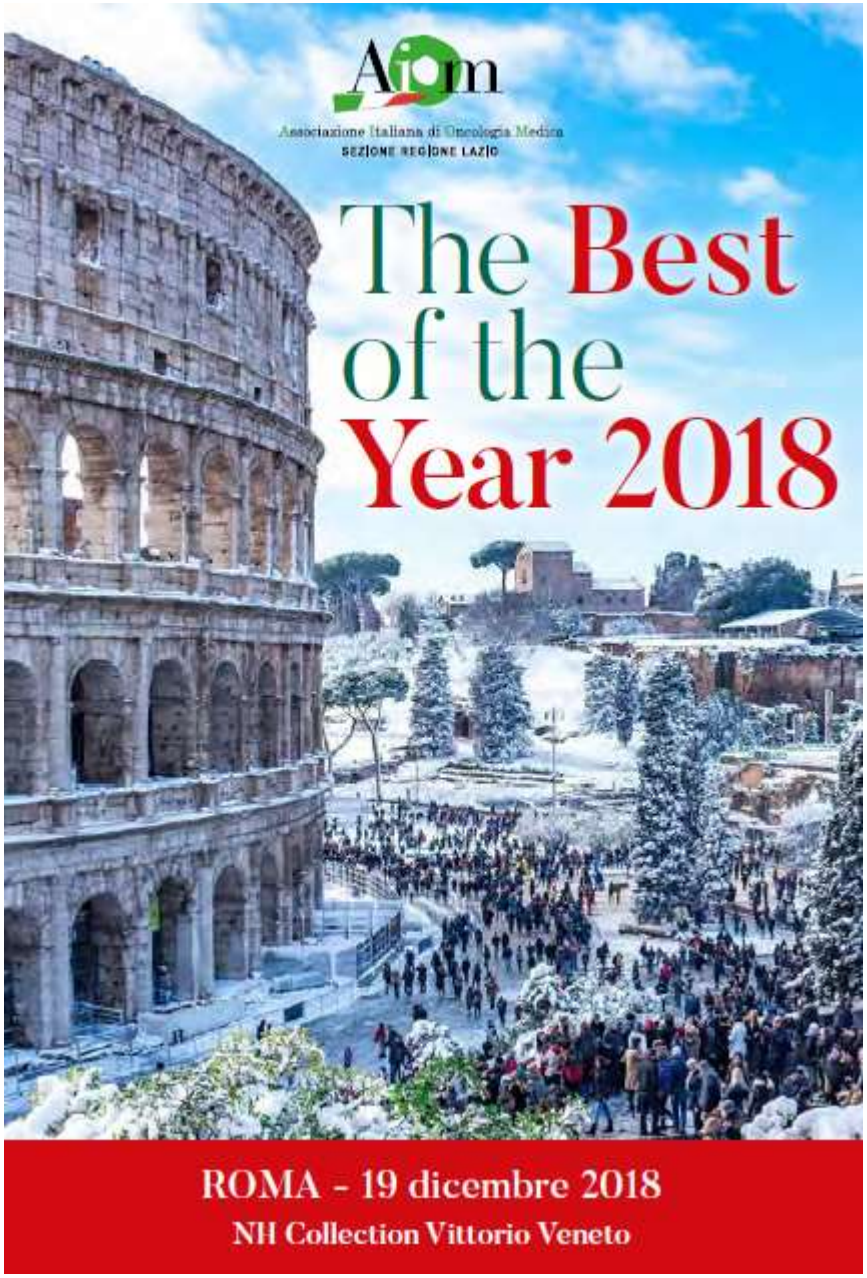


IRE
ISTITUTO NAZIONALE TUMORI
REGINA ELENA
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Tumori Ginecologici
THE BEST OF 2018

Antonella Savarese
Oncologia Medica 1

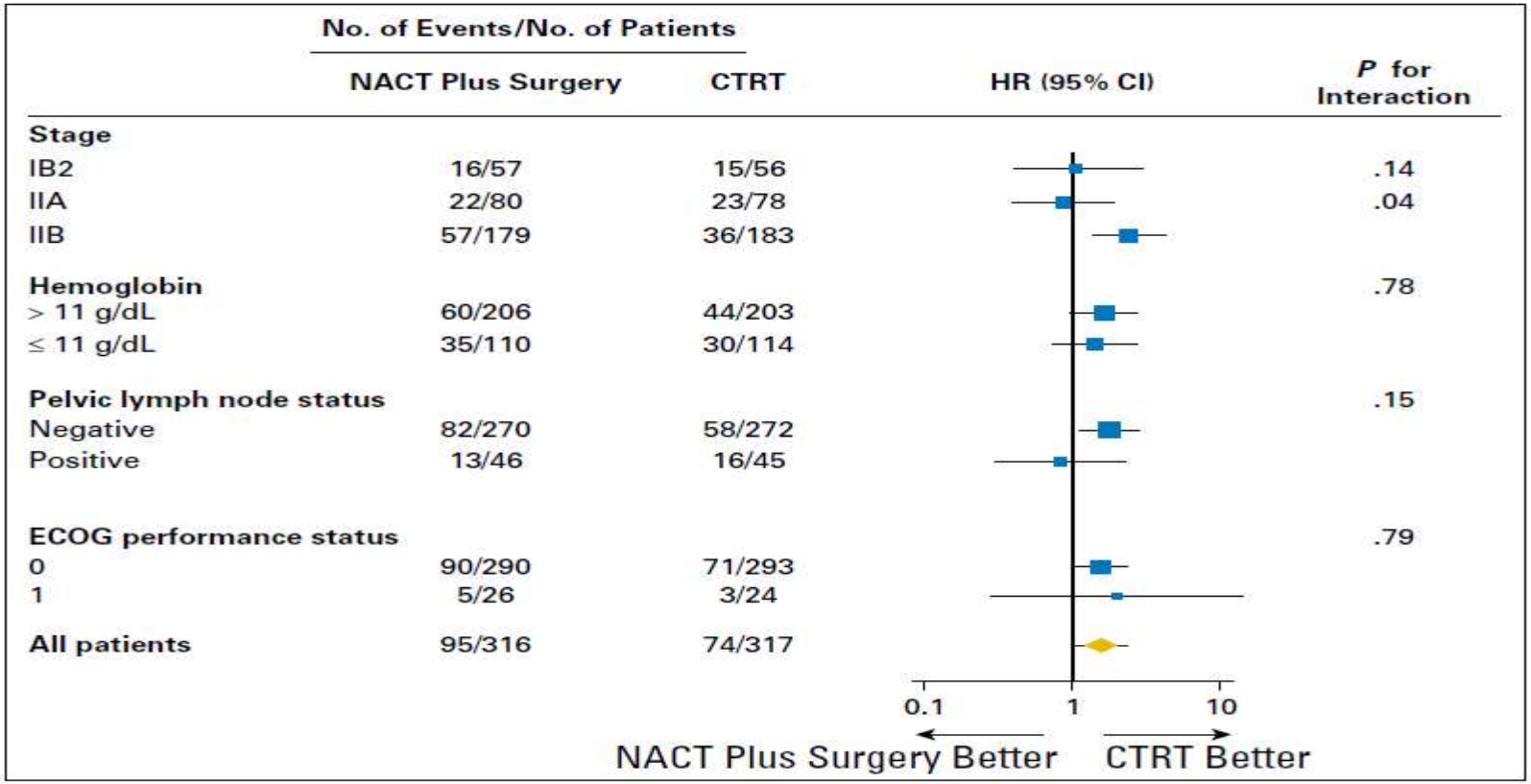
Istituto Nazionale Tumori
«Regina Elena» - Roma

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

Sudeep Gupta, Amita Maheshwari, Pallavi Parab, Umesh Mahantshetty, Rohini Hawaldar, Supriya Sastri (Chopra), Rajendra Kerkar, Reena Engineer, Hemant Tongaonkar, Jaya Ghosh, Seema Gulia, Neha Kumar, T. Surappa Shylasree, Renuka Gawade, Yogesh Kembhavi, Madhuri Gaikar, Santosh Menon, Meenakshi Thakur, Shyam Shrivastava, and Rajendra Badwe

