Ovarian-Uterine & Fallopian Tube Carcinomas

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Ovarian, Fallopian tube and Primary peritoneal Carcinoma

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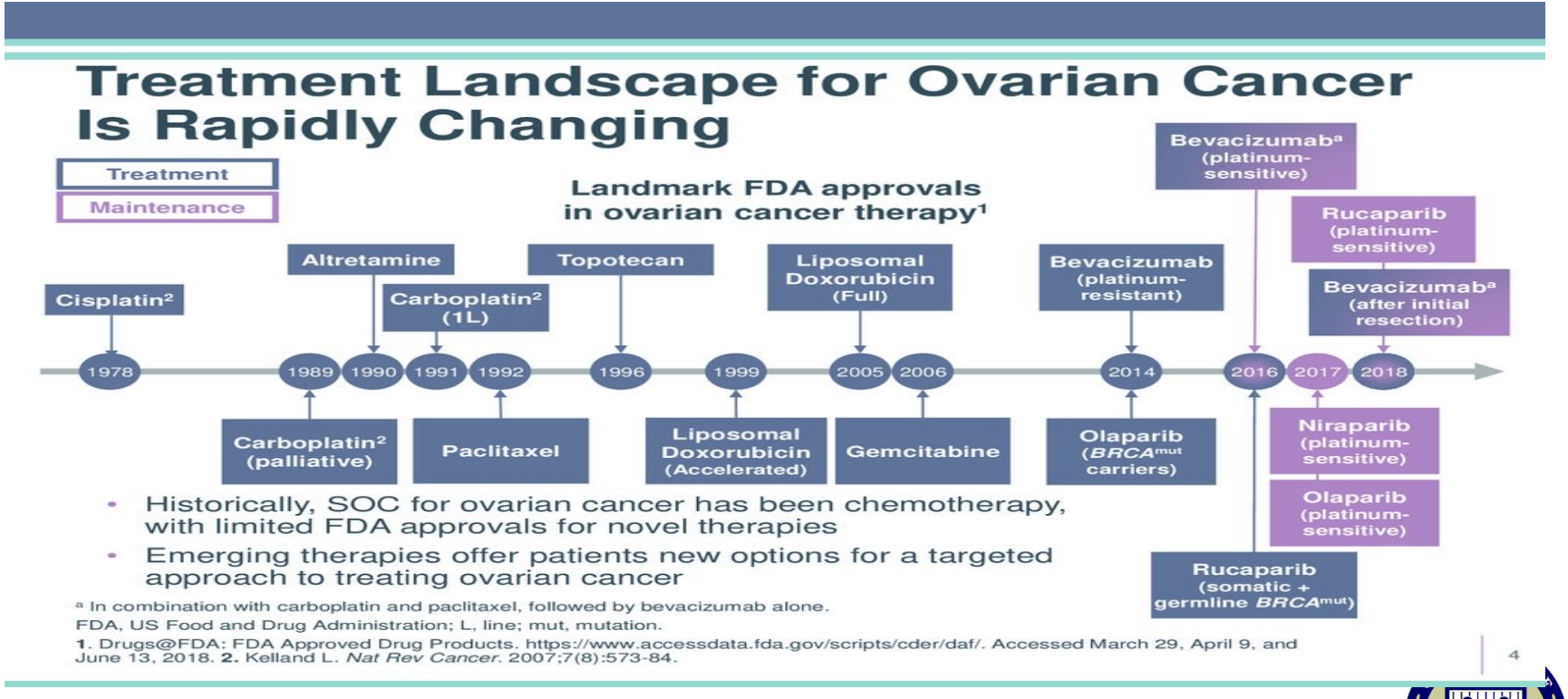
Ovarian Cancer Landscape (Systemic therapy)



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

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

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

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Targeting angiogenesis

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Rationale for Targeting VEGF Pathway in the Treatment of Ovarian Cancer

In human tumors, VEGF expression and degree of tumor angiogenesis associated with:

- Ascites formation
- Malignant progression
- Poor prognosis

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

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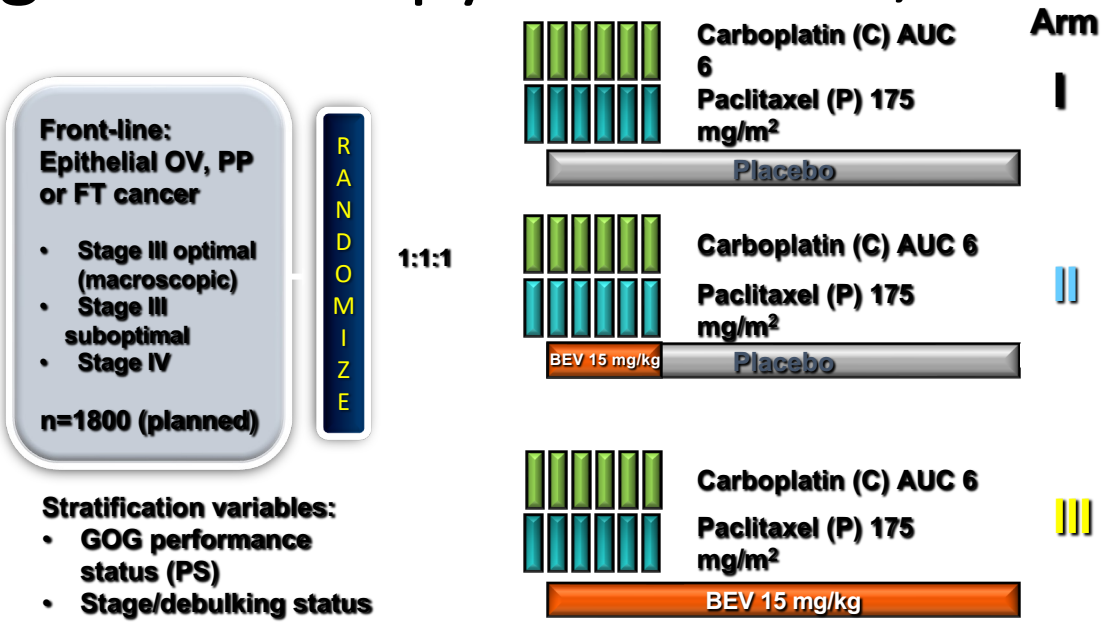
Bevacizumab (GOG 218)

Targeted therapy for ovarian, Bevacizumab



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

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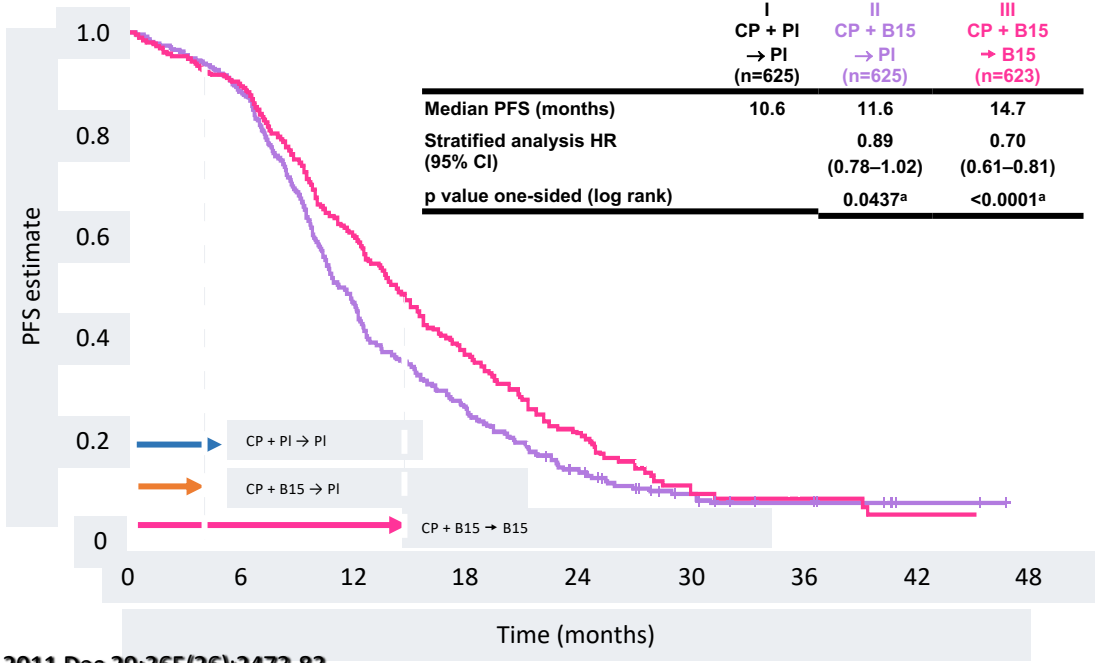
Targeted therapy for ovarian, Bevacizumab



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

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

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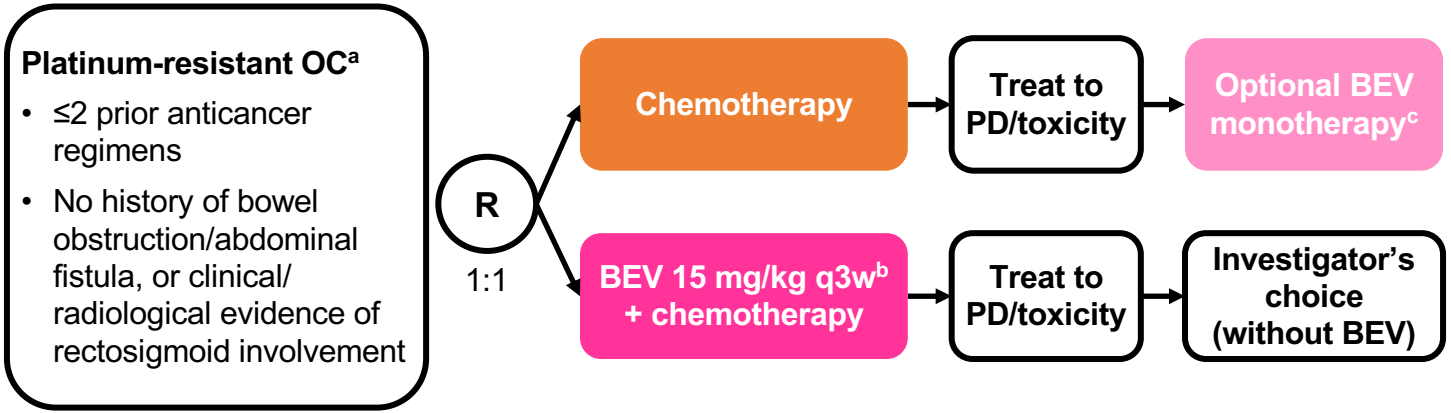
Therapy at recurrence

AURELIA trial design



Stratification factors:

- Chemotherapy selected
- Prior anti-angiogenic therapy
- Treatment-free interval (<3 vs 3–6 months from previous platinum to subsequent PD)

Chemotherapy options (investigator's choice):

- Paclitaxel 80 mg/m^2 days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m^2 days 1, 8, & 15 q4w (or 1.25 mg/m^2, days 1–5 q3w)
- PLD 40 mg/m^2 day 1 q4w

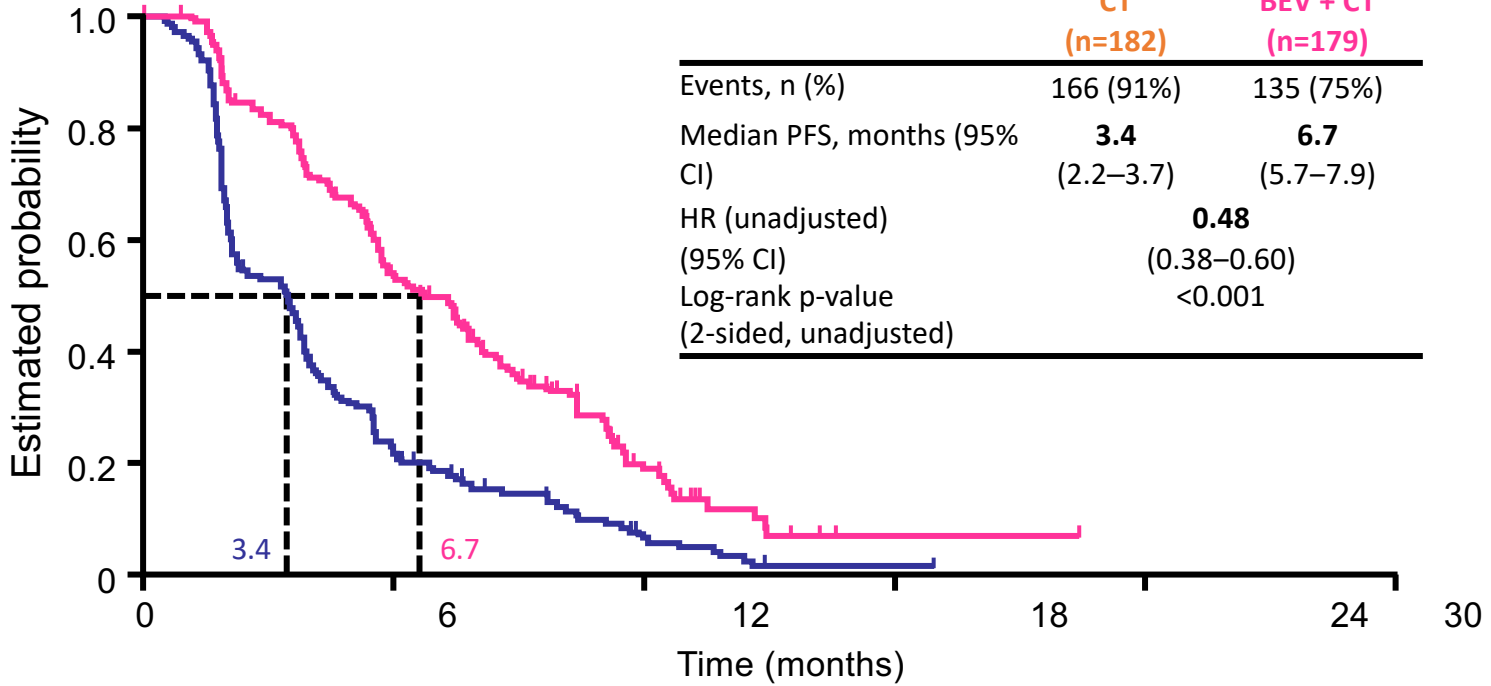
Pujade-Lauraine E. et al. J Clin Oncol 2014;32

PD = progressive disease

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer; [b]Or 10 mg/kg q2w;

[c]15 mg/kg q3w, permitted on clear evidence of progression

AURELIA - Progression-free survival



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

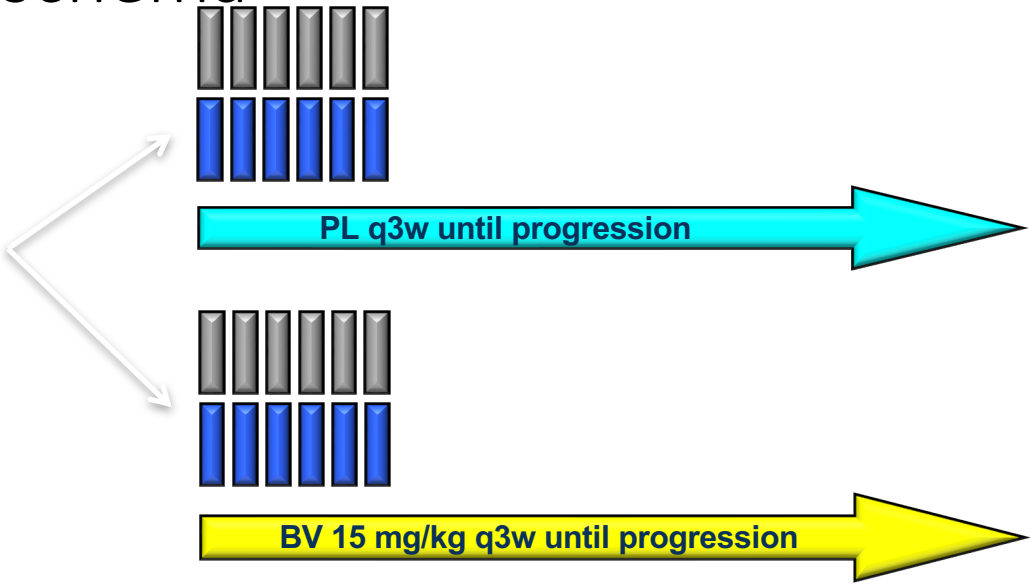
Pujade-Lauraine E. et al. LBA5002, ASCO 2012

