"The Systemic Treatment of Recurrent Ovarian Cancer revisited"

MaNGO
Mario Negri Gynecologic Oncology

XVIII ASSEMBLEA MANGO

Ricerca Clinica e Traslazionale in Ginecologia Oncologica

MILANO, 2-3 LUGLIO 2021

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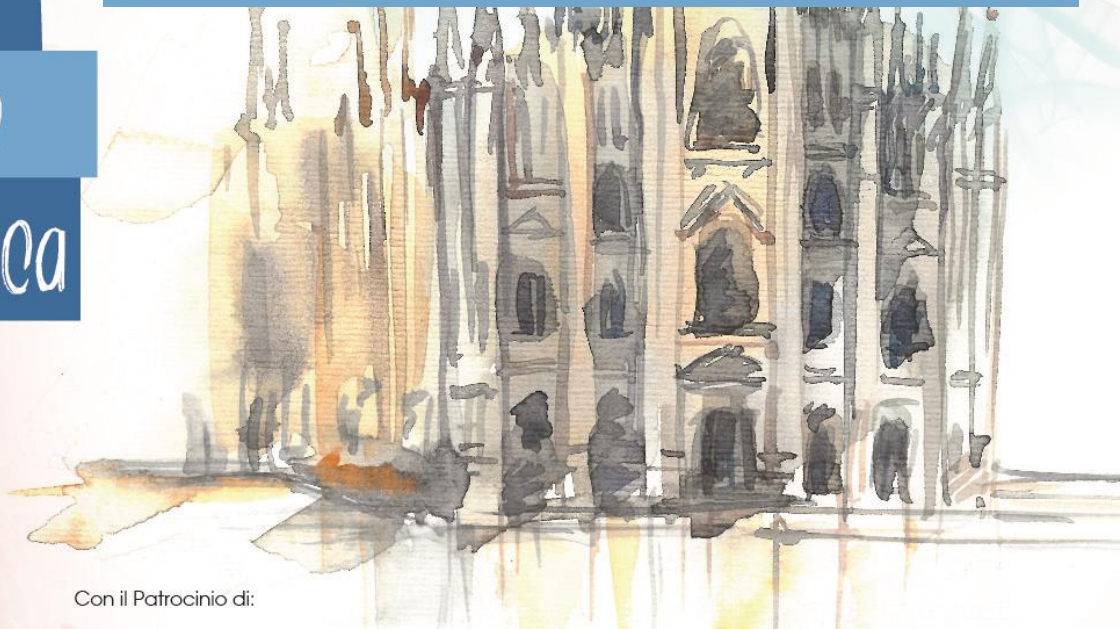

Con il Patrocinio di:

AIOM Associazione Italiana di Oncologia Medica
FICOG | Federation of Italian Cooperative Oncology Groups
SOCIETA' ITALIANA DI CANCEROLOGIA
SIGO SOCIETA' ITALIANA DI GINECOLOGIA E OSTETRICIA
ACTO ALLEANZA CONTRO il TUMORE OVARICO

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY
driving innovation in oncology

Volume 32 ■ Issue 6 ■ 2021

REVIEW

The systemic treatment of recurrent ovarian cancer revisited

T. Baert[1,2*], A. Ferrero[3], J. Sehouli[4], D. M. O'Donnell[5], A. González-Martín[6], F. Joly[7], J. van der Velden[8], P. Blecharz[9], D. S. P. Tan[10,11], D. Querleu[12], N. Colombo[13,14], A. du Bois[1†] & J. A. Ledermann[15†]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESGO European Society of Gynaecological Oncology

ESMO-ESGO Consensus Conference on Ovarian Cancer

Pathology and molecular biology, early and advanced stages, borderline ovarian tumours and recurrent disease

Milano, 12-14 April, 2018

MaNGO Milan Negri Gynecology Oncology

Ricerca Clinica e Traslazionale in Ginecologia Oncologica

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History of Platinum re-treatment

Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials

Br. J. Cancer (1989), **59**, 650–653

G. Blackledge, F. Lawton, C. Redman & K. Kelly

Table IV Response rate using interval from previous treatment to phase II therapy only

Interval (months)	*Total no.*	*No. responding*	*% responding*
<3	39	4	10
4–6	11	1	9
7–9	11	4	36
10–12	6	1	17
13–15	4	2	50
16–18	4	3	75
19–21	1	1	100
>21	16	15	94

The treatment-free interval was the most important variable predicting response to second-line chemotherapy

Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds

› Gynecol Oncol. 1990 Feb;36(2):207-11.

M E Gore [1], I Fryatt, E Wiltshaw, T Dawson

› J Clin Oncol. 1991 Mar;9(3):389-93. doi: 10.1200/JCO.1991.9.3.389.

Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin

M Markman [1], R Rothman, T Hakes, B Reichman, W Hoskins, S Rubin, W Jones, L Almadrones, J L Lewis Jr

Response rates were highest in patients with the longest treatment free interval for platinum-based chemotherapy (TFIp)

History of Platinum re-treatment

Editorial > J Clin Oncol. 1992 Apr;10(4):513-4. doi: 10.1200/JCO.1992.10.4.513.

Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated population

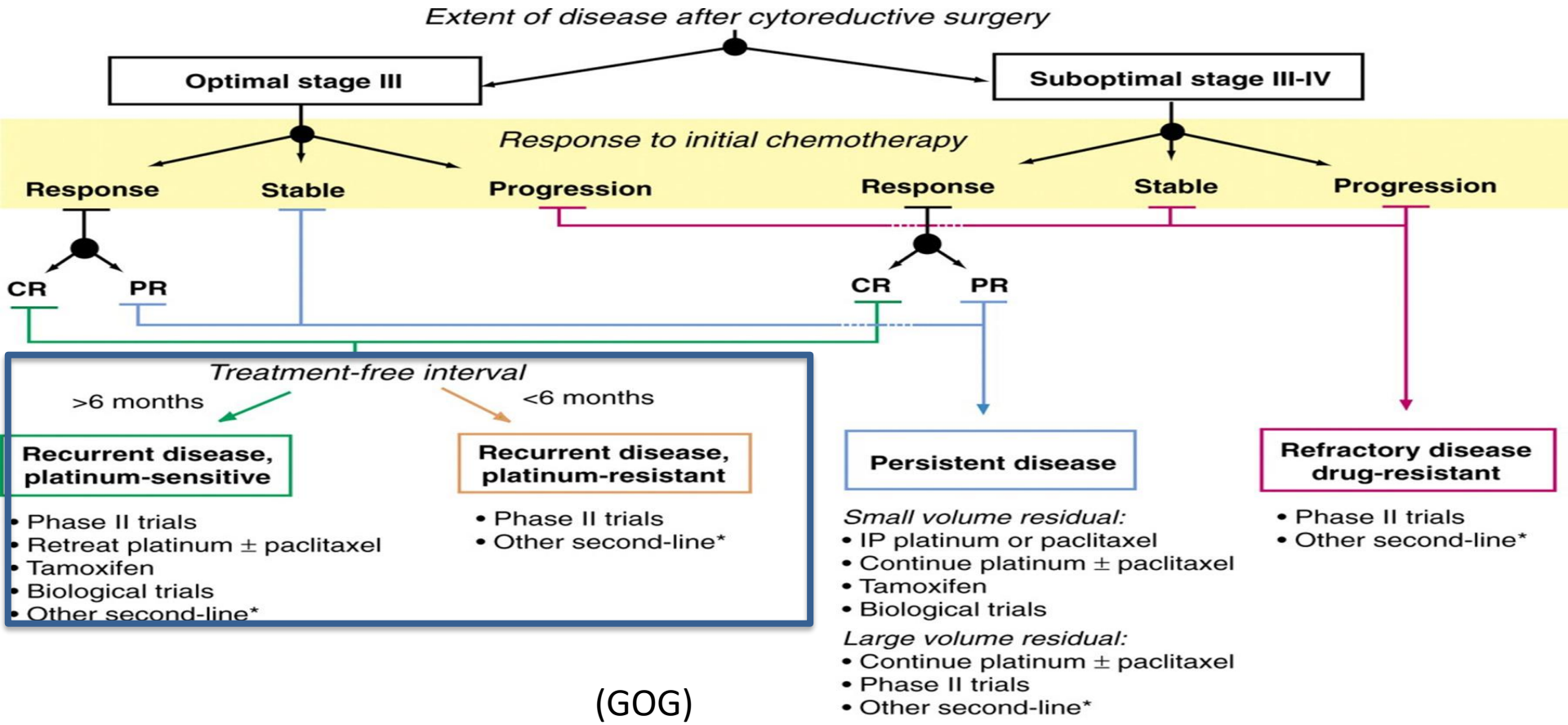
M Markman, W Hoskins

Second-Line Treatment of Ovarian Cancer

MAURIE MARKMAN,[a] MICHAEL A. BOOKMAN[b]

[a]The Cleveland Clinic Taussig Cancer Center, Cleveland, Ohio, USA; [b]Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

The Oncologist 2000;5:26-35



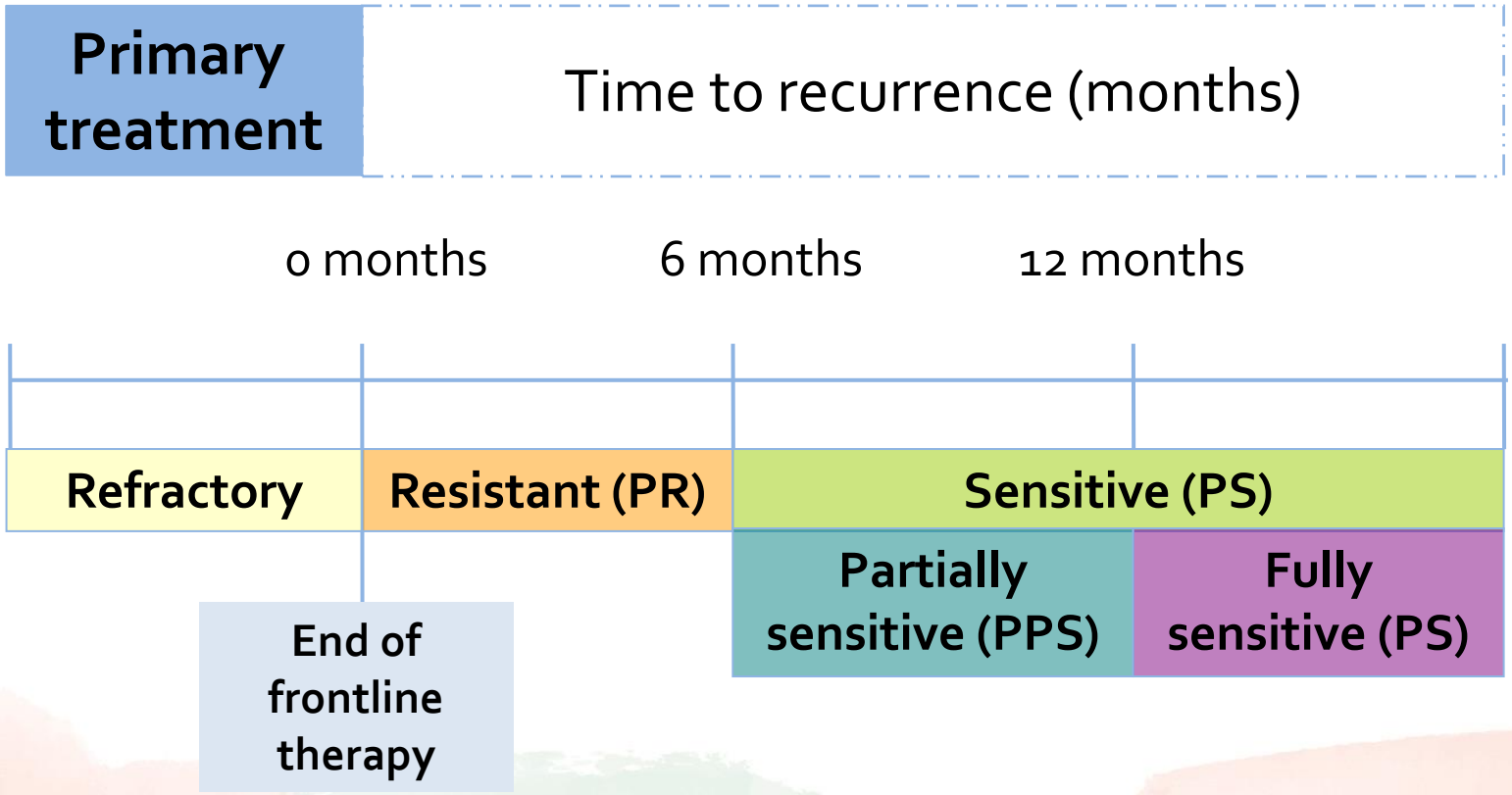
(GOG)

* Other second-line regimens include topotecan, prolonged oral etoposide, liposomal doxorubicin, weekly paclitaxel, and gemcitabine.

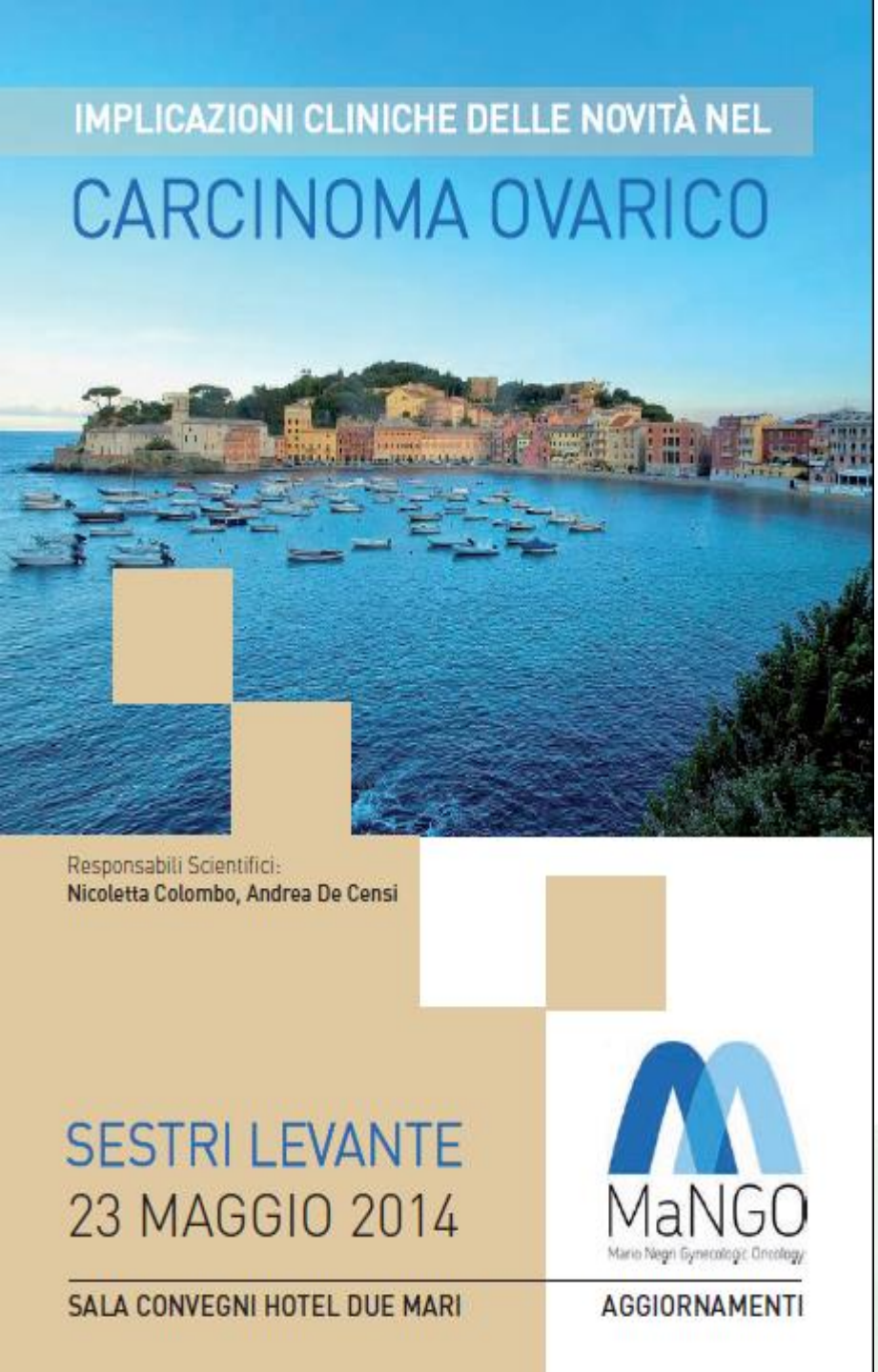
Recurrent Ovarian Cancer (ROC) Classification

4th Ovarian Cancer Consensus Conference of GCIG (Vancouver, 2010)

PFI is defined from the last day of platinum until PD



Adapted from Friedlander M, et al. Int J Gynecol Cancer. 2011;21:771-5



Malattia parzialmente platino sensibile

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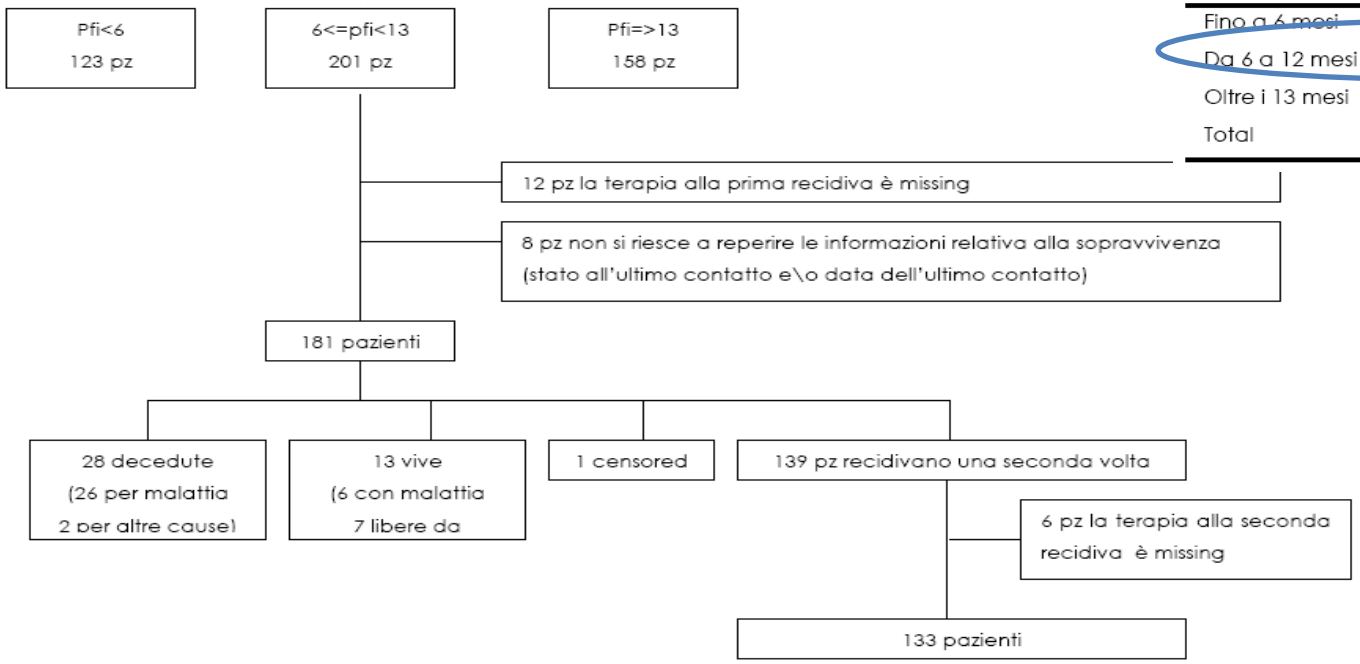
Second line treatment of partially-platinum sensitive recurrent ovarian cancer: a MANGO - Piemonte and Valle d'Aosta Cancer Network Italian multicentric retrospective study



Mesi liberi da platino	Freq	%
Fino a 6 mesi	123	25.52
Da 6 a 12 mesi	201	41.70
Oltre i 13 mesi	158	32.78
Total	482	100

