Immunotherapy and Other Systemic Therapies in Gynecologic Malignancies

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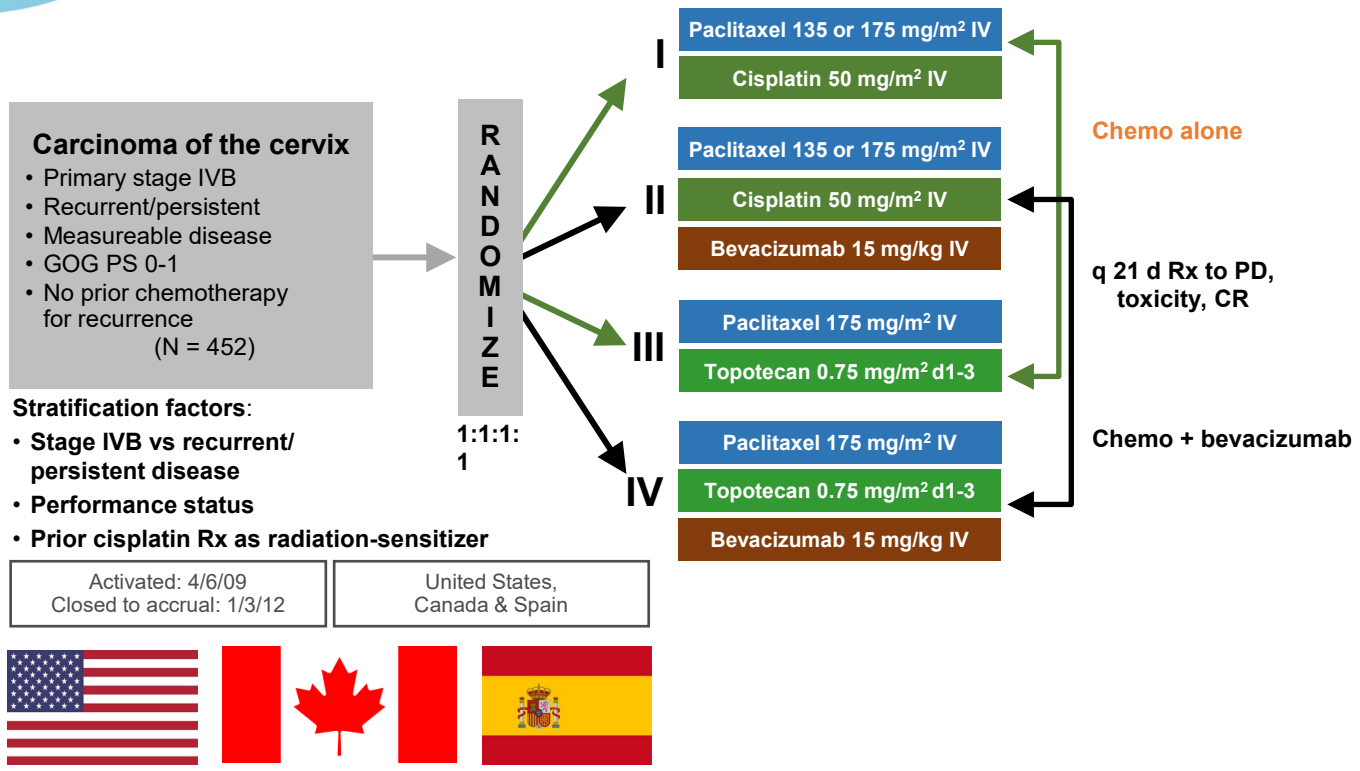
CERVICAL/VULVAR/VAGINAL CANCER

1st Line

University of Pittsburgh

GOG 240 Schema



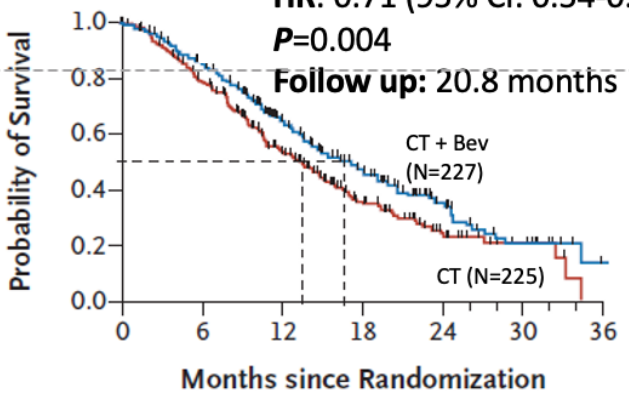
National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed 15 January 2018.

GOG-0240: Final OS/PFS

A

	Events no. (%)	Median Overall Survival mo
Chemotherapy (N=225)	140 (62)	13.3
Chemotherapy+Bev (N=227)	131 (58)	17.0

HR: 0.71 (95% CI: 0.54-0.95)
P=0.004
Follow up: 20.8 months



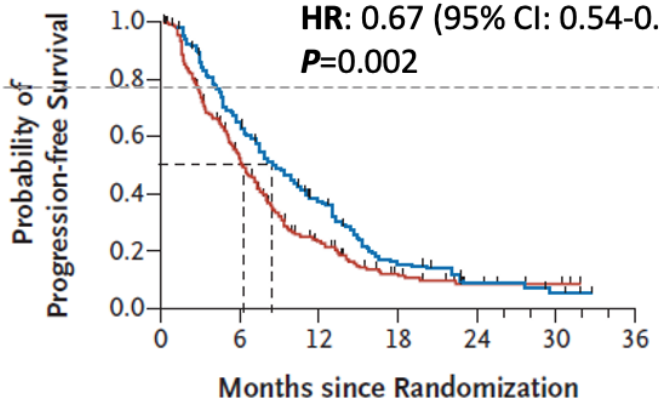
No. at Risk

Chemotherapy	225	167	94	45	17	8
Chemotherapy +bev	227	184	121	69	30	10

B

	Events no. (%)	Median Progression-free Survival mo
Chemotherapy (N=225)	184 (82)	5.9
Chemotherapy+Bev (N=227)	183 (81)	8.2

HR: 0.67 (95% CI: 0.54-0.82)
P=0.002



No. at Risk

Chemotherapy	225	103	40	14	6	3
Chemotherapy +bev	227	132	70	22	6	3

Tewari KS, et al. *N. Engl J Med* 2014;370:734-43.

ESMO 2021 LBA2

Pembrolizumab plus Chemotherapy versus Placebo plus Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Randomized, Double-Blind, Phase 3 KEYNOTE-826 Study

Nicoletta Colombo,[1] Coraline Dubot,[2] Domenica Lorusso,[3] Valeria Caceres,[4] Kosei Hasegawa,[5] Ronnie Shapira-Frommer,[6] Krishnansu S. Tewari,[7] Pamela Salman,[8] Edwin Hoyos Usta,[9] Eduardo Yañez,[10] Mahmut Gümüş,[11] Mivael Olivera Hurtado de Mendoza,[12] Vanessa Samouëlian,[13] Vincent Castonguay,[14] Alexander Arkhipov,[15] Sarper Toker,[16] Kan Li,[16] Stephen M. Keefe,[16] Bradley J. Monk,[17] on behalf of the KEYNOTE-826 Investigators

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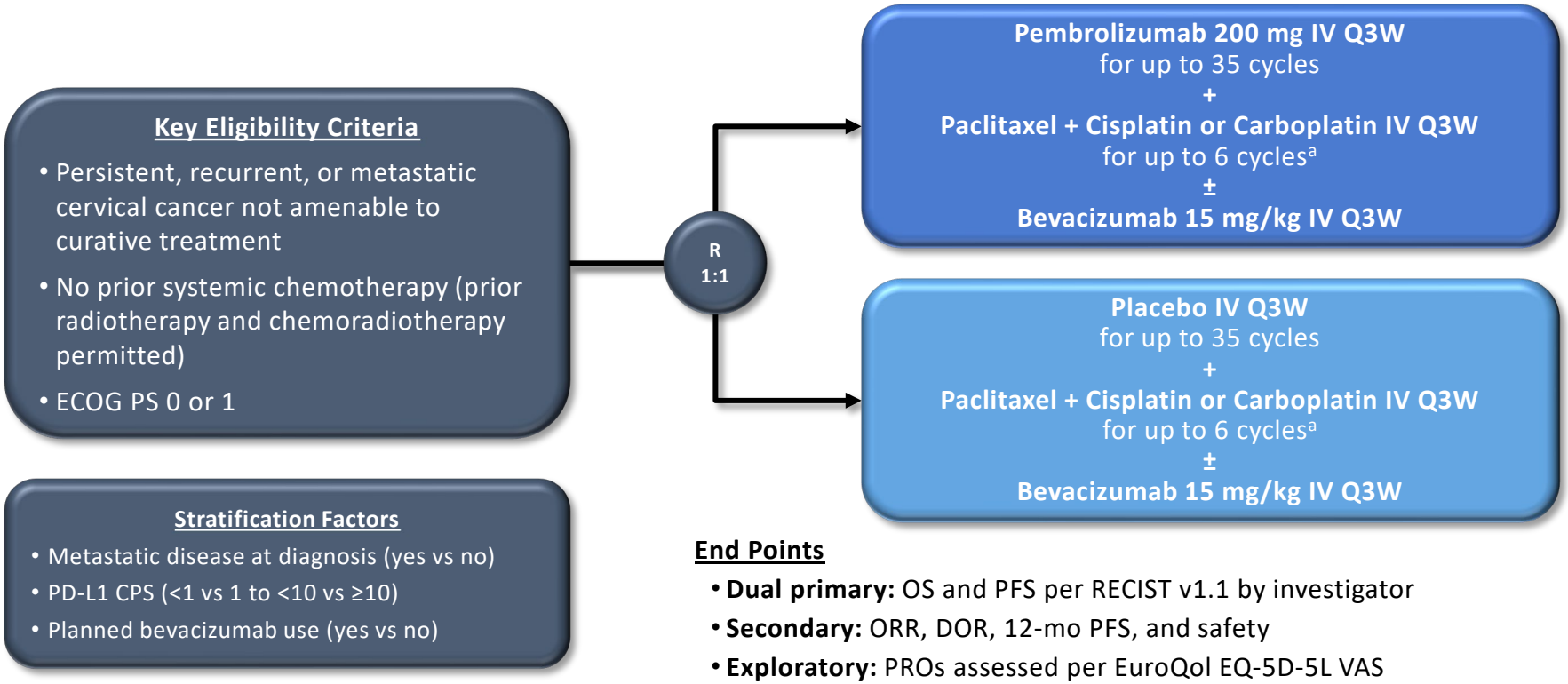
KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

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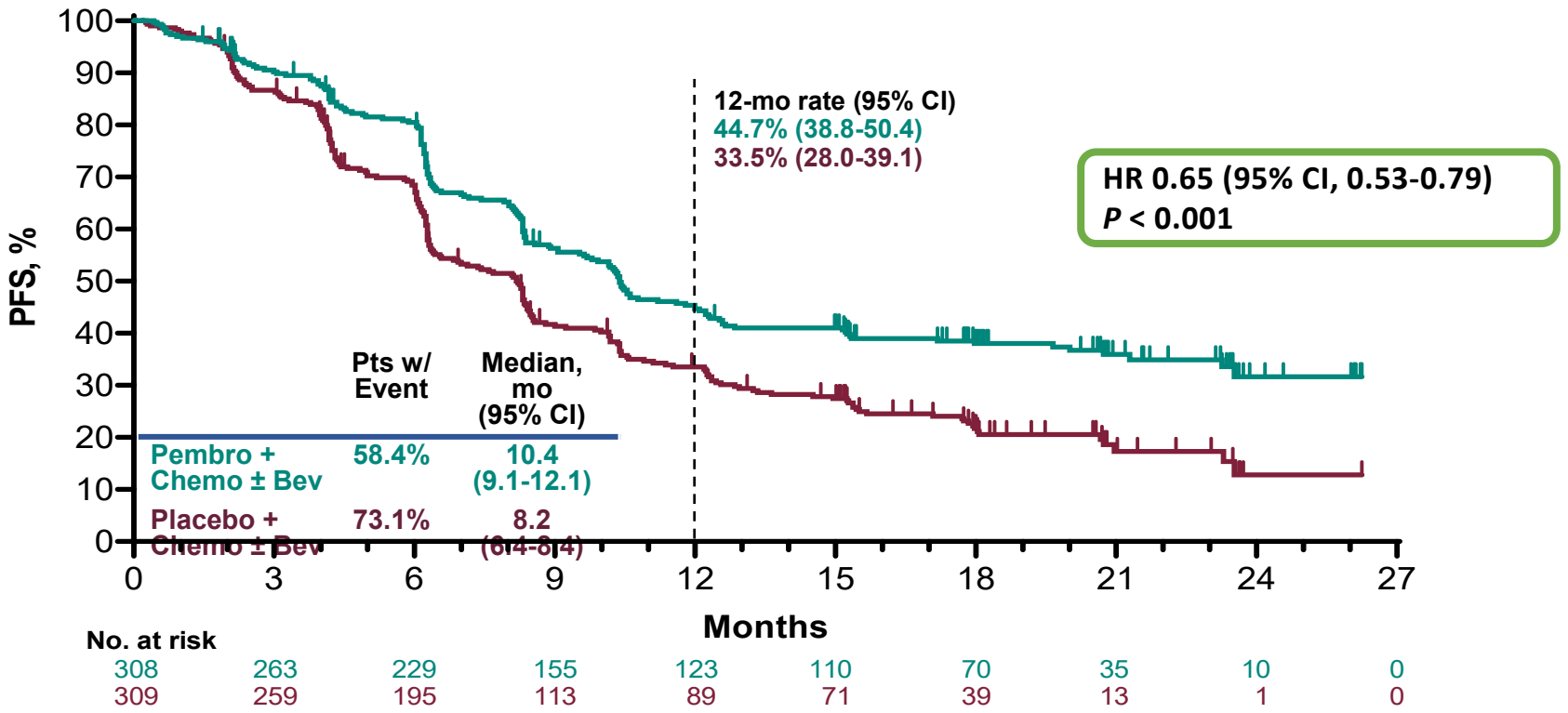
PFS: All-Comer Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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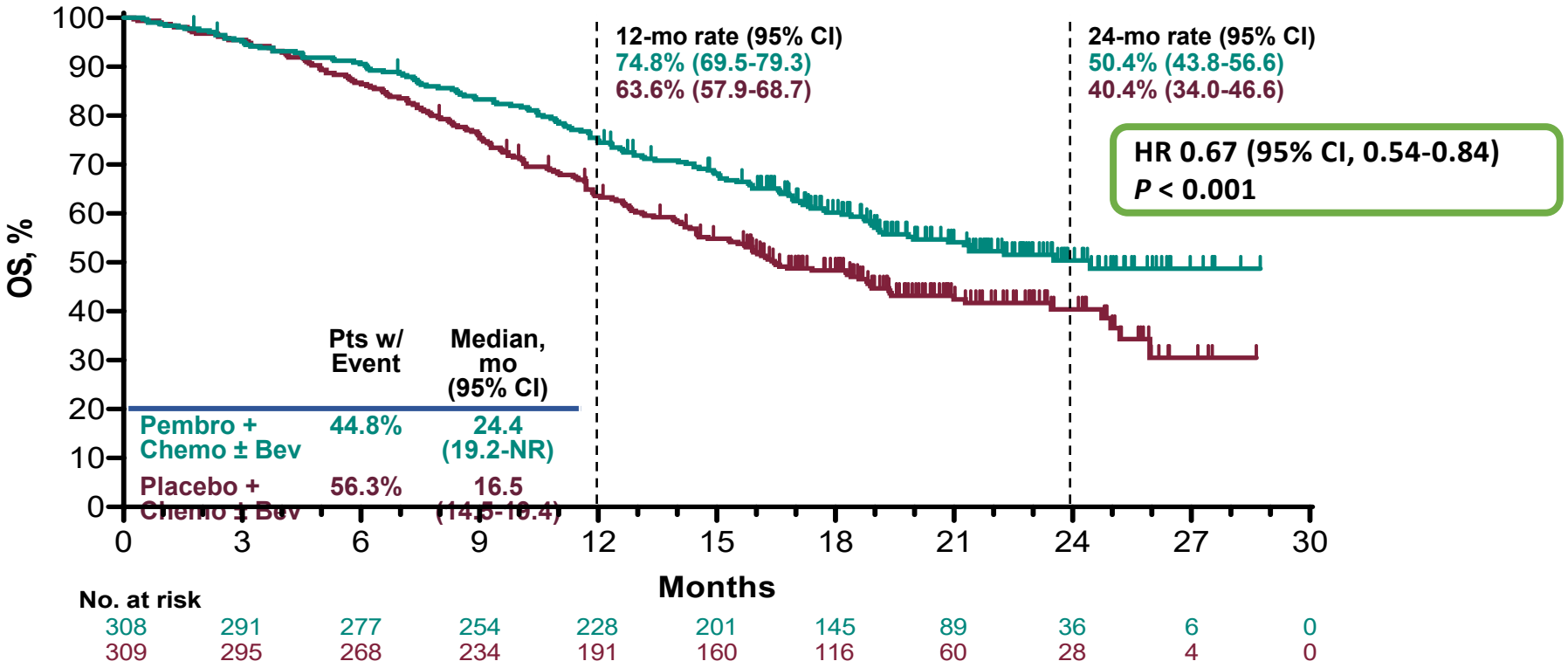
OS: All-Comer Population



Data cutoff date: May 3, 2021.