OCEANS: Study schema

Platinum-sensitive recurrent OC[a]

- **Measurable disease**
- **ECOG 0/1**
- **No prior chemo for recurrent OC**
- **No prior BV**

(n=484)



months

Aghajanian C et al. J Clin Oncol 2012;30:2039

BV = bevacizumab; PL = placebo

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer

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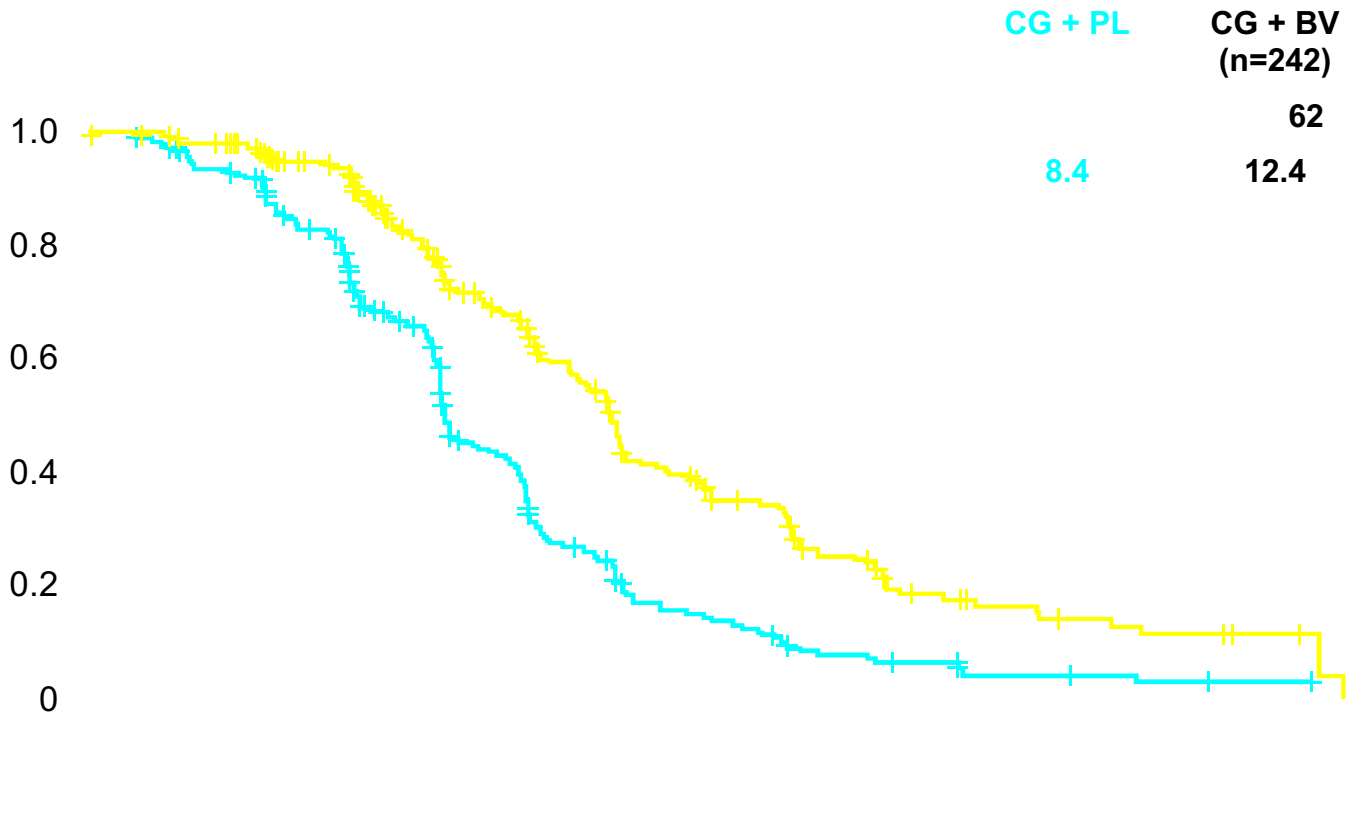
OCEANS: Primary analysis of PFS



Aghajanian C et al. J Clin Oncol. 2012; Apr 23 [Epub ahead of print]

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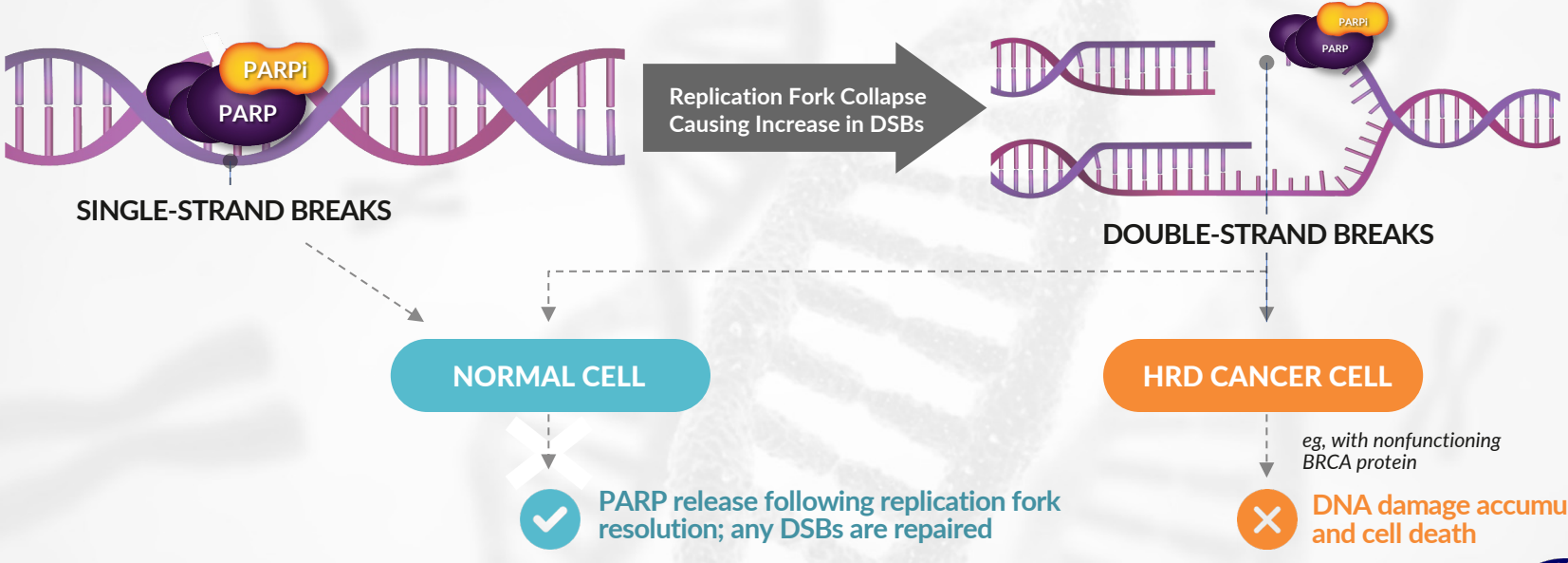
Targeting homologous recombination

PARP INHIBITORS BY BLOCKING SSB REPAIR INCREASE DSBS AND IN HRD CELLS THESE ARE NOT REPAIRED LEADING TO CELL DEATH



O'Connor MJ. Mol Cell. 2015;60:547-560.

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PARP inhibitors maintenance in recurrent ovarian cancer

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STUDY 19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib
in Platinum-Sens

Jonathan Ledermann, M.D.
Michael Friedlande
Gordon Rustin, M.D., Cl
Ronnie Shapira-Fromme
Euan Macpherson, M.Sc., C
a

BACKGROUND

From University College London, London

Olaparib (AZD2281) is an oral

NOVA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niraparib Maintenance Ther
Sensitive, Recurrent Ov

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza
M. Fabbro, J.A. Ledermann, D. Lorusso, I. Ve
C. Marth, R. Mądry, R.D. Christensen, J.S. Ber
A. du Bois, A. González-Martín, P. Follana, B. Beni
B.J. Rimel, J. Buscema, J.P. Balser, S. Agarw
for the ENGOT-OV16/NOVA Inv

ABSTRACT

BACKGROUND

Niraparib is an oral poly(adenosine diphosphate [Al
1/2 inhibitor that has shown clinical activity in pa

SOLO2

Articles

Olaparib tablets as maintenance therapy in patients with
platinum-sensitive, relapsed ovarian
mutation (SOLO2/ENGOT-Ov21): a d
randomised, placebo-controlled, pha

Eric Pujade-Lauraine, Jonathan A Ledermann, Frédéric Selle, Val Gebski, Richard T Penson,
Andrés Poveda, Sandro Pignata, Michael Friedlander, Nicoletta Colombo, Philipp Harter, K
Joyce Liu, Elizabeth S Lowe, Ralph Bloomfield, Patricia Pautier, the SOLO2/ENGOT-Ov21

Summary

Background Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibito
study when given in capsule formulation to all-comer patients with pl
ovarian cancer. We aimed to confirm these findings in patients with a B
tablet formulation of olaparib.

Methods This international, multicentre, double-blind, randomised, plac
tablet maintenance treatment in platinum-sensitive, relapsed ovarian c
had received at least two lines of previous chemotherapy. Eligible patien

ARIEL 3

Articles

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

Robert L Coleman*, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann*, on behalf of the ARIEL3 investigators†

Summary

Background Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has anticancer activity in recurrent ovarian carcinoma harbouring a *BRCA* mutation or high percentage of genome-wide loss of heterozygosity. In this trial we assessed rucaparib versus placebo after response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients from 87 hospitals and cancer centres across 11 countries. Eligible patients were aged 18 years or older, had a platinum-sensitive, hizh-

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See Online
http://dx.
S0140-6

PARP inhibitors treatment in recurrent ovarian cancer

University of Pittsburgh

University of Pittsburgh

FDA Increased Emphasis on OS in Ovarian Cancer Trials

Dear HCP Letter for NOVA Trial of Niraparib

Updated OS data from the ENGOT-OV16/NOVA study, a Phase III trial that evaluated the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer

- The primary endpoint of the study was progression free survival, which demonstrated the benefit of niraparib in patients with g*BRCA*mut and non-g*BRCA*mut ovarian cancer, including the HRD subgroups of non-g*BRCA*mut cohort.
- The observed overall survival (OS) results based on the currently available data (data cutoff date of October 1, 2020) are included below:
  - In the g*BRCA*mut cohort (N=203), the median OS was 43.6 months for patients treated with niraparib compared to 41.6 months for patients on placebo (HR = 0.93 [95% CI 0.63, 1.36])
  - In the non-g*BRCA*mut cohort (N=350), the median OS was 31.1 months for patients treated with niraparib compared to 36.5 months for patients on placebo (HR = 1.10 [95% CI 0.83, 1.46])
  - In the non-g*BRCA*mut, HRDpos subgroup (n=162), the median OS was 37.3 months for patients treated with niraparib compared to 41.4 months for patients on placebo (HR = 1.32 [95% CI 0.84, 2.06]).

  - As of the October 1, 2020 data cutoff date, 14% of patients in both the g*BRCA*mut and non-g*BRCA*mut cohorts had missing OS data. . is taking action to capture additional OS data in an effort to decrease the amount of missing survival information and intend to provide FDA with an updated OS analysis upon completion of our efforts.
- The current OS results indicate a possible OS detriment to patients in the overall non-g*BRCA*mut cohort and to patients in the non-g*BRCA*mut/HRDpos subgroup who received niraparib maintenance in this setting, as compared to placebo. The reason for this is currently unknown and additional efforts are ongoing to determine the potential etiology.
- These data are under review by the FDA.

g*BRCA*mut, germline *BRCA* mutant; HCP, healthcare provider; HR, hazard ratio; HRD, homologous recombination deficiency; OS, overall survival.
GSK Letter to HCPs: Important Drug Warning – Subject: Zejula® (Niraparib) important drug warning for the maintenance treatment in recurrent ovarian cancer (2L+).

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FDA Increased Emphasis on OS in Ovarian Cancer Trials

Dear HCP Letter for Rucaparib in *BRCA*-Mutated Ovarian Cancer After ≥2 Chemotherapies

The manufacturer of Rubraca has voluntarily withdrawn the drug for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, Fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapy lines.

The decision was made in conjunction with the FDA after detrimental OS impact was noted in patients randomized to rubraca in ARIEL4 study.

HCP, healthcare provider; OS, overall survival.
Clovis Letter to HCPs: IMPORTANT PRESCRIBING INFORMATION; Subject: Rubraca® (Rucaparib) for treatment of BRCA-mutated ovarian cancer after 2 or more chemotherapies is voluntarily withdrawn in the U.S.

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PARP inhibitors for maintenance in frontline ovarian cancer therapy

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ENGOT
European Network of Gynaecological Oncological Trial groups

GEICO
Grupo Español de Investigación en Cáncer de Ovario

GOG Gynecologic Oncology Group

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

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

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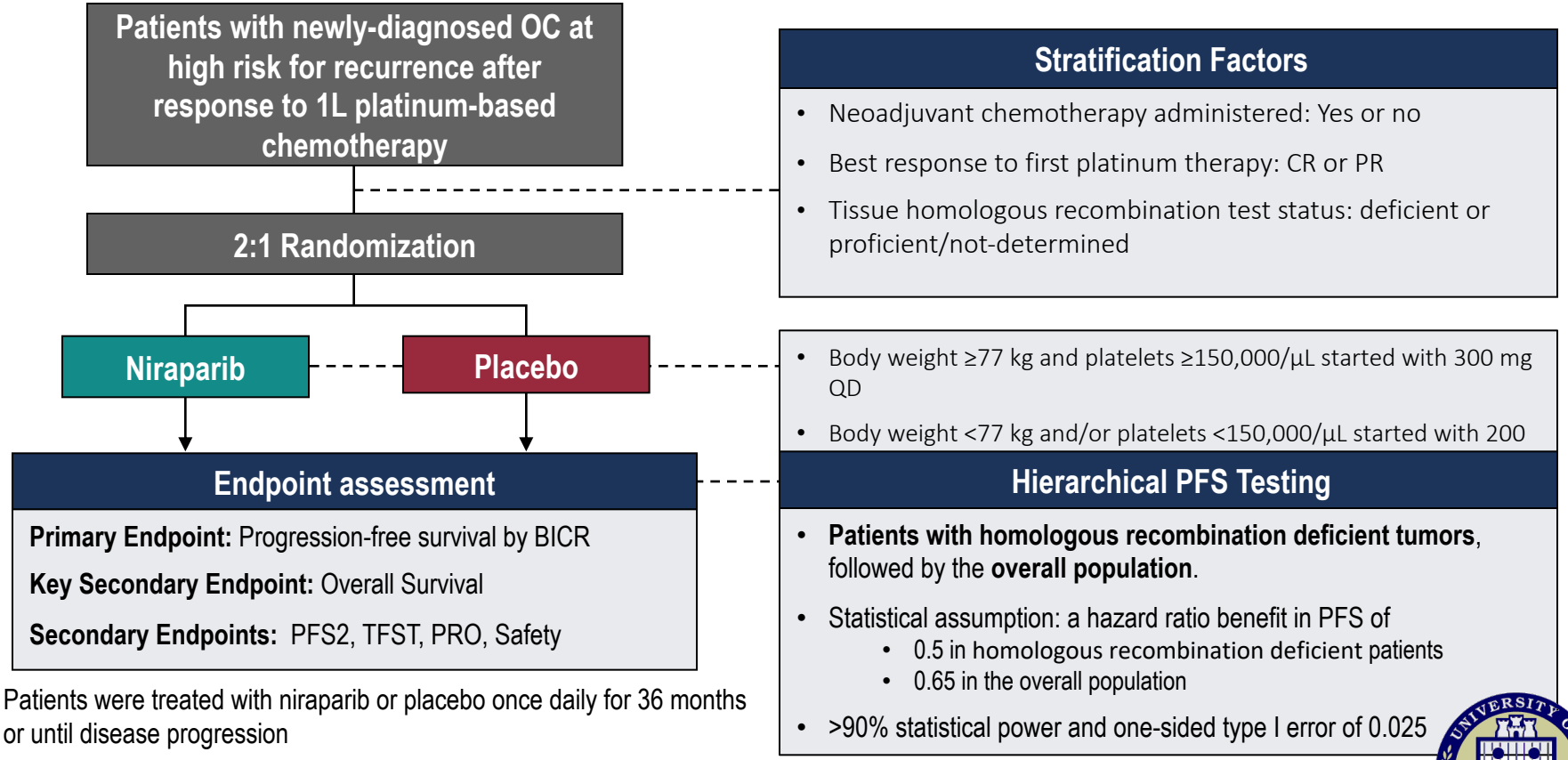
BARCELONA 2019 ESMO congress

