indications
- Review maintenance indications

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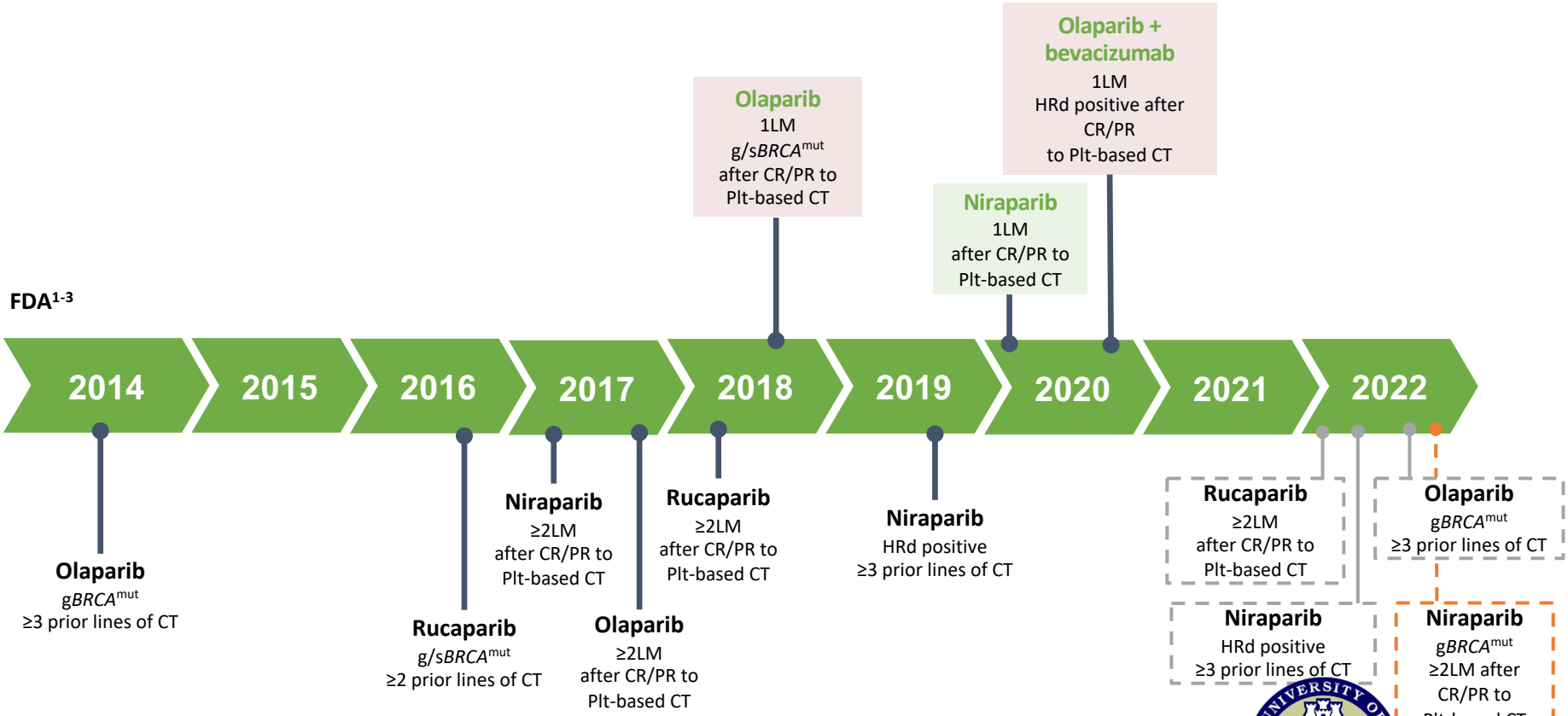
FDA Approvals of PARPi in Ovarian Cancer[1-3]



1. Niraparib. Package insert. GlaxoSmithKline; 2022. 2. Olaparib. Package insert. AstraZeneca; 2022.
3. Rucaparib. Package insert. Clovis Oncology; 2022.

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Treatment

- Seven chemo agents approved over 35 years! (1978-2013)
- All the seven agents approved for treatment indications
- Outside clinical trials, nothing else was available for ovarian cancer therapy

New FDA approvals for treatment or maintenance of ovarian cancer (Four years !, 2014 -2020)

- Treatment (three agents)
  - Olaparib
  - Rucaparib
  - Bevacizumab

- Maintenance (four agents)
  - Niraparib
  - Olaparib
  - Rucaparib
  - Bevacizumab
  - Olaparib + Bevacizumab

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Rationale for Targeting VEGF Pathway in the Treatment of Ovarian Cancer

- Human tumors
  - VEGF expression and degree of tumor angiogenesis (micro-vessel density) associated with
    - Ascites formation
    - Malignant progression
    - Poor prognosis

Yoneda et al, 1998; Ferrara, 1999; Dvorak, 2002; Gasparini et al, 1996; Hollingsworth et al, 1995; [illegible] al, 1997; Alvarez et al, 1999.

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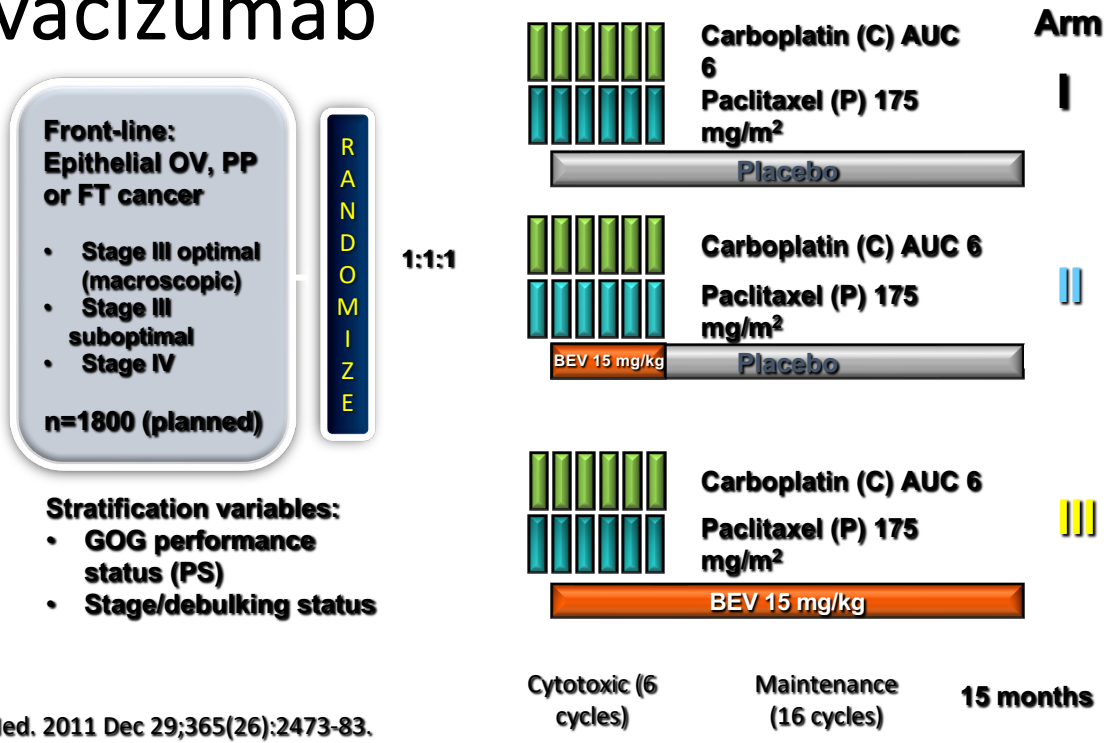
Bevacizumab (GOG 218)

Targeted therapy for ovarian, Bevacizumab



Burger, NEngl J Med. 2011 Dec 29;365(26):2473-83.

