Il punto di vista dell'esperto

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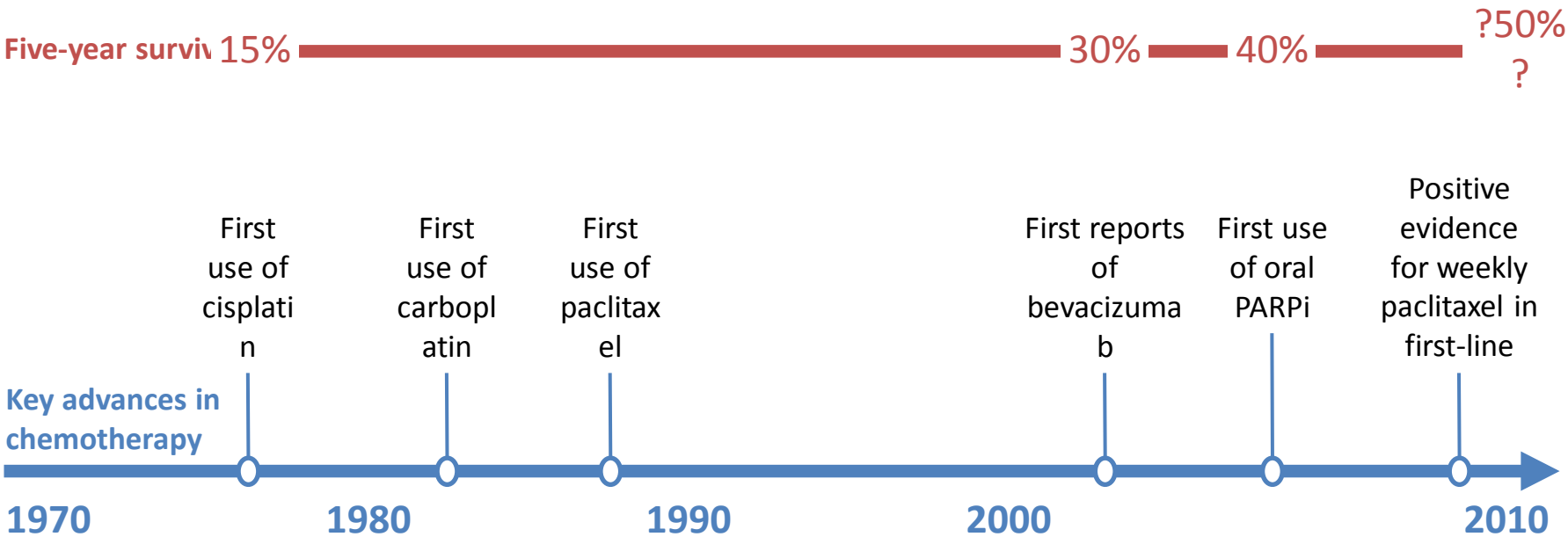
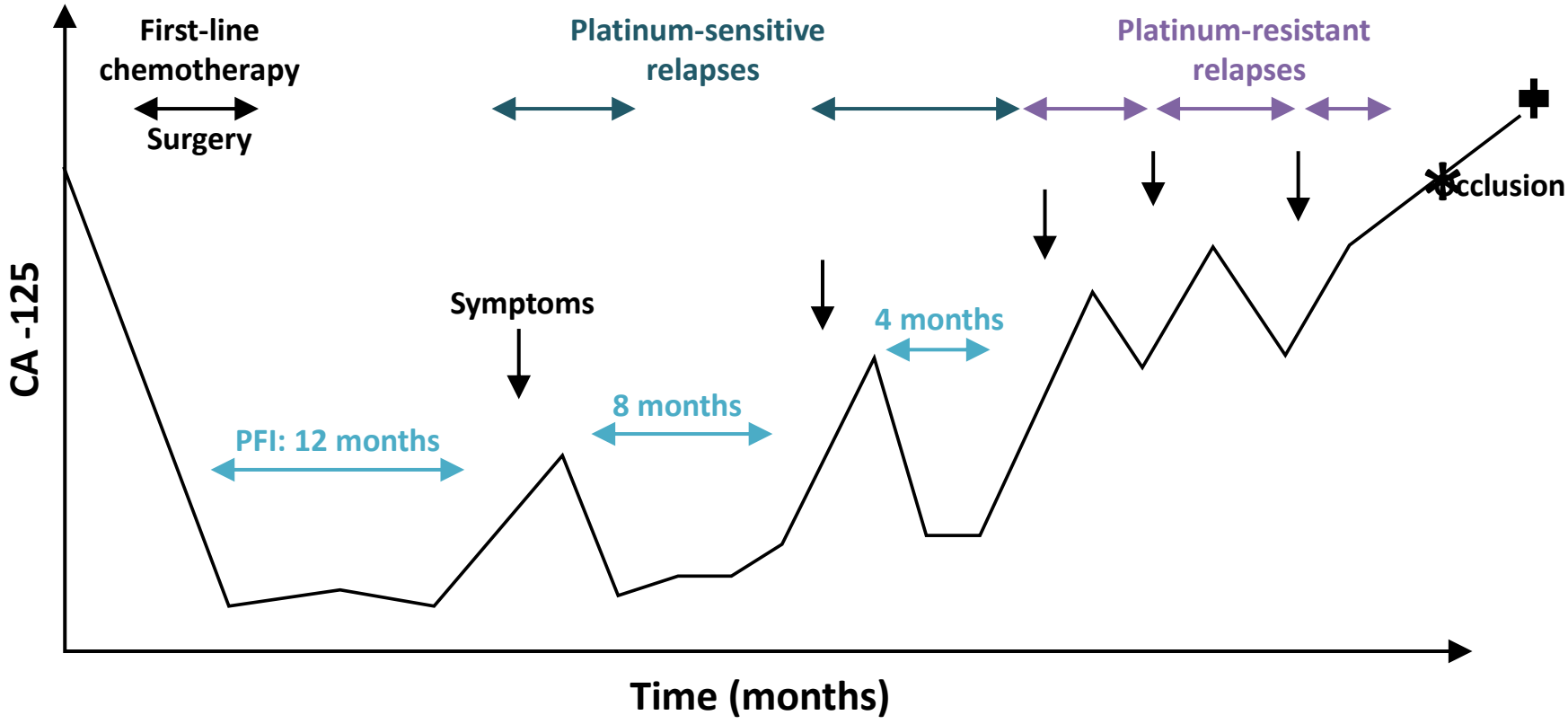
Progress in the management of ovarian cancer: Evolution over 40 years



PARPi, poly adenosine diphosphate ribose polymerase inhibitor.

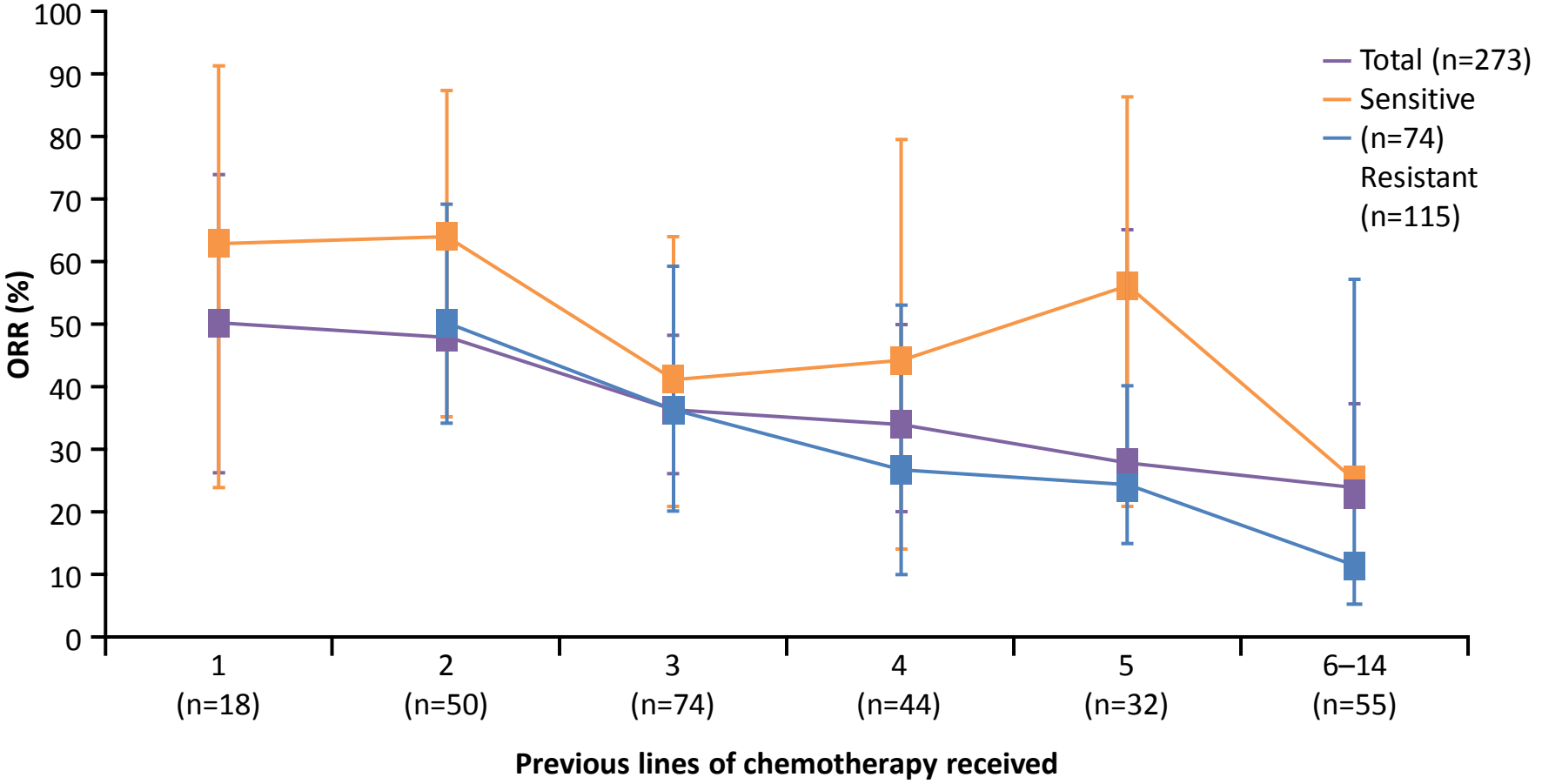
Advanced ovarian cancer: A ‘chronic’ disease with multiple relapses



PFI: platinum-free interval or duration of disease control without chemotherapy.

du Bois a, Pfisterer J. Zentralbl Gynakol. 2004;126:312-4.

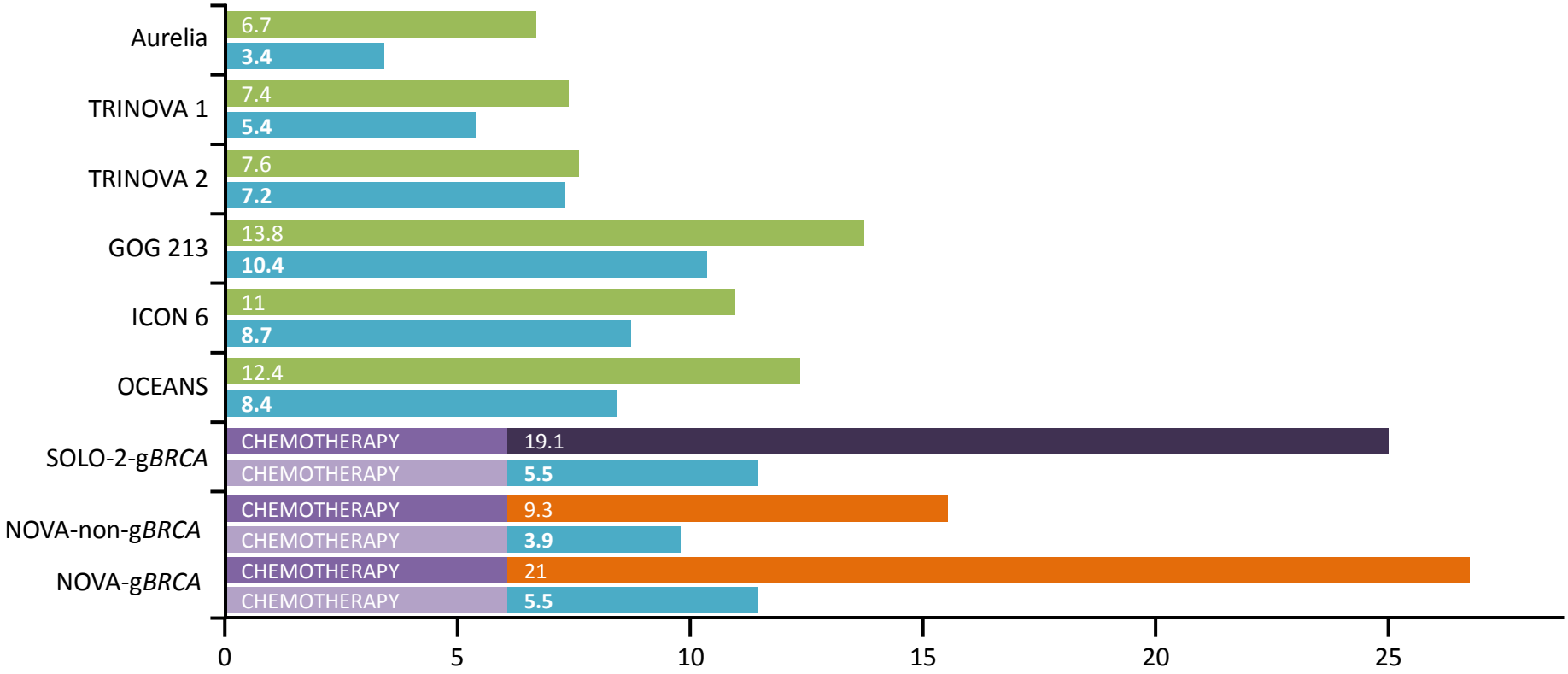
Response to treatment in patients with ovarian cancer declines with increasing disease recurrence



N numbers show total population; confidence lines represent 95% CIs for total population.
CI, confidence interval; ORR, overall response rate.

du Bois a, Pfisterer J. Zentralbl Gynakol. 2004;126:312-4.

How effective is “watchful waiting”?



Median PFS from placebo arms may provide insights.
PFS, progression-free survival.

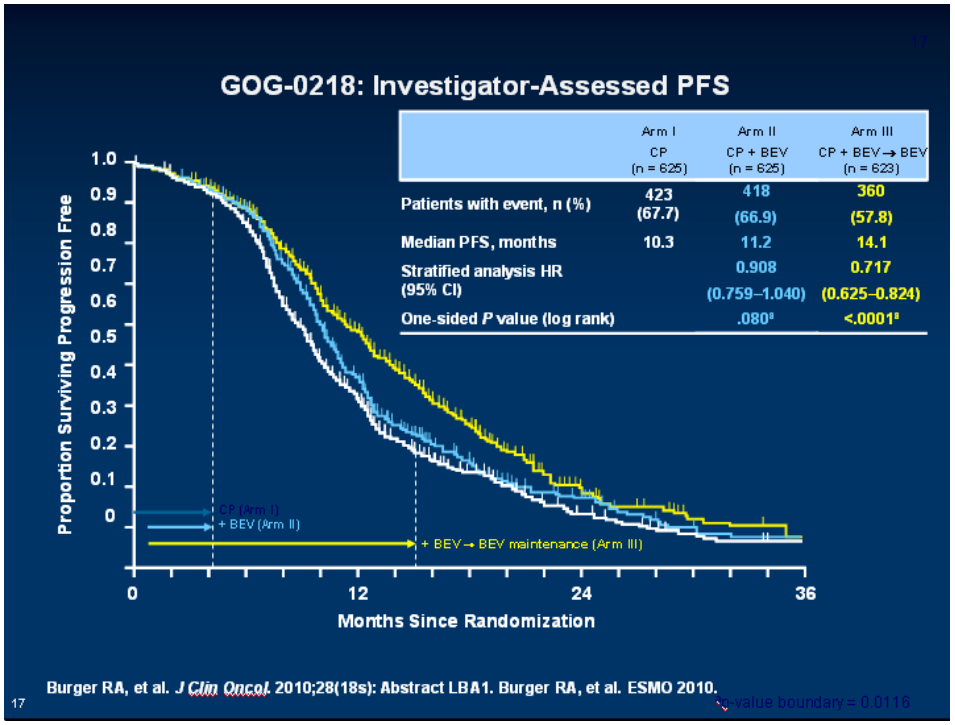
Aghajanian C et al. *J Clin Oncol.* 2012;30:2039–45; Coleman RL et al. *Gynecologic Oncol.* 2015;137:386–91; Ledermann J et al. *Lancet Oncol.* 2014;15:852–61; Ledermann JA et al. *Lancet.* 2016;387:1066–74; Marth C, et al. *European J Cancer.* 2017;70:111–121; Monk BJ et al. *Lancet Oncol.* 2014;15:799–808; Pujade-Lauraine E et al. *J Clin Oncol.* 2014;32:1302–8; Mirza MR et al. *N Engl J Med*. 2016;375:2154–64.