Ferrero et al, IGCS 2010

	Min	Max	P25	Mediana	P75	Media
Terapia senza platino	6.01	12.71	6.78	7.79	9.4	8.21
Terapia con platino	6.01	12.98	8.54	10.28	11.5	9.97
Total	6.01	12.98	7.26	8.8	10.55	9.08

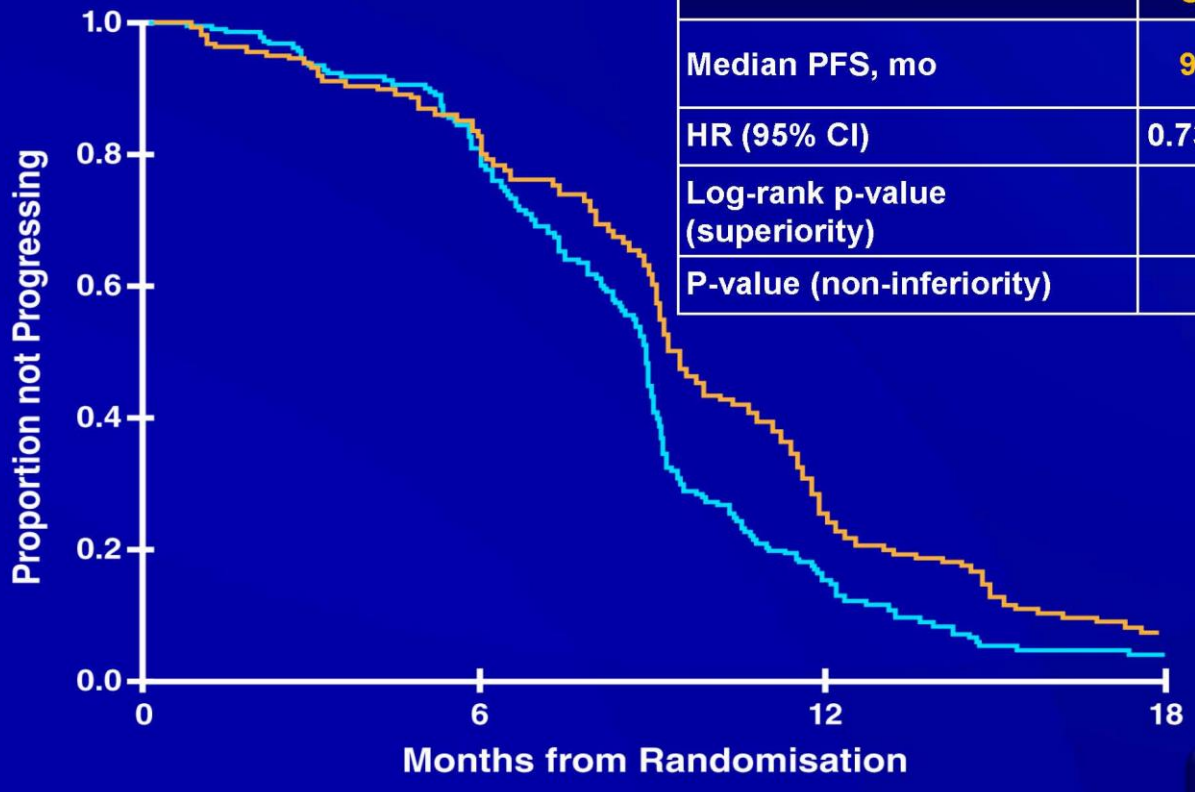
original article

Annals of Oncology
doi:10.1093/annonc/mdr441

Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial

L. Gladieff[1*], A. Ferrero[2], G. De Rauglaudre[3], C. Brown[4], P. Vasey[5], A. Reinthaller[6], E. Pujade-Lauraine[7], N. Reed[8], D. Lorusso[9], S. Siena[10], H. Helland[11], L. Elit[12] & S. Mahner[13]

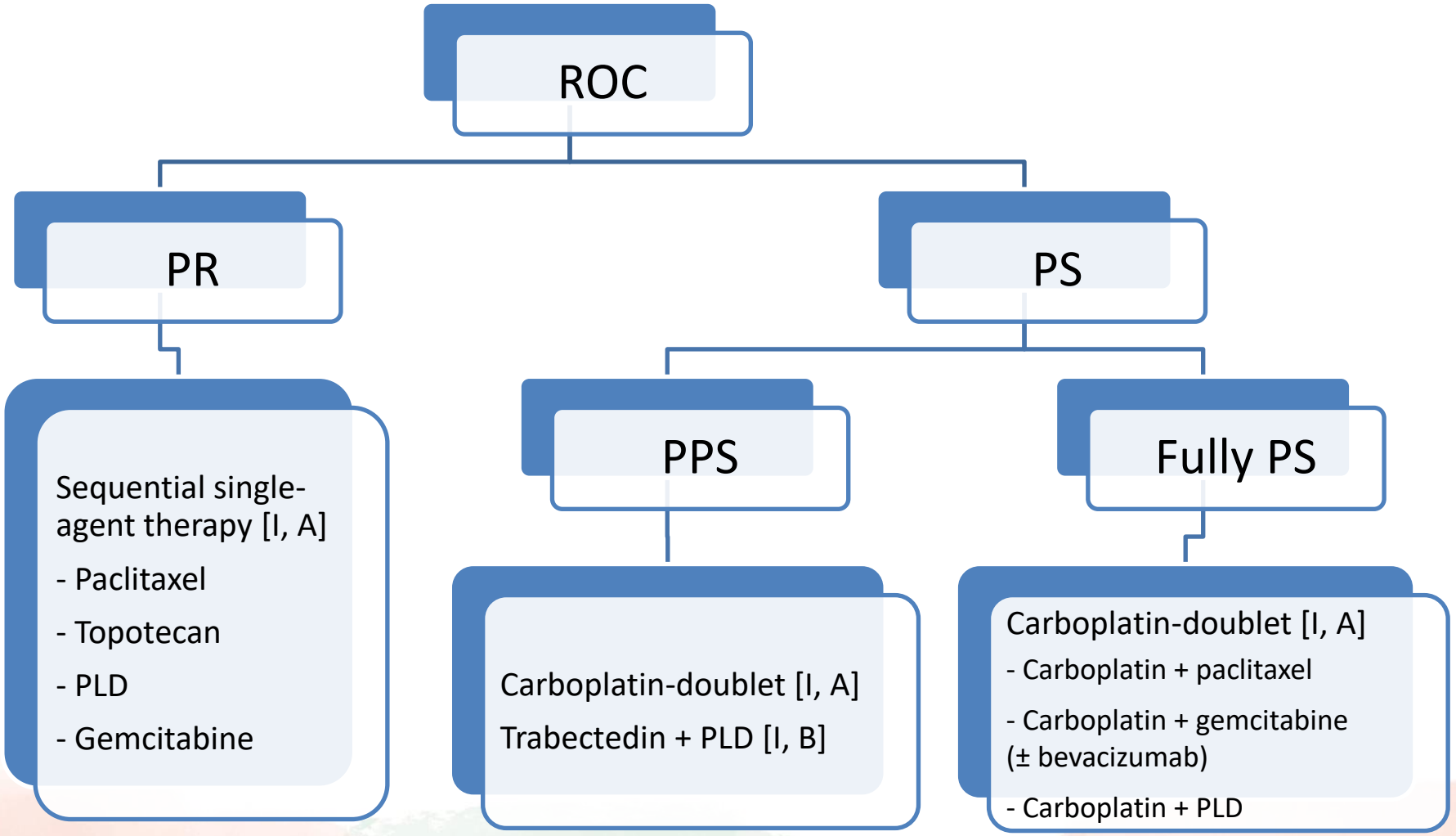
Progression-Free Survival (ITT)



	CD	CP
Median PFS, mo	9.4	8.8
HR (95% CI)	0.73 (0.58, 0.90)	
Log-rank p-value (superiority)	0.004	
P-value (non-inferiority)	<0.001	

GINECO GYNECOLOGIC CANCER INTERGROUP

ROC Treatment Algorithm (ESMO Guidelines)



Adapted from Ledermann J, et al. Ann Oncol. 2013;24 Suppl 6:vi24-32

Conclusions

- Partially platinum-sensitive disease a new entity
- "Platinum or not platinum" the dilemma

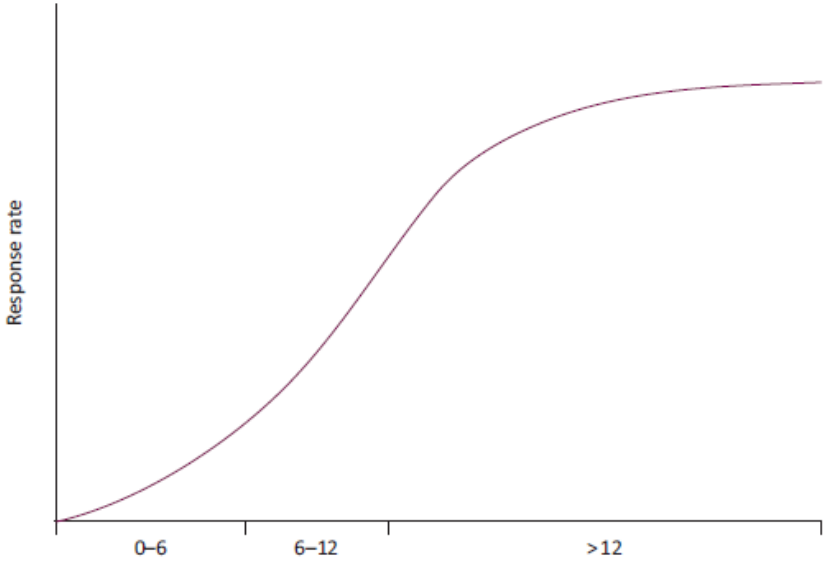
Go to clinical trials!

History of Platinum re-treatment

Annals of Oncology 28: 702–710, 2017
doi:10.1093/annonc/mdx010
Published online 24 January 2017

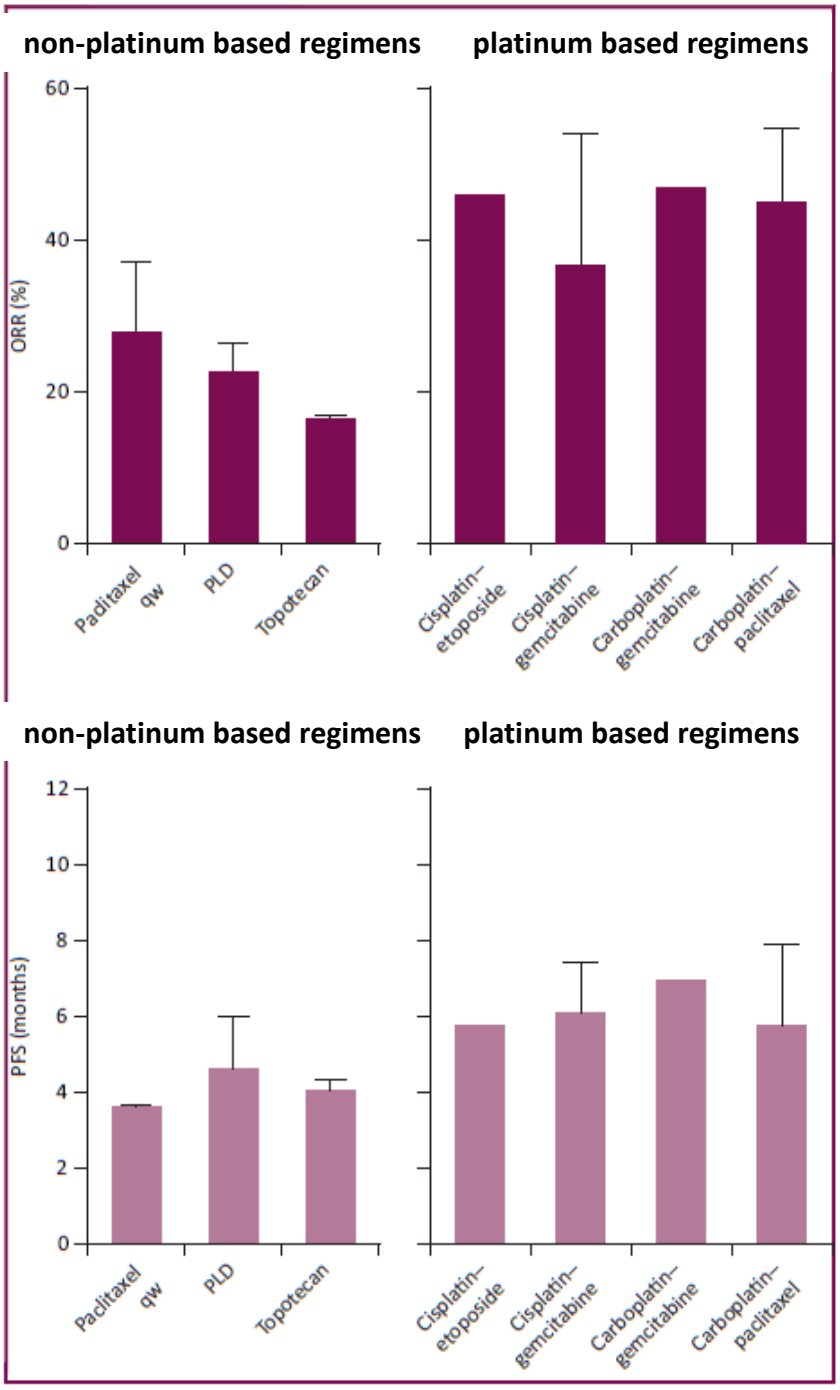
Fifth Ovarian Cancer Consensus Conference: individualized therapy and patient factors

J. McGee[1], M. Bookman[2], P. Harter[3]*, C. Marth[4], I. McNeish[5], K. N. Moore[2], A. Poveda[6], F. Hilpert[3], K. Hasegawa[7], M. Bacon[8], C. Gatsonis[9], A. Brand[10], F. Kridelka[11], J. Berek[12], N. Ottevanger[13], T. Levy[14], S. Silverberg[15], B.-G. Kim[16], H. Hirte[1], A. Okamoto[15], G. Stuart[1] & K. Ochiai[15], and on behalf of the participants of the 5th Ovarian Cancer Consensus Conference



Schematic representation of response rate to platinum-based chemotherapy based on treatment-free interval for platinum (TFIp).

- PFI following primary chemotherapy as a continuous variable
- Linear relationship between extended PFI and platinum sensitivity
- Not an arbitrary definition of ‘platinum-sensitive’ or ‘platinum-resistant’ disease based on a single fixed time point (such as 6 months)
- Future trials not limited to a fixed 6-month window (eligibility or patient cohorts according to any appropriate PFI, depending on the nature of the study)



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ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW ARTICLE

The systemic treatment of recurrent ovarian cancer revisited

T. Baert[1,2*], A. Ferrero[3], J. Sehouli[4], D. M. O'Donnell[5], A. González-Martín[6], F. Joly[7], J. van der Velden[8], P. Blecharz[9], D. S. P. Tan[10,11], D. Querleu[12], N. Colombo[13,14], A. du Bois[1†] & J. A. Ledermann[15†]

Ann Oncol 2021

- ❑ TFIp <6 months
- ❑ Overall response rates:
  - Platinum-based combination chemotherapy: 16% - 58%
  - Non-platinum-based monotherapy: 16.3% - 35%

In addition, patients that recur early (3–6 months) can have improved survival after platinum

Lindemann K et al, Gynecol Oncol 2018

Evidence for platinum re-treatment in patients with TFIp < 6 months

VOLUME 30 · NUMBER 21 · JULY 20 2012

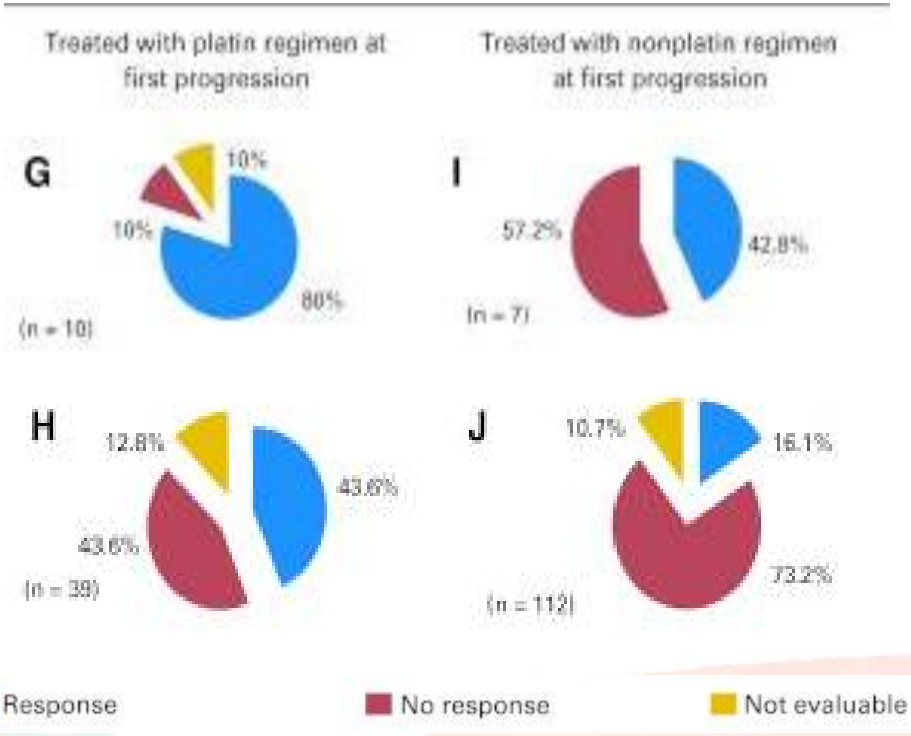
JOURNAL OF CLINICAL ONCOLOGY

BRCA Mutation Frequency and Patterns of Treatment Response in *BRCA* Mutation–Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group

Kathryn Alsop, Sian Fereday, Cliff Meldrum, Anna deFazio, Catherine Emmanuel, Joshy George, Alexander Dobrovic, Michael J. Birrer, Penelope M. Webb, Colin Stewart, Michael Friedlander, Stephen Fox, David Bowtell, and Gillian Mitchell

The highest response rate with Platinum-based chemotherapy:

- BRCA mutation carriers
- BRCA wild-type patients



Era of Targeted Therapy: Efficacy of targeted therapy is NOT related to platinum-free interval Example: Bevacizumab

	Platinum-Sensitive Disease OCEANS Aghajanian et al. 2012	Platinum-Resistant Disease AURELIA Pujade-Lauraine et al. 2014
n	802	361
Regimen	Carbo + Gem vs. Carbo + Gem + Bevacizumab	Chemo monotherapy vs. Chemo monotherapy + Bevacizumab
PFS	HR 0.48	HR 0.48
OS	NS	HR 0.85

Review of Dose-intense Platinum and/or Paclitaxel Containing Chemotherapy in Advanced and Recurrent Epithelial Ovarian Cancer

Ingrid A. Boere*, and Maria E.L. van der Burg

Department of Medical Oncology He-122, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract: Ovarian cancer is the most lethal gynecological cancer in women in the western world with a 5-year survival of 49.7%. Advanced stage ovarian cancer is treated both surgically and with chemotherapy, but despite initial high response rates of 60- 75%, many women experience disease recurrence with a dismal prognosis, 5 year overall survival for FIGO stage IIIc and IV disease being only 32 and 18%. In an attempt to improve outcome for both primary and recurrent disease, dose-intense and dose-dense chemotherapy regimens have been investigated. This overview summarizes these results in first and second-line treatment. In first-line treatment, no benefit was found of dose-intense regimes in the majority of the studies, only toxicity was increased. However, results are conflicting with the recent Japanese Gynecologic Oncology Group (JGOG) trial showing an improved progression free and overall survival in patients treated with dose-dense weekly paclitaxel combined with standard 3-weekly carboplatin. For recurrent disease dose-dense weekly combination chemotherapy seems to be very effective in patients with platinum-resistant ovarian cancer. Several phase II studies showed an increase in response rate, progression free survival and overall survival for dose-dense paclitaxel and carboplatin, compared to results of non-platinum chemotherapy. In platinum-sensitive ovarian cancer, on contrary, the results of weekly paclitaxel and carboplatin seem to be comparable with standard 3-weekly regimens.

