

NOVOSTI V SISTEMSKEM ZDRAVLJENJU RAKA JAJČNIKOV

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RAK JAJČNIKOV – BOLEZEN SE POGOSTO PONOVI

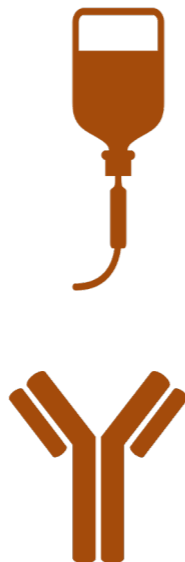
Operacija

+

Kemoterapija

+

Bevacizumab



10-18 mesecev

Mediani čas preživetja brez ponovitve bolezni^{2,3,4}

~70%

bolnic ima ponovitev bolezni 3 leta od pričetka zdravljenja¹

~40%

5-letno preživetje⁵

40 mes.

Celokupno preživetje⁴

Potrebno je izboljšati učinkovitost primarnega zdravljenja z namenom izboljšanja izhoda zdravljenja bolnic z rakom jajčnikov¹⁻⁵

NOVE EVROPSKE SMERNICE – LETA 2019



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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. Sessa², A. du Bois³, J. Ledermann⁴, W. G. McCluggage⁵, I. McNeish⁶, P. Morice⁷,
S. Pignata⁸, I. Ray-Coquard⁹, I. Vergote^{10,11}, T. Baert³, I. Belaroussi⁷, A. Dashora¹², S. Olbrecht^{10,11},
F. Planchamp¹³ & 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: olaparib¹
 - Raziskava PRIMA: niraparib²
 - Raziskava PAOLA-1: olaparib+bevacizumab³

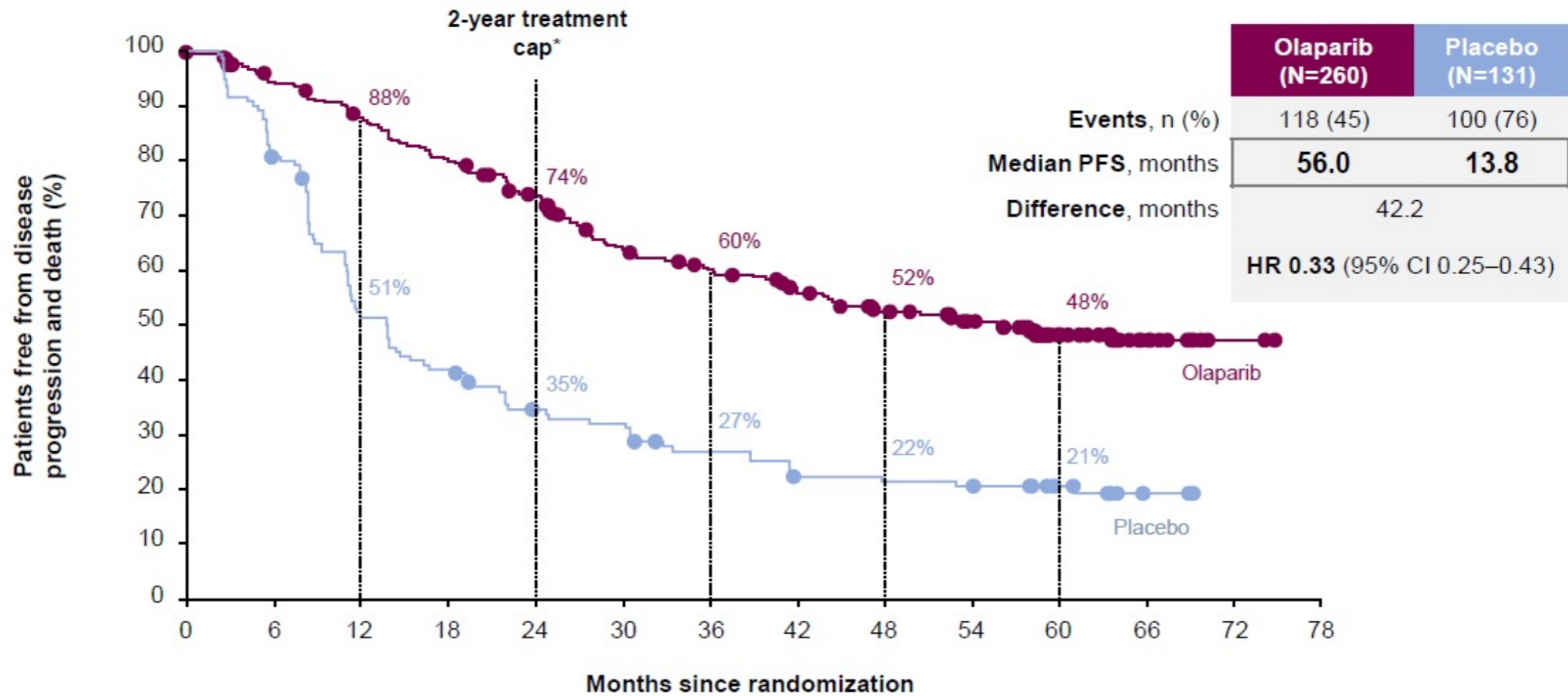
- **Določanje mutacije BRCA 1/2 – za namen zdravljenja**
 - Iz krvi (zarodna)
 - Iz tumorja (somatska/zarodna)

