NOVOSTI V SISTEMSKEM ZDRAVLJENJU RAKA JAJČNIKOV

Erik Škof

Onkološki Inštitut, Ljubljana

RAK JAJČNIKOV – BOLEZEN SE POGOSTO PONOVI

10-18 mesecev

Mediani čas preživetja brez ponovitve bolezni[2,3,4]

~70%

bolnic ima ponovitev bolezni 3 leta od pričetka zdravljenja[1]

~40%

5-letno preživetje[5]

40 mes.

Celokupno preživetje[4]

Potrebno je izboljšati učinkovitost primarnega zdravljenja z namenom izboljšanja izhoda zdravljenja bolnic z rakom jajčnikov[1-5]

NOVE EVROPSKE SMERNICE – LETA 2019

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 672–705, 2019
doi:10.1093/annonc/mdz062
Published online 2 May 2019

SPECIAL ARTICLE

ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†

N. Colombo[1*], C. Sessa[2], A. du Bois[3], J. Ledermann[4], W. G. McCluggage[5], I. McNeish[6], P. Morice[7], S. Pignata[8], I. Ray-Coquard[9], I. Vergote[10,11], T. Baert[3], I. Belaroussi[7], A. Dashora[12], S. Olbrecht[10,11], F. Planchamp[13] & D. Querleu[14*], on behalf of the ESMO–ESGO Ovarian Cancer Consensus Conference Working Group‡

Original Article

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease

N Colombo,[1] C Sessa,[2] A du Bois,[3] J Ledermann,[4] WG McCluggage,[5] I McNeish,[6] P Morice,[7] S Pignata,[8] I Ray-Coquard,[9] I Vergote,[10,11] T Baert,[3] I Belaroussi,[7] A Dashora,[12] S Olbrecht,[10,11] F Planchamp,[13] & D Querleu,[14] on behalf of the ESMO–ESGO Ovarian Cancer Consensus Conference Working Group

PRIMARNO SISTEMSKO ZDRAVLJENJE

- Novosti:
  - **Zaviralci PARP* v 1. liniji** po OP in KT – stadij III/IV
    - Raziskava SOLO-1: olaparib[1]
    - Raziskava PRIMA: niraparib[2]
    - Raziskava PAOLA-1: olaparib+bevacizumab[3]

- **Določanje mutacije BRCA 1/2 – za namen zdravljenja**
  - Iz krvi (zarodna)
  - Iz tumorja (somatska/zarodna)

- **Določanje okvare HR** -** v razvoju….