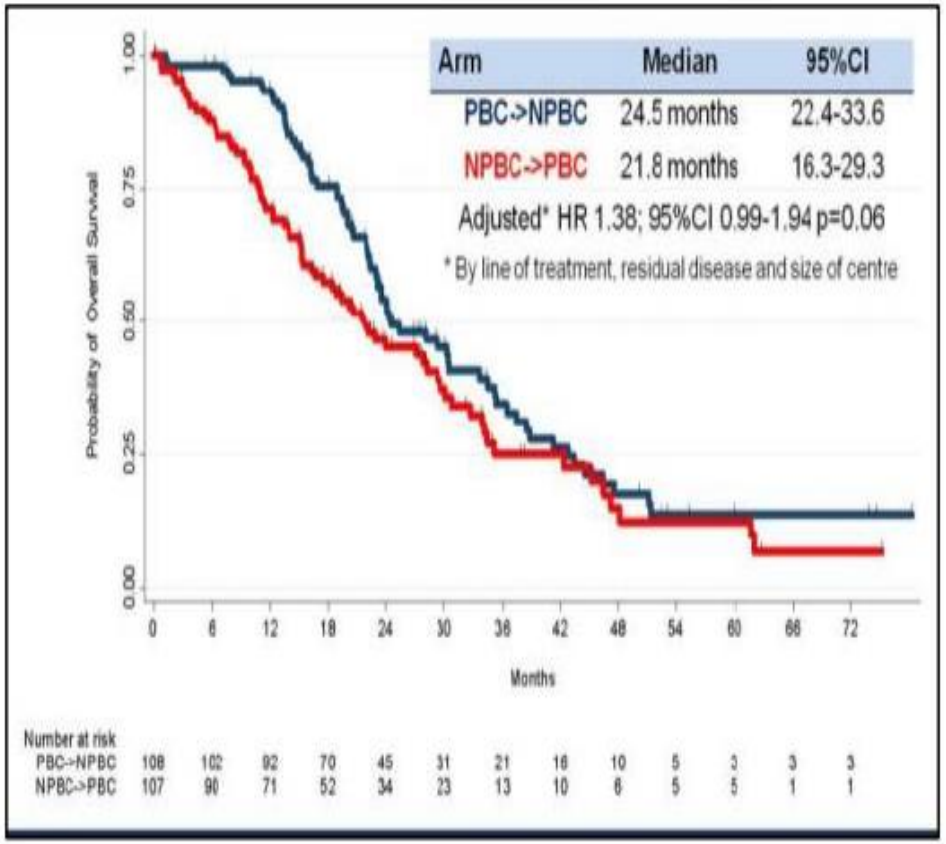
MITO-8 supports the recommendation that a platinum based chemotherapy not be delayed in favor of an non-platinum in patients with partially platinum-sensitive OC.

Randomized Controlled Trial Testing the Efficacy of Platinum-Free Interval Prolongation in Advanced Ovarian Cancer: The MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study

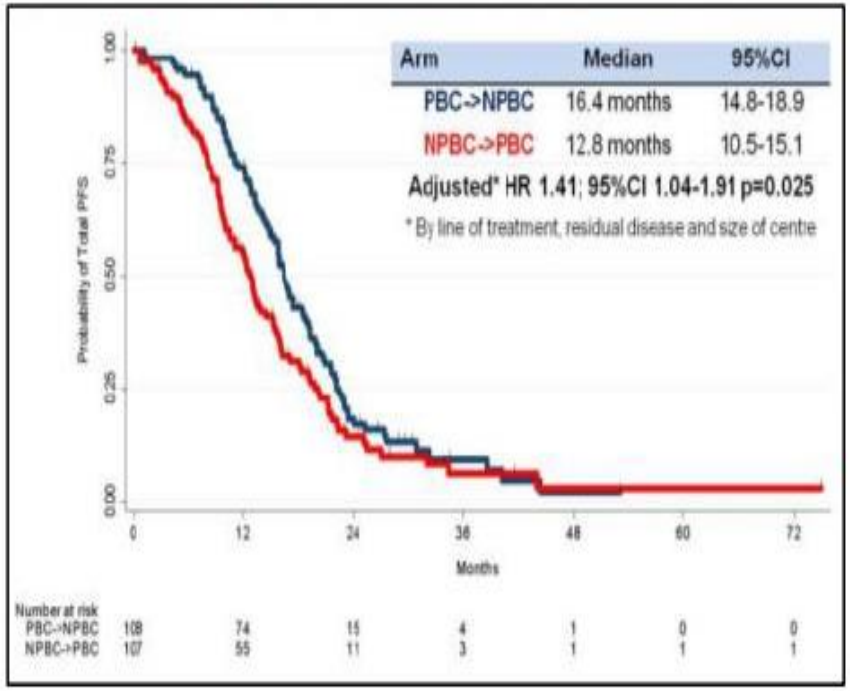
Sandro Pignata, Giovanni Scambia, Alessandra Bologna, Simona Signoriello, Ignace B. Vergote, Uwe Wagner, Domenica Lorusso, Viviana Murgia, Roberto Sorio, Gabriella Ferrandina, Cosimo Sacco, Gennaro Cormio, Enrico Breda, Saverio Cinieri, Donato Natale, Giorgia Mangili, Carmela Pisano, Sabrina Chiara Cecere, Marilena Di Napoli, Vanda Salutari, Francesco Raspagliesi, Laura Arenare, Alice Bergamini, Jane Bryce, Gennaro Daniele, Maria Carmela Piccirillo, Cito Gallo, and Francesco Perrone

J Clin Oncol 35:3347-3353. © 2017

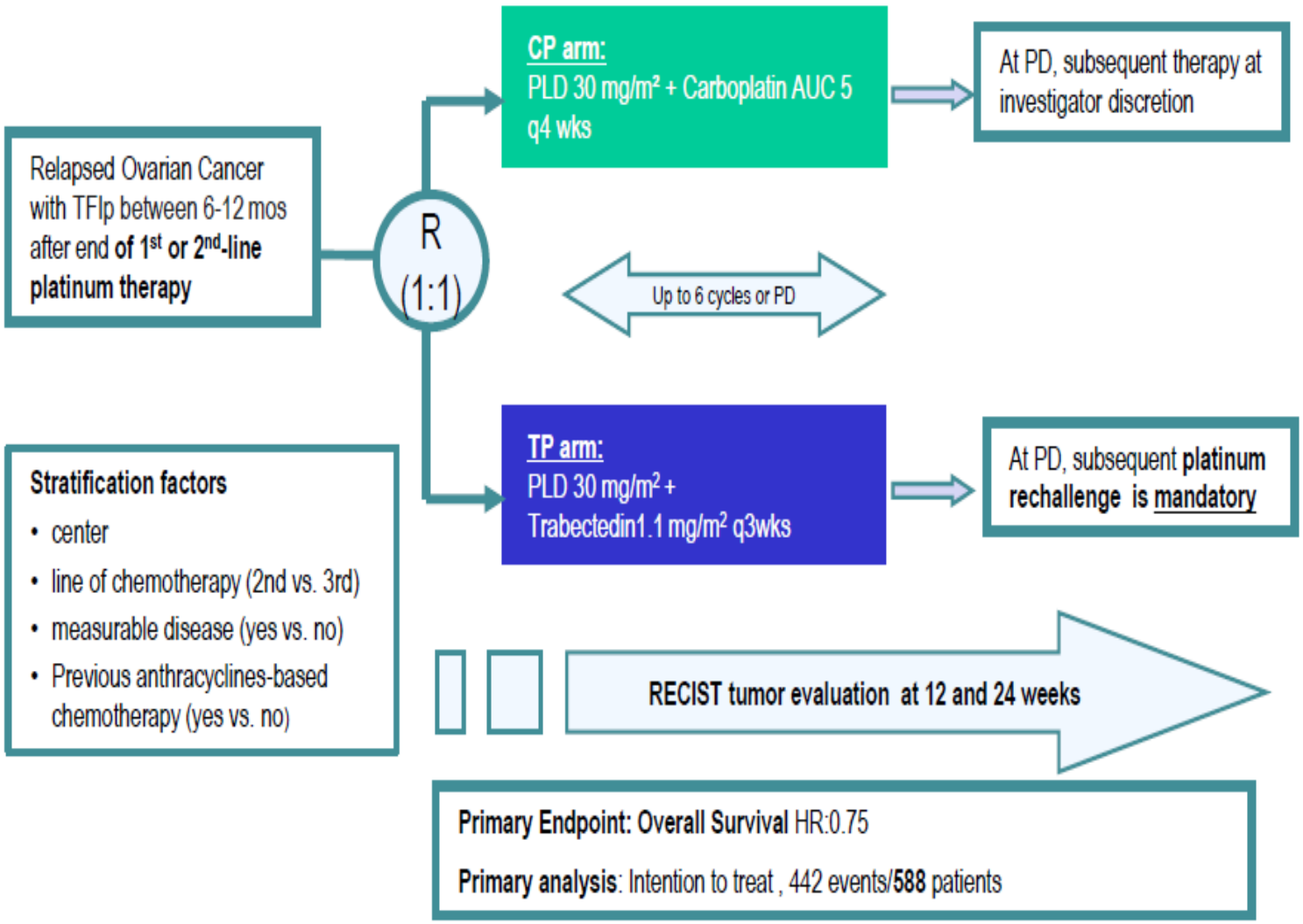
OS



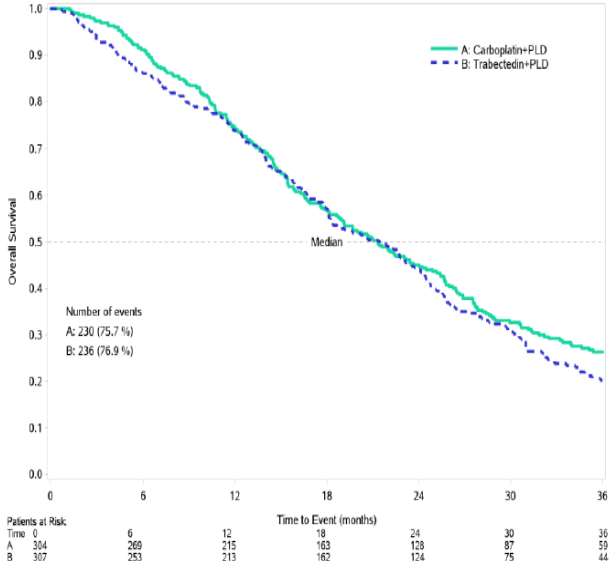
PFS2



Study Design



Primary Endpoint:Overall Survival



Median follow-up: 44mos

Median OS (Q1-Q3):

Carboplatin+PLD: 21.3 mos (11.8-37.0)

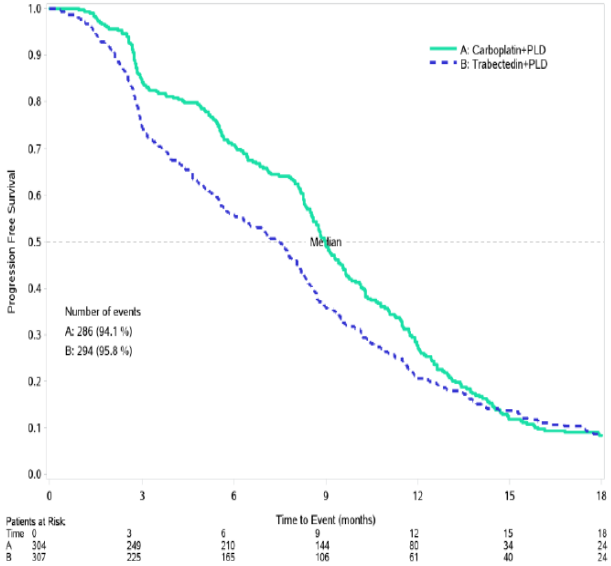
Trabectedin+PLD: 21.5 mos (11.6-32.4)

HR OS [95% CI]; p-value :

Trabectedin+PLD vs. Carboplatin+PLD

1.10 [0.92-1.32]; 0.284

Secondary Endpoint: Progression free survival



Median PFS (Q1-Q3):

Carboplatin+PLD: 9.0 mos (5.5-12.4)

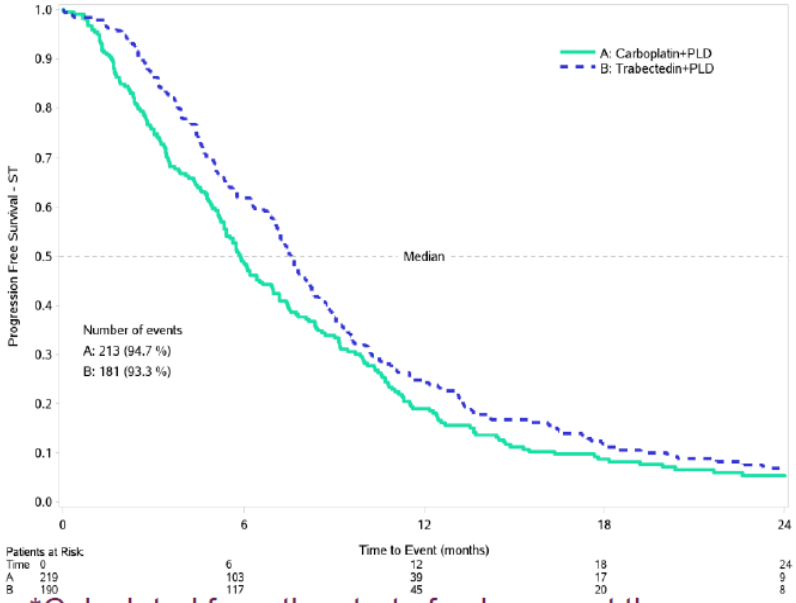
Trabectedin+PLD: 7.5 mos (3.0-11.5)

HR PFS [95% CI]; p-value :

Trabectedin+PLD vs. Carboplatin+PLD

1.26 [1.07-1.49]; 0.005

Secondary Endpoint: Progression free survival after ST*



Trabectedin+PLD → Platinum

Median PFS - ST (Q1-Q3):

Carboplatin+PLD: 5.7 mos (2.9-10.5)

Trabectedin+PLD: 7.6 mos (4.4-11.5)

HR PFS - ST [95% CI]; p-value :

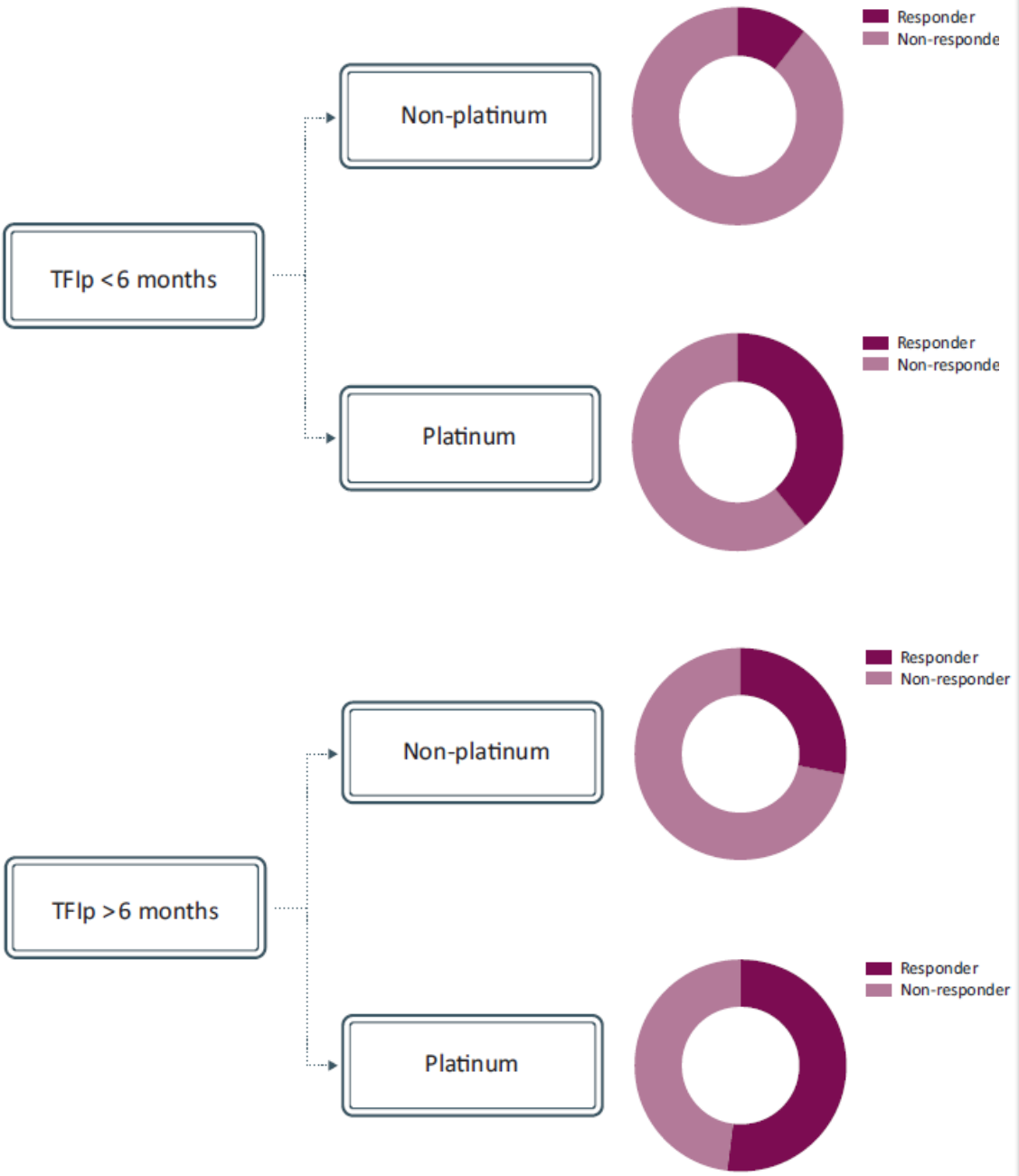
Trabectedin+PLD vs. Carboplatin+PLD

0.80 [0.65-0.98]; 0.028

*Calculated from the start of subsequent therapy

Conclusions

- This study did not meet its primary endpoint of improving OS with the sequential use of Trabectedin/PLD followed, at progression, by platinum over Carboplatin/PLD (HR:1.10; 95% CI:[0.92-1.32]; p-value:0.284).
- PFS was longer with Carboplatin/PLD (HR:1.26; 95% CI:[1.07-1.49]; p-value: 0.005) while PFS after the subsequent line (PFS-ST) was in favor of Trabectedin/PLD, particularly when platinum was administered (HR:0.80; 95%CI:[0.65-0.98]; p-value:0.028).
- No statistically significant interactions in OS were detected between treatment effect and selected subgroups. Nevertheless a qualitative, but not statistically significant, interaction was observed according to the number of prior lines.
- Carboplatin/PLD showed a better safety profile in terms of hematological, gastrointestinal, asthenia and hepatic toxicities.
- QoL assessment on Global health status, fatigue, nausea and vomiting and appetite loss, attitude to disease/treatment, hormonal/menopausal symptoms and side effects favors carboplatin/PLD
- **Platinum based regimens remain standard of care in patients with recurrent ovarian cancer progressing within 6-12 months after last platinum line**.
- The similar OS still indicates a possible role for Trabectedin/PLD in patients with multiple prior lines of platinum, who may need a longer recovery time from platinum specific toxicities.