esmo.org

PRIMA Trial Design



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

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

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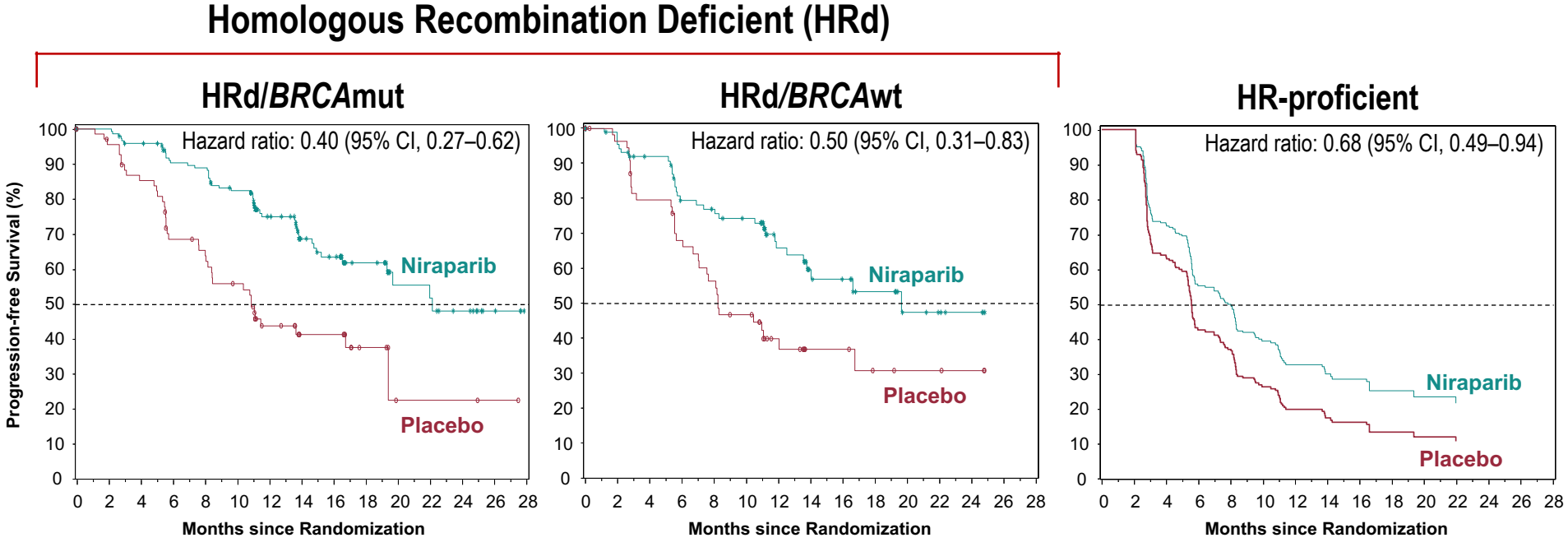
PRIMA PFS Benefit in Biomarker Subgroups



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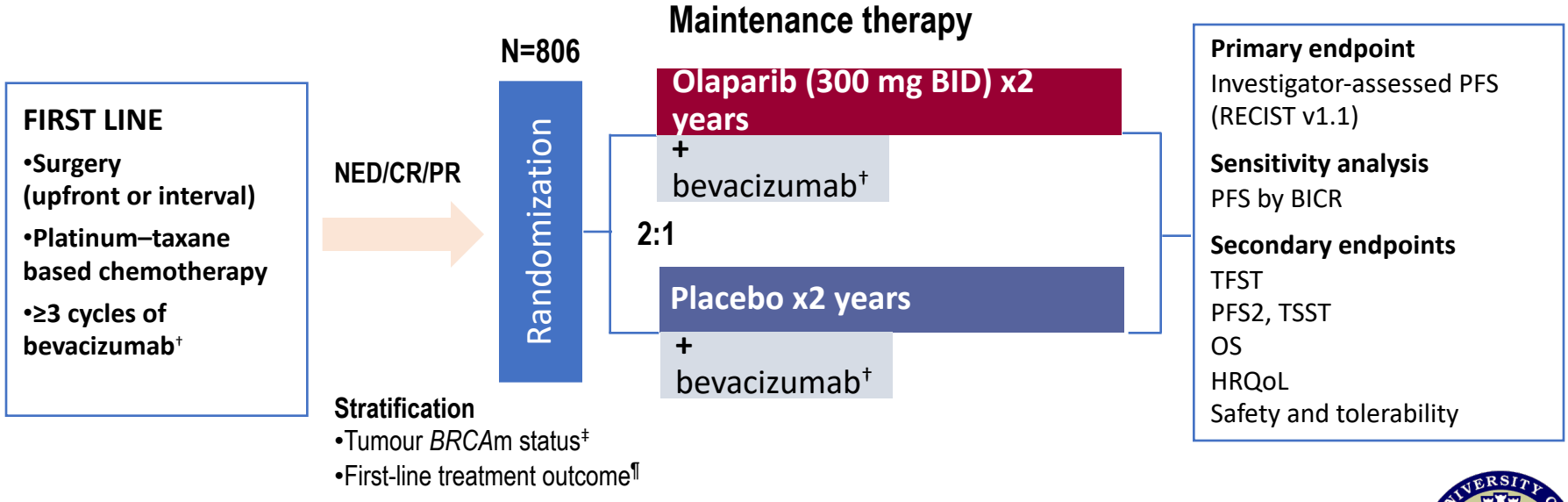
Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care

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

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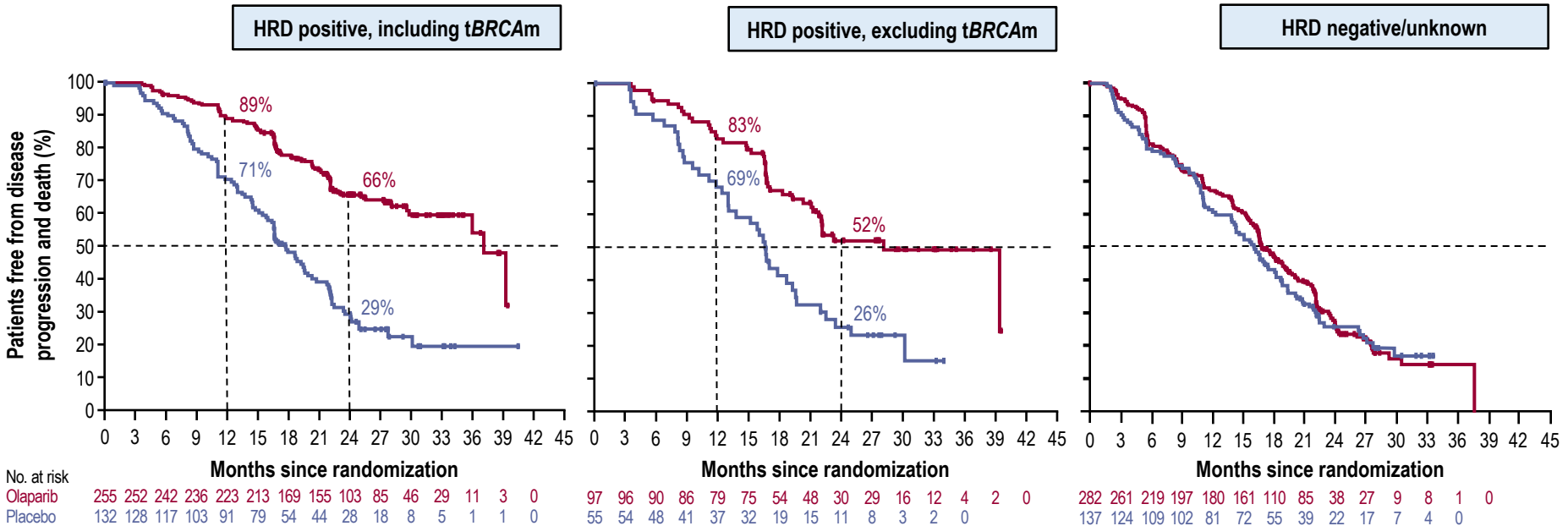
PFS by HRD status



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

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

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

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

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2022 ASCO® ANNUAL MEETING

GOG FOUNDATION®

ENGOT European Network of Gynaecological Oncological Trial groups

NRG Oncology-Japan

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

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

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

ATHENA–MONO Study Schema

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

Key Patient Eligibility

- Newly diagnosed, stage III–IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; R0/complete resection permitted)
- ECOG PS 0 or 1
- No prior treatment for ovarian cancer, including any maintenance treatment, other than frontline platinum regimen

Randomization 4:4:1:1

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

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

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

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors

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

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

Study Analyses

ATHENA–MONO

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

Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO

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

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

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

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

University of Pittsburgh

ATHENA–MONO Study Schema

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

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Arm D (n≈100)
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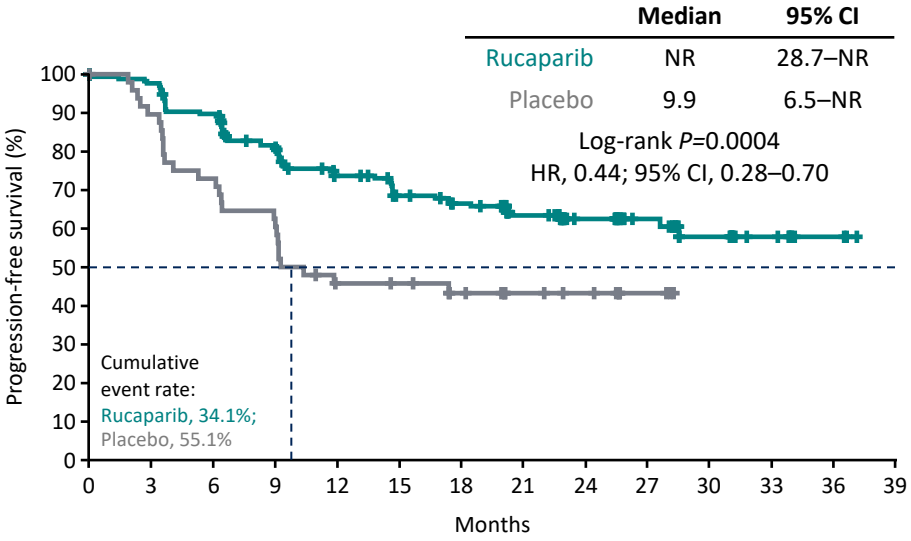
Secondary Endpoint – BICR-Assessed PFS

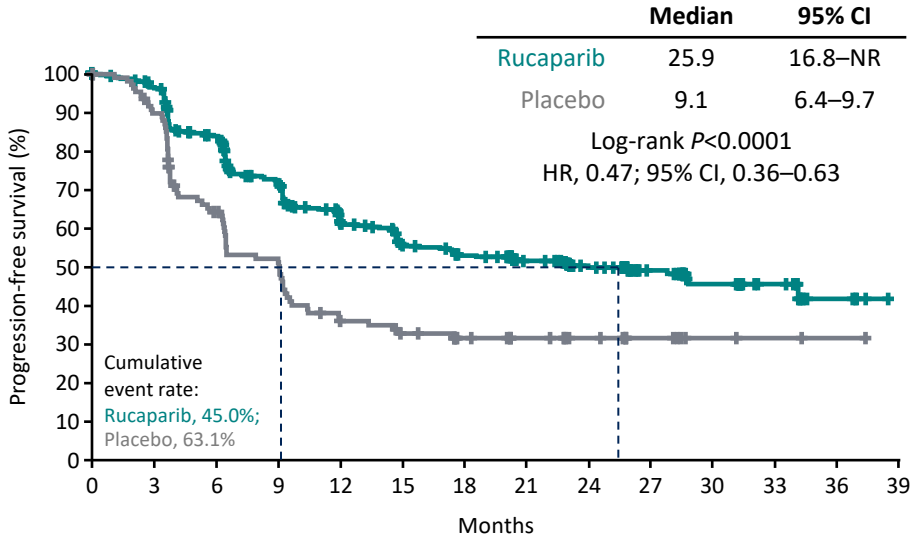
HRD



Patients at risk (events)

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

ITT



Patients at risk (events)

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

Data cutoff date: March 23, 2022.

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

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Antibody-Drug Conjugates (ADCs)

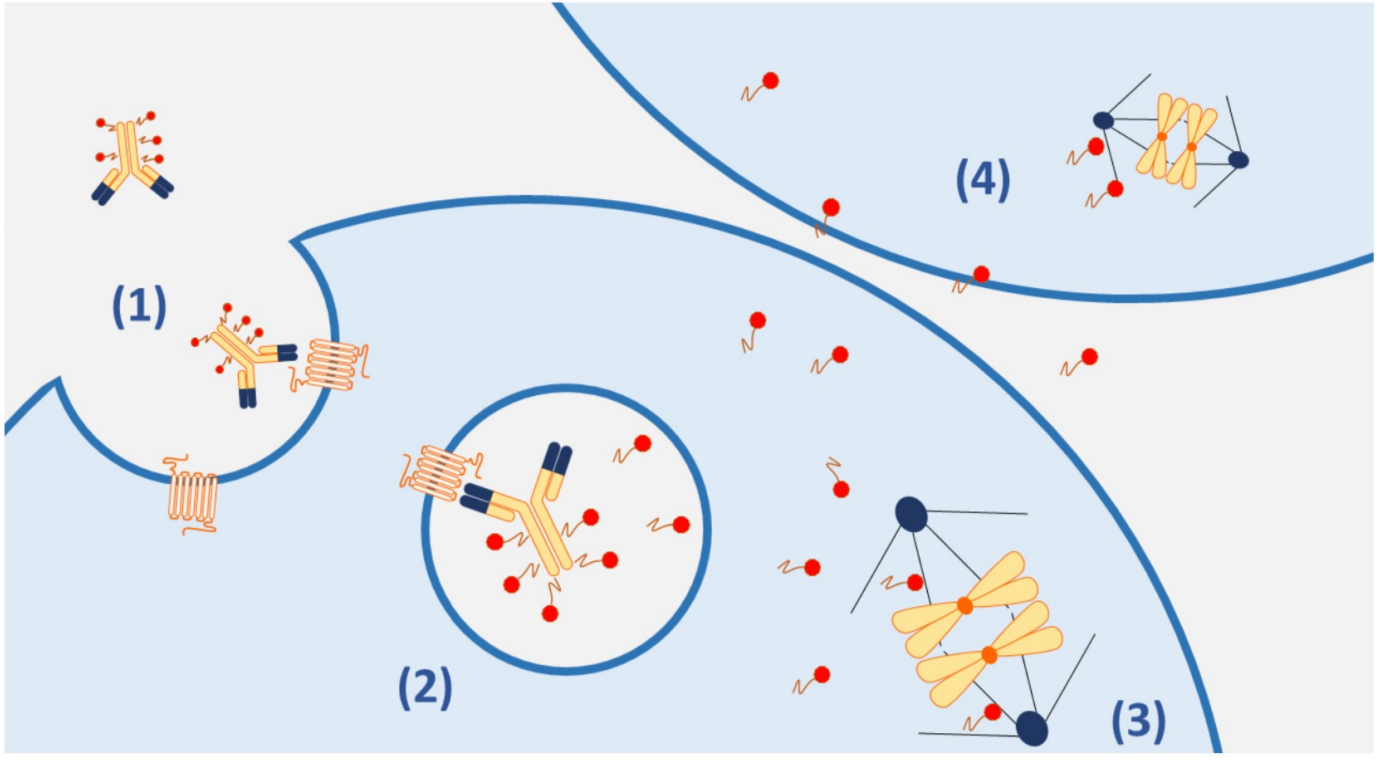


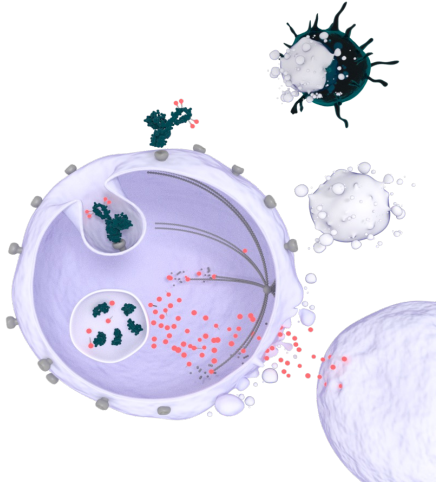
Figure 1. Main mechanisms of action of ADCs. (1). The ADC complex binds to the target antigen on the cancer cell membrane and is internalized; (2). in the lysosome, the payloads are released through linkers cleavage or antibody degradation (in case of non-cleavable linkers); (3). the cytotoxic payloads cause drug-specific microtubule inhibition; (4). the diffusion of cytotoxic payloads across the cell membranes can result in the death of neighboring antigen negative cells (bystander effect)

Nerone M, et al. Explor Target Antitumor Ther 2022; 3:149-71.

Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study

Ursula A. Matulonis,[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,[12] Brooke Esteves,[12] Michael Method,[12] Robert L. Coleman[13]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Fondazione Policlinico Universitario A. Gemelli, IRCCS and Catholic University of Sacred Heart, Rome, Italy; [3]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [4]Istituto Nazionale Tumori di Napoli Fondazione G Pascale IRCCS, Naples, Italy; [5]Ghent University Hospital, Ghent, Belgium; [6]European Institute of Oncology IRCCS, Milan, Italy and University of Milan-Bicocca, Milan, Italy; [7]University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]Institut Català d'Oncologia, Badalona, Spain; [10]Ev. Kliniken Essen-Mitte, Essen, Germany; [11]Bon Secours Hospital and Cancer Trials, Cork, Ireland; [12]ImmunoGen, Inc., Waltham, MA, USA; [13]US Oncology Research, Texas Oncology, The Woodlands, TX, USA



SORAYA

SORAYA: Study Design and Patient Population

Objective: Evaluate efficacy and safety of MIRV in patients with FRα-high platinum-resistant ovarian cancer

Primary endpoint: Confirmed ORR by investigator

- ORR by blinded independent central review for sensitivity analysis

Key secondary endpoint: Duration of response

Patient population

- Platinum-resistant ovarian cancer (recurrence within 6 months after last platinum dose) treated with 1 to 3 prior regimens
  - Primary platinum-refractory disease* was excluded
- High-grade serous histology
- All enrolled received prior bevacizumab; prior PARP inhibitor was allowed
- Tumor demonstrated FRα-high membrane staining with IHC PS2+ scoring
  - **≥75%** of cells staining positive with **≥2+** staining intensity

Treatment schedule

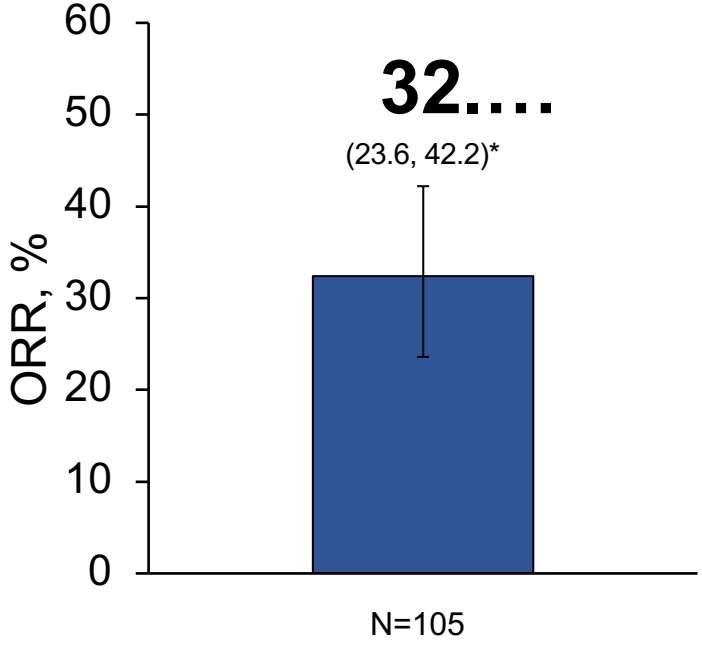
- Patients received MIRV 6 mg/kg, adjusted ideal body weight, IV once every 3 weeks

Sample size calculation: 105 patients

- 110 patients planned to result in approximately 105 efficacy-evaluable patients
- 90% power to detect a difference in ORR of 24% vs 12% using a 1-sided binomial test and a 1-sided α level of 0.025
- 12% was chosen as the ORR to rule out based on the ORR for single-agent chemotherapy reported in prior trials of platinum-resistant ovarian cancer, which ranges from 4% to 13%[1-4]

*Defined as disease that did not respond to first-line platinum therapy or progressed within 3 months of the last dose.
FRα, folate receptor alpha; IHC, immunohistochemistry; IV, intravenous; MIRV, mirvetuximab soravtansine; ORR, confirmed objective response rate; PARP, poly ADP-ribose polymerase; PS2+, sum of staining of 2+ and 3+ intensity.
1. Pujade-Lauraine E, et al. *J Clin Oncol*. 2014;32(13):1302-1308. 2. Gaillard S, et al. *Gynecol Oncol*. 2021;163(2):237-245. 3. Moore KN, et al. *Ann Oncol*. 2021;32(6):757-765. 4. Pujade-Lauraine E, et al. *Lancet Oncol*. 2021;22(7):1034-1046.

Investigator-Assessed Objective Response Rate in Overall Efficacy Evaluable Population

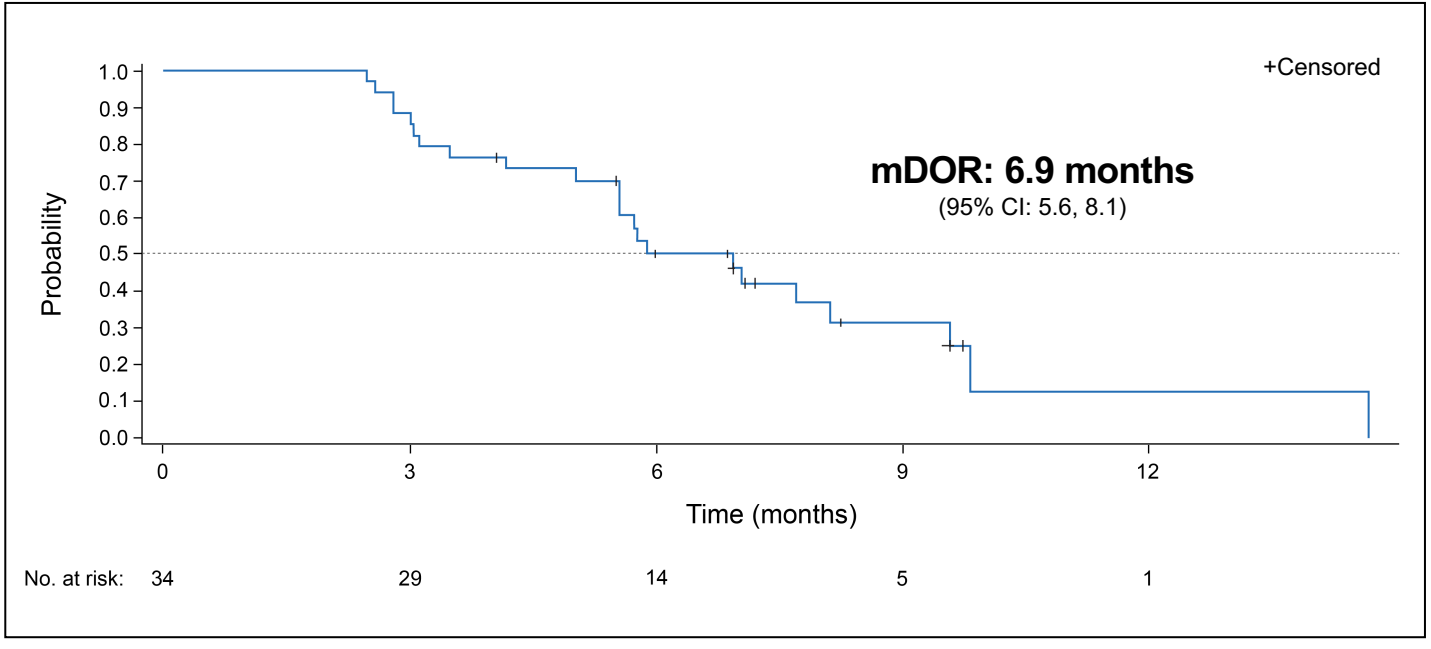


34 responders

- 5 complete responses
- 29 partial responses

Data cutoff: November 16, 2021.
The denominator for the percentage is the number of patients in the investigator-assessed efficacy evaluable population. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable.
*95% exact confidence interval is estimated by Clopper-Pearson method (Clopper-Pearson exact CI).
ORR, confirmed objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

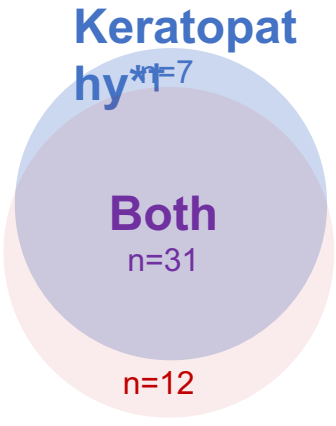
Investigator-Assessed Duration of Response



Data cutoff: March 3, 2022.
CI, confidence interval; mDOR, median duration of response.

Unique Events Specific to MIRV: Keratopathy and Blurred Vision

Events developed in 50/106 (47%) patients: mostly low grade



- **Proactive supportive care**
  - Lubricating artificial tears
  - Corticosteroid eye drops
- **Predictable**
  - Median time to onset: cycle 2 (~1.5 months)
- **Manageable with dose modifications, if needed**
  - 22% of patients (23/106) had dose delay and/or reduction
- **Reversible**
  - At data cutoff: >80% of patients with grade 2–3 events had resolved to grade 0–1
    - 9 patients still receiving MIRV or being followed up for resolution
- **<1% discontinuation due to ocular events**
  - 1 of 106 patients discontinued due to grade 4 keratopathy,† which resolved within 15 days

Data cutoff: November 16, 2021.

The grouped preferred term "Keratopathy" includes the following preferred terms: "corneal cyst," "corneal disorder," "corneal epithelial microcysts," "keratitis," "keratopathy," "limbal stem cell deficiency," "corneal opacity," "corneal erosion," "corneal pigmentation," "corneal deposits," "keratitis interstitial," "punctate keratitis," and "corneal epithelial defect." †One patient experiencing a grade 4 event recorded as keratopathy was based upon the visual acuity evaluation of one eye (20/200). This patient had confirmed grade 2 corneal changes, and both the visual acuity and these corneal changes resolved completely (grade 0) in 15 days by ophthalmic exam.

MIRV, mirvetuximab soravtansine.

Uterine cancer

Incidence, 2023 USA Estimates

Female		
Breast	297,790	31%
Lung & bronchus	120,790	13%
Colon & rectum	71,160	8%
Uterine corpus	66,200	7%
Melanoma of the skin	39,490	4%
Non-Hodgkin lymphoma	35,670	4%
Thyroid	31,180	3%
Pancreas	30,920	3%
Kidney & renal pelvis	29,440	3%
Leukemia	23,940	3%
All sites	**948,000**	

University of Pittsburgh

Mortality, 2023 USA Estimates

Female		
Lung & bronchus	59,910	21%
Breast	43,170	15%
Colon & rectum	24,080	8%
Pancreas	23,930	8%
Ovary	13,270	5%
Uterine corpus	13,030	5%
Liver & intrahepatic bile duct	10,380	4%
Leukemia	9,810	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,970	3%
All sites	**287,740**	

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Endometrial cancer is the only gynecologic cancer with rising incidence and mortality

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Adjuvant Therapy

University of Pittsburgh

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

J Clin Oncol. 2019 Jul 20; 37(21): 1810–1818.
Published online 2019 Apr 17. doi: 10.1200/JCO.18.01575

PMCID: PMC6804858
PMID: 30995174

Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early-Stage Endometrial Cancer

Marcus E. Randall, MD,[1] Virginia Filiaci, PhD,[2] D. Scott McMeekin, MD,[3,†] Vivian von Gruenigen, MD,[4] Helen Huang, MS,[2] Catheryn M. Yashar, MD,[5] Robert S. Mannel, MD,[3] Jae-Weon Kim, MD, PhD,[6] Ritu Salani, MD,[7] Paul A. DiSilvestro, MD,[8] James J. Burke, MD,[9] Thomas Rutherford, MD,[10] Nick M. Spirtos, MD,[11] Keith Terada, MD,[12] Penny R. Anderson, MD,[13] Wendy R. Brewster, MD,[14] William Small, MD,[15] Carol A. Aghajanian, MD,[16] and David S. Miller, MD[17]

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GOG 249

Key eligibility criteria

- Patients must have had staging surgery
- Endometroid adenocarcinoma meeting the GOG 99 high-intermediate risk criteria
- Clear cell or serous histology with stage I or II disease but negative washing
- Patients without lymph node assessment but negative 3-dimensional imaging for adenopathy

601 patients enrolled, 300 in each arm

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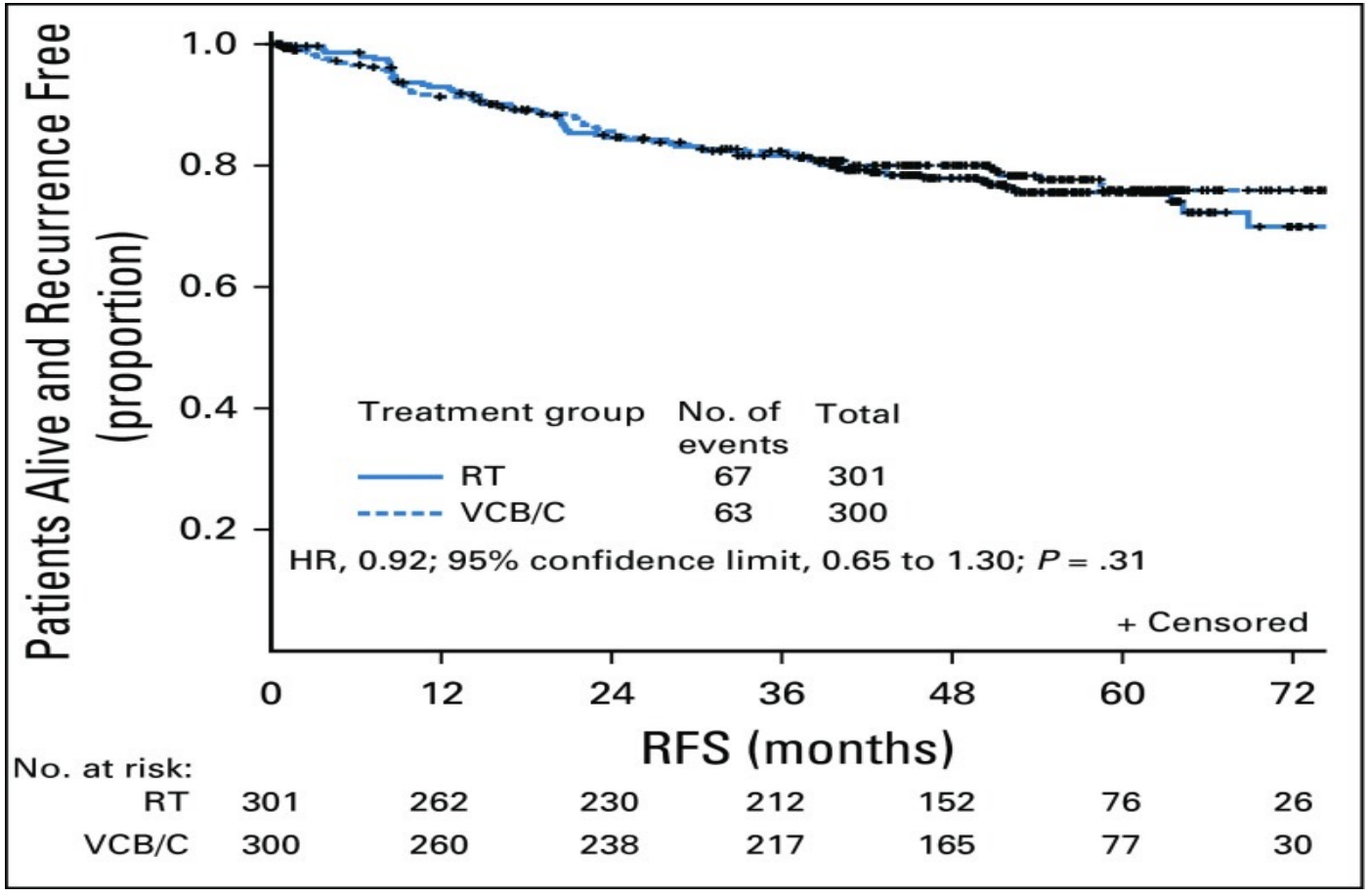