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CERVICAL/VULVAR/VAGINAL CANCER

2nd Line

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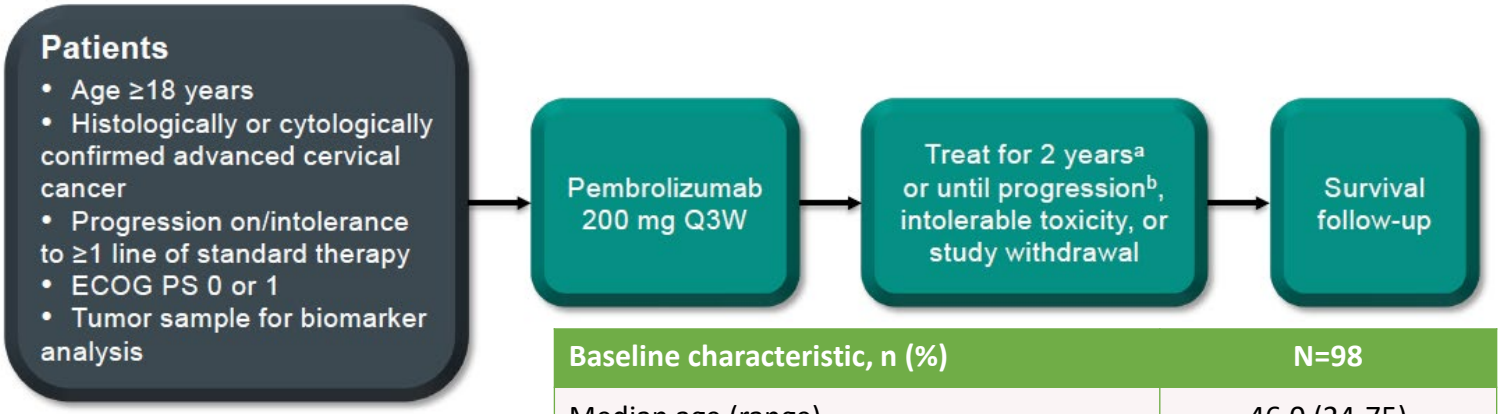
KEYNOTE 158: Study Design and Baseline Characteristics



Endpoints

- **Primary:** ORR
- **Secondary:** DOR, PFS,

Median follow-up: 36.9 months
Range: 34.3-41.0 months

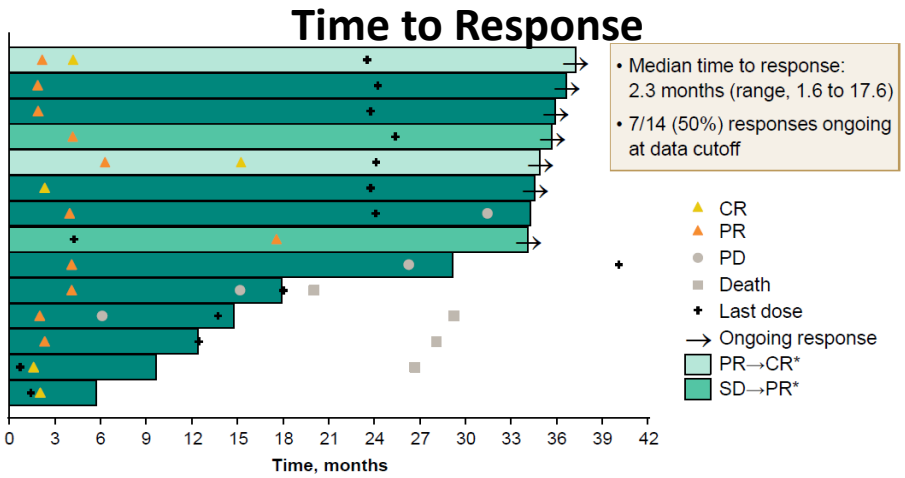
Baseline characteristic, n (%)		N=98
Median age (range)		46.0 (24-75)
ECOG PS 1		64 (65)
PD-L1+ tumor[a]		82 (84)
Number of prior therapies	1	44 (45)
	2	31 (32)
	3	13 (13)
	≥4	8 (8)

[a]CPS ≥1

Chung HC. Abstract 41. SGO Annual Meeting 2021.

KEYNOTE-158: Safety and Efficacy

Outcome	Overall[a] N=98 N = 77 PD-L1 +
ORR[d] in PDL-1+, % (95% CI)	14.3 (8.0-22.8)
Best overall response, n (%)	
CR	5 (5.1)
PR	9 (9.2)
SD	16 (16.3)
PD	55 (56.1)
Non-evaluable[e]	4 (4.1)



Safety Summary

- 65% of patients experienced any TRAE
- 12% had grade ≥3 TRAEs
- 4% had TRAEs leading to discontinuation
- ~25% of patients had any irAE; ~4% were grade ≥3, ~50% resolved
- 2% of patients discontinued pembrolizumab due to irAEs (hepatitis, n=2)

Pembrolizumab received FDA approval for the treatment of PD-L1+ r/m cervical cancer; q6w dosing approved in April 2020

[a]Includes 1 patient with unknown PD-L1 expression level. [b]CPS ≥1. [c]CPS <1. [d]At the time of analysis, all responses were confirmed. [e]Target lesions not captured on ≥1 post-baseline imaging assessment. [f]Post-baseline tumor assessment not performed. [g]TRAEs leading to discontinuation included hepatitis (n=2), diarrhea (n=1), and stomatitis (n=1)

Chung HC. Abstract 41. SGO Annual Meeting 2021.

ESMO VIRTUAL PLENARY

EMPOWER-CERVICAL 1/GOG-3016/ENGOT-CX9: RESULTS OF PHASE 3 TRIAL OF CEMIPLIMAB VS INVESTIGATOR'S CHOICE (IC) CHEMOTHERAPY (CHEMO) IN RECURRENT/METASTATIC (R/M) CERVICAL CARCINOMA

Krishnansu S Tewari,* Bradley J Monk,* Ignace Vergote, Austin Miller, Andreia Cristina de Melo, Hee Seung Kim, Yong Man Kim, Alla Lisyanskaya, Vanessa Samouëlian, Domenica Lorusso, Fernanda Damian, Chih-Long Chang, Evgeniy A Gotovkin, Shunji Takahashi, Daniella Ramone, Joanna Pikiel, Beata Maćkowiak-Matejczyk, Eva Maria Guerra, Nicoletta Colombo, Yulia Makarova,
Jingjin Li, Shaheda Jamil, Vladimir Jankovic, Chieh-I Chen, Frank Seebach, David M Weinreich, George D Yancopoulos, Israel Lowy, Melissa Mathias, Matthew G Fury, and Ana Oaknin

12 May 2021

*Contributed equally to this presentation.

This study (NCT03257267) was sponsored by Regeneron Pharmaceuticals, Inc. and Sanofi.

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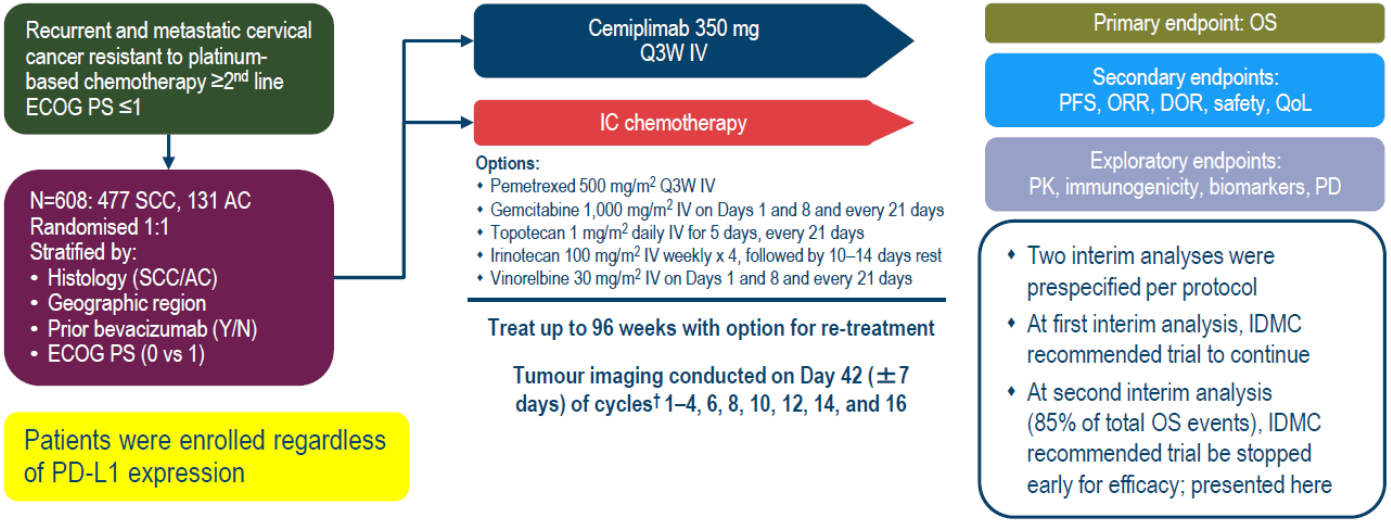
BEST PRACTICE

EMPOWER: Interim Analysis of a Phase 3 trial of Cemiplimab versus Investigator's Choice Chemotherapy in R/M Cervical Carcinoma



*Performed according to ENGOT Model C.[1] †To account for differences in drug administration schedules, one cycle is defined as 6 weeks.
AC, adenocarcinoma or adenosquamous carcinoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, investigator's choice; IDMC, Independent Data Monitoring Committee; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; QoL, quality of life; SCC, squamous cell carcinoma.

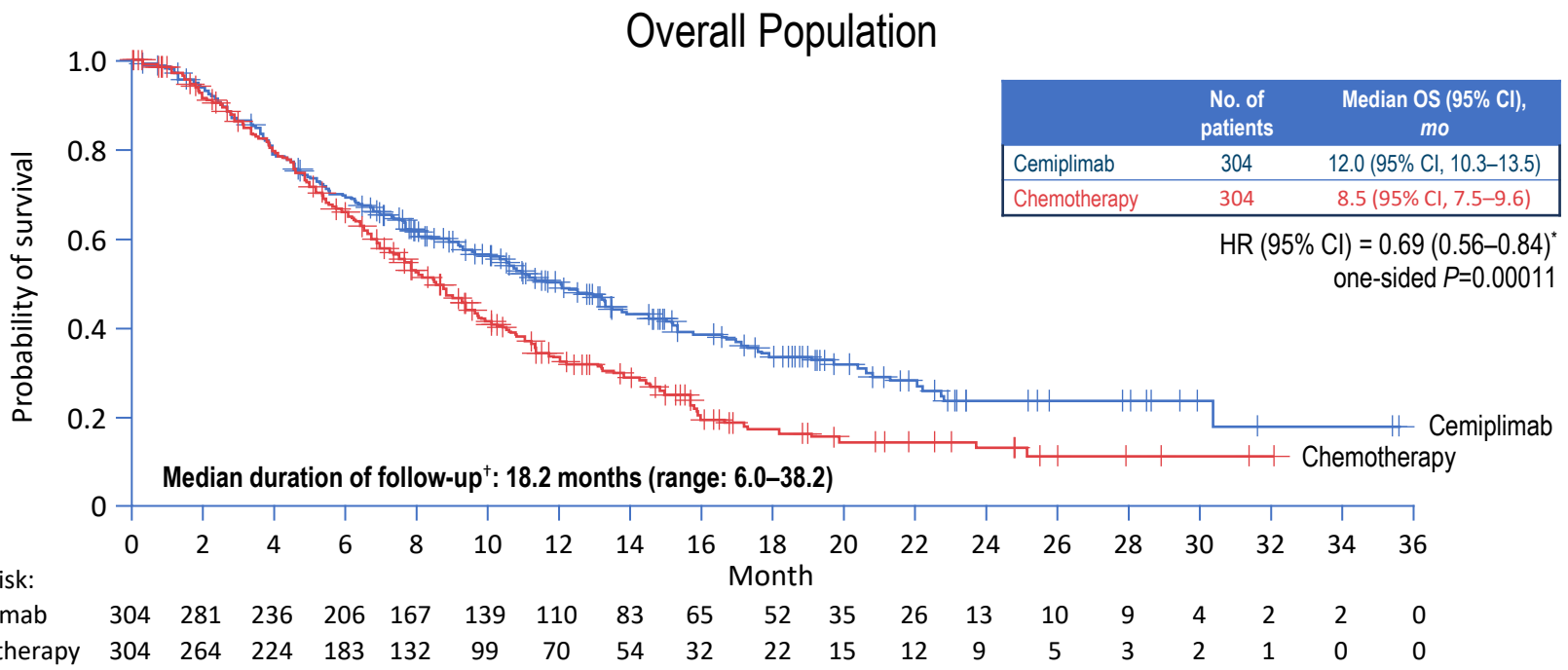
1. Vergote I et al. *Int J Gynecol Cancer*. 2019;0:1–4.

- Opened: Sept 2017
- Closed: June 2020
- N = 590
- Sites = 105

Tewari KS, et al. Presented at ESMO Virtual Plenary. 12–13 May 2021.

Overall Survival

- At second interim analysis (85% of total OS events), IDMC recommended trial be stopped early for efficacy



	No. of patients	Median OS (95% CI), *mo*
Cemiplimab	304	12.0 (95% CI, 10.3–13.5)
Chemotherapy	304	8.5 (95% CI, 7.5–9.6)

HR (95% CI) = 0.69 (0.56–0.84)*
one-sided *P*=0.00011

*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system. †From randomisation to data cutoff date.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; mo, month; ROW, rest of world; OS, overall survival.

Data cutoff date: 4 Jan 2021

2021 ESMO congress

Balstilimab (anti-PD-1) in combination with zalifrelimab (anti-CTLA-4): final results from a Phase 2 study in patients (pts) with recurrent/metastatic (R/M) cervical cancer (CC)

D.M. O'Malley[1], M. Neffa[2], B.J. Monk[3], T. Melkadze[4], A. Kryzhanivska[5], I. Bulat[6], T.M. Meniawy[7], I. Bondarenko[8], W. Ortuzar Feliu[9], M. Ancukiewicz[9], I. Lugowska[10]

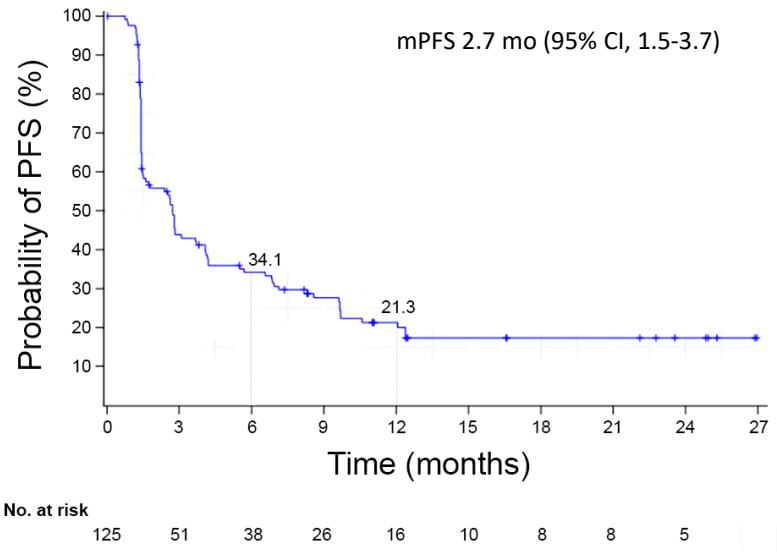
[1]Division of Gynecologic Oncology, The Ohio State University/James Comprehensive Cancer Center, Columbus, Ohio; [2]Department of Surgery, CI of Healthcare Regional Clinical Specialized Dispensary of the Radiation Protection, Kharvik, Ukraine; [3]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, Arizona; [4]Medical Oncology, Research Institute of Clinical Medicine, Tbilisi, Georgia; [5]Regional Clinical Oncology Center, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine; [6]ARENSIA Exploratory Medicine, Institute of Oncology Unit, Chisinau, Moldova; [7]Linear Clinical Research, Nedlands, Australia; [8]Department of Chemotherapy, Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine, Dnipropetrovsk, Ukraine; [9]Clinical Development, Agenus Inc., Lexington, Massachusetts; [10]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland.

