INOVATYON study

INternational OVArian cancer patients Trial with YONdelis

Randomized phase III international study comparing trabectedin/PLD followed by platinum at progression vs Carboplatin/PLD in patients with recurrent ovarian cancer progressing within 6-12 months after last platinum line.

Sponsor: MaNGO

Supporter: PharmaMar

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N. Colombo[1], A. Gadducci[2], J. Sehouli[3], E. Biagioli[4], G.-B. Nyvang[5], S. Riniker[6], A. Montes[7], N. Ottevanger[8], A. G. Zeimet[9], I. Vergote[10], G. Funari[4], A. Baldoni[11], G. Tognon[12], A. De Censi[13], C. Churruca Galaz[14], R. Chekerov[3], J. Maenpaa[15], E. Rulli[4], R. Fossati[4], A. Poveda[16]

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Abstract #2694

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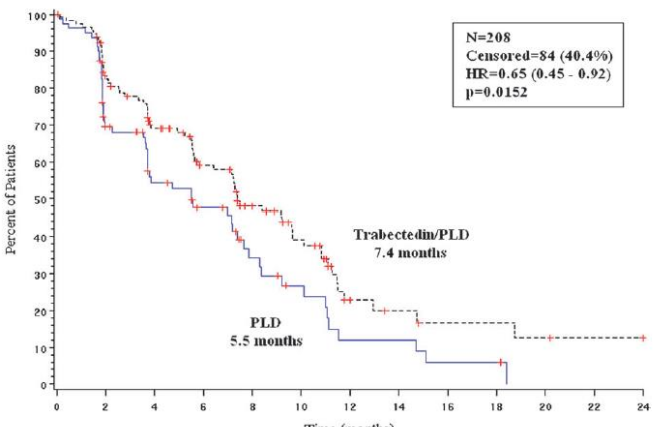
Clinical Background

- Pegylated liposomal doxorubicin (PLD) and carboplatin demonstrated an improved progression-free survival compared to carboplatin/paclitaxel therapy (HR: 0.73; 95% CI:0,58-0.90; p value 0.004) in patients with recurrent ovarian cancer (ROC) and 6-12 months (mos) platinum-free interval (TFIp) (CALYPSO trial)[1] and it is therefore considered the preferred treatment in this clinical setting
- A subgroup analysis of the OVA-301 trial in patients with TFIp between 6-12 mos showed that trabectedin/PLD was superior to PLD in terms of overall survival (OS) in particular in the subpopulation that received platinum as first subsequent line[2,3].

1.L. Gladieff et al. Annals of Oncology 23: 1185–1189, 2012
2.A. Poveda et al. Annals of Oncology 22: 39–48, 2011
3.S.B. Kaye et al. Annals of Oncology 22: 49–58, 2011

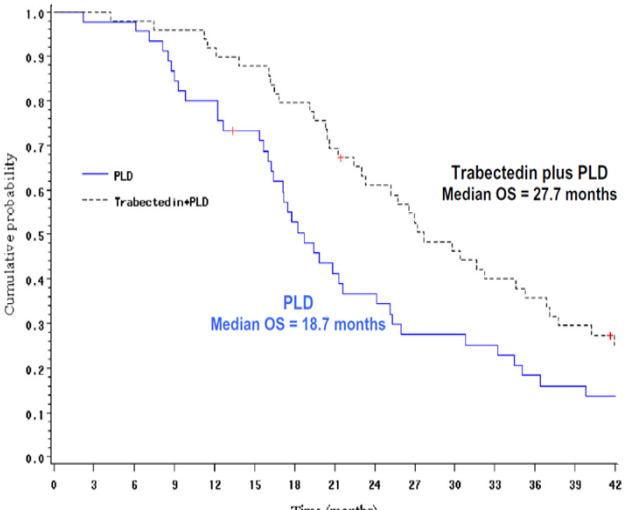
Subgroup of partially sensitive patients



Median OS: 17.2 mos for PLD; 21.0 mos for Trabe+PLD
HR:0.65 (95%CI 0.45- 0.92); p=0.0152

Poveda, Annals of Oncology 22: 39–48, 2011

Subgroup of PPS pts receiving platinum as subsequent



Median OS: 18.7 mos for PLD; 27.7 mos for Trabe+PLD
HR: 0.58 (95%CI 0.37-0.91); p=0.0153

Poveda, Cancer Treatment Reviews 40 (2014) 366–375

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A long story starting in the mid-90ies in the US