Platinum-non-eligible ovarian cancer (PNEOC)

- Progression on or immediately after their last line of platinum-based chemotherapy
- Contraindications for further platinum-based chemotherapy
- Patients who did not respond to platinum re-challenge

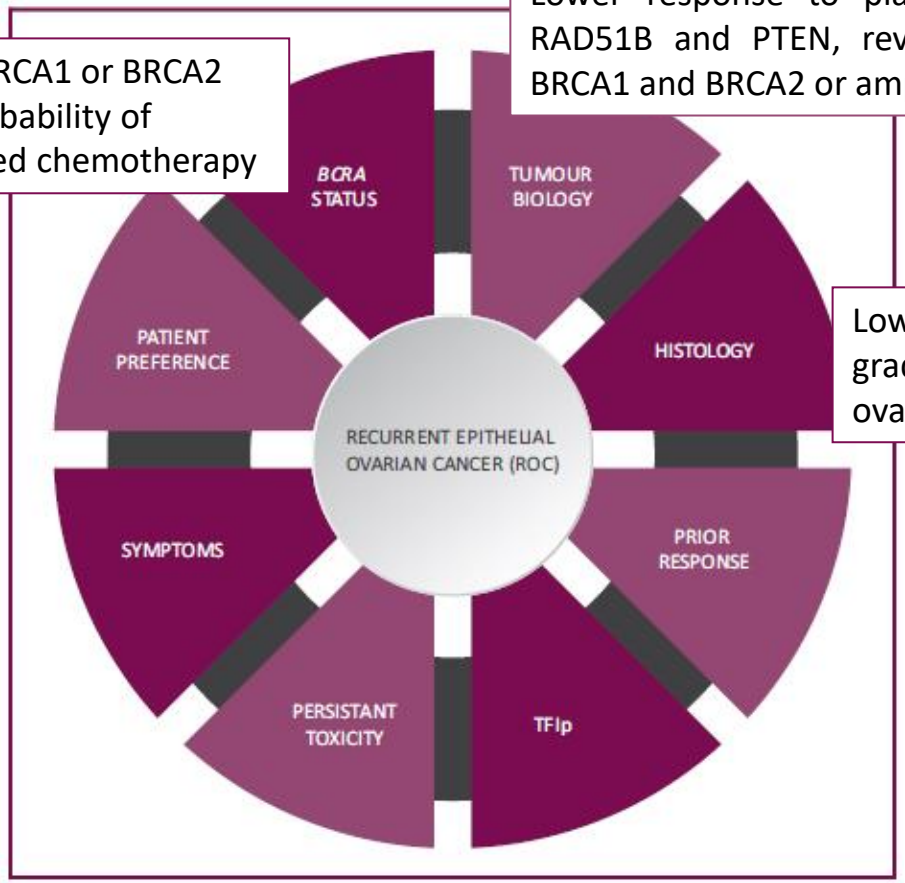
Platinum-eligible ovarian cancer (PEOC)

Baert T, Ferrero A, Sehouli J et al
The systemic treatment of recurrent ovarian cancer revisited.
Ann Oncol. 2021 Jun;32(6):710-725.

How to choose the chemotherapy?

Deleterious mutation in BRCA1 or BRCA2 associated with a high probability of response to platinum-based chemotherapy

Lower response to platinum: inactivation of RB1, NF1, RAD51B and PTEN, reversal of deleterious mutations in BRCA1 and BRCA2 or amplification of MDR1, BRD4 or CNNE1



Lower response to platinum: low-grade serous, clear cell and mucinous ovarian cancers

Figure 4. Important variables for the treatment of recurrent ovarian cancer. ROC, recurrent epithelial ovarian cancer; TFIp, treatment-free interval for platinum-based chemotherapy.

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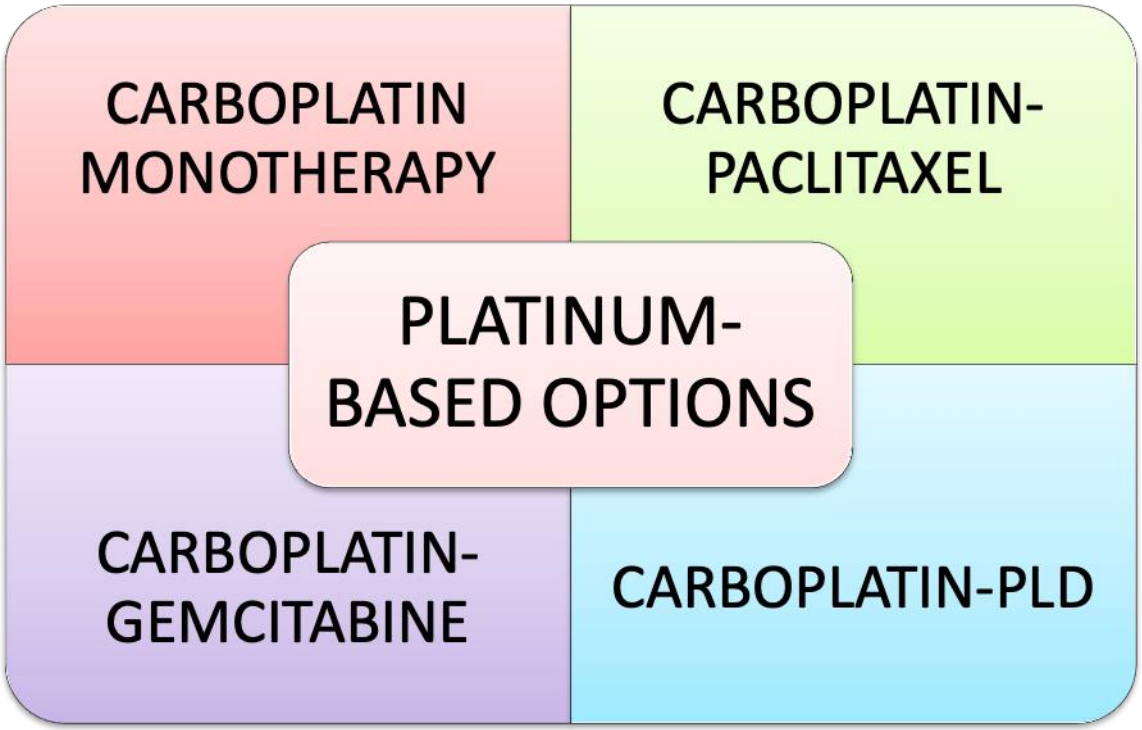
Ann Oncol. 2021 Jun;32(6):710-725.

Platinum-Eligible Ovarian Cancer - PEOC



The choice is based on:

- toxicity spectrum
- patient preference

Table 2. Overview of platinum-based chemotherapy in relapsed ovarian cancer

	ORR	PFS	Refs
Carboplatin monotherapy	29.6%-54.0%	7.3-10.0 months	4,23,25
Carboplatin–paclitaxel	66%	9.4-13.0 months	23,24
Carboplatin–gemcitabine	47.2%-62.5%	8.4-10.0 months	25,27
Carboplatin–PLD	63%	11.3 months	24,26

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Platinum- Non Eligible Ovarian Cancer - PNEOC

PNEOC ⟹ Single-agent non-platinum based chemotherapy

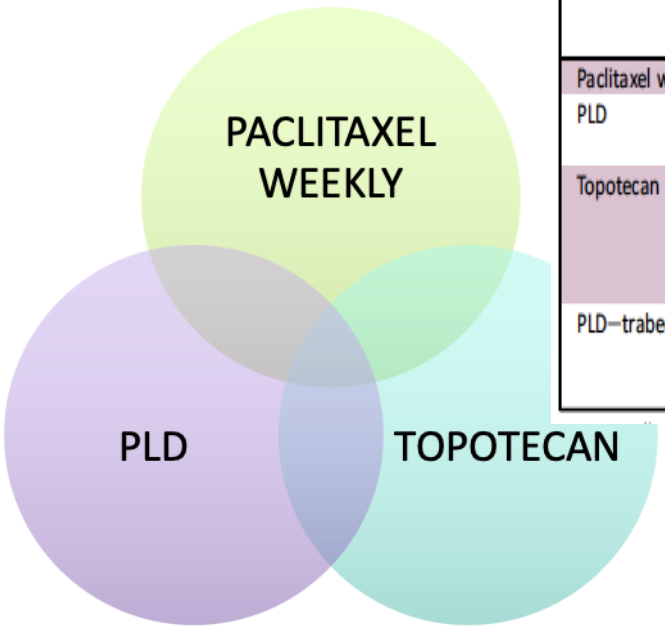

Table 3. Overview of non-platinum-based chemotherapy in relapsed ovarian cancer

	ORR	PFS	TFIp	Refs
Paclitaxel weekly	20.9%-35%	3.6-3.7 months	<6 months	22,30
PLD	19.7%-25.7%	3.7-5.7 months	Muggia et al. 29 pt <6 months-6 ≥6 months Gordon et al. 130 pt <6 months-109 ≥6 months	31,32
Topotecan	16.3%-17%	3.9-4.3 months	Gordon et al. 124 pt <6 months-111 ≥6 months Creemers et al. 62 pt <6 months-30 ≥6 months ten Bokkel Huinink et al. 60 pt <6 months-52 ≥6 months	32-34
PLD–trabectedin	27.6%	7.3-9.2 months	Poveda et al. 6-12 months Monk et al. 115 pt <6 months-218 ≥6 months	28,29

- Oral etoposide
- Tamoxifen
- Gemcitabine
- Treosulfan
- Cyclophosphamide

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Ricerca Clinica e Traslazionale in Ginecologia Oncologica

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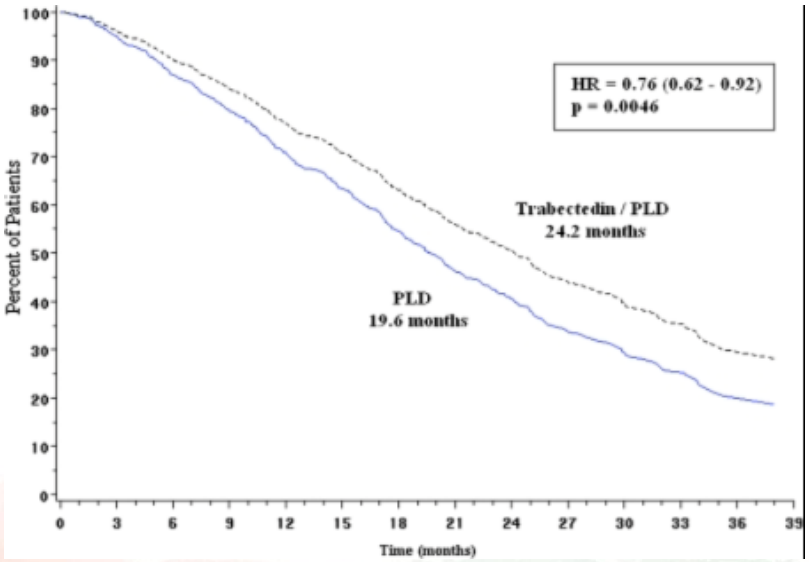
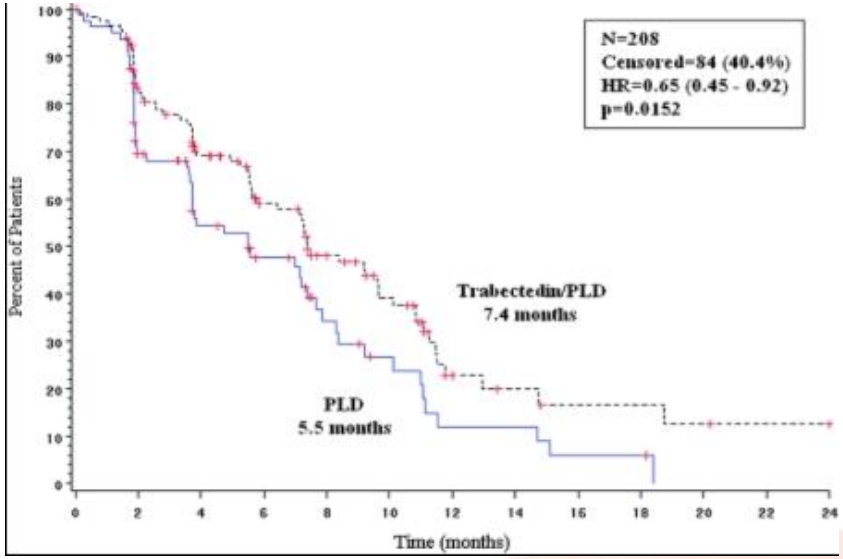
…and in patients with TFIp > 6 months but unable to receive further platinum?

PLD-TRABECTEDIN

Improved OS and PFS compared to PLD alone in a subgroup analysis of patients with a TFIp of 6-12 months in the OVA-301 trial





Poveda et al, Annal Oncol 2011

Ricerca Clinica e Traslazionale in Ginecologia Oncologica

Baert T, Ferrero A, Sehouli J et al
The systemic treatment of recurrent ovarian cancer revisited.
Ann Oncol. 2021 Jun;32(6):710-725.

ANTI-ANGIOGENIC TREATMENT

BEVACIZUMAB

Improvement in response rates and PFS if combined with chemotherapy and as maintenance

Drug	Clinical trial name	N	Inclusion criteria	Regimen	PFS	OS
Bevacizumab	OCEANS	484	Recurrence ≥6 months after front-line platinum-based therapy	Carboplatin–gemcitabine [G (1000 mg/m^2, days 1 and 8) and C (AUC 4, day 1), q 21 days for 6-10 cycles] + concurrent placebo or bevacizumab (BV 15 mg/kg q 21 days), followed by BV until progression or unacceptable toxicity	HR 0.484 (95% CI, 0.388-0.605) $P < 0.0001$–12.3 versus 8.6 months	HR 0.952 (95% CI, 0.771-1.176)–ns –32.9 versus 33.6 months
	GOG-213	674	Recurrence ≥6 months after front-line platinum-based therapy	Six 3-weekly cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC5) ± bevacizumab (15 mg/kg of bodyweight) every 3 weeks and continued as maintenance every 3 weeks until progression or unacceptable toxicity	HR 0.628 (95% CI, 0.534-0.739) $P < 0.0001$–13.8 versus 10.4 months	HR 0.829 (95% CI, 0.683-1.005) $P = 0.056$–42.4 versus 37.3 months
	AURELIA	361	First and second recurrence <6 months after last platinum-based therapy	Pegylated liposomal doxorubicin, weekly paclitaxel or topotecan as single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity or consent withdrawal	HR 0.48 (95% CI, 0.38-0.60) $P < 0.001$–6.7 versus 3.4 months	HR 0.85 (95% CI, 0.66-1.08) $P < 0.174$–16.6 versus 13.3 months

Baert T, Ferrero A, Sehouli J et al
The systemic treatment of recurrent ovarian cancer revisited.
Ann Oncol. 2021 Jun;32(6):710-725.

ANTI-ANGIOGENIC TREATMENT

AGO-OVAR 2.21
ENGOT ov18

ENGOT model A
Sponsor AGO Study Group

Bevacizumab 15mg/kg q3w until PD

Gemcitabine 1000 mg/m² d1 and 8

Carboplatin AUC 4 d 1 q3w

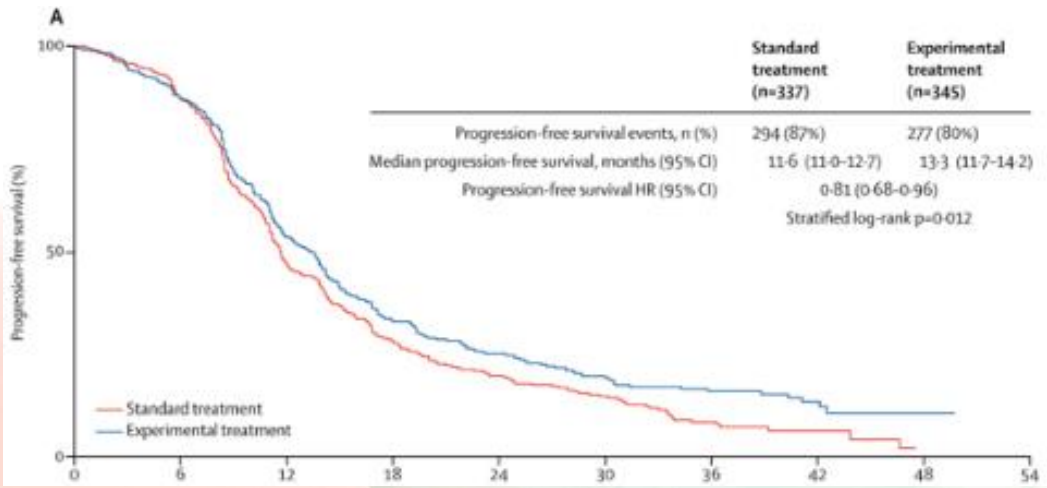
R 1:1

Bevacizumab 10mg/kg q2w

Bevacizumab 15mg/kg q3w until PD

Pegylated Liposomal Doxorubicin 30 mg/m² d1

Carboplatin AUC 5 d1 q4w

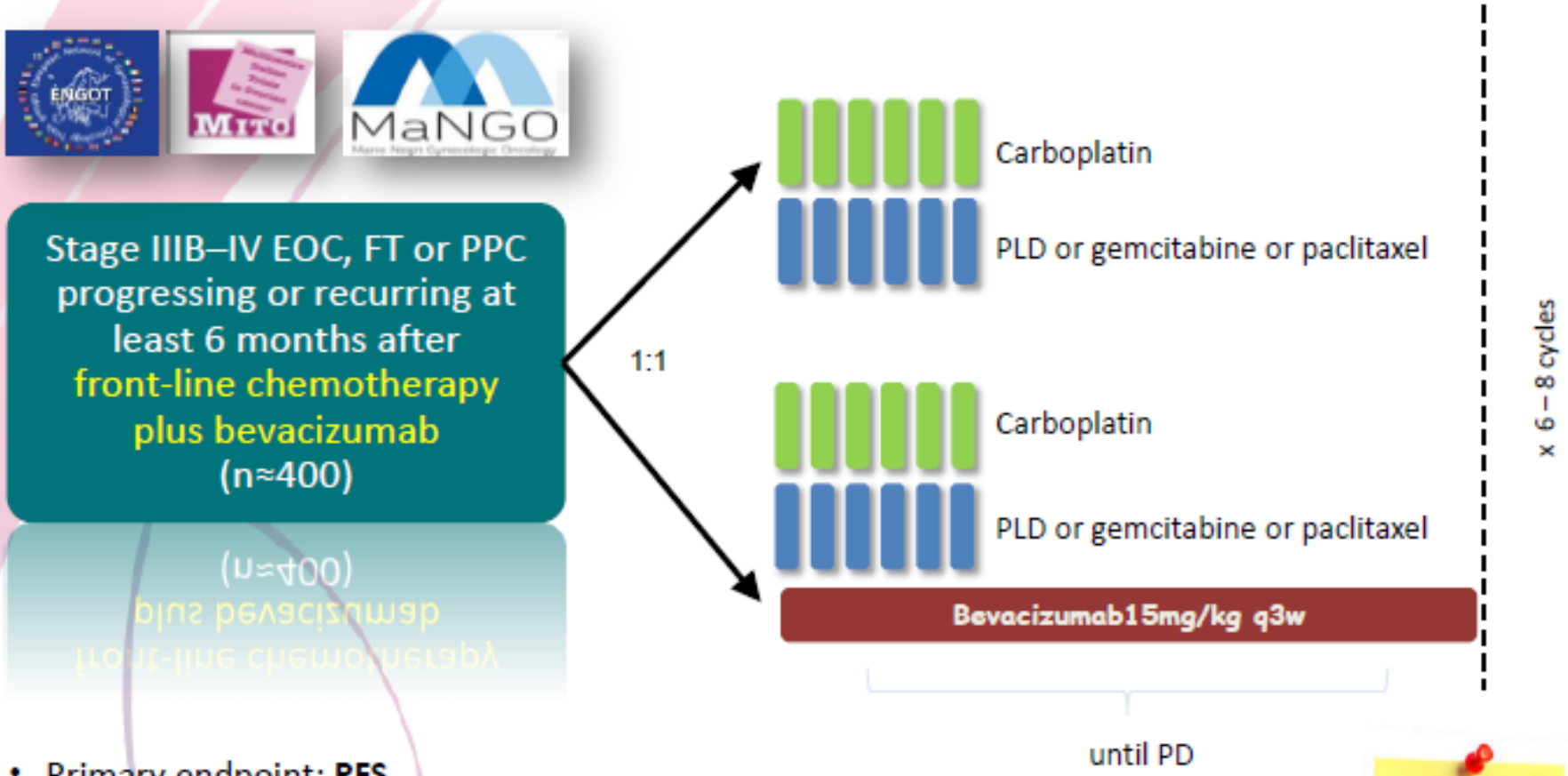


	Standard treatment (n=337)	Experimental treatment (n=345)
Progression-free survival events, n (%)	294 (87%)	277 (80%)
Median progression-free survival, months (95% CI)	11·6 (11·0–12·7)	13·3 (11·7–14·2)
Progression-free survival HR (95% CI)	0·81 (0·68–0·96)	
	Stratified log-rank p=0·012	

Advantage in **PFS** (HR 0.807, p 0.01) and **OS** (HR 0.810; p 0.03) in both patients **with and without prior bevacizumab** therapy.