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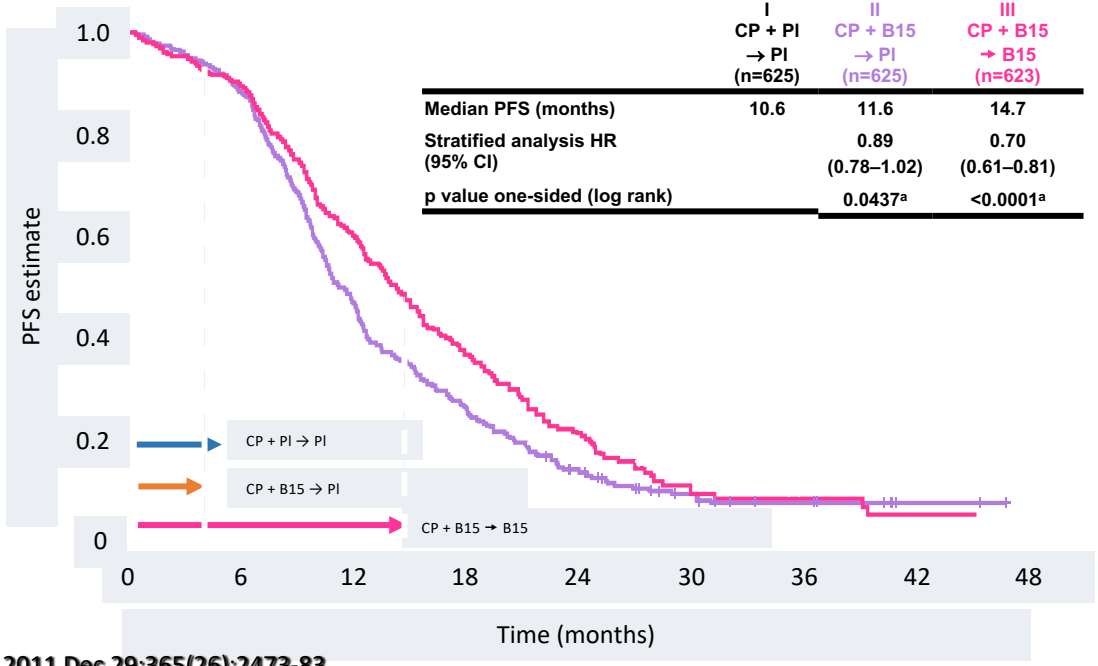
Targeted therapy for ovarian, Bevacizumab



	I CP + PI → PI (n=625)	II CP + B15 → PI (n=625)	III CP + B15 → B15 (n=623)
Median PFS (months)	10.6	11.6	14.7
Stratified analysis HR (95% CI)		0.89 (0.78–1.02)	0.70 (0.61–0.81)
p value one-sided (log rank)		0.0437[a]	<0.0001[a]

Burger, NEngl J Med. 2011 Dec 29;365(26):2473-83.

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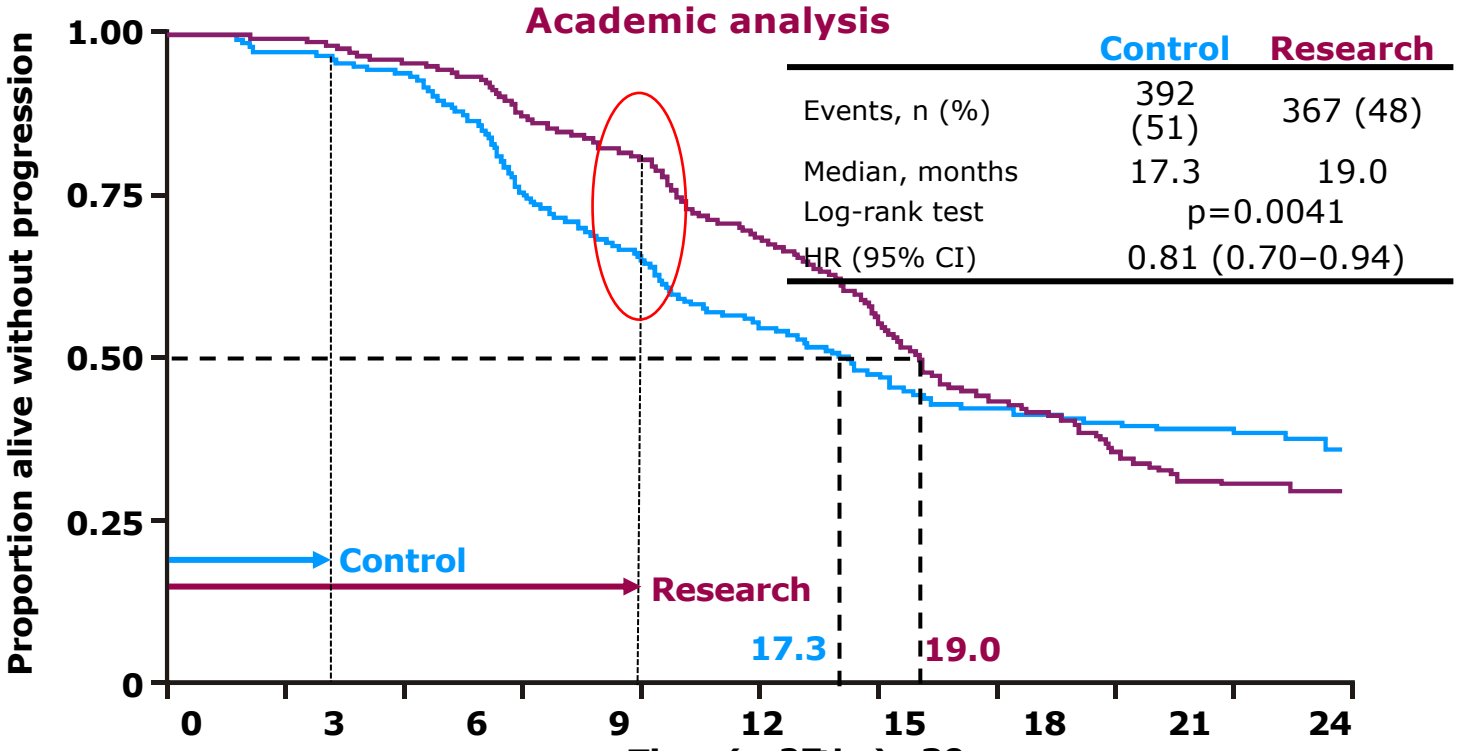
ICON7
Progression-free survival



Perren T, et al. NEJM 2011;365:2484

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Rationale for Targeting Homologous Recombination Repair in the Treatment of Ovarian Cancer

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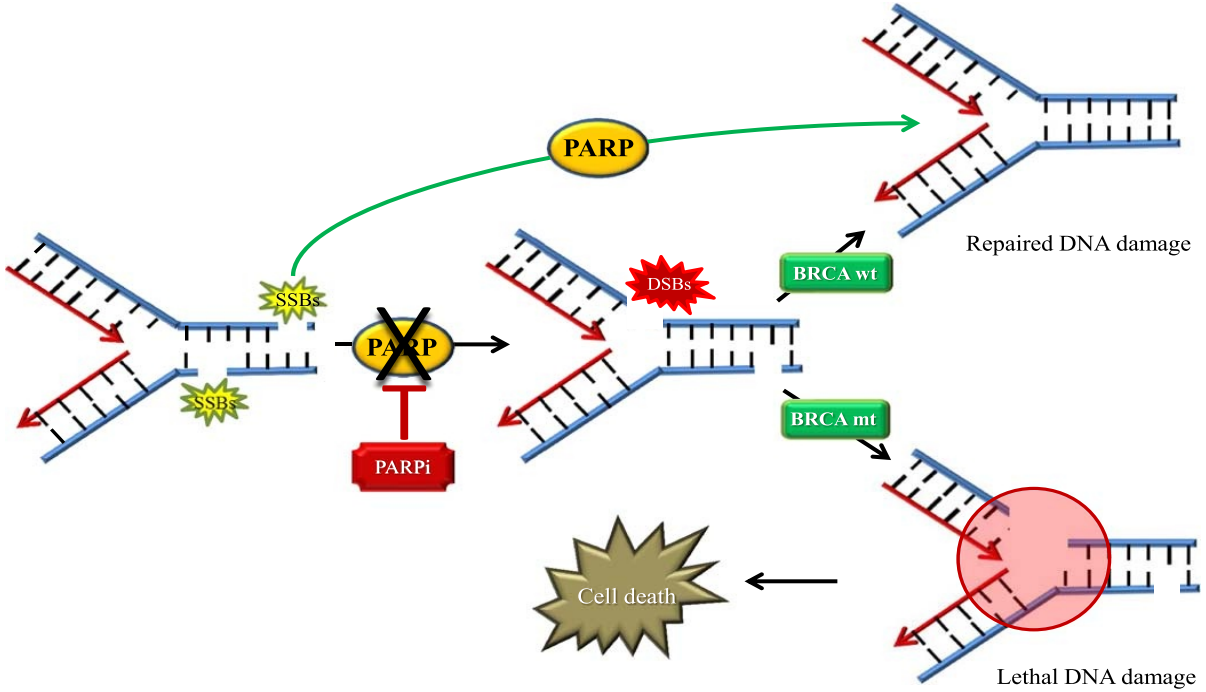
Homologous Recombination Repair