Kaplan-Meier Survival Estimates

Median duration of follow-up: 21 months

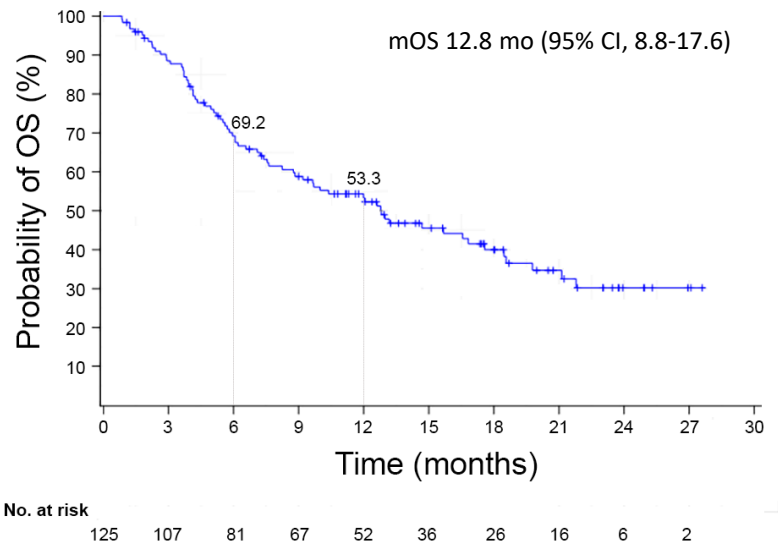
PFS

A



OS

B



PD-L1^{+} subset mOS: 15.7 mo (95% CI, 7.6, 21.1)

THE LANCET
Oncology
Volume 22, Issue 5, May 2021, Pages 609-619

Articles

Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study

Robert L Coleman MD [a], Prof Domenica Lorusso MD [b], Christine Gennigens MD [c], Prof Antonio González-Martín MD [d], Leslie Randall MD [e], David Cibula MD [f], Bente Lund MD [g], Prof Linn Woelber MD [h], Sandro Pignata MD [i], Frederic Forget MD [j], Andrés Redondo MD [k], Signe Diness Vindeløv MD [l], Menghui Chen PhD [m], Jeffrey R Harris PhD [m], Margaret Smith BA [m], Leonardo Viana Nicacio MD [n], Melinda S L Teng PhD [n], Annouschka Laenen MS [o] … Sumeet Bhatia

University of Pittsburgh

• innovaTV 204 Study Design

innovaTV 204 (NCT03438396) is a pivotal phase 2 single-arm, multicenter (United States and Europe) study evaluating tisotumab vedotin in patients with previously treated recurrent and/or metastatic cervical cancer

Key Eligibility Criteria

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] with bevacizumab, if eligible
- Received ≤2 prior systemic regimens[b]
- ECOG PS 0-1

→ **Tisotumab vedotin** 2.0 mg/kg IV Q3W →

Until PD or unacceptable toxicity

Tumor responses assessed using CT or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

Primary Endpoint

- ORR[c] per RECIST v1.1, assessed by IRC

Secondary Endpoints

- ORR, DOR, TTR, and PFS by IRC and investigator
- OS
- Safety

Exploratory Endpoints

- Biomarkers
- HRQoL

[a]Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b]Adjuvant or neoadjuvant chemotherapy or if administered with radiation therapy, was not counted as a prior systemic regimen.
[c]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment.
CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TTR, time to response.

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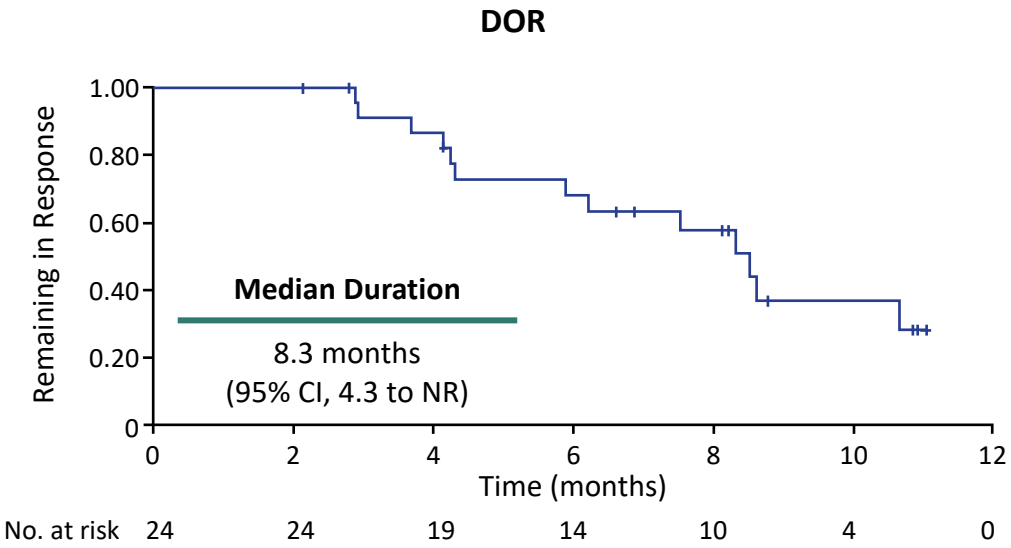
• Antitumor Activity by IRC Assessment

	N=101
Confirmed ORR (95% CI),[a] %	**24 (15.9−33.3)**
CR, n (%)	7 (7)
PR, n (%)	17 (17)
SD, n (%)	49 (49)
PD, n (%)	24 (24)
Not evaluable, n (%)	4 (4)
Disease control rate (95% CI),[b] %	72 (62.5−80.7)



Clinically meaningful and durable responses were observed

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
[a]Based on the Clopper-Pearson method. [b]Patients with a confirmed response (CR or PR confirmed at least 4 weeks later) or SD (as measured at least 5 weeks after the first dose of tisotumab vedotin).
CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PD, disease progression; PR, partial response; SD, stable disease.

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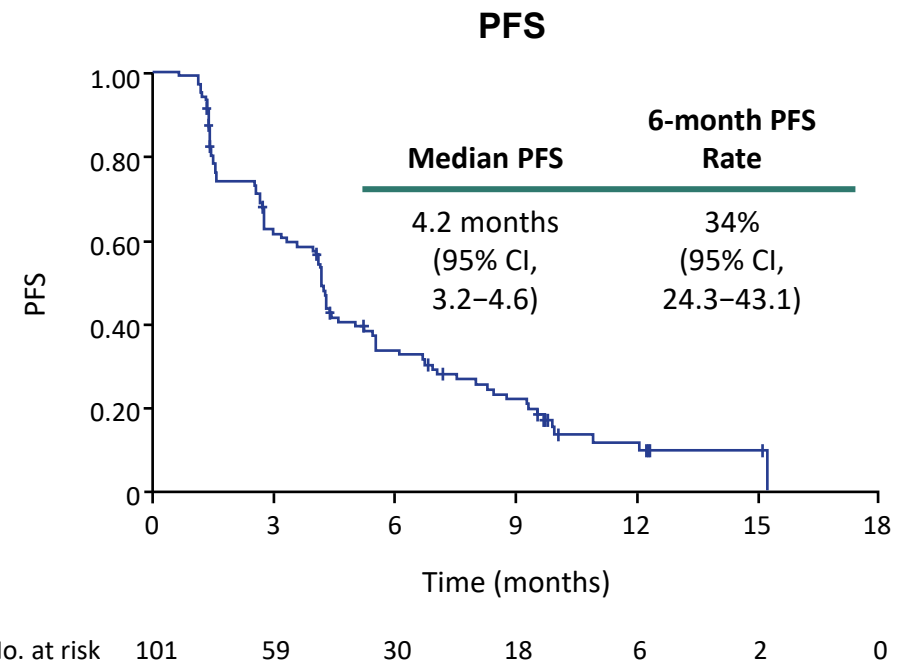
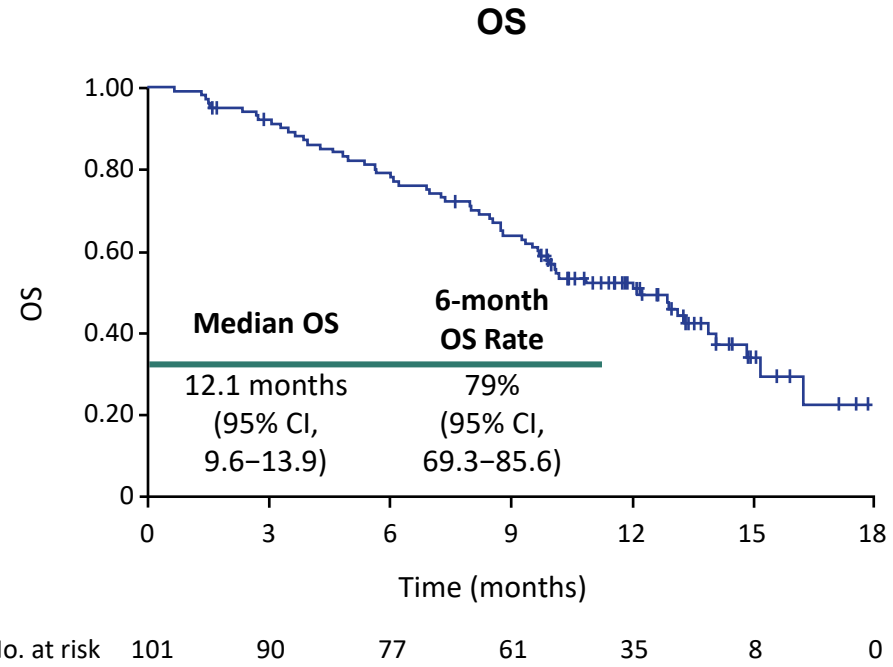
• PFS by IRC Assessment and OS





Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

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ENDOMETRIAL CANCER

1st Line

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GOG 209

Stage III/IV or recurrent endometrial cancer

- Randomized phase III non-inferiority trial

- Stage III, stage IV or recurrent endometrial carcinoma
- No prior cytotoxic chemotherapy
- ER/PR assessed on primary tumor (required)
- Patients with known LVEF <50% within 6 months of study entry are ineligible.

- Primary endpoint: Overall survival

Stratified by measurable/recurrent & prior RT

RANDOMIZE

Randomization to Regimen I requires determination of LVEF.
LVEF ≥50% receive treatment per Regimen I.
LVEF <50% crossover to Regimen II.

Regimen I — n=642

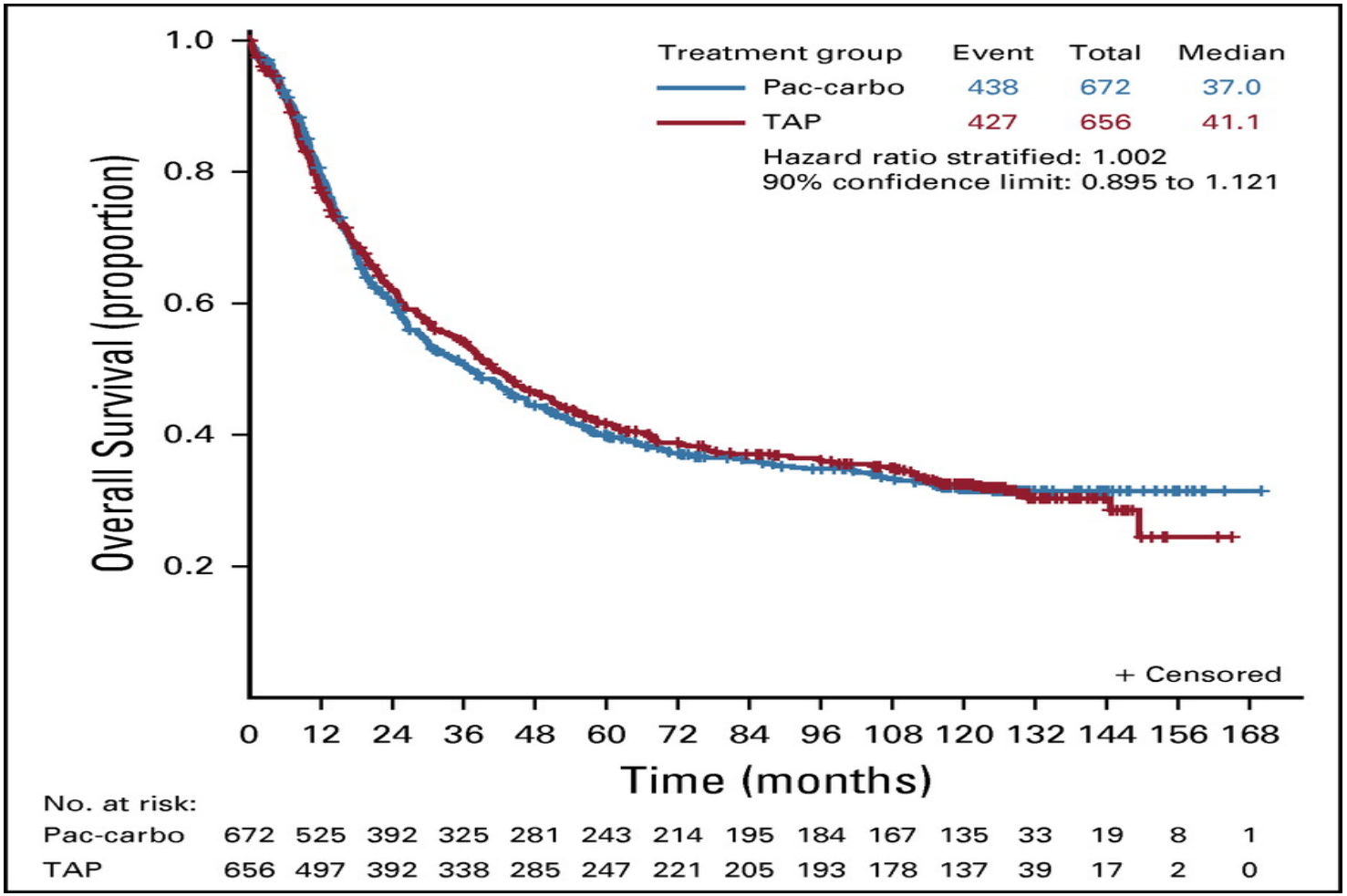
Doxorubicin
45 mg/m^2 IV day 1
Cisplatin
50 mg/m^2 day 1
Paclitaxel
3 hr 160 mg/m^2 day 2
G-CSF*
Repeated every 21 days for 7 cycles

Regimen II ** — n=663

Paclitaxel
3 hr 175 mg/m^2 day 1
Carboplatin
AUC 6 IV day 1
Repeated every 21 days for 7 cycles

Miller *et al*, SGO Annual Meeting, 2012

GOG 209 OS


Treatment group Event Total Median
Pac-carbo 438 672 37.0
TAP 427 656 41.1
Hazard ratio stratified: 1.002
90% confidence limit: 0.895 to 1.121
Overall Survival (proportion)
1.0
0.8
0.6
0.4
0.2
+ Censored
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168
Time (months)
No. at risk:
Pac-carbo 672 525 392 325 281 243 214 195 184 167 135 33 19 8 1
TAP 656 497 392 338 285 247 221 205 193 178 137 39 17 2 0

ENDOMETRIAL CANCER

2nd Line

University of Pittsburgh

A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in **combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775**

Vicky Makker[1]; Nicoletta Colombo[2]; Antonio Casado Herráez[3]; Alessandro D. Santin[4]; Emeline Colomba[5]; David S. Miller[6]; Keiichi Fujiwara[7]; Sandro Pignata[8]; Sally Baron-Hay[9]; Isabelle Ray-Coquard[10]; Ronnie Shapira-Frommer[11]; Kimio Ushijima[12]; Jun Sakata[13]; Kan Yonemori[14]; Yong Man Kim[15]; Eva M. Guerra[16]; Ulus A. Sanli[17]; Mary M. McCormack[18]; Jie Huang[19]; Alan D. Smith[20]; Stephen Keefe[21]; Lea Dutta[19]; Robert J. Orlowski[21]; Domenica Lorusso[22]

SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

Society of Gynecologic Oncology

University of Pittsburgh

Study Design

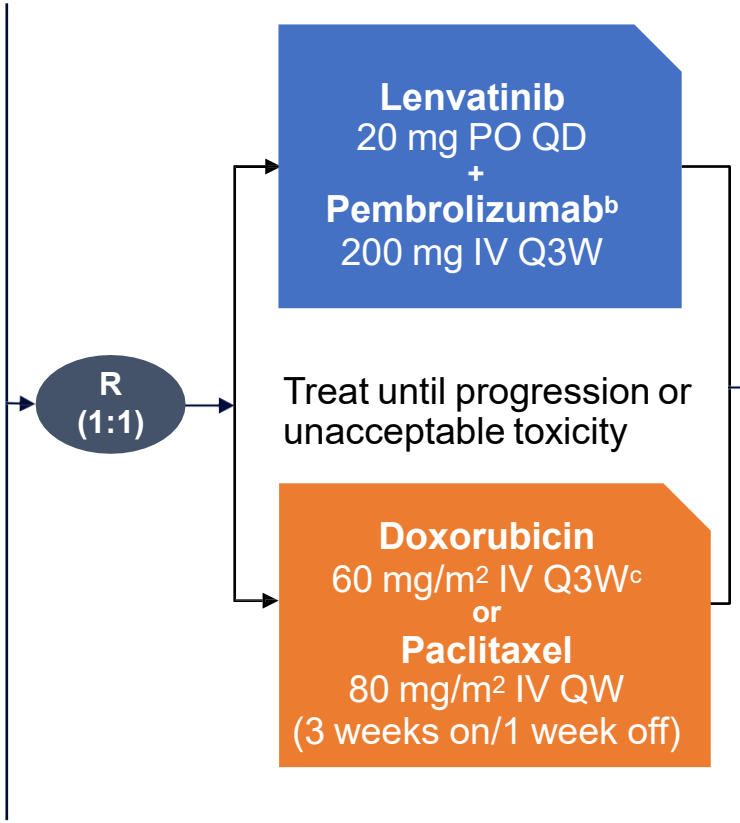
Key eligibility criteria

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:

- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)



Primary endpoints

- PFS by BICR
- Overall survival

Secondary endpoints

- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint

- Duration of response

[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m^2.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; PFS, progression-free survival; pMMR, mismatch repair-proficient; ORR, objective response rate; PO, per os (by mouth); QD, once; Q3W, every 3 weeks; QW, once weekly.