MITO-16/MaNGO OV-2:

Bevacizumab plus chemotherapy at progression after front-line Bevacizumab plus chemotherapy in platinum sensitive

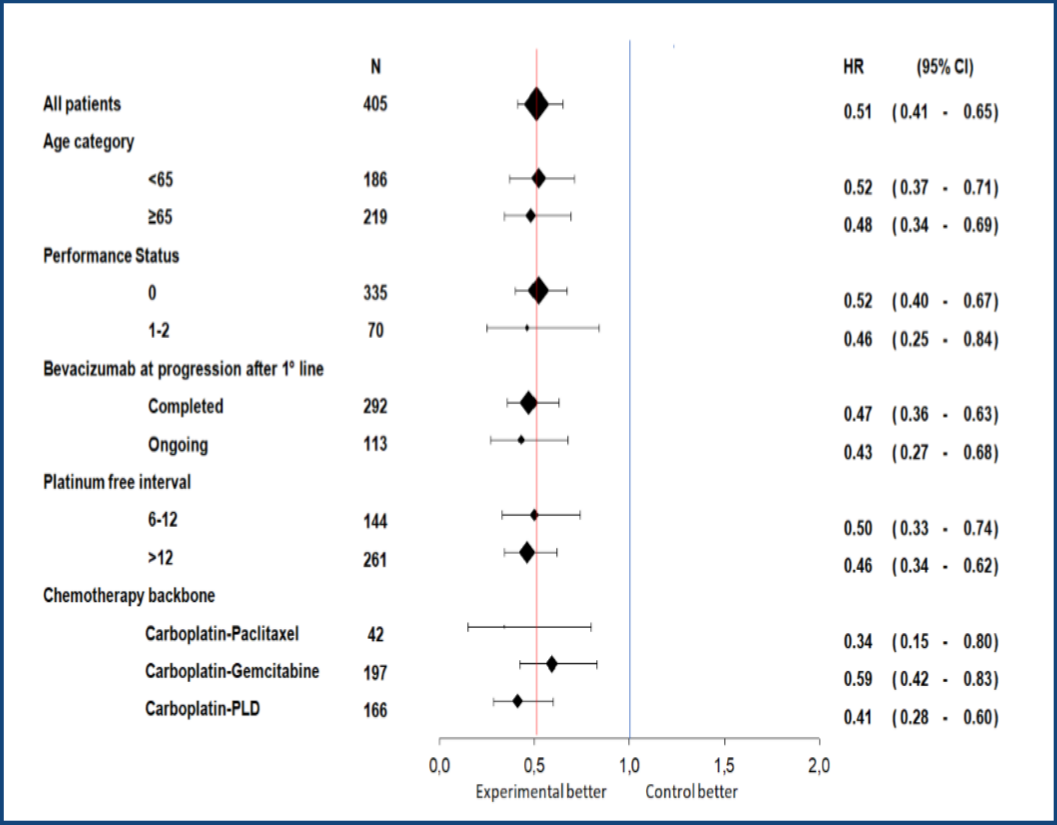


- Primary endpoint: **PFS**
- Secondary endpoint: **OS**
- 60 Italian centres involved and involvement of others European groups (ENGOT – Italy, Germany, France, Greece, Switzerland) (sponsor: INT Napoli)

Principal investigators: Sandro Pignata, Nicoletta Colombo

Phase III study

HR of PFS by major subgroups



Adjusted by: age, performance status, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Roles for PARPS: ovarian cancer

- Maintenace after first line treatment
- Treatment for platinum sensitive recurrence
- Maintenance after treatment for platinum sensitive recurrence
- Treatment for platinum resistant recurrence

Both platinum sensitive and resistant

A few more definitions

- Germline
  - from the oocyte or sperm
  - present in every cell of an organism
  - can be passed on
- Somatic
  - occur in a specific tissue (tumor)
  - not able to be passed on
- HRD
  - Homologous recombination repair pathway deficiency
  - Testing tries to quantify somatic changes in this group of pathways

Development of an European consensus guidelines for genetic testing including HRD for newly diagnosed ovarian cancer patients

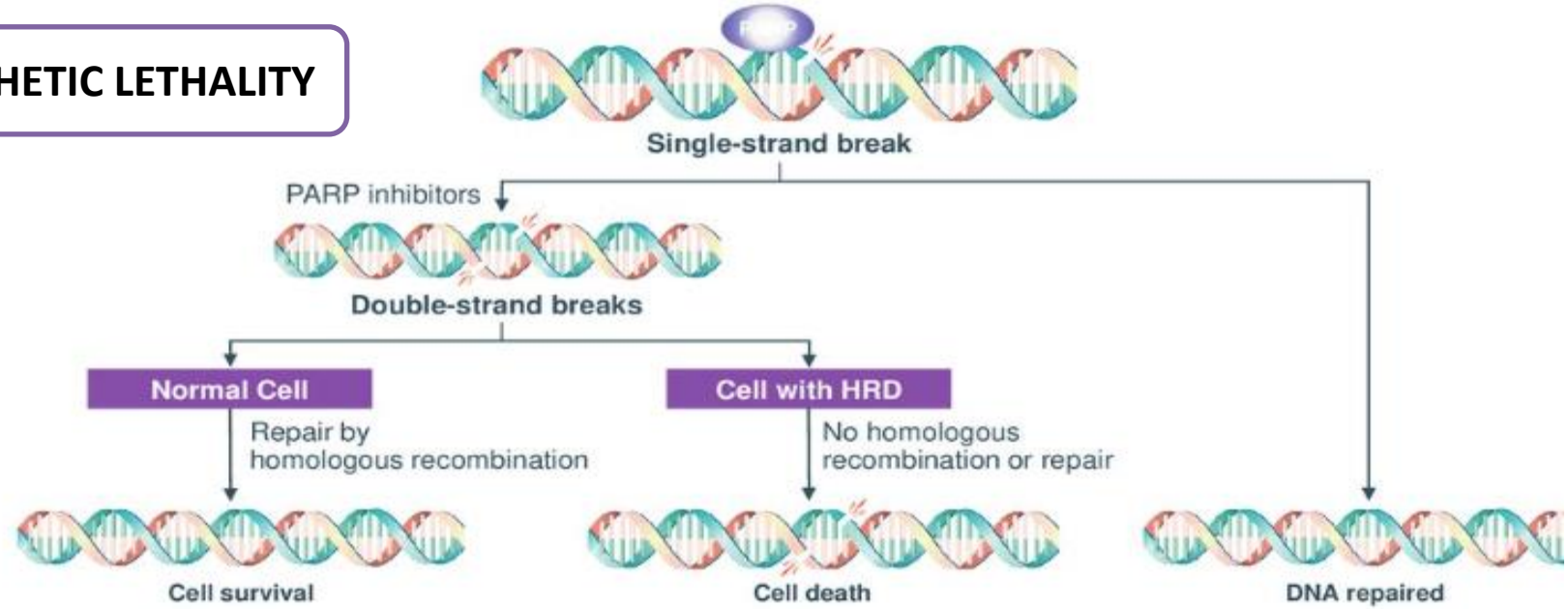
PARP INHIBITORS

OLAPARIB

NIRAPARIB

RUCAPARIB

SYTHETIC LETHALITY



- All three PARPis effective in high-grade ovarian cancers, **irrespective of the BRCA mutational status**
- Approved as **maintenance** following a response to platinum-based therapy for recurrent disease

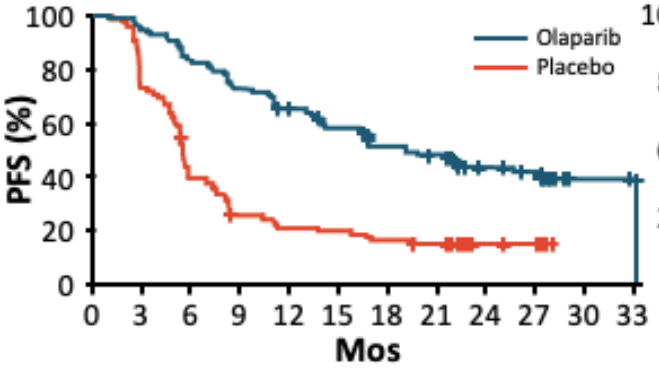
Associazione Italiana di Oncologia Medica

PARP INHIBITORS: current indications in ovarian cancer

Olaparib	Niraparib	Rucaparib
▪ First-line maintenance therapy for *BRCA*-mutated advanced ovarian cancer in CR/PR to platinum-based CT ▪ First-line maintenance therapy in combination with bevacizumab for ovarian cancer in CR/PR to platinum-based CT and with HRD (either a deleterious *BRCA* mutation or genomic instability)	▪ First-line maintenance therapy for advanced ovarian cancer in CR/PR to platinum-based CT regardless of *BRCA* mutation status	Also endometrioid histotype
▪ Maintenance therapy for recurrent ovarian cancer in CR/PR to platinum-based CT regardless of *BRCA* mutation status	▪ Maintenance therapy for recurrent ovarian cancer in CR/PR to platinum-based CT regardless of *BRCA* mutation status	▪ Maintenance therapy for recurrent ovarian cancer in CR/PR to platinum-based CT regardless of *BRCA* mutation status
▪ Fourth-line and beyond treatment for advanced ovarian cancer with germline *BRCA* mutations	▪ Fourth-line and beyond treatment for advanced ovarian cancer with HRD (either a deleterious *BRCA* mutation or genomic instability)	▪ Third-line and beyond treatment for advanced ovarian cancer with *BRCA* mutations (germline or somatic)

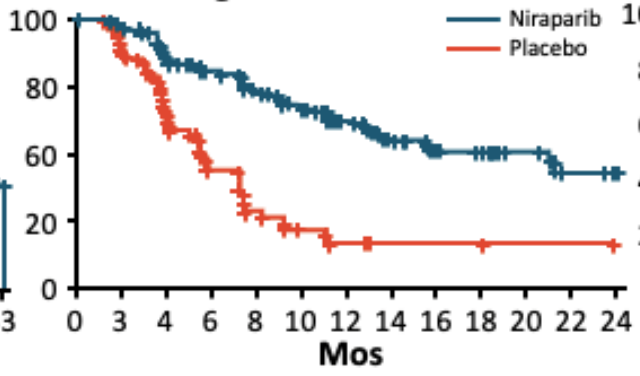
PARP INHIBITORS:
maintenance in BRCA mutated ovarian cancer

SOLO-2: Olaparib vs Placebo in g*BRCAm* Patients[1]



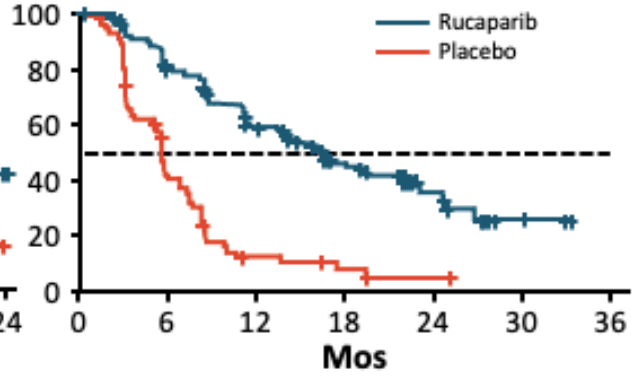
mPFS, Mos	Olaparib (n = 196)	Pbo (n = 99)	HR (95% CI)
Inv	19.1	5.5	0.30 (0.22-0.41)
BICR	30.2	5..5	0.25 (0.18-0.35)

NOVA: Niraparib vs Placebo in g*BRCAm* Patients[2,3]



mPFS, Mos	Niraparib (n = 138)	Pbo (n = 65)	HR (95% CI)
Inv	14.8	5.5	0.27 (0.18-0.40)
BICR	21.0	5.5	0.27 (0.17-0.41)

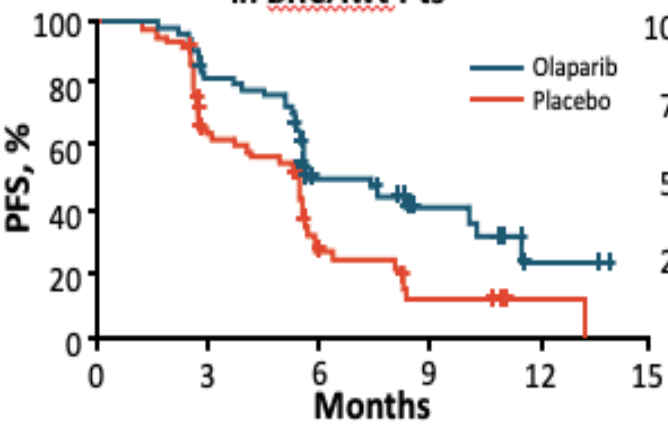
ARIEL-3: Rucaparib vs Placebo in t*BRCAm* Patients[4]



mPFS, Mos	Rucaparib (n = 130)	Pbo (n = 66)	HR (95% CI)
Inv	16.6	5.4	0.23 (0.16-0.34)
BICR	26.8	5.4	0.20 (0.13-0.32)

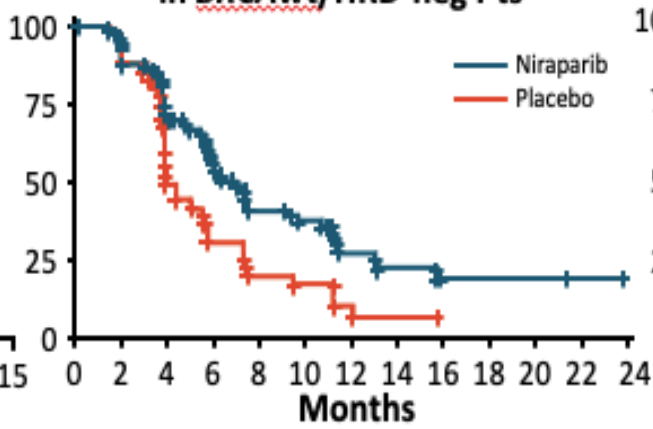
PARP INHIBITORS:
maintenance in BRCA wild type or HRD negative

STUDY 19: Olaparib vs Placebo in *BRCA*wt Pts[1]



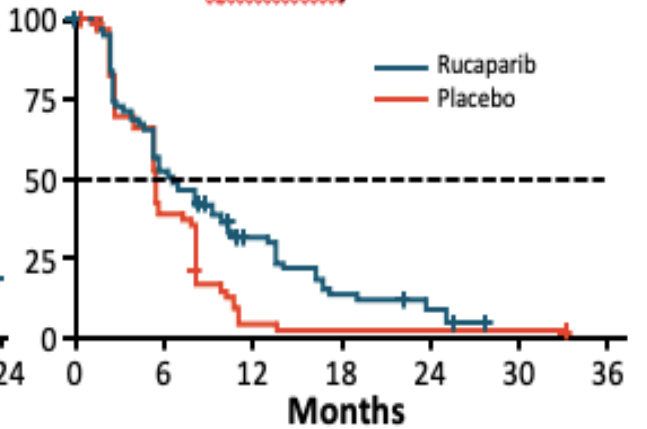
mPFS, mo	Olaparib (n = 57)	Pbo (n = 61)	HR (95% CI)
Inv	7.4	5.5	0.54 (0.34-0.85)
BICR	--	--	--

NOVA: Niraparib vs Placebo in *BRCA*wt/HRD-neg Pts[2]



mPFS, mo	Niraparib (n = 92)	Pbo (n = 42)	HR (95% CI)
Inv	--	--	--
BICR	6.9	3.8	0.58 (0.36-0.92)

ARIEL-3: Rucaparib vs Placebo in t*BRCA*wt/LOH-L Pts[3]

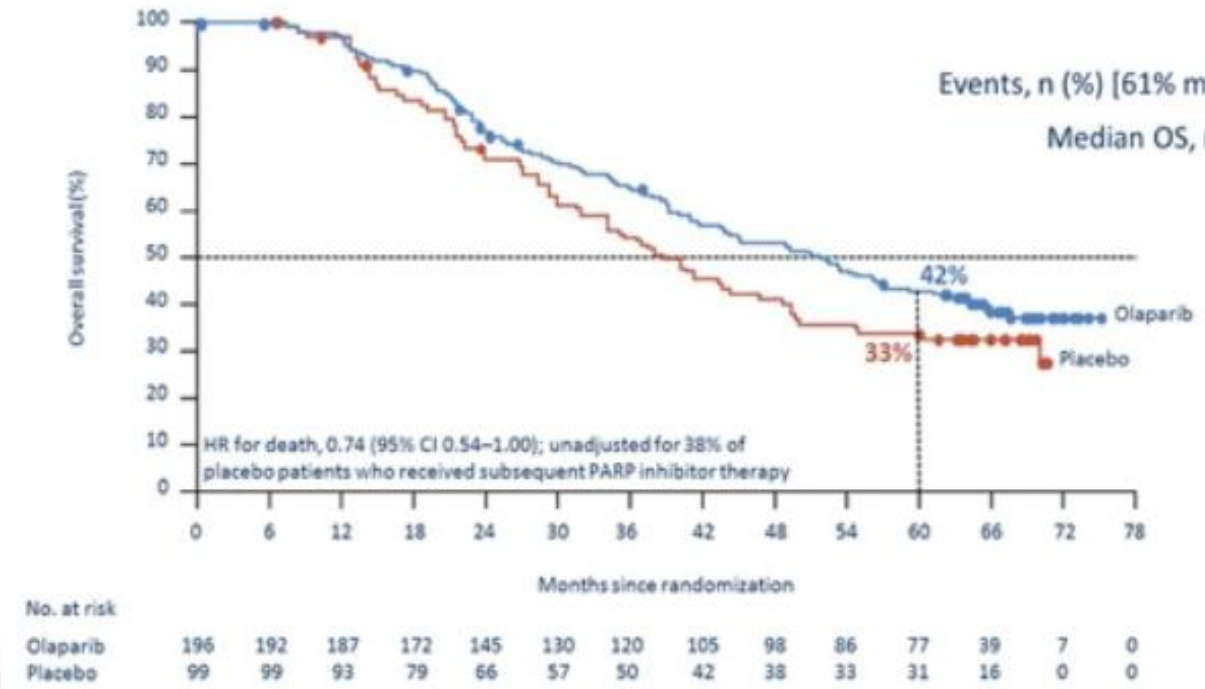


mPFS, mo	Rucaparib (n = 106)	Pbo (n = 52)	HR (95% CI)
Inv	6.7	5.4	0.58 (0.40-0.85)
BICR	--	--	--

PARP INHIBITORS:
maintenance in BRCA mutated ovarian cancer

SOLO2: final analysis of OS

Median OS improved by 12.9 months with maintenance olaparib over placebo, despite 38% of placebo patients receiving subsequent PARP inhibitor therapy



	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	51.7	38.8
HR 0.74		
95% CI 0.54–1.00; *P*=0.0537		

38% of placebo patients and 10% of olaparib patients received subsequent PARP inhibitor therapy*

OS analysis per eCRF in the full analysis set†
HR 0.70 (95% CI 0.52–0.96)

OS analysis in the Myriad gBRCAm subgroup†
HR 0.71 (95% CI 0.52–0.97)

MaNGO
Ricerca Clinica e Traslazionale in Ginecologia Oncologica

22% of patients remain on olaparib with continuing benefit for >5 years

Poveda A et al, Lancet Oncol 2021

ASCO 2021

OPINION is a Phase IIIb single-arm, open-label, multicenter study trial designed to confirm the efficacy of olaparib maintenance therapy in non-gBRCAm PSR OC

- Known non-gBRCAm status
- Relapsed, high-grade serous

or endometrioid ovarian cancer*

- ≥2 prior lines of platinum-based chemotherapy
- In complete or partial response to last platinum-based chemotherapy

N=279

Olaparib
300 mg PO
BID

Primary endpoint:
- PFS (investigator-assessed; RECIST v1.1) in overall study population

Secondary endpoints:
- PFS by predefined HRD and sBRCAm status†
- TFST
- TDT
- CT-FI
- OS
- Safety and tolerability

Patients enrolled: February 2018–April 2019[1]
Primary analysis DCO: 02 October 2020[2]

