BARCELONA 2019 ESMO congress

ONCO NOUVELLE-AQUITAINE
Réseau Régional de Cancérologie

Tumeurs gynécologiques

Dr Anne FLOQUET

Bordeaux, mardi 15 octobre 2019

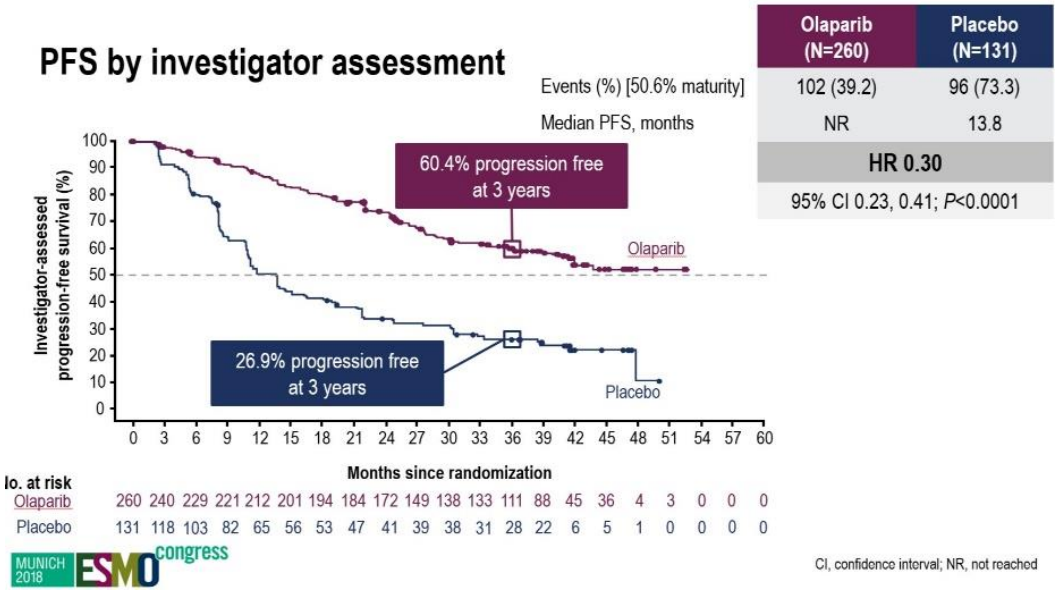
Bergonié UNICANCER NOUVELLE-AQUITAINE

SFOG société française d'onco-gynécologie

Primo traitement CO de haut grade

Ovaire

ESMO 2018
Population BRCA mutée
Et olaparib en maintenance:
Essai SOLO1



ESMO 2019
Toute population

- Essai PAOLA 1
- Essai PRIMA
- Essai VELIA

- **Place d'un anti PARP (olaparib, niraparib, veliparib)**

Soit en maintenance après CT +/- bevacizumab

Soit en association à CT sans bevacizumab

Ovaire

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

esmo.org

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¶

Primary endpoint
Investigator-assessed PFS (RECIST v1.1)

Sensitivity analysis
PFS by BICR

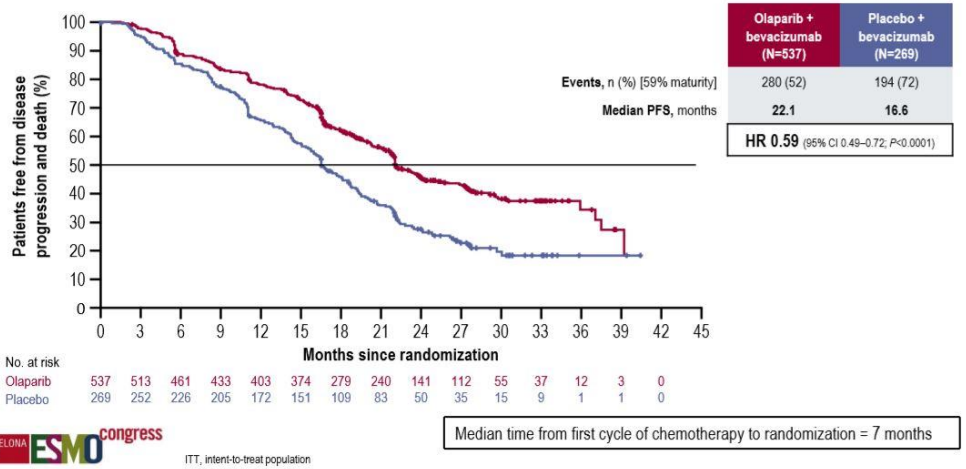
Secondary endpoints
TFST
PFS2, TSST
OS
HRQoL
Safety and tolerability

*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
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Essai PAOLA 1

Ovaire

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)

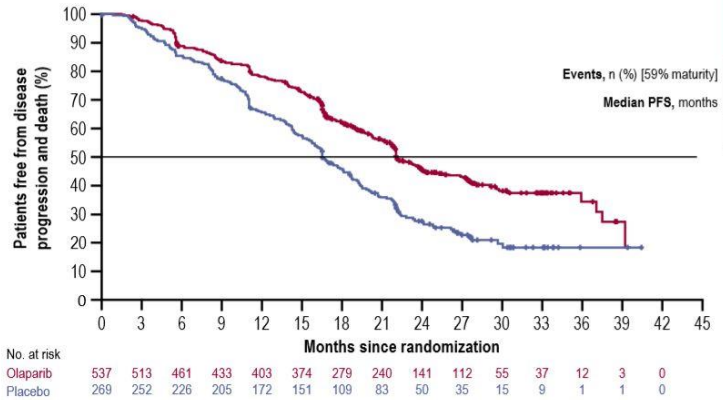
Median time from first cycle of chemotherapy to randomization = 7 months

ITT, intent-to-treat population

Essai PAOLA 1

Ovaire

PFS by investigator assessment: ITT population



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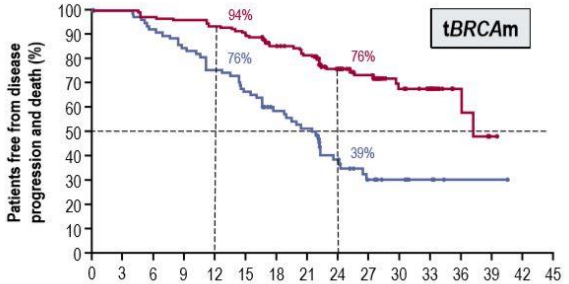
PFS by *tBRCA* mutation status



