Targeted Therapy for Ovarian and Uterine Tumors

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Discussion Outline

- Review ovarian treatment landscape
- Review uterine cancer treatment landscape
- Review new treatment indications for both

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Ovarian Cancer

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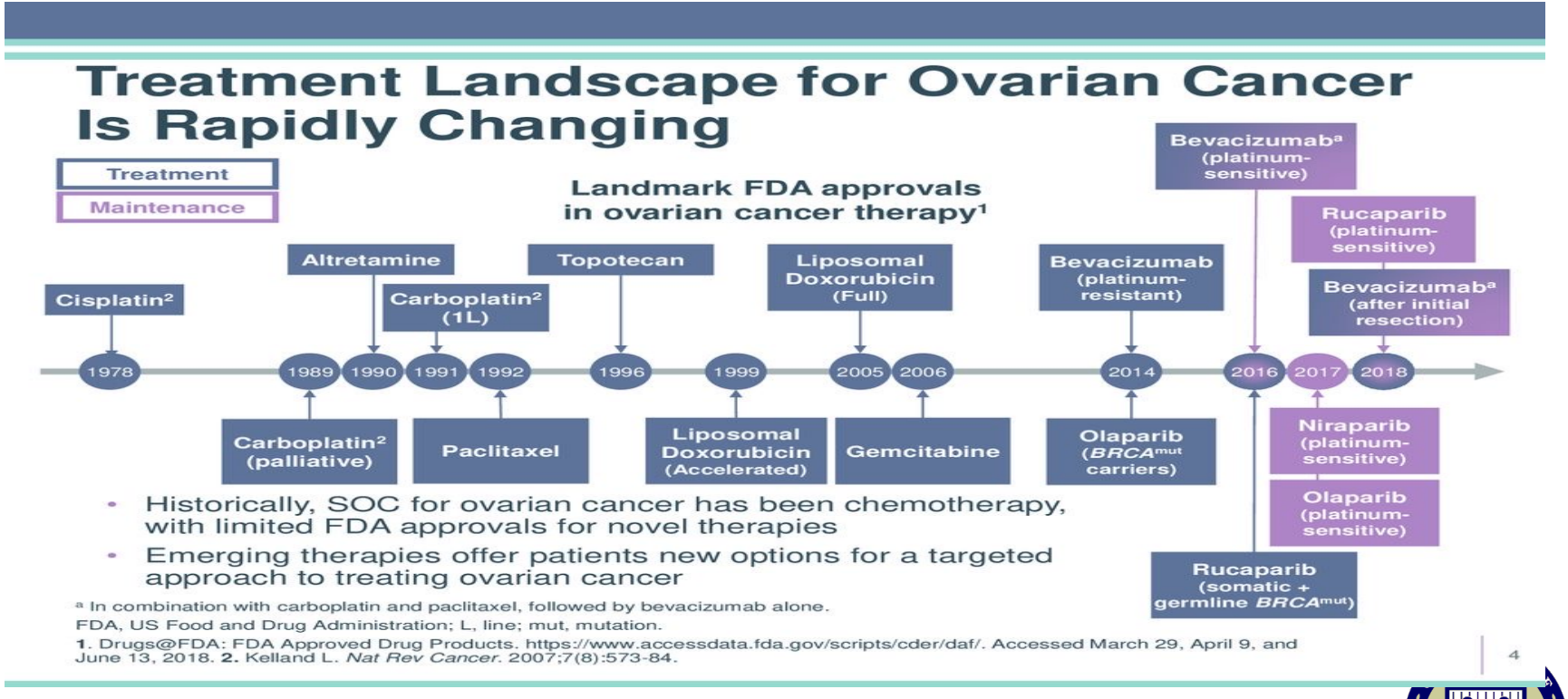
Ovarian Cancer Landscape

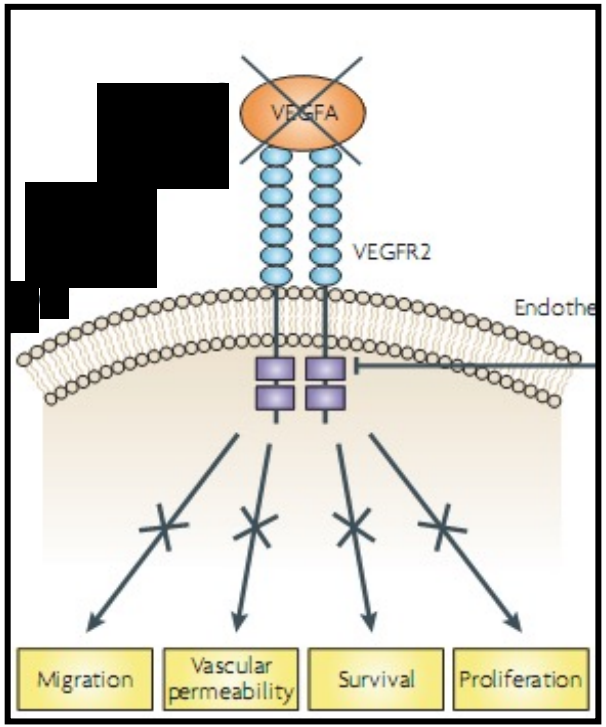


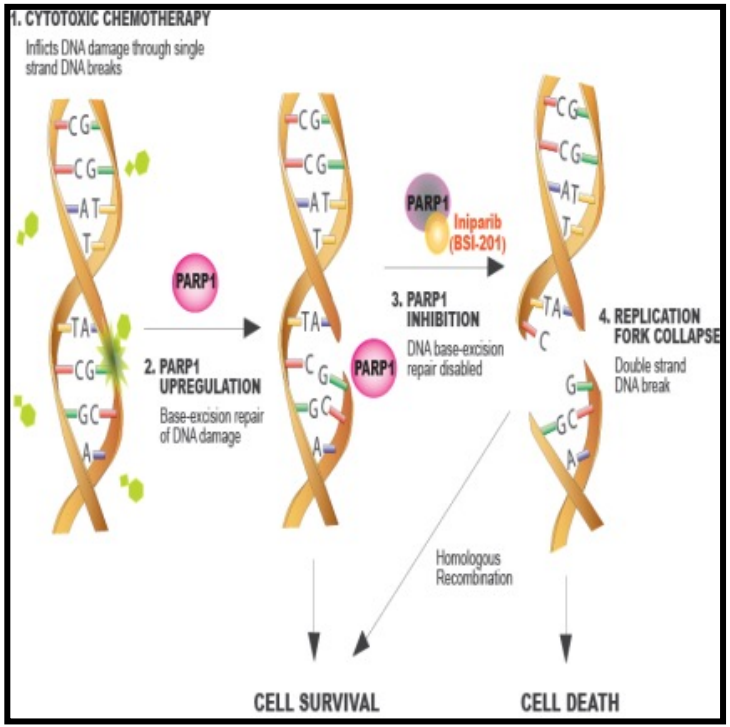
GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

4th Ovarian Cancer Consensus Conference
25 – 27 June 2010
UBC Life Sciences Institute, Vancouver, British Columbia

B-2 What Are the Promising Targets for Future Therapeutic Approaches?

- The most promising targets in clinical trials are angiogenesis and homologous recombination deficiency.





Int J Gynecol Cancer 2011:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

GOG#218

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D., for the Gynecologic Oncology Group*

The NEW ENGLAND JOURNAL of MEDICINE

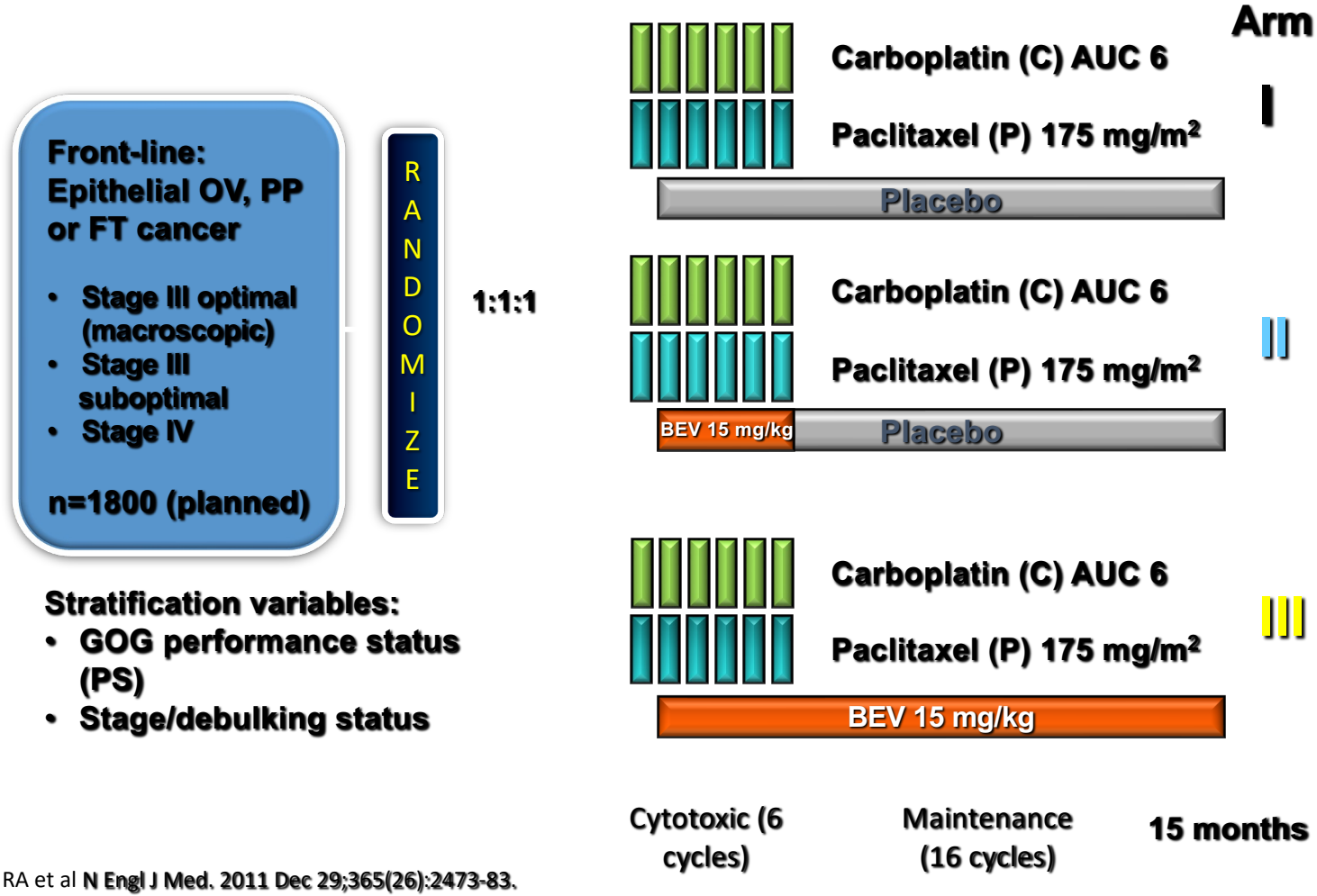
ORIGINAL ARTICLE

ICON-7

A Phase 3 Trial of Bevacizumab in Ovarian Cancer

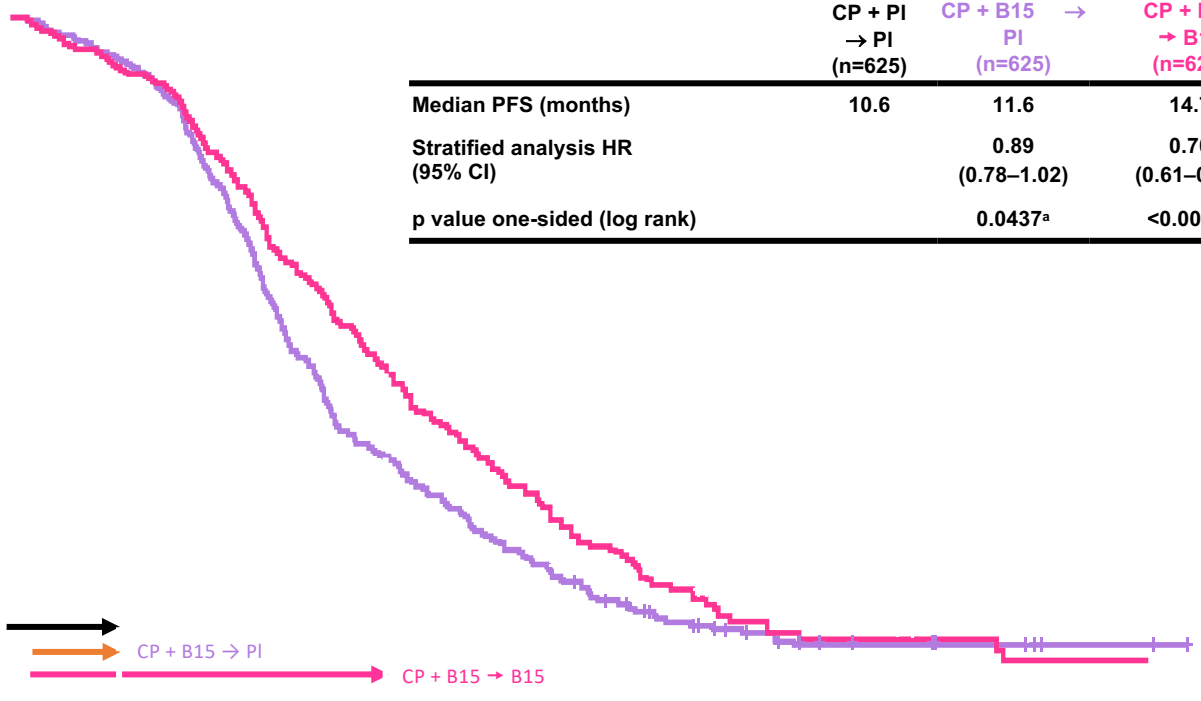
Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D., Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D., Mark S. Carey, M.D., Philip Beale, M.D., Andrés Cervantes, M.D., Christian Kurzeder, M.D., Andreas du Bois, M.D., Jalid Sehouli, M.D., Rainer Kimmig, M.D., Anne Stähle, M.D., Fiona Collinson, M.D., Sharadah Essapen, M.D., Charlie Gourley, M.D., Alain Lortholary, M.D., Frédéric Selle, M.D., Mansoor R. Mirza, M.D., Arto Leminen, M.D., Marie Plante, M.D., Dan Stark, M.D., Wendi Qian, Ph.D., Mahesh K.B. Parmar, Ph.D., and Amit M. Oza, M.D., for the ICON7 Investigators*

GOG-0218: Schema



Burger RA et al N Engl J Med. 2011 Dec 29;365(26):2473-83.