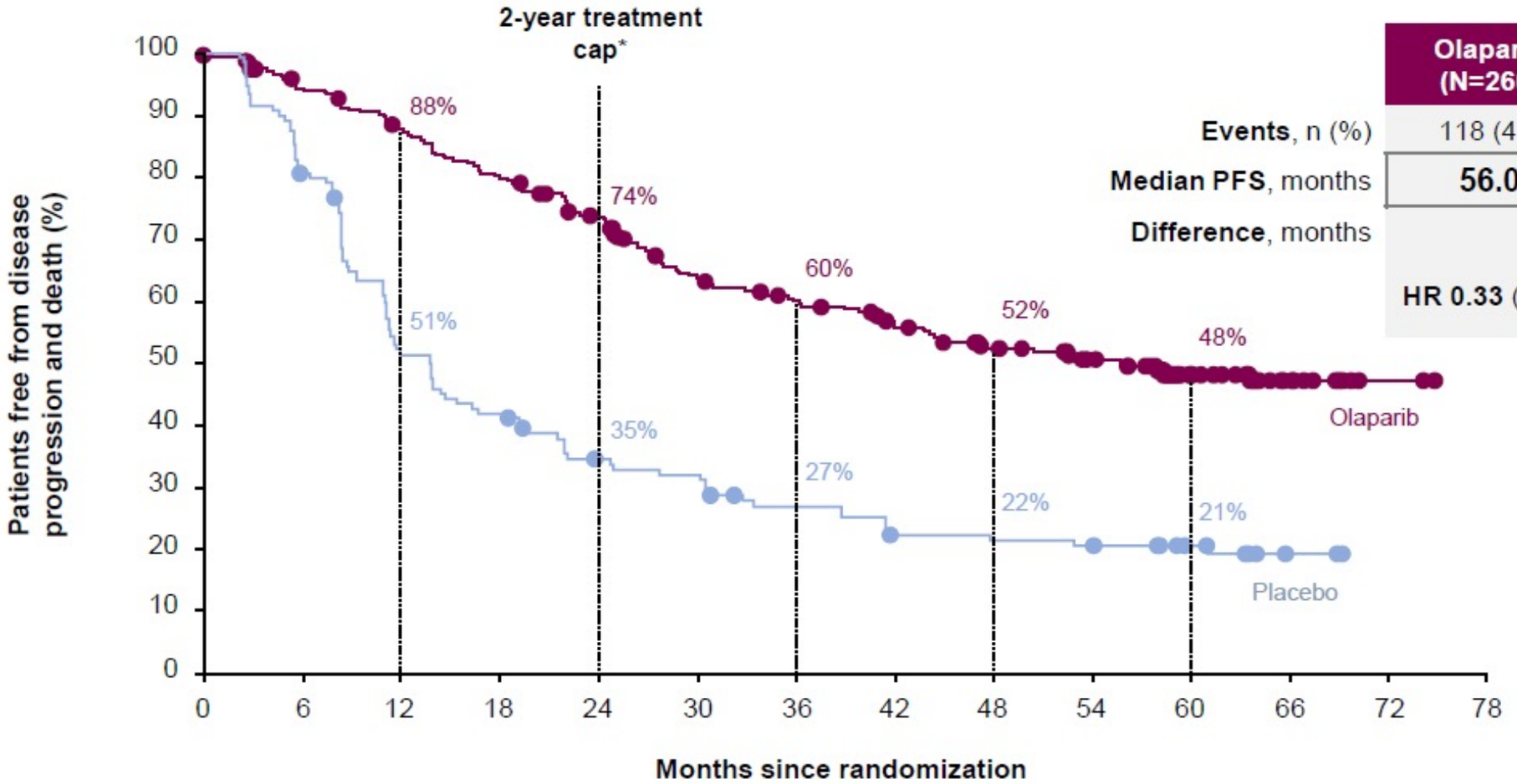
PARP – poli ADP riboza polimeraza*

*HR ** - homologna rekombinacija*

1-Moore K, et al. N Engl J Med 2018; 2- González-Martín A, et al. N Engl J Med 2019; 3-Isabelle Ray-Coquard, et al. N Engl J Med 2019

RAZISKAVA SOLO-1:
OLAPARIB V 1. LINIJI PRI BRCA 1/2 MUTIRANIH

PFS benefit of maintenance olaparib was sustained beyond the end of treatment



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
	HR 0.33 (95% CI 0.25–0.43)	

No. at risk														
Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	

*13 patients, all in the olaparib arm, continued study treatment beyond 2 years;
†n=130 (safety analysis set).
Investigator-assessed by modified RECIST v1.1. DCO: March 5, 2020.

RAZISKAVA SOLO-1:
OLAPARIB V 1. LINIJI PRI BRCA 1/2 MUTIRANIH

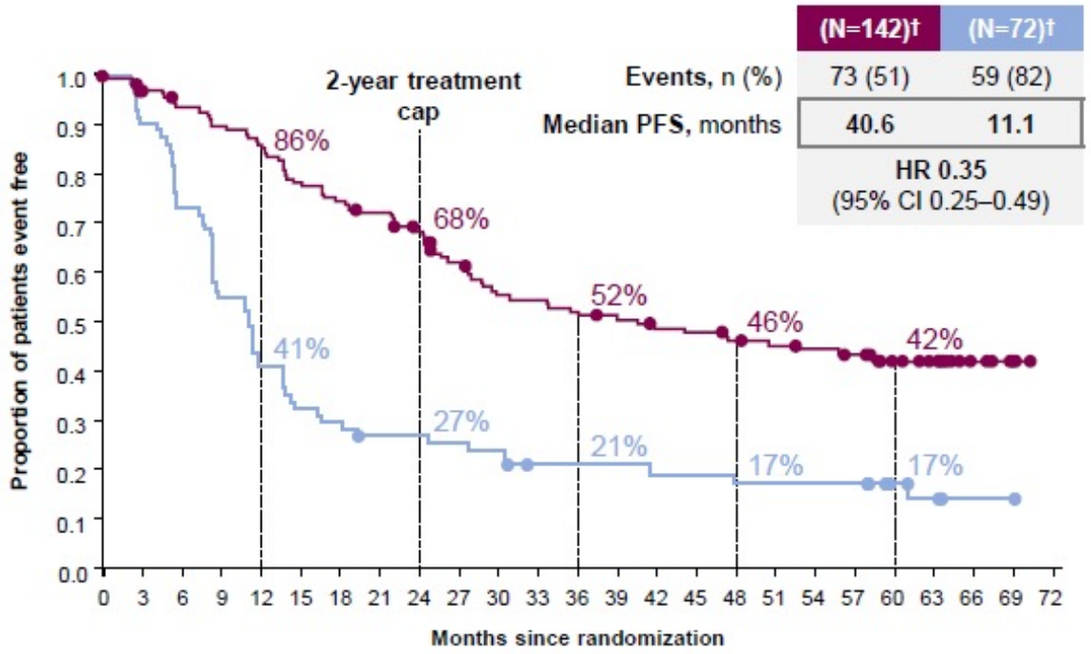
PFS benefit of maintenance olaparib was consistent in higher- and lower-risk subgroups