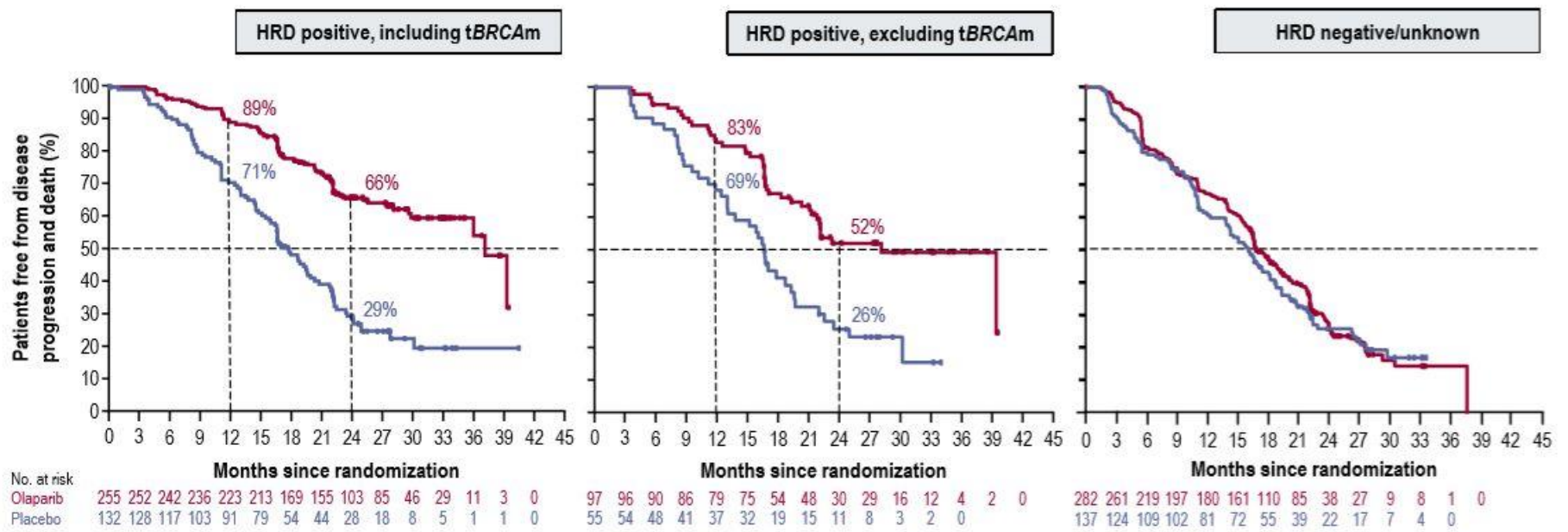
	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	41 (26)	49 (61)
Median PFS, months	**37.2***	**21.7**
HR 0.31 (95% CI 0.20–0.47)		

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. *This median is unstable due to a lack of events – less than 50% maturity

Ovaire

Essai PAOLA 1

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)
	43 (44)	40 (73)
	28.1*	16.6
	HR 0.43 (95% CI 0.28–0.66)	

	Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
	193 (68)	102 (74)
	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 than 50% maturity

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Essai PRIMA

Ovaire

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]

[1]Grupo Español de Investigación en Cáncer de Ovario (GEICO), Medical Oncology Department, Clínica Universidad de Navarra, Madrid, Spain; [2]Gynecologic Oncology Group (GOG), Department of Obstetrics/Gynecology, Perlmutter Cancer Center, NYU Langone Cancer Center, New York, NY, USA; [3]Belgium and Luxembourg Gynaecological Oncology Group (BGOG), Department of Gynaecology and Obstetrics, Division of Gynaecologic Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [4]Nordic Society of Gynaecological Oncology (NSGO), Research Unit of General Practice, Institute of Public Health, University of Southern Denmark, Odense, Denmark; [5] GOG, Gynecologic Oncology, Medical University of South Carolina, Charleston, SC, USA; [6]NSGO, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; [7]GOG, Legacy Medical Group Gynecologic Oncology, Portland, OR, USA; [8]Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO), Fondazione IRCCS National Cancer Institute of Milan, Milan, Italy; [9]US Oncology Research (USOR), Department of Medical Oncology, BC Cancer – Vancouver, Vancouver, BC, Canada; [10]Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), HCL Cancer Institute Department of Medical Oncology Lyon University, Lyon, France; [11]Division of Gynecologic Oncology, Ohio State University, Columbus, OH, USA; [12]Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), Department of Gynecology and Obstetrics, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany; [13]GEICO, Hospital Universitario La Paz-IdiPAZ, Madrid, Spain; [14]USOR, Division of Gynecologic Oncology, Wilmot Cancer Institute, Department of Obstetrics and Gynecology, University of Rochester, Rochester, NY, USA; [15]BGOG, Department of Medical Oncology and Hematology, AZ Maria Middelares, Gent, and Department of Molecular Imaging, Pathology, Radiotherapy & Oncology, Center for Oncological Research, Antwerp University, Antwerp, Belgium; [16]GOG, Gynecologic Medical Oncology, Memorial Sloan Kettering Cancer Center, and Department of Medicine, Weill Cornell Medical College, New York, NY, USA; [17]NSGO, Department of Oncology, Aalborg University, Aalborg, Denmark; [18]TESARO: A GSK Company, Waltham, MA, USA; [19]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Phoenix Creighton University School of Medicine at St. Joseph's Hospital, Phoenix, AZ, US

Essai PRIMA

Ovaire

Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer (PRIMA/ENGOT

A. González-Martín,[1] McCormick,[7] D. Lorus Moore,[14] C. Vulsteke,

[1]Grupo Español de Investigación en Cáncer de C Perlmutter Cancer Center, NYU Langone Cance Oncology, University Hospitals Leuven, Leuven (Denmark, Odense, Denmark; [5] GOG, Gynecolog Medical Group Gynecologic Oncology, Portland, Oncology Research (USOR), Department of Mec Department of Medical Oncology Lyon University Gynecology and Obstetrics, Klinikum der Stadt L Department of Obstetrics and Gynecology, Unive Pathology, Radiotherapy & Oncology, Center for Medicine, Weill Cornell Medical College, New Yo Oncology Network), University of Arizona Colleg

PRIMA Trial Design

Patients with newly-diagnosed OC at high risk for recurrence after response to 1L platinum-based chemotherapy