GOG-0218: significantly increased PFS with continued bevacizumab compared with standard chemotherapy



	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]

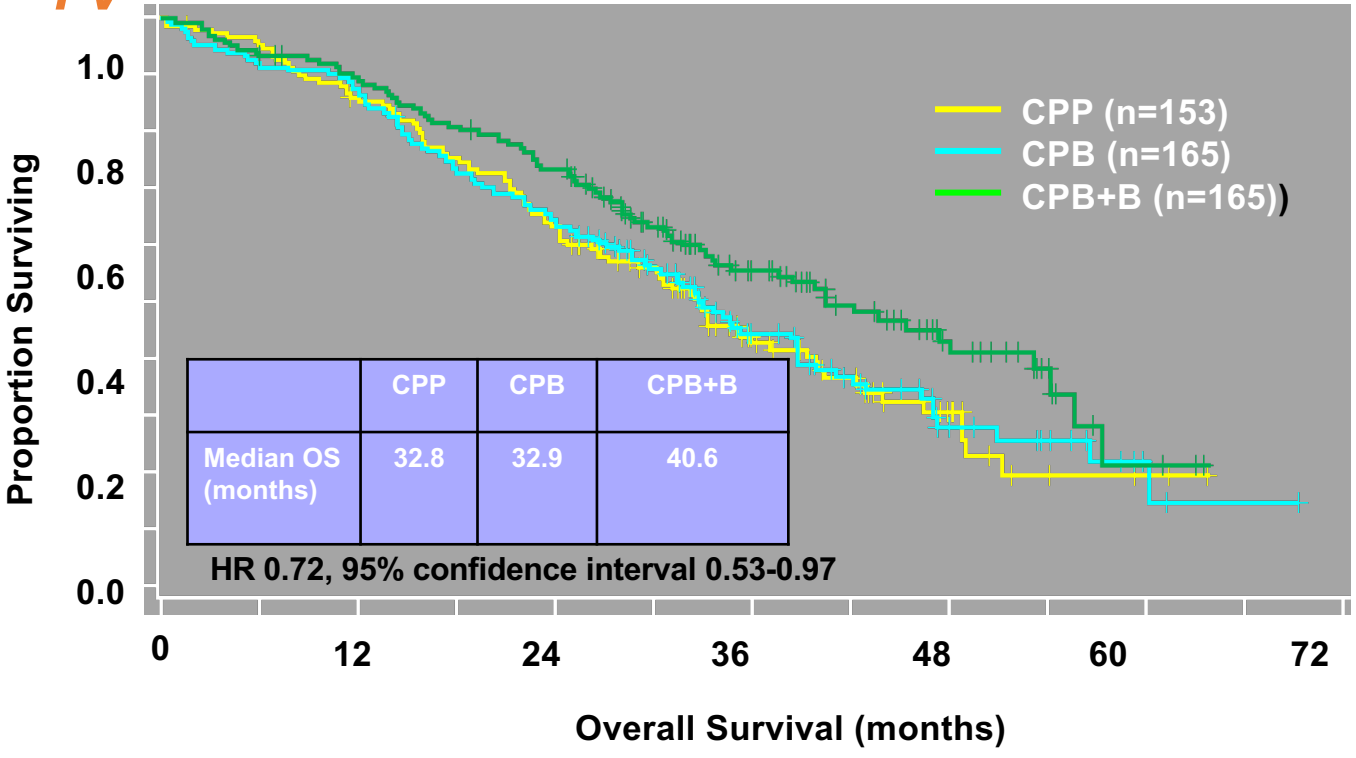
GOG-0218
CA-125 To Determine Progression

	Protocol-defined PFS analysis	CA-125-censored PFS analysis
Median PFS		
CP (Arm I)	10.3 months	12.0 months
CP + BEV → BEV (Arm III)	14.1 months	18.0 months
Absolute diff. median PFS	3.8 months	6.0 months
Hazard ratio	0.717	0.645
Censored for CA125, %		
CP (Arm I)	0	20
CP + BEV → BEV (Arm III)	0	29

Burger RA et al **N Engl J Med. 2011 Dec 29;365(26):2473-83.**

GOG-0218

Ad Hoc Survival Analysis in Stage IV



NEJM Data cut-off date August 26, 2011
(ASCO 2010 cut-off date February 5, 2010)
Randall LM et al SGO 2013

PARP inhibitors maintenance in recurrent ovarian cancer

University of Pittsburgh

NOVA: Niraparib Maintenance in Patients with Recurrent Ovarian Cancer

Phase III, multicenter, randomized, double-blind, placebo controlled study

- **Platinum-sensitive recurrent high grade serous ovarian cancer**
- **≥2 prior regimens of platinum-based chemotherapy**
- **Received at least 4 cycles platinum-based therapy and, following treatment, have an investigator-defined CR or PR with no observable residual disease of <2cm and CA-125 WNL or a decrease of >90% that was stable for at least 7 days**

N=553

Primary Endpoint: PFS by central, blinded review

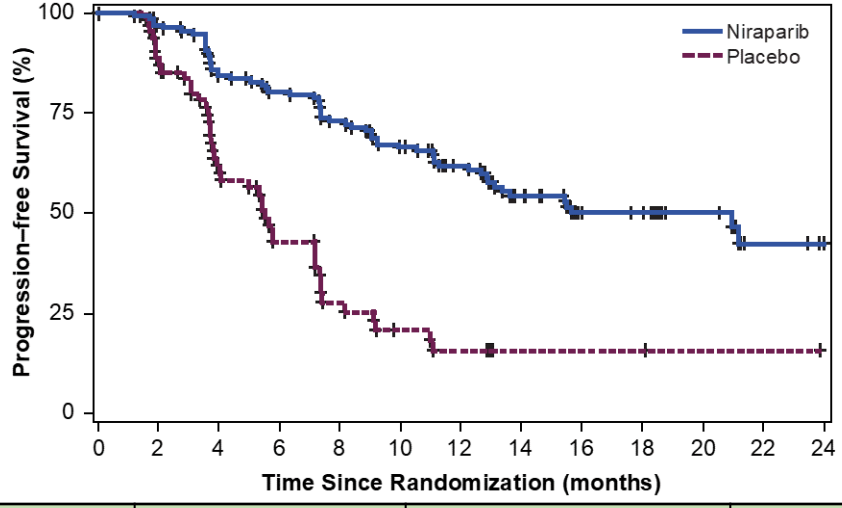
Tested at 100 events to achieve p<0.05

- **HRDpos population**
- Tested at 100 events to achieve p<0.05
- If test was positive then:
- Test overall non-gBRCAmut cohort (p<0.05

Mirza, N Engl J Med 2016; 375:2154-2164

University of Pittsburgh

NOVA: gBRCAmut Progression-Free Survival

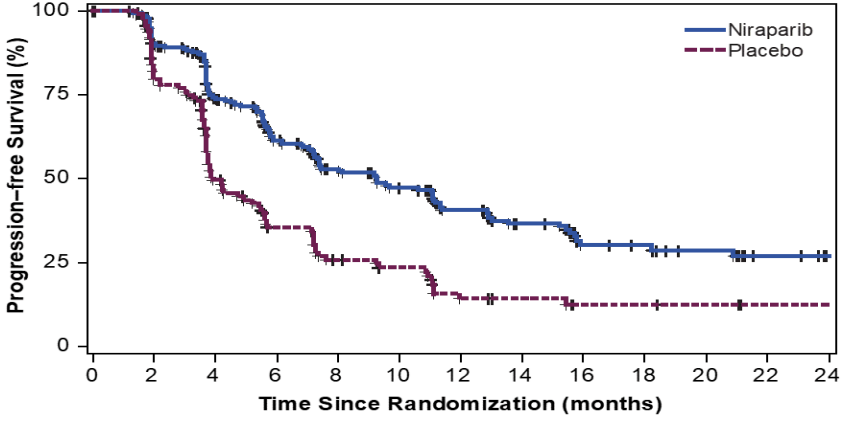


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	21.0 (12.9, NR)	0.27 (0.173, 0.410) p<0.0001	62%	50%
Placebo (N=65)	5.5 (3.8, 7.2)		16%	16%

Mirza, N Engl J Med 2016; 375:2154-2164

University of Pittsburgh

NOVA: Non-gBRCAmut Progression-Free Survival

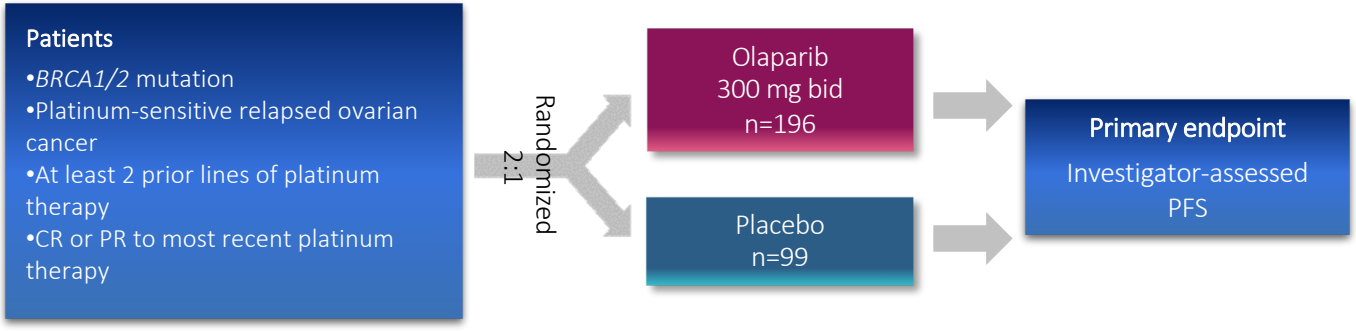


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607) p<0.0001	41%	30%
Placebo (N=116)	3.9 (3.7, 5.5)		14%	12%

Mirza, N Engl J Med 2016; 375:2154-2164

University of Pittsburgh

SOLO2/ENGOT-Ov21: Phase 3 Study Design



Sensitivity analysis: PFS by blinded independent central review (BICR)

•Key secondary endpoints:

–Time to first subsequent therapy or death (TFST), time to second progression (PFS2), time to second subsequent therapy or death (TSST), overall survival (OS)

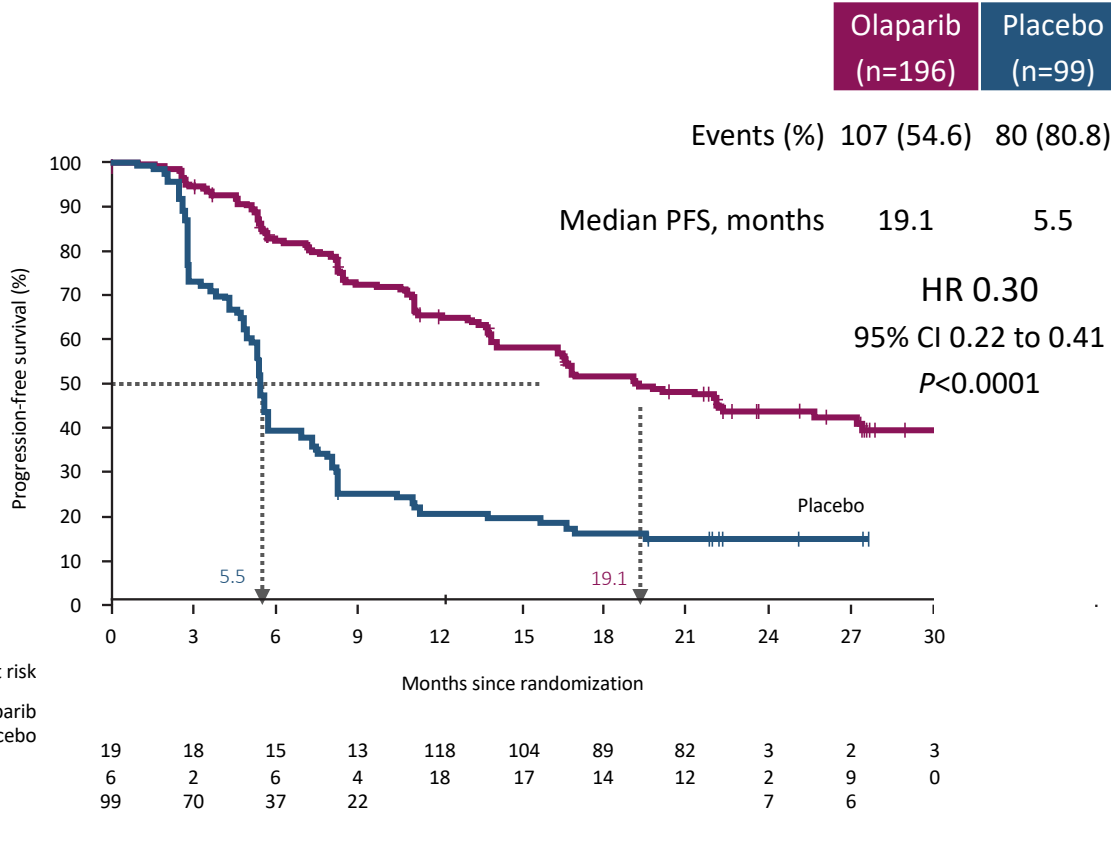
–Safety, health-related quality of life (HRQoL*)

*Primary endpoint for HRQoL was trial outcome index (TOI) of the FACT-O (Functional Assessment of Cancer Therapy – Ovarian)

Pujade-Lauraine, Lancet Oncol. 2017 Sep;18(9):1274-1284.