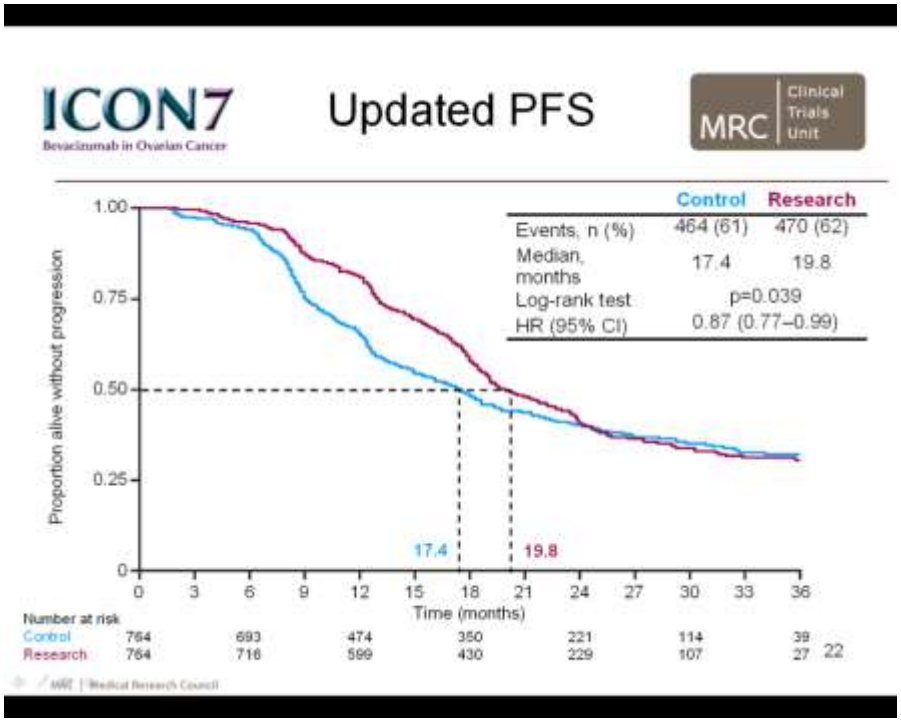
ADVANCED STAGE

What is the current role of bevacizumab in first-line treatment?

Summary of recommendations	LoE	GoR	Consensus
Bevacizumab (15mg/kg or 7.5 mg/kg every 3 weeks for maximum of 15 months) improves progression-free survival in patients with stage III-IV ovarian cancer and should be considered in addition to carboplatin and paclitaxel	I	A	Yes: 97.5% *(39 voters)* Abstain: 2.5% *(1 voter)*
Bevacizumab in the neoadjuvant setting can be considered although the additional improvement in efficacy is not proven with level I evidence	II	B	Yes: 97.5% *(39 voters)* No: 2.5% *(1 voter)*
Bevacizumab can be safely administered in the neo-adjuvant setting before and after IDS providing the interval between surgery and administration is at least 4-6 weeks	II	B	Yes: 100% *(40 voters)*

Two positive trials with bevacizumab in front line





Overall Survival

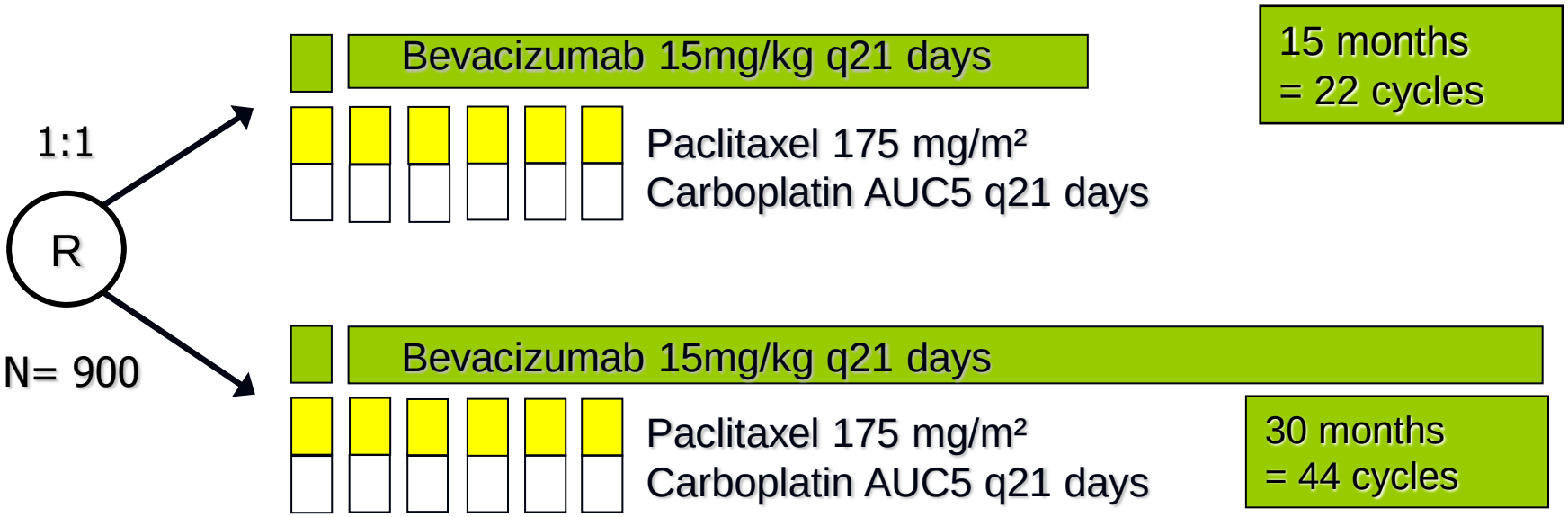
	Arm I CP (n = 625)	Arm II CP + Bev (n = 625)	Arm III CP + Bev → Bev (n = 623)
Deaths	156 (25.0%)	150 (24.0%)	138 (22.2%)
1-Year Survival	90.6%	90.4%	91.3%

Events were observed in ~ 24% of patients at the time of database lock.

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

HOW LONG?

ENGOT Ov-15 Trial
AGO-OVAR 17
Study Design



Strata

- macroscopic residual tumor (yes vs no)
- FIGO Stage (IIB-IIIC vs IV)
- Study Group

Primary endpoint:

- PFS (non inferiority -> superiority)

Main question: treatment duration Bev

Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17

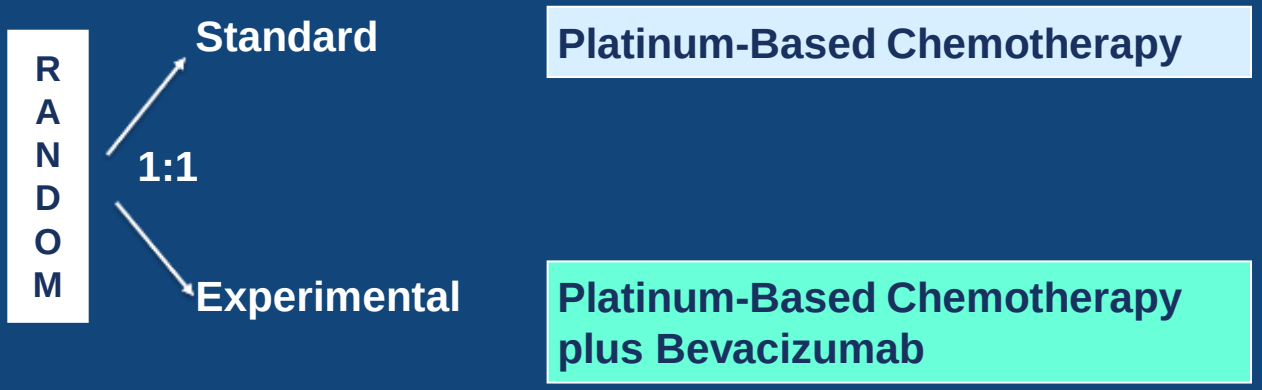
Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Carmela Pisano, Frédéric Selle, Eleonora Zaccarelli, Giovanni Scambia, Patricia Pautier, Maria Ornella Nicoletto, Ugo De Giorgi, Coraline Dubot, Alessandra Bologna, Michele Orditura, Isabelle Ray-Coquard, Francesco Perrone, Gennaro Daniele

on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY:

Study Design

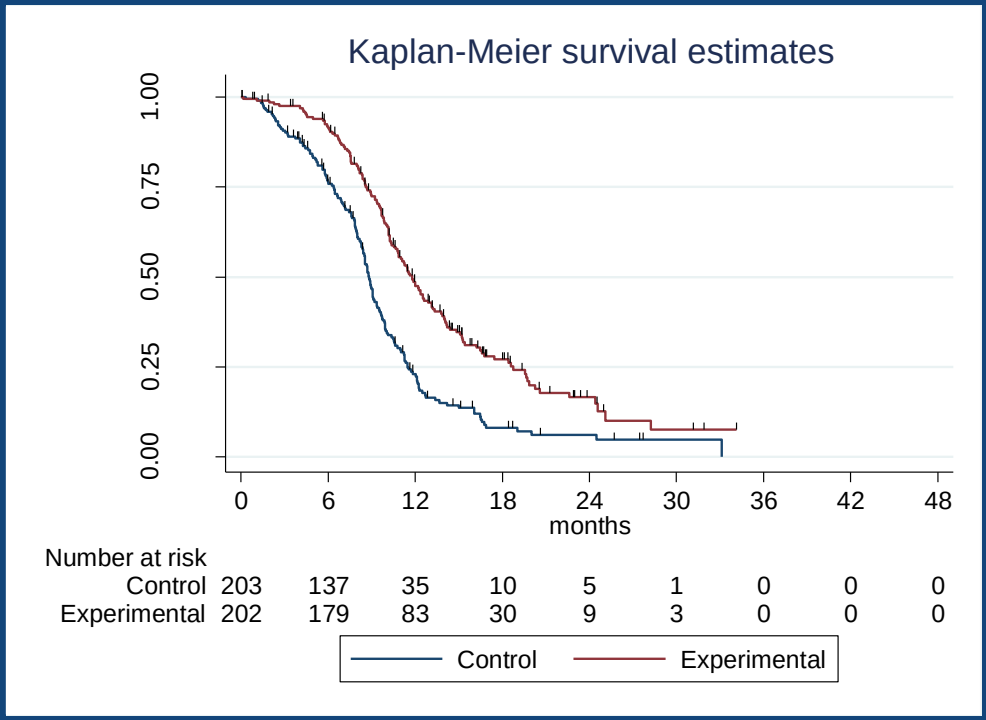


Platinum-based Chemotherapy:
- Carboplatin + Paclitaxel +/- Beva 15mg/kg q 21
- Carboplatin + Gemcitabine +/- Beva 15mg/kg q 21
- Carboplatin + PLD q 28 +/- Beva 10mg/kg q 14

Stratification:
- center
- relapse during or after 1° line Beva
- performance status
- chemo backbone

Sandro Pignata

PFS Investigator assessed (primary end-point)



	Standard	Experimental	Log Rank P
# events	161	143	
Median PFS	8.8 mos	11.8 mos	<0.001
HR* (95%CI)	0.51 (0.41-0.65)		

*adjusted by:
age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Sandro Pignata

WHICH PATIENTS?

Bevacizumab in ovarian cancer:
four pivotal trials: **Dose? Duration? Setting?**

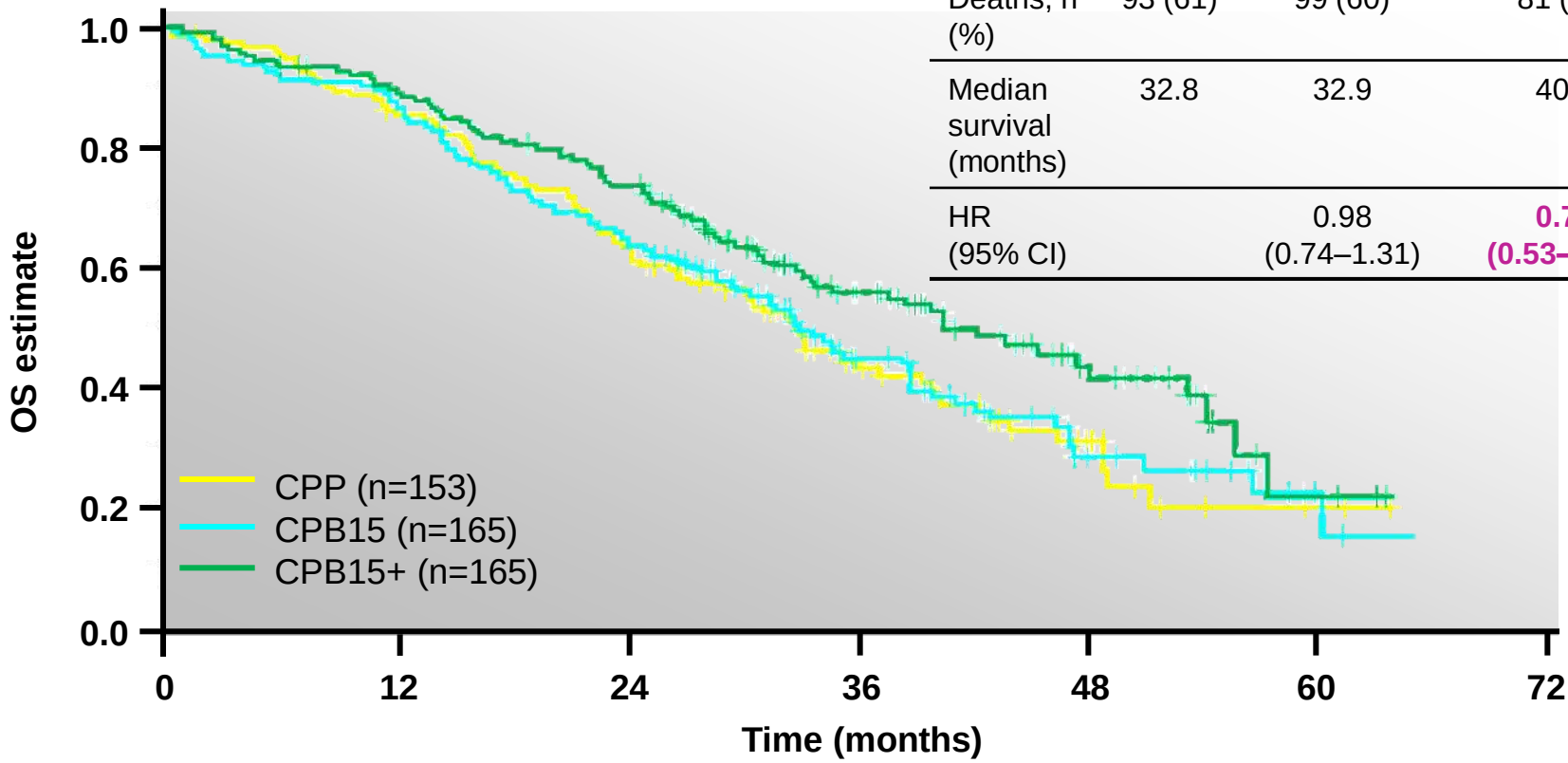
	Trial	Chemotherapy	Bevacizumab	PFS HR
First line				
	GOG-0218[1] (n=1873)	Paclitaxel Carboplatin	Concurrent and maintenance 15 mg/kg q3w (3-arm blinded)	0.72
	ICON7[2] (n=1528)	Paclitaxel Carboplatin	Concurrently only 7.5 mg/kg q3w (2 arm)	0.81
Second line				
Platinum resistant	AURELIA[3] (n=361)	Pegylated liposomal doxorubicin, Topotecan or Paclitaxel	Concurrent 10 mg/kg q2w (2 arm)	0.48
Platinum sensitive	OCEANS[4] (n=484)	Gemcitabine Carboplatin	Concurrent 15 mg/kg q3w (2 arm)	0.48

4245 patients
Which patients?
Unselected?
No biomarker

1. Burger et al. N Engl J Med 2011
2. Perren et al. N Engl J Med 2011
3. Pujade-Laurain et al. J Clin Oncol 2012
4. Aghajanian et al. J Clin Oncol 2012

OS benefit is suggested with chemotherapy + Avastin and continued single-agent Avastin in stage IV disease

	CPP	CPB	CPB15
Deaths, n (%)	93 (61)	99 (60)	81 (49)
Median survival (months)	32.8	32.9	40.6
HR (95% CI)		0.98 (0.74–1.31)	**0.72 (0.53–0.97)**

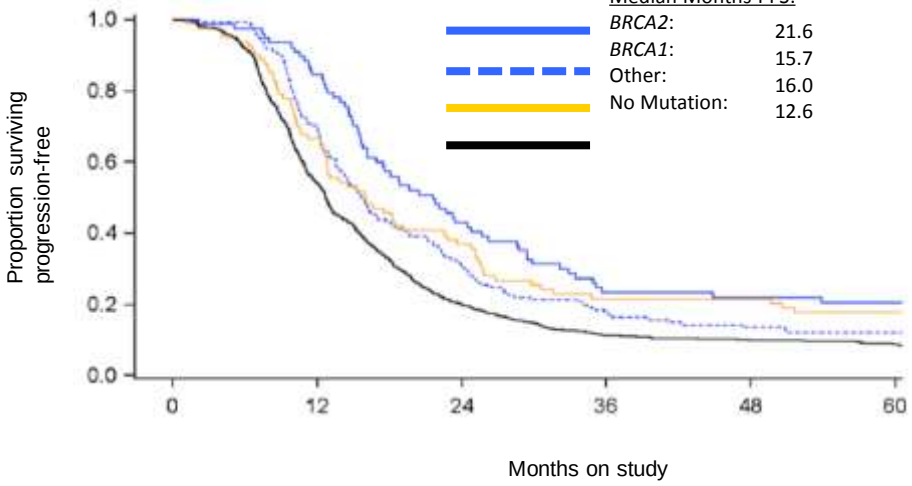


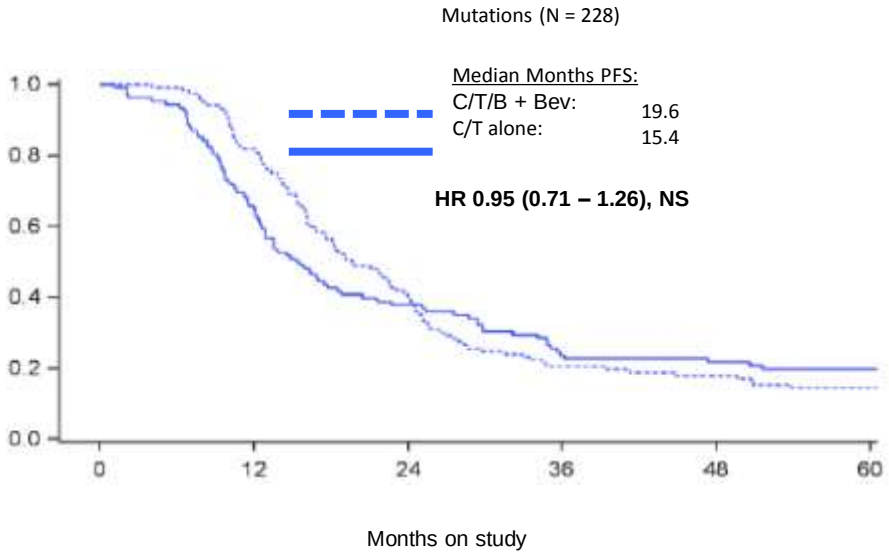
CPP	153	144	129	113	95	72	42	28	15	5	3	0	0
CPB	165	149	142	117	104	73	44	30	15	10	3	1	0
CPB15	165	154	144	130	117	83	57	37	21	10	3	0	0

Randall, et al. SGO 2013: Abstract 80

BRCA mutations confer a better prognosis – what is the outcome of these patients with 'standard of care' chemotherapy and bevacizumab?