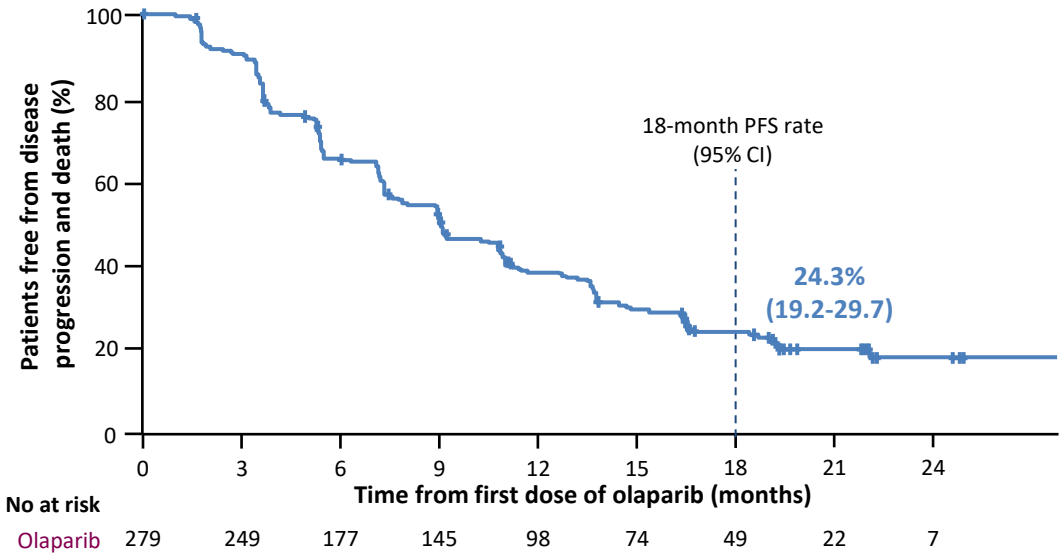
* Includes patients with primary peritoneal and/or fallopian tube cancer; † PFS analysed in the following subgroups: HRD-positive sBRCAm, HRD-positive, HRD-negative, sBRCAm, where HRD-positive is defined as genomic instability score ≥42 in the Myriad myChoice® Plus assay, and HRD-negative is defined as a score <42

BID=twice daily; DCO=data cut-off; ECOG=Eastern Cooperative Oncology Group; gBRCAm=germline mutation in BRCA1/2; HRD=homologous recombination deficiency; OC=ovarian cancer; OS=overall survival; PARPi=PARP inhibitor; PFS=progression-free survival; PO=oral; PR=partial response; PS=performance status; PSR=platinum-sensitive relapsed; RECIST=response evaluation criteria in solid tumours; sBRCAm=somatic mutation in BRCA1/2; TDT=time to discontinuation of therapy; TFST=time to first subsequent therapy; CT-FI, chemotherapy-free interval;

1. OPINION. Available at: https://clinicaltrials.gov/ct2/show/NCT03402841 (last accessed May 2021); 2. Poveda A, et al. presented at the virtual American Society of Clinical Oncology (ASCO) Annual Meeting, held on June 4–8, 2021, Poster 5545

ASCO 2021

PFS benefit was observed in the overall non-gBRCAm population and AEs were consistent with the known safety profile of olaparib



	Olaparib (N=279)
Events, n	210*
Median PFS (95% CI), months	9.2 (7.6–10.9)
Progression free at 18 months, %	24.3 (19.2–29.7)

	N = 279 n (%)
Any TEAE	267 (95.7)
CTCAE grade ≥3 TEAE	81 (29.0)
Serious TEAE	55 (19.7)
TEAE leading to dose interruption	131 (47.0)
TEAE leading to dose reduction	63 (22.6)
TEAE leading to treatment discontinuation	21 (7.5)

DCO 02 October 2020.

*Data maturity 75.3%

CI=confidence interval; DCO=data cut-off; non-gBRCAm=no germline mutation in BRCA1/2; PFS=progression-free survival

Poveda A, et al. Presented at the virtual American Society of Clinical Oncology (ASCO) Annual Meeting, held on June 4–8, 2021, Poster 5545

Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase 3 trial of niraparib in recurrent ovarian cancer

Ursula A. Matulonis, Jørn Herrstedt, Amit Oza, Sven Mahner, Andrés Redondo, Dominique Berton, Jonathan S. Berek, Bente Lund, Frederik Marme, Antonio González-Martín, Anna V. Tinker, Jonathan Ledermann, Benedict Benigno, Gabriel Lindahl, Nicoletta Colombo, Yong Li, Divya Gupta, Bradley J. Monk, Mansoor R. Mirza

Presented at the Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer

March 19–25, 2021 (virtual)

- Clinical benefit of niraparib was demonstrated in the primary PFS analysis in non-g*BRCA*m (HR 0.45) and g*BRCA*m patients (HR 0.27)
- Final PFS2 analysis indicated that the benefit of niraparib maintenance therapy extended beyond first progression
- OS interpretation is limited:
  - OS was a secondary endpoint, not statistically powered
  - Analysis was challenged by the high rate of subsequent PARPi use and missing data
  - No difference in survival was observed in patients with non-g*BRCA*m OC
  - Trend toward improved survival was observed in patients with g*BRCA*m OC, based on the adjusted analyses, with an increased survival of 9.7 months
- Long term safety analysis support use of niraparib for maintenance treatment
  - Number of hematologic adverse events decreased after the first year of maintenance

g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS2, progression-free survival 2.
Matulonis UA, et al. presented at SGO 2021, March 19–25, 2021 (virtual).

ASCO 2021

Abstract number: 5534

Efficacy of Niraparib Maintenance Therapy in Chinese Women with Platinum-Sensitive Recurrent Ovarian Cancer with and Without Secondary Cytoreductive Surgery: Results from the NORA Trial

Lingying Wu[1], Xiaohua Wu[2], Jianqing Zhu[3], Rutie Yin[4], Jiaxin Yang[5], Jihong Liu[6], Jing Wang[7], Ziling Liu[8], Yuhong Gao[9], Danbo Wang[10], Ge Lou[11], Hongying Yang[12], Qi Zhou[13], Beihua Kong[14], Yi Huang[15], Lipai Chen[16], Guiling Li[17], Ruifang An[18], Tao Tan[19], Juan Dong[19]

[1] Department of Gynecologic Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. [2] Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, Shanghai China. [3] Department of Gynecologic Oncology, Cancer Hospital of the University of Chinese Academy of Sciences/Zhejiang Cancer Hospital, Hangzhou, China. [4] Department of Obstetrics and Gynecology, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China. [5] Department of Gynecologic Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. [6] Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China. [7] Department of Gynecologic Oncology, Hunan Cancer Hospital, the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China. [8] Department of Oncology, The First Hospital of Jilin University, Changchun, China. [9] Department of Gynecology, Peking University Cancer Hospital & Institute, Beijing, China. [10] Department of Gynecology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, China. [11] Department of Gynecology Oncology, Harbin Medical University Cancer Hospital, Harbin, China. [12] Department of Gynecologic Oncology, The Third Affiliated Hospital of Kunming Medical University/Yunnan Cancer Hospital, Kunming, China. [13] Gynecological Oncology Center, Chongqing University Cancer Hospital, Chongqing, China. [14] Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University, Jinan, China. [15] Department of Gynecologic Oncology, Hubei Cancer Hospital, Wuhan, China. [16] Department of Gynecological Oncology, Affiliated Cancer Hospital of Guangzhou Medical University, Guangzhou, China. [17] Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. [18] Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. [19] R&D Department, Zai Lab (Shanghai) Co., Ltd, Shanghai, China.

Background/Objective

- Secondary cytoreductive surgery (SCS) could be beneficial to women with platinum-sensitive recurrent ovarian cancer (PSROC). [1]
- However, the use of SCS is controversial since there are limited data from randomized controlled trials (RCTs). [2,3]
- Due to relapse associated with platinum-based chemotherapy, maintenance therapy with poly (ADP-ribose) polymerase inhibitors (PARPi) is considered as the standard treatment for PSROC patients and have proven to be effective. [4–6]
- Thus, with the availability of PARPi maintenance therapy and its proven PFS benefits in PSROC, [4–6] it is important to evaluate the efficacy of these drugs in patients undergoing SCS.
- NORA is the first, phase III, RCT that demonstrated individualized starting dose regimen of niraparib significantly improved progression-free survival (PFS) in Chinese patients with PSROC.
- Based on the encouraging results obtained from NORA, we carried out a subgroup analysis to assess whether niraparib is effective and safe in this patient population who undergo SCS.

Methods

Main Inclusion Criteria

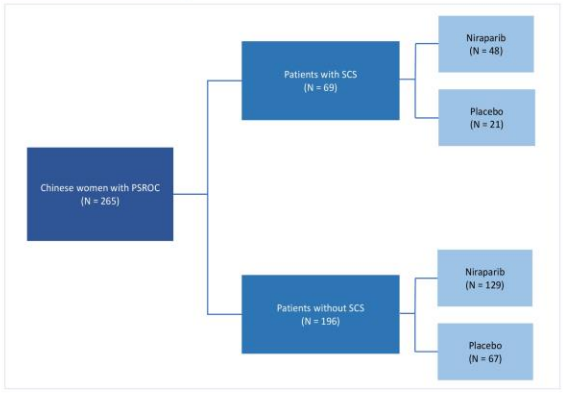
- Platinum-sensitive, recurrent ovarian cancer;
- High grade serous or high grade predominantly serous histology or known to have g*BRCA*mut;
- Completed at least 2 previous lines of platinum-containing therapy;
- Partial or complete response to the last platinum-based chemotherapy.

Randomization Stratification Factors

- g*BRCA* mutation: Yes or No
- Response to last chemotherapy: CR or PR
- Time to progression after penultimate platinum-based regimen: 6-12 months or ≥ 12 months

Statistical Analysis

- Median PFS was calculated by Kaplan-Meier estimator and P-value was generated by a stratified log-rank test (the p-value is descriptive)
- The hazard ratio was estimated with the stratified Cox proportional-hazards model.



gBRCAmut, germline *BRCA* mutation; CR, complete response; PR, partial response; PSROC, platinum-sensitive recurrent ovarian cancer, SCS, secondary cytoreductive surgery

Results

Baseline Characteristics

- Of the 265 evaluable patients, 69 (26.0%) patients received the SCS (niraparib, n = 48; placebo, n = 21), and 196 (74.0%) patients were without SCS (niraparib, n = 129; placebo, n = 67).
- Among patients with and without SCS, baseline characteristics for gBRCA*mut* were 26.1% vs 41.8%, complete response to last platinum-based chemotherapy were 68.1% vs 43.9%, and time (6-12 months) to progression after penultimate therapy were 23.2% vs 34.7%, respectively. Patient baseline characteristics are summarized in Table 1.

Efficacy outcomes

- Treatment with niraparib led to a reduction in risk of disease progression or death compared with placebo in patients with SCS (Hazard ratio [95% CI]: 0.32 [0.13–0.78]; $P = 0.0102$) and without SCS (0.34 [0.23–0.50]; $P<0.001$).
- In the subgroups of patients who received SCS, niraparib maintenance therapy had longer PFS compared with placebo (Median [95% CI]: not reached [18.33 – not estimable] vs 5.75 months [3.68 – not estimable]; P = 0.0102), considering that the event rate was low in niraparib group (Figure 1, Table 2).
- This trend was also similar in the subgroup of patients who did not receive SCS (Median [95% CI]: 10.28 months [7.49 – 18.37] vs 4.90 months [3.71 – 5.52]; P <0.0001) (Figure 1, Table 2).

Table 1: Baseline characteristics of the study population

Characteristics	Niraparib		Placebo		Total	
	With SCS (N=48)	Without SCS (N=129)	With SCS (N=21)	Without SCS (N=67)	With SCS (N=69)	Without SCS (N=196)
Age (years, mean [SD*])	53.8 (7.34)	54.5 (8.93)	55.9 (5.41)	55.3 (8.43)	54.4 (6.84)	54.8 (8.74)
Weight (kg, mean [SD*])	59.5 (9.50)	61.3 (10.64)	59.7 (7.45)	61.1 (9.83)	59.6 (8.87)	61.3 (10.34)
ECOG score, n (%)						
0	15 (31.3)	55 (42.6)	6 (28.6)	29 (43.3)	21 (30.4)	84 (42.9)
1	33 (68.8)	74 (57.4)	15 (71.4)	38 (56.7)	48 (69.6)	112 (57.1)
Best response to last platinum-containing chemotherapy, n (%)						
CR	33 (68.8)	53 (41.1)	14 (66.7)	33 (49.3)	47 (68.1)	86 (43.9)
PR	14 (29.2)	76 (58.9)	7 (33.3)	34 (50.7)	21 (30.4)	110 (56.1)
SD	1 (2.1)	0 (0)	0 (0)	0 (0)	1 (1.4)	0 (0)
gBRCA mutation status, n (%)						
g*BRCA*mut	14 (29.2)	51 (39.5)	4 (19.0)	31 (46.3)	18 (26.1)	82 (41.8)
Non-g*BRCA*mut	34 (70.8)	78 (60.5)	17 (81.0)	36 (53.7)	51 (73.9)	114 (58.2)
Time to progression after penultimate platinum therapy, n (%)						
≥12 months	38 (79.2)	83 (64.3)	15 (71.4)	45 (67.2)	53 (76.8)	128 (65.3)
6 to <12 months	10 (20.8)	46 (35.7)	6 (28.6)	22 (32.8)	16 (23.2)	68 (34.7)

BRCA, breast cancer gene; CR, complete response; ECOG, The Eastern Cooperative Oncology Group; PR, partial response; SD*, standard deviation; SD, stable disease; SCS, secondary cytoreductive surgery

Figure 1: Kaplan-Meier plot for progression free survival (PFS)

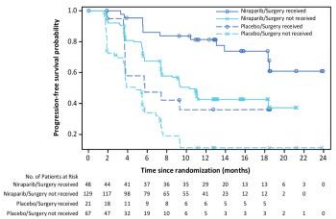


Table 2: PFS in patients with and without SCS

	With SCS (N = 69)		Without SCS (N = 196)	
	Niraparib (N = 48)	Placebo (N = 21)	Niraparib (N = 129)	Placebo (N = 67)
Event rates, n (%)	12 (25.0%)	12 (57.1%)	68 (52.7%)	54 (80.6%)
PFS, median (95% CI)	NR (18.33, NE)	5.75 (3.68, NE)	10.28 (7.49, 18.37)	4.90 (3.71, 5.52)
P value	0.0102		<0.0001	
HR (95% CI)	0.32 (0.13, 0.78)		0.34 (0.23, 0.50)	

CI; confidence interval; HR, hazard ratio; NR, not reached; NE, not estimable; PFS, progression free survival; SCS, secondary cytoreductive surgery

Safety Outcomes

- The most common treatment emergent adverse events (TEAEs) of all grade reported by patients receiving niraparib were hematological and included neutrophil count decreased (52.1% vs 38.1% in the placebo group), anemia (47.9% vs 23.8% in the placebo group), and platelet count decreased (47.9% vs 19.0% in the placebo group) in patients who received SCS.
- Similarly, patients receiving niraparib and without SCS, reported toxicities as follows; neutrophil count decreased (61.2% vs 43.3% in the placebo group), anemia (55.8% vs 29.9% in the placebo group), and platelet count decreased (57.4% vs 26.9% in the placebo group) respectively (Table 3).
- For patients receiving niraparib, with and without SCS, the incidence of grade ≥3 toxicities were in line with TEAEs of all grades.
- The overall incidence of hematological TEAEs were similar in patients who received SCS and those who did not receive SCS, and are reported in Table 3.

Table 3: Hematological TEAEs in patients with and without SCS

	Niraparib				Placebo				Total			
	With SCS (N=48) n (%)		Without SCS (N=129) n (%)		With SCS (N=21) n (%)		Without SCS (N=67) n (%)		With SCS (N=69) n (%)		Without SCS (N=196) n (%)	
Preferred Term	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3
Neutrophil count decreased[a]	25 (52.1)	11 (22.9)	79 (61.2)	25 (19.4)	8 (38.1)	0	29 (43.3)	7 (10.4)	33 (47.8)	11 (15.9)	108 (55.1)	32 (16.3)
Anaemia[b]	23 (47.9)	9 (18.8)	72 (55.8)	17 (13.2)	5 (23.8)	0	20 (29.9)	2 (3.0)	28 (40.6)	9 (13.0)	92 (46.9)	19 (9.7)
Platelet count decreased[c]	23 (47.9)	7 (14.6)	74 (57.4)	13 (10.1)	4 (19.0)	0	18 (26.9)	1 (1.5)	27 (39.1)	7 (10.1)	92 (46.9)	14 (7.1)

SCS, secondary cytoreductive surgery, TEAEs, treatment emergent adverse events, [a]The category of neutrophil count decreased includes reports of neutrophil count decreased and neutropenia. [b]The category of anaemia includes reports of anaemia and decreased hemoglobin count, [c]The category of platelet count decreased includes reports of platelet count decreased and thrombocytopenia.

Conclusion

- The results from this retrospective sub-group analysis revealed that niraparib maintenance therapy provided significant clinical efficacy in patients with PSROC, irrespective of SCS.
- Niraparib was safe and well tolerated, with similar hematological toxicities in patients with PSROC, in both patients with and without SCS.
- Thus, niraparib could be considered as a potential option in patients with PSROC, irrespective of SCS.

Acknowledgements

- This study was sponsored by Zai Lab. The study was also partially supported by the National Major Scientific and Technological Special Project for "Significant New Drugs Development" in 2018 (No. 2018ZX09736019), China.
- The authors received editorial/writing support in the preparation of this poster from Indegene Pvt Ltd., funded by Zai Lab.
- The authors also thank the patients and their families, as well as the staff and investigators at all of the study sites.

Conflicts of Interest

- Juan Dong and Tao Tan are employees of Zai Lab. The other authors have no conflict of interest.