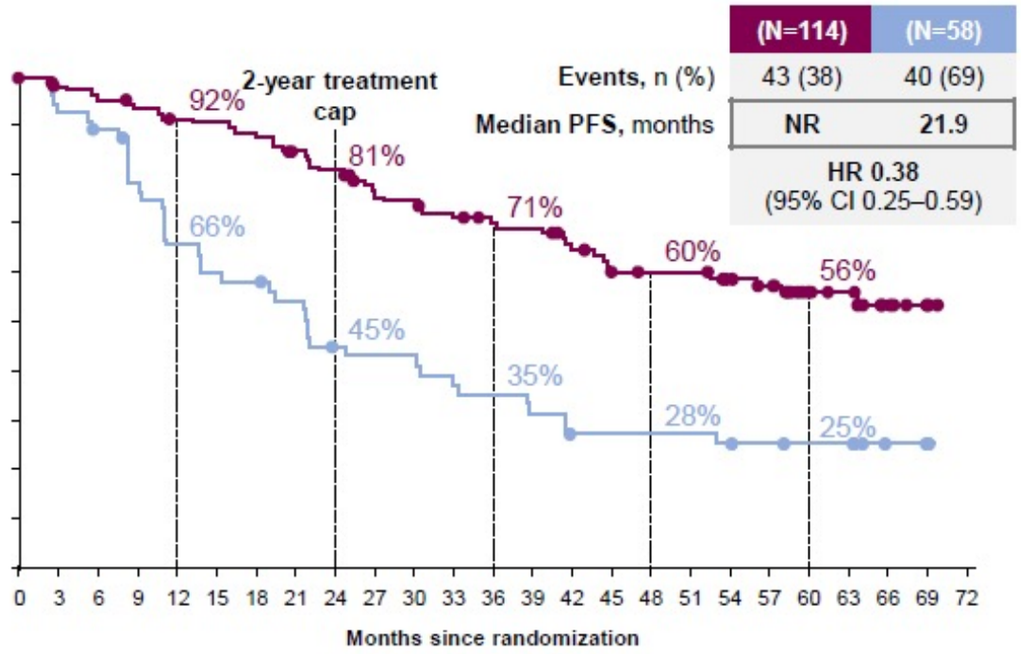
Higher-risk

Baseline characteristic, n (%)	Olaparib (N=146)	Placebo (N=73)
Interval debulking surgery	94 (64)	43 (59)
CR to prior chemotherapy*	107 (73)	54 (74)
*BRCA1*m	109 (75)	43 (59)
*BRCA2*m	36 (25)	30 (41)
*BRCA1*m and *BRCA2*m	1 (1)	0

Lower-risk

Baseline characteristic, n (%)	Olaparib (N=114)	Placebo (N=58)
Interval debulking surgery	0	0
CR to prior chemotherapy*	106 (93)	53 (91)
*BRCA1*m	82 (72)	48 (83)
*BRCA2*m	30 (26)	10 (17)
*BRCA1*m and *BRCA2*m	2 (2)	0





No. at risk

Olaparib	142	131	124	119	114	104	99	95	88	76	67	66	63	60	56	55	52	50	48	46	31	27	15	6	1
Placebo	72	64	52	39	29	23	21	18	18	17	16	12	12	12	11	11	10	10	10	10	6	4	1	1	0

114	105	102	99	96	95	93	87	83	73	71	67	64	63	57	51	47	47	43	40	27	23	15	7	1
58	53	50	43	36	33	32	29	23	22	22	19	18	16	13	13	13	13	12	11	10	10	2	1	0

*As randomized. †PFS analysis by risk excludes five patients recruited in China.
Investigator-assessed by modified RECIST v1.1. DCO: March 5, 2020.
CR, complete response.

Raziskava PRIMA:
Niraparib v 1. liniji (ne glede na mutacijo BRCA 1/2)

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]