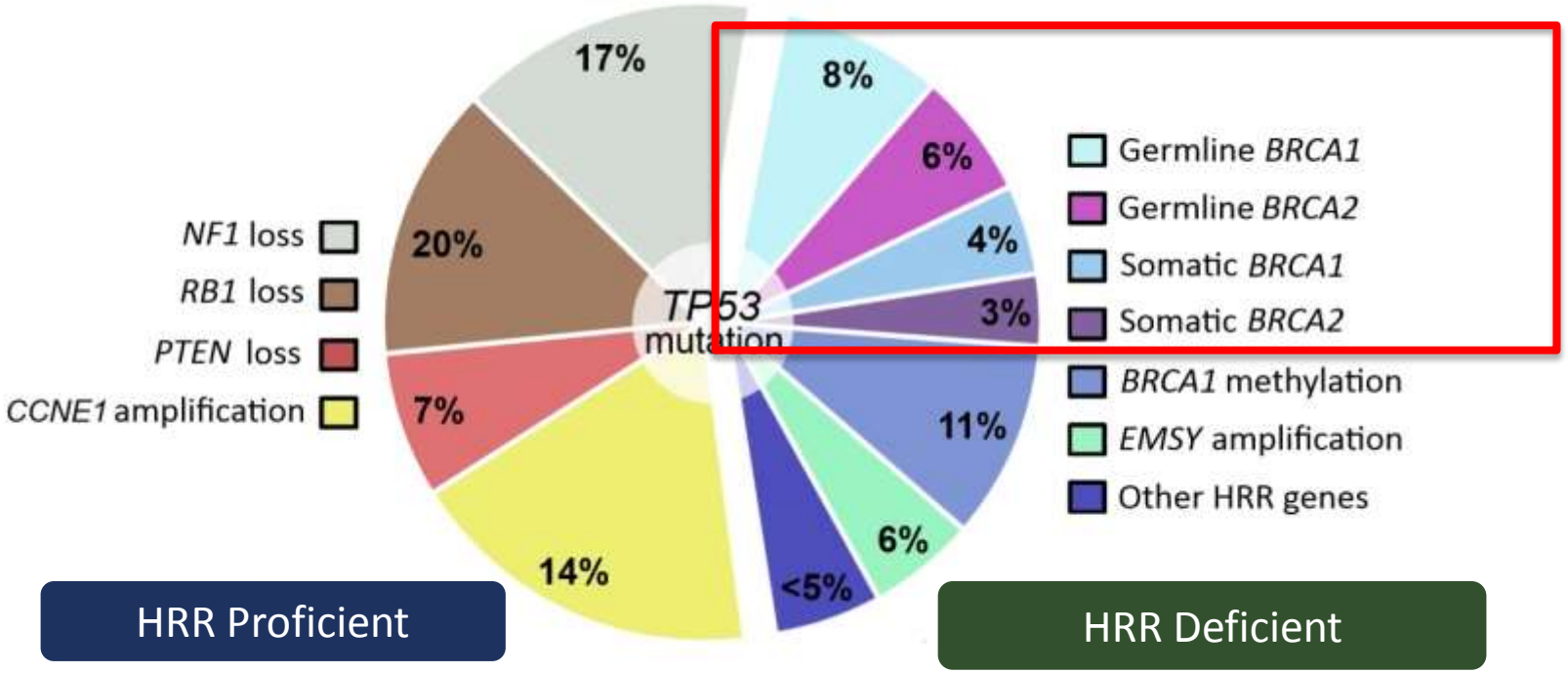
GOG 218 : Carboplatin/paclitaxel versus carboplatin/paclitaxel+ bevacizumab with bevacizumab maintenance





Norquist et al SGO 2016

Rationale for PARP inhibitors in ovarian cancer: high grade serous ovarian cancer biology



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Hollis RL, et al. Cancer Biol Med. 2016; 13:236-247

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]

[1]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK, USA; [2]University of Milan-Bicocca and IEO, European Institute of Oncology IRCCS, Milan, Italy; [3]Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica, Rome, Italy; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [5]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [6]University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia; [7]St Petersburg City Oncology Dispensary, St Petersburg, Russia; [8]Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France; [9]Gustave-Roussy Cancer Campus, Villejuif, France; [10]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [11]Cancer Research UK Edinburgh Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK; [12]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Clínica Universidad de Navarra, Madrid, Spain; [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [16]Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA; [17]AstraZeneca, Gaithersburg, MD, USA; [18]AstraZeneca, Cambridge, UK; [19]Women & Infants Hospital, Providence, RI, USA

ClinicalTrials.gov identifier: NCT01844986
This study was sponsored by AstraZeneca; part of an alliance between AstraZeneca and Merck & Co., Inc.
Conducted in partnership with the Gynecologic Oncology Group (GOG-3004)

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

Olaparib 300 mg bd (N=260)

2:1 randomization

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)

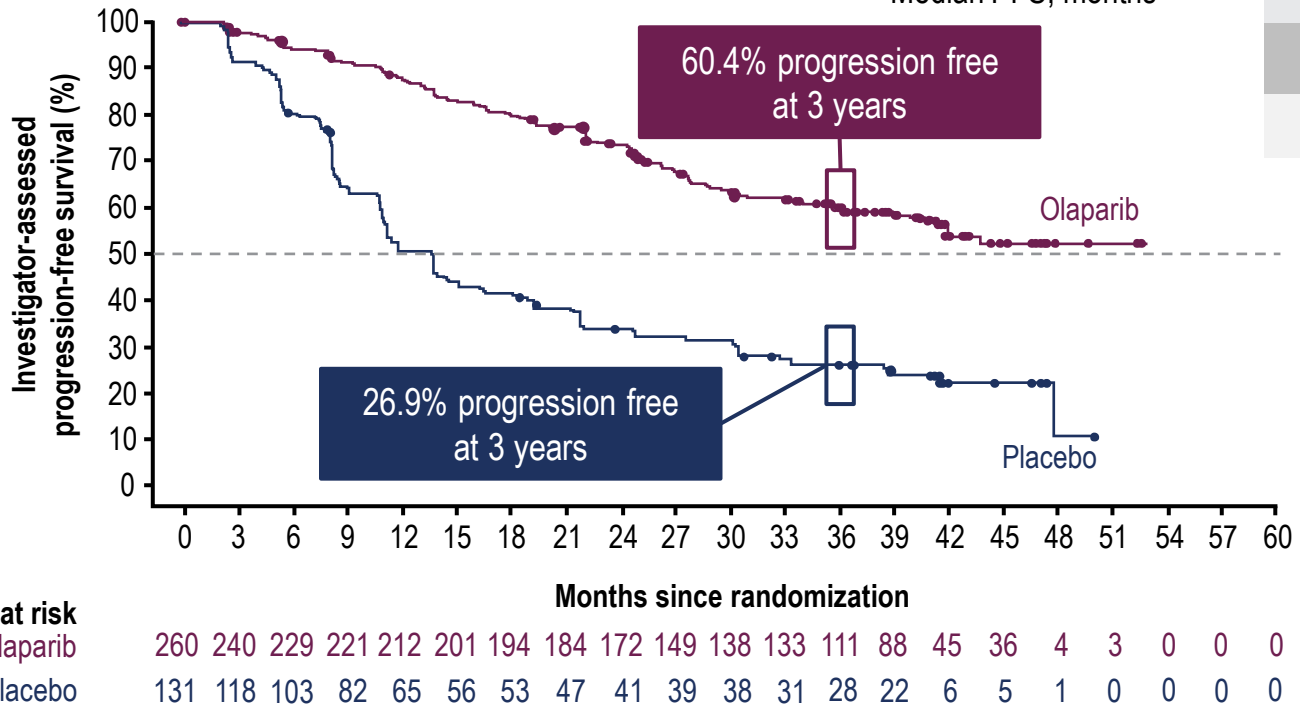
Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from 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

CI, confidence interval; NR, not reached

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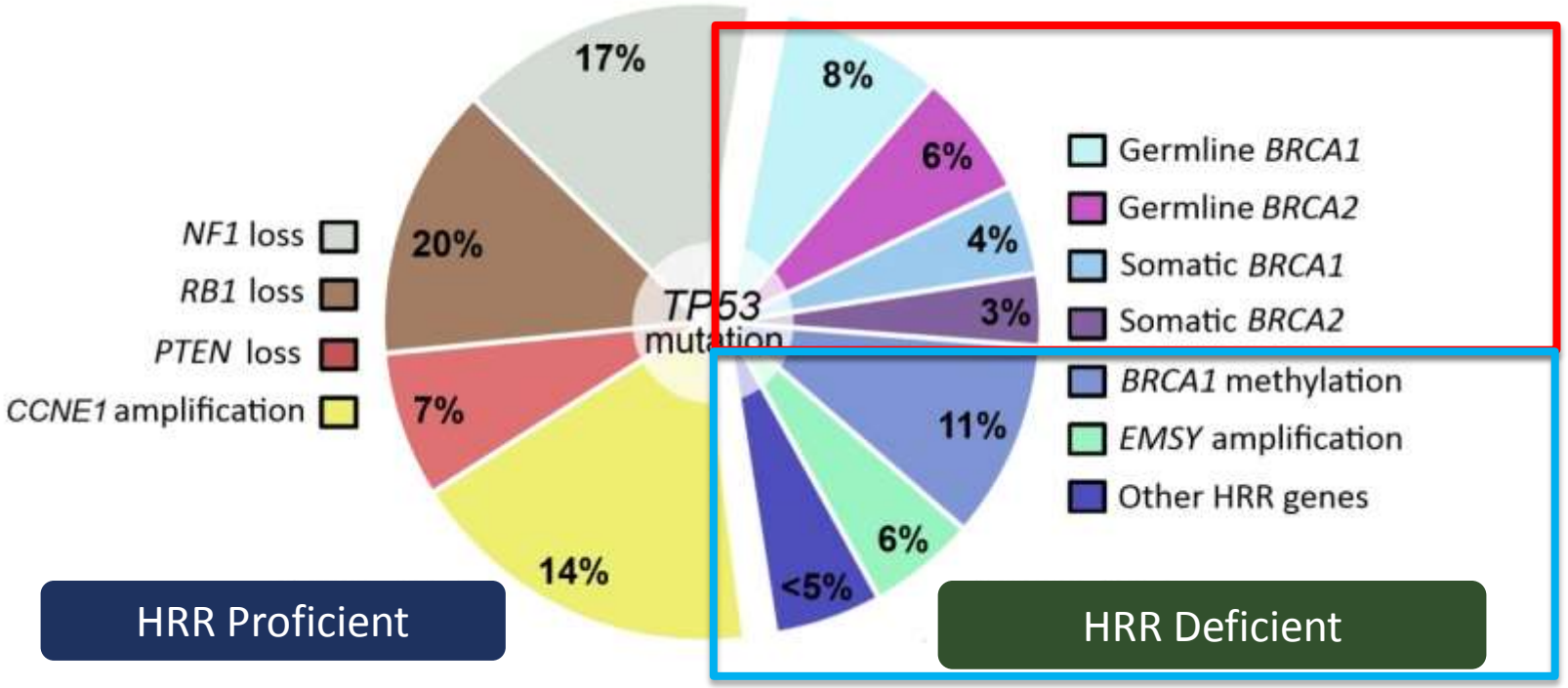
Rationale for PARP inhibitors in ovarian cancer: high grade serous ovarian cancer biology



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Hollis RL, et al. Cancer Biol Med. 2016; 13:236-247

Two Main HRD Genomic Scar Tests Have Been Developed

- **Genomic loss of Heterozygosity (LOH)**
- Foundation Medicine is developing a test in collaboration with Clovis Oncology that assesses HRD status using an algorithm comprising two elements
  - **tBRCAm status**
  - **Genomic LOH (high or low)**
- A tumour is defined as HRD negative if it is BRCAwt with low genomic LOH

- **Myriad myChoice HRD**
- Provides a score based on an assessment of three genomic scars:
  - **Loss of heterozygosity (LOH)**
  - **Telomeric allelic imbalance**
  - **Large-scale state transitions**
- A score ≥42 (on a scale of 0-100) represents a positive score (loss of DNA repair function), while a score <42 reflects a negative score (intact DNA repair function)
- Also tests for t*BRCA*m

Jenner ZB, Sood AK and Coleman RL. Future Oncol. 2016 Jun; 12(12): 1439–1456.