University of Pittsburgh

PFS by Investigator Assessment



Mirza, N Engl J Med 2016; 375:2154-2164

University of Pittsburgh

STUDY 19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

Jonathan Lederman *et al.* N Engl J Med 2012; 366:1382-1392

University of Pittsburgh

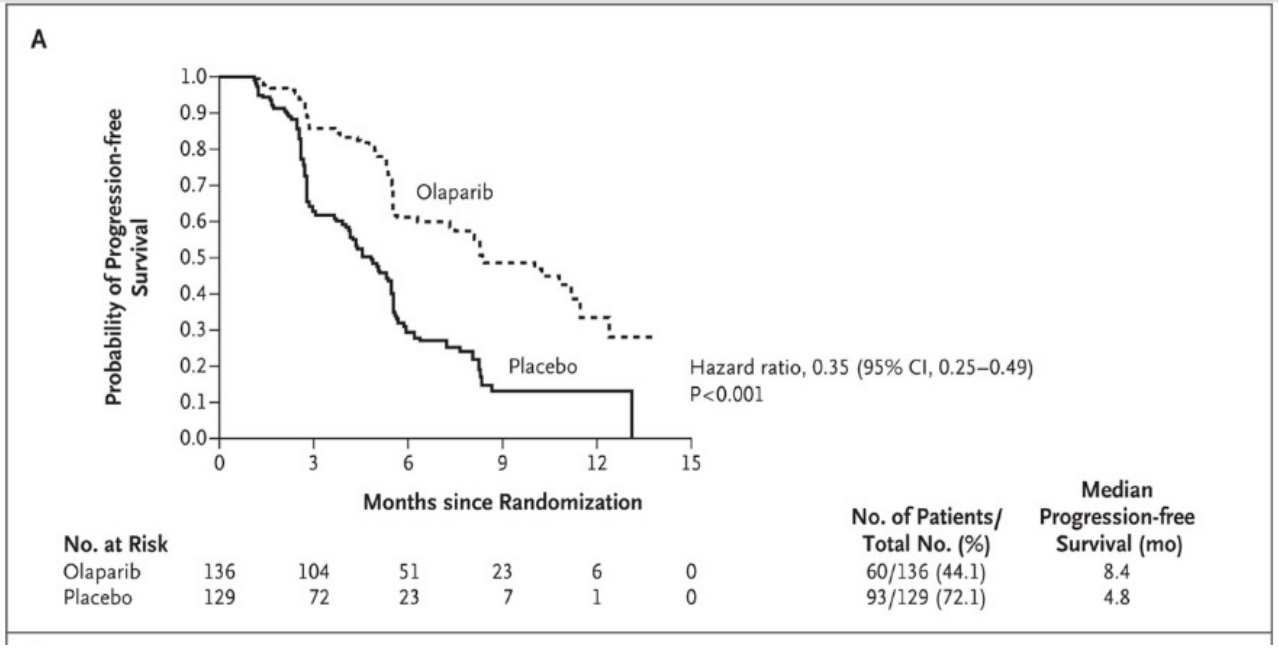
Study design

Randomized, double blind, placebo-controlled phase II study
Drug: Olaparib, 400mg PO twice/day

Jonathan, N Engl J Med 2012; 366:1382-1392

University of Pittsburgh

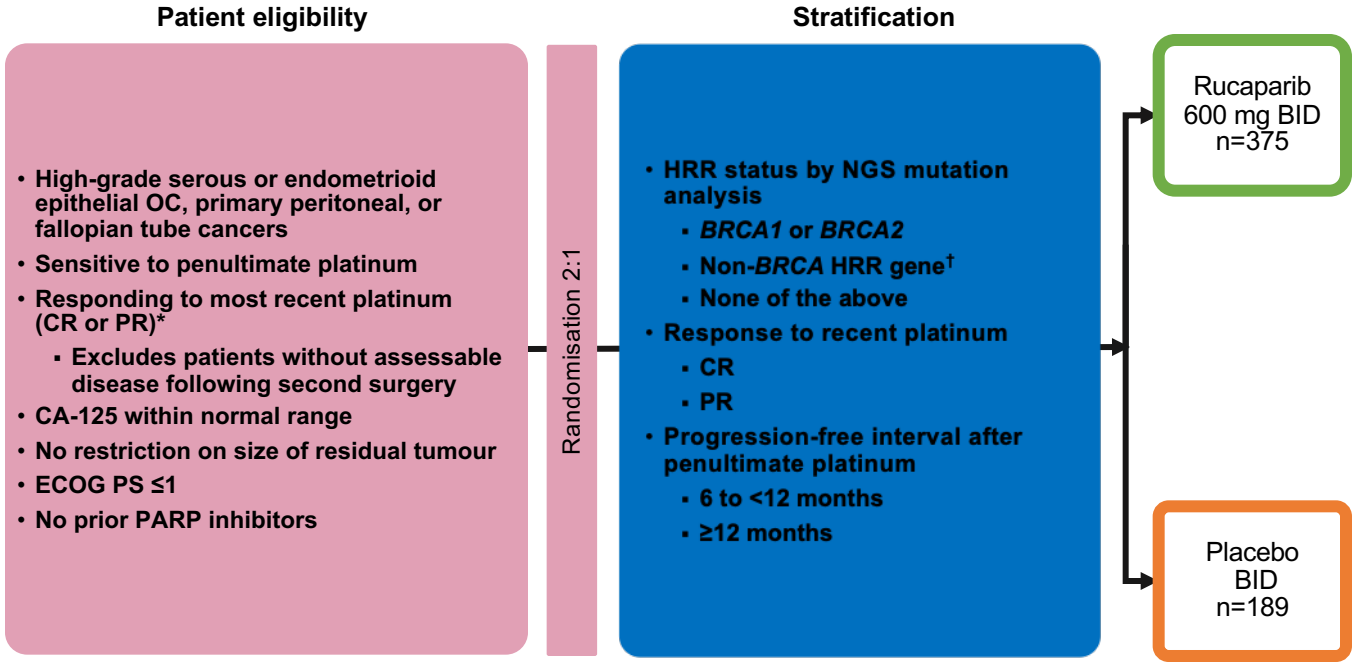
Result



Jonathan, N Engl J Med 2012; 366:1382-1392

University of Pittsburgh

ARIEL3: Study Design

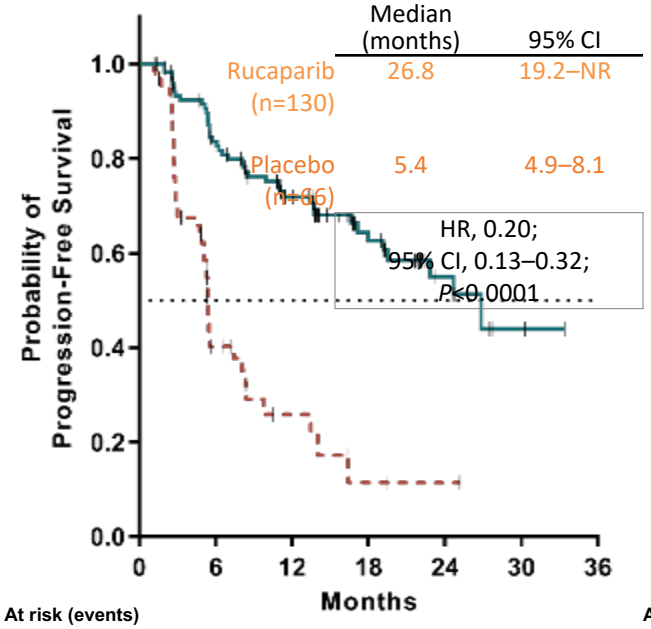


Lancet. 2017 Oct 28;390(10106):1949-1961

University of Pittsburgh

ARIEL3: BICR-Assessed Progression-Free Survival

BRCA mutant

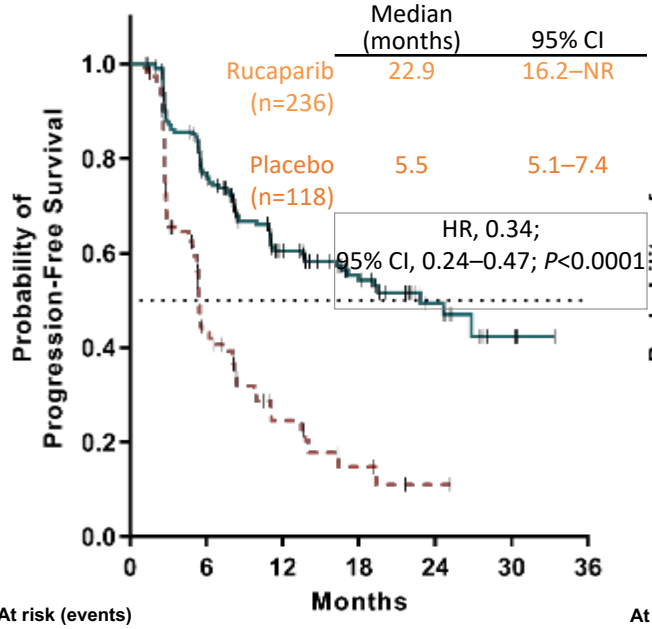


At risk (events)

Rucaparib	130 (0)	93 (19)	62 (31)	35 (36)	15 (40)	2 (42)	0 (42)
Placebo	66 (0)	18 (34)	6 (39)	2 (42)	1 (42)	0 (42)	

Rucaparib, 68% censored Placebo, 36% censored

HRD

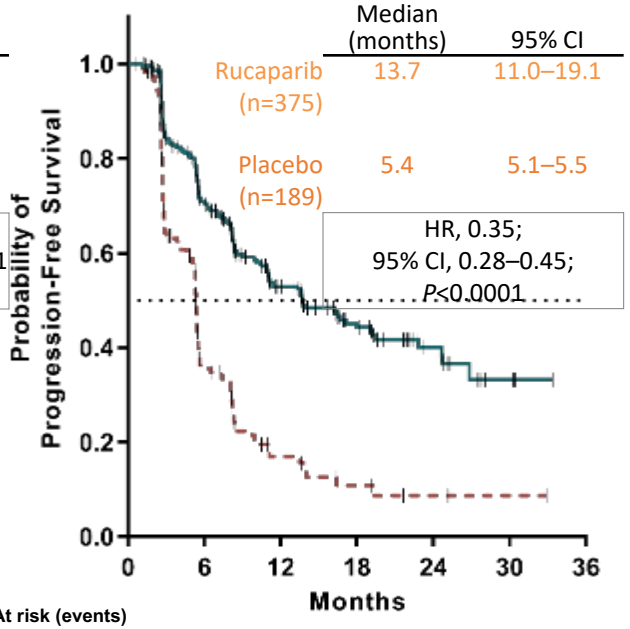


At risk (events)

Rucaparib	236 (0)	152 (49)	87 (78)	53 (84)	21 (88)	4 (90)	0 (90)
Placebo	118 (0)	34 (57)	12 (69)	5 (73)	1 (74)	0 (74)	

Rucaparib, 62% censored Placebo, 37% censored

ITT



At risk (events)

Rucaparib	375 (0)	213 (95)	114 (143)	60 (157)	24 (162)	4 (165)	0 (165)
Placebo	189 (0)	50 (106)	13 (128)	6 (132)	2 (133)	1 (133)	0 (133)

Rucaparib, 56% censored Placebo, censored

[Lancet.](#) **2017 Oct 28;390(10106):1949-1961**

University of Pittsburgh

PARP inhibitors treatment in recurrent ovarian cancer

University of Pittsburgh

THE LANCET
Oncology

Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial

Elizabeth Swisher *et al* Lancet Oncol 2017; 18: 75–87

University of Pittsburgh

Study design

ARIEL2 is an international, multicentre, two-part, phase 2, open-label study.
Drug: Rucaparib, 600mg PO twice/day