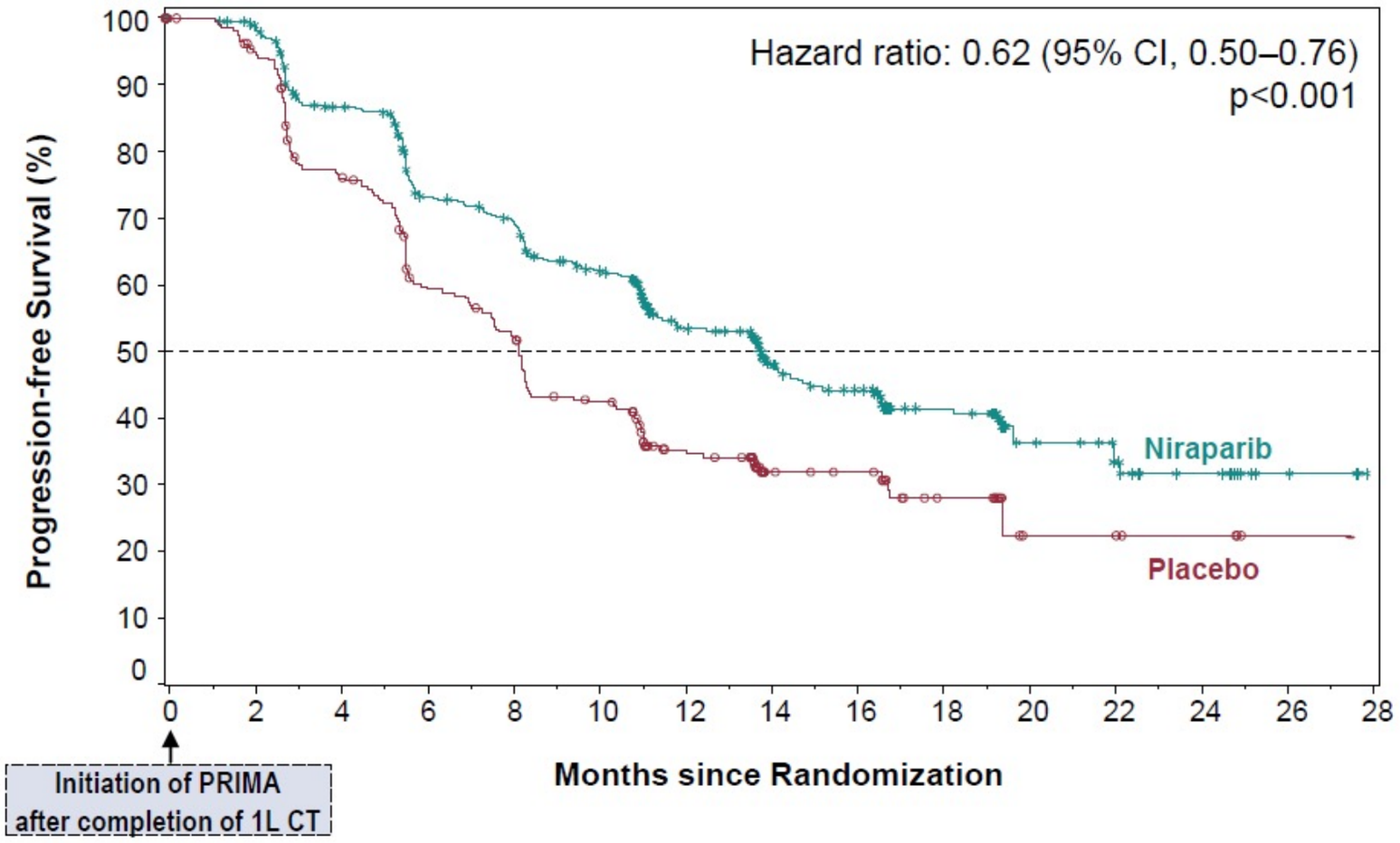
[1]Grupo Español de Investigación en Cáncer de Ovario (GEICO), Medical Oncology Department, Clínica Universidad de Navarra, Madrid, Spain; [2]Gynecologic Oncology Group (GOG), Department of Obstetrics/Gynecology, Perlmutter Cancer Center, NYU Langone Cancer Center, New York, NY, USA; [3]Belgium and Luxembourg Gynaecological Oncology Group (BGOG), Department of Gynaecology and Obstetrics, Division of Gynaecologic Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [4]Nordic Society of Gynaecological Oncology (NSGO), Research Unit of General Practice, Institute of Public Health, University of Southern Denmark, Odense, Denmark; [5] GOG, Gynecologic Oncology, Medical University of South Carolina, Charleston, SC, USA; [6]NSGO, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; [7]GOG, Legacy Medical Group Gynecologic Oncology, Portland, OR, USA; [8]Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO), Fondazione IRCCS National Cancer Institute of Milan, Milan, Italy; [9]US Oncology Research (USOR), Department of Medical Oncology, BC Cancer – Vancouver, Vancouver, BC, Canada; [10]Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), HCL Cancer Institute Department of Medical Oncology Lyon University, Lyon, France; [11]Division of Gynecologic Oncology, Ohio State University, Columbus, OH, USA; [12]Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), Department of Gynecology and Obstetrics, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany; [13]GEICO, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain; [14]USOR, Division of Gynecologic Oncology, Wilmot Cancer Institute, Department of Obstetrics and Gynecology, University of Rochester, Rochester, NY, USA; [15]BGOG, Department of Medical Oncology and Hematology, AZ Maria Middelares, Gent, and Department of Molecular Imaging, Pathology, Radiotherapy & Oncology, Center for Oncological Research, Antwerp University, Antwerp, Belgium; [16]GOG, Gynecologic Medical Oncology, Memorial Sloan Kettering Cancer Center, and Department of Medicine, Weill Cornell Medical College, New York, NY, USA; [17]NSGO, Department of Oncology, Aalborg University, Aalborg, Denmark; [18]TESARO: A GSK Company, Waltham, MA, USA; [19]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Phoenix Creighton University School of Medicine at St. Joseph's Hospital, Phoenix, AZ, US

BARCELONA 2019 ESMO congress

esmo.org

Raziskava PRIMA:
Niraparib v 1. liniji (ne glede na mutacijo BRCA 1/2)