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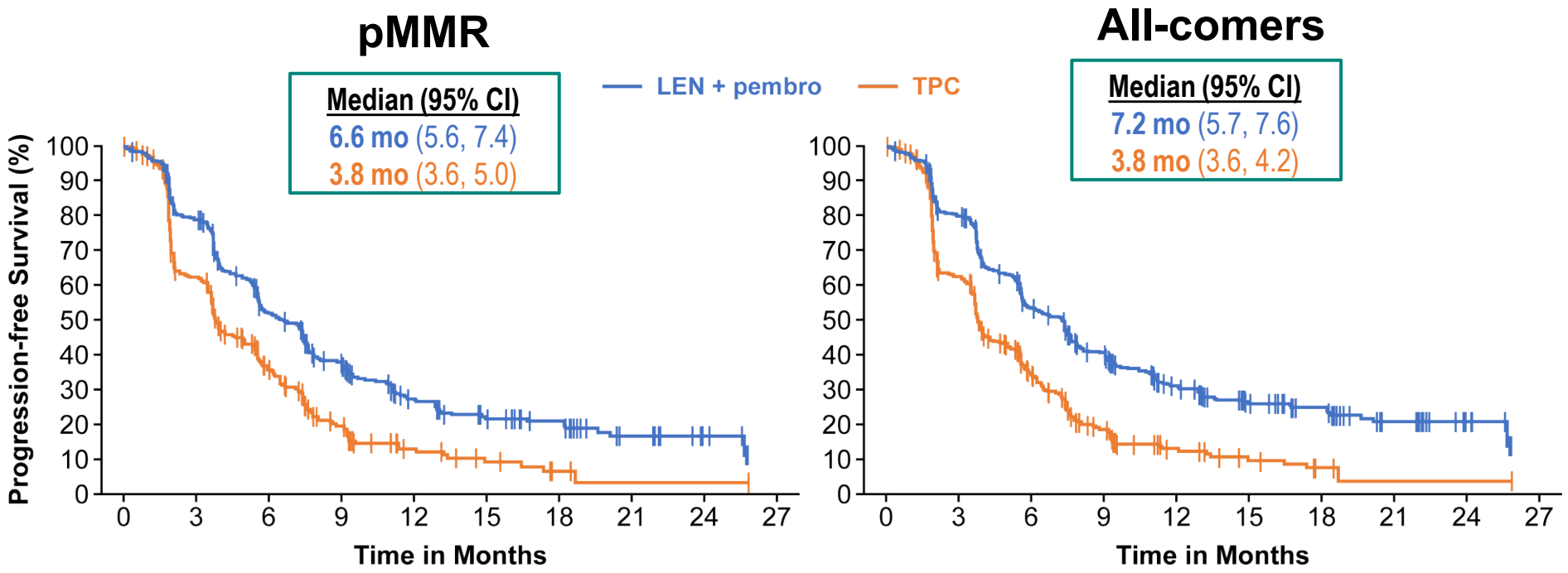
Progression-free Survival[a]



	Events	HR (95% CI)	*P*-value
LEN + pembro	247	**0.60** (0.50, 0.72)	< 0.0001
TPC	238		

	Events	HR (95% CI)	*P*-value
LEN + pembro	281	**0.56** (0.47, 0.66)	< 0.0001
TPC	286		

[a]By BICR per Response Evaluation Criteria in Solid Tumors version 1.1.

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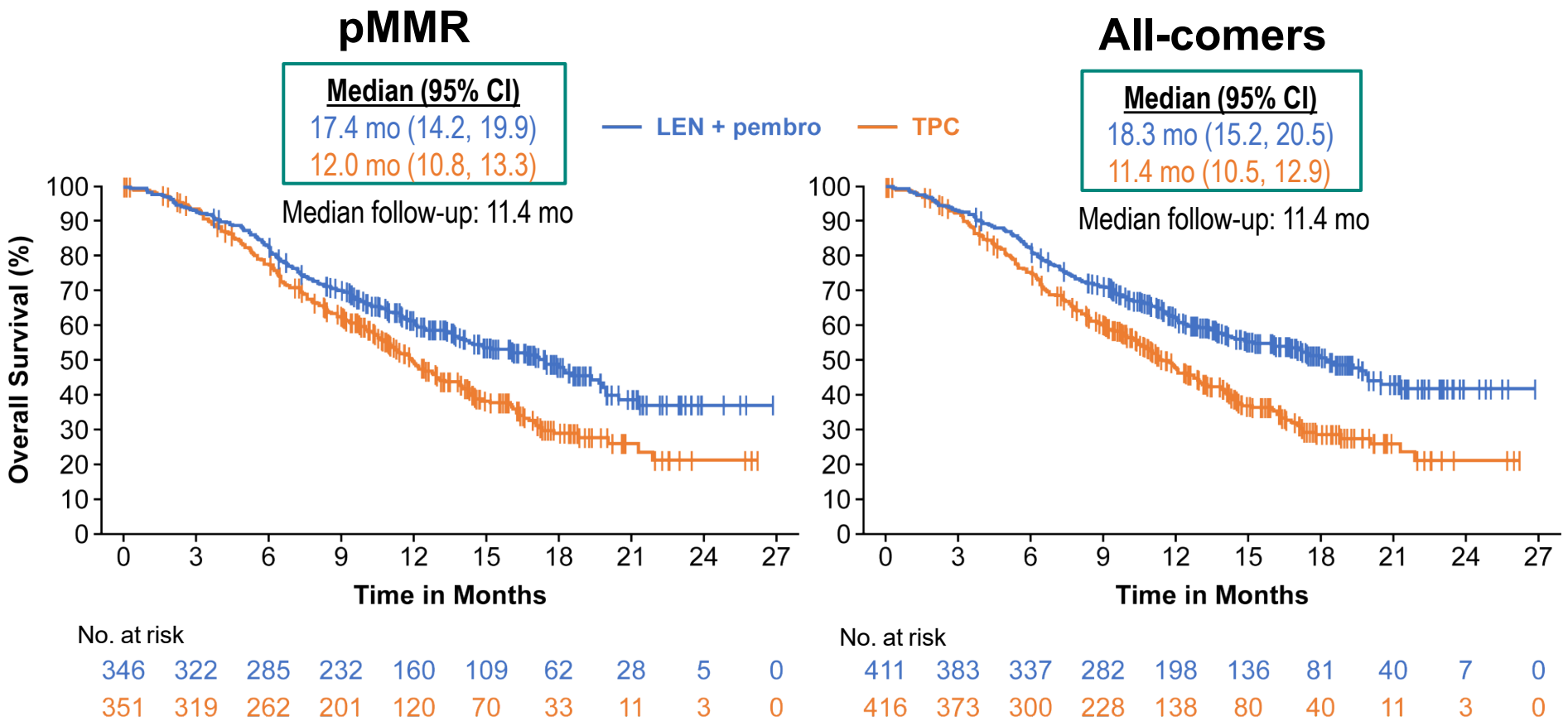
Overall Survival



	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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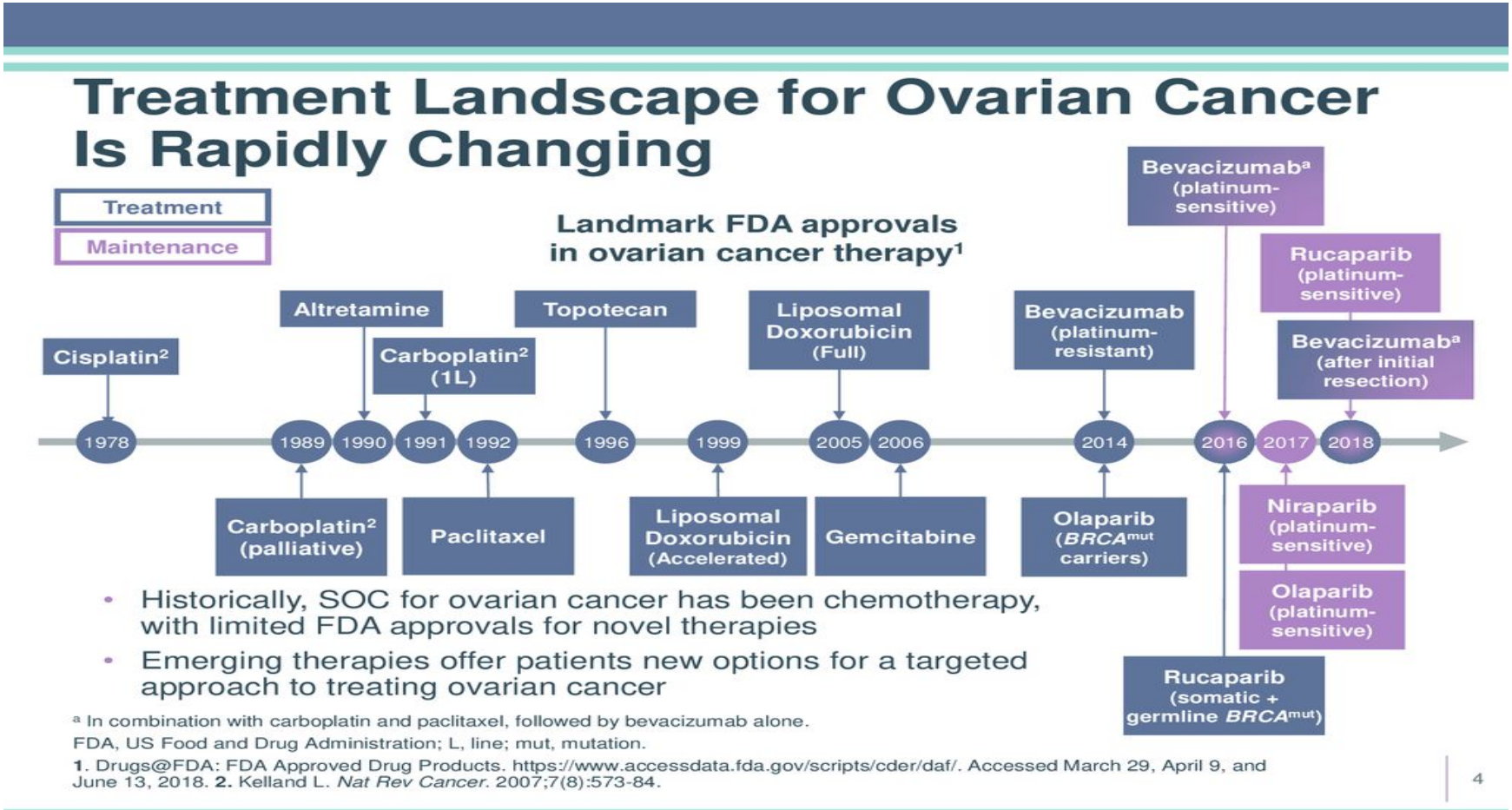
OVARIAN CANCER

LANDSCAPE



University of Pittsburgh

GOG 258

Phase III Trial of Carboplatin and Paclitaxel Compared With Cisplatin and Paclitaxel in Patients With Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study

By Robert F. Ozols, Brian N. Bundy, Benjamin E. Greer, Jeffrey M. Fowler, Daniel Clarke-Pearson, Robert A. Burger, Robert S. Mannel, Koen DeGeest, Ellen M. Hartenbach, and Rebecca Baergen

University of Pittsburgh

GOG 218

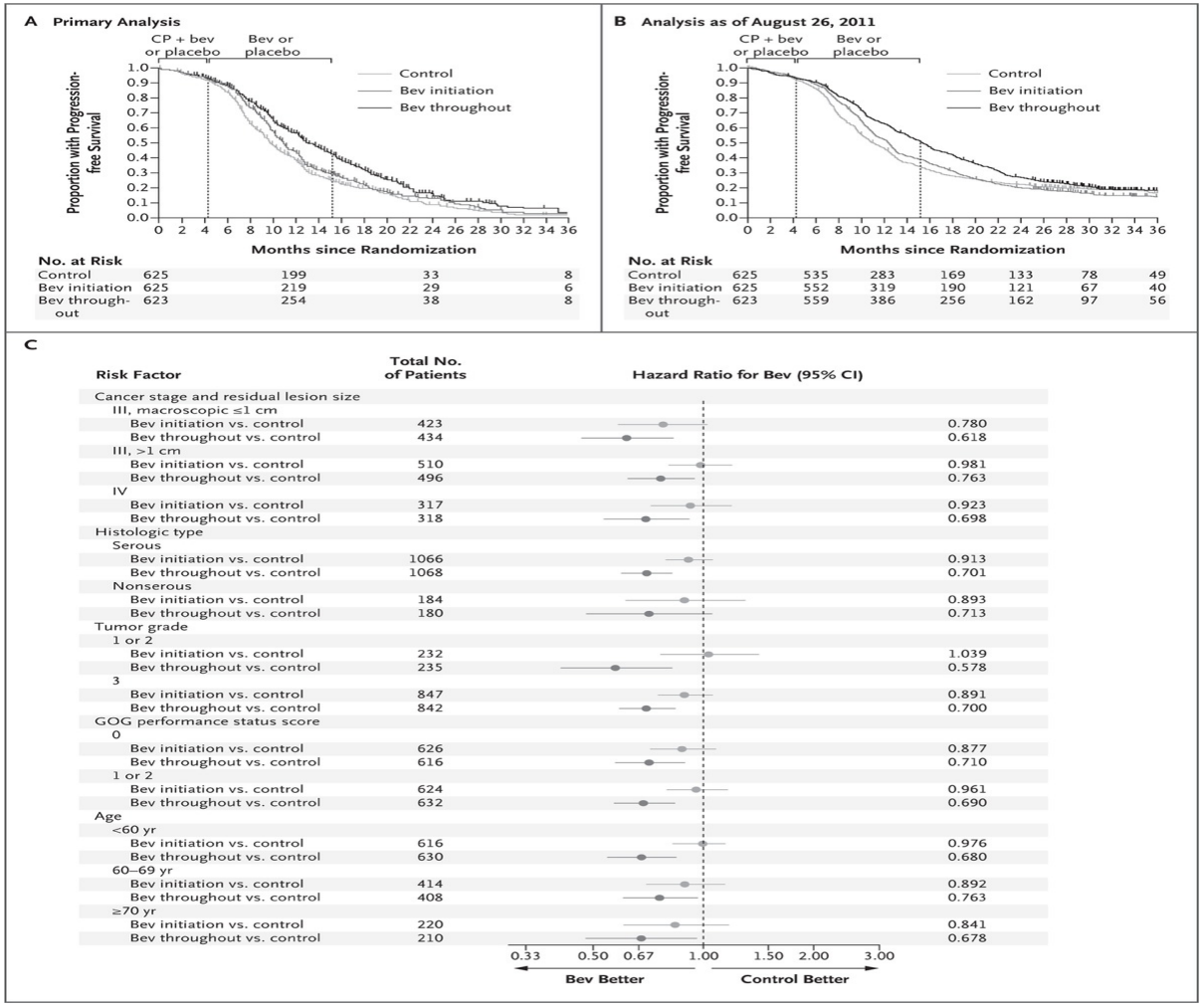
Clinical Trial > N Engl J Med. 2011 Dec 29;365(26):2473-83. doi: 10.1056/NEJMoa1104390.