Swisher, Lancet Oncol 2017; 18: 75–87

University of Pittsburgh

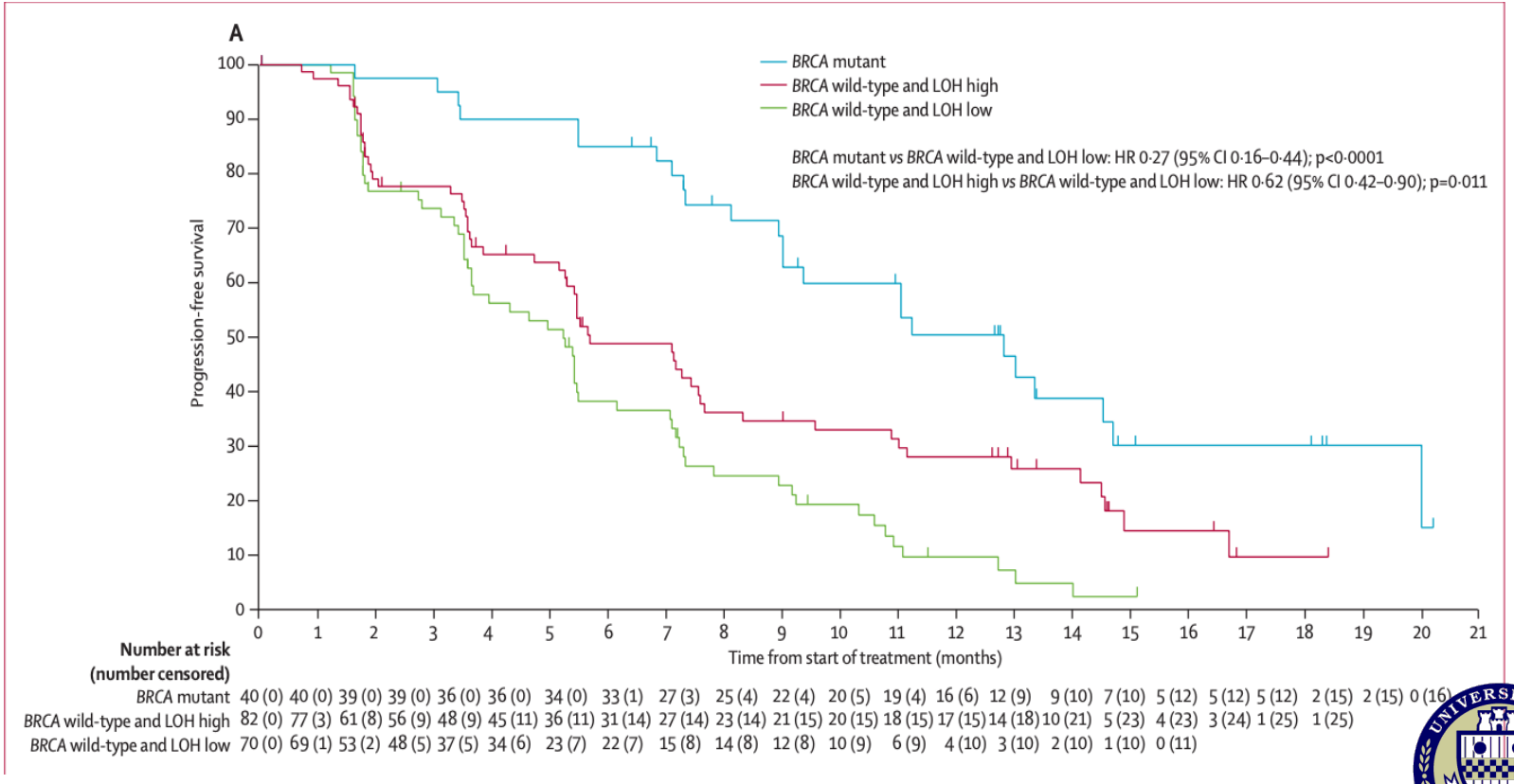
Result 1

- 192 treated patients could be classified into one of the three subgroups: BRCA mutant (n=40), LOH high (n=82), or LOH low (n=70)
- Median PFS after rucaparib treatment was;
  - 12·8 months BRCA mutant subgroup
  - 5·7 months in the LOH high subgroup
  - 5·2 months in the LOH low subgroup

Swisher, Lancet Oncol 2017; 18: 75–87

University of Pittsburgh

Result 2



Swisher, Lancet Oncol 2017; 18: 75–87

University of Pittsburgh

Olaparib Monotherapy versus Chemotherapy for Germline BRCA-Mutated Platinum-Sensitive Relapsed Ovarian Cancer Patients: Phase III SOLO3 Trial

Richard T Penson,[1] Ricardo Villalobos Valencia,[2] David Cibula,[3] Nicoletta Colombo,[4] Charles A Leath III,[5] Mariusz Bidziński,[6] Jae-Weon Kim,[7] Joo Hyun Nam,[8] Radoslaw Madry,[9] Carlos Hernández,[10] Paulo AR Mora,[11] Sang Young Ryu,[12] Tsveta Milenkova,[13] Elizabeth S Lowe,[14] Laura Barker,[13] Giovanni Scambia[15]

[1]Massachusetts General Hospital, Boston, MA, USA; [2]Centro Medico Dalinde, Mexico City, Mexico; [3]First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [4]University of Milan-Bicocca and IEO European Institute of Oncology IRCCS, Milan, Italy; [5]University of Alabama, Birmingham, AL, USA; [6]Faculty of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland; [7]Seoul National University Hospital, Seoul, South Korea; [8]Asan Medical Center, Seoul, South Korea; [9]Medical University K. Marcinkowski and the Clinical Hospital of the Transfiguration, Poznań, Poland; [10]Oaxaca Site Management Organization, Oaxaca de Juarez, Mexico; [11]Instituto COI de Educação e Pesquisa, Rio de Janeiro, Brazil; [12]Korea Institute of Radiological and Medical Sciences, Seoul, South Korea; [13]AstraZeneca, Cambridge, UK; [14]AstraZeneca, Gaithersburg, MD, USA; [15]Università Cattolica del Sacro Cuore-Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy

ClinicalTrials.gov identifier: NCT02282020
This study was sponsored by AstraZeneca; part of an alliance between AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, USA

Study Design

- Relapsed, high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer
- Germline BRCAm
- ECOG performance status 0–2
- ≥2 previous lines of platinum-based chemotherapy*
- Platinum sensitive†

Open-label

Study treatment administered until disease progression

Olaparib tablets 300 mg bid (n=178)

2:1 randomization

Stratified by:
- Selected chemotherapy‡
- Number of prior lines of chemotherapy
- Time to progression after previous platinum-based chemotherapy

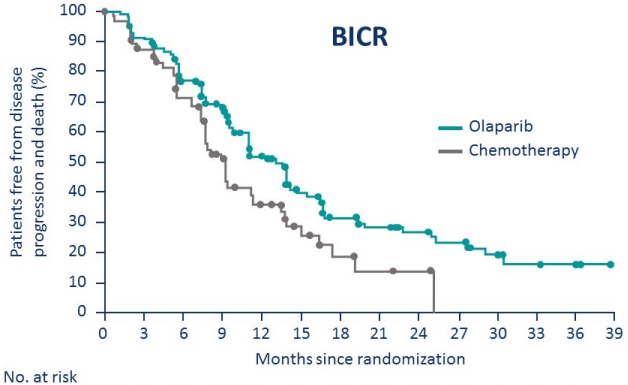
Non-platinum chemotherapy§ (n=88)
- **PLD (n=47)**
- **Paclitaxel (n=20)**
- **Gemcitabine (n=13)**
- **Topotecan (n=8)**

Primary endpoint
- ORR by BICR (RECIST v1.1)

Secondary endpoints
- PFS
- PFS2
- OS
- TFST
- TSST
- HRQoL
- Safety

*Prior treatment with a PARP inhibitor was not permitted;
†Fully platinum sensitive: progression >12 months after platinum-based chemotherapy; partially platinum sensitive: progression 6–12 months after platinum-based chemotherapy;
‡For each patient, the investigator declared their choice of non-platinum chemotherapy before randomization;
§PLD, 50 mg/m^2 on day 1 q4w; paclitaxel, 80 mg/m^2 on days 1, 8, 15, and 22 q4w; gemcitabine, 1000 mg/m^2 on days 1, 8, and 15 q4w; topotecan, 4 mg/m^2 on days 1, 8, and 15 q4w
BICR, blinded independent central review; BRCAm, *BRCA1* or *BRCA2* mutation; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; PLD, pegylated liposomal doxorubicin; q4w, every 4 weeks; RECIST, response evaluation criteria in solid tumors; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

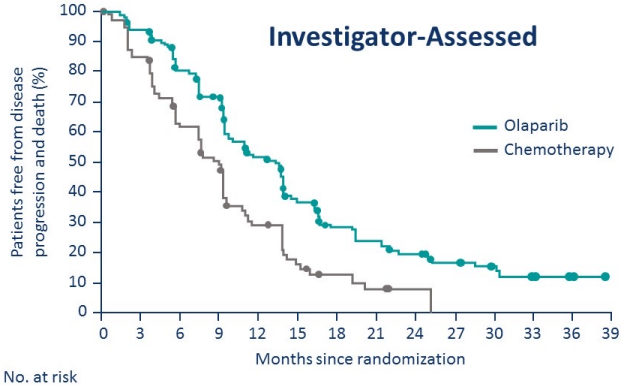
PFS (Intention-To-Treat Population)



No. at risk

Olaparib	178	156	126	108	71	47	30	25	18	14	8	5	2	0
Chemotherapy	88	63	47	31	18	9	5	3	2	0	0	0	0	0

	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	110 (62)	49 (56)
Median PFS, months	**13.4**	**9.2**
HR (95% CI), *P* value	**0.62 (0.43, 0.91); *P*=0.013**	



No. at risk

Olaparib	178	155	126	110	72	48	31	26	19	12	8	6	2	0
Chemotherapy	88	62	43	34	18	9	5	3	1	0	0	0	0	0

	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	123 (69)	63 (72)
Median PFS, months	**13.2**	**8.5**
HR (95% CI), *P* value	**0.49 (0.35, 0.70); *P*<0.001**	

Presented By Richard Penson at 2019 ASCO Annual Meeting

University of Pittsburgh

PARP inhibitors maintenance after 1st line treatment of ovarian cancer

University of Pittsburgh

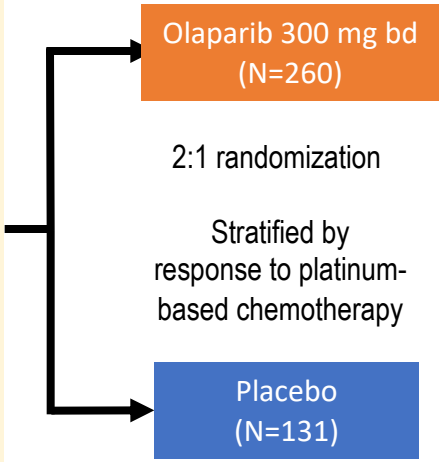
SOLO1: Phase III trial of maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients with advanced ovarian cancer and a *BRCA1/2* mutation

- 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]

University of Pittsburgh

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)

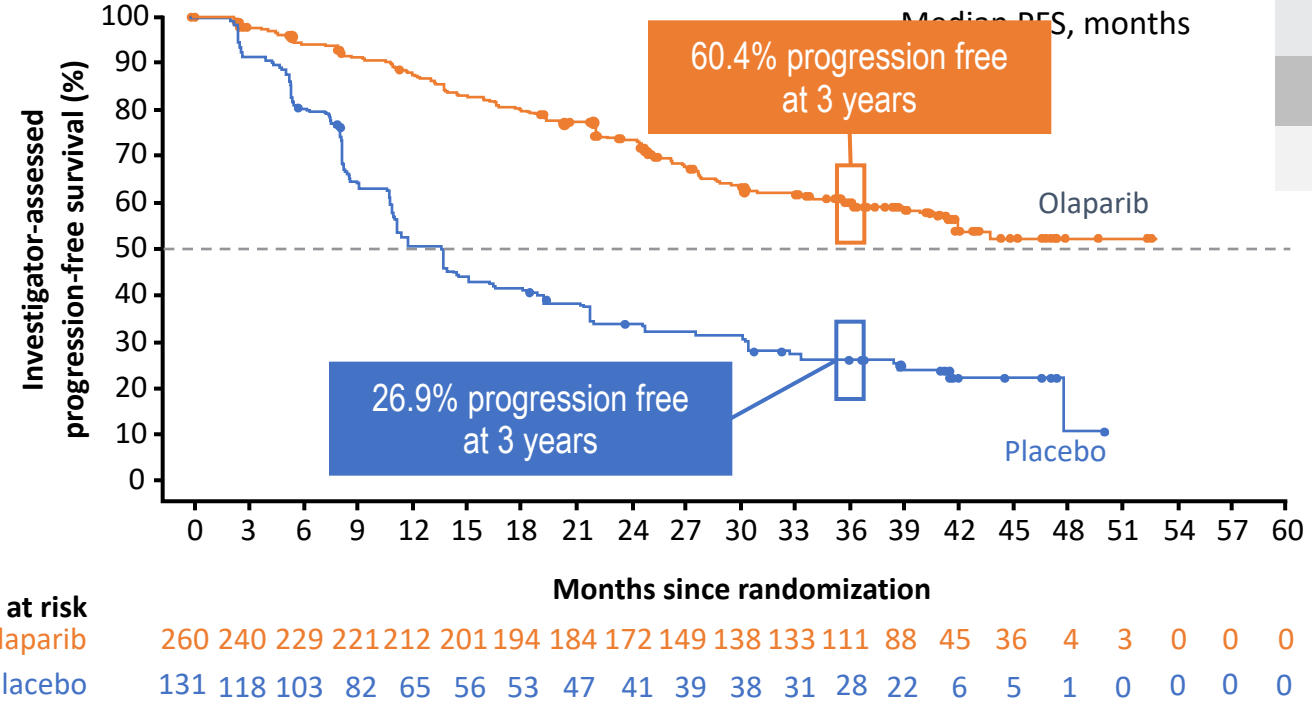
Secondary endpoints

- 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

University of Pittsburgh

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)