J Clin Oncol 36:1548-1555,2018

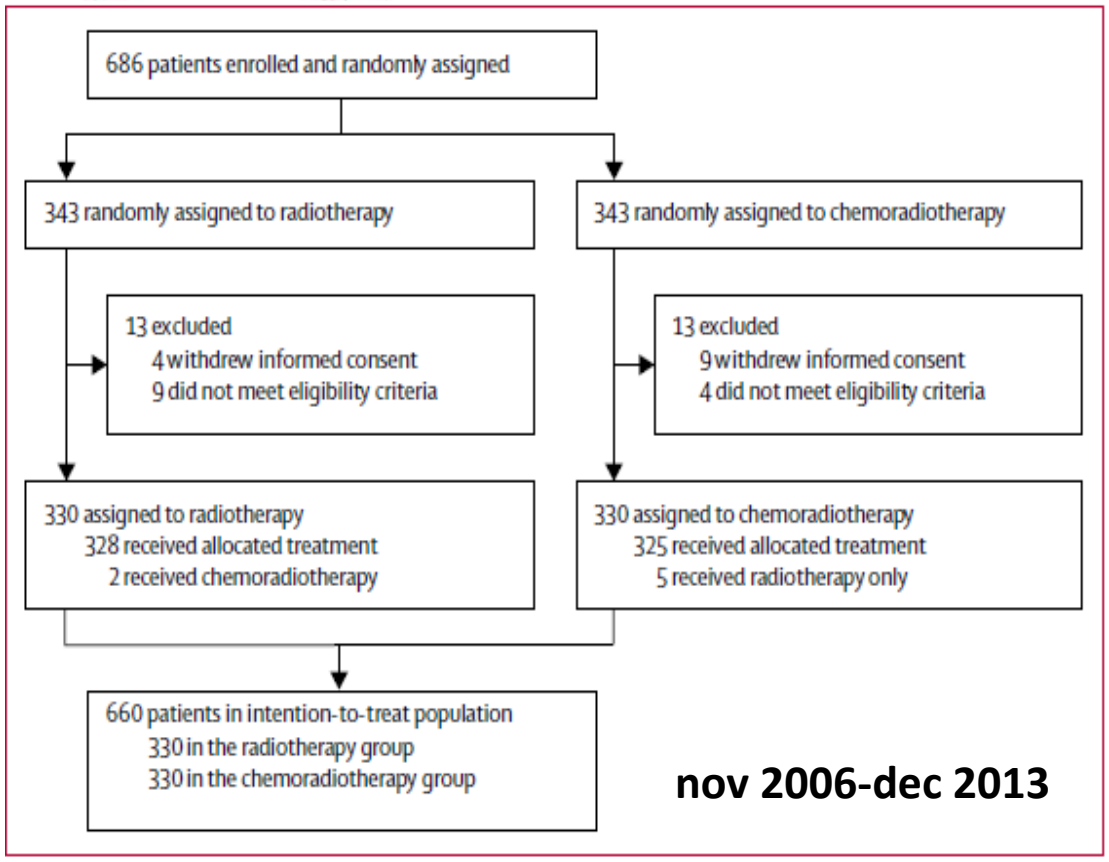
Sep 2003 – Feb 2015 / 635 pts, accrual not reached / median f-u time 58.5 mos



Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial

Lancet Oncol 2018; 19: 295–309

*Stephanie M de Boer, Melanie E Powell, Linda Mileshkin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B Ottevanger, Jonathan A Ledermann, Pearly Khaw, Alessandro Colombo, Anthony Fyles, Marie-Helene Baron, Ina M Jürgenliemk-Schulz, Henry C Kitchener, Hans W Nijman, Godfrey Wilson, Susan Brooks, Silvestro Carinelli, Diane Provencher, Chantal Hanzen, Ludy C H W Lutgens, Vincent T H B M Smit, Naveena Singh, Viet Do, Romerai D'Amico, Remi A Nout, Amanda Feeney, Karen W Verhoeven-Adema, Hein Putter, Carien L Creutzberg, on behalf of the PORTEC study group**



nov 2006-dec 2013

Pts characteristics:

Endometrioid stage I G3 LVSI+, II, III
Serous /clear cell stage I-III
Age >18
PS 0-2

Treatment plan:

✓ **External pelvic RT 48.6 Gy in 5 w**

✓ **External pelvic RT 48.6 Gy in 5 w+**
DDP 50mg/m2 w 1 and 4 of RT
followed by
4 cycles of
CBDCA AUC5 + Taxol 175 mg/m2 q21

PORTEC 3: Evidence before this study

- Jan 1980-Dec 2006: 6 randomized trials comparing chemotherapy vs radiotherapy in high risk or advanced endometrial cancer: no difference in OS
- Because of increased pelvic relapse with CT alone, combination of CT + RT has been explored
- Since 2006 (PORTEC-3 starts) three randomized trials of RT alone vs CT+RT have been published, with no difference in OS