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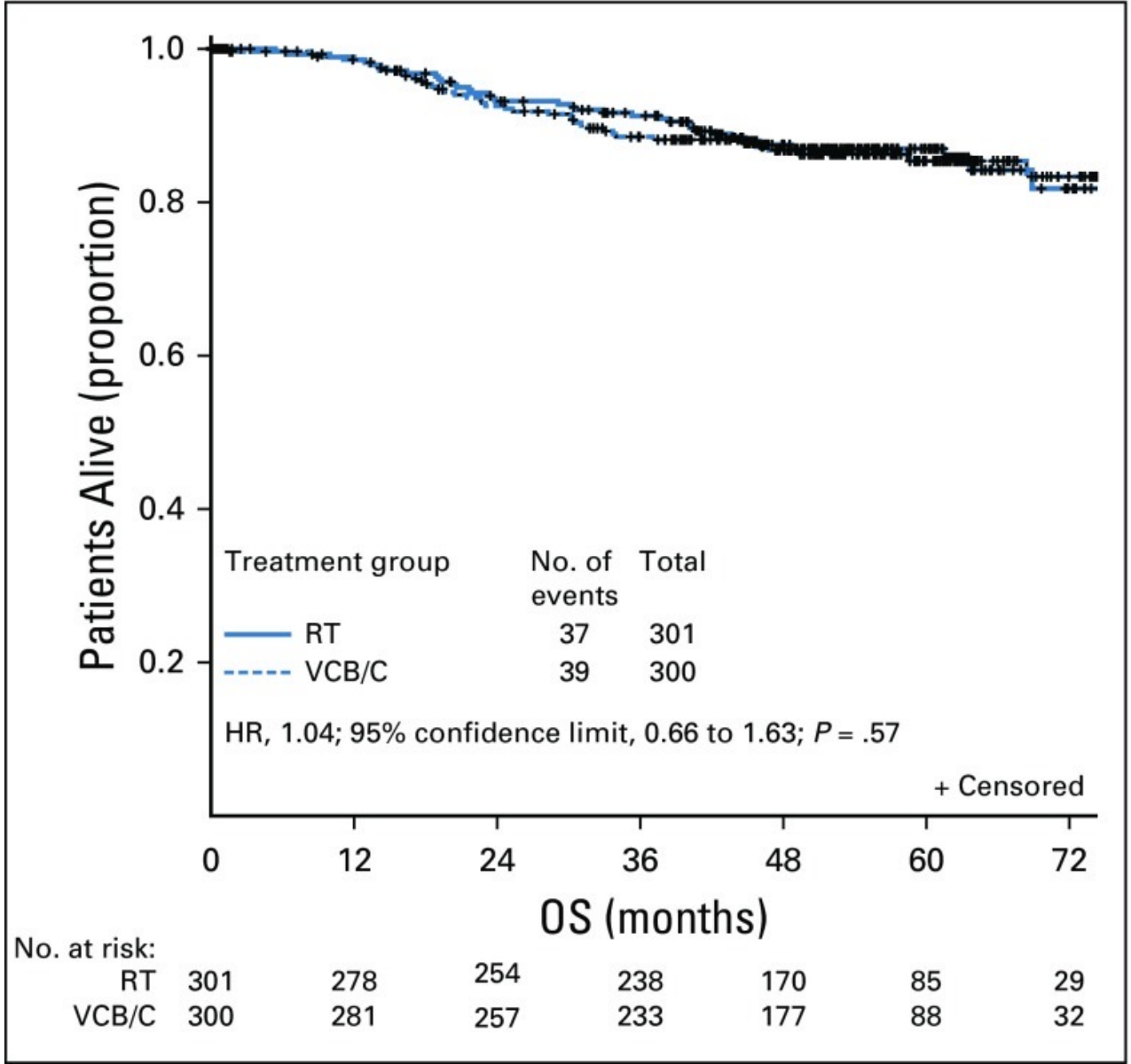

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer

Daniela Matei, M.D., Virginia Filiaci, Ph.D., Marcus E. Randall, M.D., David Mutch, M.D., Margaret M. Steinhoff, M.D., Paul A. DiSilvestro, M.D., Katherine M. Moxley, M.D., Yong M. Kim, M.D., Ph.D., Matthew A. Powell, M.D., David M. O'Malley, M.D., Nick M. Spirtos, M.D., William Small, Jr., M.D., Krishnansu S. Tewari, M.D., William E. Richards, M.D., John Nakayama, M.D., Ursula A. Matulonis, M.D., Helen Q. Huang, M.S., and David S. Miller, M.D.

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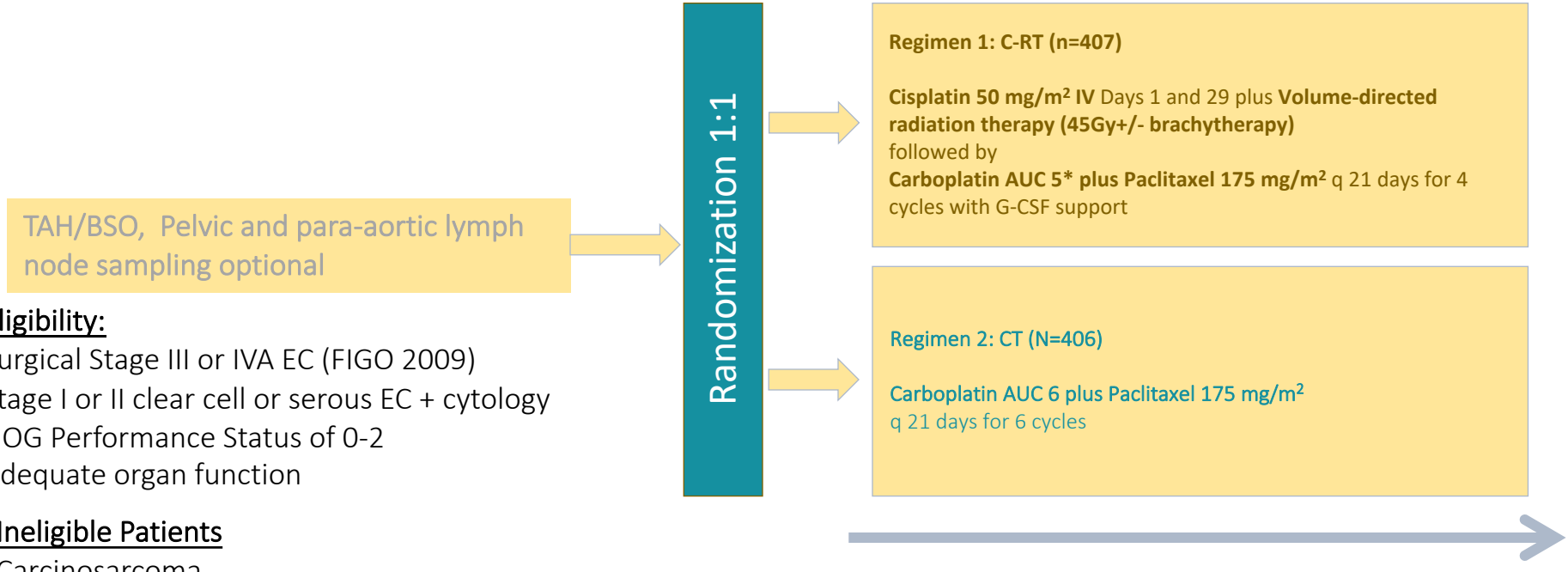
Study Schema



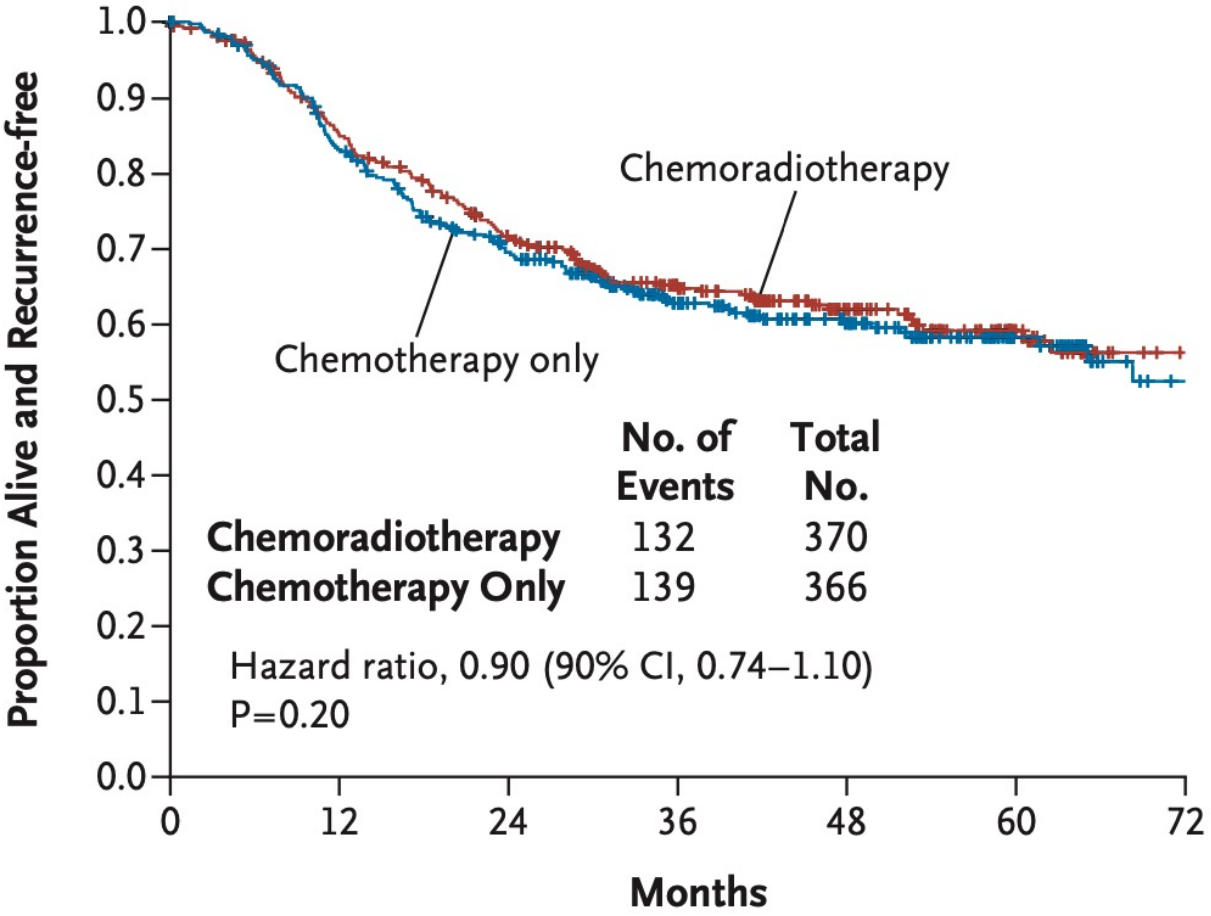
Eligibility:

Surgical Stage III or IVA EC (FIGO 2009)
Stage I or II clear cell or serous EC + cytology
GOG Performance Status of 0-2
Adequate organ function

Ineligible Patients

Carcinosarcoma
Recurrent EC
Residual tumor after surgery > 2 cm

Presented by: Daniela Matei, MD



No. at Risk

Chemoradiotherapy	370	295	235	164	103	45	19
Chemotherapy only	366	293	230	159	113	55	17

rgh

Sytemic therapy for stage III/IV and recurrent disease

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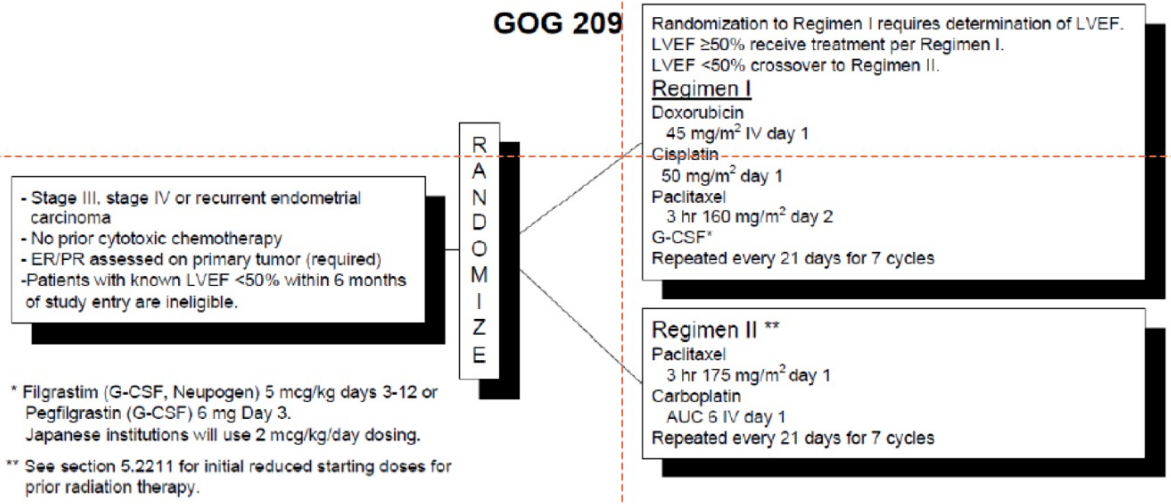
GOG 209

Established carboplatin and paclitaxel as the chemotherapy backbone for patients with advanced stage or recurrent disease



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GOG 209

- **Key eligibility criteria**
  - **Stage III, Stage IV or recurrent endometrial carcinoma** whose potential for cure by radiation therapy or surgery alone or in combination is very poor
    - No mandate for measurable disease
  - Pathological confirmation and Estrogen Receptor (ER)/Progesterone Receptor (PR) status of the primary tumor is mandatory
  - **NO prior cytotoxic chemotherapy**, including chemotherapy used for radiation sensitization
  - Patients may have received prior radiation therapy, hormonal therapy, or therapy with biologic agents, but such therapies must be discontinued prior to entry on this study
  - GOG PS 0,1 or 2

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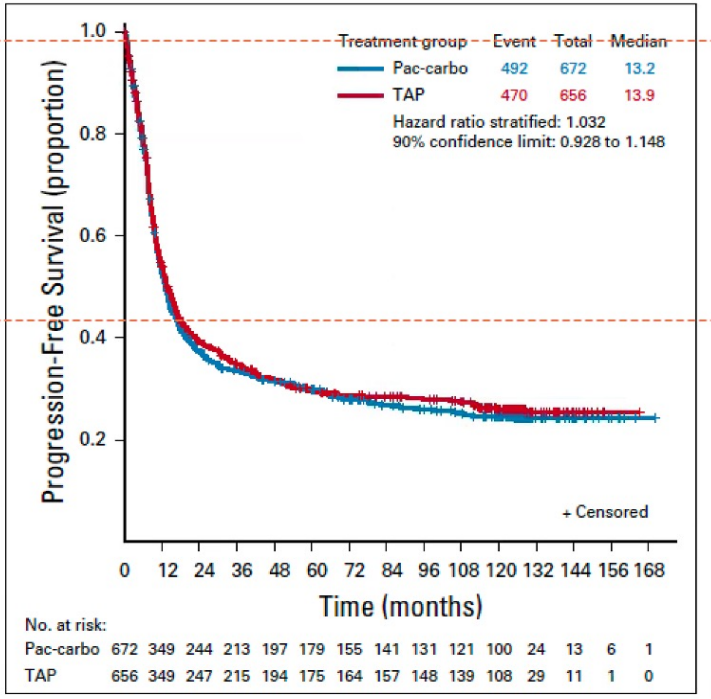
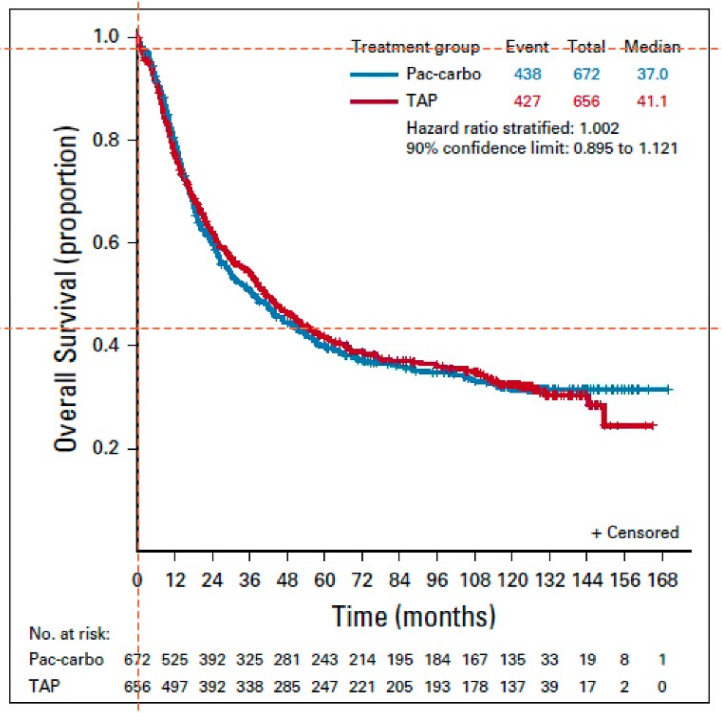
GOG 209: Survival Outcomes



Progression Free Survival



Overall Survival

Miller DS, et al. J Clin Oncol. 2020 Nov 20;38(33):3841-3850.