PRIMA Primary Endpoint, PFS Benefit in the Overall Population



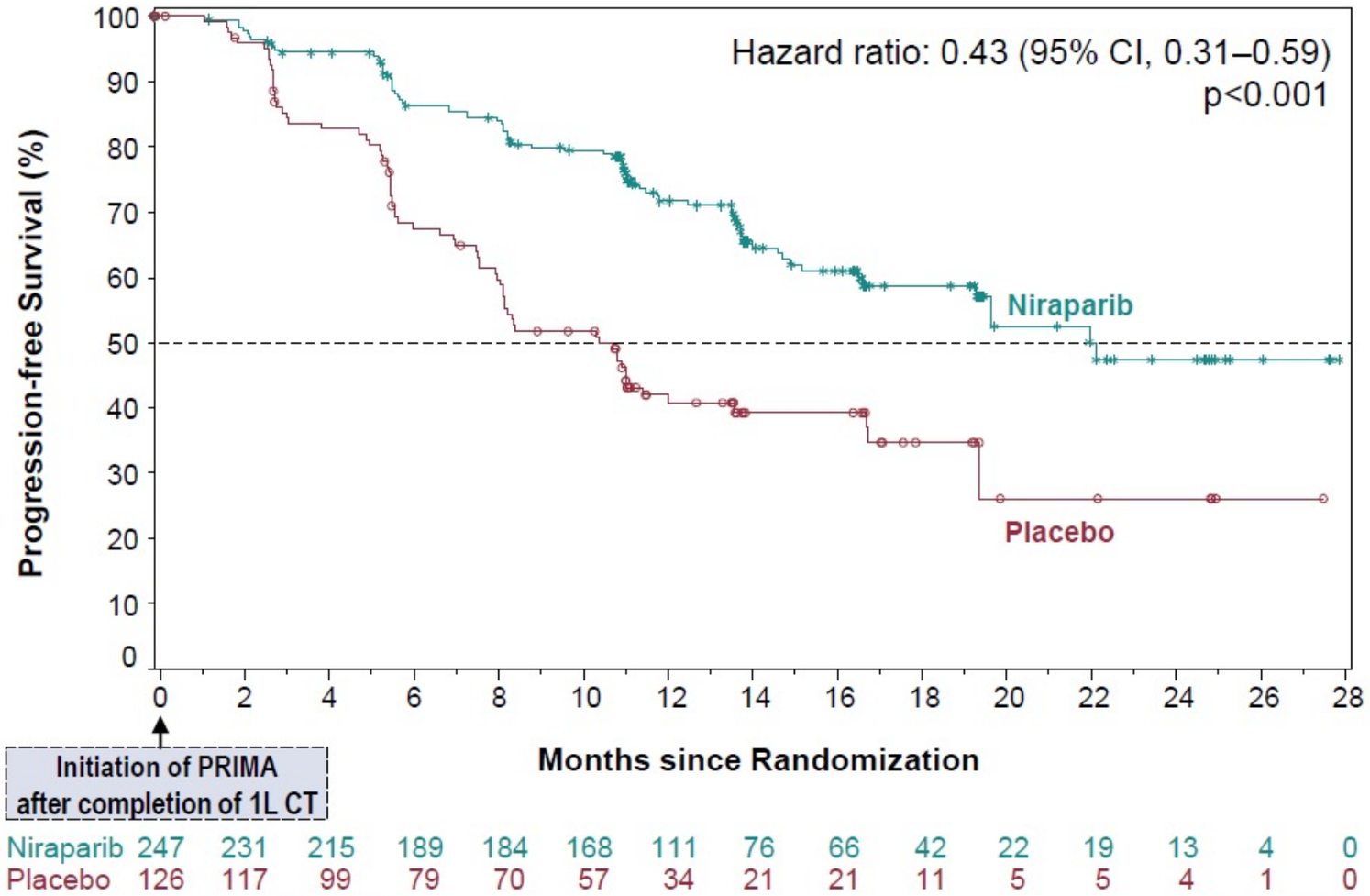
38% reduction in hazard of relapse or death with niraparib		
	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

BARCELONA 2019 ESMO congress

1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.

Raziskava PRIMA:
Niraparib v 1. liniji (ne glede na mutacijo BRCA 1/2)

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%

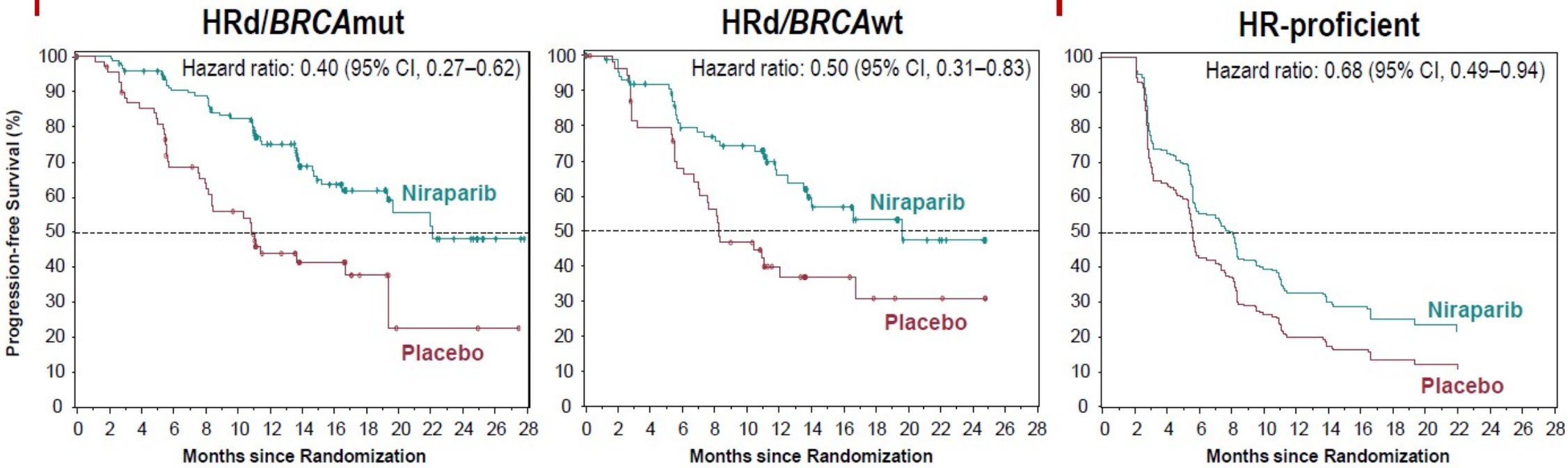
BARCELONA 2019 ESMO congress

1L, first-line; CI, confidence interval; CT, chemotherapy; HR, homologous recombination; 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.