Incorporation of bevacizumab in the primary treatment of ovarian cancer

Robert A Burger [1], Mark F Brady, Michael A Bookman, Gini F Fleming, Bradley J Monk, Helen Huang, Robert S Mannel, Howard D Homesley, Jeffrey Fowler, Benjamin E Greer, Matthew Boente, Michael J Birrer, Sharon X Liang, Gynecologic Oncology Group

University of Pittsburgh

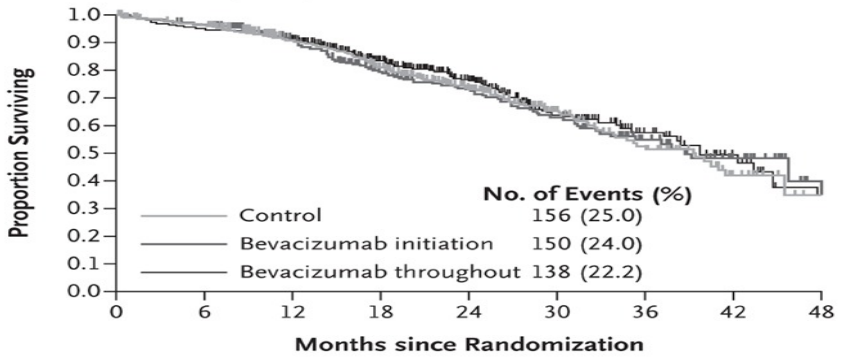
PFS



University of Pittsburgh

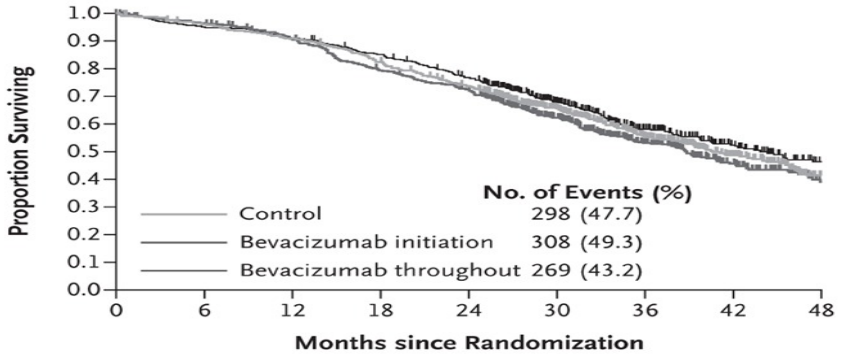
OS

A Analysis at Time of Primary Analysis



No. at Risk				
Control	625	442	173	46
Bevacizumab initiation	625	432	162	39
Bevacizumab throughout	623	437	171	40

B Analysis as of August 26, 2011



No. at Risk									
Control	625	595	558	506	446	322	200	116	56
Bevacizumab initiation	625	598	557	486	440	304	191	108	54
Bevacizumab throughout	623	587	561	519	463	321	201	114	62

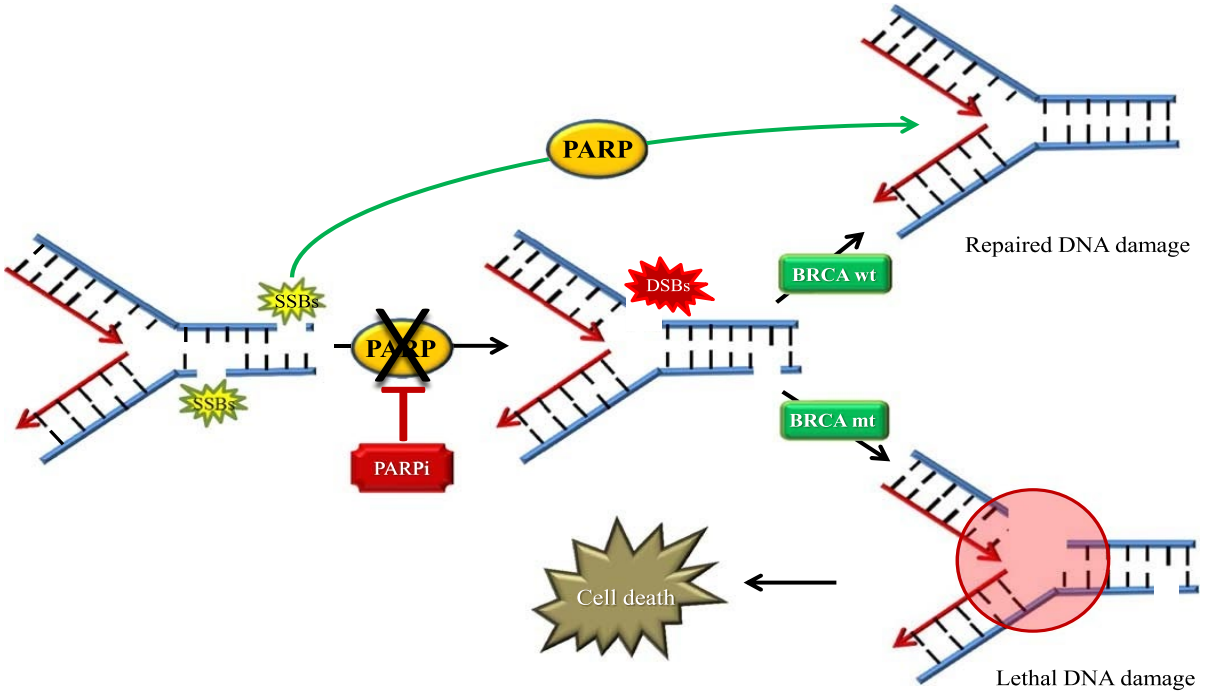
University of Pittsburgh

OVARIAN /FALLOPIAN/PRIMARY PERITONEAL CANCERS

PARP Inhibition- - maintenance
Platinum sensitive recurrent disease

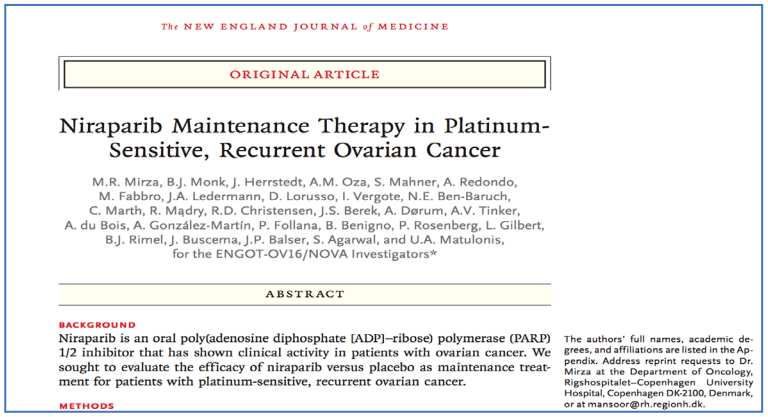
University of Pittsburgh

Homologous Recombination Repair



University of Pittsburgh

Targeted therapy for ovarian, PARP inhibitors



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*

ABSTRACT

BACKGROUND

Niraparib is an oral poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) 1/2 inhibitor that has shown clinical activity in patients with ovarian cancer. We sought to evaluate the efficacy of niraparib versus placebo as maintenance treatment for patients with platinum-sensitive, recurrent ovarian cancer.

METHODS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mirza at the Department of Oncology, Rigshospitalet–Copenhagen University Hospital, Copenhagen DK-2100, Denmark, or at mansoor@rh.regionh.dk.

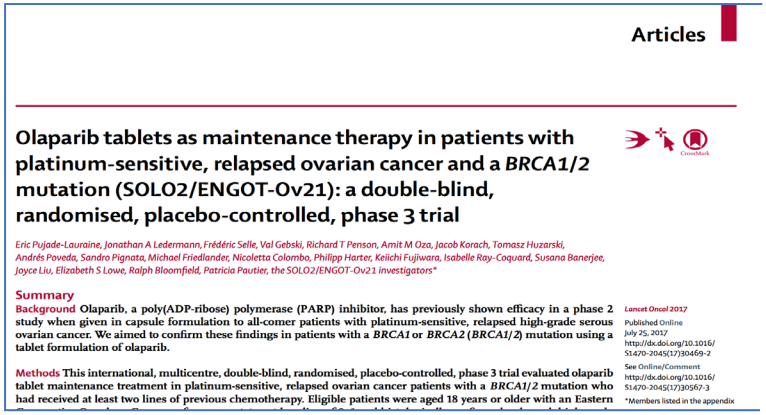
THE LANCET

Log in

ARTICLES | VOLUME 390, ISSUE 10106, P1949-1961, OCTOBER 28, 2017

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

Prof Robert L Coleman, MD • Prof Amit M Oza, MD • Domenica Lorusso, MD • Carol Aghajanian, MD • Ana Oaknin, MD • Andrew Dean, MD • et al. Show all authors



Articles

Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

*Eric Pujade-Lauraine, Jonathan A Ledermann, Frédéric Selle, Val Gebski, Richard T Penson, Amit M Oza, Jacob Korach, Tomasz Huzarski, Andrés Poveda, Sandro Pignata, Michael Friedlander, Nicoletta Colombo, Philipp Harter, Keiichi Fujiwara, Isabelle Ray-Coquard, Susana Banerjee, Joyce Liu, Elizabeth S Lowe, Ralph Bloomfield, Patricia Pautier, the SOLO2/ENGOT-Ov21 investigators**

Summary

Background Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has previously shown efficacy in a phase 2 study when given in capsule formulation to all-comer patients with platinum-sensitive, relapsed high-grade serous ovarian cancer. We aimed to confirm these findings in patients with a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation using a tablet formulation of olaparib.

Methods This international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial evaluated olaparib tablet maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with a *BRCA1/2* mutation who had received at least two lines of previous chemotherapy. Eligible patients were aged 18 years or older with an Eastern

Lancet Oncol 2017

Published Online July 25, 2017 http://dx.doi.org/10.1016/S1470-2045(17)30469-2

See Online/Comment http://dx.doi.org/10.1016/S1470-2045(17)30567-3

*Members listed in the appendix

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

Jonathan Ledermann, M.D., Philipp Harter, M.D., Charlie Gourley, M.B., Ph.D., Michael Friedlander, M.B., Ph.D., Ignace Vergote, M.D., Ph.D., Gordon Rustin, M.D., Clare Scott, M.B., Ph.D., Werner Meier, M.D., Ph.D., Ronnie Shapira-Frommer, M.D., Tamar Safra, M.D., Daniela Matei, M.D., Euan Macpherson, M.Sc., Claire Watkins, M.A., M.Sc., James Carmichael, M.D., and Ursula Matulonis, M.D.

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

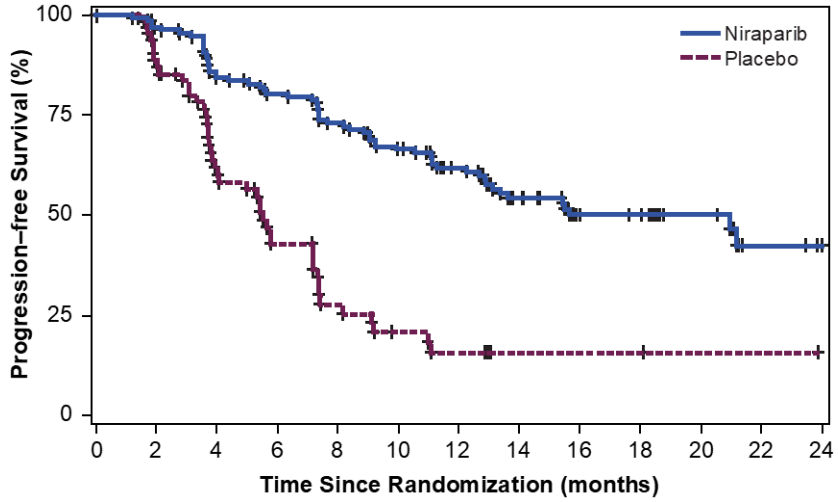
Tested at 100 events to achieve p<0.05

- **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

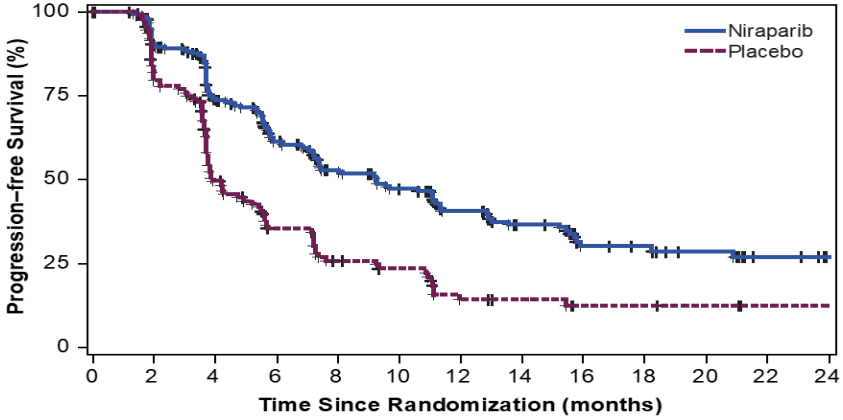


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	21.0 (12.9, NR)	0.27 (0.173, 0.410) p<0.0001	62%	50%
Placebo (N=65)	5.5 (3.8, 7.2)		16%	16%

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

University of Pittsburgh

NOVA: Non-gBRCAmut Progression-Free Survival

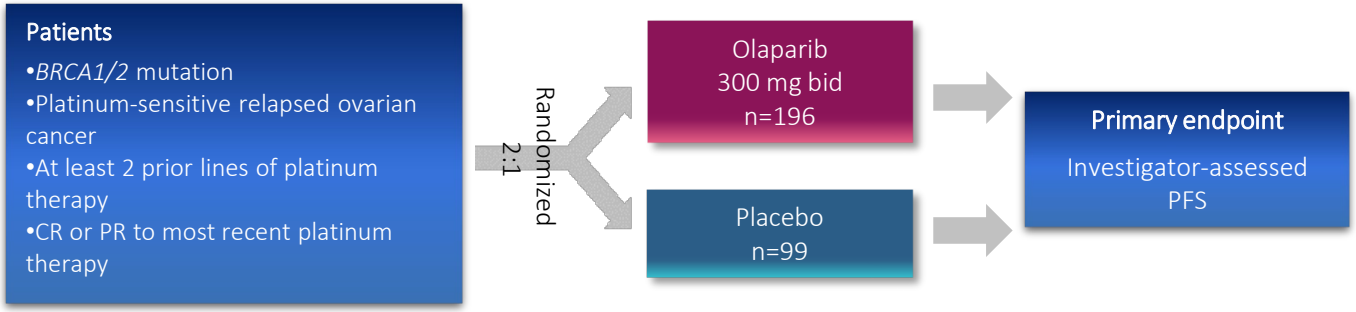


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607) p<0.0001	41%	30%
Placebo (N=116)	3.9 (3.7, 5.5)		14%	12%

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)

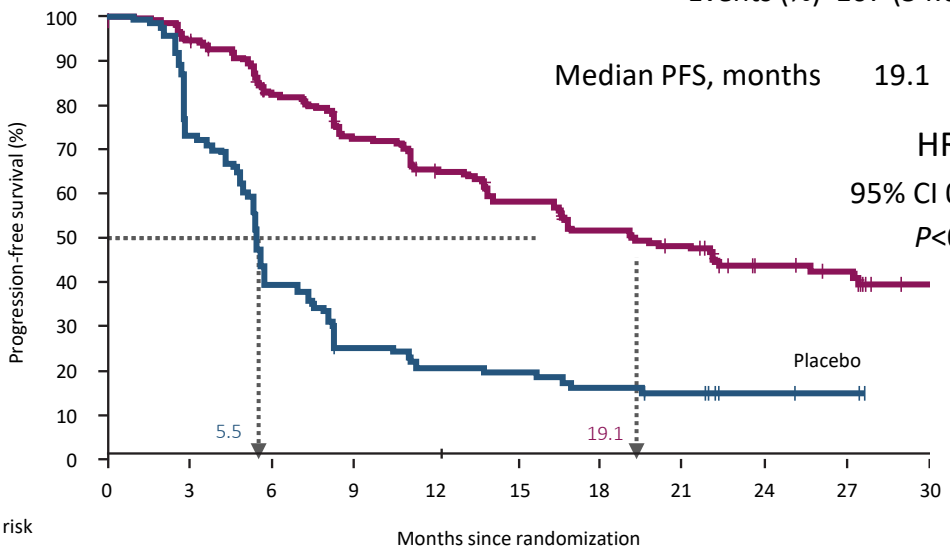
Pujade-Lauraine, Lancet Oncol. 2017 Sep;18(9):1274-1284.