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA exploratory analyses

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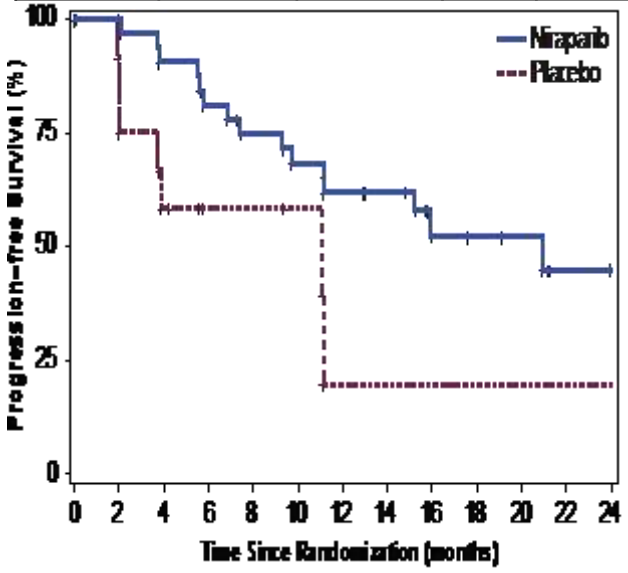
HRD-positive

HRD-negative

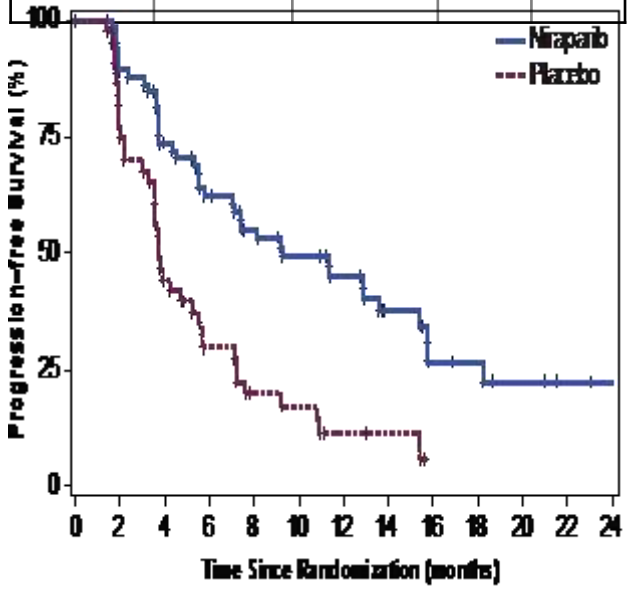
sBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=35)	**20.9** (9.7, NR)	**0.27** (0.081, 0.903) p=0.0248	62%	**52%**
Placebo (N=12)	**11.0** (2.0, NR)		19%	19%

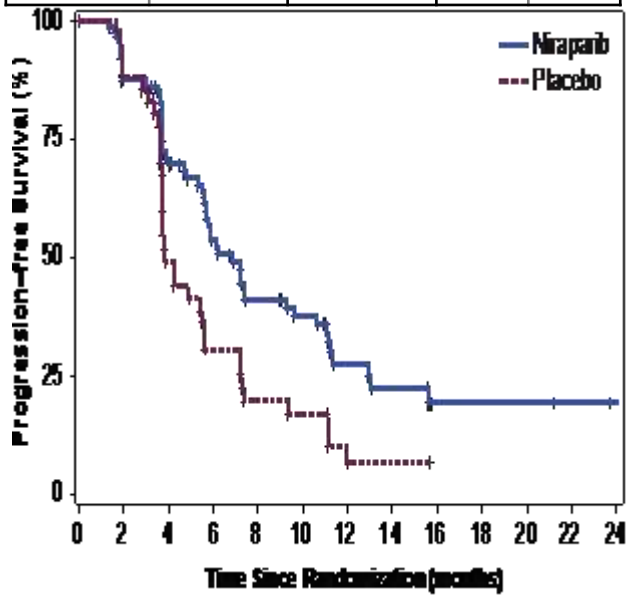


BRCAwt

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=71)	**9.3** (5.8, 15.4)	**0.38** (0.231, 0.628) p=0.0001	45%	**27%**
Placebo (N=44)	**3.7** (3.3, 5.6)		11%	6%

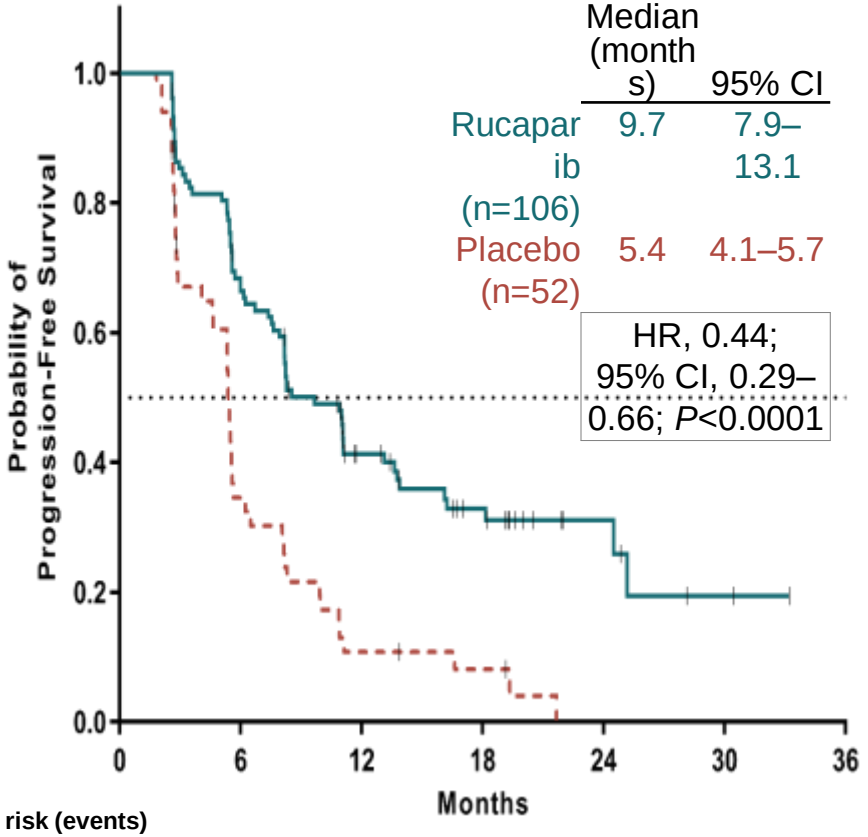


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=92)	**6.9** (5.6, 9.6)	**0.58** (0.361, 0.922) p=0.0226	27%	**19 %**
Placebo (N=42)	**3.8** (3.7, 5.6)		7%	7%



ARIEL3: Investigator-Assessed Progression-Free Survival: Patients with *BRCA* Wild-Type OC (Exploratoy Analysis)

LOH high



	Median (months)	95% CI
Rucaparib (n=106)	9.7	7.9–13.1
Placebo (n=52)	5.4	4.1–5.7

HR, 0.44; 95% CI, 0.29–0.66; *P*<0.0001

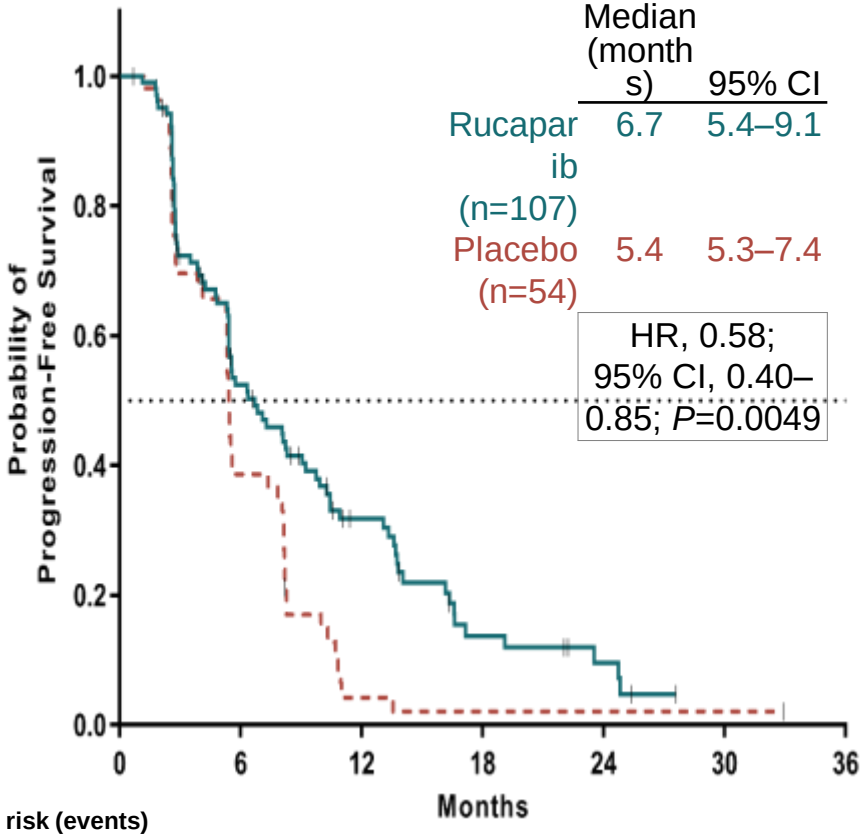
At risk (events)

Rucaparib	106 (0)	68 (32)	33 (58)	19 (64)	6 (65)	2 (67)	0 (67)
Placebo	52 (0)	16 (31)	5 (42)	3 (43)	0 (45)		

Rucaparib, 37% censored

Placebo, 13% censored

LOH low



	Median (months)	95% CI
Rucaparib (n=107)	6.7	5.4–9.1
Placebo (n=54)	5.4	5.3–7.4

HR, 0.58; 95% CI, 0.40–0.85; *P*=0.0049

At risk (events)

Rucaparib	107 (0)	49 (47)	23 (65)	8 (77)	4 (79)	0 (81)	
Placebo	54 (0)	20 (32)	2 (49)	1 (50)	1 (50)	1 (50)	0 (50)

Rucaparib, 24% censored

Placebo, 7% censored

Visit cutoff date: 15 April 2017.

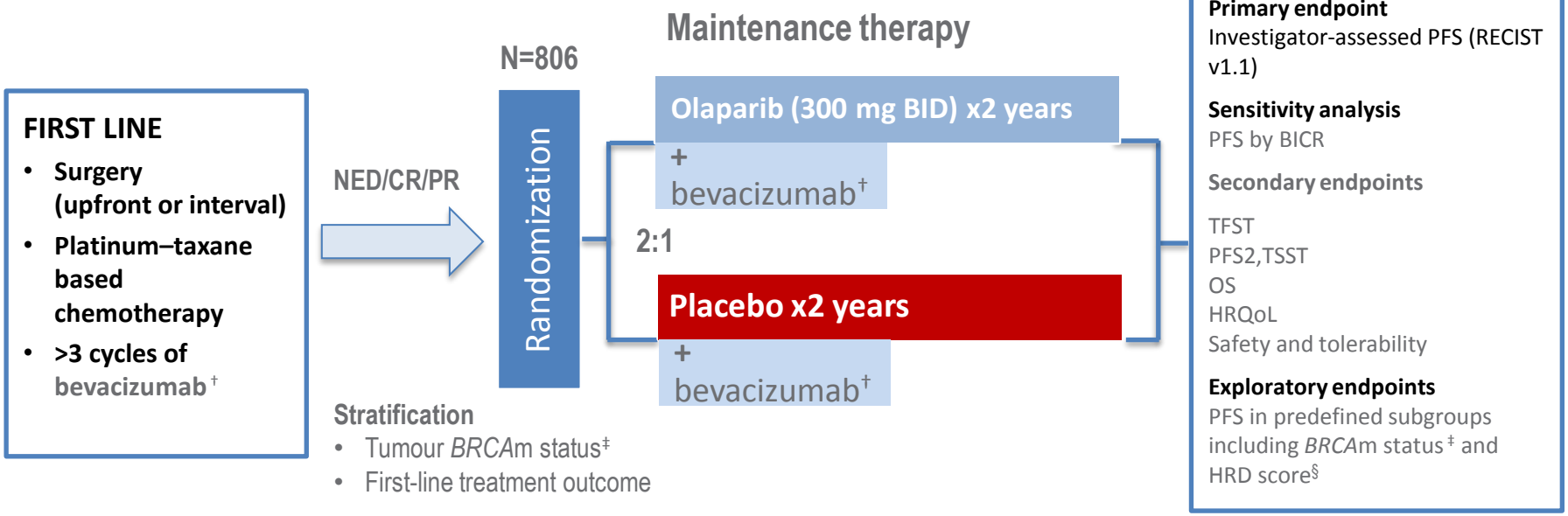
Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care

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 or endometrioid ovarian, fallopian tube or primary peritoneal cancer*



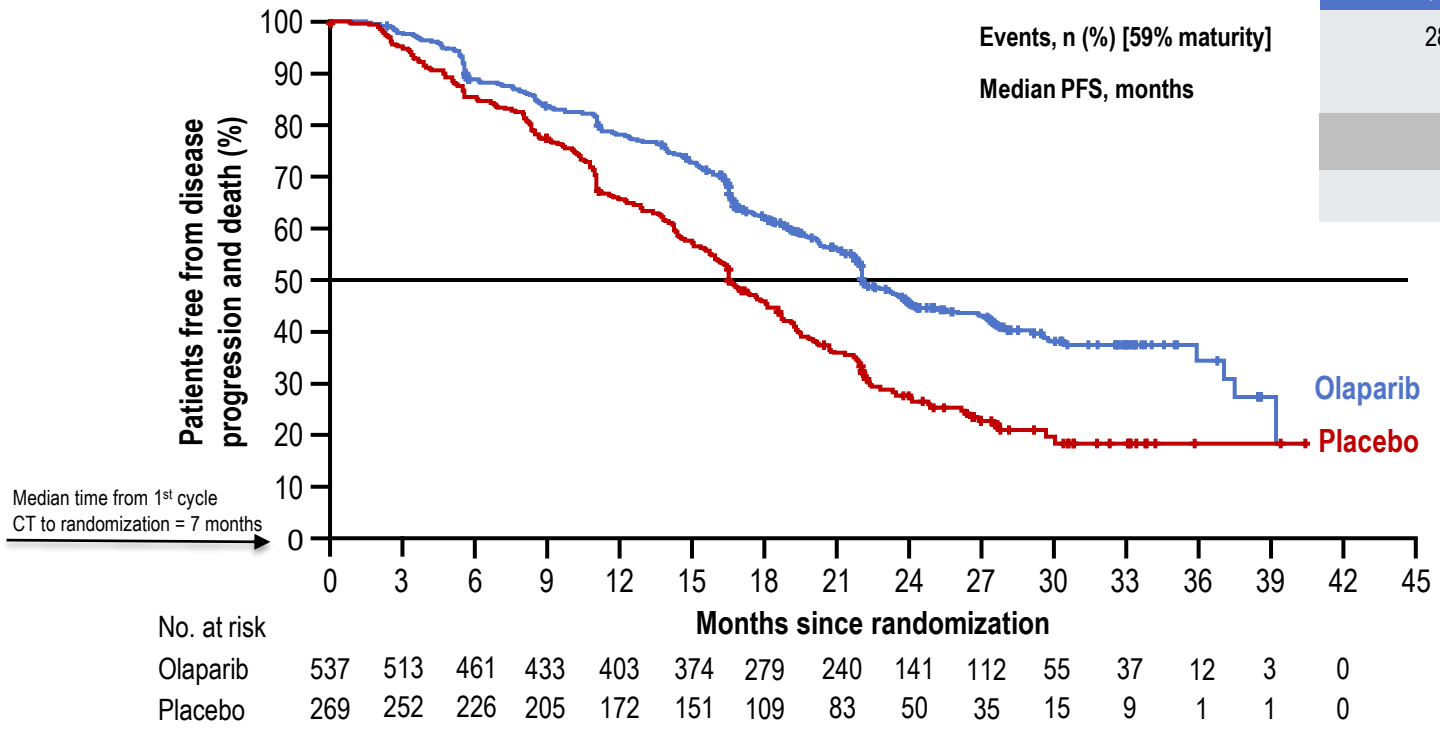
*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline BRCA1 and/or BRCA2 mutation

†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy ; ‡ by central labs; §by Myriad myChoice HRD plus

CR, complete response; HRD, homologous recombination deficiency; 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 to first subsequent therapy or death; TSST, time to second subsequent therapy or death

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		



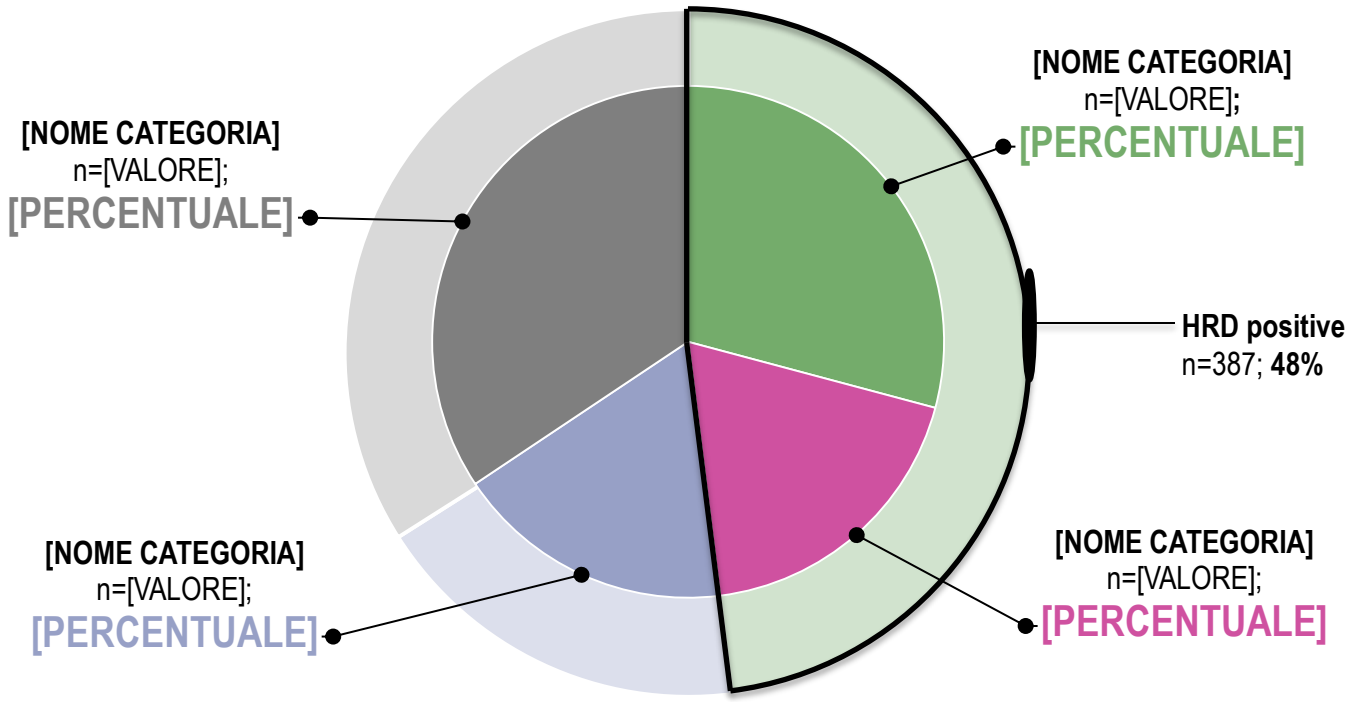
ITT, intention-to-treat population; Median follow-up was 24.0 months in the olaparib + bevacizumab arm and 22.7 months in the placebo + bevacizumab arm