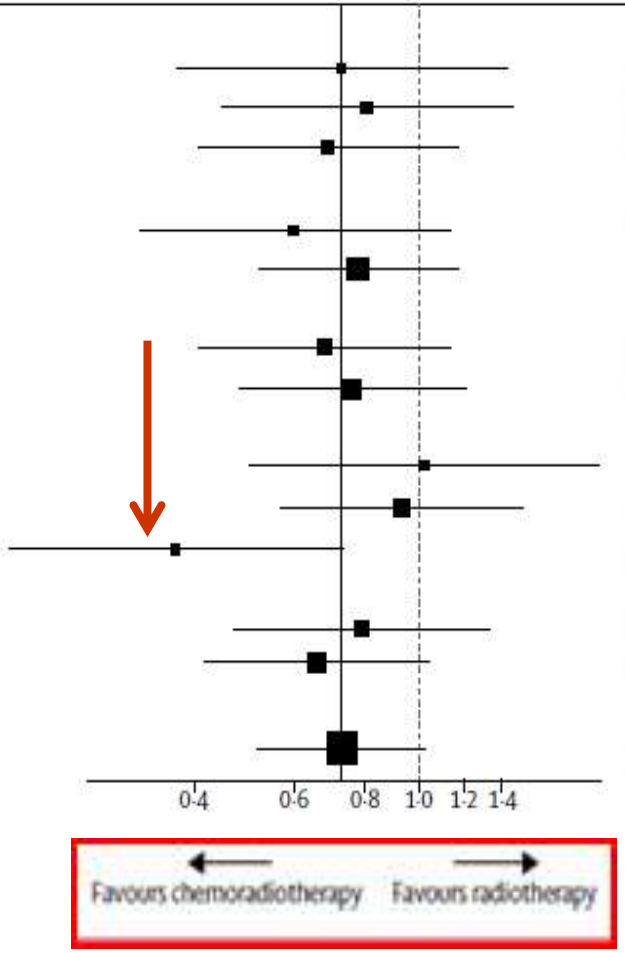
PORTEC 3

Forest plot of multivariable analysis for overall survival

77%

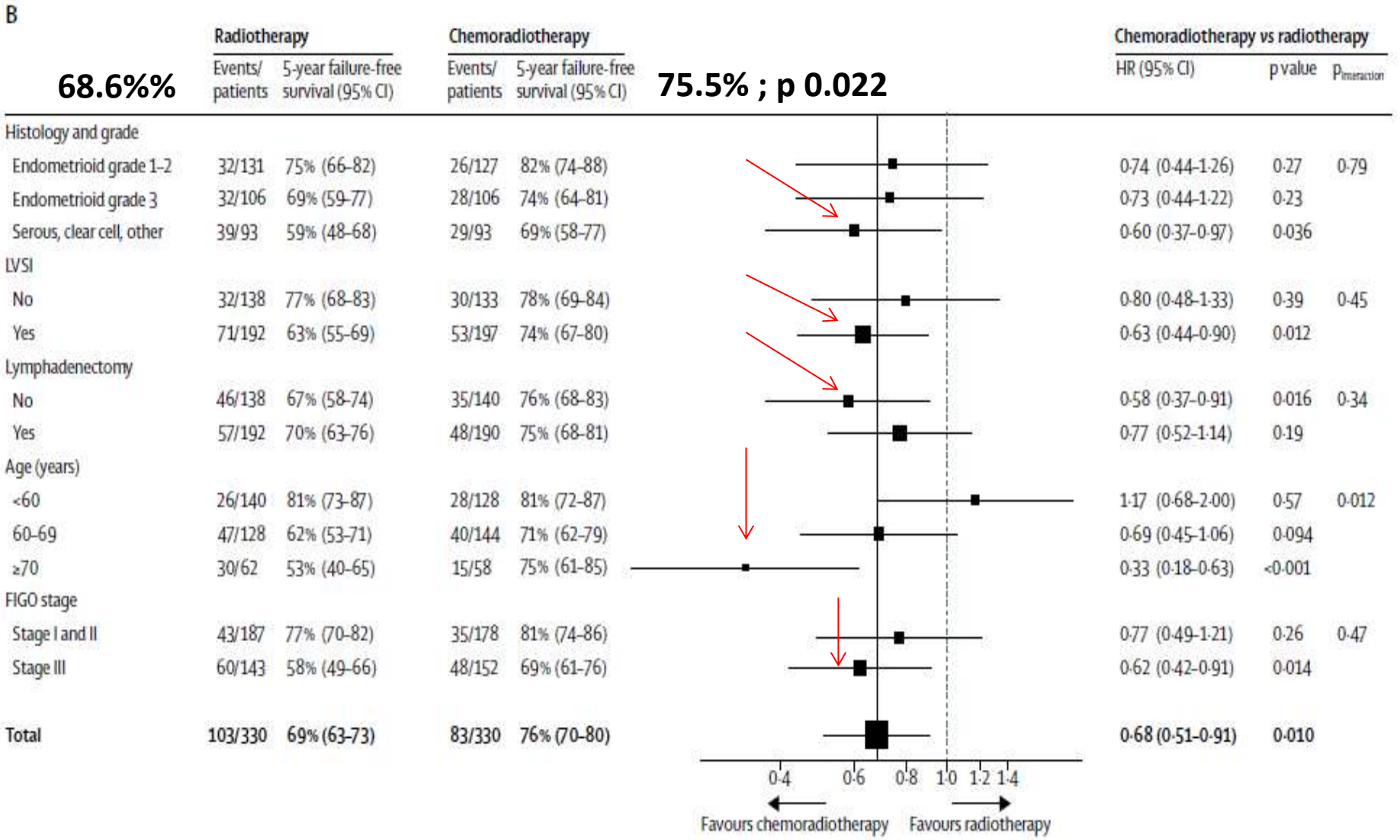
82%; p 0.075

A	Radiotherapy		Chemoradiotherapy		Chemoradiotherapy vs radiotherapy		
	Events/ patients	5-year overall survival (95% CI)	Events/ patients	5-year overall survival (95% CI)	HR (95% CI)	p value	$p_{interaction}$
Histology and grade							
Endometrioid grade 1–2	21/131	84% (78–91)	15/127	88% (82–94)	0·73 (0·37–1·42)	0·35	0·93
Endometrioid grade 3	23/106	77% (69–86)	22/107	80% (73–89)	0·81 (0·45–1·47)	0·49	
Serous, clear cell, other	31/93	66% (56–76)	24/96	76% (68–85)	0·69 (0·41–1·19)	0·19	
LVSI							
No	25/138	82% (76–89)	18/133	88% (82–94)	0·60 (0·32–1·13)	0·11	0·50
Yes	50/192	73% (67–80)	43/197	77% (71–84)	0·78 (0·52–1·18)	0·25	
Lymphadenectomy							
No	33/138	75% (67–83)	28/140	78% (71–86)	0·68 (0·41–1·14)	0·15	0·78
Yes	42/192	78% (72–85)	33/190	84% (79–90)	0·76 (0·48–1·20)	0·24	
Age (years)							
<60	16/140	89% (83–94)	15/128	89% (84–95)	1·02 (0·50–2·08)	0·96	0·059
60–69	33/128	72% (64–81)	33/144	78% (71–85)	0·93 (0·57–1·52)	0·77	
≥70	26/62	58% (47–72)	13/58	76% (65–89)	0·37 (0·19–0·74)	0·004	
FIGO stage							
Stage I and II	32/187	82% (76–88)	27/178	84% (79–90)	0·79 (0·47–1·33)	0·38	0·61
Stage III	43/143	70% (62–78)	34/152	79% (72–86)	0·66 (0·42–1·04)	0·074	
Total	**75/330**	**77% (72–82)**	**61/330**	**82% (78–86)**	**0·73 (0·52–1·03)**	**0·075**	



PORTEC 3

Forest plot of multivariable analysis for failure- free survival



PORTEC-3 Trial

GRADE 3 Toxicity: radiotherapy alone events 12%

chemotherapy + radiotherapy 60% (p <0.001)

Linee guida

NEOPLASIE DELL'UTERO: ENDOMETRIO E CERVICE

2018

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Bassa	*In caso di malattia ad alto rischio di metastasi la chemioterapia puòessere considerata in associazione con la radioterapia.* ** La valutazione complessiva della qualità delle evidenze ad oggi disponibili circa "l'efficacia della chemioterapia in associazione con la radioterapia in pazienti ad alto rischio di recidiva", la valutazione del rapporto tra i benefici ed i rischi correlati e la formulazione della raccomandazione relativa al quesito posto, sono state analizzate secondo metodologia GRADE (vedere capitolo 15).*	**Positiva debole**

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	La chemioterapia può essere presa in considerazione in aggiunta alla radioterapia nelle pazienti ad alto rischio riducendo il rischio di recidiva pur non essendo in grado di migliorare la sopravvivenza complessiva. Le pazienti dovrebbero essere informate sulla non conclusività delle evidenze (5-8)	**Positiva debole**

LA CHEMIOIPERTERMIA I.P. NEL TRATTAMENTO DEL CA. OVARICO

ULTERIORE OPZIONE PER LA CHIRURGIA SECONDARIA

- LA CHEMIOIPERTERMIA I.P. HA UNO SPAZIO TERAPEUTICO IN PZ. CON RECIDIVA PLATINO SENSIBILE IN COMBINAZIONE CON

CHIRURGIA CITORIDUTTIVA OTTIMALE
(livello II di evidenza)

(1° italian consensus conference on HIPEC, 2015)

Educazionale AIOM 2017

OVARIAN
& GYNECOLOGIC CANCER UNIT

The NEW ENGLAND JOURNAL of MEDICINE

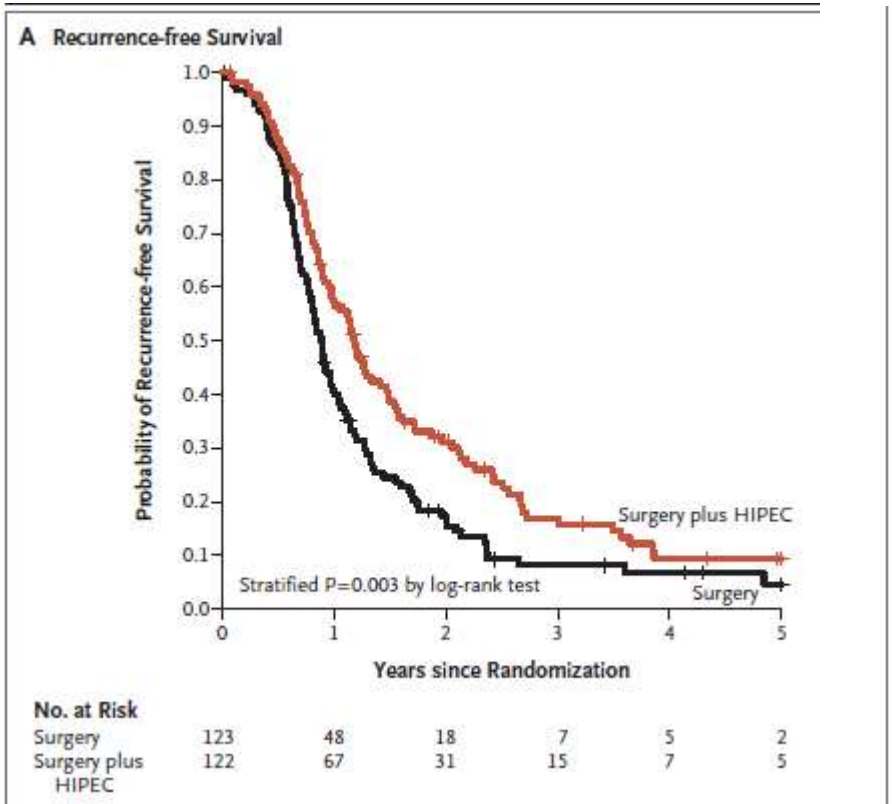
ORIGINAL ARTICLE

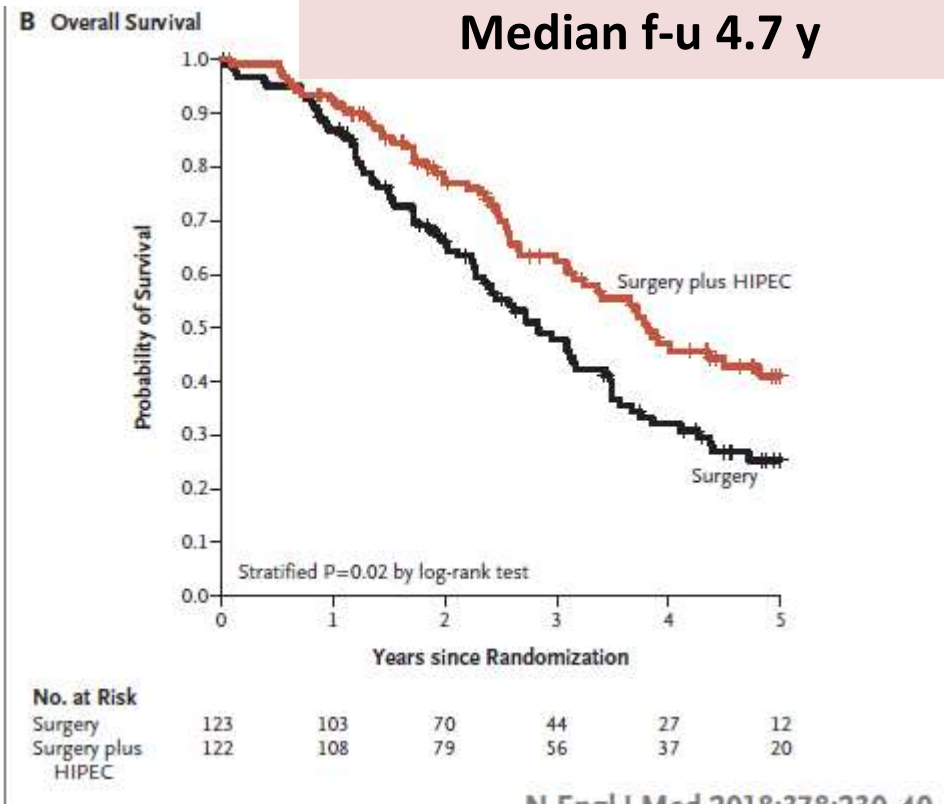
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.J.T. de Hingh, J. van der Velden, H.J. Arts, L.F.A.G. Massuger, A.G.J. Aalbers, V.J. Verwaal, J.M. Kieffer, K.K. Van de Vijver, H. van Tinteren, N.K. Aaronson, and G.S. Sonke

245 pts randomized (2007-2016)
All hystologies
HIPEC arm:
CBDCA+Taxol q 21 x3 cycles before surgery +HIPEC (DDP 100 mg/m2 IP followed by CBDCA+Taxol q 21 x3 cycles