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2. Du Bois A, et al. *J Clin Oncol*. 2017;35(15_suppl):5501-5501.
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PARP INHIBITORS as monotherapy

Phase 2 Study of Olaparib in Patients With Advanced Cancer and a Germline *BRCA*1/2 Mutation (Study 42)

	Ovarian (n = 193)	Breast (n = 62)	Pancreas (n = 23)	Prostate (n = 8)	Other (n = 12)	Total (n = 298)
Tumor response rate, n (%)	60 **(31.1)**	8 (12.9)	5 (21.7)	4 (50.0)	1 (8.3)	78 (26.2)
95% CI	24.6, 38.1	5.7, 23.9	7.5, 43.7	15.7, 84.3	0.02, 38.5	21.3, 31.6
CR	6 (3)	0 (0)	1 (4)	0 (0)	0 (0)	7 (2)
PR	54 (28)	8 (13)	4 (17)	4 (50)	1 (8)	71 (24)

Kaufman et al, J Clin Oncol 2015

Treatment with olaparib 400 mg twice daily was associated with clinical responses in heavily pretreated patients with *BRCA1/2* mutations and recurrent, treatment-refractory cancer

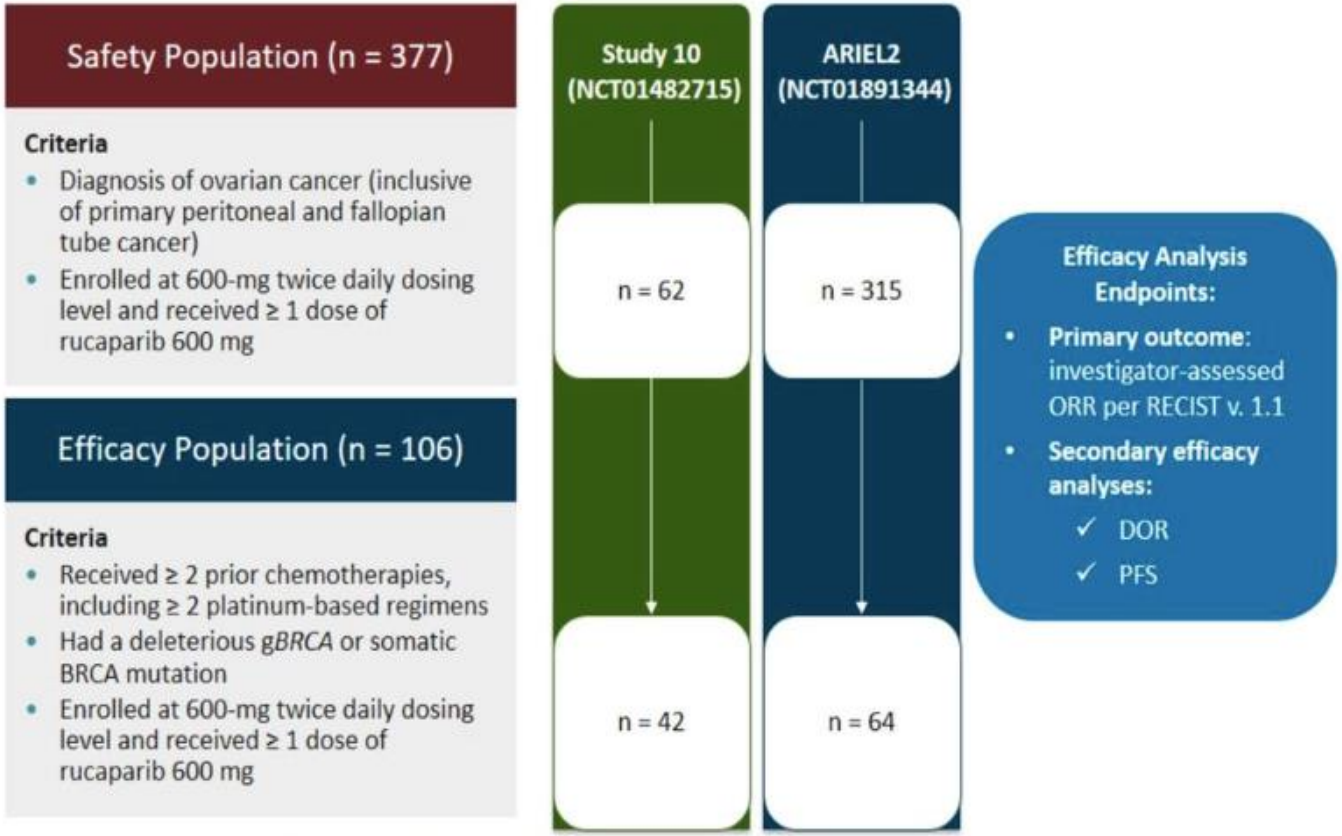
PARP INHIBITORS as monotherapy

CCR Drug Updates

Clinical Cancer Research

FDA Approval Summary: Rucaparib for the Treatment of Patients with Deleterious *BRCA* Mutation–Associated Advanced Ovarian Cancer

- *≥ 2 prior lines of platinum-based chemotherapy*
- *Unable to receive further platinum based chemotherapy*



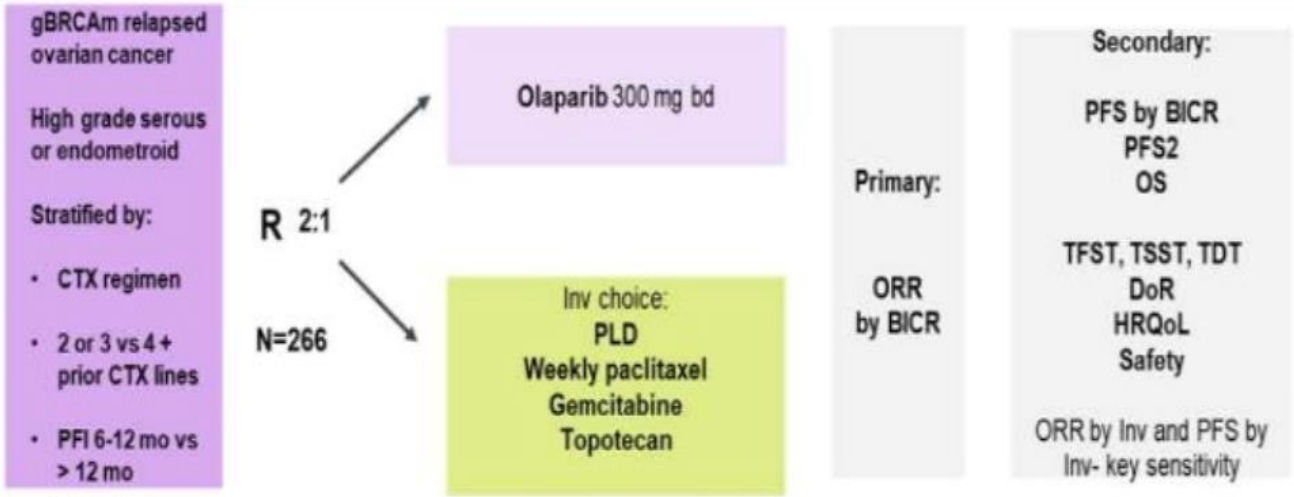
Oza AM, et al. *Gynecol Oncol*. 2017;147:267-275.

Response rate: 54%
Duration of response: 9.2 months

Phase III SOLO3 Trial of Olaparib vs Chemotherapy in Platinum-Sensitive Relapsed Ovarian Cancer and Germline *BRCA* Mutation

solo3 BRCAm Ovarian Cancer

is the first Phase III study to evaluate the efficacy of single agent treatment with a PARP inhibitor (olaparib tablets) in *BRCA*m OC patients who have progressed at least six months after last platinum treatment and have received at least 2 prior platinum treatments[1]



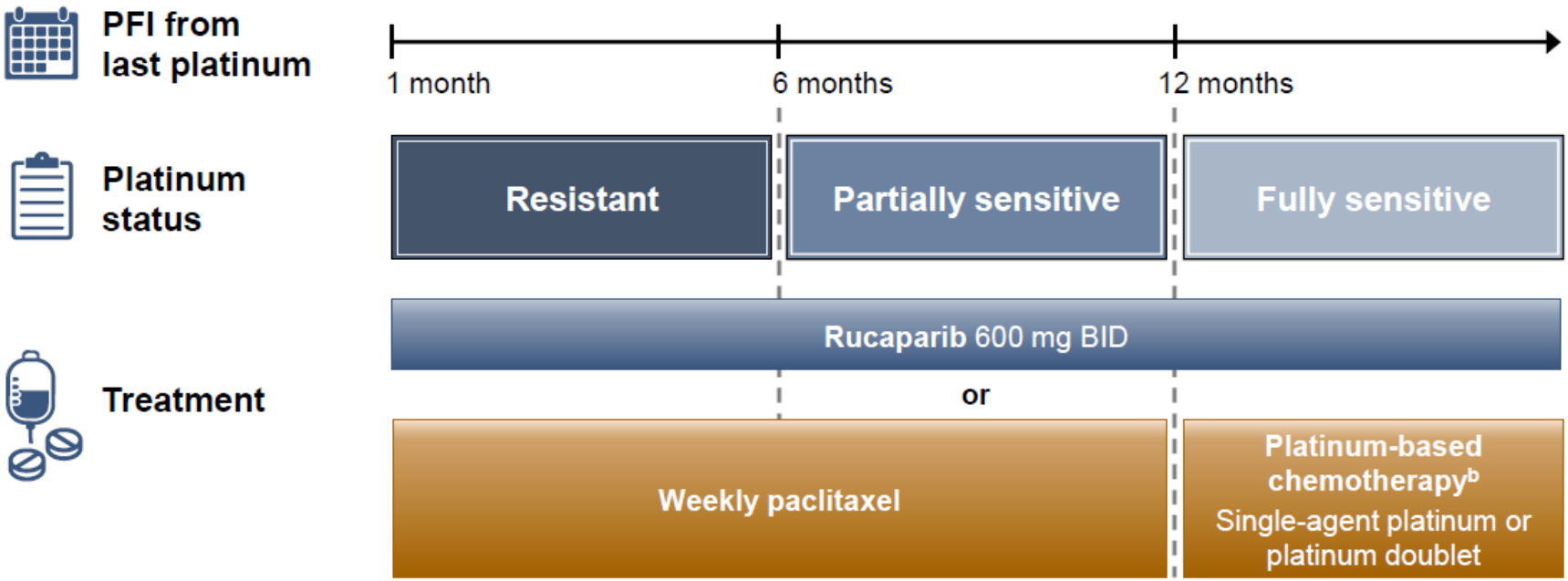
- **Overall response rate** in the olaparib group **72.2%** versus **51.4%** in the chemotherapy group (HR2.53; p 0.002)
- **PFS 13.4** vs **9.2 months** (HR 0.62, p 0.013)

Penson RT et al, JCO 2020

ARIEL4 Study Population

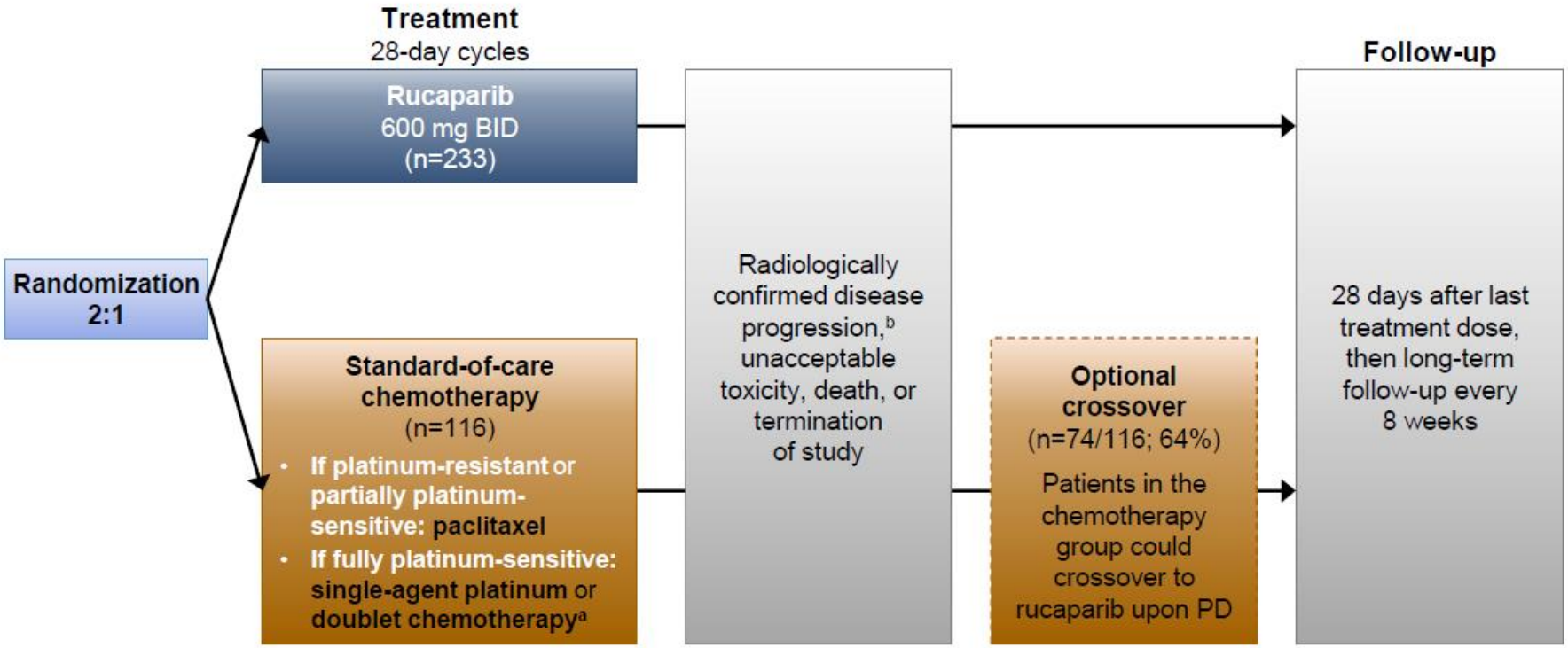
Patients with:

- Relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- ≥2 prior chemotherapy regimens, including ≥1 platinum-based regimen[a]
- Deleterious germline or somatic BRCA mutation
- No prior PARP inhibitor or single-agent paclitaxel treatment



[a]With treatment-free interval ≥6 months following first chemotherapy received. [b]At investigator's discretion.
BID, twice daily; BRCA, *BRCA1* or *BRCA2*; PARP, poly(ADP-ribose) polymerase; PFI, progression-free interval.

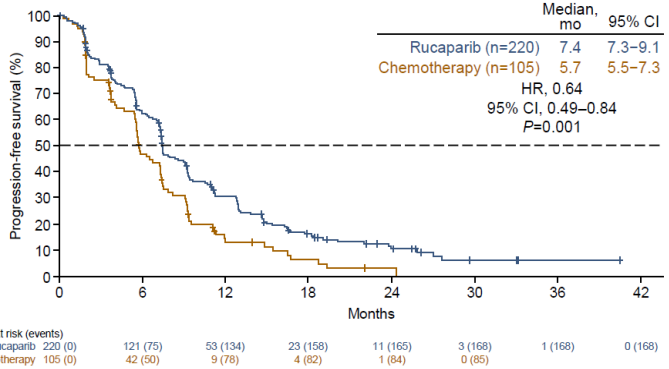
ARIEL4 Study Schema



Randomization stratification factor: Platinum status (platinum-resistant, partially platinum-sensitive, fully platinum sensitive)[c]

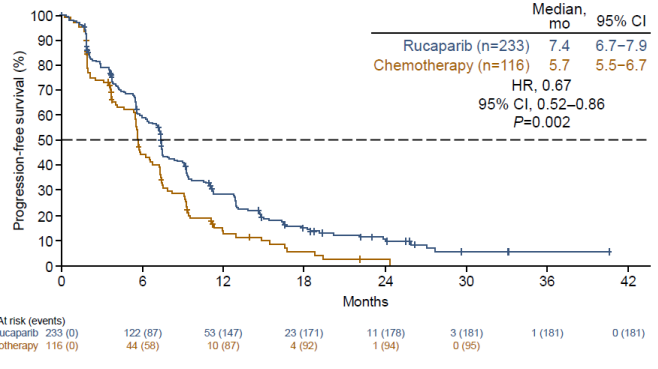
[a]At investigator's discretion. [b]Per RECIST. [c]Platinum resistant: PFI ≥1–<6 months, partially platinum sensitive: PFI ≥6–<12 months, fully platinum sensitive: PFI ≥12 months. BID, twice daily; BRCA, *BRCA1* or *BRCA2;* PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFI, progression-free interval; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

Primary Endpoint – Investigator-assessed PFS: Efficacy Population



Visit cutoff September 30, 2020.
HR and associated *P* value calculated using a stratified Cox proportional hazards model.
HR, hazard ratio; PFS, progression-free survival.

Primary Endpoint – Investigator-assessed PFS: ITT Population

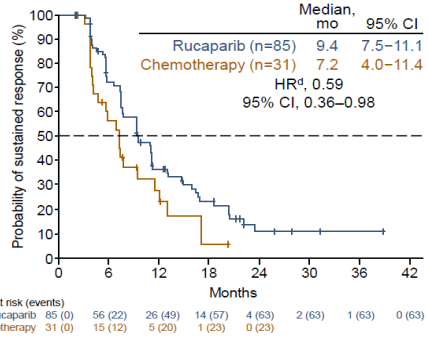


Visit cutoff September 30, 2020.
HR and associated *P* value calculated using a stratified Cox proportional hazards model.
HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival.

Secondary Endpoints – Response: Efficacy Population

	Rucaparib	Chemotherapy
RECIST ORR, n/N (%) [95% CI][a]	**85/211 (40.3) [33.6–47.2]**	**31/96 (32.3) [23.1–42.6]**
	P=0.13[b]	
Complete response	10 (4.7)	2 (2.1)
Partial response	75 (35.5)	29 (30.2)
Stable disease	77 (36.5)	38 (39.6)
Progressive disease	25 (11.8)	15 (15.6)
Not evaluable	24 (11.4)	12 (12.5)
RECIST and/or CA-125 response, n/N (%) [95% CI][c]	**110/217 (50.7) [43.8–57.5]**	**44/101 (43.6) [33.7–53.8]**

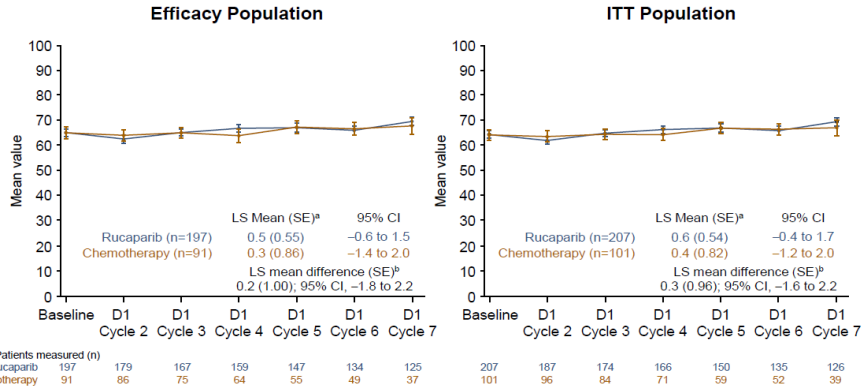
DOR



- Data were similar for the ITT population:
  - RECIST ORR: rucaparib, 37.9% (95% CI, 31.6–44.7) vs chemotherapy, 30.2% (95% CI, 21.7–39.9)
  - Median DOR: rucaparib, 9.4 months vs chemotherapy, 7.2 months (HR,[d] 0.56 [95% CI, 0.34–0.93])

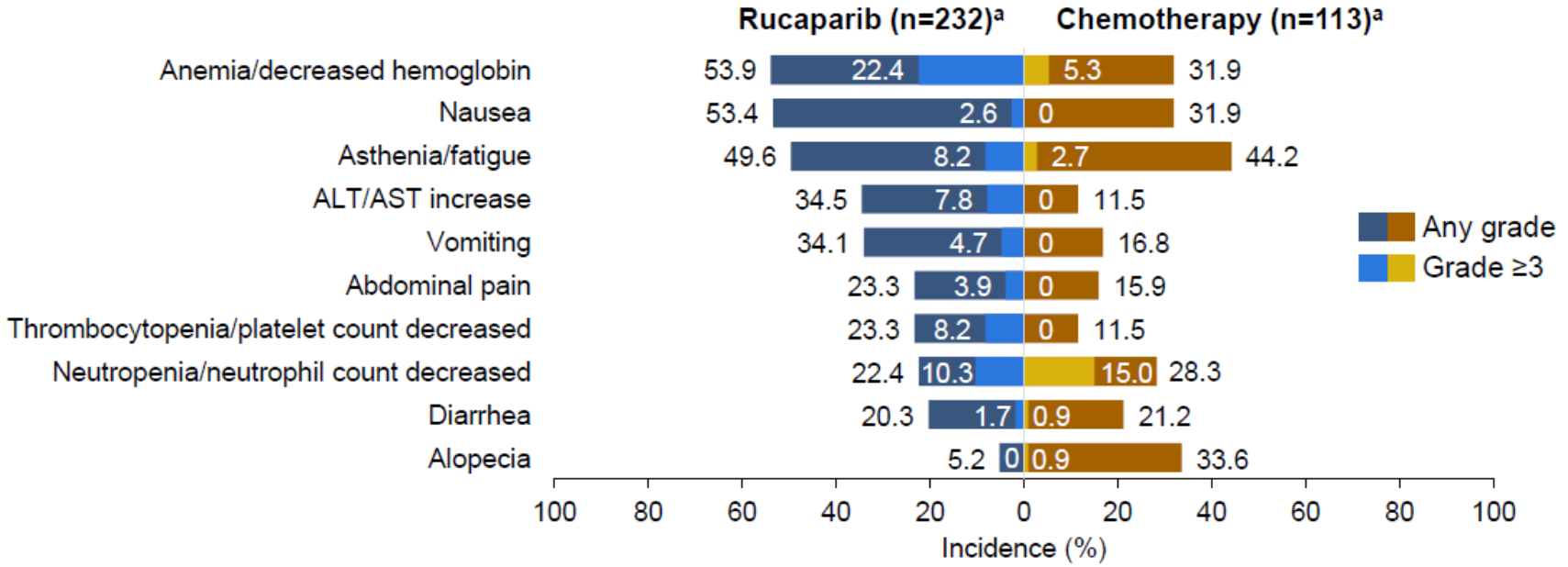
Visit cutoff September 30, 2020.
[a]Patients with measurable disease at baseline. [b]Per Stratified Cochran-Mantel-Haenszel test. [c]Patients with measurable disease at baseline and/or evaluable by CA-125.
[d]Per Cox proportional hazards model. CA-125, cancer antigen 125; DOR, duration of response; HR, hazard ratio; ITT, intent to treat; ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

Secondary Endpoint – Change From Baseline in EORTC QLQ-C30 Global Health Status



Visit cutoff September 30, 2020.
Data were analyzed using a repeated measures ANCOVA model, with the baseline value as a covariate, and treatment and randomization stratification as factors.
[a]LS mean change from baseline during first 6 cycles. [b]Rucaparib vs chemotherapy.
ANCOVA, analysis of covariance; D, day; EORTC QLQ, European Organization for Research and Treatment of Cancer quality of life questionnaire; ITT, intent to treat; LS, least square; SE, standard error.