Patient disposition

		Olaparib + bevacizumab	Placebo + bevacizumab
Randomized, n		537	269
Treated, n (%)		535 (99.6)	267 (99.3)
Discontinued study treatment, n (%)		331 (62)	194 (73)
	Disease progression per RECIST	182 (34)	155 (58)
	Disease progression non-RECIST	14 (3)	13 (5)
	Toxicity	109 (20)	13 (5)
	Patient decision	4 (<1)	4 (1)
	Death	1	3
	Other*	21 (4)	6 (2)
Patients receiving treatment at data-cut-off, n (%)		56 (10)	20 (7)
Median duration of treatment, months	Olaparib/placebo	17.3	15.6
	Bevacizumab	11.0	10.6

*Other includes lost to follow-up and other

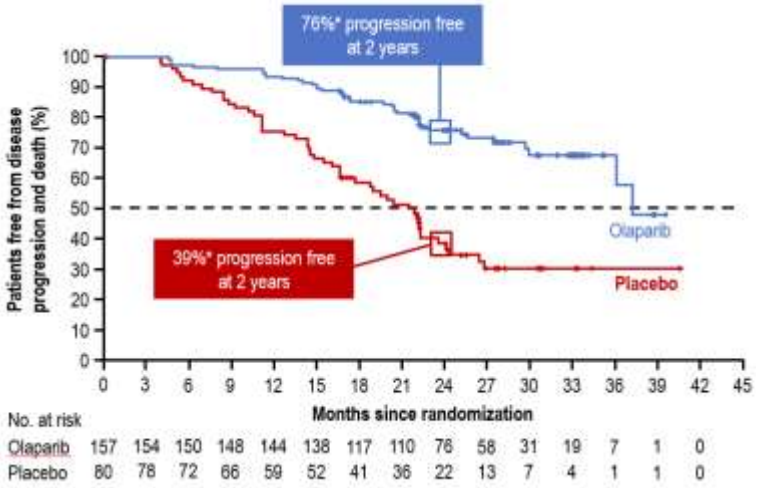
Myriad biomarker subgroups in PAOLA-1

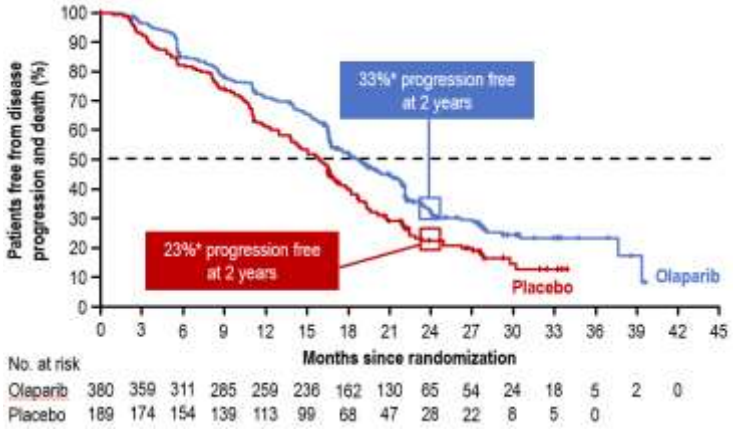


HRD positive is either tumour BRCA mutation and/or HRD score ≥42

Reasons for HRD status unknown: 3% no tumour sample available; 3% insufficient tumour sample to test; 12% HRD test failure:86 low tumour content (n=86); low DNA quality (n=1); insufficient heterozygosity (n=4)

PFS by BRCA mutation status





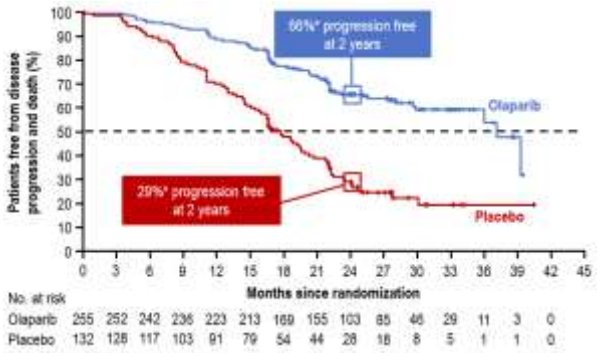
tBRCAm	Olaparib (n=157)	Placebo (n=80)
Events, n (%)	41 (26)	49 (61)
Median PFS, months	37.2	21.7
	HR 0.31	
	95% CI 0.20–0.47	

Non-tBRCAm	Olaparib (n=380)	Placebo (n=189)
Events, n (%)	239 (63)	145 (77)
Median PFS, months	18.9	16.0
	HR 0.71	
	95% CI 0.58–0.88	

*based on Kaplan-Meier estimates

PFS by HRD status

HRD-positive, including tBRCA (48%)

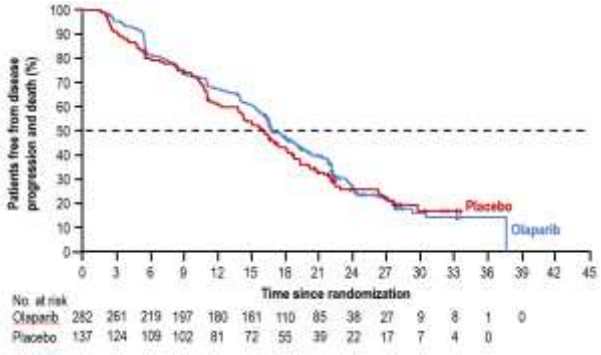


	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	37.2	17.7
	HR 0.33	
	95% CI 0.25–0.45	

HRD-positive, excluding tBRCA (19%)

	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	

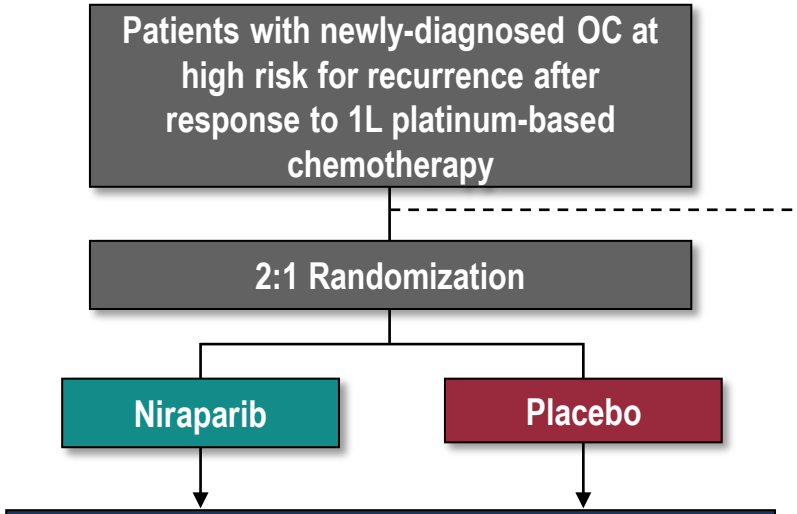
HRD-negative/unknown (34%)



	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	

HRD-positive is an HRD score ≥42 *based on Kaplan-Meier estimates

PRIMA/ENGOT-OV26/GOG-3012 Trial Design



Stratification Factors

- Neoadjuvant chemotherapy administered: Yes or no
- Best response to first platinum therapy: CR or PR
- Tissue homologous recombination test status: deficient or proficient/not-determined

Endpoint assessment

Primary Endpoint: Progression-free survival by BICR

Key Secondary Endpoint: Overall Survival
Secondary Endpoints: PFS2, TFST, PRO, Safety

Body weight ≥77 kg and platelets ≥150,000/µL started with 300 mg QD;
Body weight <77 kg and/or platelets <150,000/µL started with 200 mg QD

- A **hierarchical testing** method was performed for the **primary endpoint** in the **homologous recombination deficient patients**, followed by the **overall population**.
  - Statistical assumption: a hazard ratio benefit in PFS of
    - 0.5 in homologous recombination deficient patients
    - 0.65 in the overall population
  - >90% statistical power and one-sided type I error of 0.025

1L, first-line; BICR, blinded independent central review; CR, complete response; OC, ovarian cancer; OS, overall survival; PFS2, progression-free survival 2; PR partial response; PRO, patient-reported outcomes; TFST, time to first subsequent therapy.

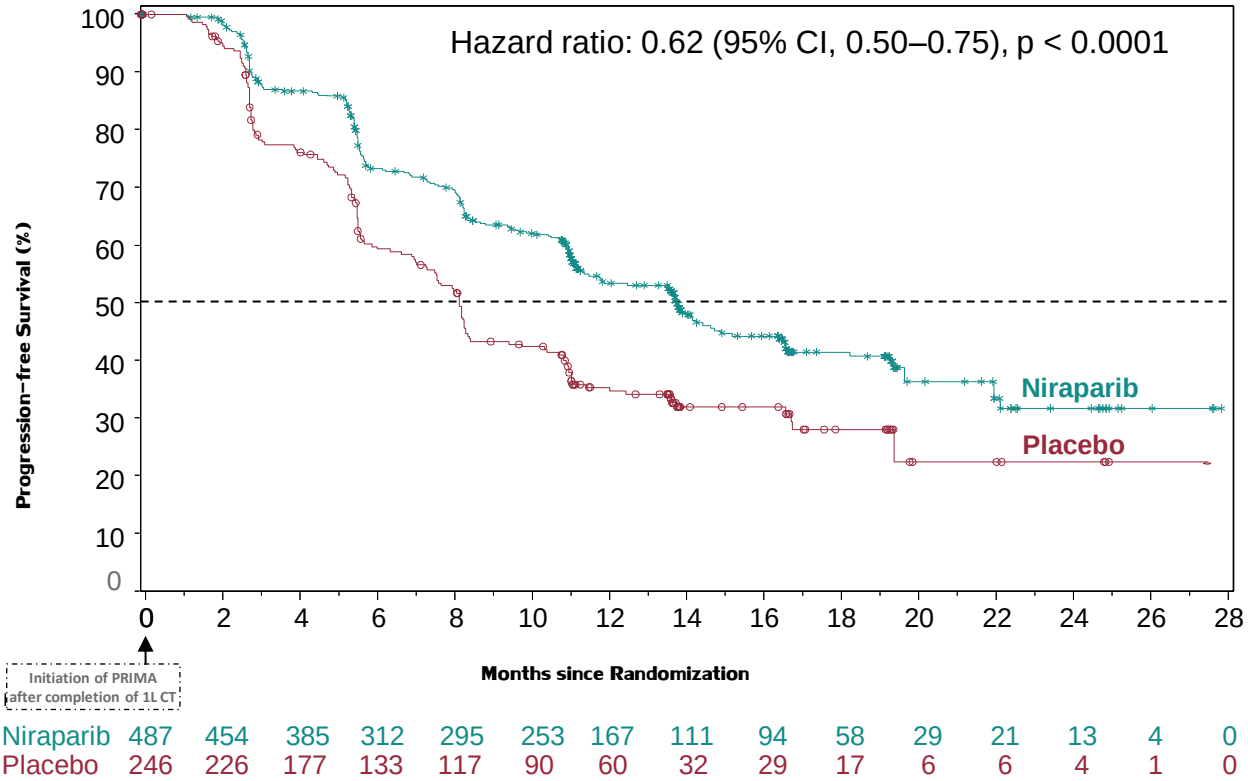
PRIMA Patient Characteristics and Baseline Demographics

Characteristic	Niraparib (n=487)	Placebo (n=246)	Overall (N=733)
Age, median (range), years	62 (32, 85)	62 (33,88)	62 (32, 88)
Weight, median, kg	66	66	66
Stage at initial diagnosis, n (%)			
III	318 (65)	158 (64)	476 (65)
IV	169 (35)	88 (36)	257 (35)
Prior NACT, n (%)			
Yes	322 (66)	167 (68)	489 (67)
No	165 (34)	79 (32)	244 (33)
Best response to platinum-based CT, n (%)			
CR	337 (69)	172 (70)	509 (69)
PR	150 (31)	74 (30)	224 (31)
Homologous recombination test status, n (%)			
HRd	247 (51)	126 (51)	373 (51)
*BRCA*mut	152 (31)	71 (29)	223 (30)
*BRCA*wt	95 (20)	55 (22)	150 (20)
HRp	169 (35)	80 (33)	249 (34)
HRnd	71 (15)	40 (16)	111 (15)

- 35% of patients were Stage IV
- 67% received NACT
- 99.6% with Stage III had residual disease post PDS
- 31% achieved a PR to 1L CT
- 51% had HRd tumors
- 30% had *BRCA*mut tumors

1L, first-line; CR, complete response; CT, chemotherapy; HRd, homologous recombination deficient; HRp, homologous recombination proficient; HRnd, Homologous recombination not determined; mut, mutation; NACT, neoadjuvant chemotherapy; PR, partial response; wt, wild-type.

PRIMA Primary Endpoint, PFS Benefit in the Overall Population

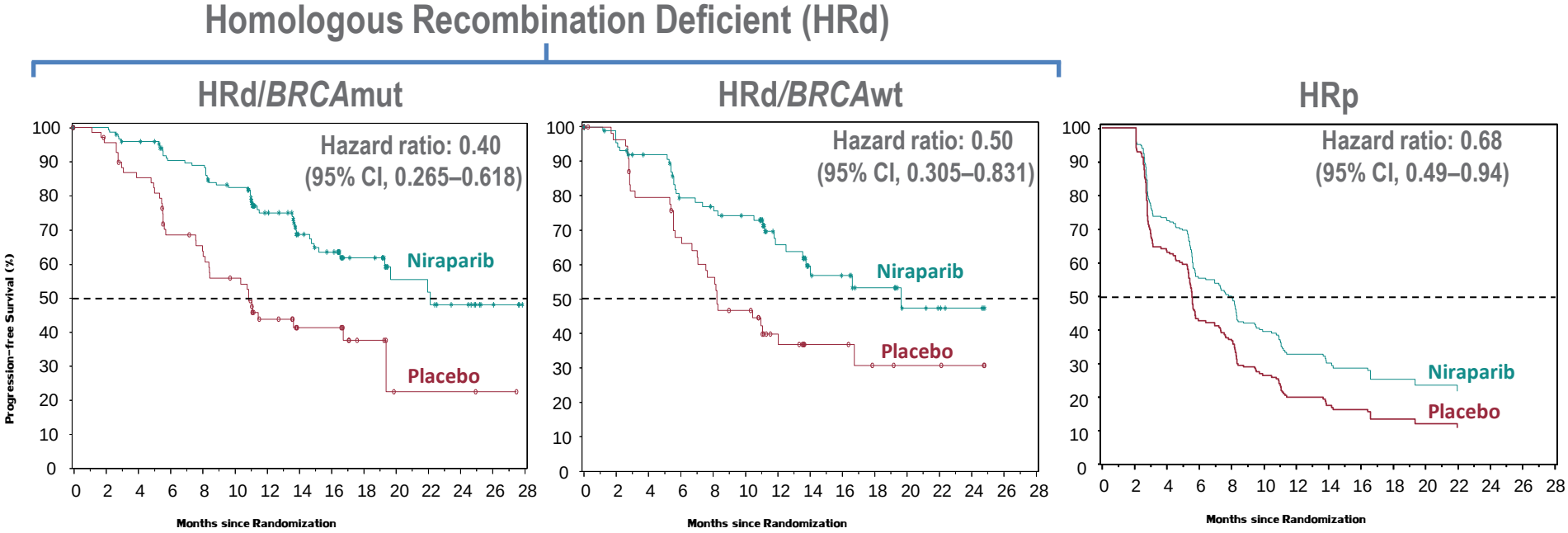


	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	**13.8 (11.5–14.9)**	**8.2 (7.3–8.5)**
Patients without PD or death (%)		
6 months	**73%**	**60%**
12 months	**53%**	**35%**
18 months	**42%**	**28%**

38% reduction in risk of relapse or death with niraparib

CI, confidence interval; Tx, Treatment; NE, not estimable; PD, progressive disease; PFS, progression-free survival
Discordance in PFS event between investigator assessment vs BICR ≈12%

PRIMA: PFS Benefit in Biomarker Subgroups



- Niraparib provided similar clinical benefit in the HRd subgroups (*BRCA*mut and *BRCA*wt)
- A continuum of niraparib benefit was observed across biomarker subgroups
  - HRd/*BRCA*mut > HRd/*BRCA*wt > HRp

CI, confidence interval; CR, complete response; HRd, homologous recombination deficient; HRp, homologous recombination proficient; HRnd, Homologous recombination not determined; mut, mutation; PFS, Progression-free survival PR, partial response; wt, wild-type.