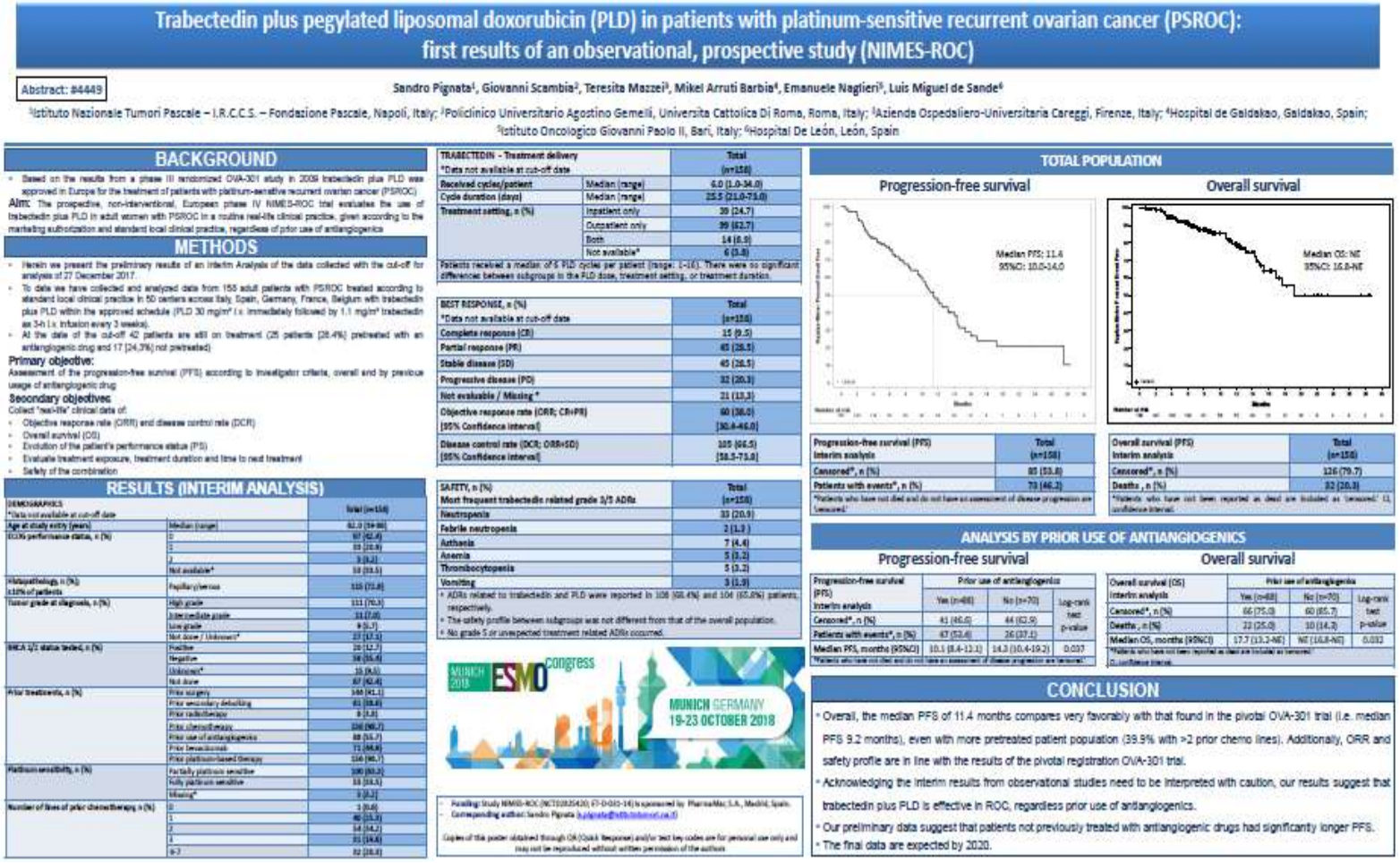
Median f-u 4.7 y





N Engl J Med 2018;378:230-40.

Trabectedin plus PLD in patients with platinum-sensitive recurrent ovarian cancer (PSROC): first results of an observational, prospective study (NIMES-ROC)



Trabectedin plus pegylated liposomal doxorubicin (PLD) in patients with platinum-sensitive recurrent ovarian cancer (PSROC): first results of an observational, prospective study (NIMES-ROC)

Abstract: #4449

Sandro Pignata[1], Giovanni Scambia[2], Teresita Mazzei[3], Mikel Arruti Barbia[4], Emanuele Naglieri[5], Luis Miguel de Sande[6]

[1]Istituto Nazionale Tumori Pascale – I.R.C.C.S. – Fondazione Pascale, Napoli, Italy; [2]Policlinico Universitario Agostino Gemelli, Universita Cattolica Di Roma, Roma, Italy; [3]Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy; [4]Hospital de Galdakao, Galdakao, Spain; [5]Istituto Oncologico Giovanni Paolo II, Bari, Italy; [6]Hospital De León, León, Spain

BACKGROUND

- Based on the results from a phase III randomized OVA-301 study in 2009 trabectedin plus PLD was approved in Europe for the treatment of patients with platinum-sensitive recurrent ovarian cancer (PSROC)

Aim: The prospective, non-interventional, European phase IV NIMES-ROC trial evaluates the use of trabectedin plus PLD in adult women with PSROC in a routine real-life clinical practice, given according to the marketing authorization and standard local clinical practice, regardless of prior use of antiangiogenics

METHODS

- Herein we present the preliminary results of an interim Analysis of the data collected with the cut-off for analyses of 27 December 2017
- To date we have collected and analyzed data from 158 adult patients with PSROC treated according to standard local clinical practice in 50 centers across Italy, Spain, Germany, France, Belgium with trabectedin plus PLD within the approved schedule (PLD 30 mg/m² i.v. immediately followed by 1.1 mg/m² trabectedin as 3-h i.v. infusion every 3 weeks).
- At the date of the cut-off 42 patients are still on treatment (25 patients [28.4%] pretreated with an antiangiogenic drug and 17 [24.3%] not pretreated)

Primary objective:
Assessment of the progression-free survival (PFS) according to investigator criteria, overall and by previous usage of antiangiogenic drug

Secondary objectives:
Collect "real-life" clinical data of:

- Objective response rate (ORR) and disease control rate (DCR)
- Overall survival (OS)
- Evolution of the patient's performance status (PS)
- Evaluate treatment exposure, treatment duration and time to next treatment
- Safety of the combination

RESULTS (INTERIM ANALYSIS)

DEMOGRAPHICS *Data not available at cut-off date		Total (n=158)
Age at study entry (years)	Median (range)	61.0 (34-86)
ECOG performance status, n (%)	0	97 (62.4)
	1	33 (21.9)
	2	3 (1.9)
	Not available*	19 (12.1)
Histopathology, n (%); ≥10% of patients	Papillary/serous	115 (72.8)
Tumor grade at diagnosis, n (%)	High grade	111 (70.3)
	Intermediate grade	11 (7.0)
	Low grade	9 (5.7)
	Not done / Unknown*	27 (17.1)
BRCA 1/2 status tested, n (%)	Positive	20 (12.7)
	Negative	58 (36.4)
	Unknown*	15 (9.5)
	Not done	67 (42.4)
Prior treatments, n (%)	Prior surgery	148 (93.7)
	Prior secondary debulking	81 (51.3)
	Prior radiotherapy	9 (5.7)
	Prior chemotherapy	158 (100.0)
	Prior use of antiangiogenics	88 (55.7)
	Prior bevacizumab	71 (44.9)
	Prior platinum-based therapy	158 (100.0)
Platinum sensitivity, n (%)	Partially platinum sensitive	100 (63.3)
	Fully platinum sensitive	53 (33.5)
	Missing*	5 (3.2)
Number of lines of prior chemotherapy, n (%)	0	1 (0.6)
	1	46 (29.1)
	2	54 (34.2)
	3	31 (19.6)
	≥3	26 (16.5)

TRABECTEDIN – Treatment delivery *Data not available at cut-off date		Total (n=158)
Received cycles/patient	Median (range)	6.0 (1.0-34.0)
Cycle duration (days)	Median (range)	25.5 (21.0-73.0)
Treatment setting, n (%)	Inpatient only	39 (24.7)
	Outpatient only	99 (62.7)
	Both	14 (8.9)
	Not available*	6 (3.8)

Patients received a median of 6 PLD cycles per patient (range: 1-16). There were no significant differences between subgroups in the PLD dose, treatment setting, or treatment duration

BEST RESPONSE, n (%) *Data not available at cut-off date	Total (n=158)
Complete response (CR)	15 (9.5)
Partial response (PR)	45 (28.5)
Stable disease (SD)	45 (28.5)
Progressive disease (PD)	32 (20.3)
Not evaluable / Missing *	21 (13.3)
Objective response rate (ORR; CR+PR) [95% Confidence interval]	60 (38.0) [30.4-46.0]
Disease control rate (DCR; ORR+SD) [95% Confidence interval]	105 (66.5) [58.5-73.8]

SAFETY, n (%) Most frequent trabectedin related grade 3/5 ADRs	Total (n=158)
Neutropenia	33 (20.9)
Febrile neutropenia	2 (1.3)
Asthenia	7 (4.4)
Anemia	5 (3.2)
Thrombocytopenia	5 (3.2)
Vomiting	3 (1.9)

- ADRs related to trabectedin and PLD were reported in 108 (68.4%) and 104 (65.8%) patients, respectively.
- The safety profile between subgroups was not different from that of the overall population.
- No grade 5 or unexpected treatment related ADRs occurred.

Funding: Study NIMES-ROC (NCT02825420; 47-D-010-14) is sponsored by PharmaMar, S.A., Madrid, Spain.