University of Pittsburgh

PFS by Investigator Assessment

	Olaparib (n=196)	Placebo (n=99)
Events (%)	107 (54.6)	80 (80.8)
Median PFS, months	19.1	5.5

HR 0.30
95% CI 0.22 to 0.41
P<0.0001



No. at risk

Olaparib	19	18	15	13	118	104	89	82	3	2	3
Placebo	6	2	6	4	18	17	14	12	2	9	0
	99	70	37	22					7	6	

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

University of Pittsburgh

STUDY 19

The NEW ENGLAND JOURNAL of MEDICINE

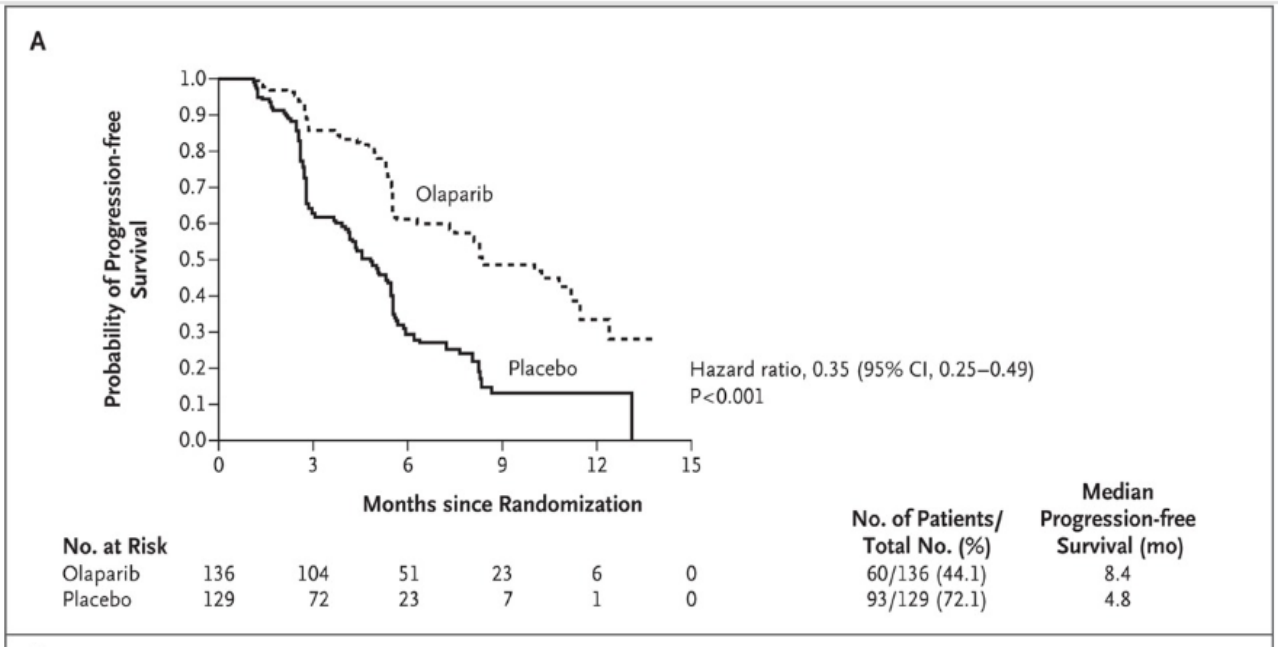
ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

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

University of Pittsburgh

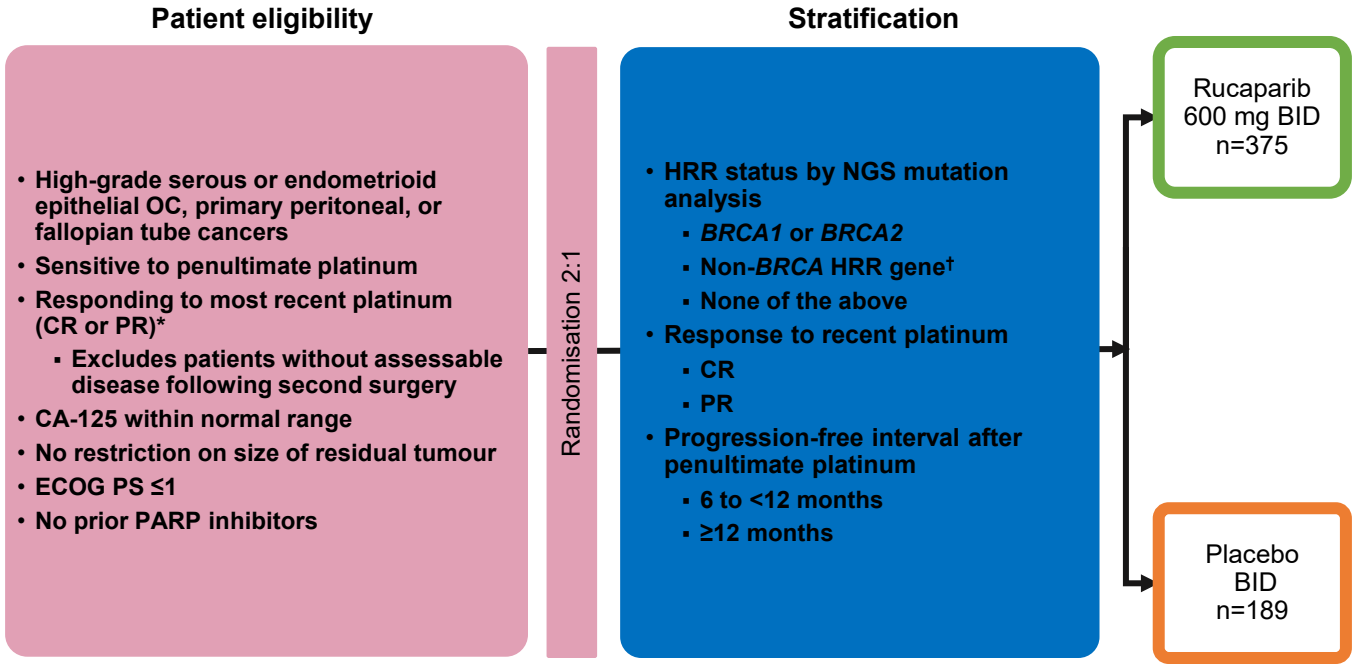
Result



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

University of Pittsburgh

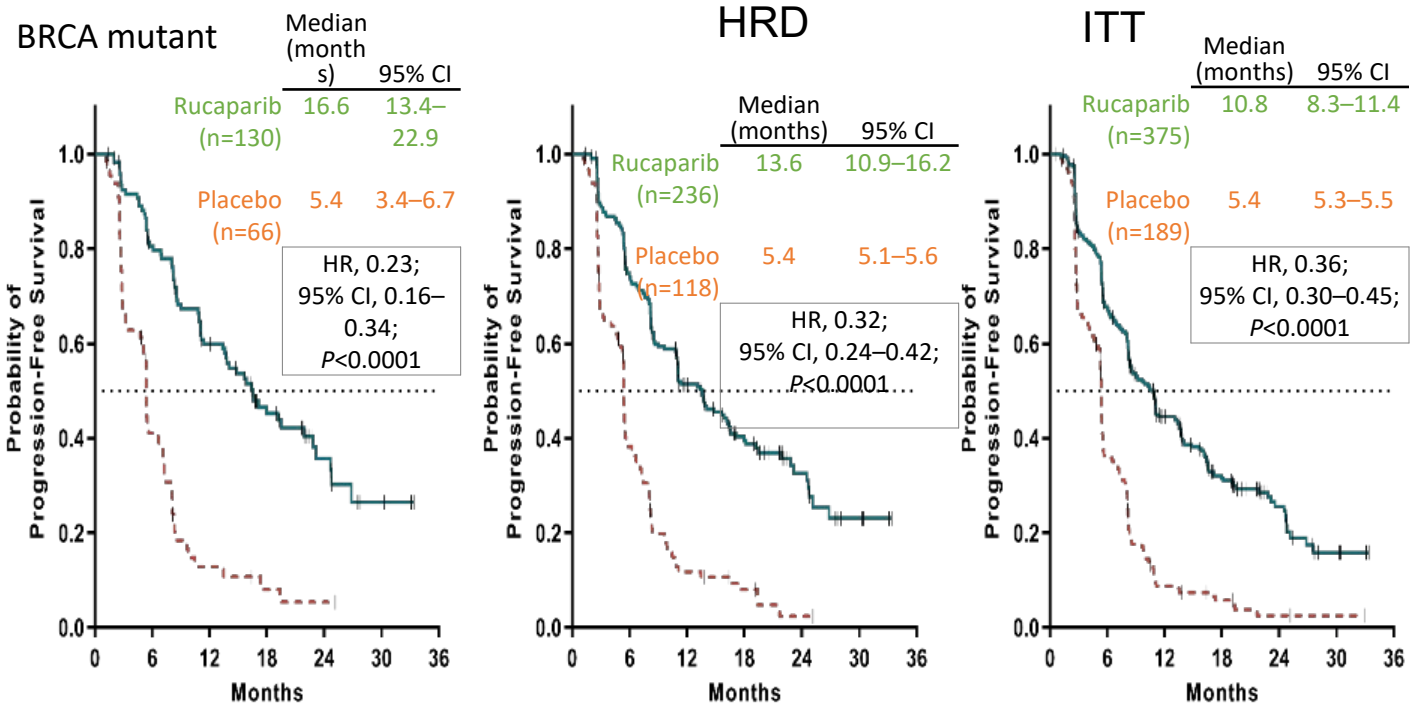
ARIEL3: Study Design



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

University of Pittsburgh

ARIEL3: Investigator-Assessed Progression-Free Survival

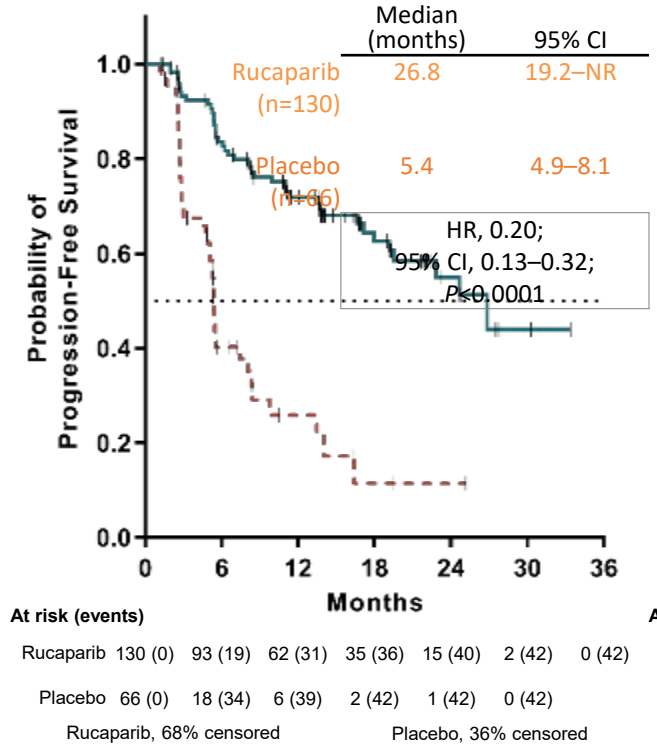


Lancet. 2017 Oct 28;390(10106):1949-1961

University of Pittsburgh

ARIEL3: BICR-Assessed Progression-Free Survival

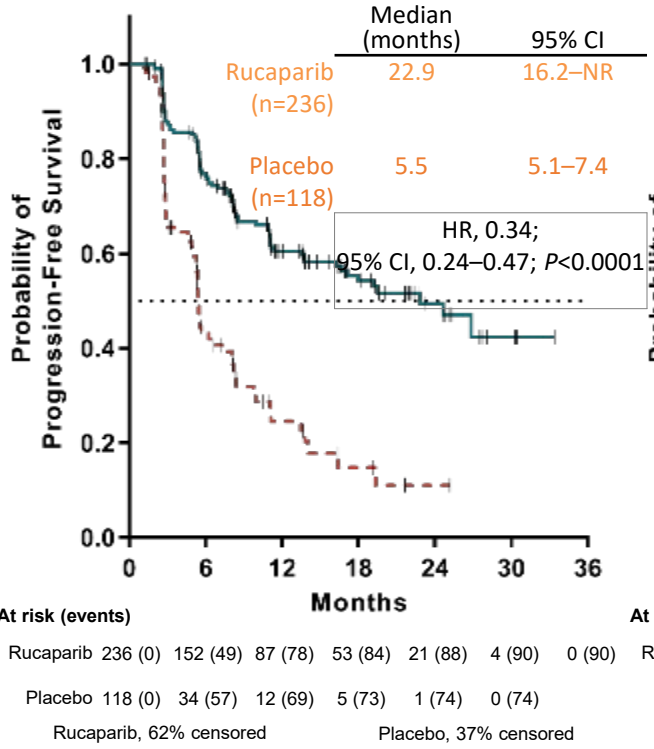
BRCA mutant



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

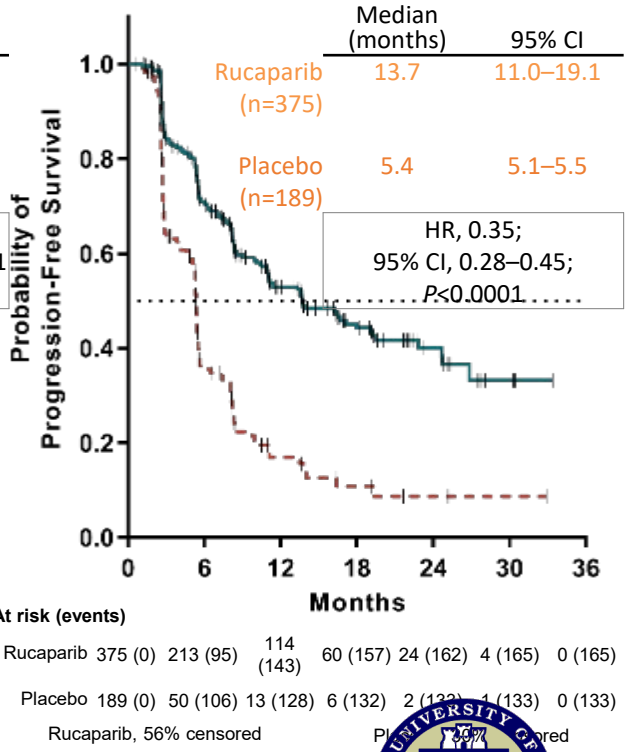
HRD



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 Pl[illegible] 20%] ored

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

University of Pittsburgh

PARP Inhibition- - treatment
Platinum sensitive recurrent disease

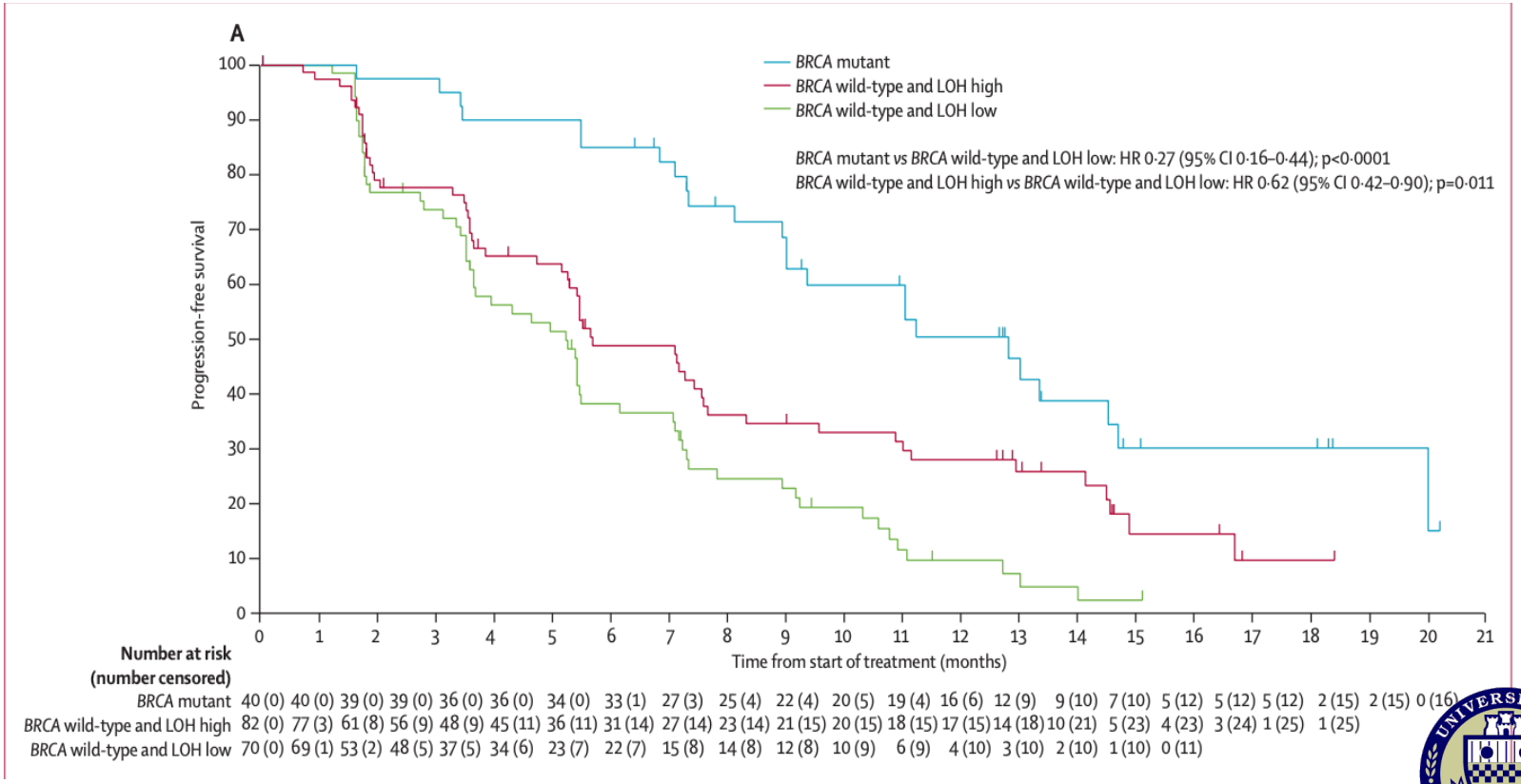
Study design

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 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)