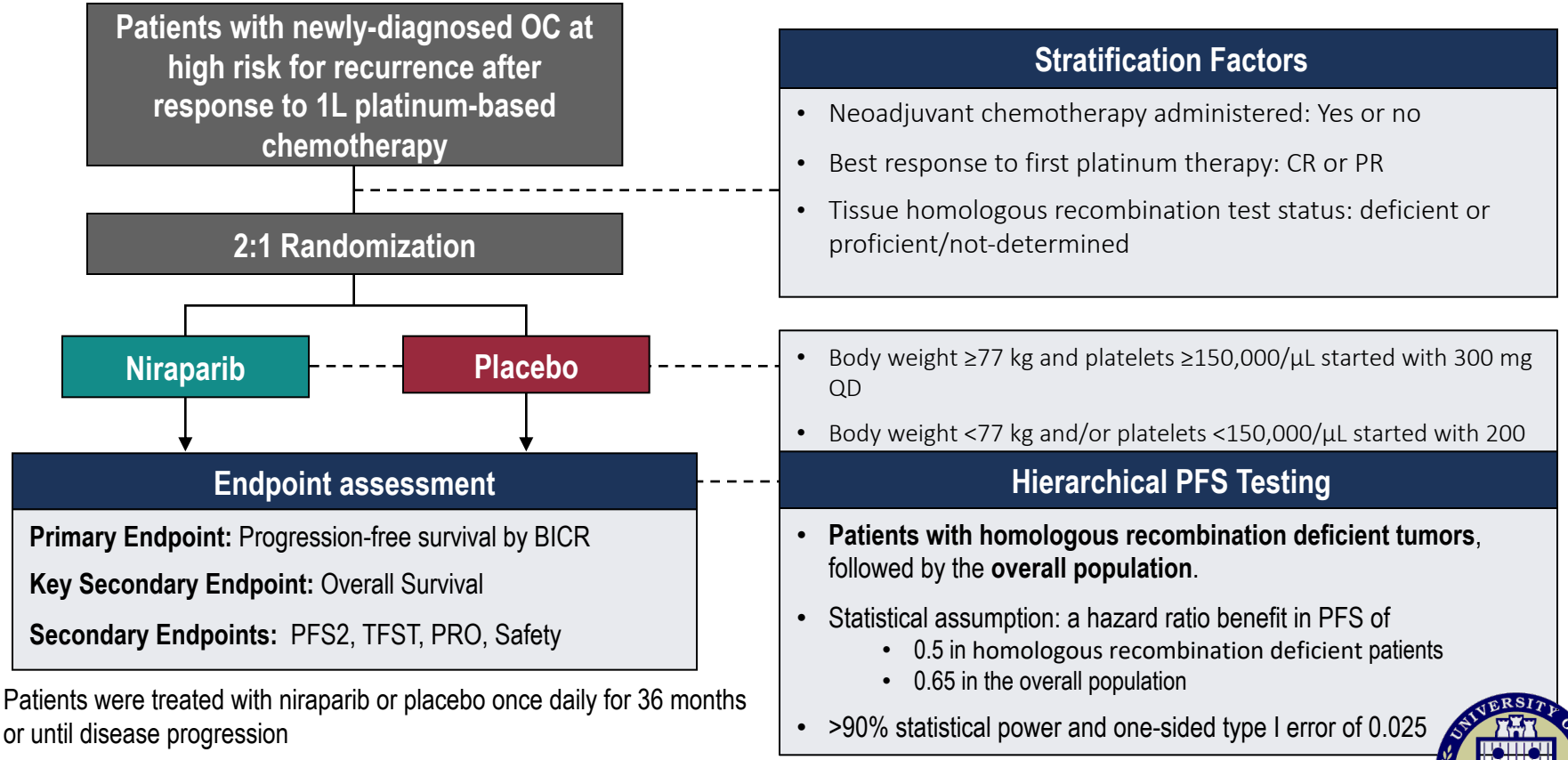
A. González-Martín,[1] B. Pothuri,[2] I. Vergote,[3] R.D. Christensen,[4] W. Graybill,[5] M.R. Mirza,[6] C. McCormick,[7] D. Lorusso,[8] P. Hoskins,[9] G. Freyer,[10] F. Backes,[11] K. Baumann,[12] A. Redondo,[13] R. Moore,[14] C. Vulsteke,[15] R.E. O'Cearbhaill,[16] B. Lund,[17] Y. Li,[18] D. Gupta,[18]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

University of Pittsburgh

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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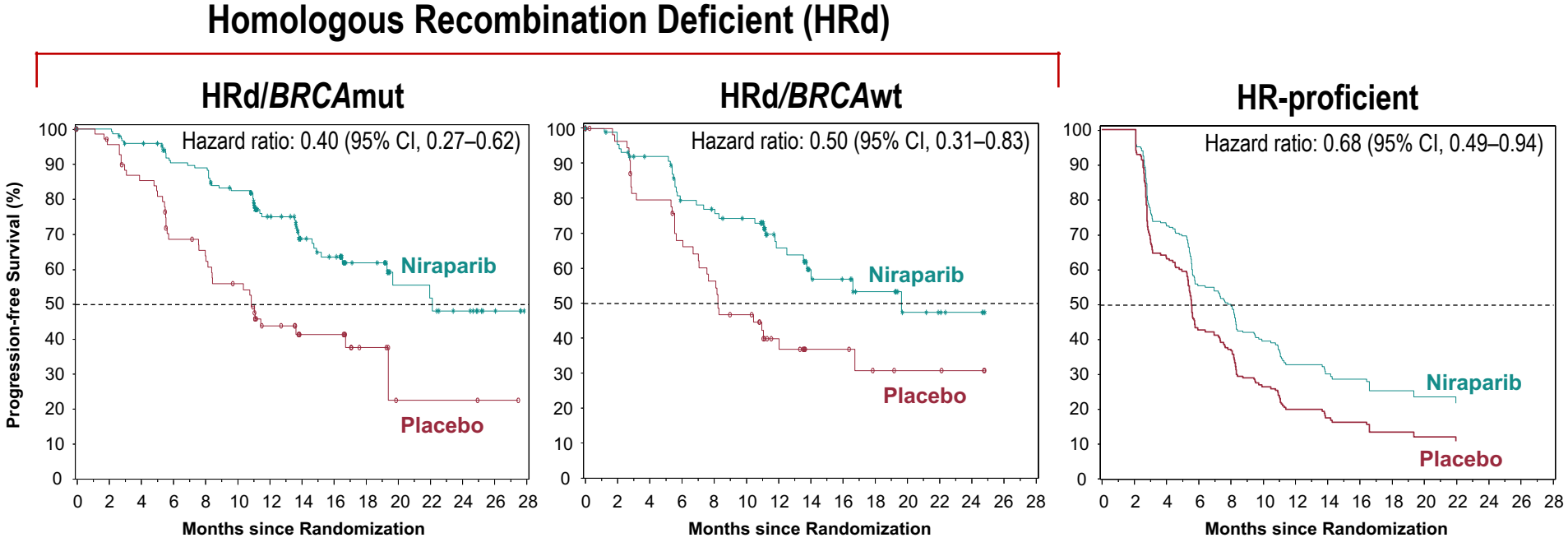
PRIMA PFS Benefit in Biomarker Subgroups



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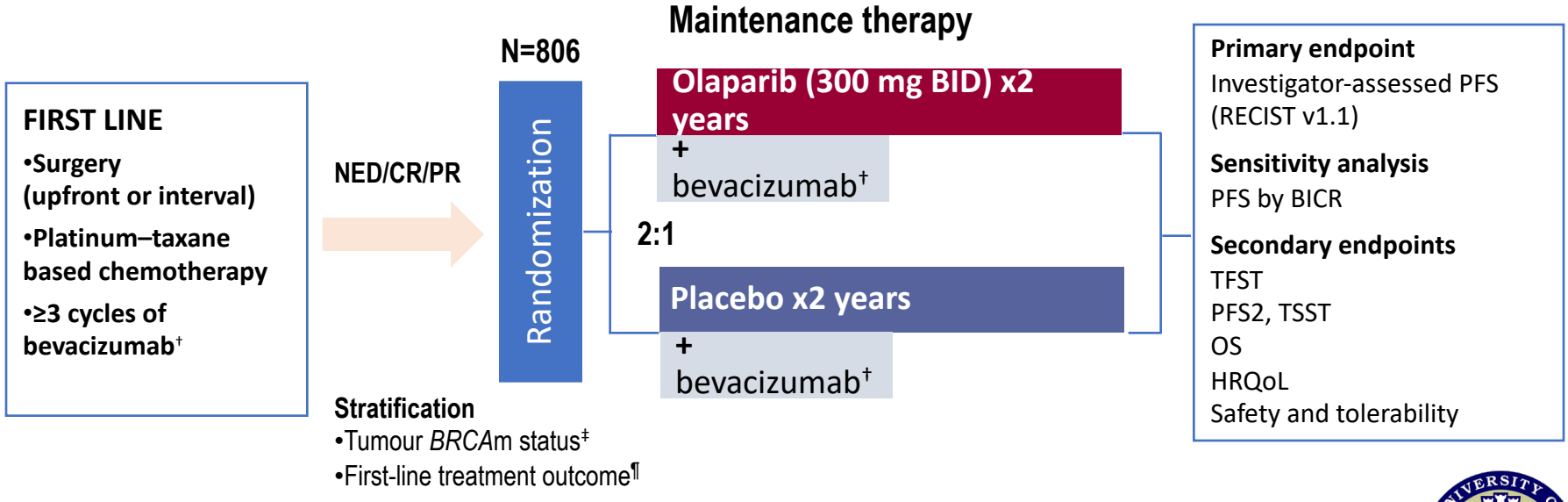
Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care

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

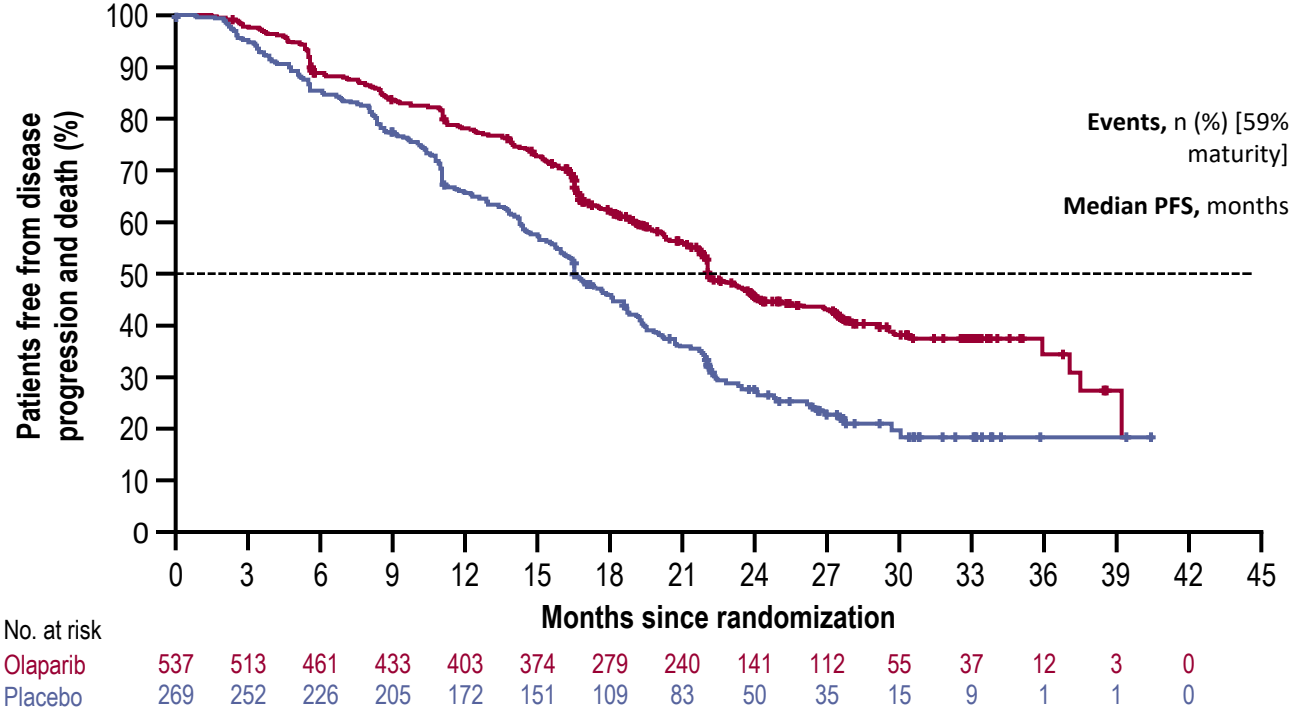
Newly diagnosed FIGO stage III–IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer*