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Molecular classification & immunotherapy in EC

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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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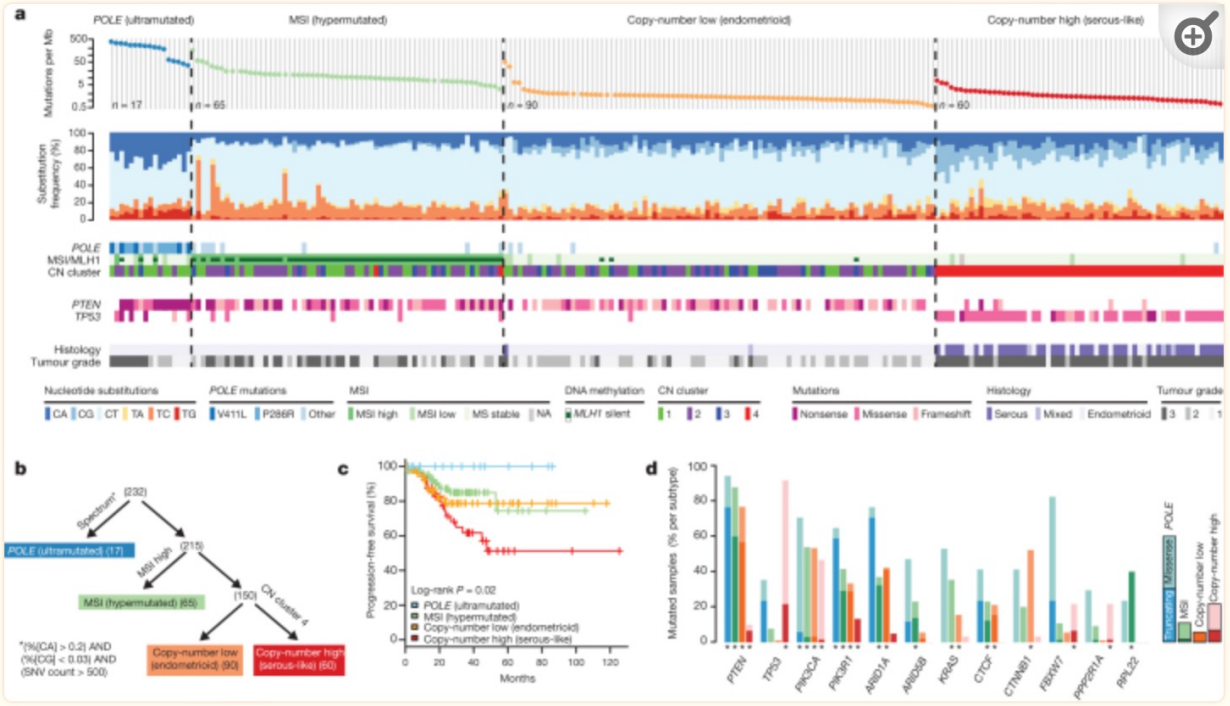
Genomic Characterization of EC



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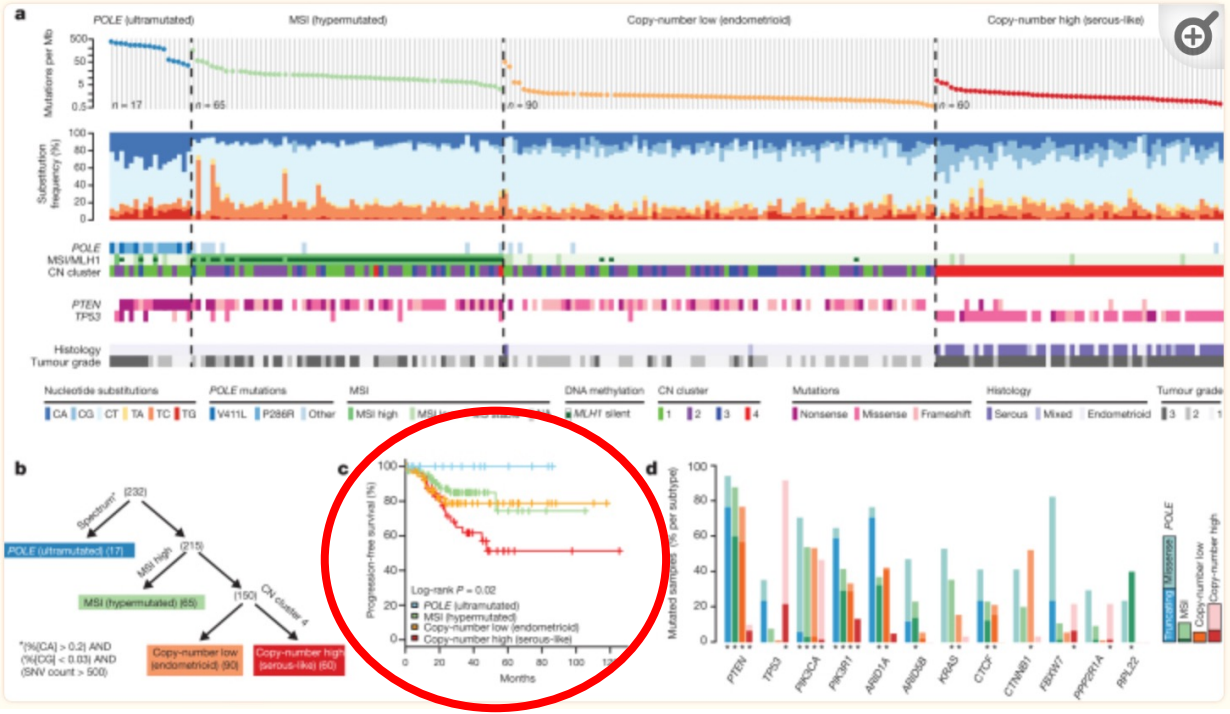
Genomic Characterization of EC



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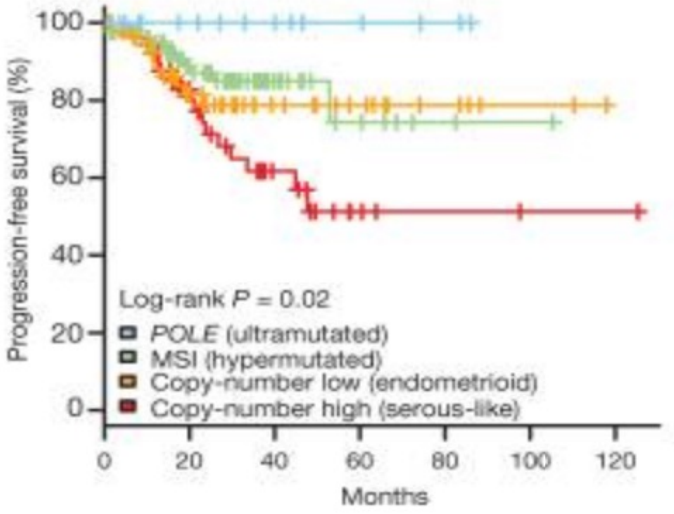
Genomic Characterization of EC



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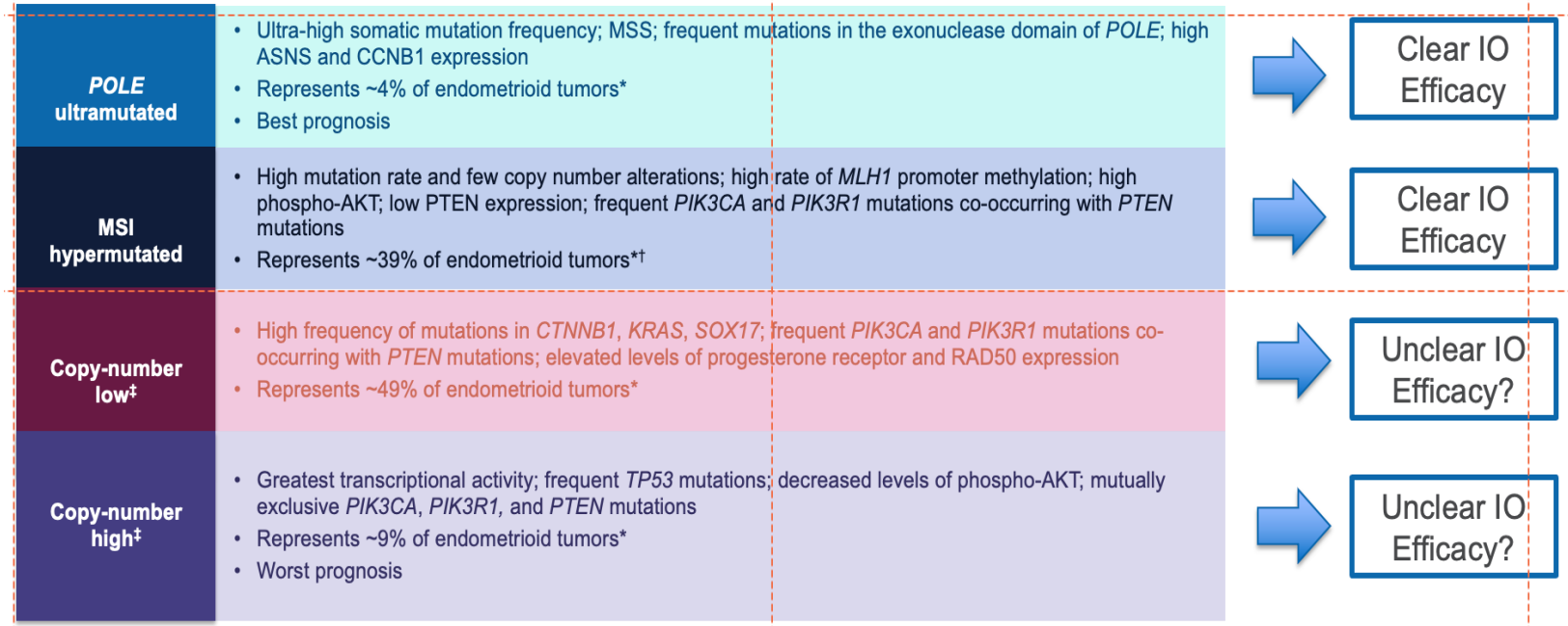
Endometrial Cancer: Molecular Subtypes



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

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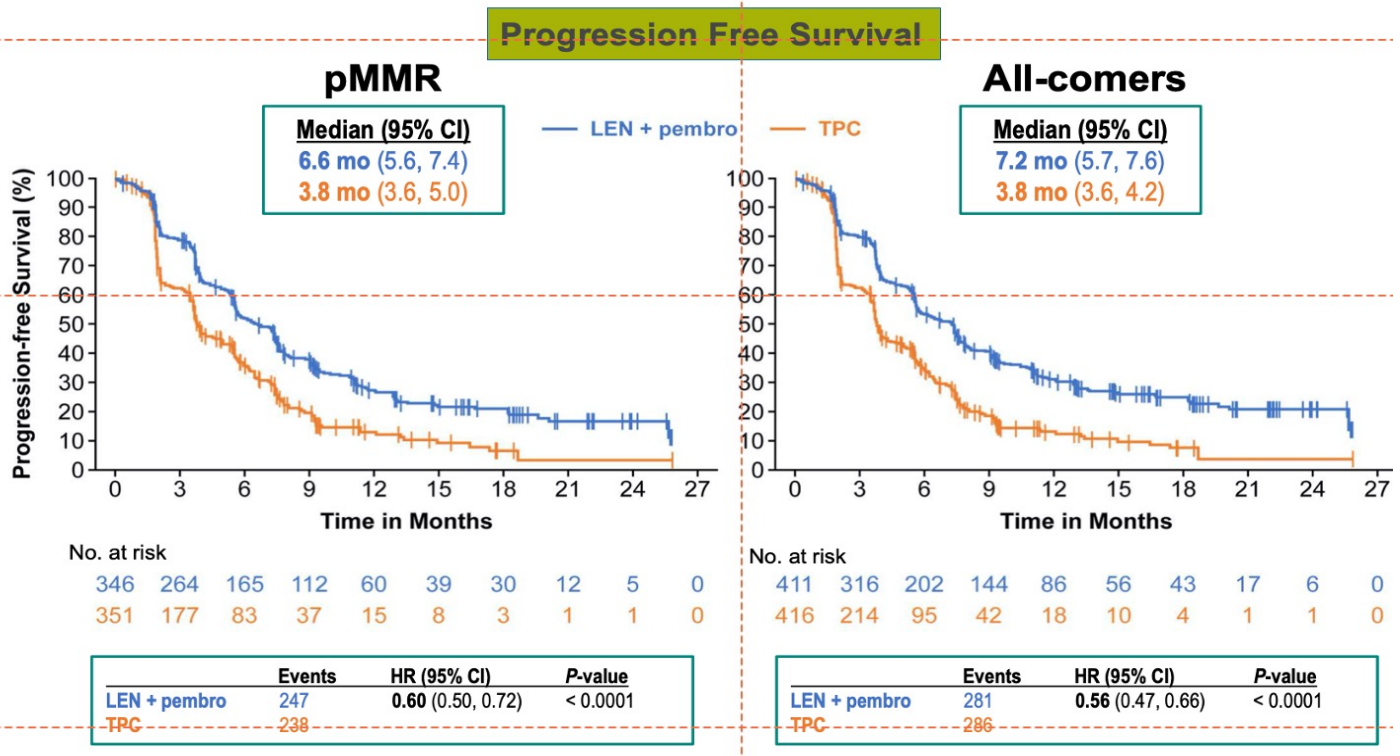
Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)



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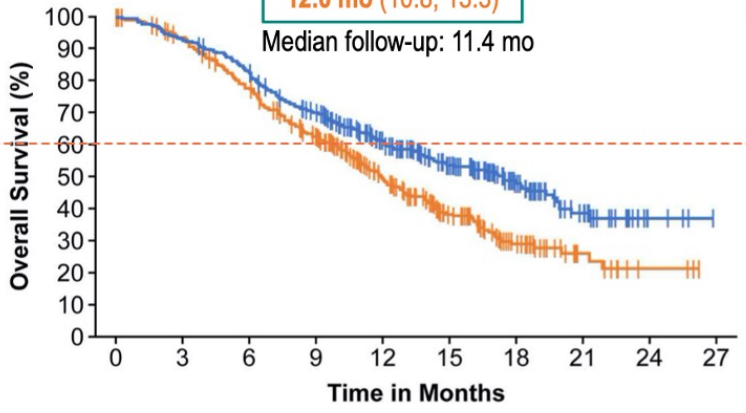
Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)