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PARP inhibitors maintenance after 1st line treatment of ovarian cancer

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SOLO1: Phase III trial of maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients with advanced ovarian cancer and a *BRCA1/2* mutation

- Kathleen Moore,[1] Nicoletta Colombo,[2] Giovanni Scambia,[3] Byoung-Gie Kim,[4] Ana Oaknin,[5] Michael Friedlander,[6]
  Alla Lisyanskaya,[7] Anne Floquet,[8] Alexandra Leary,[9] Gabe S. Sonke,[10] Charlie Gourley,[11] Susana Banerjee,[12] Amit Oza,[13] Antonio González-Martín,[14] Carol Aghajanian,[15] William Bradley,[16] Elizabeth S. Lowe,[17] Ralph Bloomfield,[18] Paul DiSilvestro[19]

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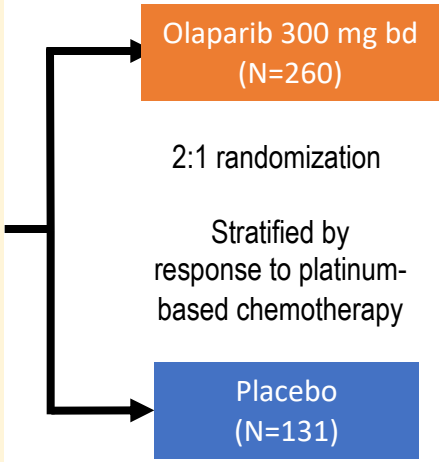
Study design

- 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



- 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)

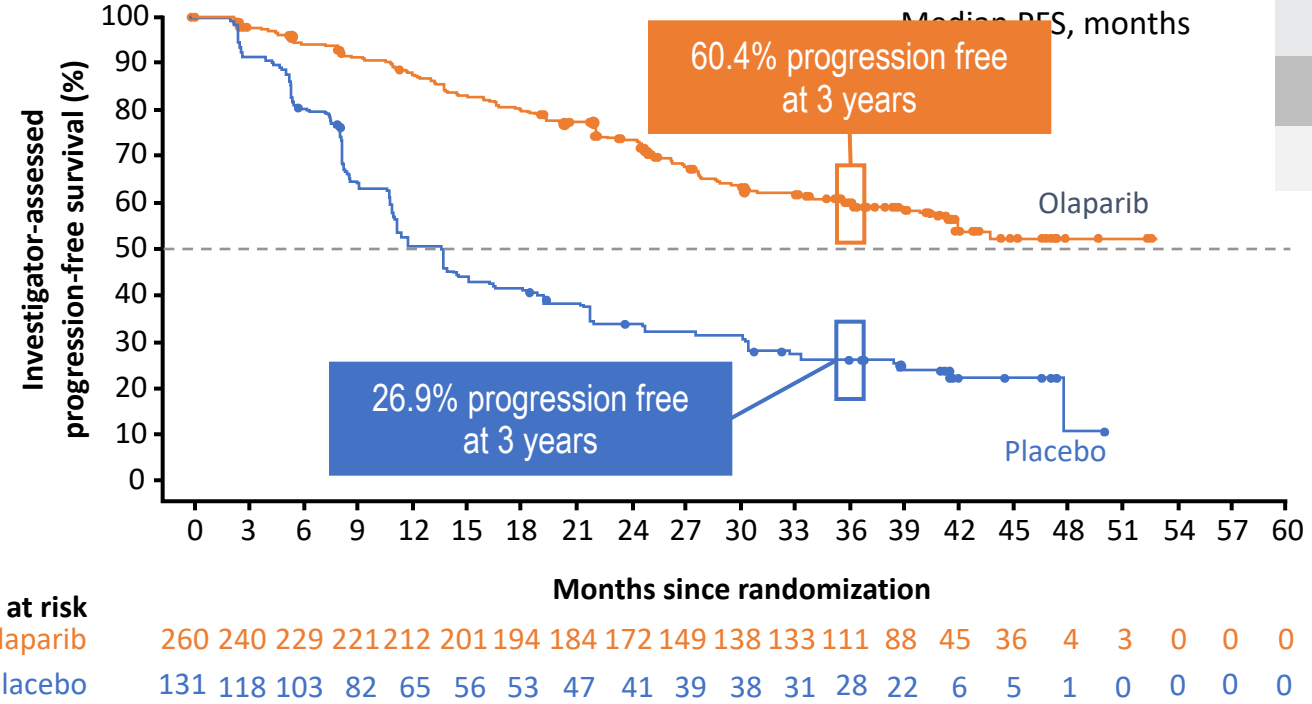
Secondary endpoints

- 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

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		



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

ESMO Congress, Munich 2018

CI, confidence interval; M

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ENGOT
European Network of Gynaecological Oncological Trial groups

GEICO
Grupo Español de Investigación en Cáncer de Ovario

GOG Gynecologic Oncology Group

Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer (PRIMA/ENGOT-OV26/GOG-3012)

A. González-Martín,[1] B. Pothuri,[2] I. Vergote,[3] R.D. Christensen,[4] W. Graybill,[5] M.R. Mirza,[6] C. McCormick,[7] D. Lorusso,[8] P. Hoskins,[9] G. Freyer,[10] F. Backes,[11] K. Baumann,[12] A. Redondo,[13] R. Moore,[14] C. Vulsteke,[15] R.E. O'Cearbhaill,[16] B. Lund,[17] Y. Li,[18] D. Gupta,[18] B.J. Monk[19]

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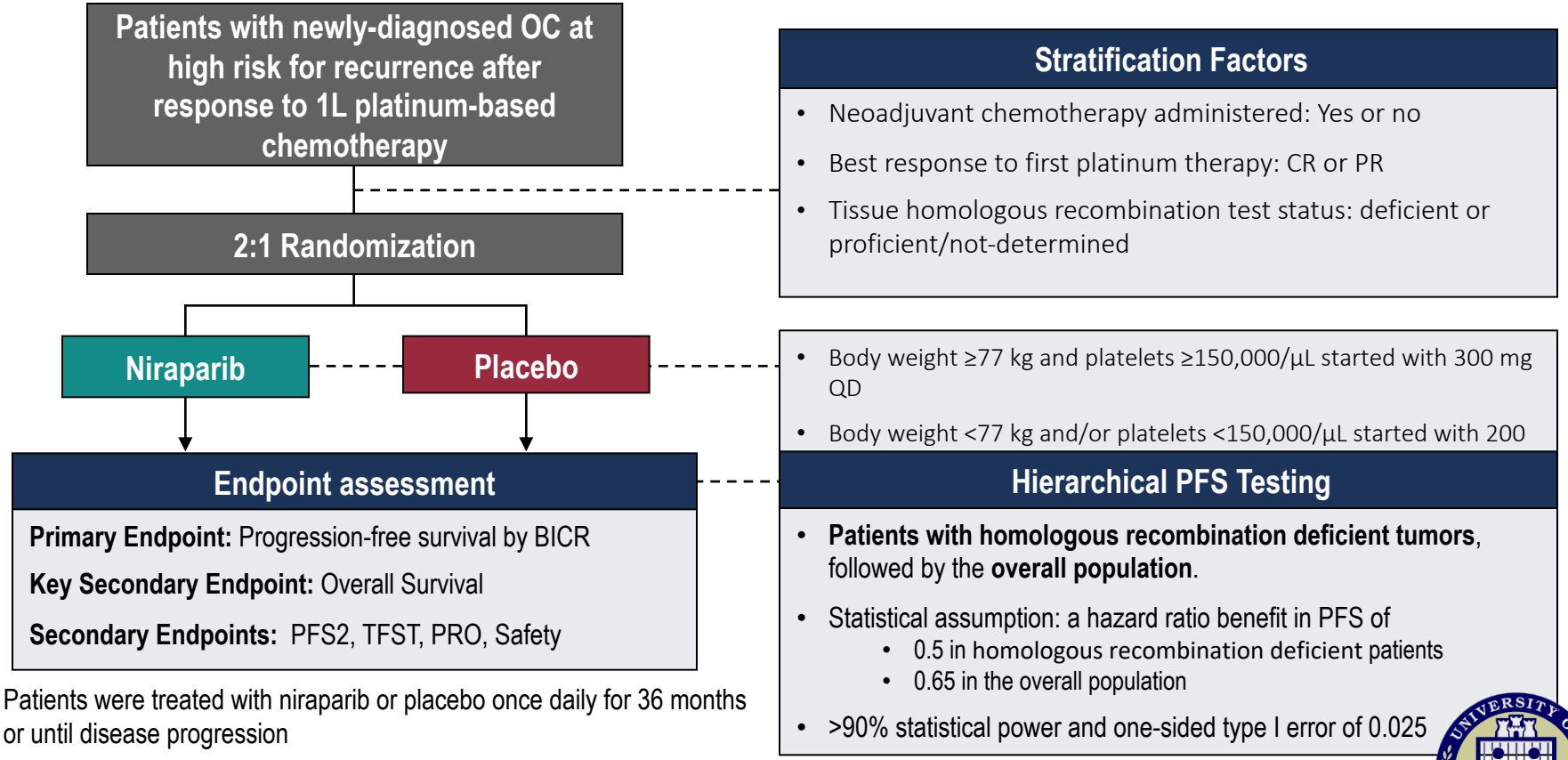
BARCELONA 2019 ESMO congress