- **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



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	0

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

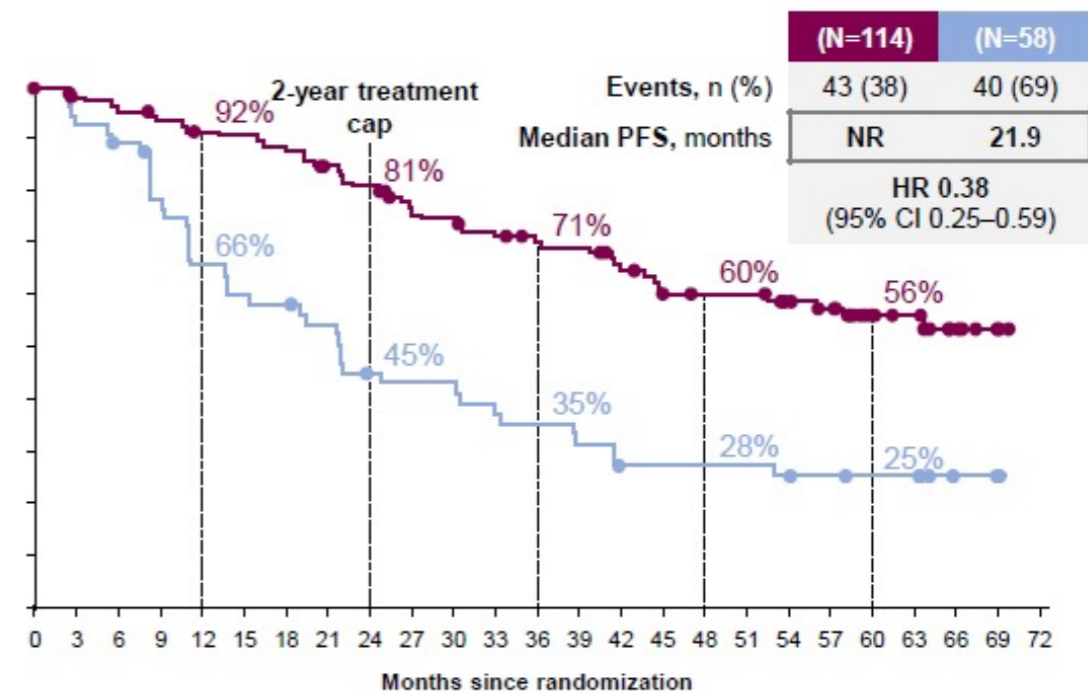
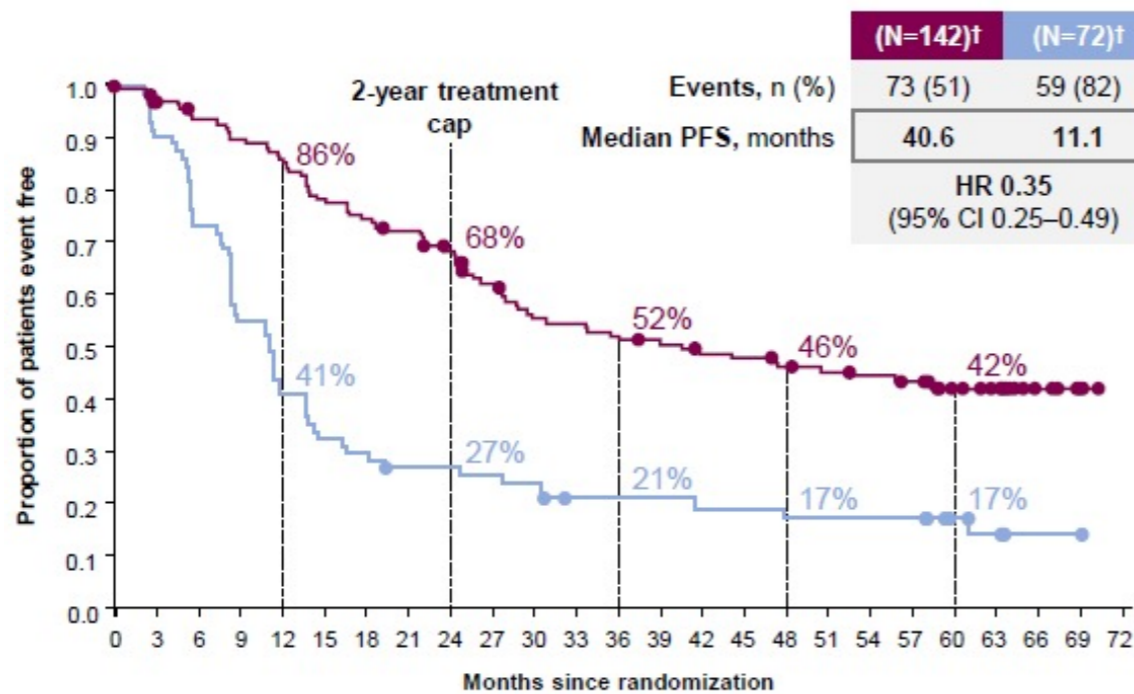
PFS benefit of maintenance olaparib was consistent in higher- and lower-risk subgroups