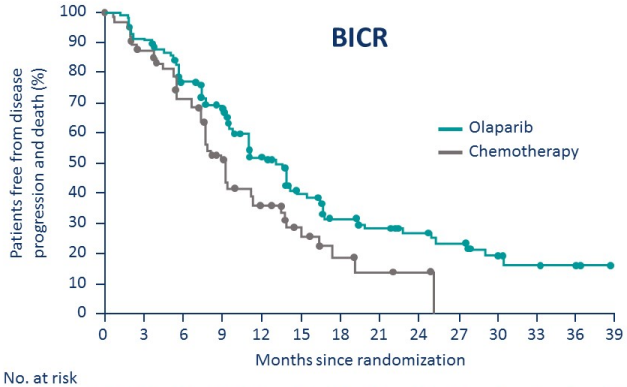
Secondary endpoints
- PFS
- PFS2
- OS
- TFST
- TSST
- HRQoL
- Safety

*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/m² on day 1 q4w; paclitaxel, 80 mg/m² on days 1, 8, 15, and 22 q4w; gemcitabine, 1000 mg/m² on days 1, 8, and 15 q4w; topotecan, 4 mg/m² 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

Presented By Richard Penson at 2019 ASCO Annual Meeting

University of Pittsburgh

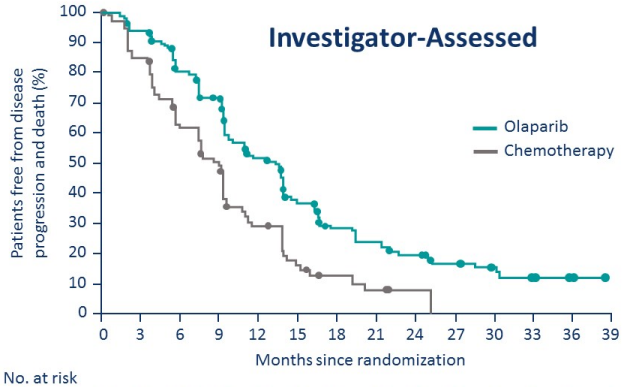
PFS (Intention-To-Treat Population)



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

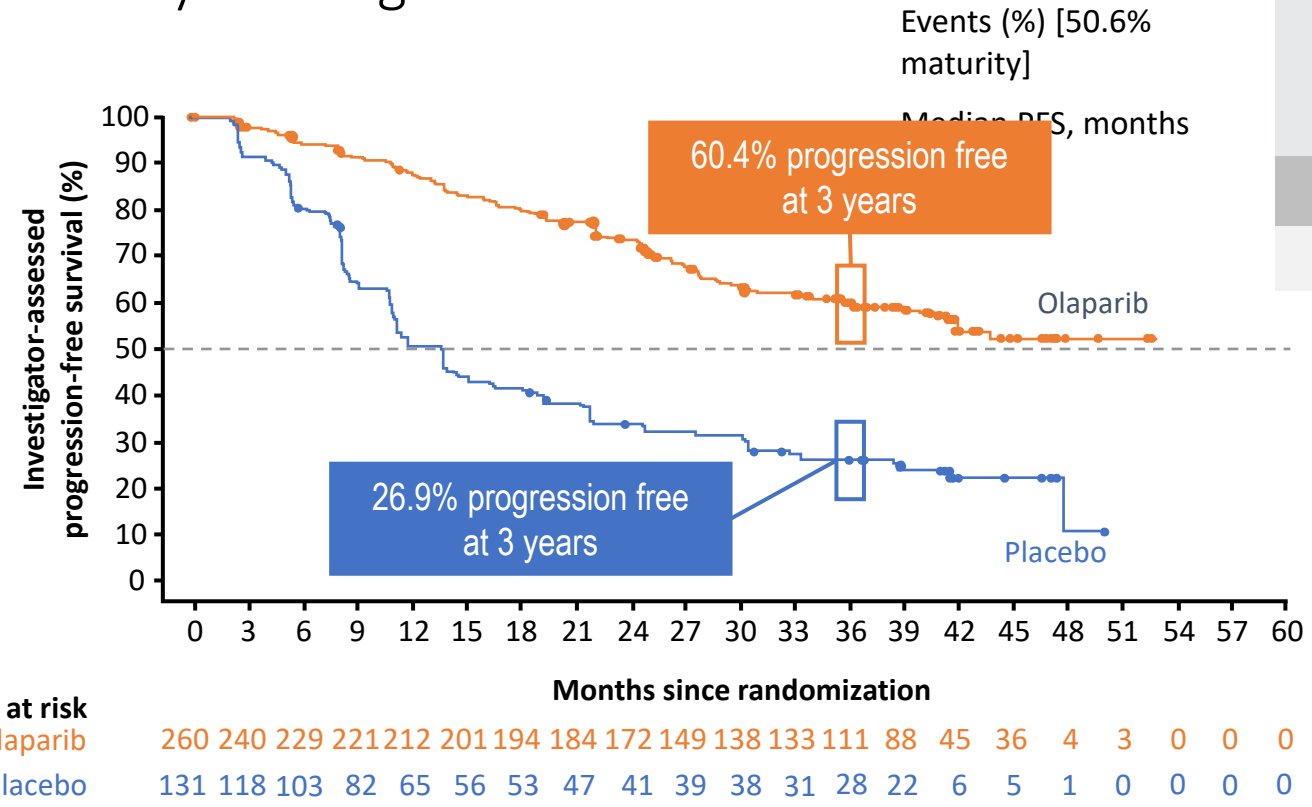
SOLO1: Phase III trial of maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients with advanced ovarian cancer and a *BRCA1/2* mutation

- 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

ESMO Congress, Munich 2018

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

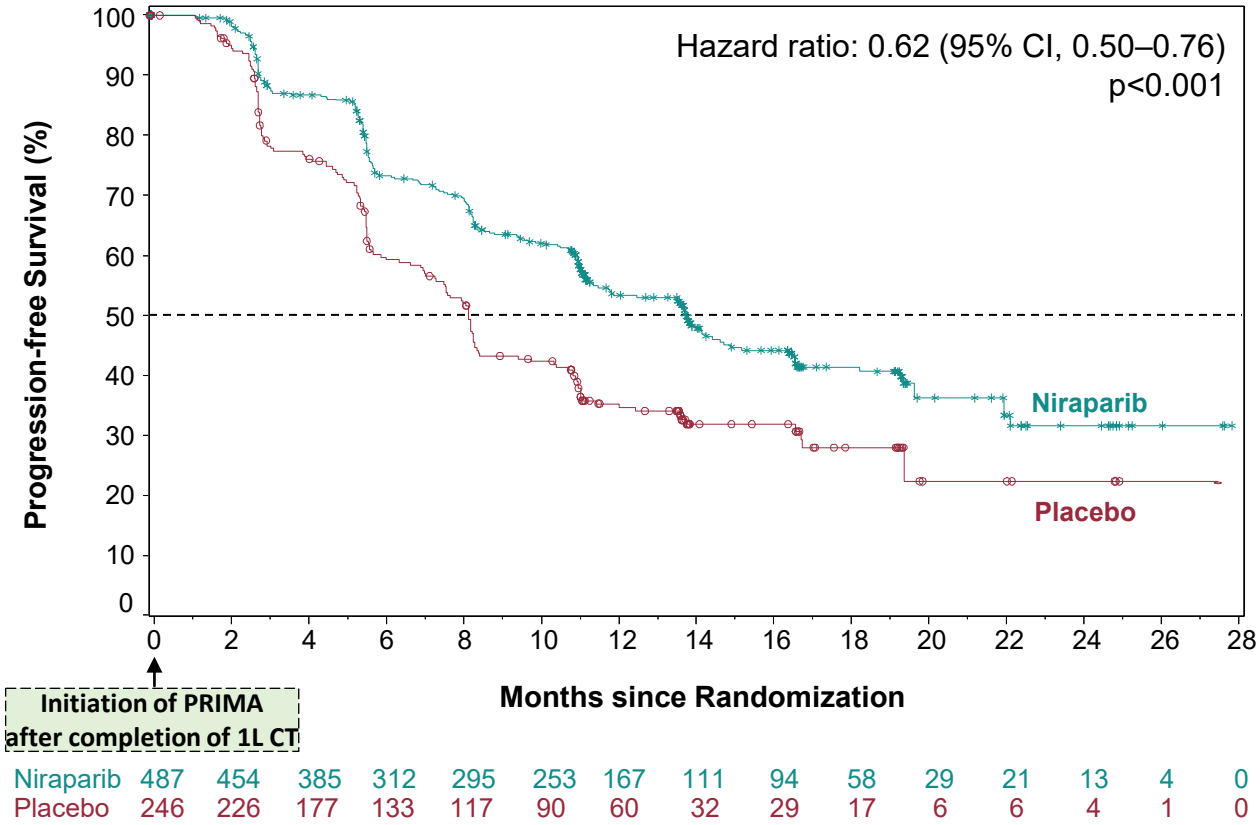
ESMO Congress, Munich 2018

CI, confidence interval; NR, not reached

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]

PRIMA Primary Endpoint, PFS Benefit in the Overall Population



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

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

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

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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*

FIRST LINE

- **Surgery (upfront or interval)**
- **Platinum–taxane based chemotherapy**
- **≥3 cycles of bevacizumab†**

NED/CR/PR

N=806

Randomization

2:1

Maintenance therapy

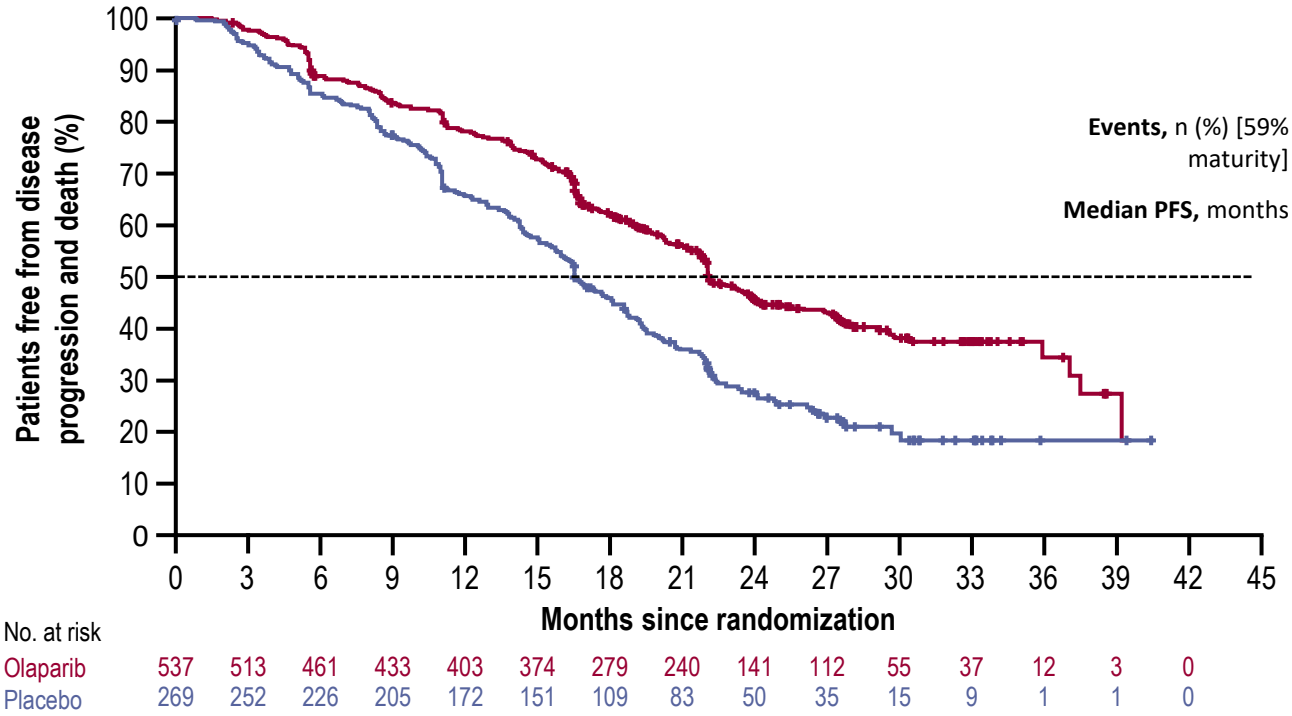
Olaparib (300 mg BID) x2 years
+
bevacizumab†

Placebo x2 years
+
bevacizumab†

Stratification
- Tumour *BRCA*m status‡
- First-line treatment outcome¶

*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 timing of surgery and NED/CR/PR
BID, twice daily; *BRCA*m, *BRCA1* and/or *BRCA2* mutation; CR, complete response; NED, no evidence of disease; PR, partial response

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

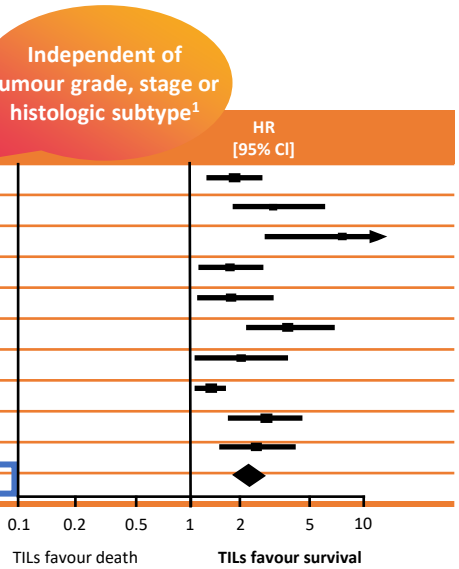
ITT, intent-to-treat population

Immunotherapy

Immunotherapy in Ovarian Cancer: What is the rationale? Correlation between TILs and Survival

Independent of tumour grade, stage or histologic subtype[1]

Study or Subgroup	Log [HR]	SE	Weight (%)	HR [95% CI]
Zhang (2003)	0.61	0.18	12.5	1.84 [1.29–2.62]
Sato (2005)	1.11	0.307	8.8	3.03 [1.66–5.54]
Hamanishi (2007)	2.031	0.518	4.8	7.62 [2.76–21.04]
Callahan (2008)	0.548	0.222	11.2	1.73 [1.12–2.67]
Han (2008)	0.563	0.258	10.1	1.76 [1.06–2.91]
Tomsova (2008)	1.308	0.296	9.1	3.70 [2.07–6.61]
Adams (2009)	0.694	0.315	8.6	2.00 [1.08–3.71]
Clarke (2009)	0.282	0.106	14.5	1.33 [1.08–1.63]
Leffers (2009)	1.02	0.251	10.3	2.77 [1.70–4.54]
Stumpf (2009)	0.895	0.258	10.1	2.45 [1.48–4.06]
Total (95% CI)			**100.0**	**2.24 [1.71–2.92]**



Test for overall effect: p<0.00001
CI, confidence interval; HR, hazard ratio; OC, ovarian cancer;
SE, standard error; TILs, tumour-infiltrating lymphocytes

Hwang et al. Gynecol Oncol 2012

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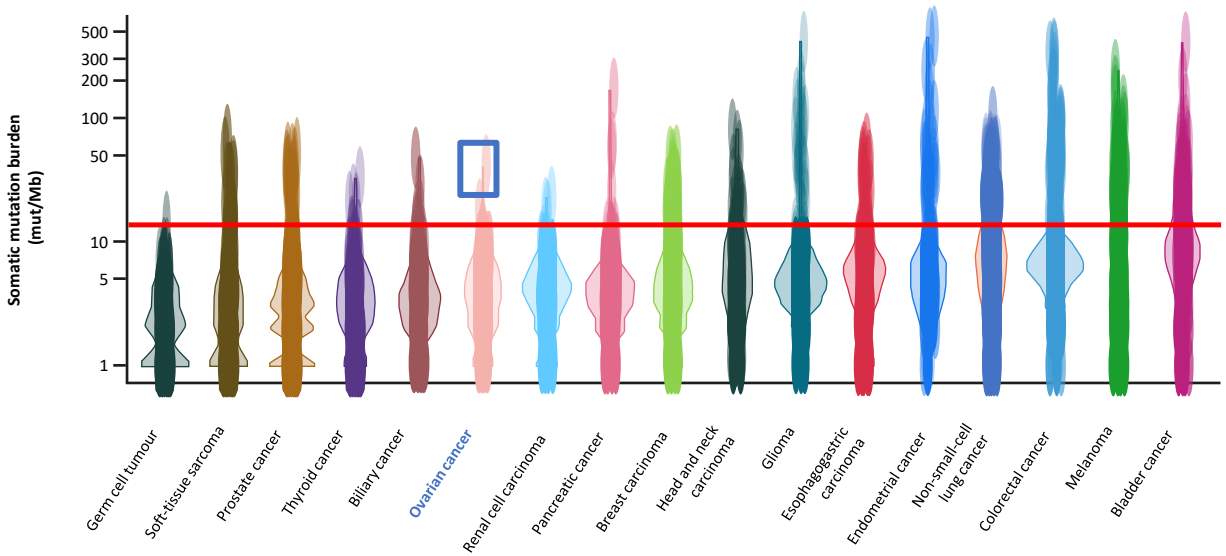
Immunotherapy in Ovarian Cancer: What is the rationale?