esmo.org

PRIMA Trial Design



Patients were treated with niraparib or placebo once daily for 36 months or until disease progression

1L, first-line; BICR, blinded independent central review; CR, complete response; OC
PFS2, progression-free survival 2; PR partial response; PRO, patient-reported outcomes; TFST, time to first subs

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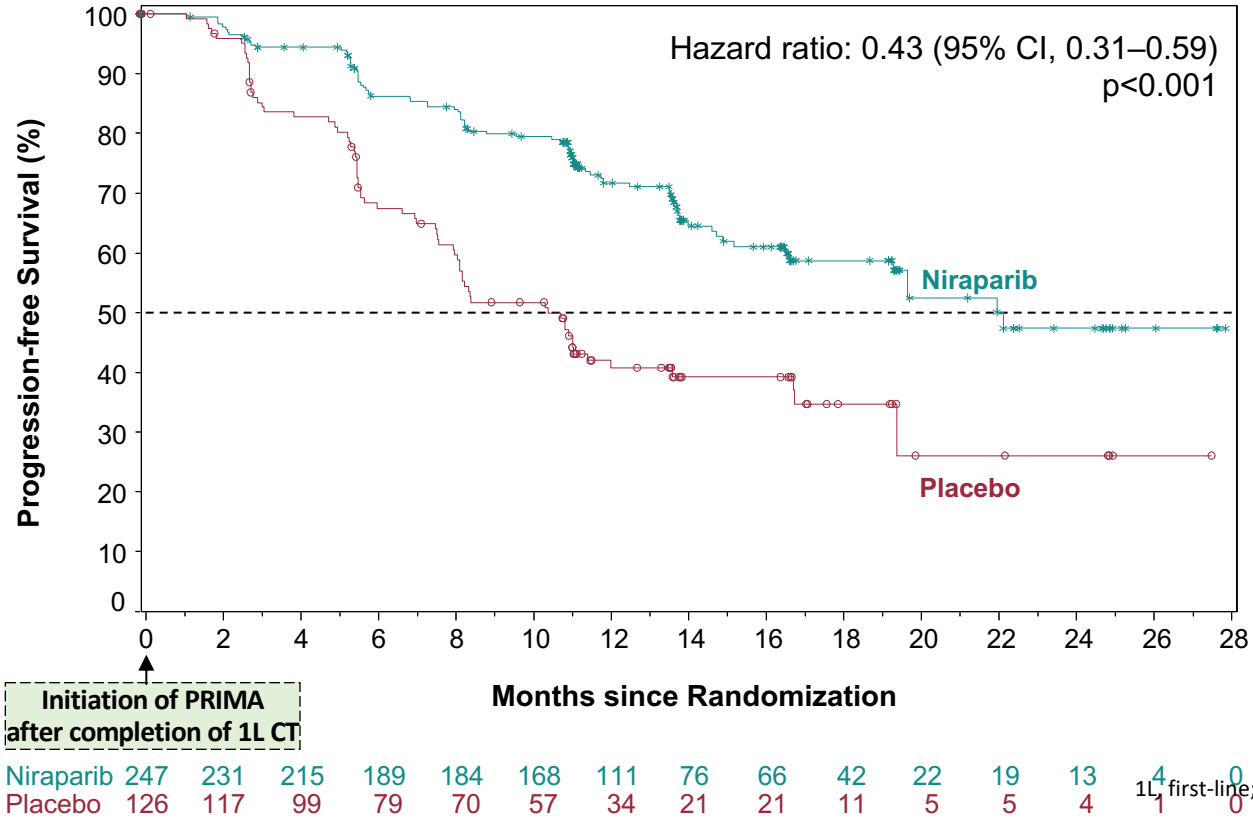
PRIMA Primary Endpoint, PFS Benefit in the HR-deficient Population



57% reduction in hazard of relapse or death with niraparib		
	Niraparib (n=247)	Placebo (n=126)
Median PFS		
months (95% CI)	21.9 (19.3–NE)	10.4 (8.1–12.1)
Patients without PD or death (%)		
6 months	86%	68%
12 months	72%	42%
18 months	59%	35%

1L, first-line; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

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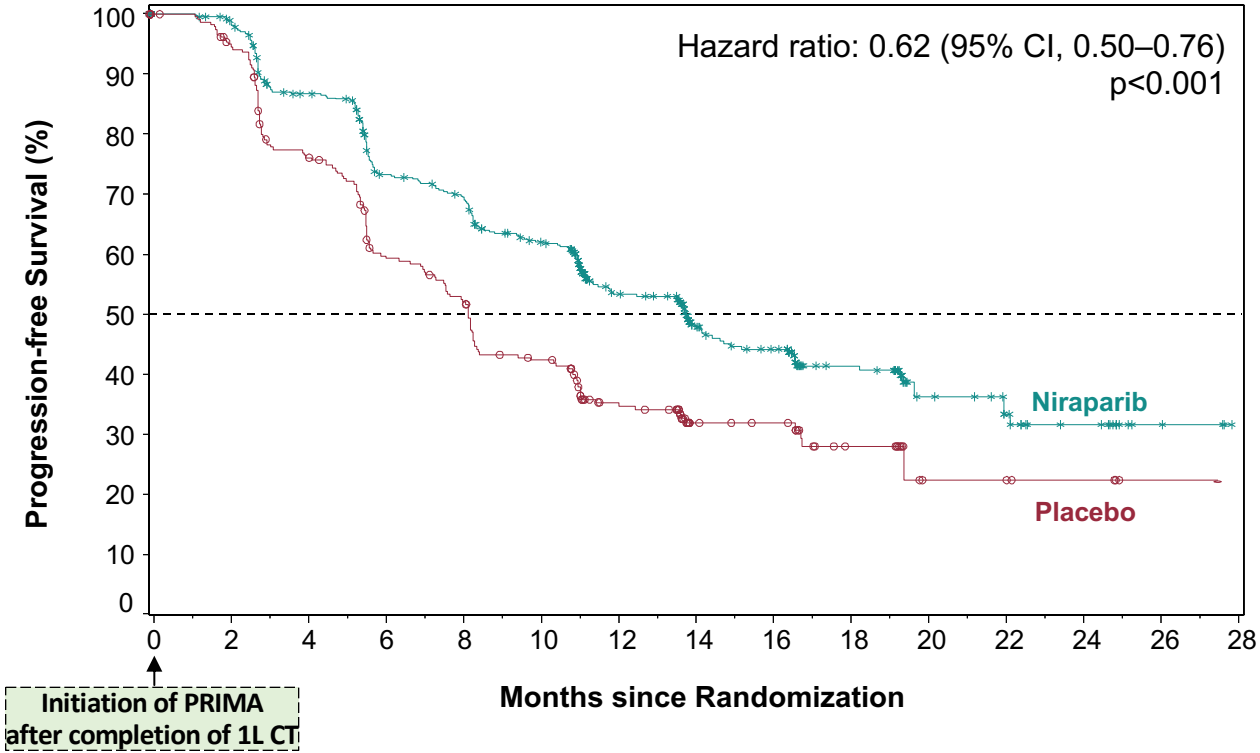
PRIMA Primary Endpoint, PFS Benefit in the Overall Population