*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

University of Pittsburgh

PFS by investigator assessment: ITT population



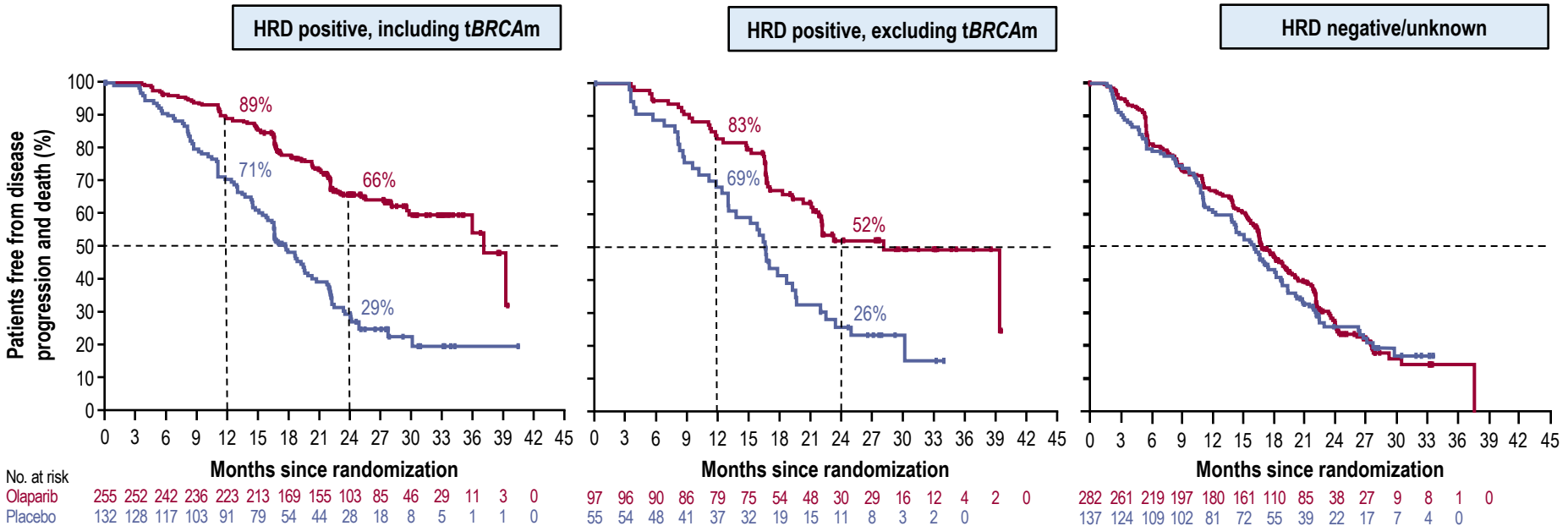
	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	**22.1**	**16.6**

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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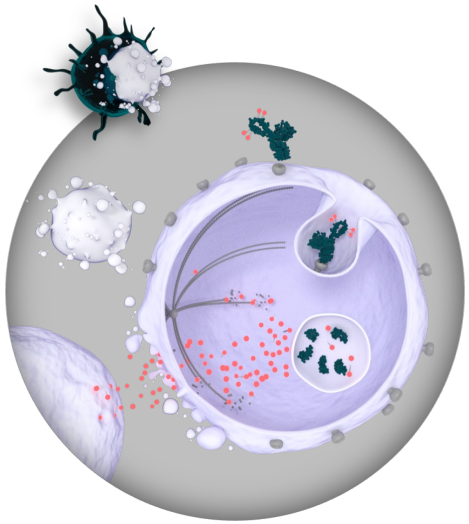
Clinical Benefit of Mirvetuximab Soravtansine in Ovarian Cancer Patients With High Folate Receptor Alpha Expression: Results From the SORAYA Study

Robert L. Coleman,[1] Domenica Lorusso,[2] Ana Oaknin,[3] Sandro Pignata,[4] Hannelore Denys,[5] Nicoletta Colombo,[6] Toon Van Gorp,[7] Jason A. Konner,[8] Margarita Romeo Marin,[9] Philipp Harter,[10] Conleth G. Murphy,[11] Jiuzhou Wang,[12] Elizabeth Noble,[13] Brooke Esteves,[14] Michael Method,[14] **Ursula Matulonis[15]**

[1]US Oncology Research, Gynecologic Oncology, The Woodlands, TX, USA; [2]Fondazione IRCCS National Cancer Institute of Milan, Division of Gynecologic Oncology, Milan, Italy; [3]Vall d'Hebron University Hospital, Gynaecologic Cancer Programme, Barcelona, Spain; [4]IRCCS National Cancer Institute, Uro-Gynaecology, Naples, Italy; [5]UZ Gent, Medical Oncology, Gent, Belgium; [6]Istituto Europeo Oncologia, Gynecologic Oncology, Milan, Italy; [7]University Hospital Leuven, Division of Gynaecological Oncology, Leuven, Belgium; [8]Memorial Sloan Kettering Cancer Center, Medical Oncology, New York, NY, USA; [9]ICO - Institut Català d'Oncologia Badalona, Medical Oncology, Barcelona, Spain; [10]Kliniken Essen Mitte Evang, Gynecology and Gynecologic Oncology, Essen, Germany; [11]Bon Secours Hospital, Oncology, Cork, Ireland; [12]ImmunoGen, Inc., Biostatistics, Waltham, MA, USA; [13]ImmunoGen, Inc., Clinical Operations, Waltham, MA, USA; [14]ImmunoGen, Inc., Clinical Development, Waltham, MA, USA; [15]Dana-Farber Cancer Institute, Medical Oncology, Boston, MA, USA

Mirvetuximab Soravtansine (MIRV)



- Treatment options for PROC are limited, consisting primarily of single-agent chemotherapy, and the majority of patients will have received prior bevacizumab (BEV)[3,4]
  - Single-agent chemotherapy has limited activity (ORR, 4%–13%) along with considerable toxicity[5-8]
- FRα, also known as folate receptor 1 (FOLR1), has limited expression on normal tissues but is elevated in most ovarian cancers, which makes FRα an attractive target for the development of novel therapies[9,10]
- MIRV is an antibody-drug conjugate (ADC) comprising an FRα-binding antibody, cleavable linker, and a maytansinoid DM4 payload, a potent tubulin-targeting agent[11]
- SORAYA is a global, single-arm, phase 3 study that evaluated MIRV for the treatment of PROC in patients with high FRα expression who received 1 to 3 prior therapies, including required prior BEV[1,2,12]
- Treatment with MIRV demonstrated clinically meaningful antitumor activity regardless of the number of prior lines of therapy or prior PARPi use[1,2]
  - Previous data for ORR: 32.4% (34 of 105) of patients, including 5 CR[1,a]
  - Previous data for mDOR: 6.9 months (95% CI, 5.6–9.7)[1,a]

MIRV is the first biomarker-directed agent demonstrating antitumor activity in patients with folate receptor alpha (FRα)-high platinum-resistant ovarian cancer (PROC)[1,2]

Here we report updated data on the clinical benefit of MIRV, including tumor reduction and disease control rate[a]

[ADP]-ribose) polymerase inhibitor.

[a]Data cutoff: April 29, 2022.

References: 1. Matulonis UA, et al. Poster presented at: ASCO 2022 Annual Meeting; June 3-7, 2022; Chicago, IL. **2**. Matulonis UA, et al. Presented at: SGO 2022 Annual Meeting on Women's Cancer; March 18-21, 2022; Phoenix, AZ. **3.** Indini A, et al. *Cancers (Basel).* 2021;13(7):1663. **4.** McClung EC, Wenham RM. *Int J Womens Health.* 2016;8:59-75. **5.** Pujade-Lauraine E, et al. *J Clin Oncol*. 2014;32(13):1302-1308. **6.** Gaillard S, et al. *Gynecol Oncol*. 2021;163(2):237-245. **7.** Hamanishi J, et al. *J Clin Oncol*. 2021;39(33):3671-3681. **8.** Pujade-Lauraine E, et al. *Lancet Oncol*. 2021;22(7):1034-1046. **9.** Birrer MJ, et al. *Oncologist*.

Clinical Benefits

Investigator Assessment per RECIST

	Overall (N=105[a])	Exposure			
		PARPi naïve (n=51)	Prior PARPi (n=50)	1–2 prior lines (n=51)	3 prior lines (n=53)
ORR, %	32.4	27.5	38.0	35.3	30.2
Best overall response, %					
CR	4.8	3.9	4.0	3.9	5.7
PR	27.6	23.5	34.0	31.4	24.5
SD	45.7	58.8	34.0	47.1	45.3
PD	19.0	9.8	26.0	17.6	18.9
NE	2.9	3.9	2.0	0	5.7
mDOR[b], mo	6.9	6.4[c]	5.7[d]	5.9[e]	7.4[f]
DCR[g], %	51.4	51.0	54.0	58.8	45.3
Tumor reduction, %	71.4	70.6	74.0	76.5	67.9

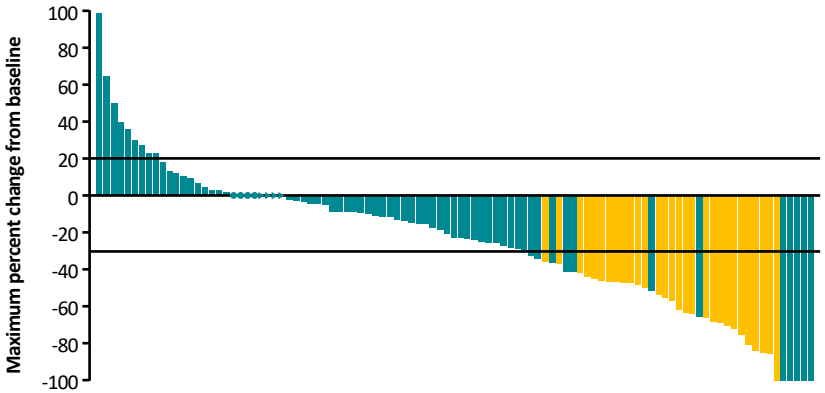
51% had disease control (CR, PR, or SD for ≥12 weeks)[g]

polymerase inhibitor; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

[a]Efficacy-evaluable population. [b]mDOR for overall patients was calculated among patients with CR (n=5) or PR

Best Tumor Response by RECIST

Patients (n=102[h])



71% had tumor reduction as their best response

Summary

- MIRV monotherapy for the treatment of PROC resulted in **clinically meaningful antitumor activity** including: disease control rate with durable response in heavily pretreated patients with FRα-high expression
  - **71%** experienced **tumor reduction**
  - **51%** had **disease control** (CR, PR, or SD for ≥12 weeks)

- **Safety and tolerability of MIRV in SORAYA are consistent** with that observed in previous studies[1]
  - Adverse events were primarily low-grade gastrointestinal and ocular events that generally resolved with supportive care or, if needed, dose modifications
  - The discontinuation rate due to TRAEs was 9%

In the SORAYA study, MIRV demonstrated a favorable benefit-risk profile in patients with FRα-high PROC

These results demonstrate that MIRV has the potential to be a practice-changing, biomarker-driven therapy

CR, complete response; FRα, folate receptor alpha; MIRV, mirvetuximab soravtansine; PR, partial response; PROC, platinum-resistant ovarian cancer; SD, stable disease; TRAEs, treatment-related adverse events.

Reference: Moore KN, et al. Poster presented at: ASCO 2022 Annual Meeting; June 3-7, 2022; Chicago, IL.

Endometrial Cancer

University of Pittsburgh

Genomic Characterization of EC

Nature

Nature Publishing Group

THIS ARTICLE HAS BEEN CORRECTED.

See the correction in volume 500 on page 242.