VELIA/GOG-3005: Integration of veliparib (V) with front-line chemotherapy and maintenance in women with high-grade serous carcinoma of ovarian, fallopian tube, or primary peritoneal origin (HGSC)

Robert L. Coleman[1], Gini F. Fleming[2], Mark F. Brady[3], Elizabeth M. Swisher[4], Karina D. Steffensen[5], Michael Friedlander[6], Aikou Okamoto[7], Kathleen N. Moore[8], Noa Ben-Baruch[9], Theresa L. Werner[10], Ana Oaknin[11], Joo-Hyun Nam[12], Charles A. Leath III[13], Shibani Nicum[14], David Cella[15], Danielle M. Sullivan[16], Peter J. Ansell[16], Minh H. Dinh[16], Carol Aghajanian[17], Michael A. Bookman[18]

[1]The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [2]The University of Chicago Medicine, Chicago, IL, USA;[3]NRG Oncology Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY, USA; [4]University of Washington, Seattle, Washington, USA; [5]Vejle University Hospital of Southern Denmark, Vejle, Denmark; [6]Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia; [7]The Jikei University School of Medicine, Tokyo, Japan; [8]Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [9]Kaplan Medical Center, Rehovot, Israel;[10]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA;[11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [13]University of Alabama at Birmingham, Birmingham, AL, USA; [14]Oxford University Hospitals, Oxford, United Kingdom;[15]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA;[16]AbbVie Inc., North Chicago, IL, USA; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA;[18]Kaiser Permanente Northern California, San Francisco, CA, USA

Study Design: VELIA/GOG-3005 (NCT02470585)

Patient Population

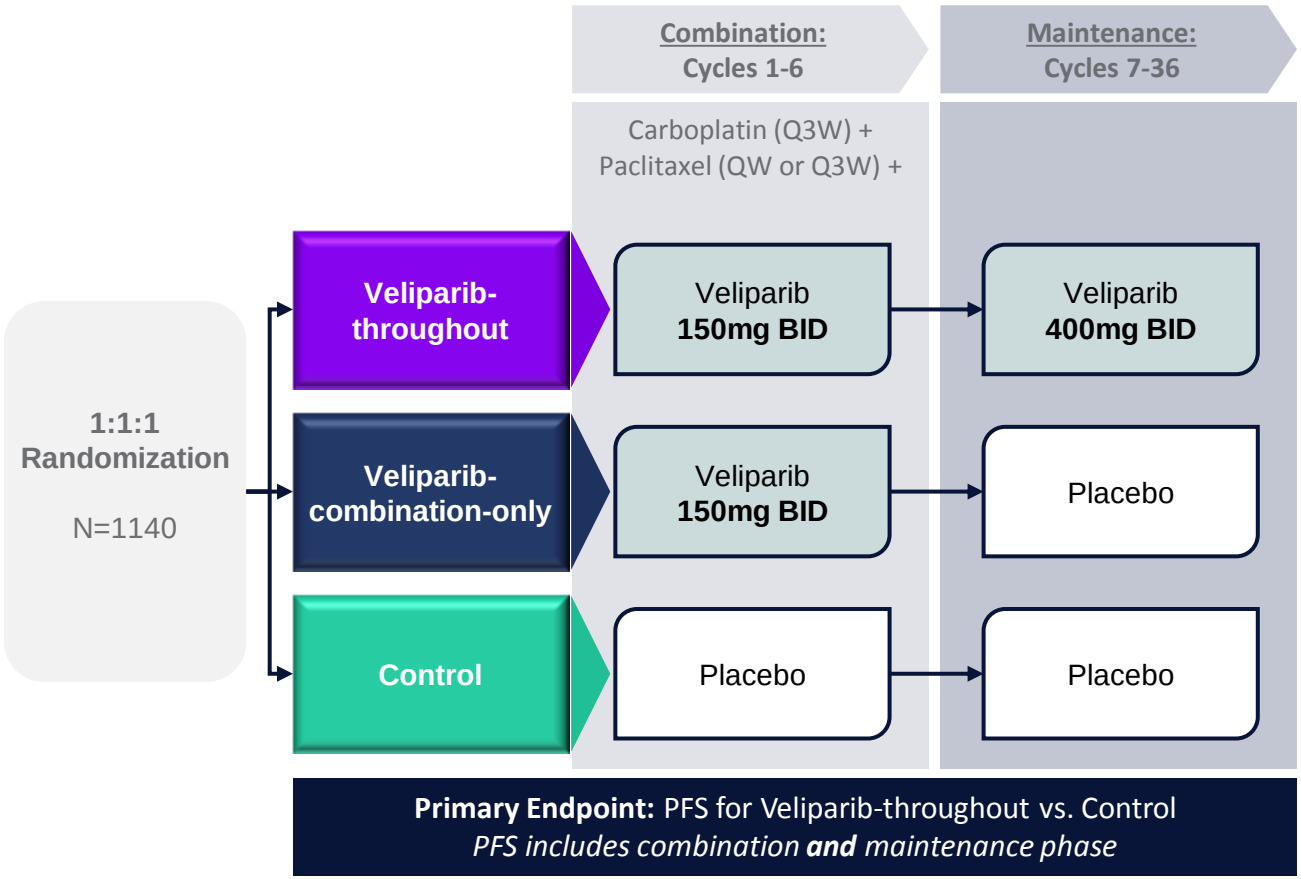
- High-Grade Serous Cancer
- FIGO Stage III or IV
- No Prior Systemic Therapy
- ECOG 0 to 2
- No CNS Metastases

Stratification Factors

- Stage of Disease
- Region
- Primary vs Interval Cytoreduction
- Residual Disease
- Chemotherapy Regimen*
- g*BRCA* Status **

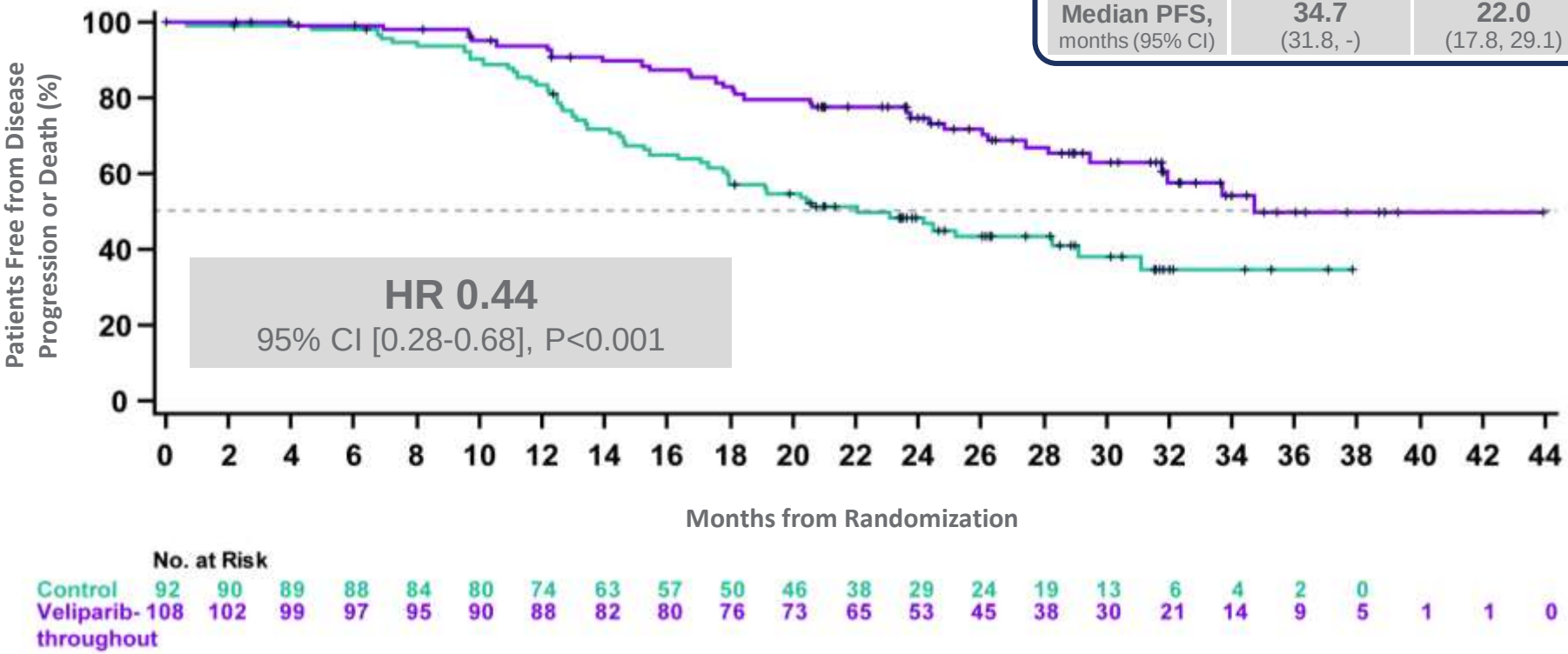
* Carboplatin AUC 6 Q3W + Paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W

** Added as stratification factor ~14 months after trial initiation due to noted imbalance



PFS by Investigator Assessment *BRCA*m Population

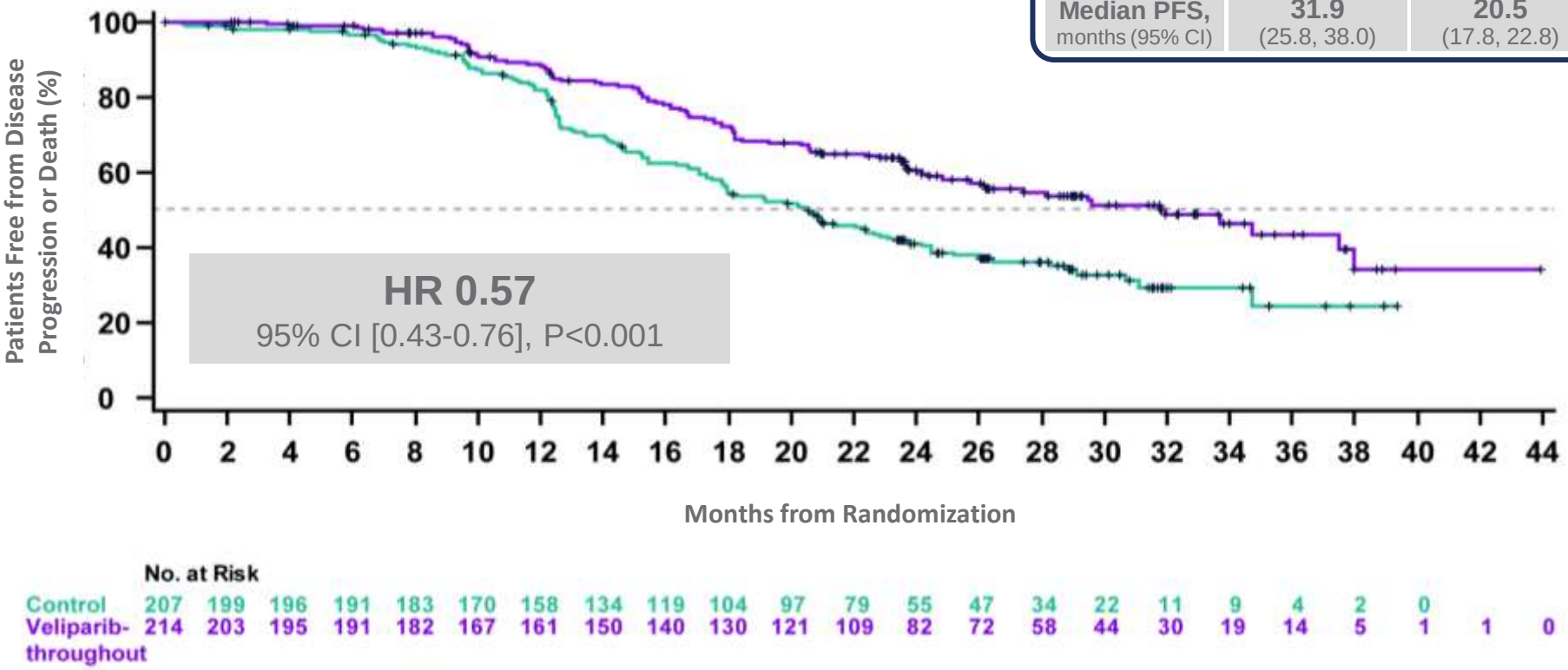
*BRCA*m	Veliparib-throughout	Control
Events (%)	34/108 (31.5)	51/92 (55.4)
Median PFS, months (95% CI)	**34.7** (31.8, -)	**22.0** (17.8, 29.1)



Median duration of follow-up was 28 months at the time of database lock.

PFS by Investigator Assessment HRD Population

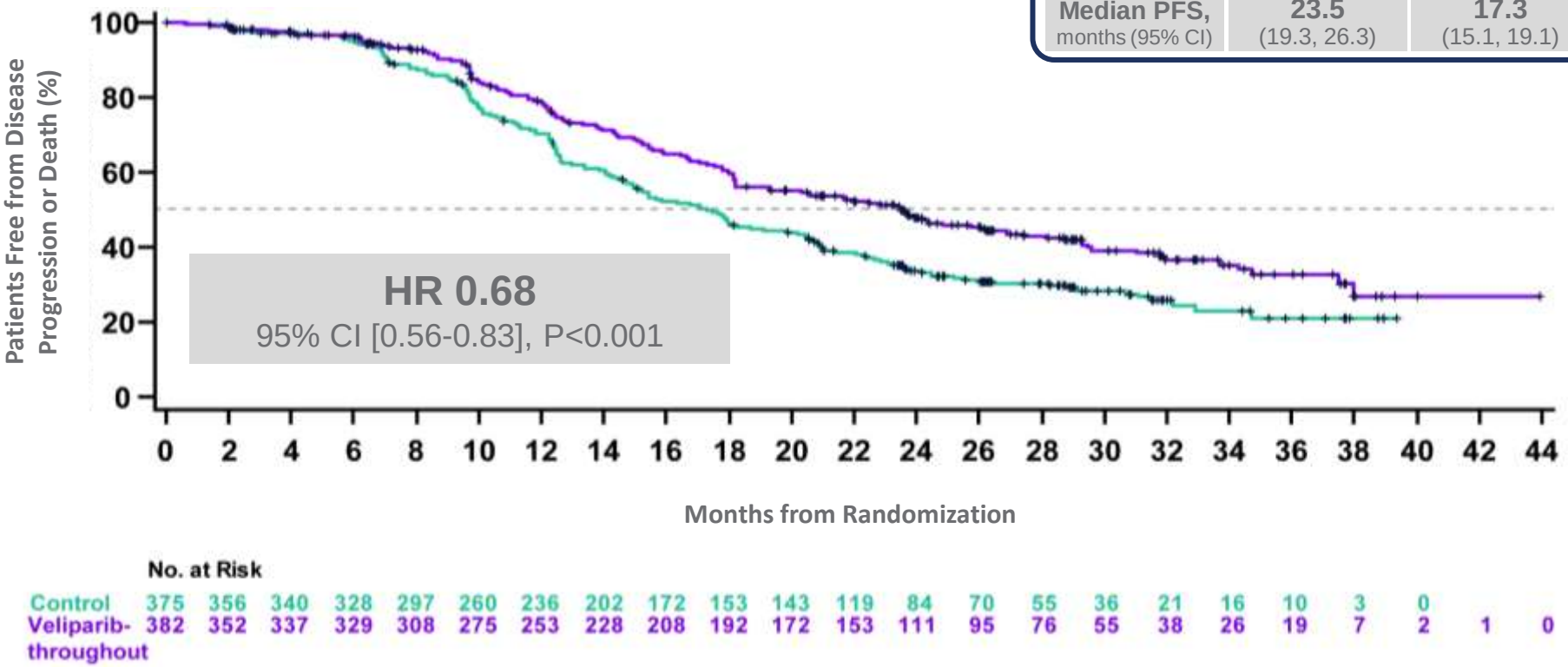
HRD	Veliparib-throughout	Control
Events (%)	87/214 (40.7)	124/207 (59.9)
Median PFS, months (95% CI)	**31.9** (25.8, 38.0)	**20.5** (17.8, 22.8)



Median duration of follow-up was 28 months at the time of database lock.

PFS by Investigator Assessment
ITT Population

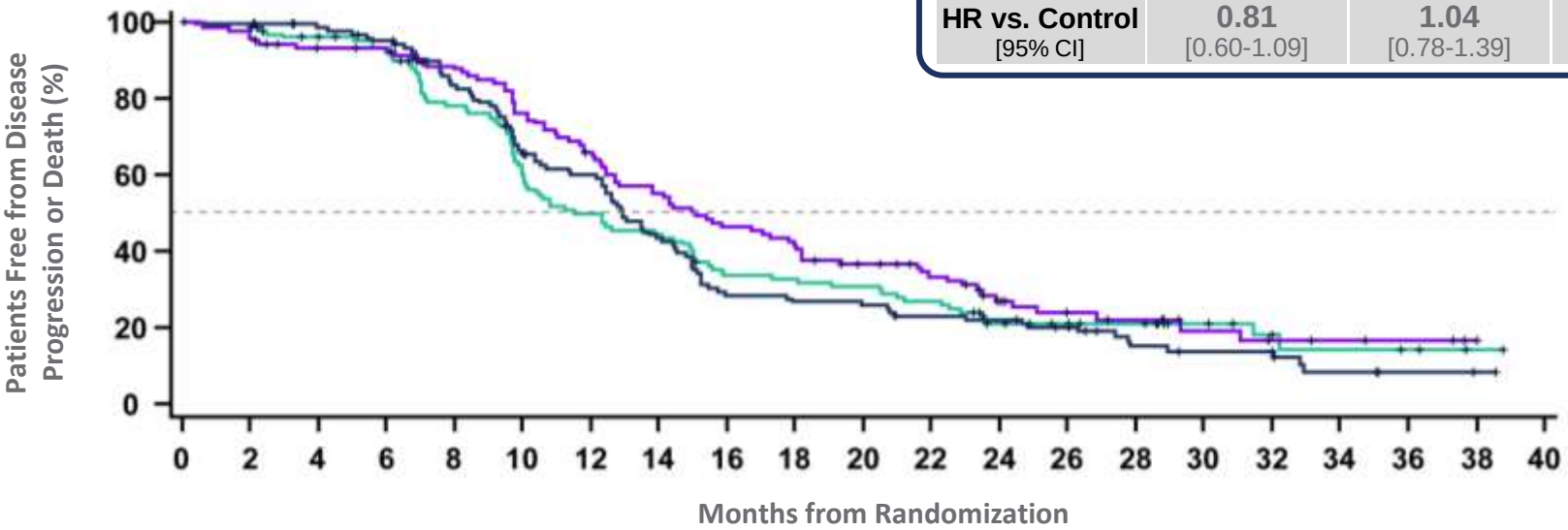
ITT	Veliparib-throughout	Control
Events (%)	191/382 (50.0)	237/375 (63.2)
Median PFS, months (95% CI)	**23.5** (19.3, 26.3)	**17.3** (15.1, 19.1)



Median duration of follow-up was 28 months at the time of database lock.