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

38% reduction in hazard of relapse or death with niraparib

	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progress

Discordance in PFS event between investigator assessme

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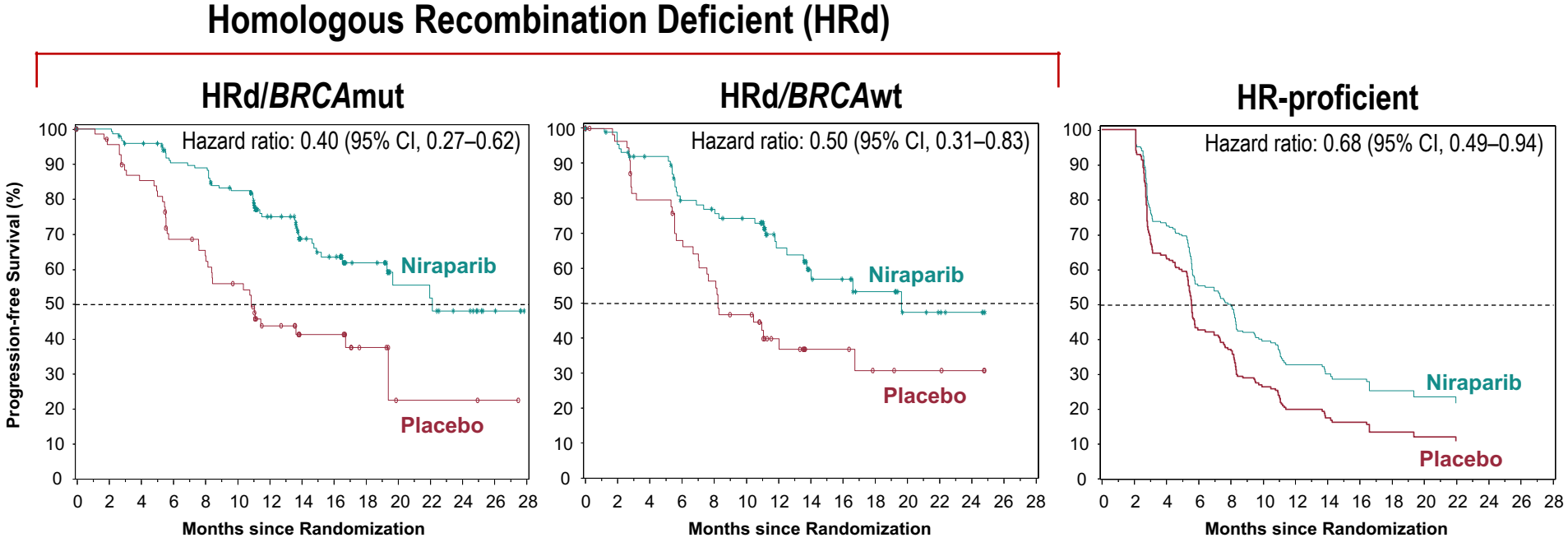
PRIMA PFS Benefit in Biomarker Subgroups



- Niraparib provided similar clinical benefit in the HRd subgroups (*BRCA*mut and *BRCA*wt)
- Niraparib provide clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

CI, confidence interval; HR, homologous recombination; mut, mutation; PFS, progression-free survi

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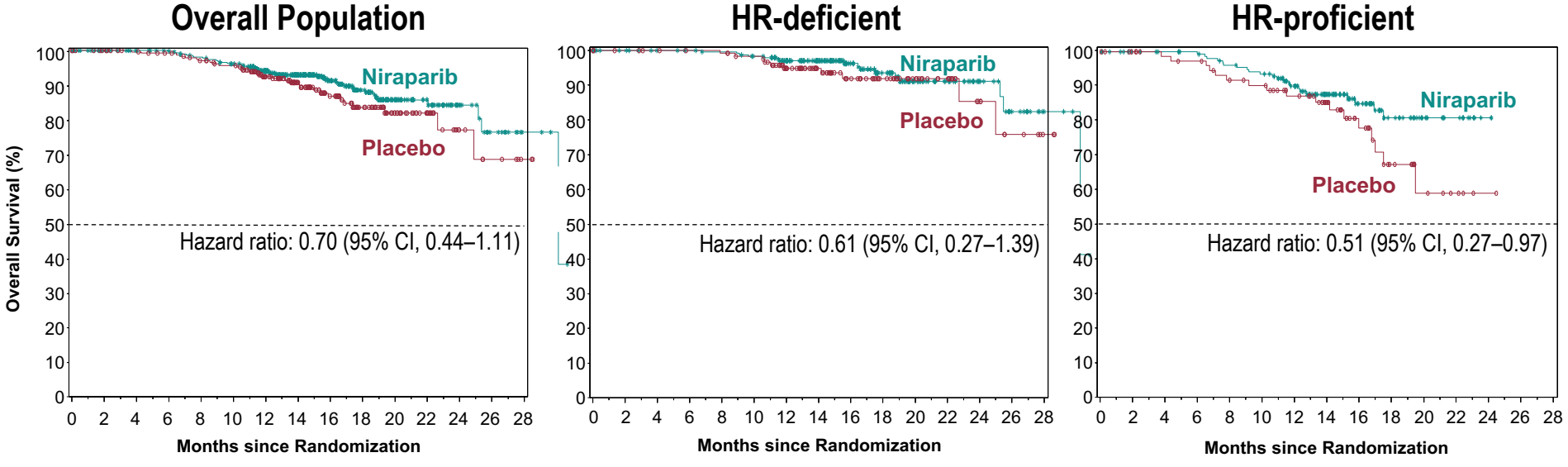
PRIMA Key Secondary Endpoint, Overall Survival (11% data maturity)



- **Pre-planned** interim analysis of overall survival numerically favors niraparib over placebo
  - Overall population 84% vs 77% alive at 2 years
  - HR-deficient 91% vs 85% alive at 2 years
  - HR-proficient 81% vs 59% alive at 2 years

CI, confidence interval; HR, homologous recombination.

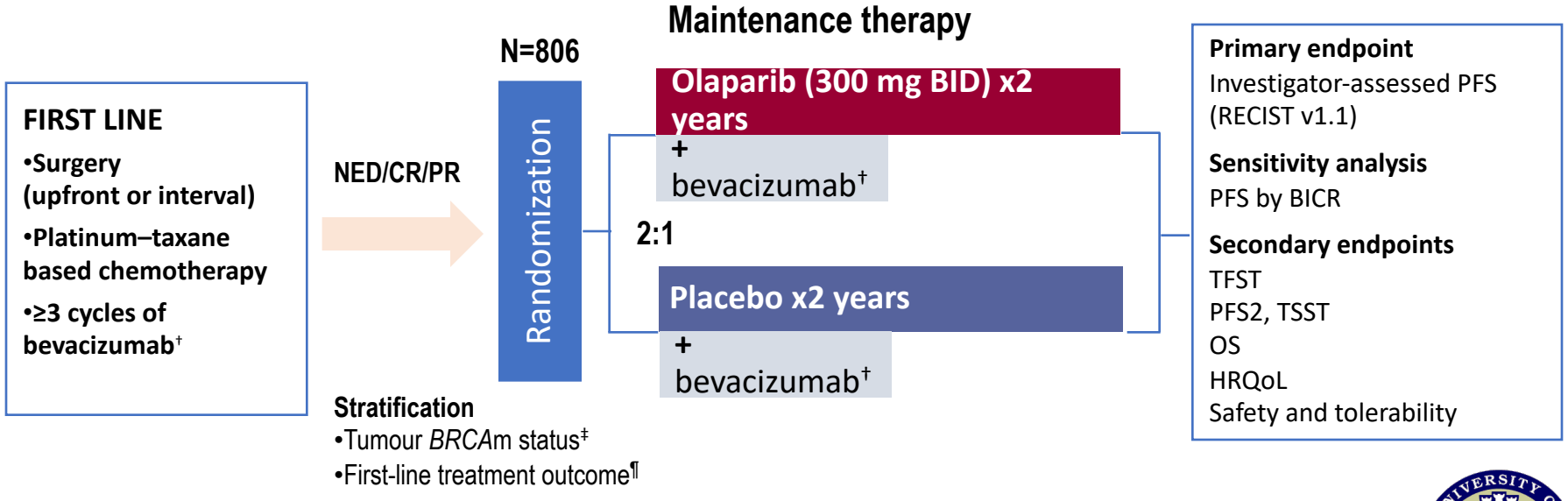
Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care