RAZISKAVA PRIMA:
NIRAPARIB V 1. LINIJI (NE GLEDE NA MUTACIJO BRCA 1/2)

PRIMA PFS Benefit in Biomarker Subgroups

Homologous Recombination Deficient (HRd)



- 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

BARCELONA 2019 ESMO congress

CI, confidence interval; HR, homologous recombination; mut, mutation; PFS, progression-free survival wt, wild-type.

RAZISKAVA PAOLA-1:
OLAPARIB + BEVACIZUMAB V 1. LINIJI (NE GLEDE NA MUTACIJO BRCA 1/2)

BARCELONA 2019 ESMO congress

ARCAGY - GINECO

ENGOT European Network of Gynaecological Oncological Trial groups

GYNECOLOGIC CANCER INTERGROUP An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

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

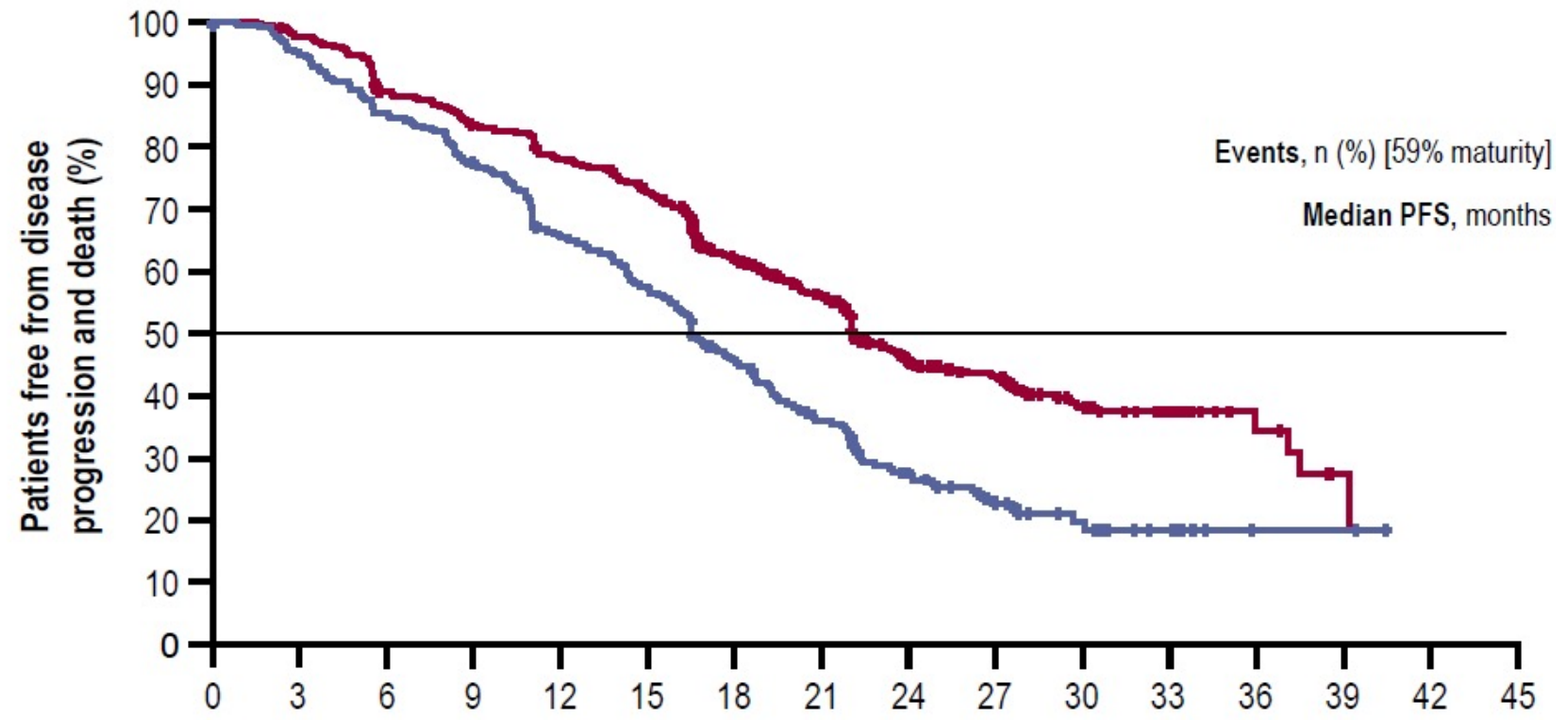
AGO AUSTRIA · AGO Study Group · BGOG · GEICO · GOTIC · MaNGO · MITO · NSGO-CTU

esmo.org

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

RAZISKAVA PAOLA-1: OLAPARIB + BEVACIZUMAB V 1. LINIJI (NE GLEDE NA MUTACIJO BRCA 1/2)

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)		

No. at risk															
Olaparib	537	513	461	433	403	374	279	240	141	112	55	37	12	3	0
Placebo	269	252	226	205	172	151	109	83	50	35	15	9	1	1	0