Corresponding author: Sandro Pignata (s.pignata@tiscali.net)

TOTAL POPULATION

Progression-free survival

Overall survival

Progression-free survival (PFS) Interim analysis	Total (n=158)
Censored*, n (%)	85 (53.8)
Patients with events*, n (%)	73 (46.2)

*Patients who have not died and do not have an assessment of disease progression are censored.

Overall survival (PFS) Interim analysis	Total (n=158)
Censored*, n (%)	126 (79.7)
Deaths , n (%)	32 (20.3)

*Patients who have not been reported as dead are included as 'censored'. CI, confidence interval.

ANALYSIS BY PRIOR USE OF ANTIANGIOGENICS

Progression-free survival

Progression-free survival (PFS) Interim analysis	Prior use of antiangiogenics: Yes (n=88)	No (n=70)	Log-rank test p-value
Censored*, n (%)	41 (46.6)	44 (62.9)	
Patients with events*, n (%)	47 (53.4)	26 (37.1)	
Median PFS, months (95%CI)	10.1 (8.4-12.1)	14.3 (10.4-19.2)	0.037

*Patients who have not died and do not have an assessment of disease progression are censored.

Overall survival

Overall survival (OS) Interim analysis	Prior use of antiangiogenics: Yes (n=88)	No (n=70)	Log-rank test p-value
Censored*, n (%)	66 (75.0)	60 (85.7)	
Deaths , n (%)	22 (25.0)	10 (14.3)	
Median OS, months (95%CI)	17.7 (13.2-NE)	NE (16.8-NE)	0.032

*Patients who have not been reported as dead are included as censored.
CI, confidence interval.

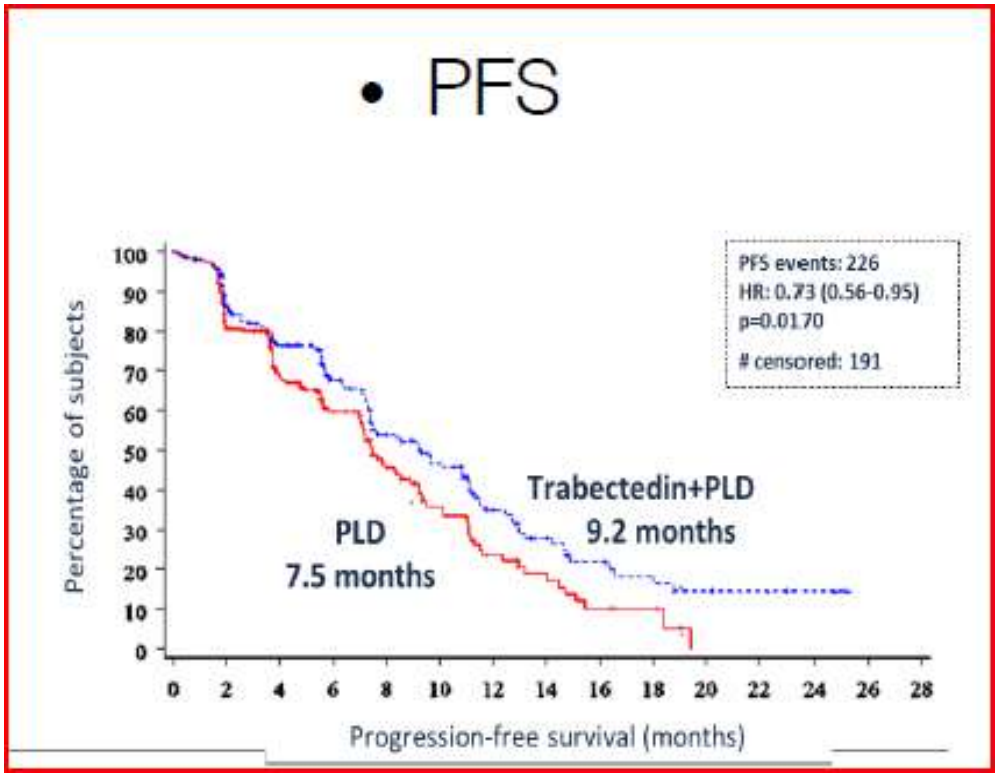
CONCLUSION

- Overall, the median PFS of 11.4 months compares very favorably with that found in the pivotal OVA-301 trial (i.e. median PFS 9.2 months), even with more pretreated patient population (39.9% with >2 prior chemo lines). Additionally, ORR and safety profile are in line with the results of the pivotal registration OVA-301 trial.
- Acknowledging the interim results from observational studies need to be interpreted with caution, our results suggest that trabectedin plus PLD is effective in ROC, regardless prior use of antiangiogenics.
- Our preliminary data suggest that patients not previously treated with antiangiogenic drugs had significantly longer PFS.
- The final data are expected by 2020.

Pignata et al. ESMO 2018 Absract #4449Trabectedin plus PLD in patients with platinum-sensitive recurrent ovarian cancer (PSROC): first results of an observational, prospective study (NIMES-ROC)

OVA 301 : trabectedine+PLD vs PLD in platinum sensitive ROC.

Monk B, Eur J Cancer 2012

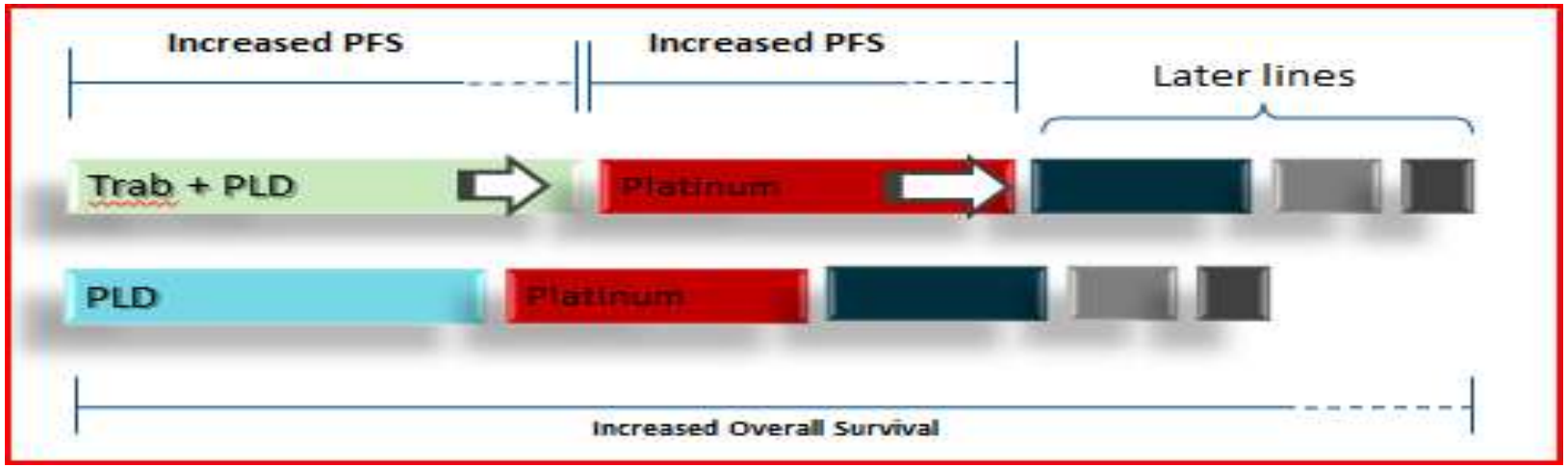


Prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients: the MITO 15 trial

D. Lorusso[1], G. Scambia[2], S. Pignata[3], R. Sorio[4], G. Arnaldi[5], S. Lapori[6], A. Mosconi[7], C. Pisano[8], G. Mangili[9], G. Mattioni[10], P. Sabbatini[11], G. Arnolfi[12], T. Gamucci[13], M. Di Napoli[14], E. Capobianco[15], V. Ludovini[16], F. Raspagliesi[1] & G. Ferrandina[2]

Response to trabectedin according to BRCA mutational status

BRCA 1-2	N.	ORR (CR+PR)
WT	48	19 (39.6%)
MUT	21	12 (57.1%)



Effectivenes of Chemotherapy + antiangiogenetics at 1st relapse of OC

Armbruster S, Hematol/Oncol Clin North Am 2018

Table 1
Phase III trials of cytotoxic chemotherapy in patients with platinum-sensitive recurrent disease

Trial	Treatment	RR (%)	PFS (mo)	HR	OS (mo)	HR
ICON 4[5]	Platinum	54	9	0.76 ($P < .001$)	24	0.82 ($P = .023$)
	Platinum and paclitaxel	66	12		29	
AGO[6]	Carboplatin	31	5.8	0.72 ($P = .003$)	17.3	0.96 ($P = .73$)
	Gemcitabine and carboplatin	47	8.6		18	
CALYPSO	Carboplatin and Paclitaxel	–	9.4	0.82 ($P = .005$)	33.0	0.99 ($P = .94$)
	Carboplatin and PLD	–	11.3		30.7	
OVA-301	PLD	33	7.5	0.73 ($P = .017$)	24.1	0.83 ($P = .11$)
	PLD and Trabectedin	42	9.2		27.0	