Most Common TEAEs (≥20% in Either Group)



- Median treatment duration: rucaparib, 7.3 months (range <1–41); chemotherapy, 3.6 months (range <1–25)
- Nineteen (8.2%) patients in the rucaparib group and 14 (12.4%) in the chemotherapy group discontinued due to TEAE[b]
- MDS/AML was reported by 4 patients in the rucaparib group (1 during treatment, 3 during long-term follow-up) and no patients in the chemotherapy group

Visit cutoff September 30, 2020.
[a]Four patients (rucaparib, 1; chemotherapy, 3) discontinued before receiving study treatment and are excluded from the safety population. [b]Excluding disease progression. ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

Rechallenge with PARP INHIBITORS

- No license is available for re-treatment with PARPis
- It is currently unclear whether PARPi retreatment is beneficial

OReO

Olaparib Retreatment in Ovarian Cancer

- Previously successfully treated with a PARPi
- Response to most recent line of platinum-based chemotherapy after disease progression

Strategies for future

PARPi + ANTI-ANGIOGENIC

- *Hypoxia increases the sensitivity of cancer cells to PARPis due to reduced efficacy of homologous recombination repair mechanism*
- *Direct effect on DNA repair via platelet-derived growth factor receptor inhibition (Cediranib)*

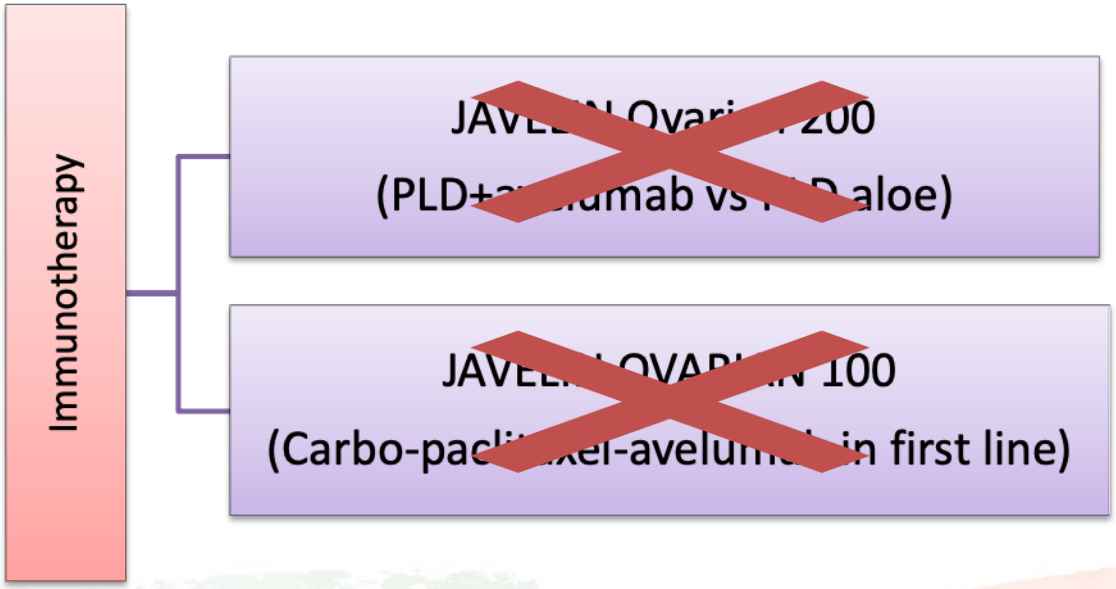
Proposed Strategy	Trials
Maintenance combinations Additive effects ←	• **PAOLA 1:** (olaparib/bevacizumab) first-line • **ICON9:** cediranib/olaparib v olaparib • **AVANOVA: Niraparib + bevacizumab**
Combinations versus chemotherapy	**NRG-GYN 004:** olaparib + cediranib v platinum-based chemotherapy

- Cediranib added to the effect of olaparib in both gBRCAmut and BRCAwt groups
- The study was negative as the chemotherapy-free regimen was not superior to chemotherapy

Liu JF, Ann Oncol 2019 and JCO 2020

Immunotherapy

- Immune systemis thought to play an important role in ovarian cancer, but the results of trials of immune checkpoint inhibitor monotherapy have shown **little activity**
- Available biomarkers identify only **10-15% of patient** benefiting
- The highest expectation is focused now in the combination of immunotherapy with antiangiogenic agents and/or PARPi



Coosemans A, Eur J Cancer 2019;
Ledermann JA, SGO 2020

PARPi + IMMUNOTHERAPY

PARPis can activate STING (stimulator of interferon genes) pathway to increase T-cell infiltration in the tumor

TAPACIO/KEYNOTE-162 (phase I-II)
(niraparib+pembrolizumab)

MEDIOLA trial
(olaparib-durvalumab)

Response rates were **encouraging**, especially for patients without deleterious BRCA mutations or homologous recombination deficiency

Konstantinoupoulos PA, JAMA Oncol 2019; Drew J, Ann Onco 2019

PARPi + IMMUNOTHERAPY

ENGOT-OV41/GEICO 69-O/ANITA

N= 414 patients

- Recurrent high- grade serous or endometrioid, or undifferentiated ovarian, primary peritoneal or tubal carcinoma
- TFIp >6 months
- ≤ 2 prior lines
- Measurable disease
- ECOG≤ 1

RANDOMIZATION 1:1

A: Platinum doublet+ Placebo 6 cycles

B: Platinum-doublet + Atezolizumab 6 cycles

RECIST v1.1 CT SCAN

If CR, PR or SD

Niraparib+ Placebo until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination by sponso

Niraparib+ Atezolizumab disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination by sponso

Primary Endpoint:

- PFS by RECIST v.1.1

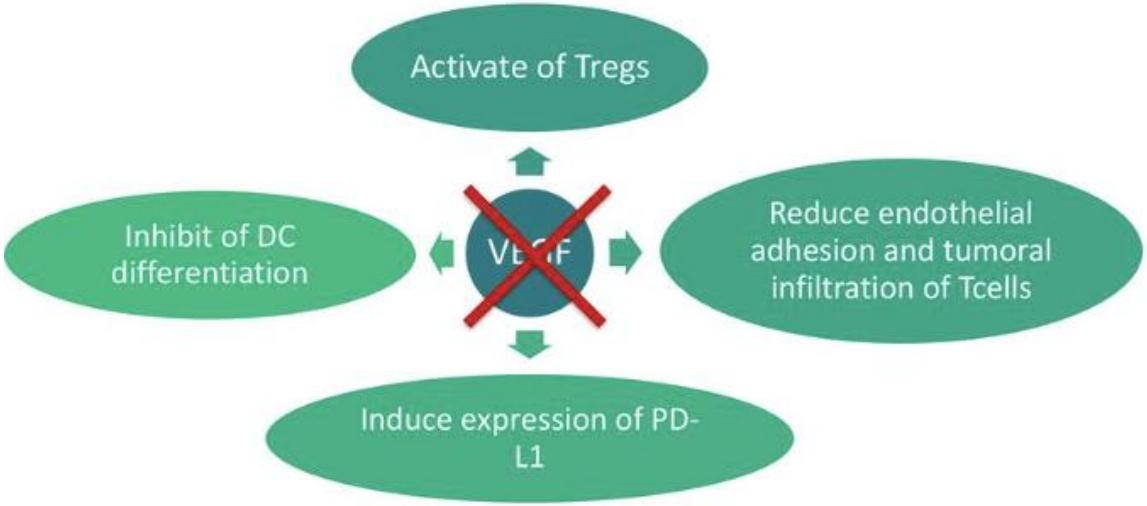
Secondary endpoints:

- Safety and tolerability
- TFST, TSST,PFS2,OS
  ORR, DOR
  QoL/PRO

The addition of atezolizumab is expected to increase the median PFS of Arm A from 16 months to 22.9 months, corresponding to a 30% reduction of the risk of progression (**average HR of 0.70**)

ANTIANGIOGENIC + IMMUNOTHERAPY

VEGF has immunosupressive properties



ATALANTE/ENGOT OV-29
(Atezolizumab and Avastin in Late recurreNT diseasE)

AGO-OVAR 2.29/ENGOT OV-34
(chemotherapy + atezolizumab + bevacizumab)

TRIAL ONGOING

Work in Progress

Symptom Identification and Management in Epithelial Ovarian Cancer

#5554

AD Hickman[1], KJ Ruddy[2], DR Pachman[3], K Fischer[4], P Rahman[5], KM Goergen[5], M Lee[5], AL Cheville[6], AE Wahner Hendrickson[2]

Department of Internal Medicine[1], Department of Medical Oncology[2], Department of Palliative Medicine[3], Kern Center for the Science of Healthcare Delivery[4], Division of Biomedical Statistics and Informatics[5], Department of Physical Medicine and Rehabilitation[6]

Mayo Clinic, Rochester, MN

ASCO 2021

Introduction

A better understanding regarding the burden of treatment side effects in patients with gynecological malignancies could help guide symptom interventions and oncologic therapy decision-making. We aim to inform understanding of symptom burden in epithelial ovarian cancer (EOC) by analyzing patient-reported symptom data from patients treated for this condition over a 16-month period.

Objectives:

1. Determine which symptoms are most distressing to patients receiving care for EOC
2. Identify risk factors for increased symptom burden

Methods

- Patients receiving medical oncology care at Mayo Clinic Rochester and Midwest Mayo Clinic Health System community sites received symptom-focused surveys prior to each medical oncology visit since March 28, 2019 through the Enhanced Electronic Health Record Facilitated Cancer Symptom Control Study (E2C2)
- Surveys were administered either through the electronic medical record portal or on a clinic tablet prior to each oncology office visit; no more frequently than every 2 weeks
- Surveys for patients with epithelial ovarian cancer were collected from March 2019-July 2020

Surveys by Symptom Severity

	Sleep Disturbance	Pain	Anxiety	Emotional Distress	Fatigue	Physical Dysfunction
Mild (0-3)	71.8%	77.9%	74.9%	79.6%	60.0%	69.4%
Moderate (4-6)	20.5%	16.3%	18.7%	15.5%	27.8%	22.7%
Severe (7-10)	7.7%	5.8%	6.4%	4.9%	12.2%	7.9%

Surveys by Symptom Severity: The percentage of surveys that report symptom severity as mild, moderate, or severe. Mild defined as scores of 0-3, moderate defined as scores 4-6, and severe defined as scores 7-10.

Results

- 2974 encounter-based surveys from 762 patients.
- The number of surveys completed by each patient ranged from 1-20.
- 40% report moderate to severe fatigue
- Patients aged 30-49 years old appear to have the greatest burden of symptoms

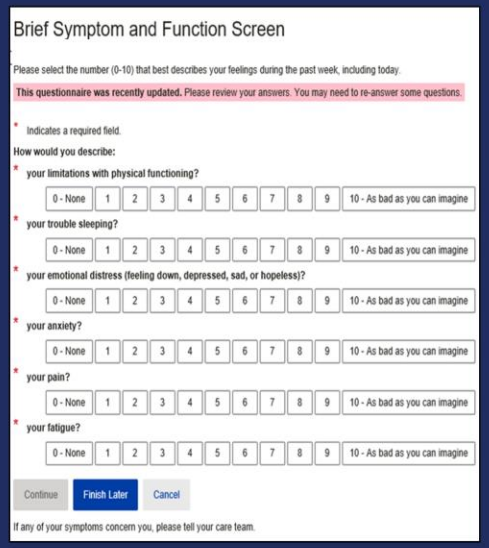
Conclusions

- Survey based symptom assessment is an effective tool to understanding symptom burden in patients undergoing oncologic care
- Patients undergoing treatment for EOC report significant fatigue
- Patients age 30-49 years old experience a higher than average symptom burden in each category

Future Directions for Research

- Determine barriers to survey completion
- Identify risk factors for increased symptoms (age, treatment regimen)
- Implement individualized resources for symptom management

E2C2 Survey


Brief Symptom and Function Screen

Please select the number (0-10) that best describes your feelings during the past week, including today.

This questionnaire was recently updated. Please review your answers. You may need to re-answer some questions.

* Indicates a required field.

How would you describe:

* your limitations with physical functioning?
* your trouble sleeping?
* your emotional distress (feeling down, depressed, sad, or hopeless)?
* your anxiety?
* your pain?
* your fatigue?

0 - None | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 - As bad as you can imagine

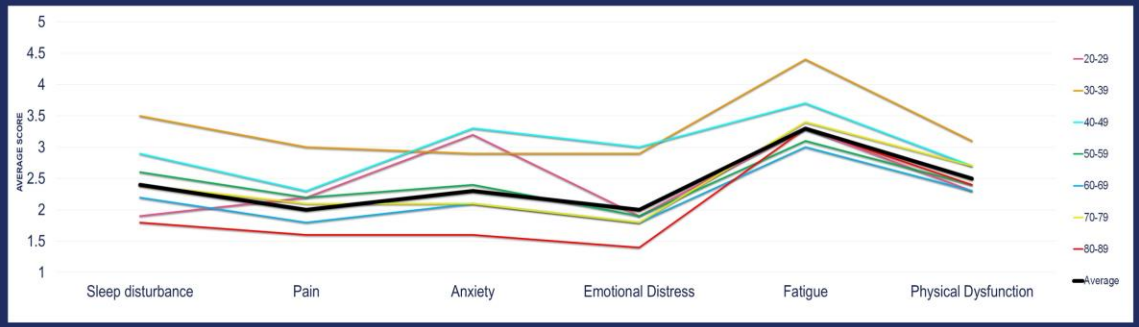
Continue | Finish Later | Cancel

If any of your symptoms concern you, please tell your care team.

EOC Surveys Per Patient

Number of Surveys	Number of Patients
1	240
2	145
3	79
4	56
5	58
6	45
7	38
8	27
9	22
≥ 10	52

Average Symptom Scores by Age in Decades



Average Symptom Scores by Age: the average score for each symptom separately reported for patients in each decade of age.

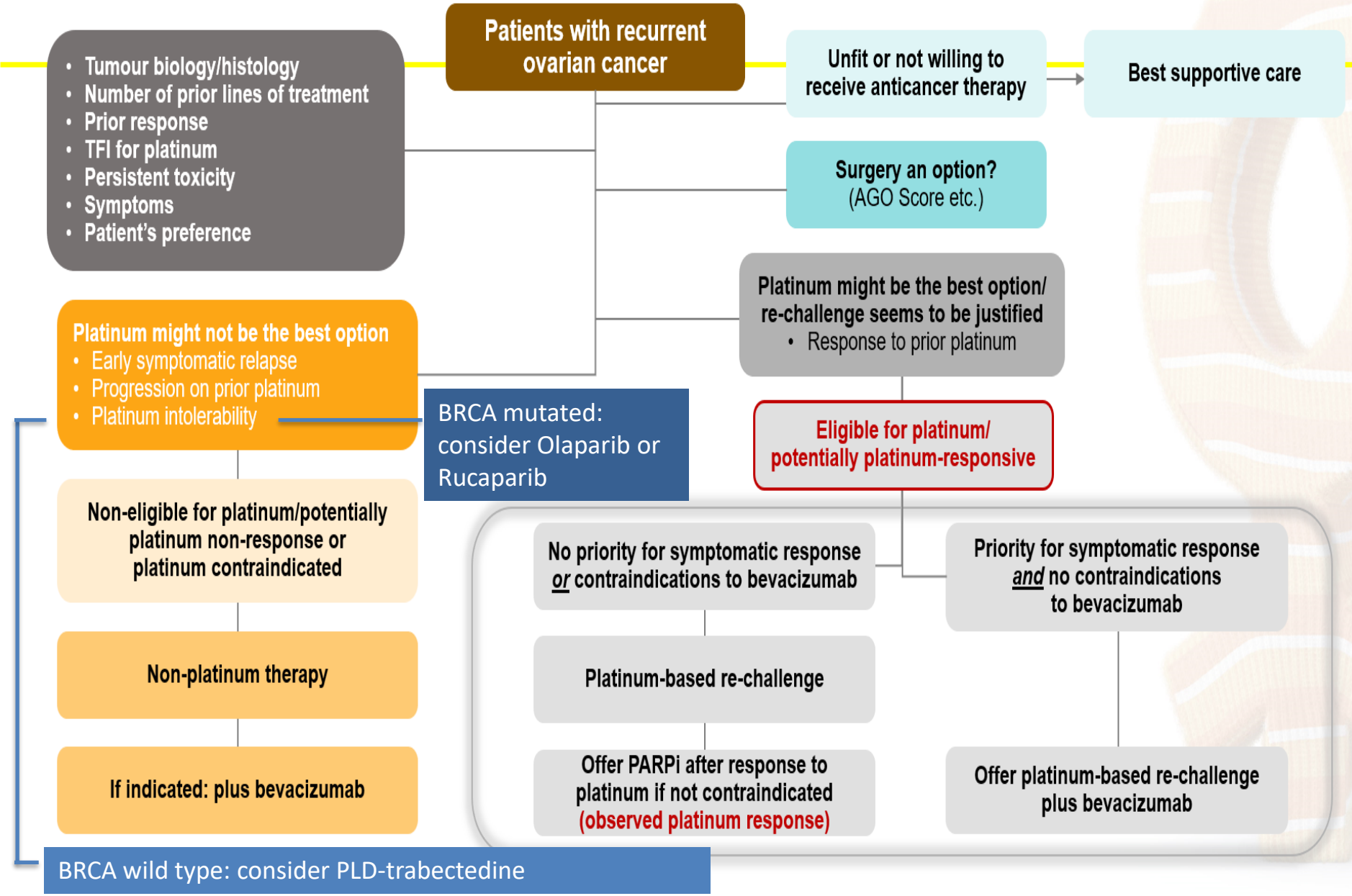
Acknowledgments

Thank you to the E2C2 research team for allowing our participation in this research

References

1. Finney Rutten *et al.* Trials. 2020 Jun 5;21(1):480.
2. ClinicalTrials.gov Identifier: NCT03892967

ESMO – ESGO Recommendations



Conclusioni

ANNALS OF ONCOLOGY
driving innovation in oncology
Volume 32 ■ Issue 6 ■ 2021

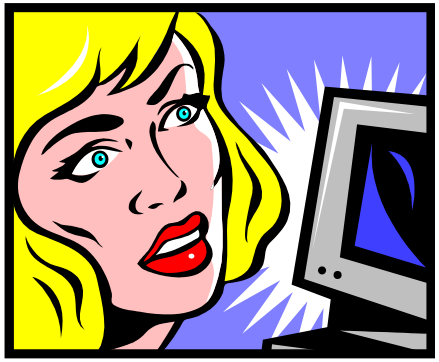
REVIEW

The systemic treatment of recurrent ovarian cancer revisited

T. Baert[1,2*], A. Ferrero[3], J. Sehouli[4], D. M. O'Donnell[5], A. González-Martín[6], F. Joly[7], J. van der Velden[8], P. Blecharz[9], D. S. P. Tan[10,11], D. Querleu[12], N. Colombo[13,14], A. du Bois[1†] & J. A. Ledermann[15†]

- Treatment approaches for relapsed ovarian cancer have evolved over the past decade from a calendar-based decision tree to a patient-oriented biologically driven algorithm
- Platinum-based chemotherapy should be offered to all patients with a reasonable chance of responding
- A more pratical approach should be therapy-oriented and therefore classified as platinum eligible (PEOC) or non-eligible (PNOC)
- Targeted therapy (anti-angiogenic and PARP-inhibitors) are milestones

OUTCOME E QUALITA' DI VITA



Grazie per l'attenzione!