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)
BRCA1m	109 (75)	43 (59)
BRCA2m	36 (25)	30 (41)
BRCA1m and BRCA2m	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)
BRCA1m	82 (72)	48 (83)
BRCA2m	30 (26)	10 (17)
BRCA1m and BRCA2m	2 (2)	0



No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
Olaparib	142	131	124	119	114	104	99	95	88	78	67	66	63	60	56	55	52	50	48	46	31	27	15	8	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

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
Olaparib	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
Placebo	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

Raziskava PRIMA:

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



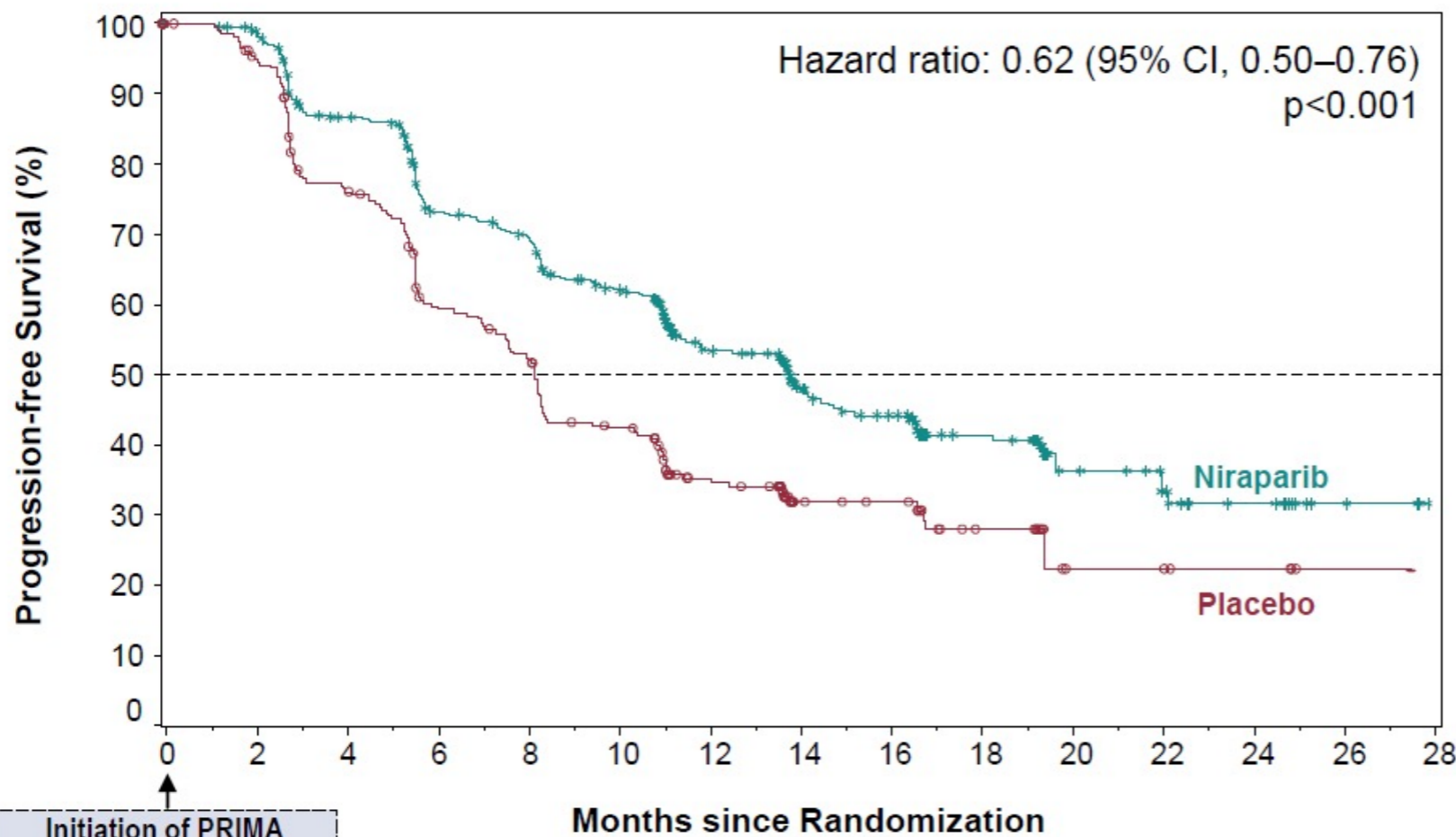
Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer (PRIMA/ENGOT-OV26/GOG-3012)

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. Monk¹⁹

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

PRIMA Primary Endpoint, PFS Benefit in the Overall Population



	Niraparib (n=487)	Placebo (n=246)
38% reduction in hazard of relapse or death with niraparib		
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%