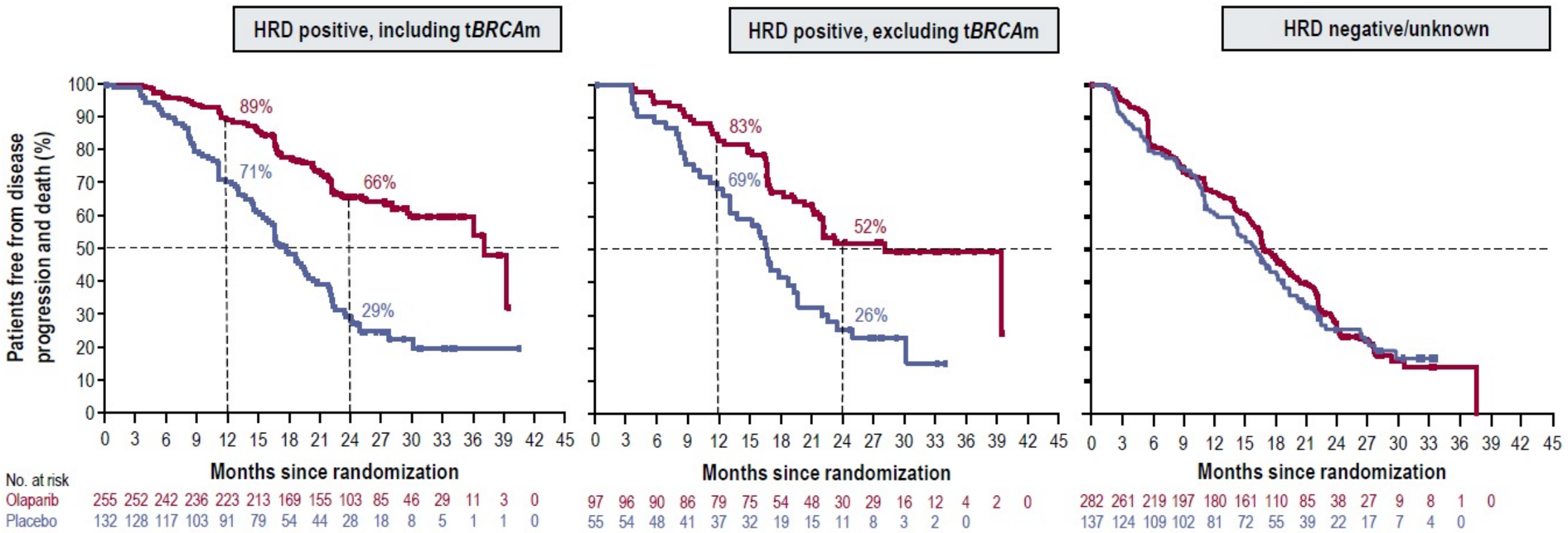
BARCELONA 2019 ESMO congress

ITT, intent-to-treat population

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

RAZISKAVA PAOLA-1: OLAPARIB + BEVACIZUMAB V 1. LINIJI (NE GLEDE NA MUTACIJO BRCA 1/2)

PFS by HRD status



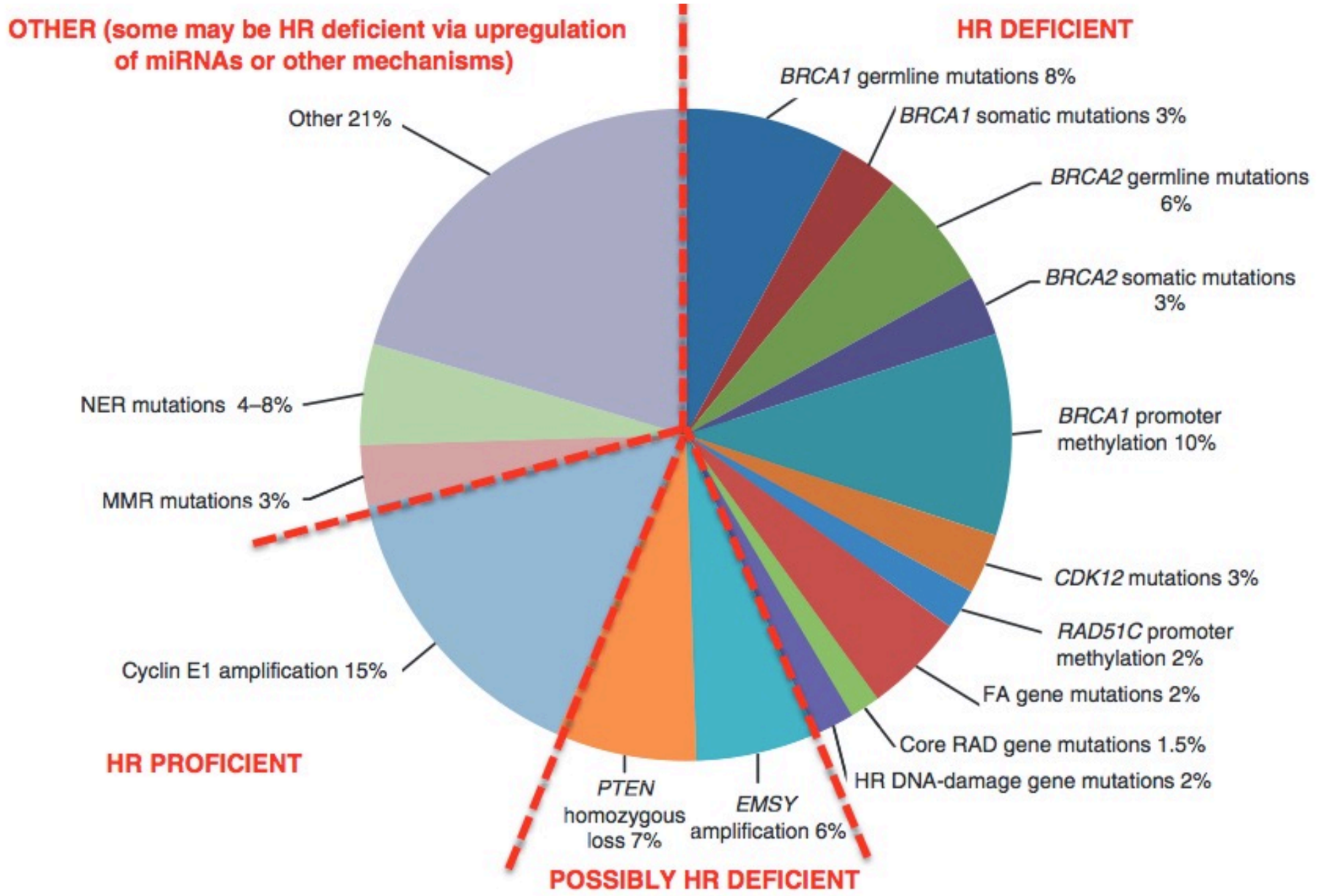
	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	**37.2***	**17.7**
	HR 0.33 (95% CI 0.25–0.45)	