PFS: Non-HRD Population

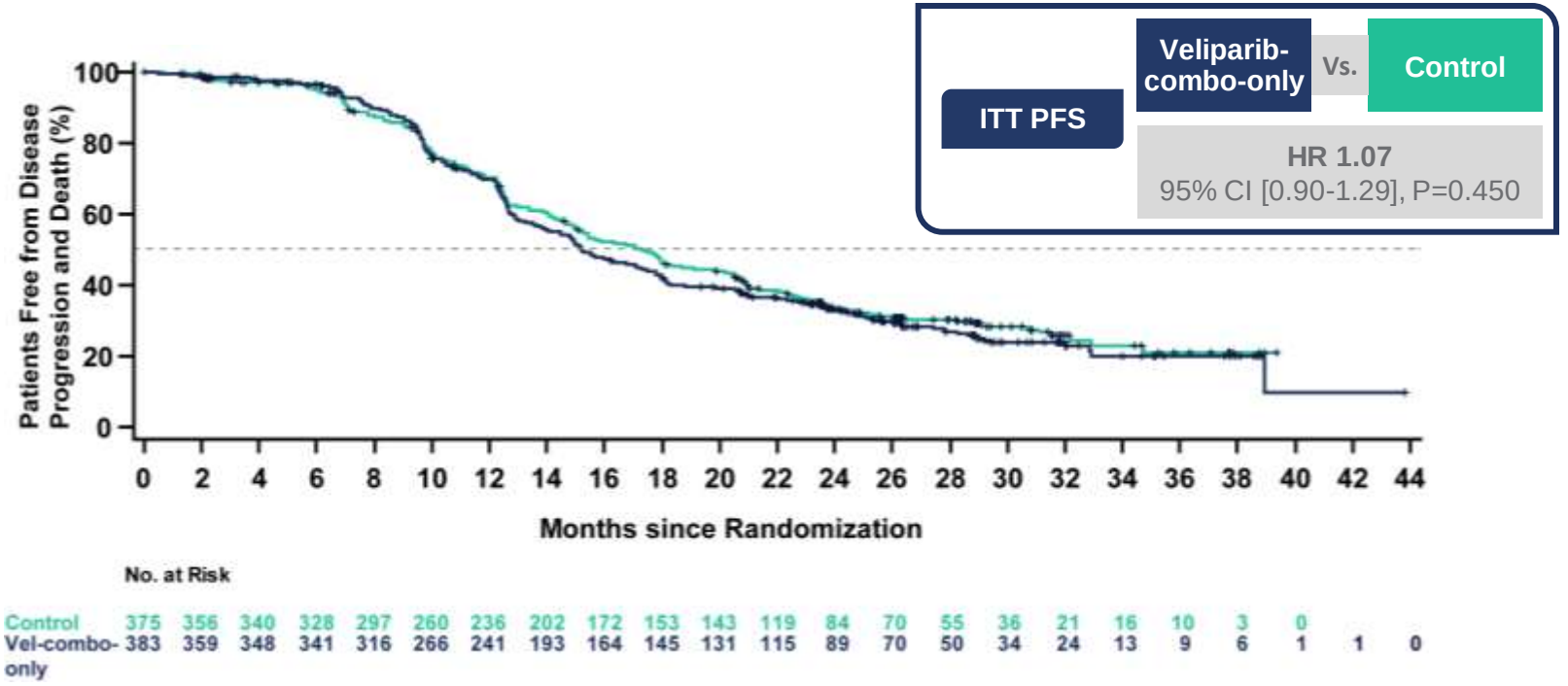
Non-HRD	Veliparib-throughout	Veliparib-combo-only	Control
Median PFS, months (95% CI)	15.0 (12.7, 18.0)	12.9 (12.2, 14.5)	11.5 (10.1, 14.9)
HR vs. Control [95% CI]	0.81 [0.60-1.09]	1.04 [0.78-1.39]	–



No. at Risk

Control	124	118	111	105	87	66	55	49	36	35	33	29	19	16	14	9	6	4	3	1	0
Vel-combo	123	118	113	108	93	73	65	47	31	29	28	24	23	19	12	10	10	4	2	1	0
Veliparib-throughout	125	110	103	102	94	81	68	57	48	43	35	29	18	13	11	7	5	4	3	1	0

PFS for Veliparib-combo-only vs. Control



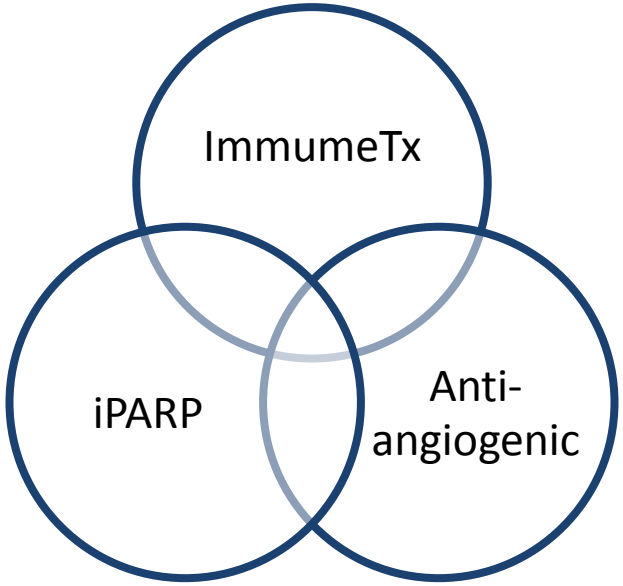
Across *BRCA*m, HRD, and ITT, the veliparib-combo-only arm and the control arm demonstrated similar PFS

Summary of Adverse Events

	Veliparib-throughout N = 377	Veliparib-combo-only N = 376	Control N = 371
Any Treatment-Emergent AE	377 (100)	376 (100)	371 (100)
Grade 3 or 4 AEs	332 (88)	329 (88)	285 (77)
Serious AEs	141 (37)	129 (34)	141 (38)
AEs Leading to Discontinuation of Veliparib/Placebo	97 (26)	49 (13)	43 (12)
Related to Disease Progression	6 (2)	11 (3)	18 (5)
Not Related to Disease Progression (Combination: Cycles 1-6)	40 (11)	29 (8)	22 (6)
Not Related to Disease Progression (Maintenance: Cycles 7-36) *	53 (14)	9 (3)	3 (1)
AEs Leading to Death	8 (2)	7 (2)	6 (2)

* Most discontinuations of veliparib occurred during Cycles 7-8

OC TREATMENT: FUTURE APPROACHES



The combinations

Studies with immune checkpoint inhibitors in ovarian cancer

Checkpoint inhibitor	Inclusion	Phase	N	Prior Therapy (no. lines)	Response Rate	Reference
Anti-CTLA-4						
Ipilimumab	recurrent OC	I	9	Vaccination and >1	10% PR, 33% SD	Hodi et al. 2008
Anti-PD-1						
Nivolumab	PROC	II	20	≥4 (55%)	10% CR, 5% PR, 30% SD	Hamanishi et al. 2015
Pembrolizumab (KEYNOTE-28)	Recurrent OC	Ib	26	≥3 (65%)	4% CR 8% PR 23% SD	Varga et al. 2015
Pembrolizumab (KEYNOTE-100)	Recurrent OC Cohort A: TFI of ≥ 3 to 12 months Cohort B: TFI of ≥ 3 months	II	376	A: 1-3 B: 4-6	8% ORR (17.3% ORR CPS>10)	Matulonis et al. 2018
Anti-PD-L1						
Avelumab	PROC	Ib	124	≥3 (58%)	9.7% PR 44% SD	Disis et al. 2016
Atezolizumab	Recurrent OC	Ib	12	>6 (58%)	25% ORR	Infante et al. 2016
BMS-936559	Recurrent OC	I	17	>1	6% PR, 18% SD	Brahmer et al. 2012

Marth et al., IJGC 2019

Studies with immune checkpoint inhibitors in ovarian cancer

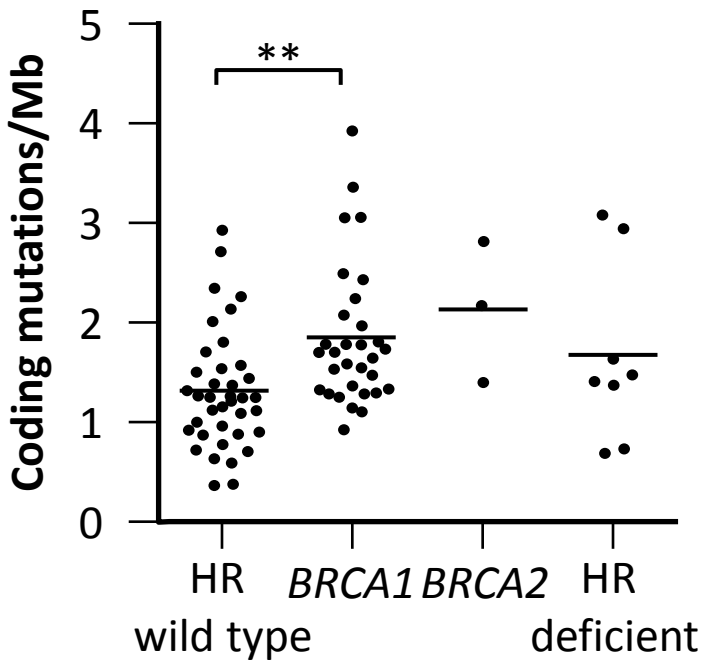
Checkpoint inhibitor	Inclusion	Phase	N	Prior Therapy (no. lines)	Response Rate	Reference
Anti-CTLA-4						
Ipilimumab	recurrent OC	I	9	Vaccination and >1	10% PR, 33% SD	Hodi et al. 2008
Anti-PD-1						
Nivolumab	PROC	II	20	≥4 (55%)	10% CR, 5% PR,	Hamanishi et al. 2015
Pembrolizumab (KEYNOTE-28)	Recurrent					Varga et al. 2015
Pembrolizumab (KEYNOTE-100)	Recurrent Cohort A: TFI of months Cohort B: TFI of ≥ 3 months			B: 4-6	(17.3% ORR CPS>10)	Matulonis et al. 2018
Anti-PD-L1						
Avelumab	PROC	Ib	124	≥3 (58%)	9.7% PR 44% SD	Disis et al. 2016
Atezolizumab	Recurrent OC	Ib	12	>6 (58%)	25% ORR	Infante et al. 2016
BMS-936559	Recurrent OC	I	17	>1	6% PR, 18% SD	Brahmer et al. 2012

ORR 6%-25%

Marth et al., IJGC 2019

PARP Inhibitors in Combination with Immuno-Oncology Agents: Rationale

- Tumours with deleterious mutations in DNA repair genes (including *BRCA1/2*) have a high mutational load and a higher number of protein-coding mutations (neoepitopes) due to the inability of the cancer cell to repair DNA damage effectively[1]
- *BRCA1/2* mutant and HR-deficient tumours are correlated with higher PD-L1 expression and CD8 T-cell infiltration that predict PD-(L)1 mAb response[2]



1. Patch AM et al. *Nature.* 2015;521:489–494;
2. Strickland K et al. ASCO 2015; Abstract 5512

	PRIMA	Imagyn050 ENGOT OV39	Athena	First	ENGOT OV43	Duo-O	Total
Sponsor	Tesaro	Roche	Clovis	Tessaro	Merck	Astra Zeneca	
Group leader	GEICO(GOG)	GOG(MITO)	GOG(NCRI)	GINECO (GOG??)	BGOG(leading) – unsure whether GOG will join as supporting groups	AGO(GOG)	
ENGOT Model	**C**	C	C		C	C	
Randomisation	After CT	Upfront	Maintenance	Upfront	Upfront	Upfront	
Bev in Standardarm	No	Yes	No	Optional	Optional	Yes	
Exp. Arm	Nira	- TC-Bev-Atezo	- Ruca-Nivolu - Ruca - Nivolu	- Nira - Nira + O42	BRCA+: Ola + Pembro BRCA-: Pembro Pembro+Ola	- Durva - Durva+Ola	
NACT allowed	Yes	Yes	Yes	Yes	Yes	Yes	
RT=0	**NO after PDS** **YES after IDS**	No but Under discussion	CR/NED after CT	No	Yes	Yes	
Endpoint	PFS	PFS + OS	PFS	PFS	PFS+OS	PFS	
MITO	X 9	X 12	6	A 8	C 10	B 10	

Rationale for Combining Cancer Immunotherapy With Anti-VEGF

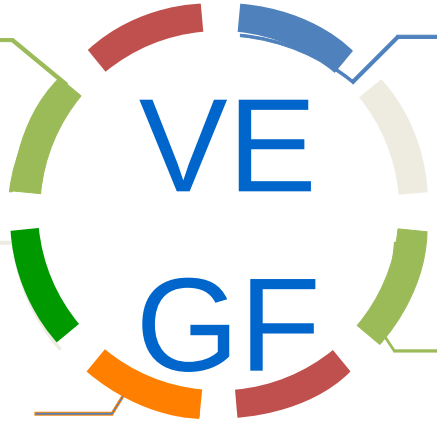
Reduce TILs

Induces abnormal tumor vasculature

Reducing T-cell trafficking and infiltration into the tumor bed[5,6]

Reduces lymphocyte adhesion to vessel walls

Decreases immune-cell recruitment to the tumor site[4]



Immunosuppressive

Inhibits T-cell function

Binds to VEGFR2 on T cells[1]

Kills T cells by tumor endothelium-produced FasL[2]

Stimulates immunosuppressive regulatory T cells[2]

Inhibits dendritic cell function

Drives them into an immature state[3]

VEGF(R), vascular endothelial growth factor (receptor)

1. Gavalas NG, et al. *Br J Cancer.* 2012;107(11):1869-1875. 2. Terme M, et al. *Cancer Res.* 2013;73(2):539-549. 3. Coukos G, et al. *Br J Cancer.* 2005;92(7):1182-1187 4. Bouzin C, et al. *J Immunol.* 2007;178(3):1505-1511. 5. Shrimali RK, et al. *Cancer Res.* 2010;70(15):6171-6180. 6. Chen DS, et al. *Immunity.* 2013;39(1):1-10.

Imagyn trial

- Previously untreated ovarian, fallopian tube, or peritoneal cancer
- Post-operative Stage III w/macroscopic residual disease, Stage IV
- ECOG PS 0-2

R
1:1

Carboplatin AUC 6 q3wk
Paclitaxel 175 mg/m^2 q3wk
Bev 15 mg/kg q3wk
Bev 15 mg/kg X 16 cycles
Placebo q3w X 22 cycles

Carboplatin AUC 6 q3wk
Paclitaxel 175 mg/m^2 q3wk
Bev 15 mg/kg q3wk
Bev 15 mg/kg X 16 cycles
Atezo 1200 mg q3w X 22 cycles

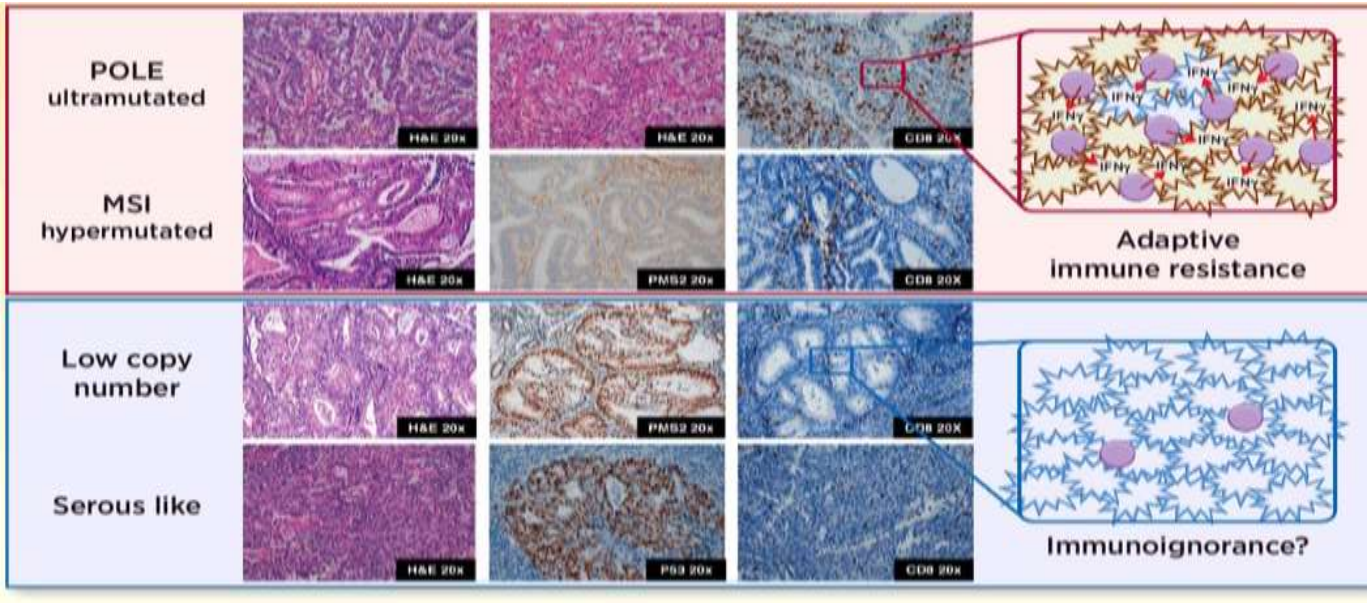
No cross-over

Stratification variables

- Stage/debulking status
- ECOG PS
- PDL1 IC0 vs IC1+
- Adjuvant/Neo-adjuvant

GOG Foundation/Partners

Immunotherapy in endometrial cancer



- Piulats, JM. Clin Cancer Res. 2016;22(23):5623-5; Sharma, P. and Allison, JP. Science. 2015;348(6230):56-61.