Isabelle Ray-Coquard, Patricia Pautier, Sandro Pignata, David Pérol, Antonio González-Martin, Paul Sevelda, Keiichi Fujiwara, Ignace Vergote, Nicoletta Colombo, Johanna Mäenpää, Frédéric Selle, Jalid Sehouli, Domenica Lorusso, Eva Maria Guerra Alia, Claudia Lefeuvre-Plesse, Ulrich Canzler, Alain Lortholary, Frederik Marmé, Eric Pujade-Lauraine, Philipp Harter

ClinicalTrials.gov identifier: NCT02477644
This study was sponsored by ARCAGY Research

Study design

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



*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to [illegible] and NED/CR/PR
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evalu[illegible] in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

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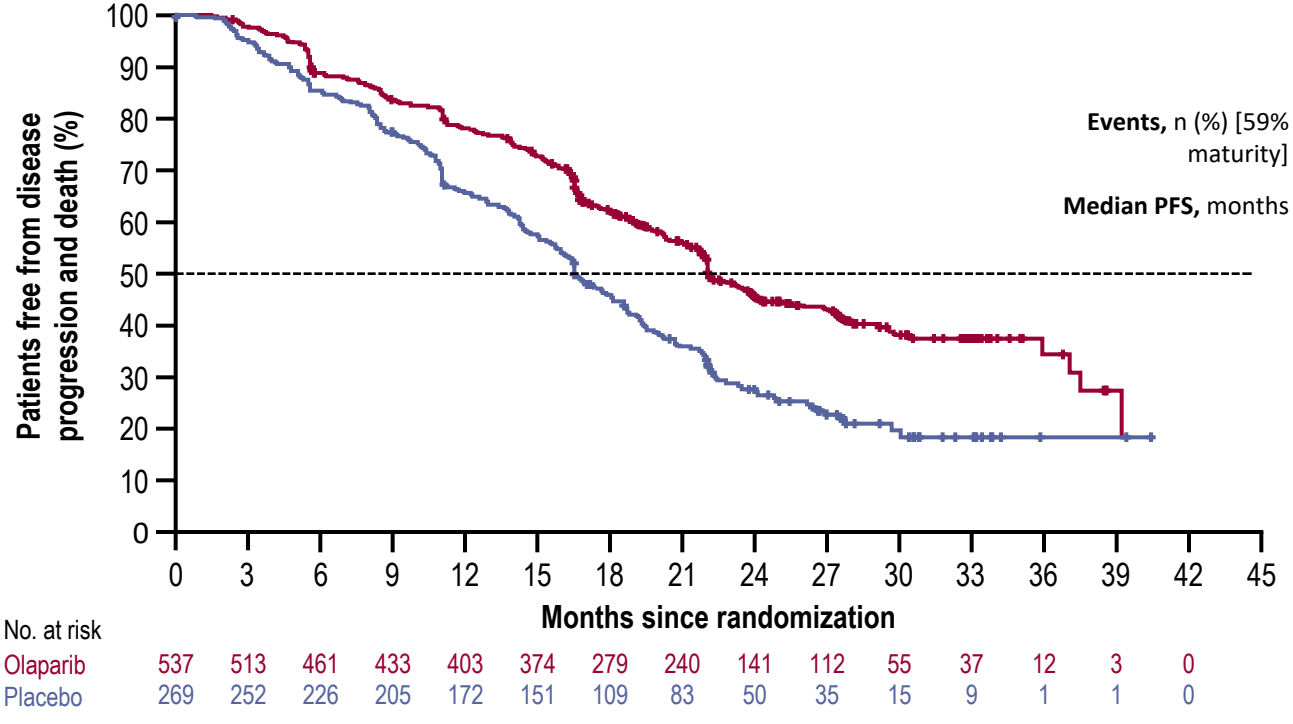
PFS by investigator assessment: ITT population



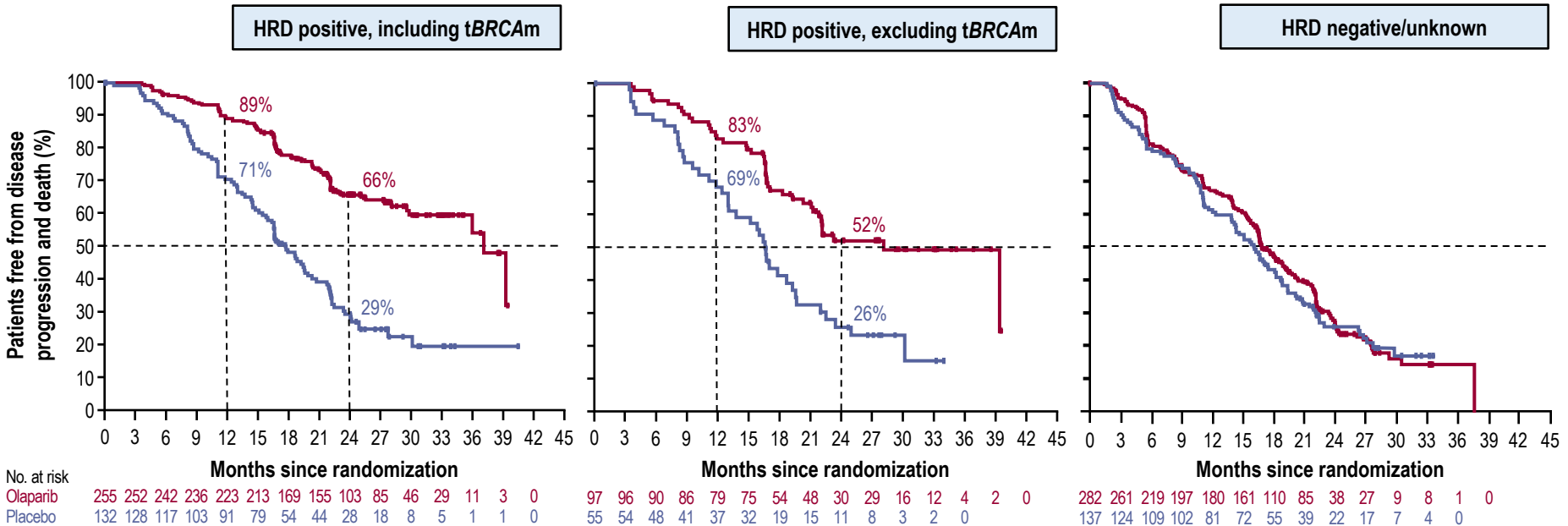
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	**22.1**	**16.6**

HR 0.59 (95% CI 0.49–0.72; *P*<0.0001)

Median time from first cycle of chemotherapy to randomization = 7 months

ITT, intent-to-treat population

PFS by HRD status



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

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

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

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42. *This median is unstable due to a lack of events – less mature

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2022 ASCO® ANNUAL MEETING

GOG FOUNDATION®

ENGOT European Network of Gynaecological Oncological Trial groups

NRG Oncology-Japan

ATHENA–MONO (GOG-3020/ENGOT-ov45): A Randomized, Double-blind, Phase 3 Trial Evaluating Rucaparib Monotherapy Vs Placebo As Maintenance Treatment Following Response To First-line Platinum-based Chemotherapy In Ovarian Cancer