Overall Survival

pMMR

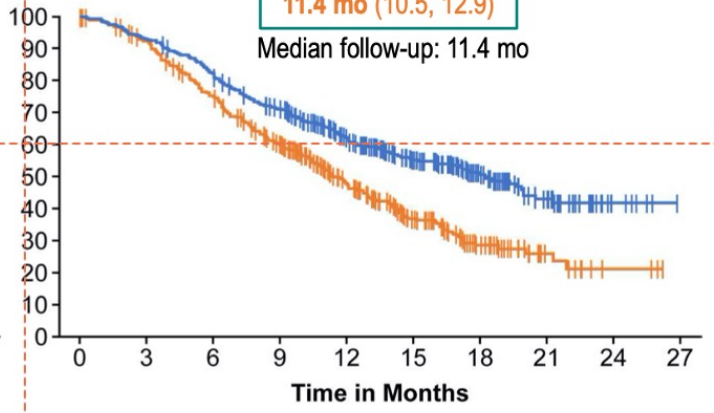


No. at risk

346	322	285	232	160	109	62	28	5	0
351	319	262	201	120	70	33	11	3	0

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

All-comers



No. at risk

411	383	337	282	198	136	81	40	7	0
416	373	300	228	138	80	40	11	3	0

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

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The NEW ENGLAND JOURNAL of MEDICINE

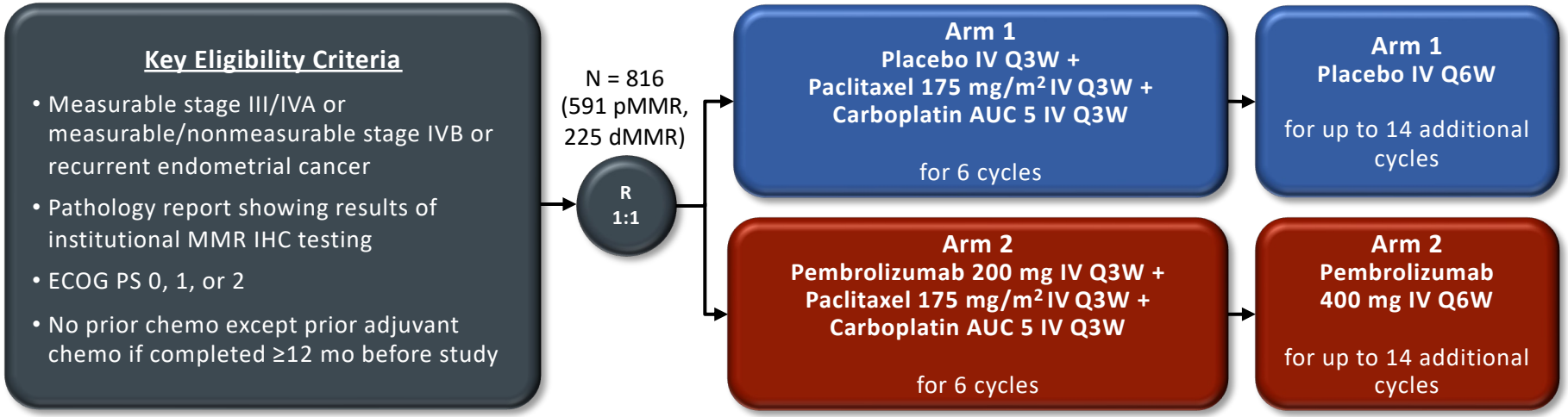
ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie Mayer Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath, III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

University of Pittsburgh

NRG-GY018 (NCT03914612)



Stratification Factors

- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

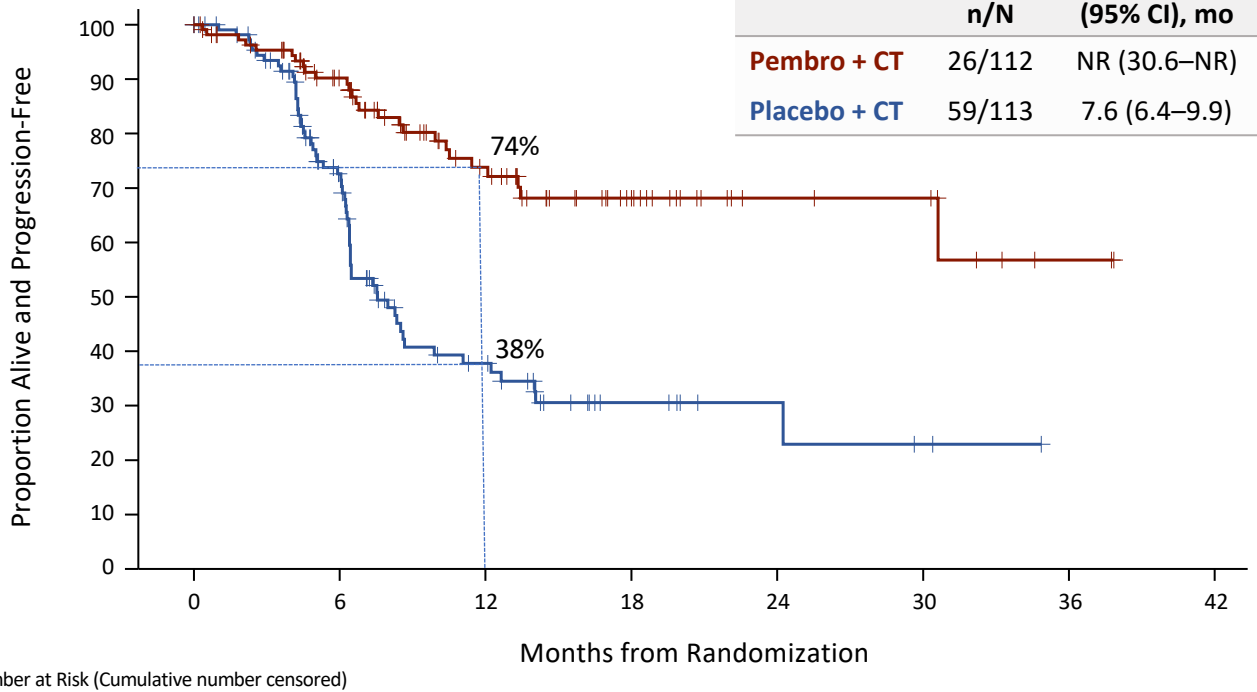
Endpoints

- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary:** Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of institutional vs central MMR IHC testing results

BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; PRO, patient-reported outcomes; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid T

PFS per RECIST v1.1: dMMR Population

	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	26/112	NR (30.6–NR)	0.30 (0.19–0.48)
Placebo + CT	59/113	7.6 (6.4–9.9)	*P* = <0.00001



Number at Risk (Cumulative number censored)

Placebo + CT	113 (2)	62 (24)	24 (35)	8 (47)	4 (51)	2 (52)	0 (54)	
Pembro + CT	112 (1)	80 (22)	44 (46)	22 (65)	9 (78)	8 (79)	2 (84)	0 (86)

Data cutoff date: December 16, 2022.

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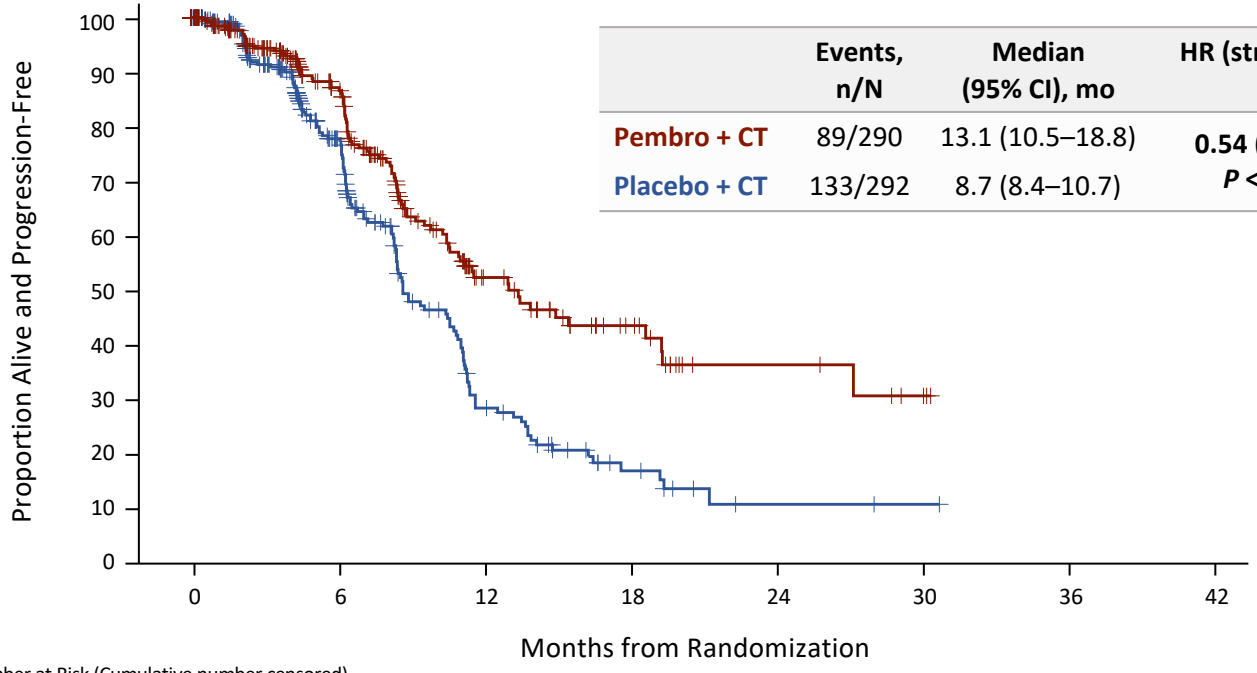
PFS per RECIST v1.1: pMMR Population



	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	89/290	13.1 (10.5–18.8)	**0.54 (0.41–0.71)**
Placebo + CT	133/292	8.7 (8.4–10.7)	***P* < 0.00001**

Number at Risk (Cumulative number censored)

Placebo + CT	292 (14)	129 (115)	33 (141)	10 (152)	2 (157)	1 (158)	0 (159)
Pembro + CT	290 (15)	150 (112)	45 (167)	20 (185)	7 (195)	3 (198)	0 (201)

University of Pittsburgh

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ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

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ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients

- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted[a]
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification

- MMR/MSI status[b]
- Prior external pelvic radiotherapy
- Disease status

R1:1

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2
Q3W for 6 cycles

Dostarlimab IV 1000 mg
Q6W up to 3 years[c]

Placebo
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2
Q3W for 6 cycles

Placebo IV
Q6W up to 3 years[c]

Follow -up

Primary endpoint

- PFS by INV
- OS

Secondary endpoints

- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by Investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later, or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care. [a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; IV, administered intravenously; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

ENGOT-EN6-NSGO/GOG-3031/RUBY presented by Mansoor R Mirza

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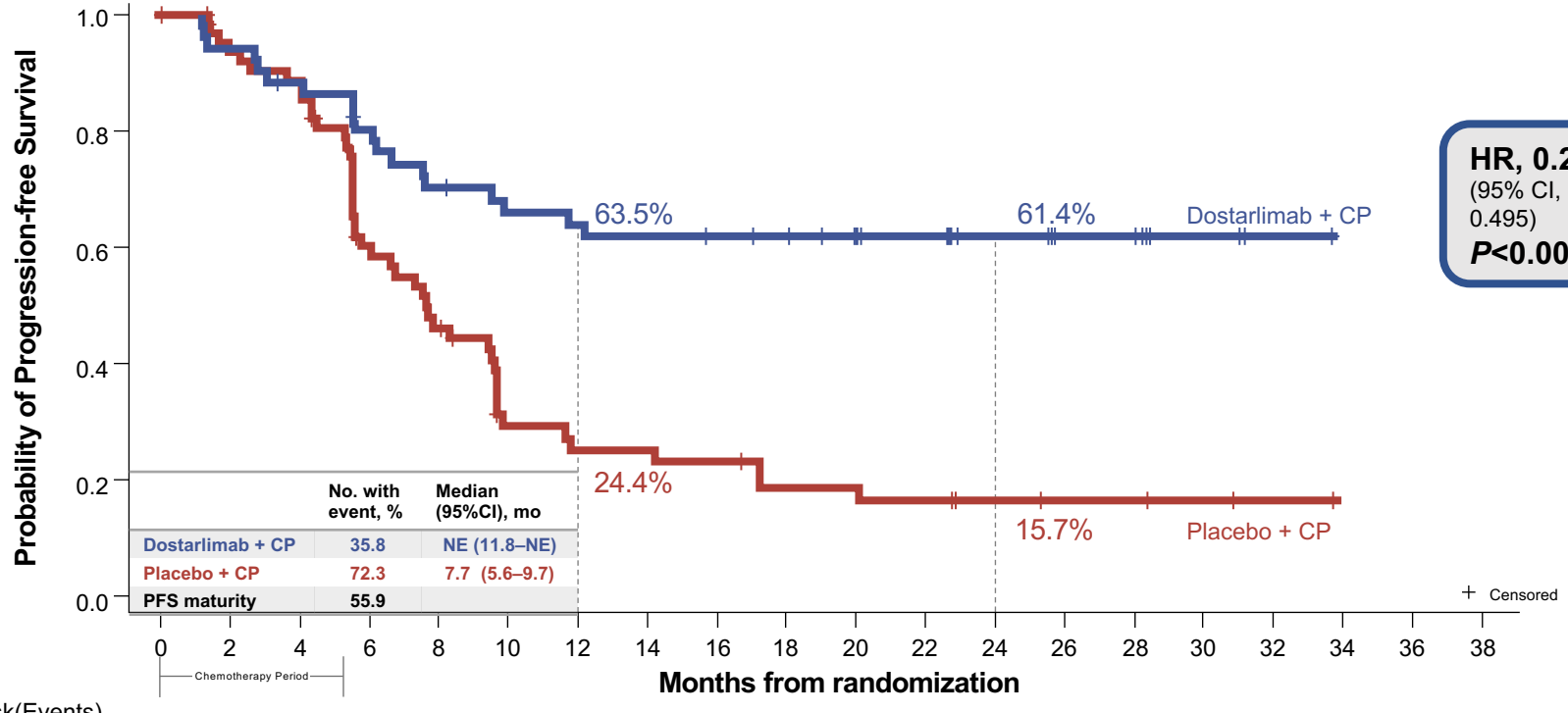
Primary Endpoint: PFS in dMMR/MSI-H Population



HR, 0.28
(95% CI, 0.162–0.495)
***P*<0.0001**

At Risk(Events)

Dostarlimab + CP	53(0)	48(3)	44(6)	39(10)	34(15)	31(17)	30(18)	29(19)	28(19)	27(19)	25(19)	19(19)	13(19)	9(19)	9(19)	4(19)	1(19)	0(19)
Placebo + CP	65(0)	57(4)	54(7)	34(24)	26(32)	14(41)	12(43)	12(43)	11(44)	8(46)	8(46)	7(47)	4(47)	3(47)	3(47)	2(47)	1(47)	0(47)

Median duration of follow-up 24.79 months.

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival.