2:1 Randomization

Niraparib — **Placebo**

Stratification Factors

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

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

Endpoint assessment

Primary Endpoint: Progression-free survival by BICR

Key Secondary Endpoint: Overall Survival

Secondary Endpoints: PFS2, TFST, PRO, Safety

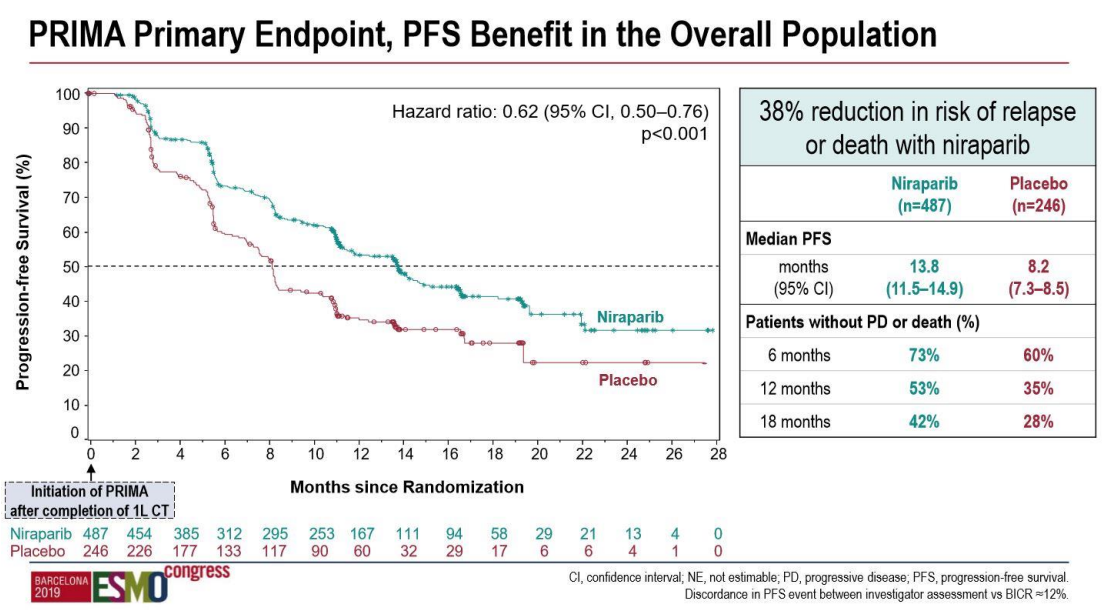
Hierarchical PFS Testing

- **Patients with homologous recombination deficient tumors**, followed by the **overall population**.
- Statistical assumption: a hazard ratio benefit in PFS of
  - 0.5 in homologous recombination deficient patients
  - 0.65 in the overall population
- >90% statistical power and one-sided type I error of 0.025

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

Essai PRIMA

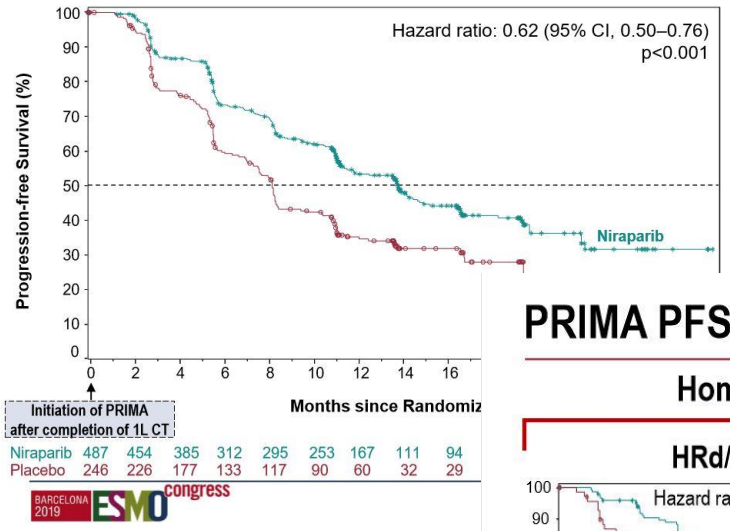
Ovaire



Essai PRIMA

Ovaire

PRIMA Primary Endpoint, PFS Benefit in the Overall Population

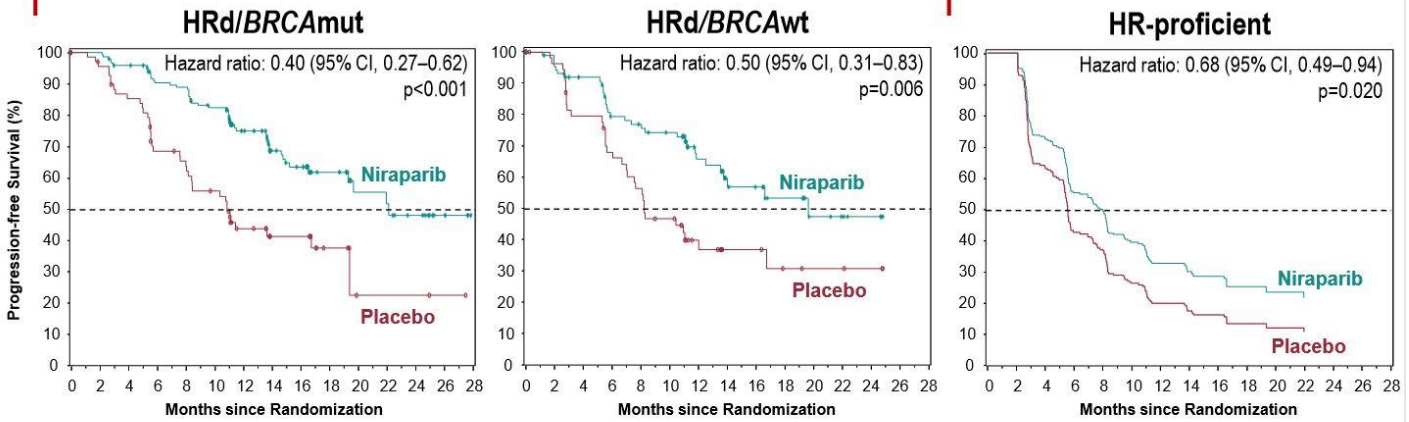


38% reduction in risk of relapse or death with niraparib

	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 (%)		

PRIMA PFS Benefit in Biomarker Subgroups

Homologous Recombination Deficient (HRd)



- 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; HRd, homologous recombination deficient; mut, mutation; PFS, progression-free survival wt, wild-type.