Integrated genomic characterization of endometrial carcinoma

Douglas A. Levine and The Cancer Genome Atlas Research Network

Nature **497**, 67–73 (2013)

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Genomic Characterization of EC

Using a combination of;

- **nucleotide substitutions**
- **MSI**
- **SCNAs**

Endometrial carcinomas were characterized into 4 groups;

1. **Ultramutated group (*POLE*-EDM*)***
2. **Hypermutated group (MSH)**
3. **Copy number low (NSMP)**
4. **Copy number high (Serous-like)**

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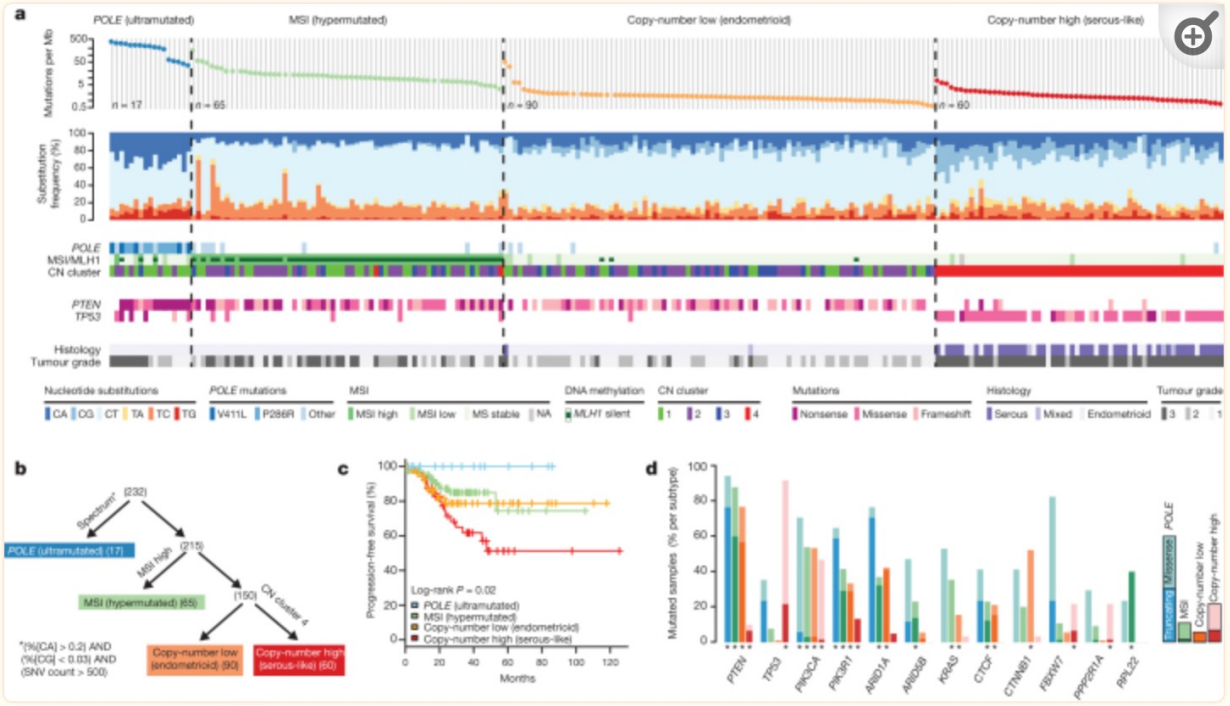
Genomic Characterization of EC



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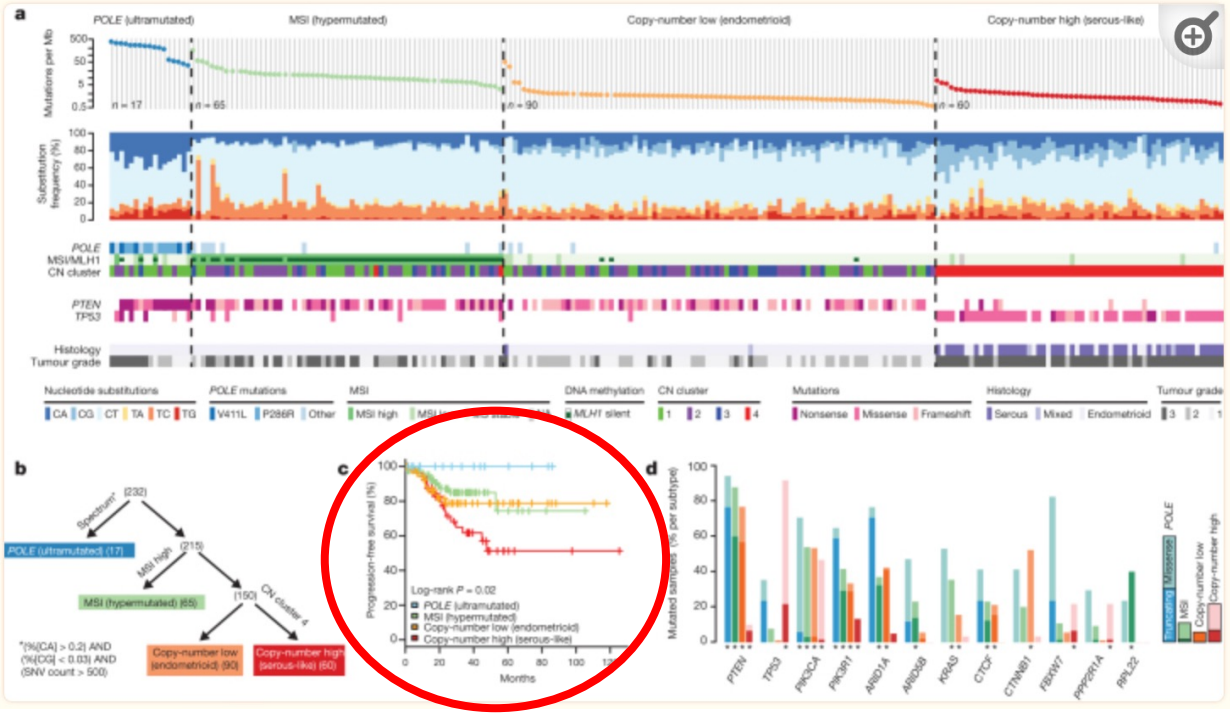
Genomic Characterization of EC



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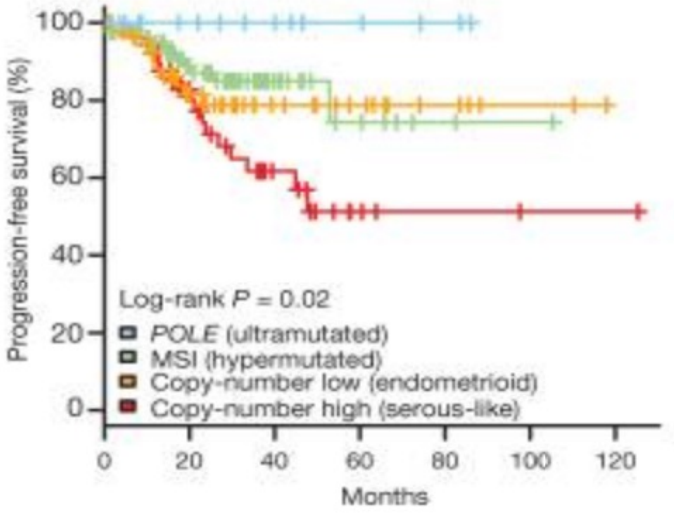
Genomic Characterization of EC



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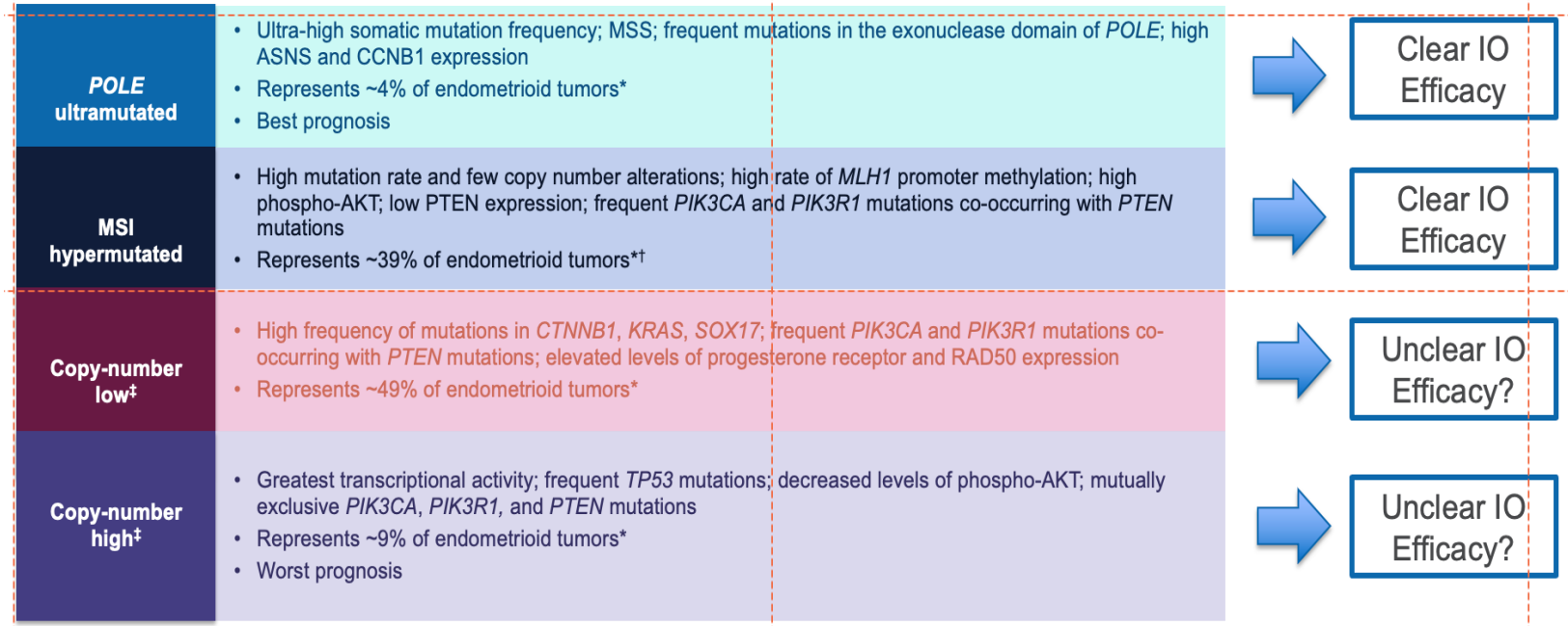
Endometrial Cancer: Molecular Subtypes



G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

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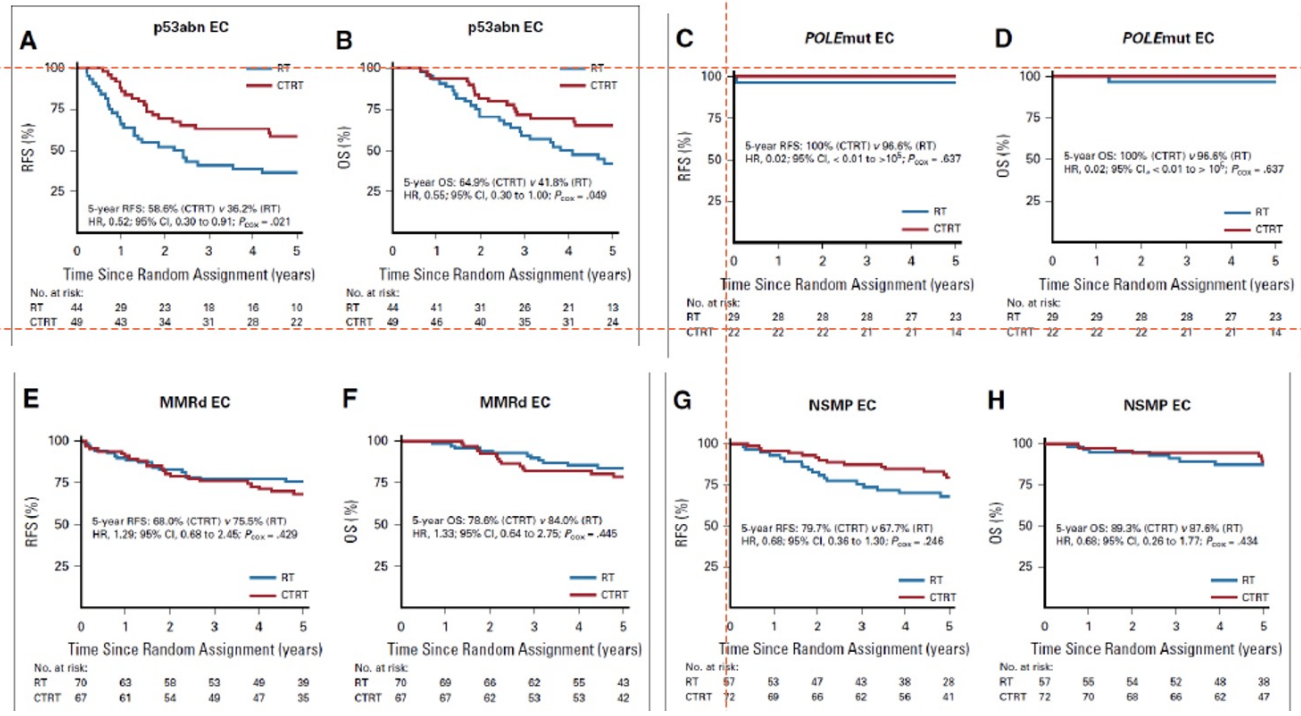
Endometrial Cancer: Molecular Subtypes are Important & Relevant



Leon-Castillo et al, JCO 2020.