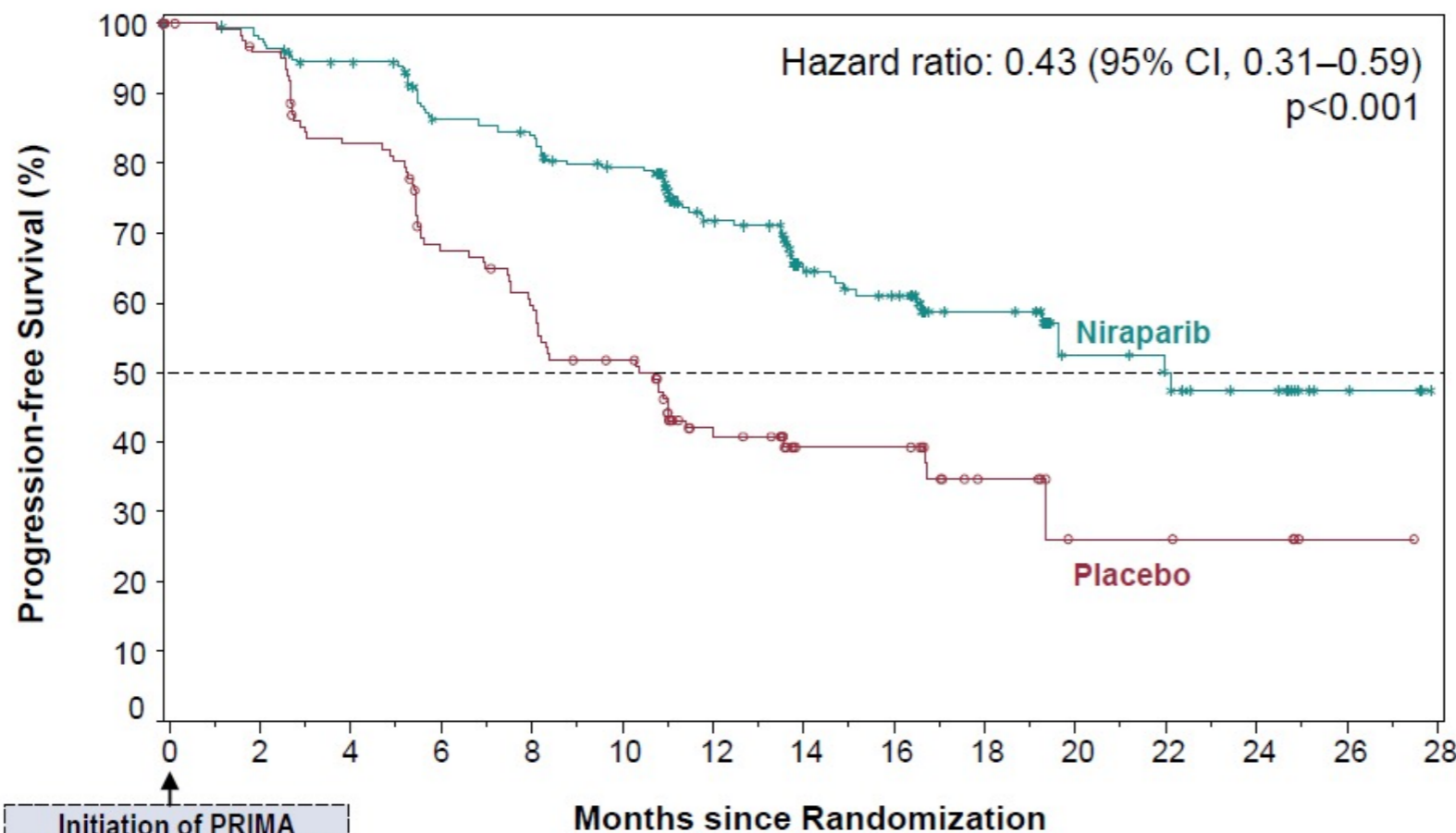
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Niraparib	487	454	385	312	295	253	167	111	94	58	29	21	13	4	0
Placebo	246	226	177	133	117	90	60	32	29	17	6	6	4	1	0



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



	Niraparib (n=247)	Placebo (n=126)
57% reduction in hazard of relapse or death with niraparib		
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%

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
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