Ovaire

Essai VELIA

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

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

Study Design: VELIA/GOG-3005 (NCT02470585)

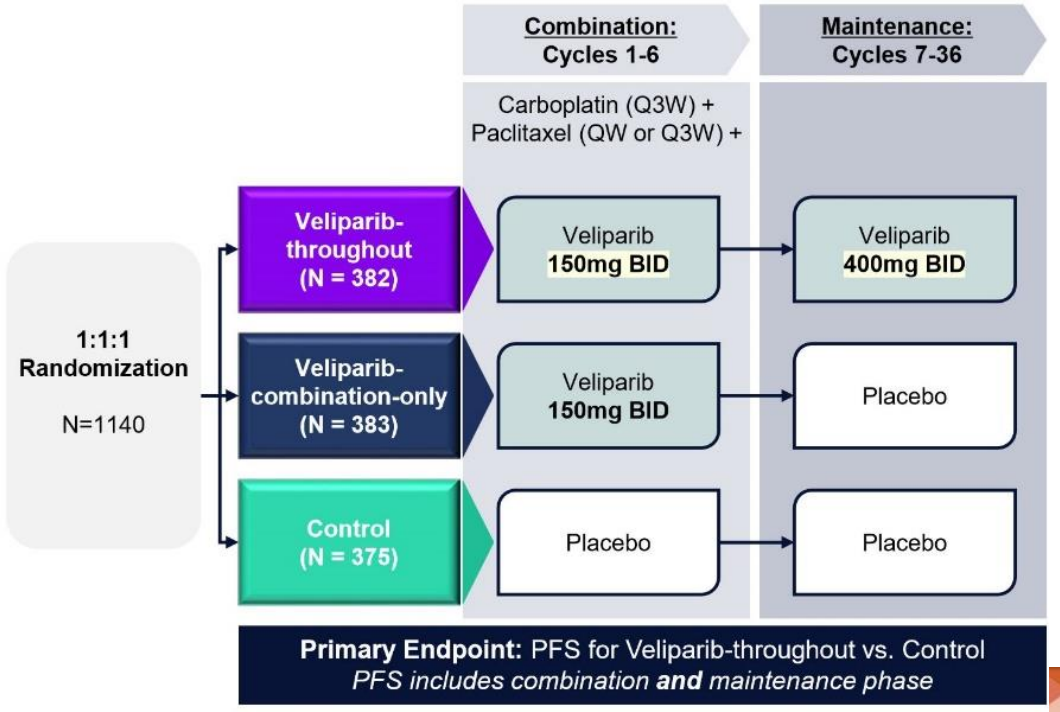
Patient Population

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

Stratification Factors

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

Carboplatin AUC 6 Q3W +
Paclitaxel 80 mg/m² QW or 175 mg/m² Q3W
* Added as stratification factor ~14 months after trial initiation due to noted imbalance

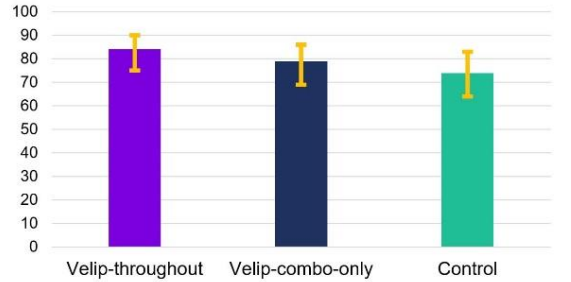


Essai VELIA

Ovaire

Objective Response Rates at End of Combination Phase

ORR at End of Combination Phase in ITT Patients with Primary Surgery and Measurable Disease



N = 290 (25% of ITT Patients)

ORR (CR+PR), n / N %, [95% CI]		
Veliparib-throughout	Veliparib-combo-only	Control
82/98	78/99	69/93
84% [75, 90]	**79%** [69, 86]	**74%** [64, 83]

For both veliparib-containing arms, numerically higher response rates were observed at the end of chemotherapy

Essai VELIA

Ovaire

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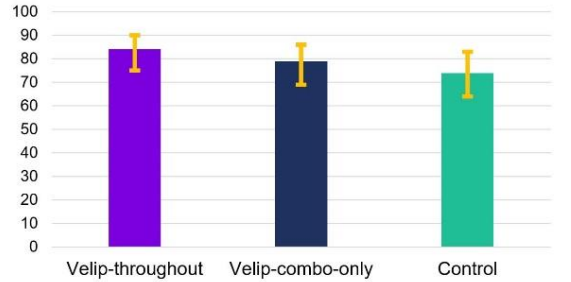

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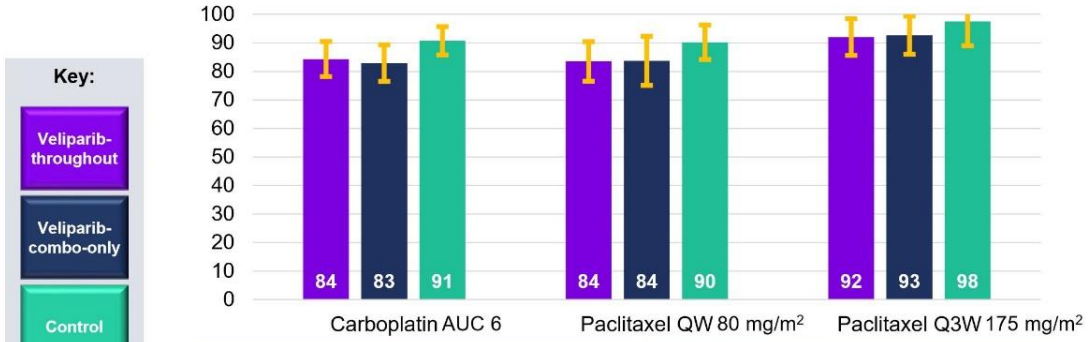
Relative Dose Intensity of Chemotherapy

Relative Dose Intensity: Mean % of Actual/Planned Doses



Dosing of veliparib/placebo during combination phase (Cycles 1-6)	Velip-throughout	Velip-combo-only	Control
Median Cycles	6 cycles	6 cycles	6 cycles
Dose Reductions	5%	6%	3%