Bradley J. Monk,[1] Christine Parkinson,[2] Myong Cheol Lim,[3] David M. O'Malley,[4] Ana Oaknin,[5] Michelle K. Wilson,[6] Robert L. Coleman,[7] Domenica Lorusso,[8] Amit Oza,[9] Sharad Ghamande,[10] Athina Christopoulou,[11] Emily Prendergast,[12] Fuat Demirkiran,[13] Ramey D. Littell,[14] Anita Chudecka-Głaz,[15] Mark A. Morgan,[16] Sandra Goble,[17] Stephanie Hume,[17] Keiichi Fujiwara,[18] Rebecca S. Kristeleit[19]

[1]GOG Foundation, HonorHealth Research Institute, University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA; [2]Addenbrooke's Hospital, Cambridge, UK; [3]National Cancer Center Korea, Goyang-si, Gyeonggi-do, Republic of Korea; [4]The Ohio State University, James Cancer Center, Columbus, OH, USA; [5]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [6]Auckland City Hospital, Auckland, New Zealand; [7]US Oncology Research, The Woodlands, TX, USA; [8]MITO and Fondazione Universitario A. Policlinico Gemelli IRCCS and Catholic University of Sacred Heart, Rome, Italy; [9]Princess Margaret Hospital Cancer Centre, Toronto, Ontario, Canada; [10]Augusta University, Augusta, GA, USA; [11]St. Andrews General Hospital, Patras, Greece; [12]Minnesota Oncology and Metro-Minnesota Community Oncology Research Consortium, Minneapolis, MN, USA; [13]Istanbul University, Cerrahpaşa, Istanbul, Turkey; [14]Kaiser Permanente Northern California Gynecologic Cancer Program, San Francisco, CA, USA; [15]Pomeranian Medical University, Szczecin, Poland; [16]University of Pennsylvania Health System, Philadelphia, PA, USA; [17]Clovis Oncology, Inc., Boulder, CO, USA; [18]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [19]Guy's and St Thomas' NHS Foundation Trust, London, UK

ATHENA–MONO Study Schema

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
  - Received cytoreductive surgery (primary or interval; R0/complete resection permitted)
- 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 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors

- Tumor HRD test status†
- Disease status post-chemotherapy
- Timing of surgery

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

Study Analyses

ATHENA–MONO

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

*After initiation of oral/IV combination study treatment (IV drug was initiated cycle 2 day 1; 28-day cycles). †Centrally assessed, determined by FoundationOne CDx ($BRCA^{mut}$, $BRCA^{wt}/LOH^{high}$ [LOH ≥16%], $BRCA^{wt}/LOH^{low}$ [LOH <16%], $BRCA^{wt}/LOH^{indeterminate}$). BID, twice daily; BRCA, *BRCA1* or *BRCA2*; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; mut, mutant; PO, by mouth; PR, partial response; wt, wild type.

Bradley J. Monk, MD, FACS, FACOG (LBA5500)

University of Pittsburgh

ATHENA–MONO Study Schema

Athena
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF NIVOLUMAB AND RUCAPARIB

Key Patient Eligibility

- Newly diagnosed, stage III–IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
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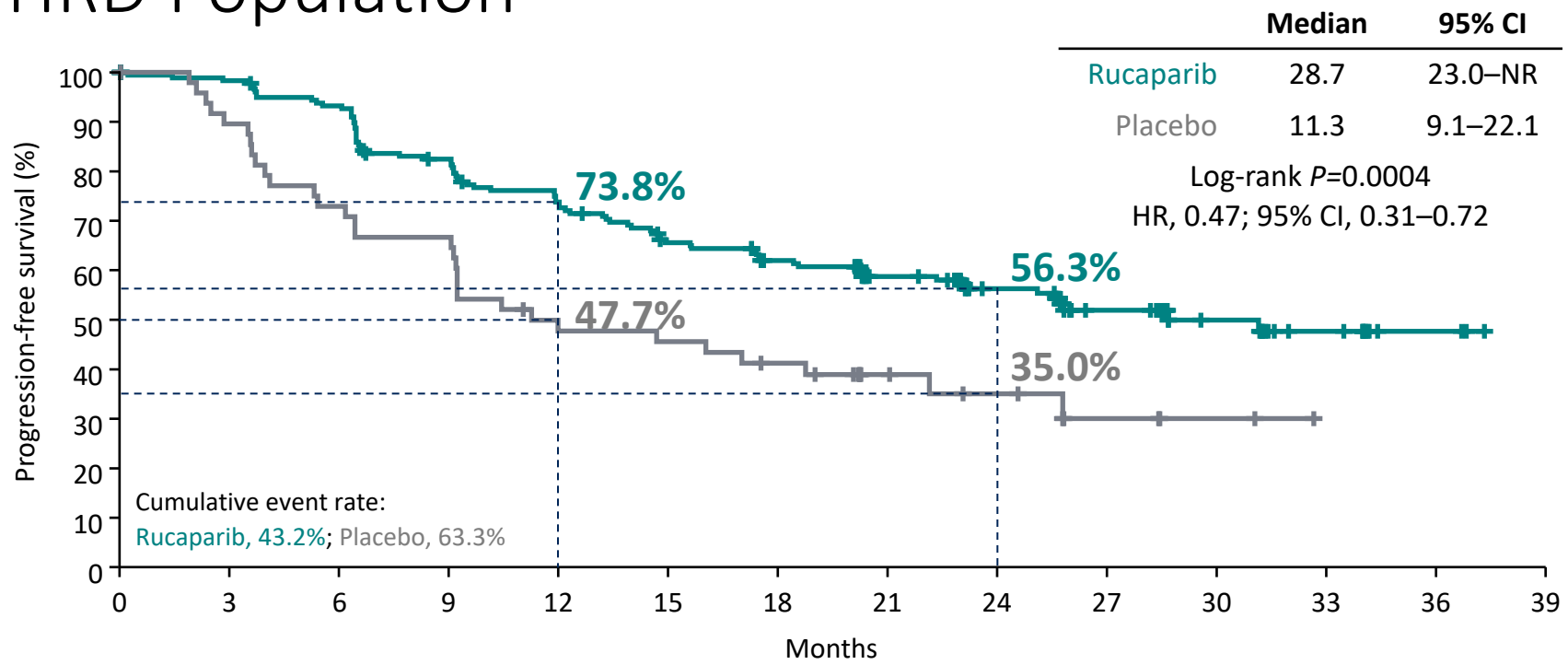
Primary Endpoint – Investigator-Assessed PFS: HRD Population



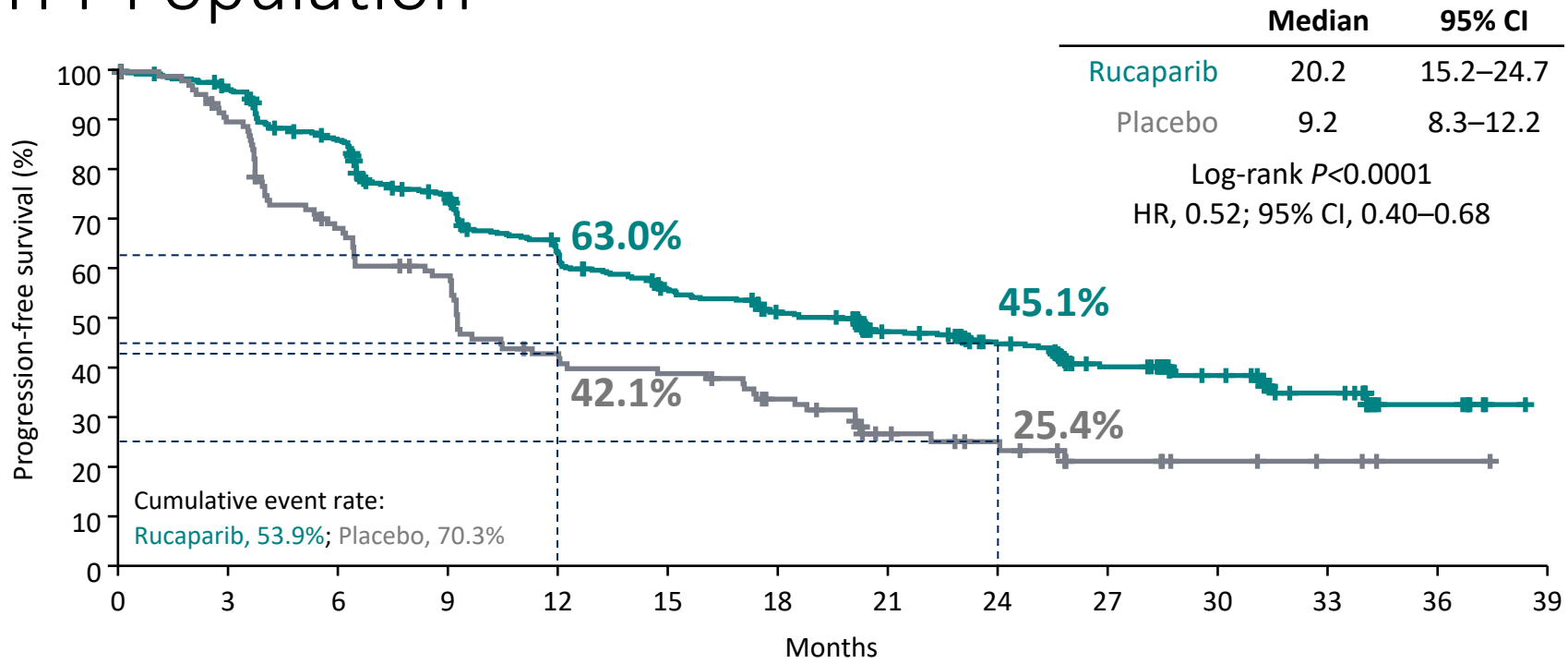
Patients at risk (events)