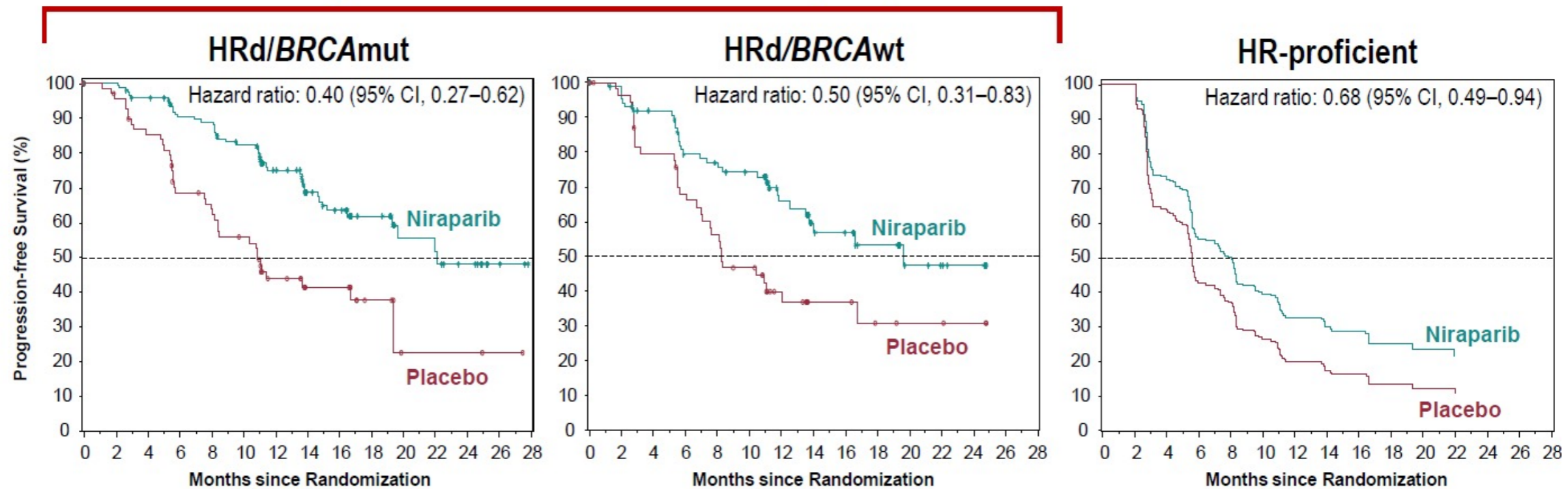


1L, first-line; CI, confidence interval; CT, chemotherapy; HR, homologous recombination; NE, not estimable; PD, progressive disease; PFS, progression-free survival. Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

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 (*BRCAmut* and *BRCAwt*)