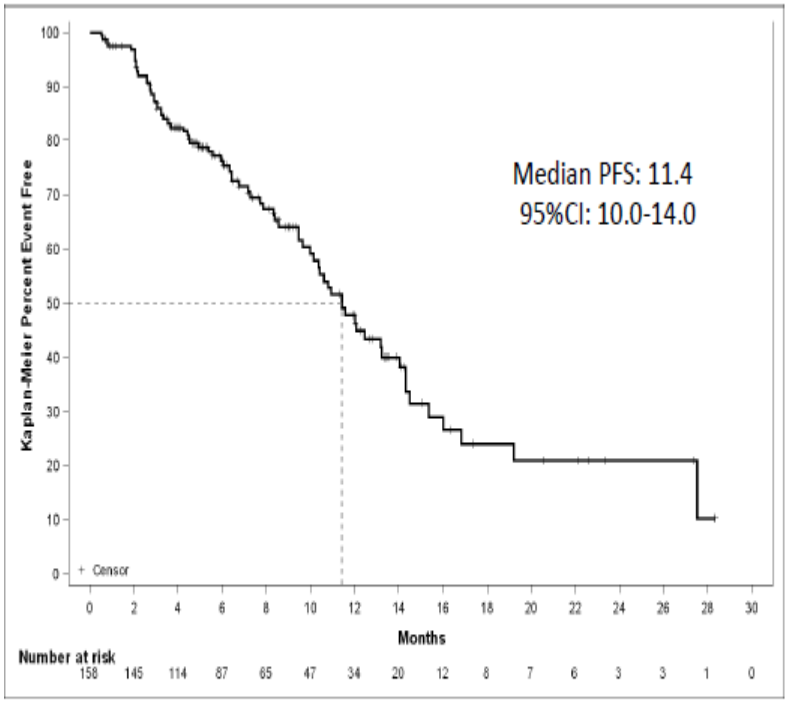
Table 3
Phase III trials of antiangiogenic agents in women with recurrent epithelial ovarian cancer

Trial	Treatment	Population	RR (%)	PFS (mo)	HR	OS	HR (mo)	US FDA Approval
OCEANS[20,21]	Gemcitabine and carboplatin	Platinum sensitive	57	8.4	0.48 ($P < .001$)	33.7	0.96 ($P = .73$)	Yes
	Gemcitabine, carboplatin, bevacizumab		79	12.4		33.4		
GOG 213[22]	Paclitaxel, carboplatin	Platinum sensitive	59	10.4	0.61 ($P < .001$)	37.3	0.82 ($P = .056$)	Yes
	Paclitaxel, carboplatin, bevacizumab		79	13.8		42.2		
ICON 6[23,24]	Paclitaxel, carboplatin (A)	Platinum sensitive	—	8.7	A vs C: 0.57 ($P < .001$)	19.9	A vs C: 0.85 ($P = .21$)[a]	No
	Paclitaxel, carboplatin, cediranib (B)		—	9.9		—		
	Paclitaxel, carboplatin, cediranib (maintenance) (C)		—	11.1		27.3		
TRINOVA-1[19,35]	Paclitaxel weekly	Platinum sensitive,	—	5.4	0.66 ($P < .001$)	18.3	0.95 ($P = .52$)	No
	Paclitaxel weekly, trebananib	platinum resistant	—	7.2		19.3		

Trabectedin plus PLD in patients with PSROC: first results of an observational, prospective study (NIMES-ROC)

TOTAL POPULATION

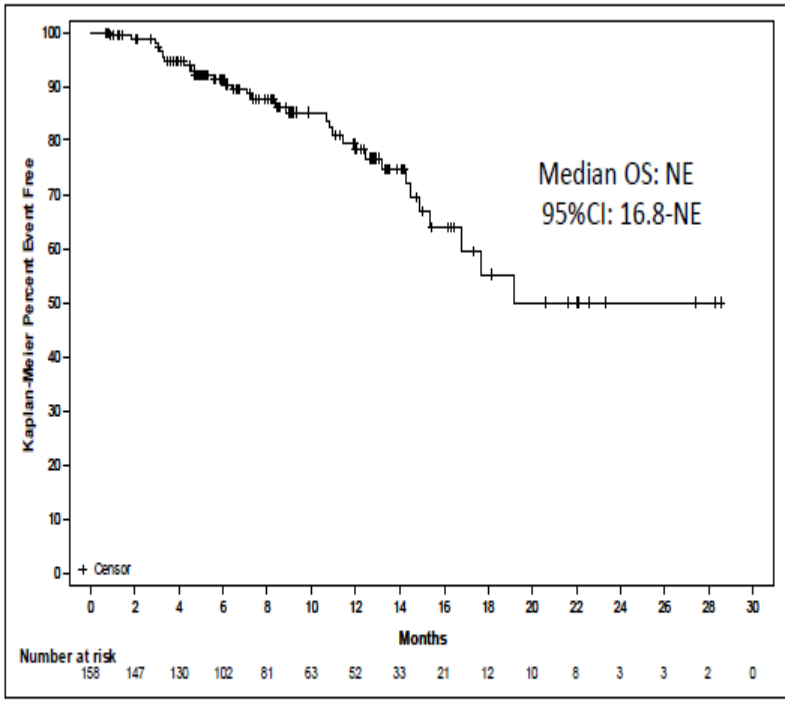
Progression-free survival



Progression-free survival (PFS) Interim analysis	Total (n=158)
Censored*, n (%)	85 (53.8)
Patients with events*, n (%)	73 (46.2)

*Patients who have not died and do not have an assessment of disease progression are 'censored.'

Overall survival



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Deaths , n (%)	32 (20.3)

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Pignata et al. ESMO 2018 Absract #4449Trabectedin plus PLD in patients with platinum-sensitive recurrent ovarian cancer (PSROC): first results of an observational, prospective study (NIMES-ROC)

Trabectedin plus PLD in patients with PSROC: first results of an observational, prospective study (NIMES-ROC)

ANALYSIS BY PRIOR USE OF ANTIANGIOGENICS

Progression-free survival

Progression-free survival (PFS) Interim analysis	Prior use of antiangiogenics		
	Yes (n=88)	No (n=70)	Log-rank test p-value
Censored*, n (%)	41 (46.6)	44 (62.9)	
Patients with events*, n (%)	47 (53.4)	26 (37.1)	
Median PFS, months (95%CI)	10.1 (8.4-12.1)	14.3 (10.4-19.2)	0.037

*Patients who have not died and do not have an assessment of disease progression are 'censored.'

Overall survival

Overall survival (OS) Interim analysis	Prior use of antiangiogenics		
	Yes (n=88)	No (n=70)	Log-rank test p-value
Censored*, n (%)	66 (75.0)	60 (85.7)	
Deaths , n (%)	22 (25.0)	10 (14.3)	
Median OS, months (95%CI)	17.7 (13.2-NE)	NE (16.8-NE)	0.032

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CONCLUSION

- Overall, the median PFS of 11.4 months compares very favorably with that found in the pivotal OVA-301 trial (i.e. median PFS 9.2 months), even with more pretreated patient population (39.9% with >2 prior chemo lines). Additionally, ORR and safety profile are in line with the results of the pivotal registration OVA-301 trial.
- Acknowledging the interim results from observational studies need to be interpreted with caution, our results suggest that trabectedin plus PLD is effective in ROC, regardless prior use of antiangiogenics.
- Our preliminary data suggest that patients not previously treated with antiangiogenic drugs had significantly longer PFS.
- The final data are expected by 2020.

Pignata et al. ESMO 2018 Absract #4449Trabectedin plus PLD in patients with platinum-sensitive recurrent ovarian cancer (PSROC): first results of an observational, prospective study (NIMES-ROC)

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ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

Figure S6. Stage Distribution (%) for Ovarian Cancer by Histology, US, 2007-2013

SOPRAVVIVENZA a 5 anni per carcinoma OVAIO in EUROPA

Paese	1991–1993	2000–2003
FINLANDIA	30.9	43.4
GERMANIA	37.4	39
POLONIA	26.7	38.1
GRAN BRETAGNA	29.4	30
ITALIA	31.9	37.2
media europea	32.4	36.3