Rucaparib	185(0)	175(3)	165(12)	143(31)	127(46)	110(60)	100(66)	82(71)	59(74)	36(78)	22(79)	12(80)	3(80)	0(80)
Placebo	49(0)	43(5)	35(13)	32(16)	22(25)	21(26)	18(28)	11(29)	8(30)	4(31)	2(31)	0(31)		

Data cutoff date: March 23, 2022.

HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.

Primary Endpoint – Investigator-Assessed PFS: ITT Population



Patients at risk (events)

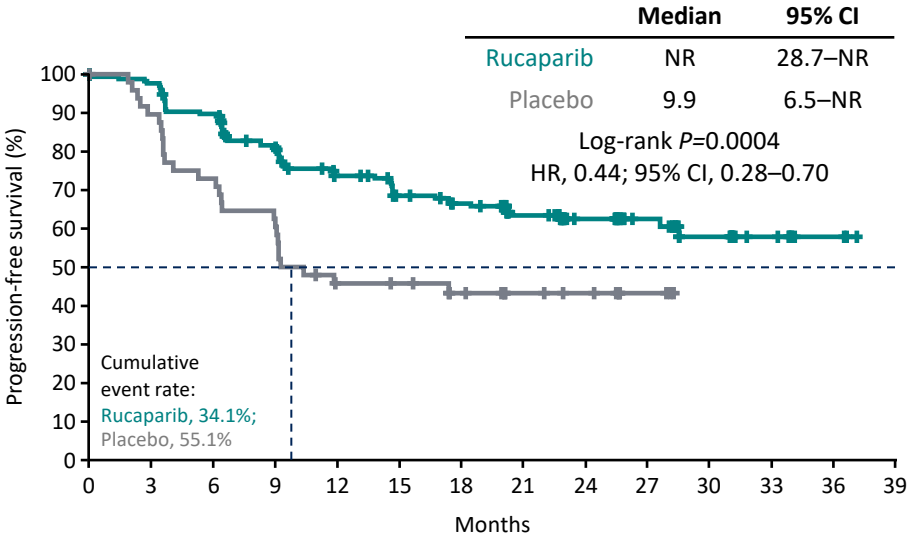
Rucaparib	427 (0)	398 (15)	351 (57)	298 (101)	245 (149)	213 (176)	190 (193)	151 (207)	114 (214)	67 (224)	42 (226)	23 (229)	7 (230)	0 (230)
Placebo	111 (0)	97 (11)	72 (34)	60 (44)	42 (61)	39 (64)	31 (69)	18 (75)	14 (76)	8 (78)	5 (78)	3 (78)	1 (78)	0 (78)

Data cutoff date: March 23, 2022.

HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Secondary Endpoint – BICR-Assessed PFS

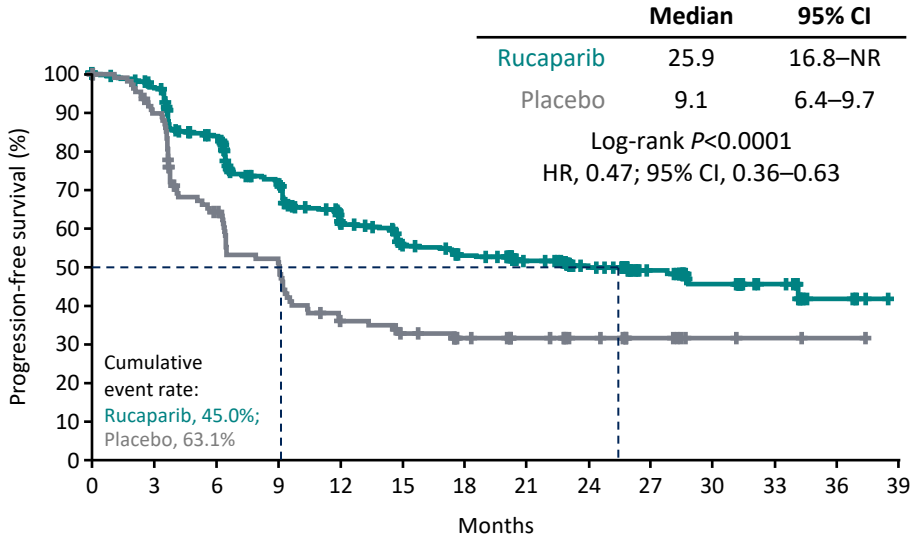
HRD



Patients at risk (events)

Rucaparib	185 (0)	158 (18)	117 (45)	97 (56)	51 (61)	20 (63)	3 (63)
Placebo	49 (0)	35 (13)	20 (26)	15 (27)	8 (27)	0 (27)	

ITT



Patients at risk (events)

Rucaparib	427 (0)	334 (66)	220 (149)	174 (179)	100 (187)	34 (191)	5 (192)
Placebo	111 (0)	65 (38)	34 (66)	22 (70)	12 (70)	3 (70)	1 (70)

Data cutoff date: March 23, 2022.

BICR, blinded independent central radiology review; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

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FDA Approval with indications

1. Olaparib
   - ❖ 1st line switch maintenance, germline *BRCA* (June 2019)
2. Olaparib + Bevacizumab
   - ❖ 1st line switch maintenance, HRD(May 2020)
3. Niraparib
   - ❖ 1st line switch maintenance, All comers (April 2020)

Advanced Ovarian Cancer post 1st line Chemotherapy ,Additional New Options

All comers: (maintenance)
BRCA ½ mutation/somatic mutation:
- **Olaparib**
- **Niraparib**
- **Olaparib + bevacizumab**

HRD: (maintenance)
- **Niraparib**
- **Olaparib + bevacizumab**

HRP and BRCA wt:
- **Observation**

Important considerations in ovarian cancer frontline maintenance therapy (HRD)

STUDY	NUMBER OF DRUGS	DURATION OF THERAPY (I)	DELTA PFS GAIN (Y)	Y/I RATIO (%)
GOG 2018	1	15 months	3.1 months	21%
SOLO1	1	24 months	N/A	
PRIMA	1	36 months	11.5 months	32%
PAOLA 1	2	24 months	11.5 months	48%

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Important considerations in ovarian cancer frontline maintenance therapy (HRP)

STUDY	NUMBER OF DRUGS	DURATION OF THERAPY (I)	DELTA PFS GAIN (Y)	Y/I RATIO (%)
GOG 2018	1	15 months	3.1 months	21%
SOLO1	1	24 months	N/A	
PRIMA	1	36 months	2.7 months	8%
PAOLA 1	2	24 months	0.9 months	4%

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Conclusions

- Advances in the understanding of ovarian cancer biology have led to significantly expanded options for women diagnosed with advanced ovarian cancer.
- Most of the studies leading to these advances have no matured overall survival data yet.
- As therapeutic options increase, burden of each therapeutic option must be carefully balanced with its potential benefits.

Thank you