- Niraparib provide clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

RAZISKAVA PAOLA-1:

OLAPARIB + BEVACIZUMAB V 1. LINIJI (NE GLEDE NA MUTACIJO BRČA 1/2)



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 Sevela, 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



esmo.org

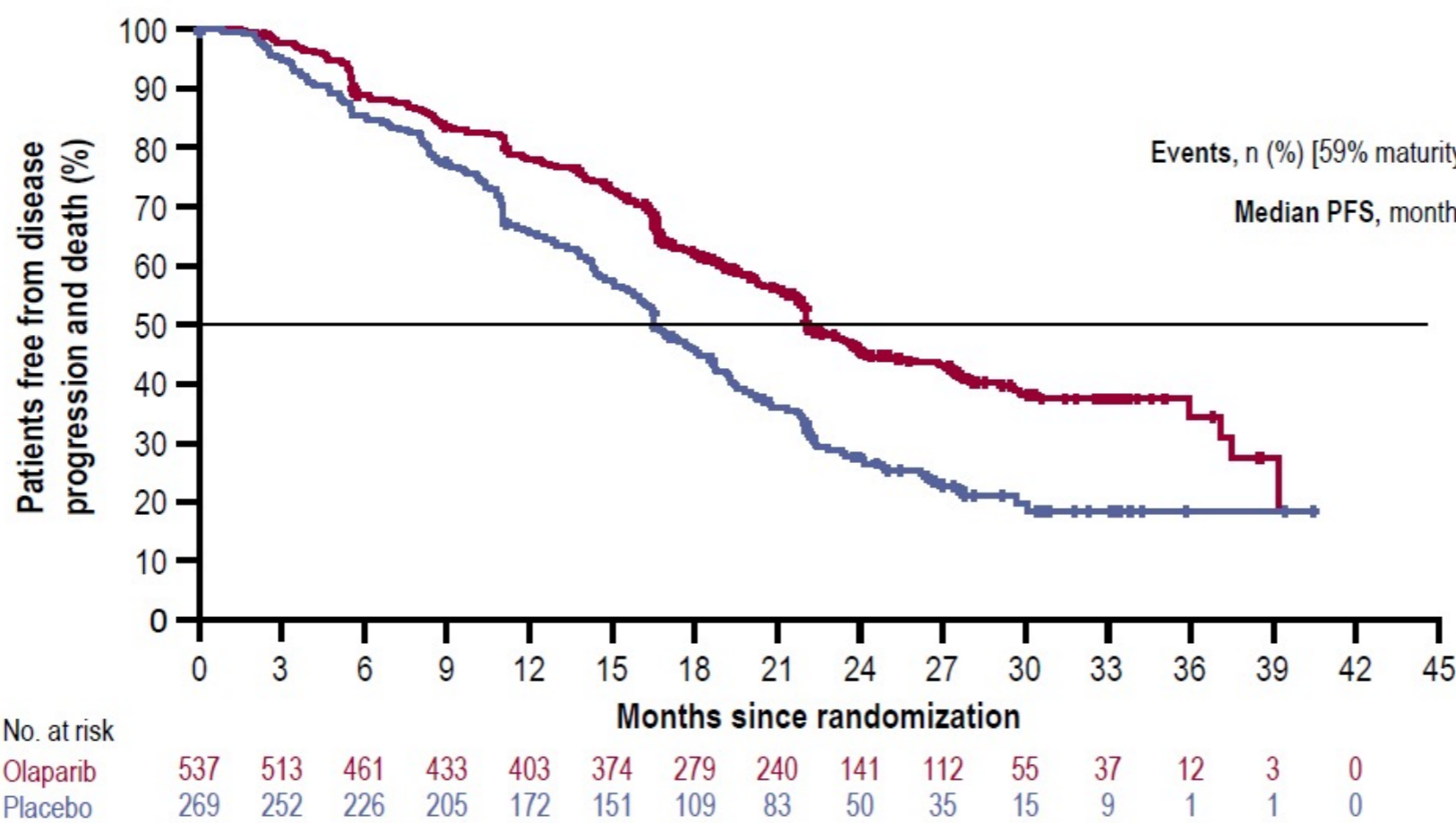
ClinicalTrials.gov identifier: NCT02477644