Checkpoint Inhibitors in Endometrial Cancer

Author	Patient Population	IO	Results
Le et al. (2018)	MMRd tumors incl. 2 EC	Pembrolizumab	ORR 71%
Ott et al. (2017) Keynote 028	24 PD-L1+ pts.	Pembrolizumab	ORR 13%
Keynote 158	Multicohort MSI-high incl 17 EC	Pembrolizumab	ORR 38%
Fader et al. (2018)	MMRd tumors recurrent EC	Pembrolizumab	ORR 56% DCR 89%
Santin et al. (2016)	2 pts POLE and MSI-high	Nivolumab	Prolonged Response
Hasegava et al (2018)	23 metastatic EC pts.	Atezolizumab	ORR 13%
Oankin et al. (2019) GARNET	MSI-high/advanced EC	Dostarlimab	ORR 52%
Antill et al. (2019) PHAEDRA	Advanced/recurrent EC	Durvalumab	ORR MMR-d 43% ORR MMR-p 3%
Konstaninopoulos et al. (2019)	Recurrent/persisten EC	Avelumab	ORR MMR-d 27% ORR MMR-p 6%

Checkpoint Inhibitors in Endometrial Cancer

Author	Patient Population	IO	Results
Le et al. (2018)	MMRd tumors incl. 2 EC	Pembrolizumab	ORR 71%
Ott et al. (2017) Keynote 028	24 PD-L1+ pts.	Pembrolizumab	ORR 13%
Keynote 15		Pembrolizumab	ORR 38%
Fader et al.		Pembrolizumab	ORR 56% DCR 89%
Santin et al		Nivolumab	Prolonged Response
Hasegava et al (2018)	23 metastatic EC pts.	Atezolizumab	ORR 13%
Oankin et al. (2019) GARNET	MSI-high/advanced EC	Dostarlimab	ORR 52%
Antill et al. (2019) PHAEDRA	Advanced/recurrent EC	Durvalumab	ORR MMR-d 43% ORR MMR-p 3%
Konstaninopoulos et al. (2019)	Recurrent/persisten EC	Avelumab	ORR MMR-d 27% ORR MMR-p 6%

MMR-deficient: ORR 27%-71%
MMR-proficient: ORR 3%-13%

Clinical Cancer Research

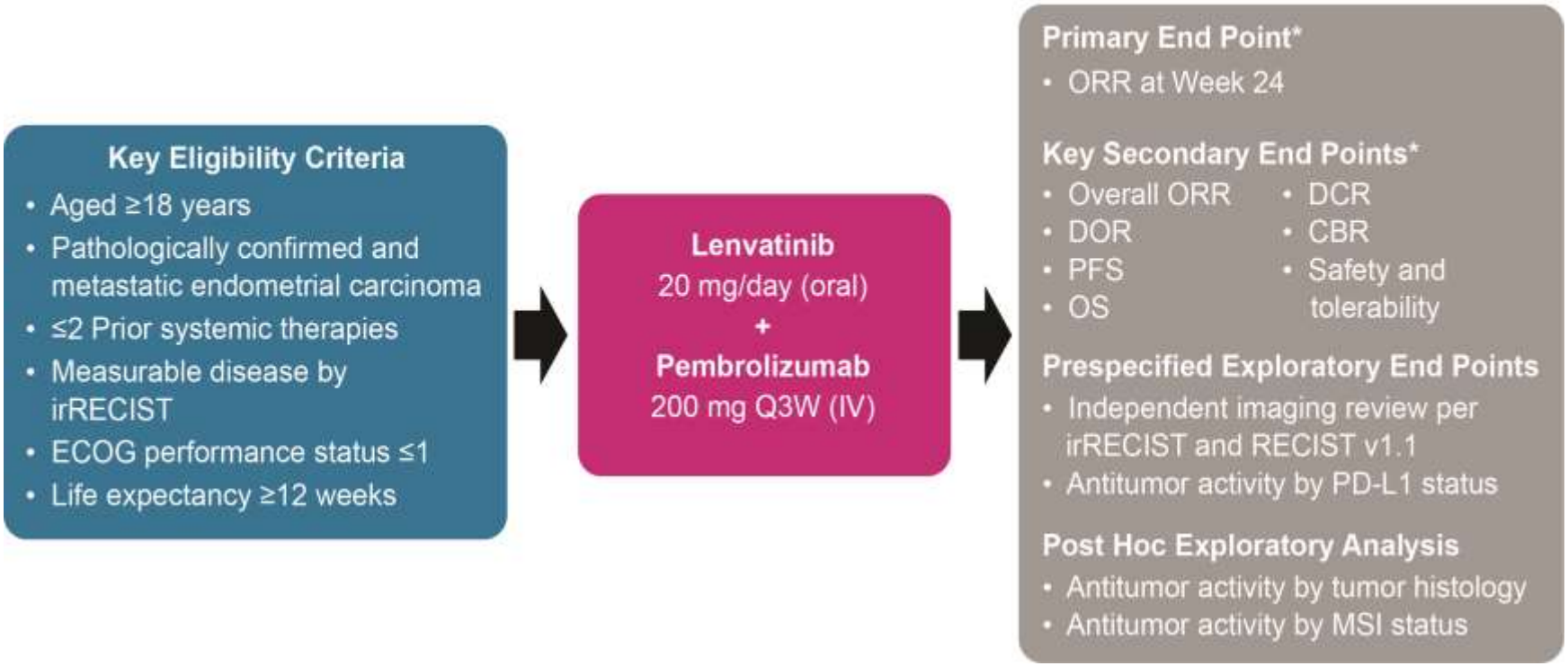
CCR Drug Updates

FDA Approval Summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors

2017 THE FIRST AGNOSTIC APPROVAL IN THE HISTORY OF ONCOLOGY

Lenvatinib and Pembrolizumab in Patients With Advanced Endometrial Cancer

Phase 2, Open-label, Single-arm Study (NCT02501096)



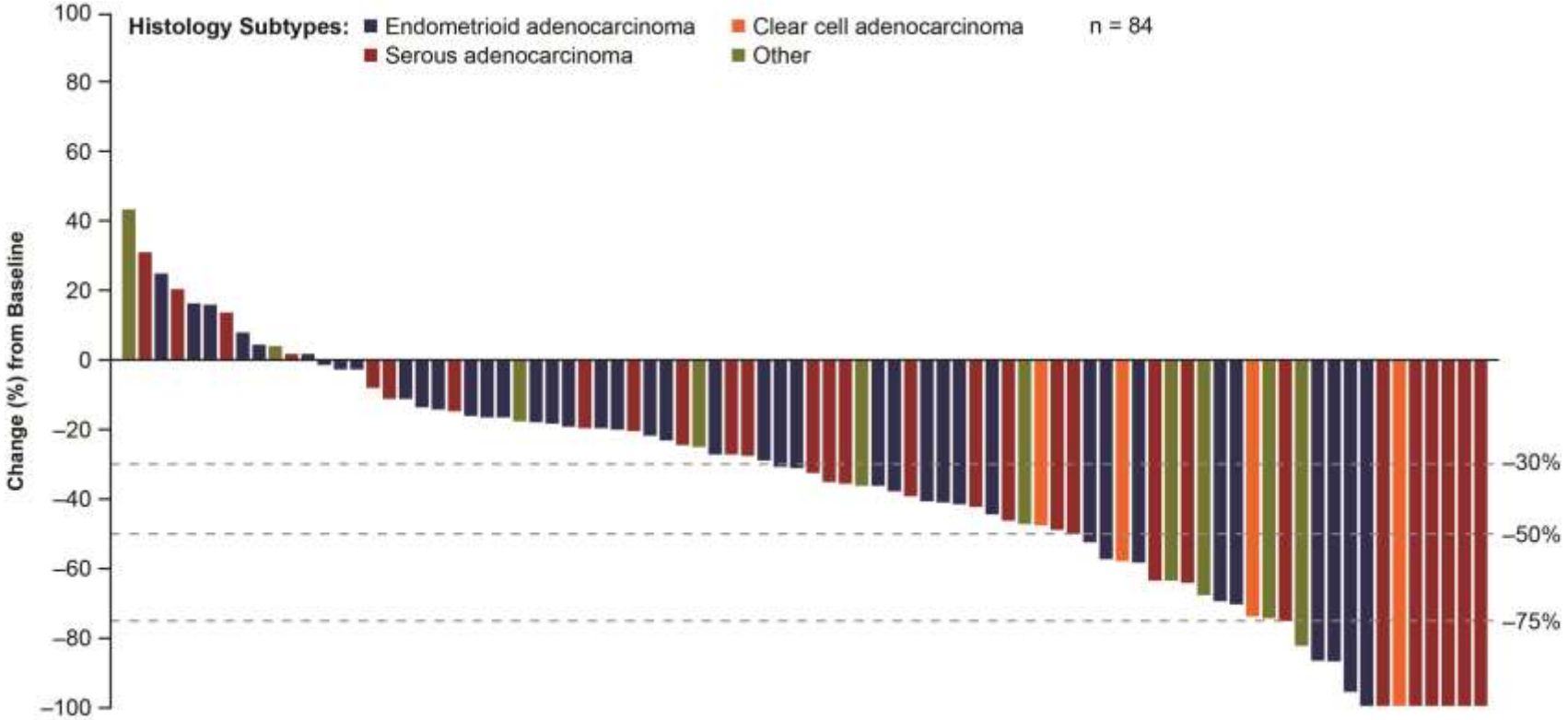
*Tumor responses for primary and secondary end points were assessed by the investigator per irRECIST.

Tumor Response (Investigator Assessment; irRECIST)

Response Category	Total (n = 108)[a]	Not MSI-H or dMMR (n = 94)	MSI-H / dMMR (n = 11)
	Week 24		
Objective response rate (complete response + partial response), n (%)[b]	41 (38.0)	34 (36.2)	7 (63.6)
95% CI	28.8, 47.8	26.5, 46.7	30.8, 89.1
Response Category	**At Data Cutoff**		
Best overall response, n (%)			
Complete response	8 (7.4)	7 (7.4)	1 (9.1)
Partial response	34 (31.5)	28 (29.8)	6 (54.5)
Stable disease	49 (45.4)	44 (46.8)	3 (27.3)
Progressive disease	12 (11.1)	10 (10.6)	1 (9.1)
Not evaluable	5 (4.6)	5 (5.3)	0
Objective response rate (complete response + partial response), n (%)	42 (38.9)	35 (37.2)	7 (63.6)
95% CI[c]	29.7, 48.7	27.5, 47.8	30.8, 89.1
Duration of response (months), median (range)[d]	21.2 (1.2+, 35.6+)	NE (1.2+, 33.8+)	21.2 (6.1+, 35.6+)

[a]The MSI or MMR status was not available for 3 patients; [b]ORR_{wk24} and the exact 95% CIs were calculated with the Clopper-Pearson method; [c]95% CIs were calculated with the Clopper-Pearson method; [d]Duration of response was estimated with the Kaplan-Meier method.

Percentage Change in Sum of Diameters of Target Lesions at Postbaseline Nadir by Histologic Subtype (Independent Imaging Review; RECIST version 1.1)



n = the number of previously treated not-MSI-H or dMMR patients with both baseline and at least 1 postbaseline target lesion assessment.

Accelerated Approval

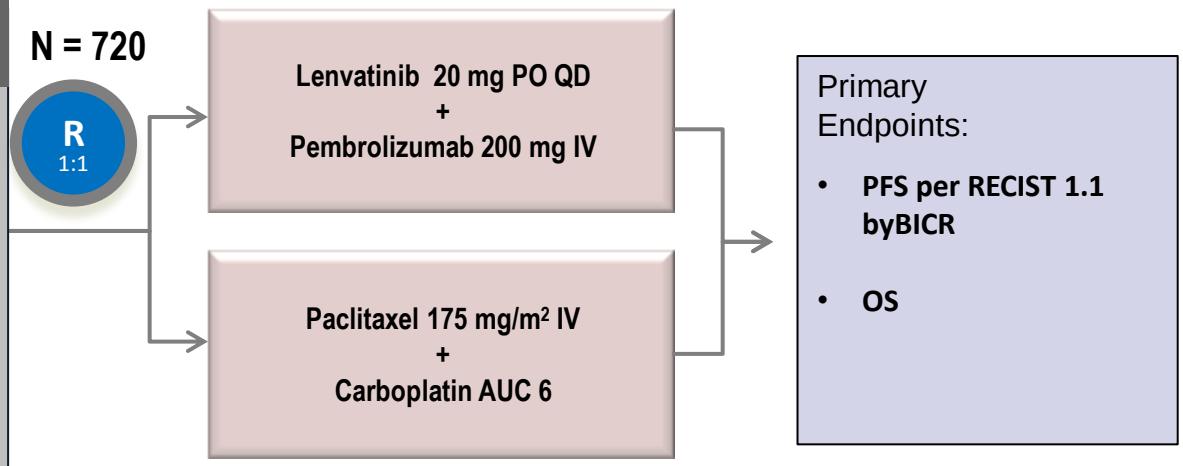
- The FDA, the Australian Therapeutic Goods Administration, and Health Canada granted simultaneous review decisions in all 3 countries on September 17, 2019
- Lenvatinib plus pembrolizumab was granted accelerated approval for the treatment of advanced endometrial carcinoma that is not MSI-H or dMMR
- Patients must have had disease progression following prior systemic therapy and must not be candidates for curative surgery or radiation

ENGOT-en9 / LEAP-001

NCT03884101 : A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma

KEY ELEGIBILITY

- Stage III, Stage IV or recurrent endometrial cancer
- Measurable disease or radiographically apparent disease by BICR
- May have received prior chemotherapy only if administered concurrently with radiation
- May have received prior radiation
- May have received prior hormonal therapy for treatment of endometrial carcinoma, provided that it was discontinued ≥1 week prior to randomization
- ECOG 0-1
- Adequate Controlled Blood pressure within 7 days prior randomization
- Available tumor tissue for determination of MMR status



Principal Investigator: Marth
Sponsor: AGO-A
Planned No. of patients: 720

Source : clinicaltrials.gov

New Proposals

- **"RAINBO" TransPORTEC Umbrella trials for HR (I-IVa) (TransPORTEC Coll.; N=1800)**
  Refining **A**djuvant treatment **IN** endometrial cancer **B**ased **O**n molecular features
  Umbrella trials (4)
- **"DOMINO" Adjuvant Immuno for MMRd HR (III) (CCTG; N=170)**
  Durvalumab as part of Post-**O**perative Therapy for **MI**smatch Repair-deficient E**N**d**O**metrial Ca *Rand. Phase II trial CTRT + observ. vs CTRT + Durvalumab maint. in resect. St. III endo MMRd*
- **"ADELE" Adjuvant Immuno in HR (III-IVa) (ANZGOG; N=60+170+400)** CTRT+CT(Portec3) + antiPD1 vs CTRT+CT (Portec3)
  Feasibility study + non-comp. phase II + phase III
- **DUAL HER2 Adjuv. Immuno in HG serous HER2+ve (III-IVa) (ANZGOG; N=81+375)**
  Rand. phase II (CT vs CT + Trastuzumab vs CT + Trastuzumab + Pertuzumab) (PFS) followed by rand. phase III (two winners)

POST ESMO: conclusions

- In ovarian cancer treatment according to histotype is the future!

- Antiangiogenic agents and parp inhibitors are changing the natual history of ovarian cancer disease.

- The best treatment algorytm is the one which allows patients to receive all the available and effective treatment options in combination or sequence.

- Immunotherapy the raising star in endometrial cancer alone or in combination with TKI's