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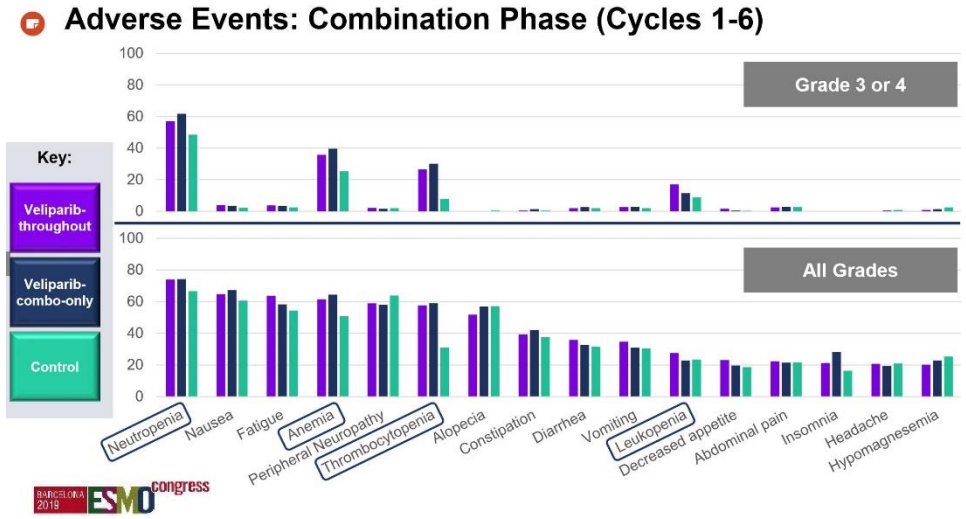

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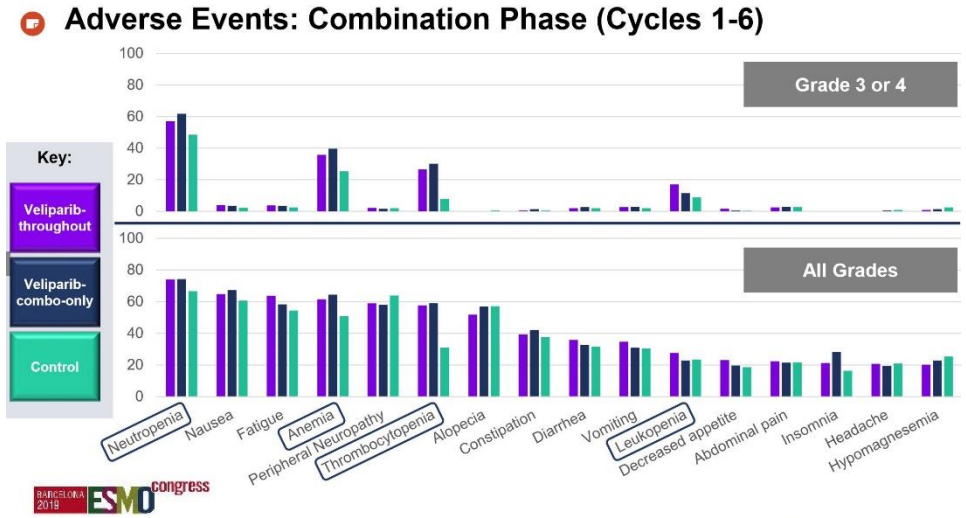