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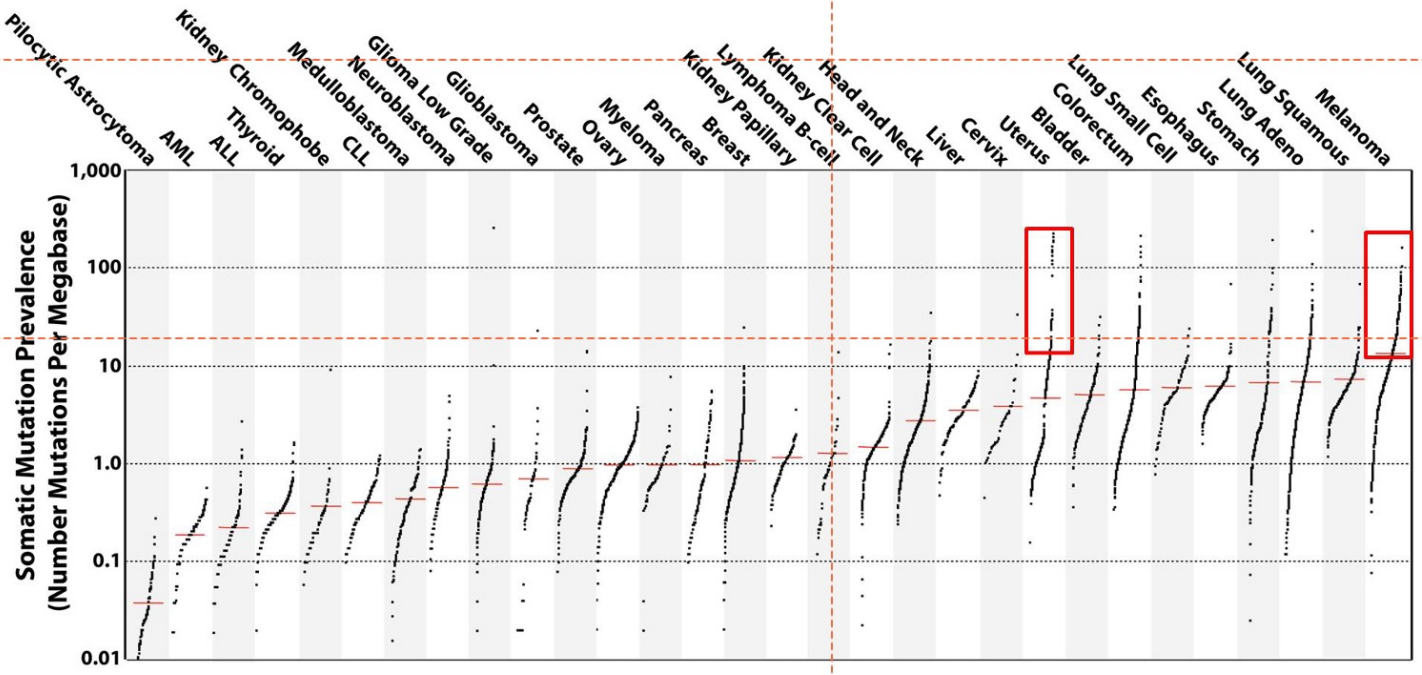
Immune Checkpoint Inhibitors in Endometrial Cancer



Alexandrov et al,Nature 2013

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"Biomarker" Guided Therapy in Endometrial Cancer

- **MMR deficient & MSI-H population**
  - Harbor hundreds to thousands of somatic mutations that encode potential neoantigens and are thus immunogenic
- **Phase II Keynote 158 Study** (27 independent tumor types)
  - Endometrial (n=49), gastric (n=24), cholangiocarcinoma and pancreatic cancer most common
  - In the entire cohort: ORR 34.3%, (95% CI, 28.3% to 40.8%). Median PFS 4.1 months (95% CI, 2.4 to 4.9 months) and median OS 23.5 months (95% CI, 13.5 months to not reached).

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

Marabelle A, et al. J Clin Oncol, 2019

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Single Agent IO in "non-biomarker" Selected Endometrial Cancer Populations

- Response to single agent IO in pMMR or MSI-stable endometrial cancer has been modest

Study & Drug	Patient Population	Outcome
Keynote 28: Pembrolizumab (N=24)	Advanced stage or metastatic PD-L1 + endometrial cancer	ORR: 13%
PHAEDRA trial: Durvalumab (N=36 pMMR)	Advanced stage or metastatic endometrial cancer	ORR in pMMR: 3%
GARNET study: Dostarlimab (N=94)	Previously treated, recurrent advanced stage endometrial cancer	ORR in pMMR: 13.9%
Ph II Avelumab study (N= 16 pMMR)	Advanced stage or metastatic endometrial cancer	ORR: 6.25%

Ott PA et al. J Clin Oncol 2017
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Gynecol Oncol 2019
Konstantinopoulos PA et al. J Clin Oncol 2019
Pothuri et al. SGO Annual Meeting 2021

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Single Agent IO in "biomarker" Selected Endometrial Cancer Populations (dMMR)

- **Response to single agent IO in dMMR or MSI-high endometrial**

Study & Drug	Patient Population	Outcome
Keynote 158: Pembrolizumab (N=90)	Advanced stage or metastatic dMMR endometrial cancer	ORR: 48%
PHAEDRA trial: Durvalumab (N=35 dMMR)	Advanced stage or metastatic endometrial cancer	ORR in dMMR: 43%
GARNET study: Dostarlimab (N=129)	Previously treated, recurrent advanced stage endometrial cancer	ORR in dMMR: 43.5%
Ph II Avelumab study (N= 15 dMMR)	Advanced stage or metastatic endometrial cancer	ORR: 26.7%

O'Malley D, et al. J Clin Oncol, 2022
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Journal for ImmunoTherapy of Cancer 2022
Konstantinopoulos PA et al. J Clin Oncol 2019

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Combinatorial IO approach: Lenvatinib + Pembrolizumab
Keynote 775 (NCT03517449)

- Advanced, recurrent or metastatic endometrial
- Progressive disease 1-2 prior platinum regimens
- Measurable disease per RECIST 1.1
- Available archival tumor tissue
- Performance status of 0 to1
- Adequate organ function

Stratification:
1. MMR status (pMMR or dMMR)
2. ECOG performance status (0 or 1)
3. Geographic region
4. Prior history of pelvic radiation (yes or no)

R

1:1

Pembrolizumab 200 mg IV q 3 weeks plus lenvatinib 20 mg PO once daily (QD) during each 21-day cycle for up to 35 cycles.

EITHER: Doxorubicin 60 mg/m2 IV q 3 weeks (max cumulative dose of 500 mg/m2) OR Paclitaxel 80 mg/m2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel.

Primary endpoints:

1) Progression-free Survival (PFS) by RECIST 1.1 by BICR
2) Overall Survival (OS).

Secondary endpoints:

1) ORR, DOR, TTF, AEs, PK, PROs

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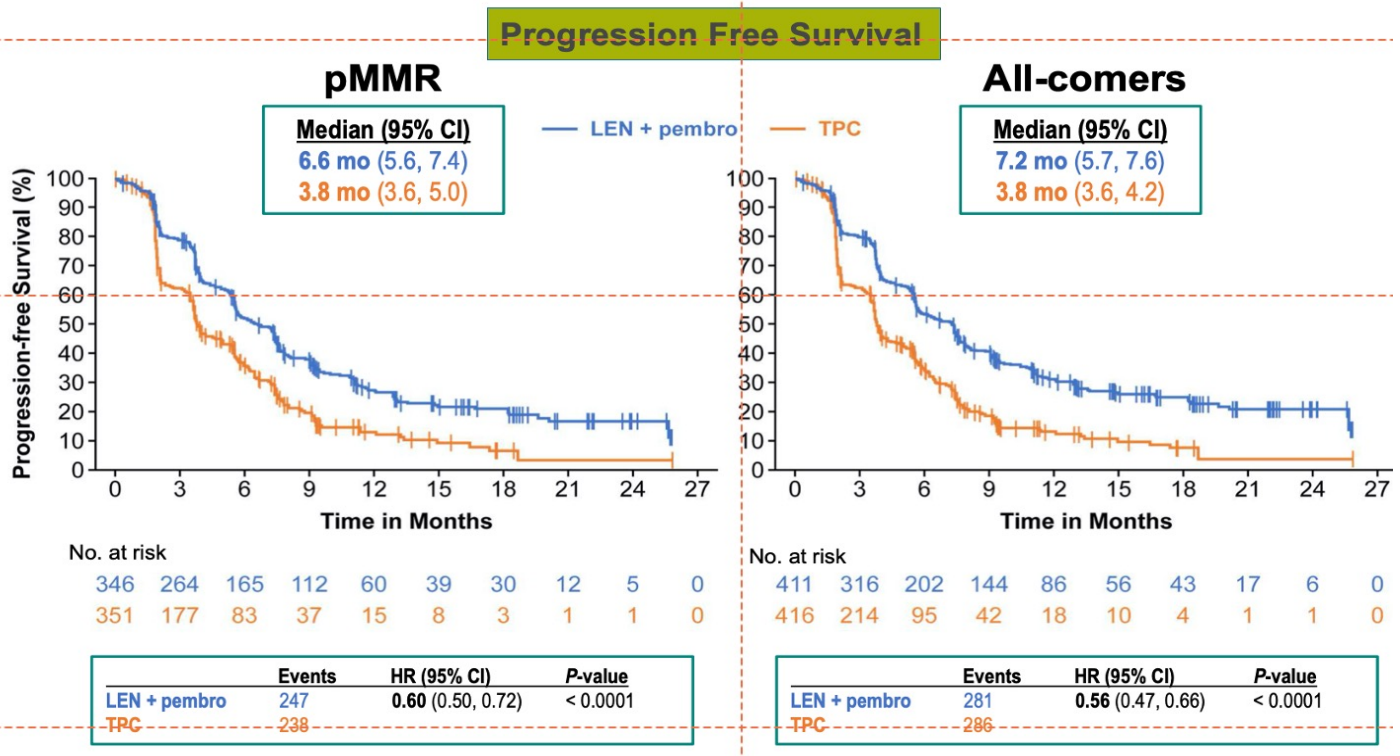
Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)



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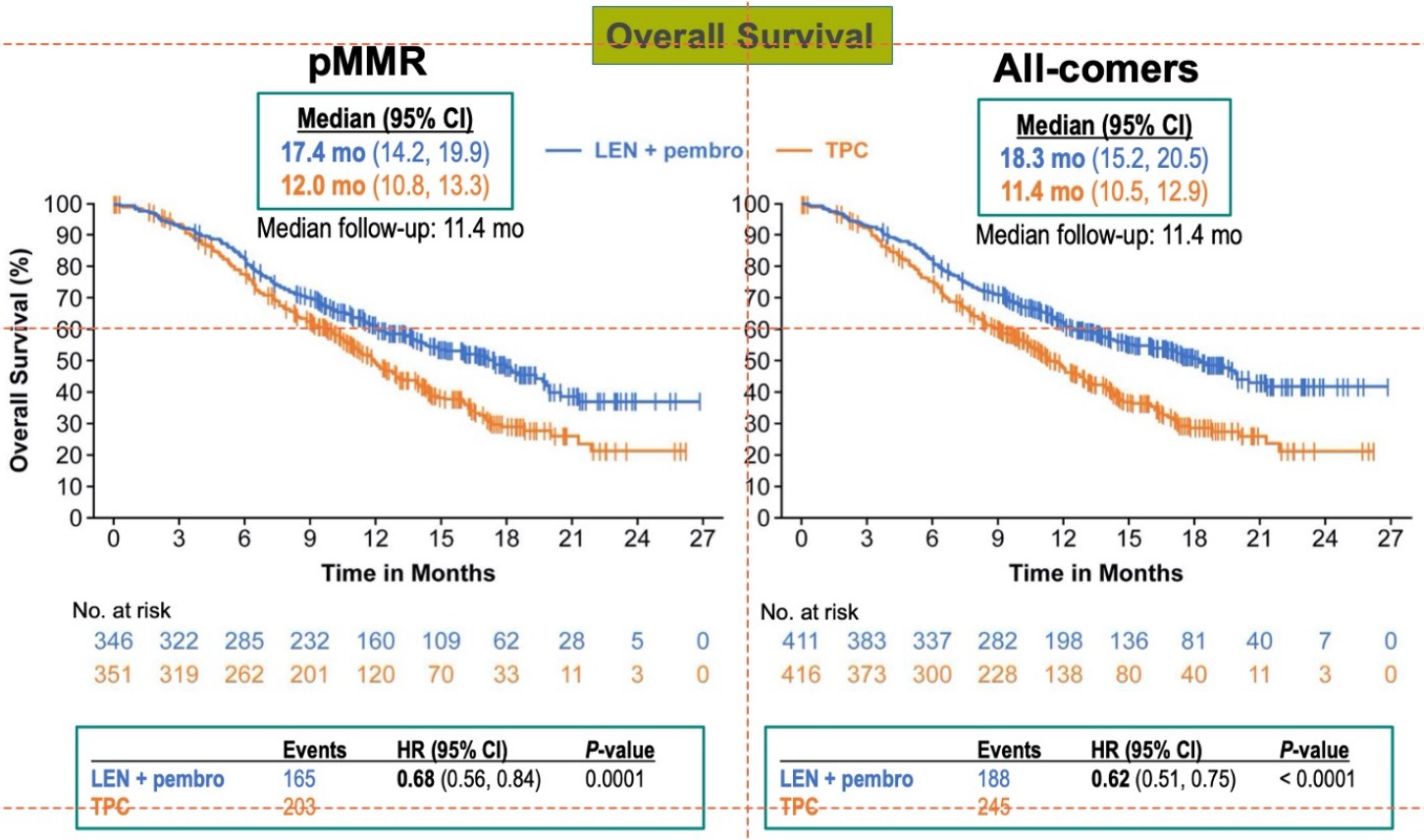
Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)



	Events	HR (95% CI)	*P*-value
LEN + pembro	165	**0.68** (0.56, 0.84)	0.0001
TPC	203		

	Events	HR (95% CI)	*P*-value
LEN + pembro	188	**0.62** (0.51, 0.75)	< 0.0001
TPC	245		

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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.
- It is quite possible and highly likely that the proportion of women cured of advanced ovarian cancer has increased (data awaited)
- Advances in the understanding of endometrial cancer molecular biology have led to improved prognostication
- Advances in the understanding of endometrial cancer molecular biology have expanded treatment options for advanced and recurrent disease

Thank you