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)		

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

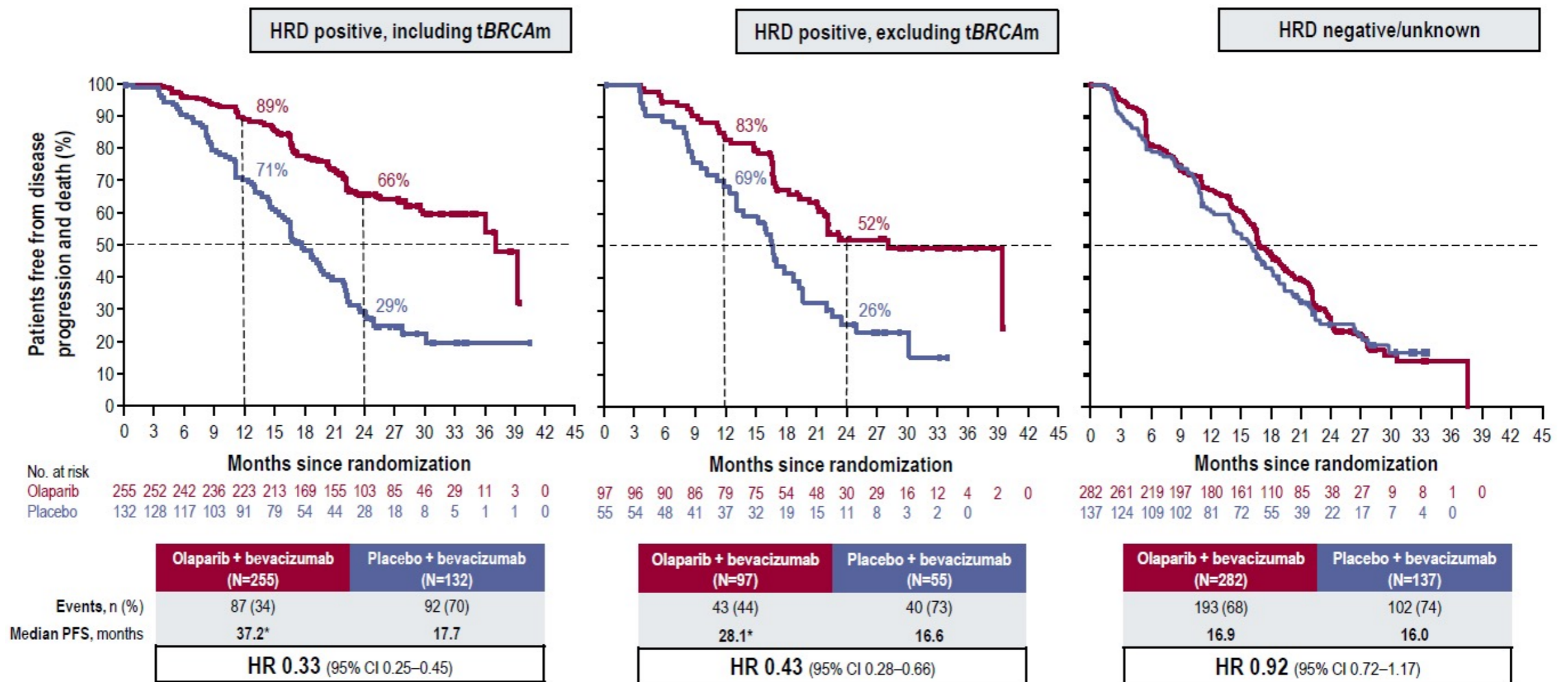


ITT, intent-to-treat population

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

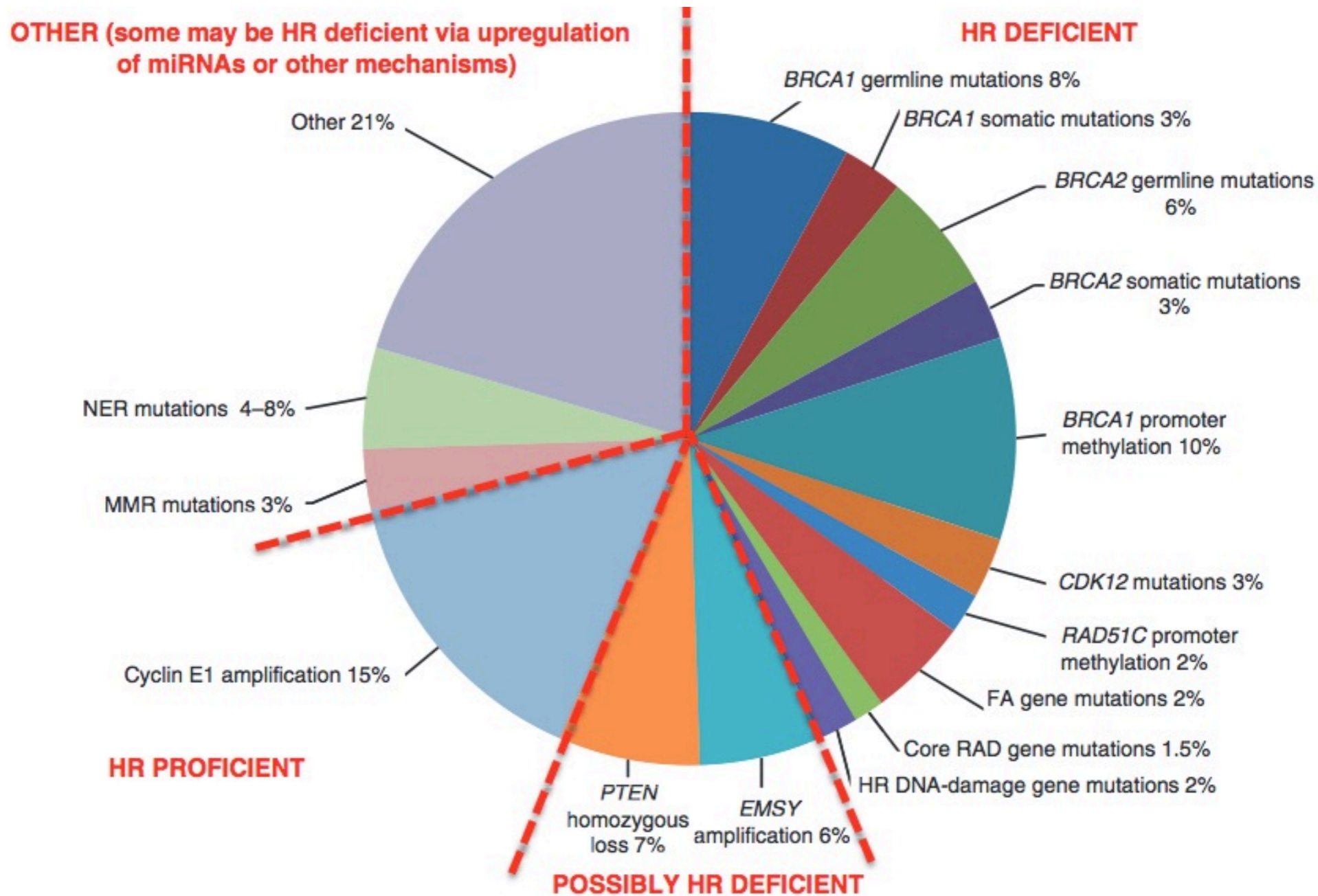


PFS by HRD status



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 PONOVIČNE 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-2¹
 - ▶ niraparib - raziskava NOVA²
 - ▶ rucaparib - raziskava ARIEL 3³
 - ▶ Biološko podobno zdravilo bevacizumaba

* *PARP* – poli ADP riboza polimeraza

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 epiteljskega 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 Erik¹