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

	Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
	193 (68)	102 (74)
	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 than 50% maturity

Dejavniki, ki vplivajo na homologno rekombinacijo



SISTEMSKO ZDRAVLJENJE PONOVITVE BOLEZNI

- Novosti:
  - Uporaba izraza „občutljivost oz. rezistenca na platino“ samo na osnovi PFI (platinum-free intervala) je „zastarelo“, namesto tega:
  - **Platinum is an option** vs. **platinum is not an option**

- **Zaviralci PARP*** - vzdrževalno, ne glede na BRCA (EMA)
  - olaparib - raziskavi SOLO-2[1]
  - niraparib - raziskava NOVA[2]
  - rucaparib - raziskava ARIEL 3[3]

- **Biološko podobno zdravilo** bevacizumaba

** PARP – poli ADP riboza polimeraza*

1-Pujade-Lauraine E, et al. Lancet 2017; 2- Mirza MR, et al. NEJM 2016, 3- Coleman RL, et al. Lancet 2017

SISTEMSKO ZDRAVLJENJE – NOVOSTI V SLOVENIJI (1)

- Primarno sistemsko zdravljenje
  - Vzdrževalno zdravljenje (po OP in KT) – stadij III/IV
    - olaparib (pri BRCA mutiranih) – 2 leti
    - niraparib (ne glede na BRCA) – 3 leta
    - bevacizumab (ne glede na BRCA) – 15 mesecev
      - **biološko podobno zdravilo** bevacizumaba (MVASI®)
    - olaparib + bevacizumab – sprožen postopek za odobritev ZZS

- Zdravljenje ponovitve bolezni
  - Vzdrževalno zdravljenje (po odgovoru na KT s platino)
    - olaparib (pri BRCA mutiranih)
    - niraparib (ne glede na BRCA)
    - bevacizumab (ne glede na BRCA)
      - **biološko podobno zdravilo** bevacizumaba (MVASI®)

SISTEMSKO ZDRAVLJENJE – NOVOSTI V SLOVENIJI (2)

- Od januarja 2019:
  - Določanje mutacije BRCA 1/2
    - Iz tumorja (somatska/zarodna)
    - Iz krvi (zarodna)*

- Namen testiranja BRCA je:
  - **Izbor optimalnega vzdrževalnega zdravljenja** (olaparib, niraparib, bevacizumab)
  - preventiva raka dojk in jajčnikov

- Posodobljena klinična pot za testiranje mutacije v genih BRCA 1/2

- Določanje okvare HR (poleg BRCA) – v fazi raziskovanja…

** po predhodnem genetskem svetovanju*

SISTEMSKO ZDRAVLJENJE – NOVOSTI V SLOVENIJI (3)

➤ Naše izkušnje s testiranjem BRCA

Research article | Open Access | Published: 02 April 2019

Cytology material is equivalent to tumor tissue in determining mutations of *BRCA 1/2* genes in patients with tubo-ovarian high grade serous carcinoma

Andreja Gornjec, Srdjan Novakovic, Vida Stegel, Marko Hocevar, Ziva Pohar Marinsek, Barbara Gazic, Mateja Krajc & Erik Skof

BMC Cancer **19**, Article number: 296 (2019) | Cite this article

Aktualno v primeru, če testiranje iz tumorskega tkiva (FFPA) ni možno

- neprimeren material

- operacija/biopsija ni možna

SISTEMSKO ZDRAVLJENJE – NOVOSTI V SLOVENIJI (4)

➤ Naše izkušnje z zdravilom olaparib

12 | ONKOLOGIJA | ISSN 1408-1741 | IZVIRNI ZNANSTVENI ČLANEK | LETO XXV | ŠT. 1 | JUNIJ 2021

Izkušnje z zdravilom olaparib pri zdravljenju recidivnega epitelijskega raka jajčnikov z mutacijami v genih BRCA 1 in BRCA 2

Experience with olaparib in the treatment of recurrent ovarian epithelial cancer with mutations in the BRCA 1 and BRCA 2 genes

Škof Erik[1]