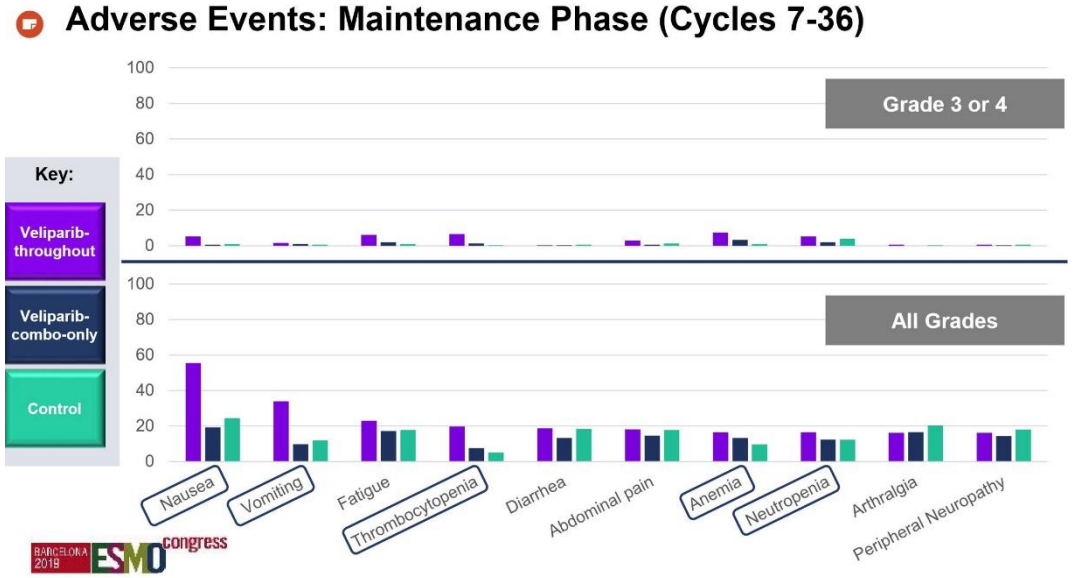

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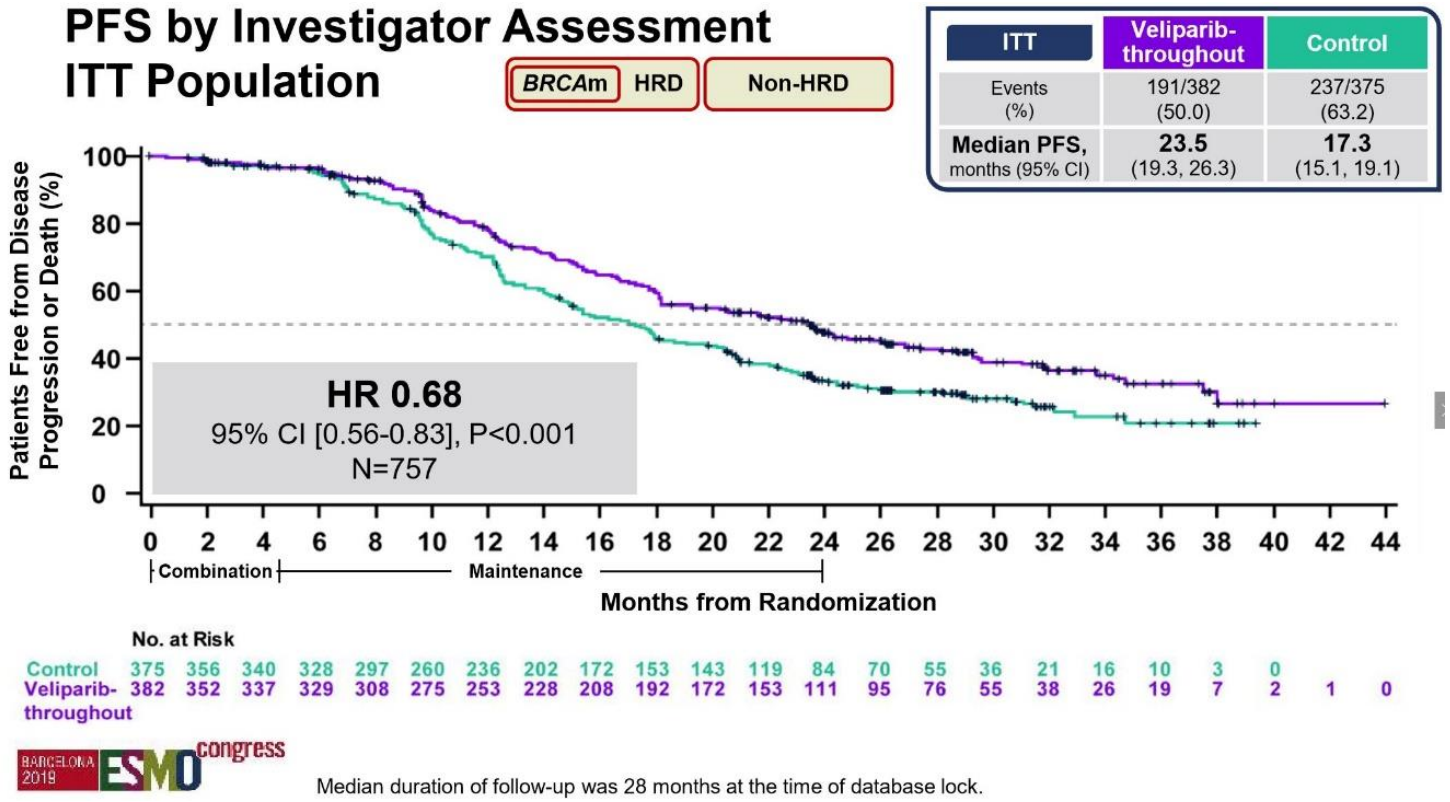

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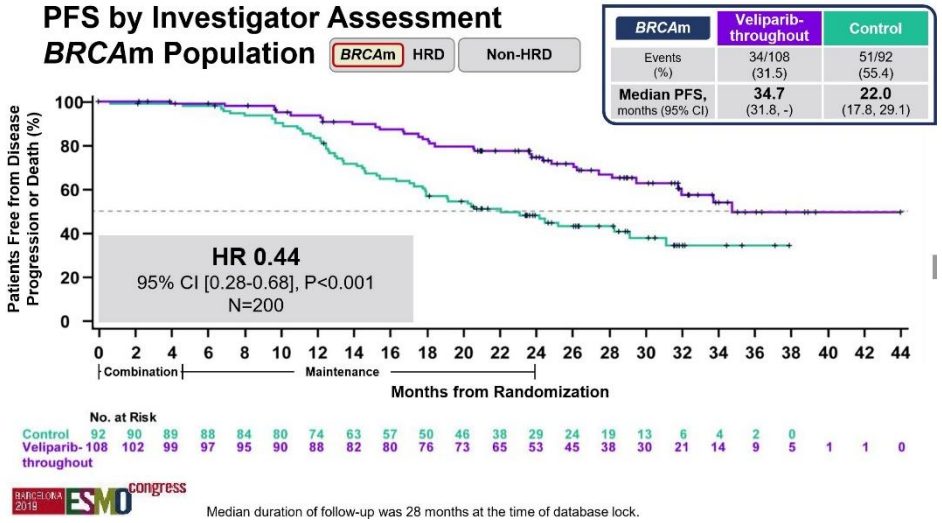
Median duration of follow-up was 28 months at the time of database lock.

Essai VELIA

Ovaire



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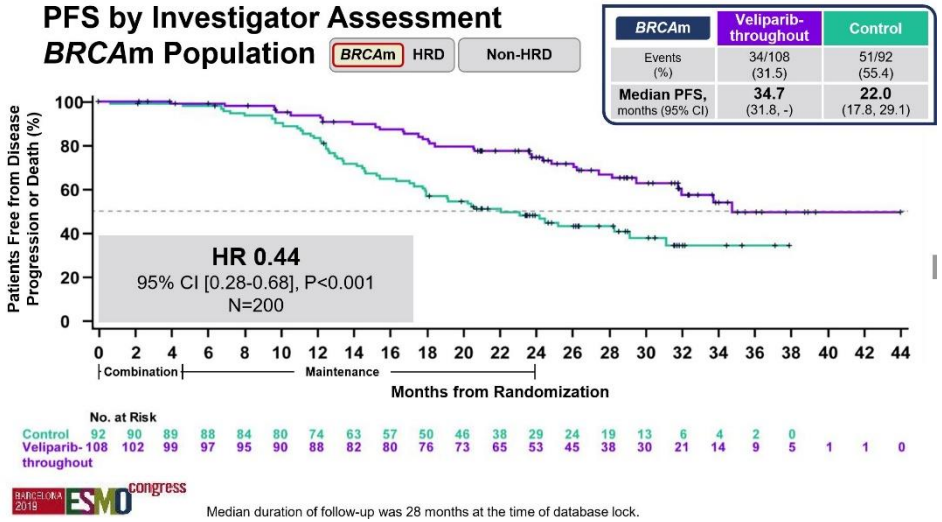