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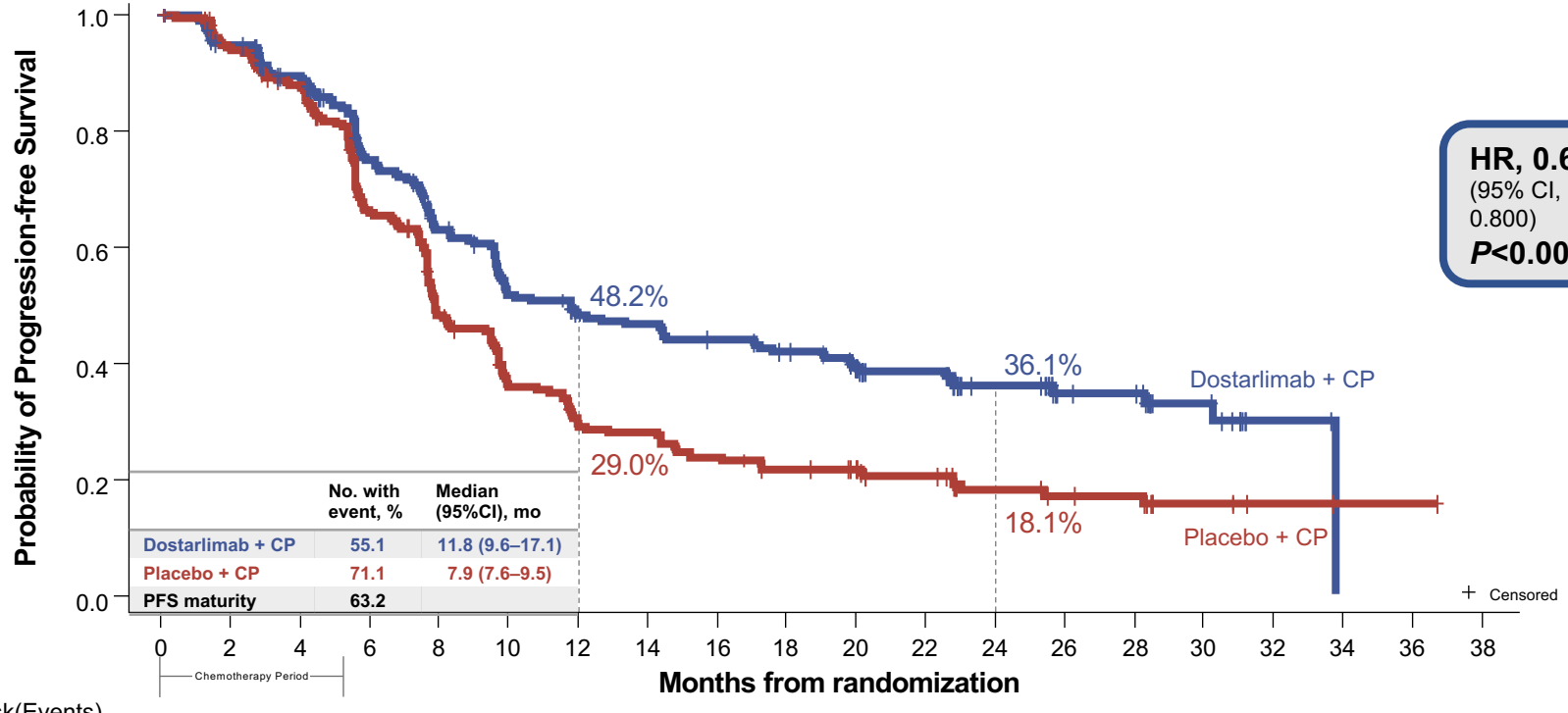
Primary Endpoint: PFS in Overall Population



HR, 0.64
(95% CI, 0.507–0.800)
***P*<0.0001**

At Risk(Events)

Dostarlimab + CP	245(0)	220(12)	197(25)	157(55)	130(80)	105(103)	94(110)	90(113)	84(118)	78(122)	66(127)	52(128)	34(131)	23(132)	22(132)	12(133)	2(134)	0(135)	
Placebo + CP	249(0)	219(14)	200(29)	144(77)	103(115)	74(141)	59(155)	57(157)	48(166)	42(170)	39(170)	32(172)	20(175)	14(176)	13(176)	5(177)	2(177)	1(177)	1(177)	0(177)

Median duration of follow-up 25.38 months.

CP, carboplatin/paclitaxel; HR, hazard ratio; PFS, progression-free survival.

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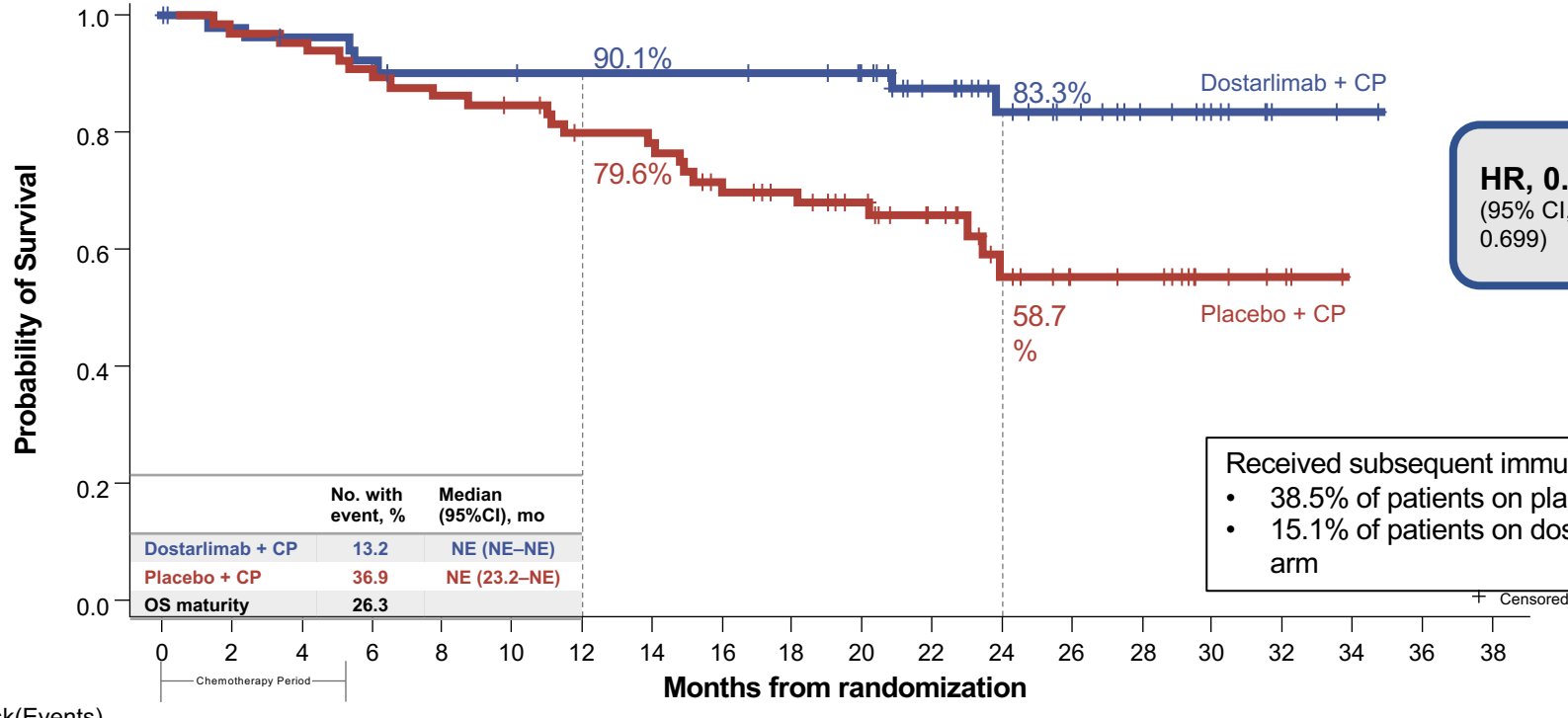
OS in dMMR/MSI-H Population



	No. with event, %	Median (95%CI), mo
Dostarlimab + CP	13.2	NE (NE–NE)
Placebo + CP	36.9	NE (23.2–NE)
OS maturity	26.3	

HR, 0.30
(95% CI, 0.127–0.699)

Received subsequent immunotherapy:
- 38.5% of patients on placebo arm
- 15.1% of patients on dostarlimab arm

At Risk(Events)

Dostarlimab + CP	53(0)	50(1)	48(2)	46(4)	44(5)	44(5)	43(5)	43(5)	43(5)	42(5)	41(5)	29(6)	20(7)	16(7)	12(7)	8(7)	2(7)	1(7)	0(7)
Placebo + CP	65(0)	63(2)	62(3)	59(6)	55(9)	53(10)	48(13)	47(14)	41(18)	37(19)	32(20)	25(21)	16(23)	12(24)	10(24)	5(24)	3(24)	0(24)	

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival.

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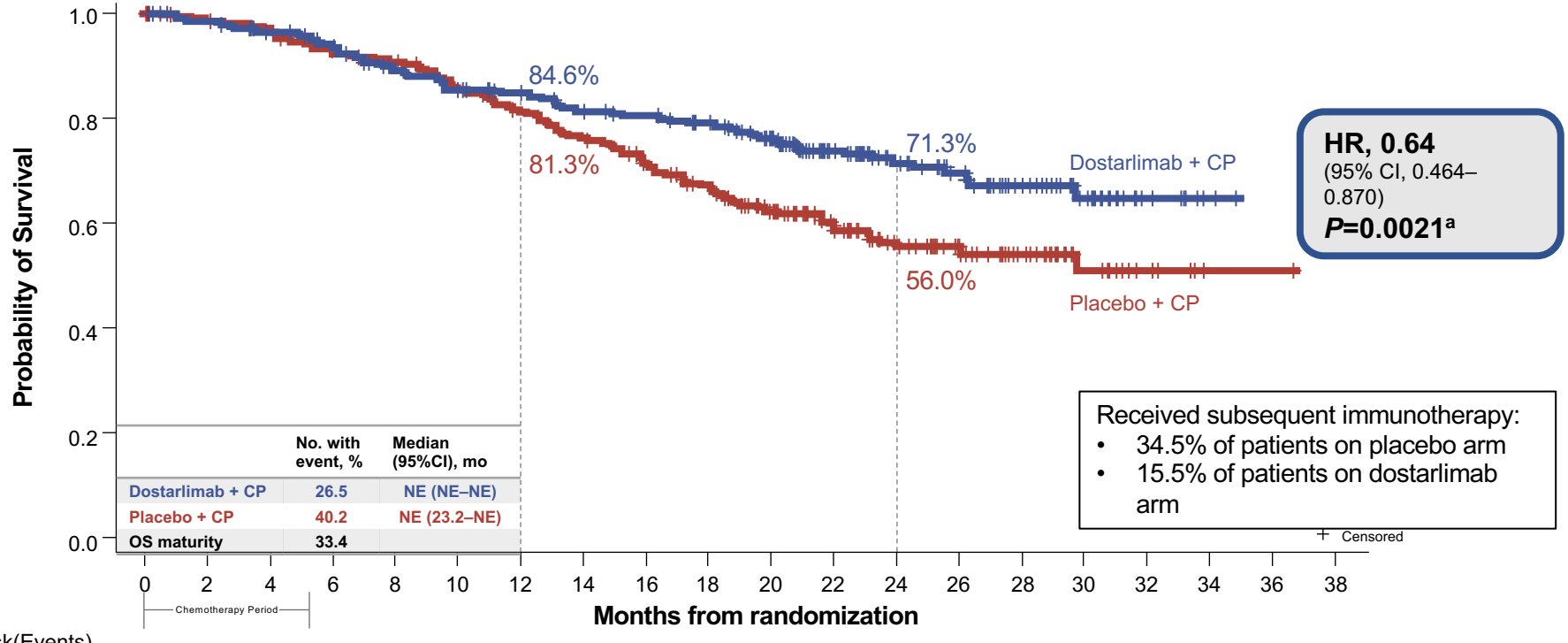
Primary Endpoint: OS in Overall Population (33% maturity)



At Risk(Events)

Dostarlimab + CP	245(0)	235(3)	224(8)	214(15)	198(25)	190(33)	183(35)	174(42)	169(44)	162(47)	145(53)	110(57)	83(60)	64(62)	45(64)	25(65)	7(65)	2(65)	0(65)	
Placebo + CP	249(0)	242(3)	237(7)	226(17)	219(22)	203(35)	189(45)	177(57)	162(68)	147(78)	125(88)	88(93)	65(97)	48(98)	33(99)	15(100)	6(100)	1(100)	1(100)	0(100)

Median duration of follow-up 25.38 months.

[a]P≤0.00177 required to declare statistical significance at first interim analysis.
CP, carboplatin/paclitaxel; HR, hazard ratio; NE, not estimable; OS, overall survival.

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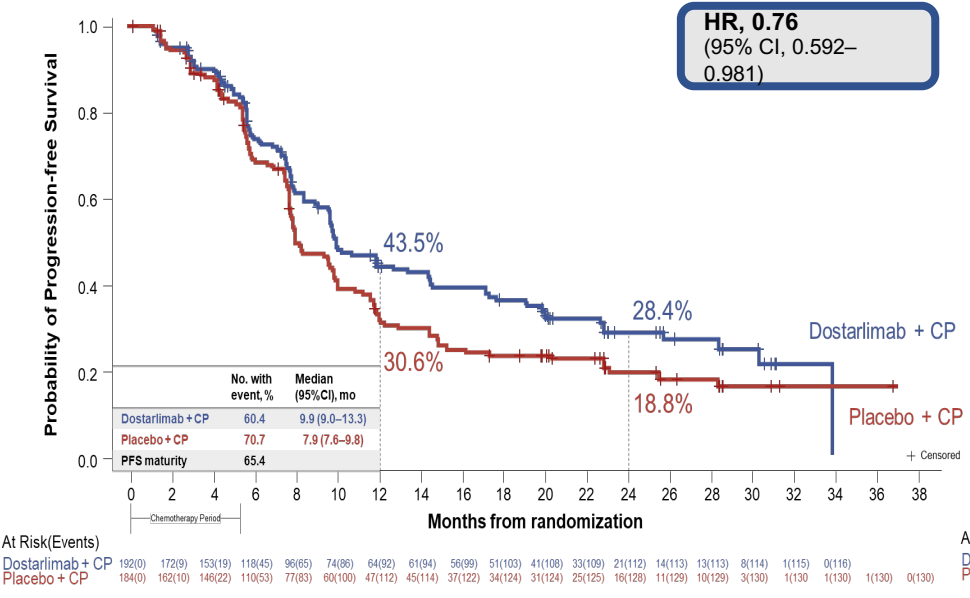
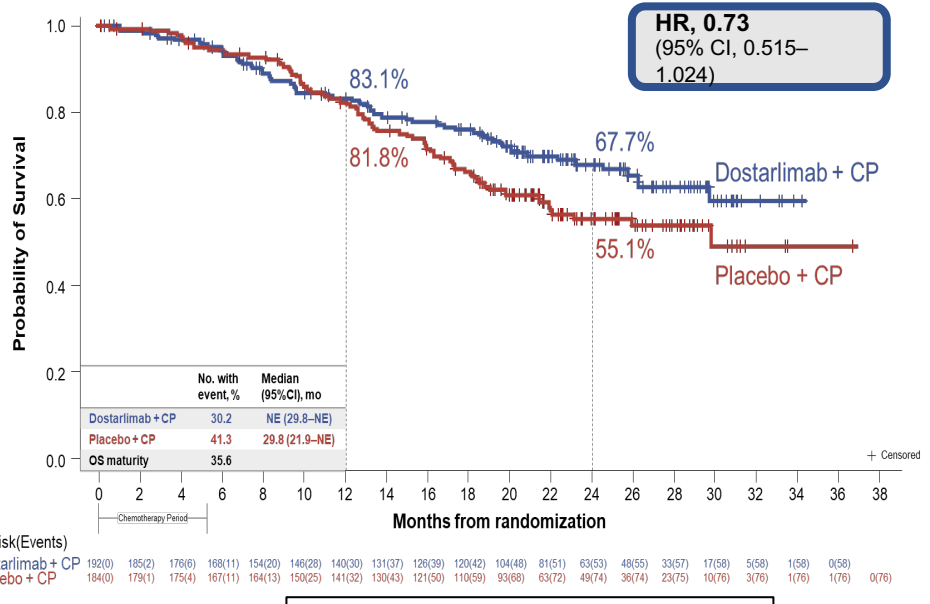
PFS and OS in MMRp/MSS Population

PFS



OS



Received subsequent immunotherapy:
- 33.2% of patients on placebo arm
- 15.6% of patients on dostarlimab arm

CP, carboplatin/paclitaxel; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; OS, overall survival; PFS, progression-free survival.

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Conclusions

- Advances in the understanding of uterine and ovarian cancer biology have led to significantly expanded options for women diagnosed with advanced disease.
- 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 uterine and ovarian cancer has increased (data awaited)

Thank you