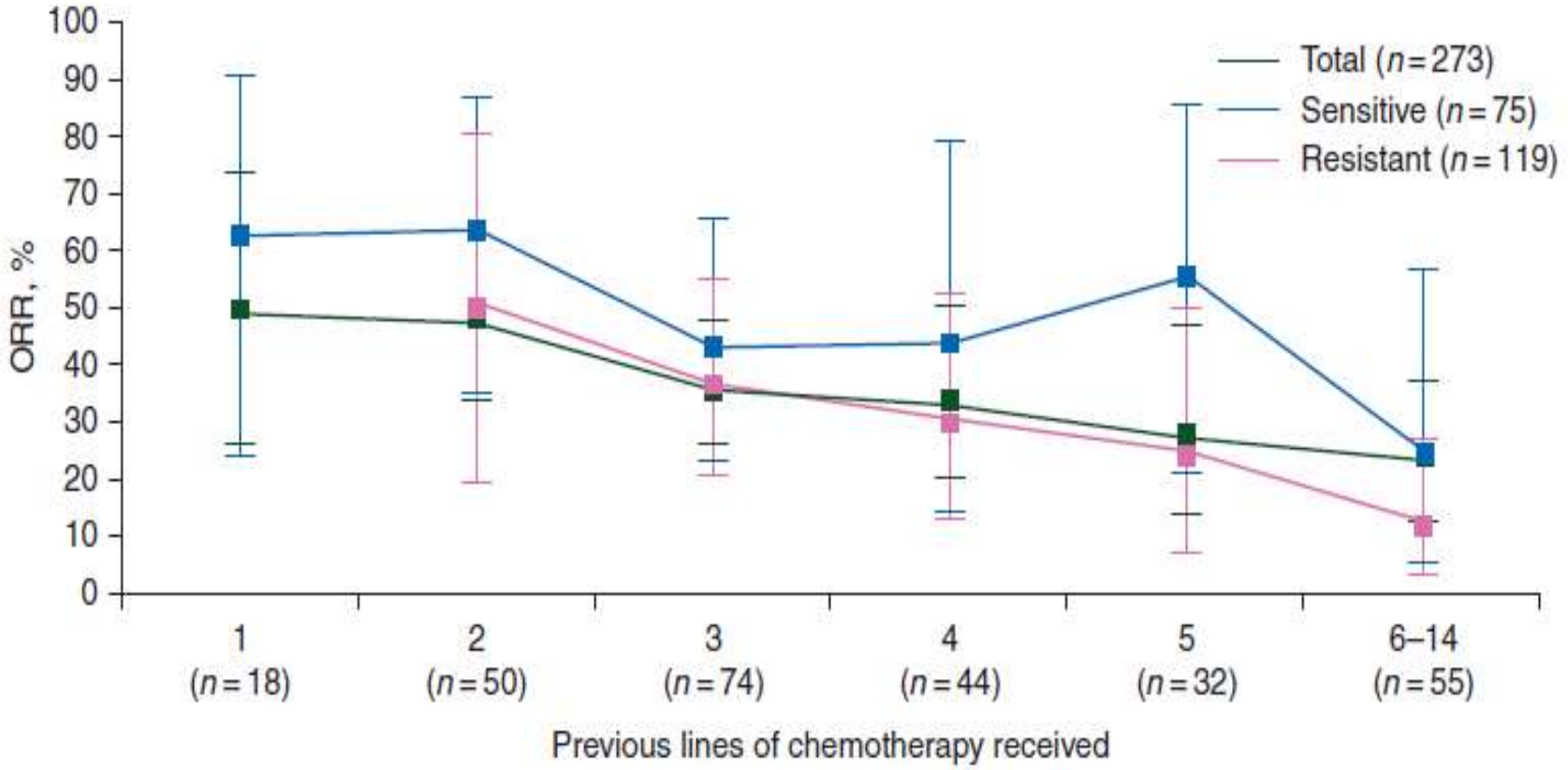
(Eurocare database 2017)

OVARIAN
& GYNECOLOGIC CANCER UNIT

Source: Howlader N, Noone AM, Krapcho M, et al. (eds). *SEER Cancer Statistics Review 1975-2014*, National Cancer Institute, Bethesda, MD, www.seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER website April 2017 (all ovarian cancers); SEER 18 Registries, National Cancer Institute, 2017 (subtypes).

Clinical response as a continuum in ROC

Ritardare la progressione!



Matulonis , Ann Oncol 2016

Study design

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

391 pts

Olaparib 300 mg bd (N=260)

2:1 randomization

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease.
BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TOI, Trial Outcome Index

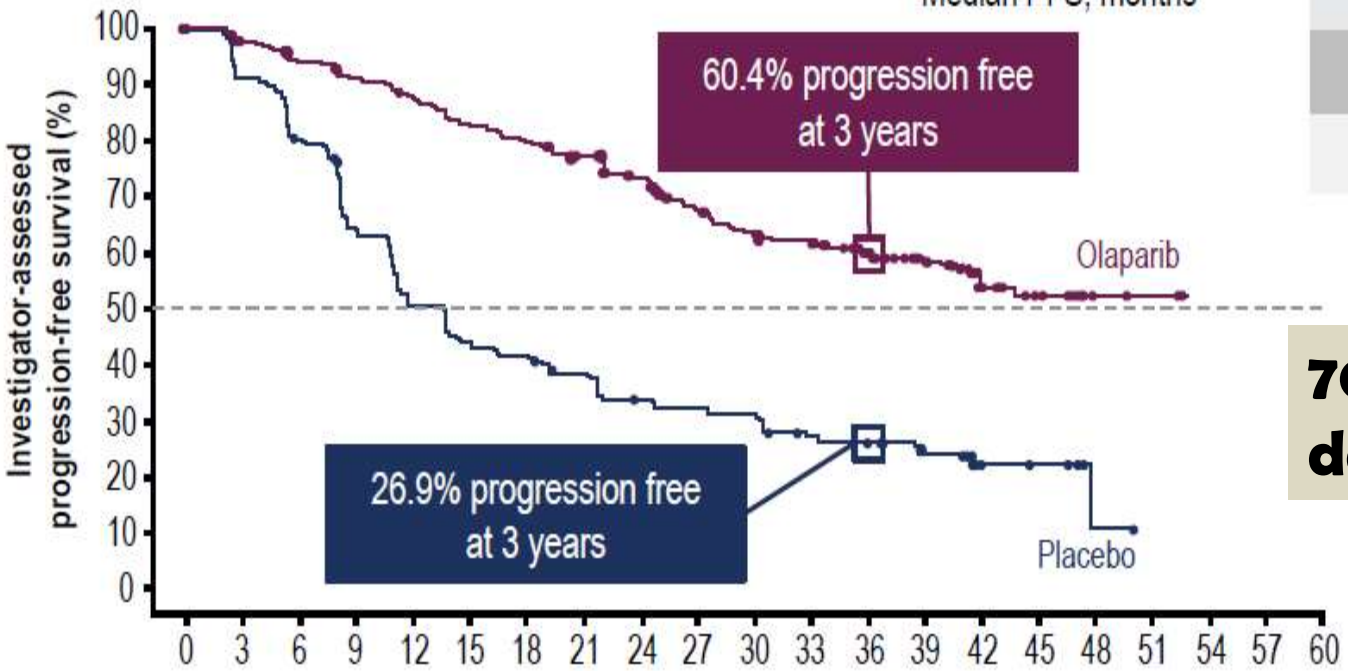
Patient disposition

	Olaparib	Placebo
Randomized, n	260	131
Treated, n	260	130
Discontinued treatment before 2 years	111 (42.7)	92 (70.8)
Completed treatment at 2 years per protocol	123 (47.3)	35 (26.9)
Continued treatment beyond 2 years	26 (10.0)	3 (2.3)
Still receiving treatment at data cut-off	13 (5.0)	1 (0.8)
Discontinued treatment for reason other than protocol-defined 2-year stopping rule	124 (47.7)	94 (72.3)
Objective disease progression	51 (19.6)	78 (60.0)
Adverse event	30 (11.5)	3 (2.3)
Patient decision	22 (8.5)	2 (1.5)
Other*/unknown reason	21 (8.1)	11 (8.5)
Median (range) duration of treatment, months	24.6 (0–52.0)	13.9 (0.2–45.6)
Median (IQR) duration of follow-up, months	40.7 (34.9–42.9)	41.2 (32.2–41.6)

*Other includes study-specific discontinuation criteria, severe non-compliance to protocol and lost to follow-up, among other reasons. IQR, interquartile range