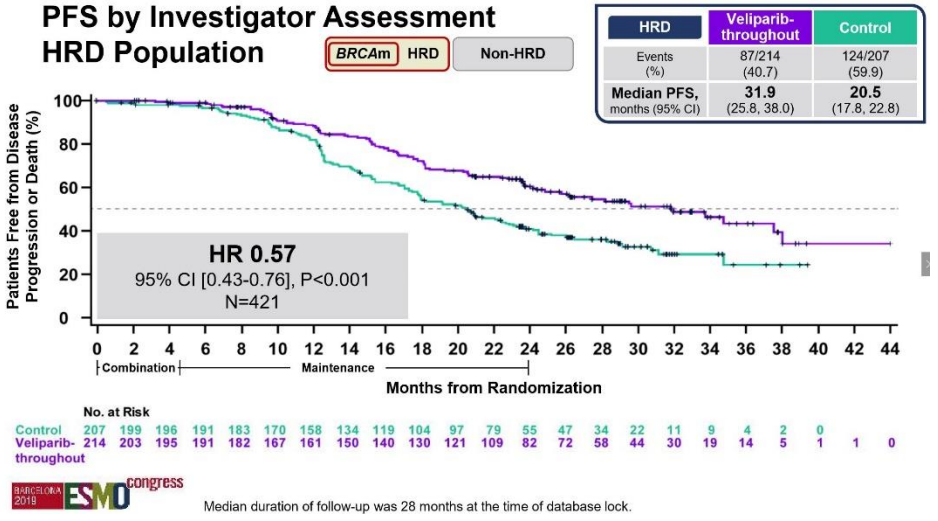

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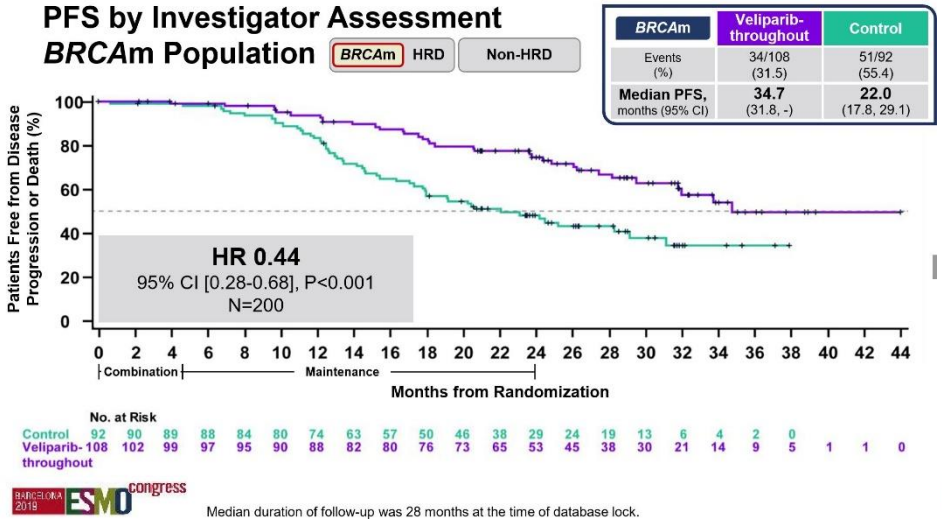

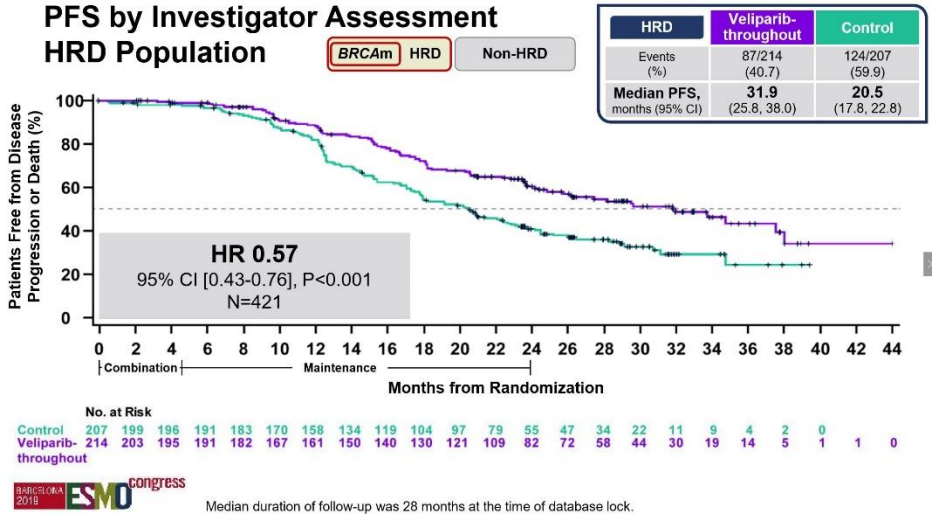

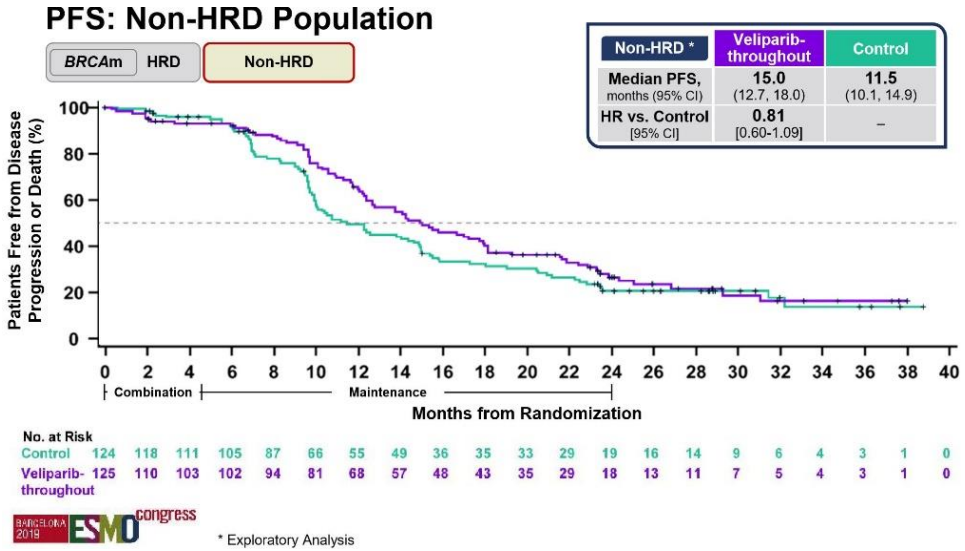

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Conclusions

Ovaire

Bras expérimental Des études	GOG 218 N= 623	PRIMA N=487	PAOLA1 N=537
Age médian (ans)	60 (22-89)	62 (32-85)	61 (32-87)
Statut BRCA, n (%) BRCA mut BRCA wt/HRP/HR UK	 92 (23 %) 307(77 %)	 152 (**31 %**) 335 (69 %)	 157 (**29%**) 380 (71%)
Stade au diagnostic, n (%) III IV	 458 (73,5%) 165 (26,5 %)	 318 (65 %) 169 (**35%**)	 378 (70%) 159 (30%)
Chirurgie - **initiale** • Résidu macro • Pas de résidu macro - **intervalle** • Résidu macro • Pas de résidu macro	 663 (100%) 458 (73,5%) NA **NA**	 244 (34%) NA 322 (**66%**)	 217 (50%) 111 (41%) 160 (59%) 228 (**42%**) 65 (29%) 163 (71%)
Réponse après chirurgie +chimio avec platine, n (%) • NED • RC • RP	NA	 NA 337 (69 %) 150 (31 %)	 290 (**54 %**) 106 (20%) 141 (26%)