OC carries significant levels of mutational load



Red line indicates the threshold for samples with a high mutational burden (13.8 mutations/Mb)
Mb, megabase; OC, ovarian cancer

Zehir et al. Nat Med 2017

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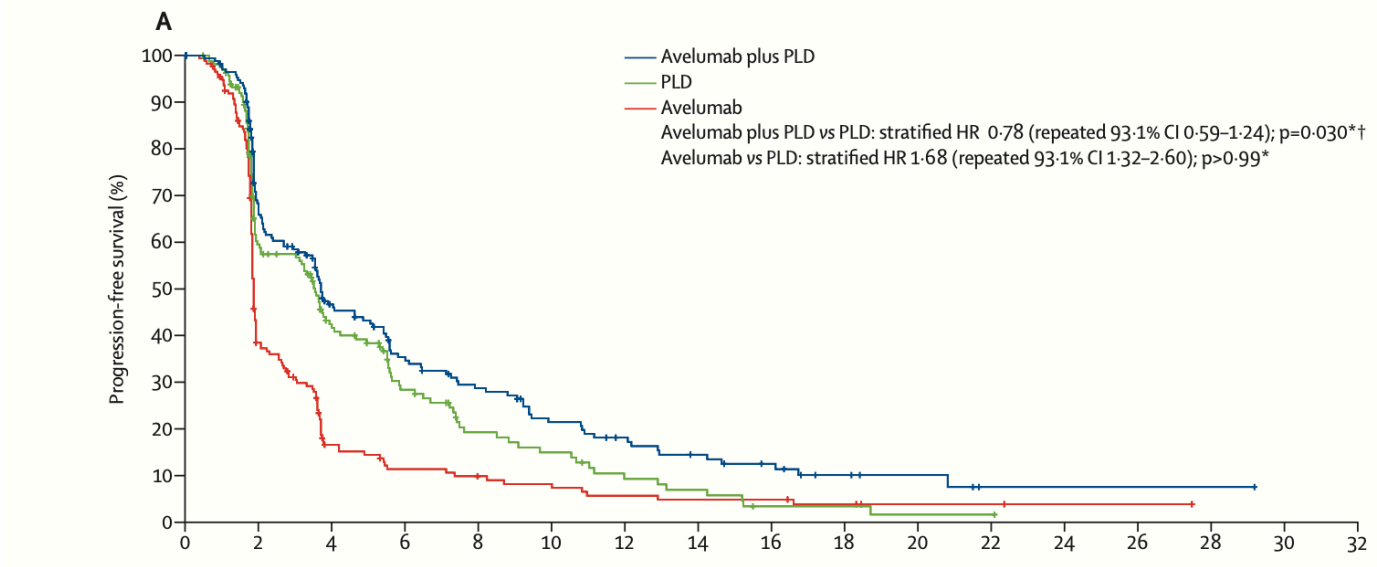
Javelin 200: Avelumab vs. PLD vs. PLD+Avelumab PROC-Progression-Free Survival



1: Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study.
Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard IL, Richardson GE, Sessa C, Yonemori K, Banerjee S, Leary A, Tinker AV, Jung KH, Madry R, Park SY, Anderson CK, Zohren F, Stewart RA, Wei C, Dychter SS, Monk BJ.
Lancet Oncol. 2021 Jul;22(7):1034-1046.

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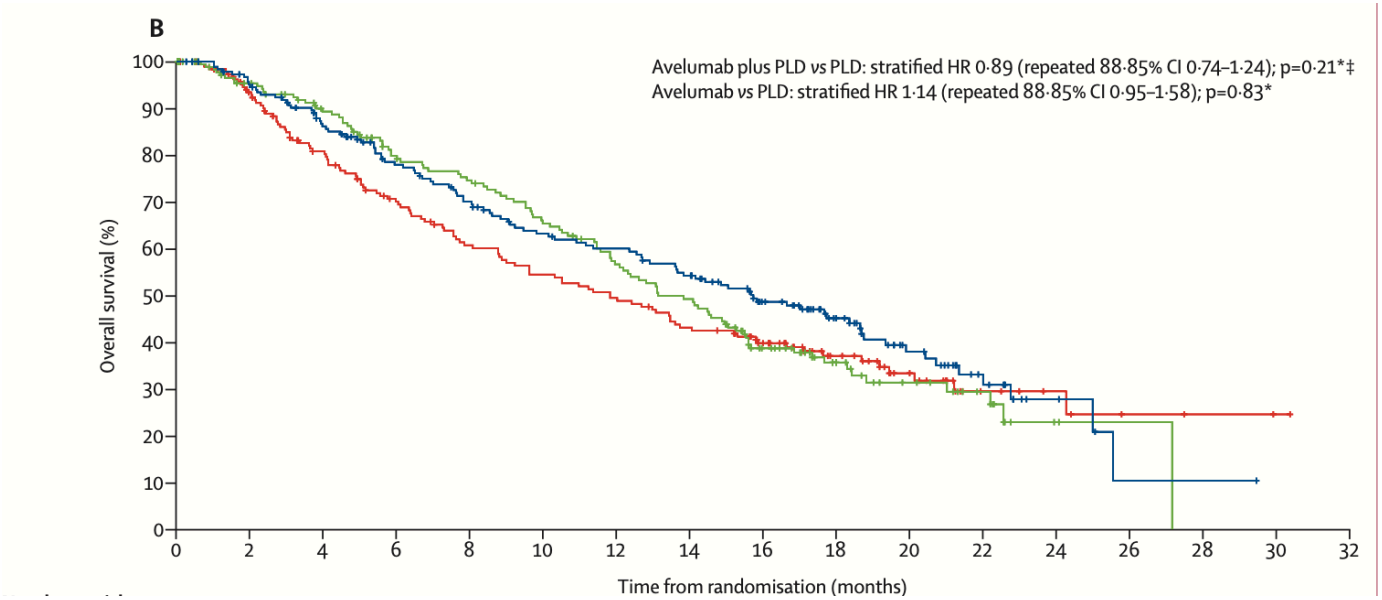
Javelin 200: Avelumab vs. PLD vs. PLD+Avelumab PROC-Overall Survival



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Lancet Oncol. 2021 Jul;22(7):1034-1046.

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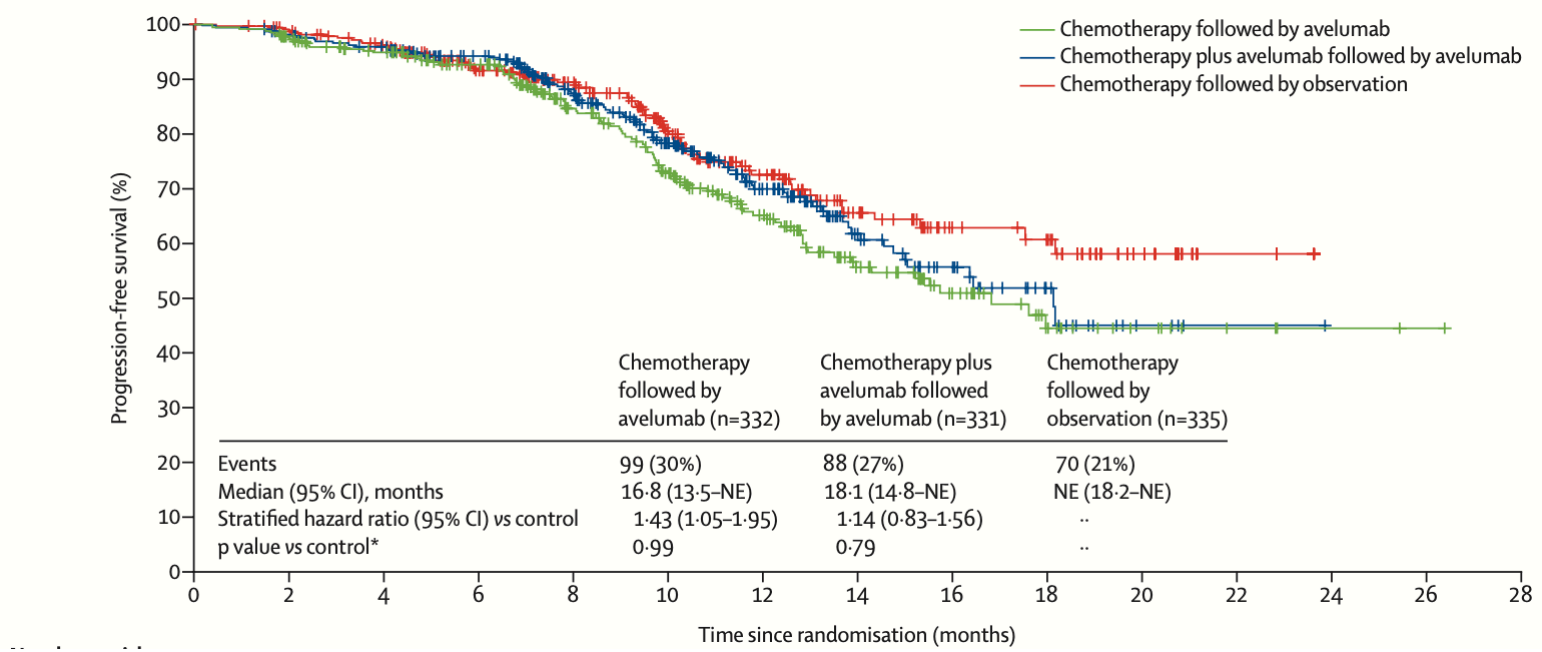
Javelin 100: CT vs CT+ avelumab vs CT followed by avelumab



	Chemotherapy followed by avelumab (n=332)	Chemotherapy plus avelumab followed by avelumab (n=331)	Chemotherapy followed by observation (n=335)
Events	99 (30%)	88 (27%)	70 (21%)
Median (95% CI), months	16·8 (13·5–NE)	18·1 (14·8–NE)	NE (18·2–NE)
Stratified hazard ratio (95% CI) *vs* control	1·43 (1·05–1·95)	1·14 (0·83–1·56)	..
p value *vs* control*	0·99	0·79	..

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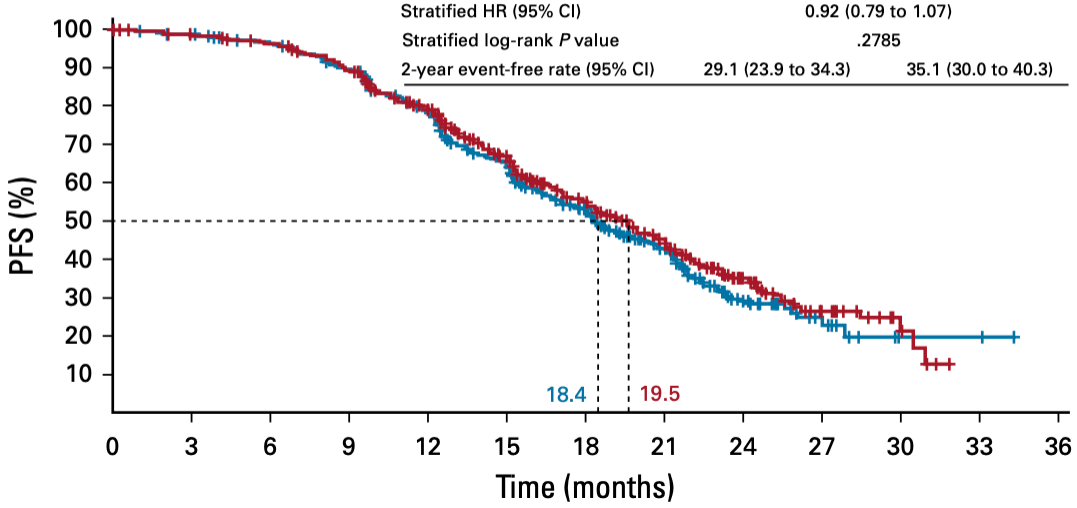
IMAGYN 50

PFS in ITT

PFS	Placebo Plus CP Plus Bevacizumab (n = 650)	Atezolizumab Plus CP Plus Bevacizumab (n = 651)
Events, n (%)	341 (52.5)	323 (49.6)
Median PFS, months (95% CI)	18.4 (17.2 to 19.8)	19.5 (18.1 to 20.8)
Stratified HR (95% CI)	0.92 (0.79 to 1.07)	
Stratified log-rank *P* value	.2785	
2-year event-free rate (95% CI)	29.1 (23.9 to 34.3)	35.1 (30.0 to 40.3)



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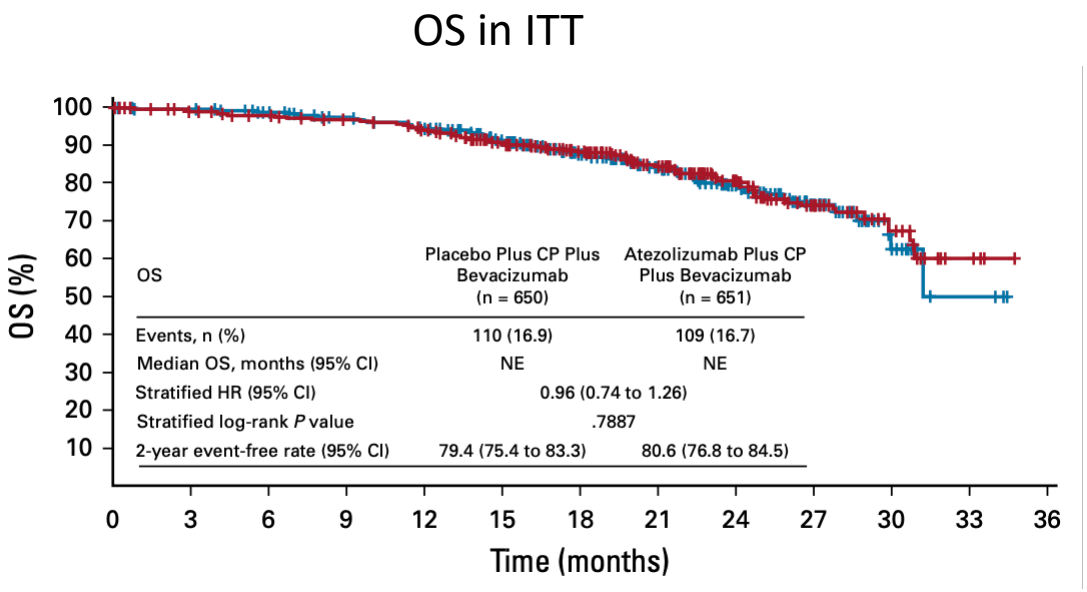
IMAGYN 50



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Conclusions

- **Immunomodulation is a viable treatment strategy for gynecologic cancers**
- **When tumor responds, the response durable**
- **There are opportunities to be explored for optimizing immune therapy benefits in gynecologic cancers**
- **Combination of chemotherapy with immune therapy is an attractive strategy that should be explored further**

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Thank you