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

70% di riduzione del rischio di PD

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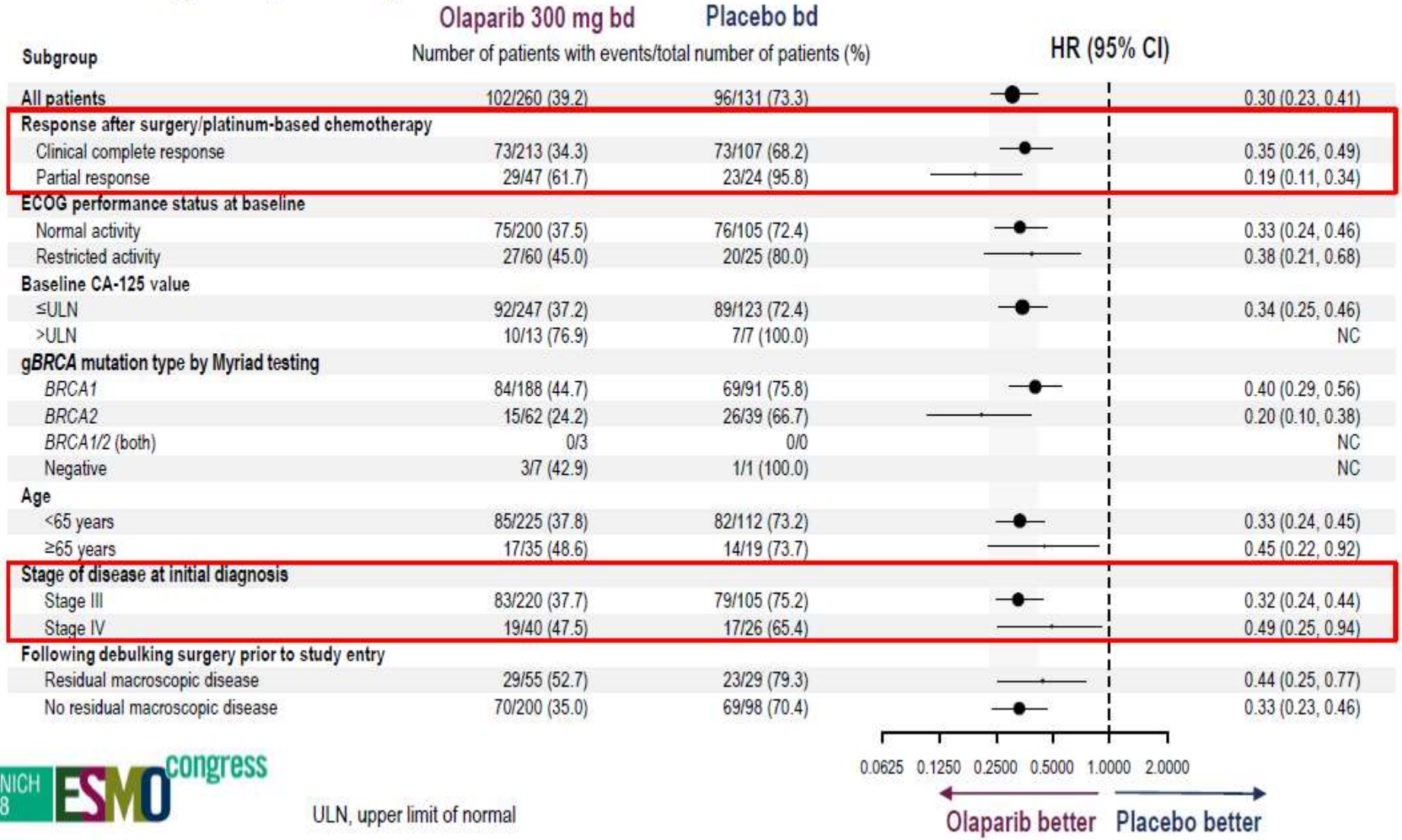
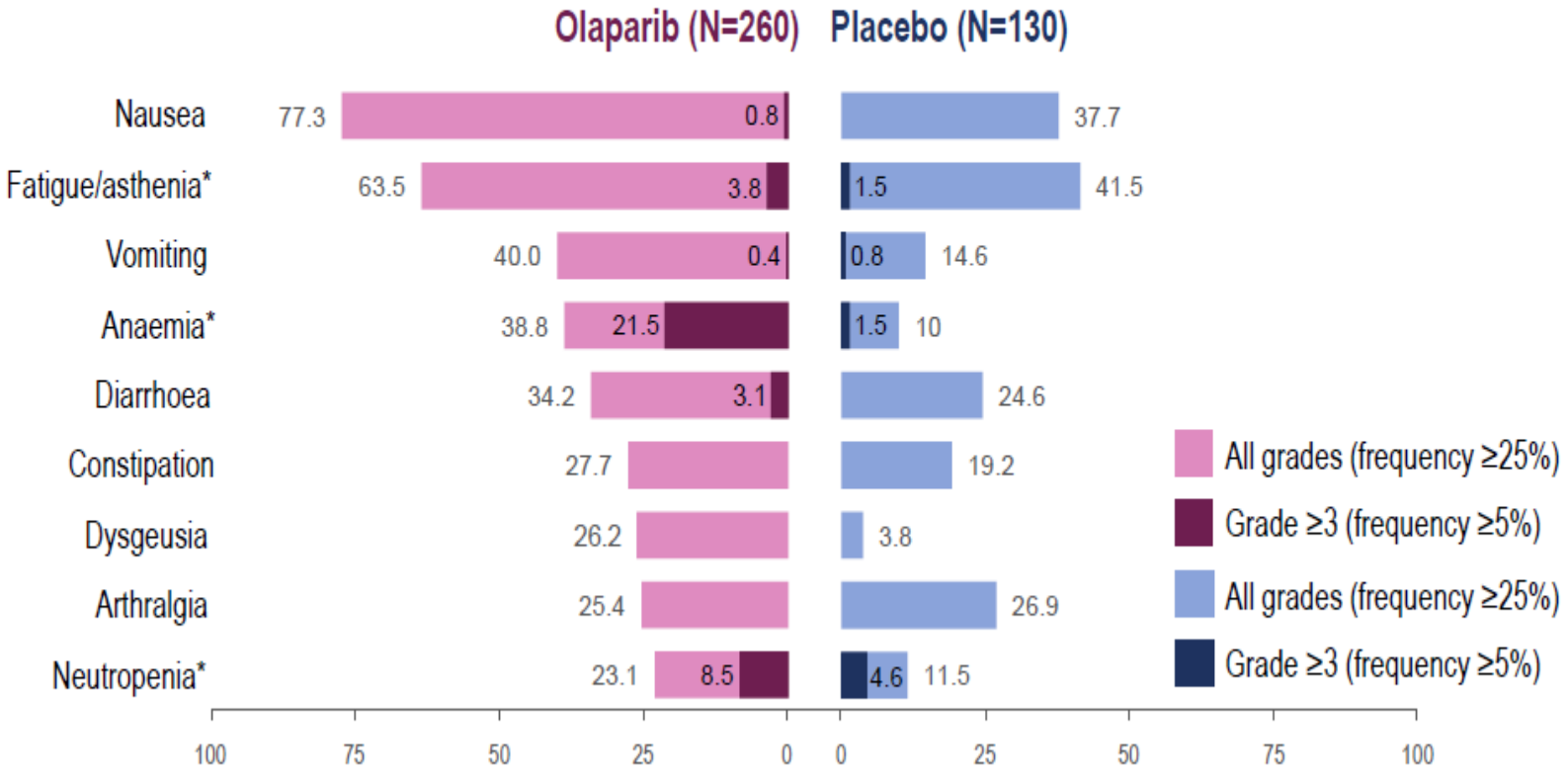
CI, confidence interval; NR, not reached

PFS subgroup analysis



ULN, upper limit of normal

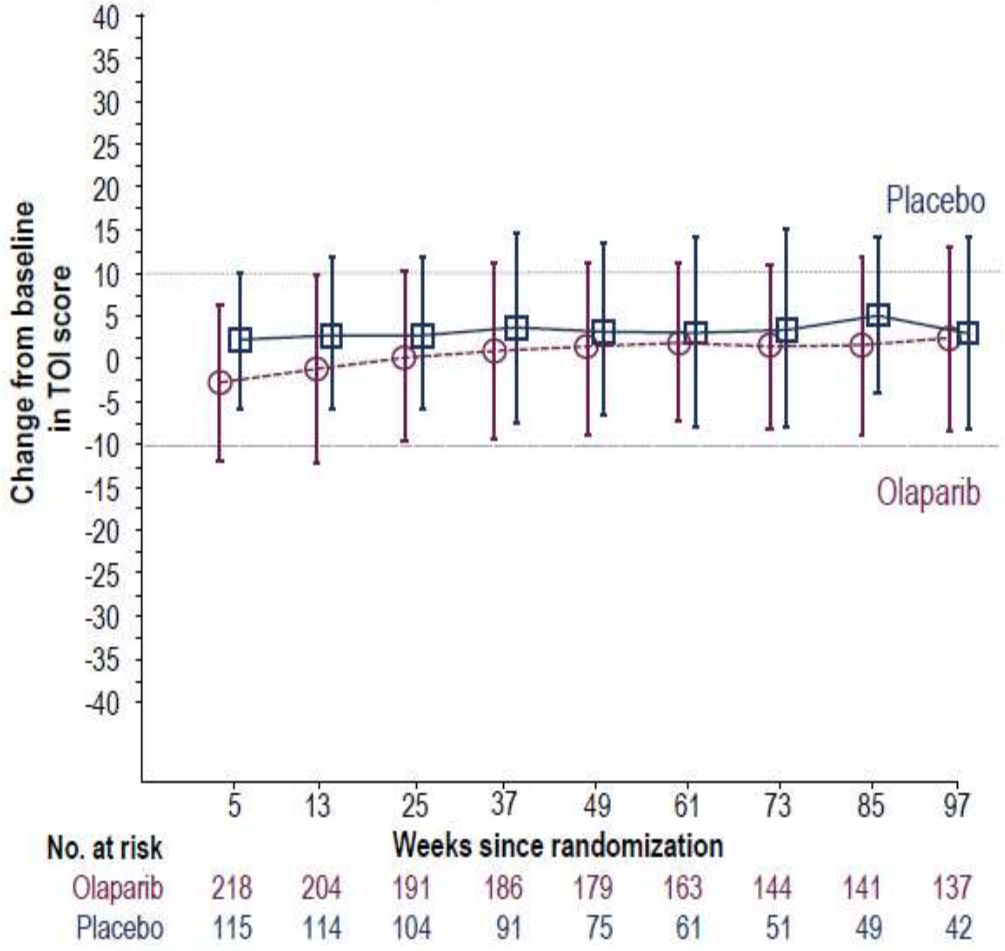
Most common treatment-emergent adverse events



Adverse events of special interest

	Olaparib (N=260)	Placebo (N=130)
MDS/AML,* n (%)	3 (1.2)	0
New primary malignancies,† n (%)	5 (1.9)	3 (2.3)
Pneumonitis/ILD, n (%)	5 (1.9)	0

Health-related quality of life: FACT-O TOI score*



The difference between olaparib and placebo in the mean change from baseline in TOI score over 24 months (−3.00; 95% CI −4.779, −1.216) was not clinically meaningful

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*TOI scores range from 0 to 100, with higher scores indicating better HRQoL and a clinically meaningful difference defined as ±10 points

Conclusions

- Maintenance olaparib led to a substantial, unprecedented improvement in PFS in patients with newly diagnosed, advanced ovarian cancer and a *BRCA*m, with a difference in median PFS for olaparib versus placebo of approximately 3 years
  - There was no obvious change in Kaplan-Meier curves after 2 years in the olaparib group, indicating an apparent enduring treatment benefit after stopping treatment
- There was a statistically significant improvement in PFS2, suggesting that olaparib did not diminish patients' ability to benefit from subsequent therapy
- Olaparib was generally well tolerated, with a safety profile consistent with that observed in the relapsed disease setting
- Maintenance olaparib should be considered standard treatment following platinum-based chemotherapy for women with newly diagnosed, advanced ovarian cancer and a *BRCA*m