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Conclusions

Ovaire

- 3 études de phase III positives :
  - Il existe une place pour les PARPi dans le primo-traitement du CEO

    mBRCA > HRD positif > HRD UK et nég
- Au-delà de l'altération des gènes BRCA, les tests HRD (ici MyChoice, Myriad) ont permis d'augmenter la population susceptible de bénéficier des PARPi mais **il persiste une difficulté à identifier celle qui n'en bénéficie pas**
- Une chirurgie complète initiale, principal facteur pronostique à ce jour, ne permet pas d'évaluer la platino sensibilité…principal facteur clinique actuel de réponse aux PARPi
- La combinaison CT et PARPI (veliparib) est possible
- Pas de nouveau signal pour le profil de tolérance
- Demain, **rien ne change en pratique**
  - mBRCA: Carbo-taxol et maintenance si réponse par olaparib (schéma SOLO1)
  - Les autres: Carbo taxol +/- Bev
- En recherche clinique: amendement en cours pour les essais de phase III en cours

Conclusions

Ovaire

- 3 études de p
  - Il existe u t du CEO
- Au-delà de l'a MyChoice, Myriad) ont permis d' énéficier des PARPi mais **il persis bénéficie pas**
- Une chirurgie tique à ce jour, ne permet pas d eur clinique actuel de réponse aux
- La combinais
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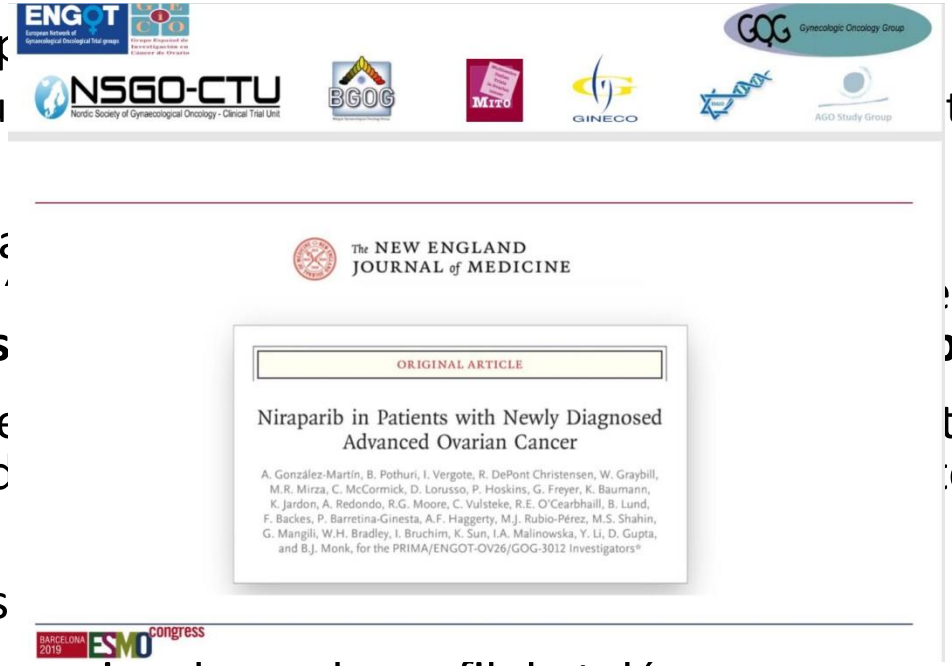

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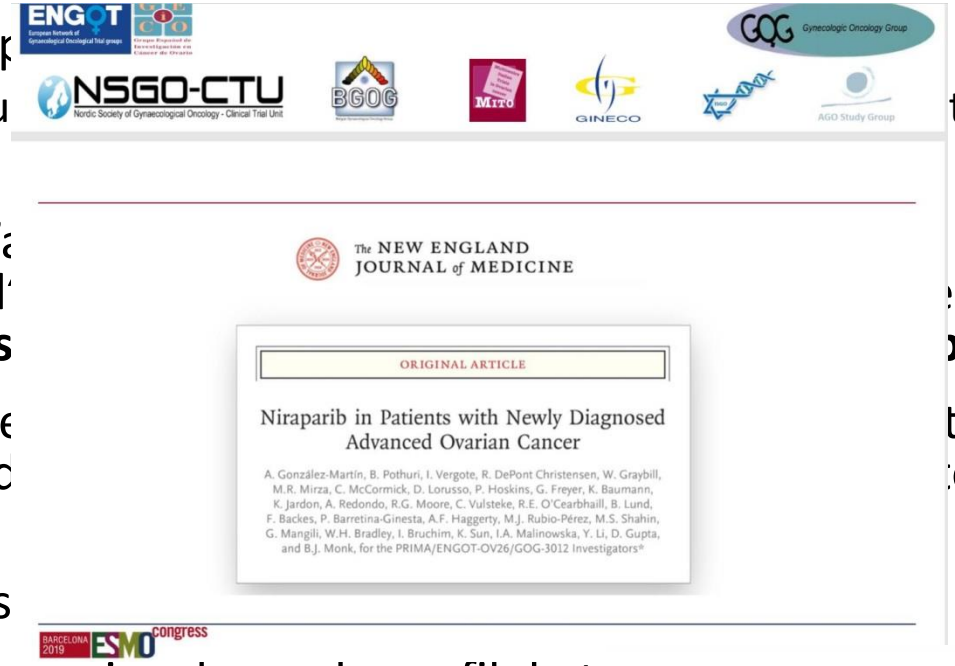
- La combinais
- Pas de nouveau signal pour le profil de t
- Demain, **rien ne change en pratique**
  - mBRCA: Carbo-taxol et maintenance si r
  - Les autres: Carbo taxol +/- Bev
- En recherche clinique: amendement en c cours



Conclusions

Ovaire

- 3 études de p
  - Il existe u t du CEO
- Au-delà de l'a MyChoice, Myriad) ont permis d' énéficier des PARPi mais **il persis bénéficie pas**
- Une chirurgie tique à ce jour, ne permet pas d eur clinique actuel de réponse aux
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- Pas de nouveau signal pour le profil de t
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- En re nent en c cours

Essai PAOLA 1
En attente de publication