Carboplatin Reinduction After Taxane in Patients With Platinum-Refractory Epithelial Ovarian Cancer

By J. Kavanagh, D. Tresukosol, C. Edwards, R. Freedman, C. Gonzalez de Leon, A. Fishman, R. Mante, M. Hord, and A. Kudelka

J Clin Oncol 1995

Extending the Platinum-Free Interval in Recurrent Ovarian Cancer: The Role of Topotecan in Second-Line Chemotherapy

MICHAEL A. BOOKMAN

The Oncologist 1999

…promoted in the late 90ies

Retrospective review: re-treatment of patients with ovarian cancer with carboplatin after platinum resistance

H.T. SEE*, R.S. FREEDMAN†, A.P. KUDELKA*, T.W. BURKE†, D.M. GERSHENSON†, S. TANGJITGAMOL* & J.J. KAVANAGH*

*Departments of *Gynecologic Medical Oncology and †Gynecological Oncology, M.D. Anderson Cancer Center, Houston, Texas*

Int J Gynecol Cancer 2005

…amplified´in the 2000s

Extending platinum-free interval in partially platinum-sensitive recurrent ovarian cancer by a non-platinum regimen: Its possible clinical significance

Yin-Ting Chuang [a], Chih-Long Chang [a,b,*]

Taiwanese Journal of Obstetrics & Gynecology 51 (2012)

…and spread to the World thereafter

Trabectedin and its mechanism of action

- It has been demonstrated both in vitro and in vivo that cancer cell lines made resistant to trabectedin by prolonged drug exposure become more sensitive to ultraviolet light and to platinum compounds.
- the reason is that cells resistant to trabectedin often present defects of the mechanism of DNA repair named transcription-coupled Nucleotide Excision Repair

B. Colmegna et al. BJC (2015) 113, 1687–1693

- Trabectedin can induce the selection of cell clones that are hypersensitive to platinum compounds because of their NER deficiency.
- Therefore, trabectedin should enhance the subsequent antitumor activity of platinum treatment

Review Article

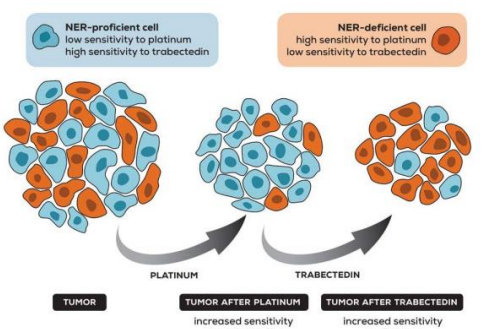

Figure 2. This is an illustration of the rationale for the sequential administration of trabectedin followed by platinum compounds. NER indicates nucleotide excision repair.

Tomao, Cancer September 15, 2017

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Study Objectives

The INOVATYON phase III trial aimed at demonstrating an improvement in OS for the sequential use of trabectedin/PLD (TP) followed, at progression, by platinum re-challenge, over carboplatin/PLD (CP).

Secondary objectives include the evaluation of:

1) progression free survival
2) progression free survival from subsequent therapy
3) treatment safety
4) quality of life (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) and the Quality of Life Questionnaire-OV28 (QLQ-OV28)

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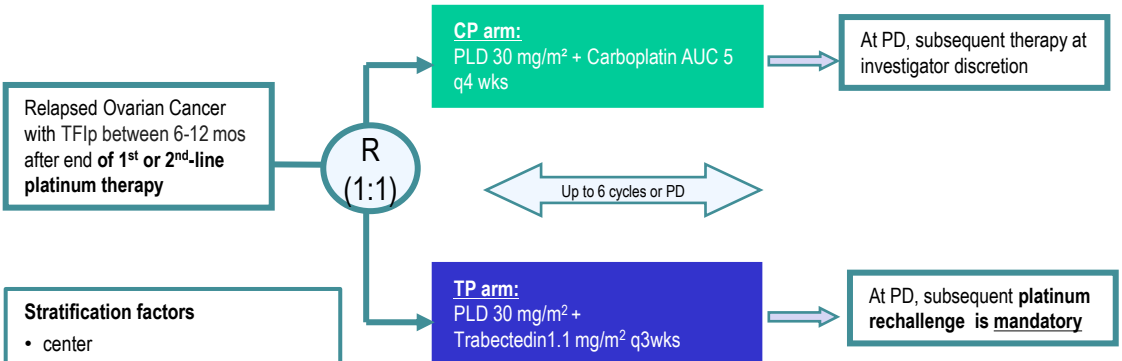
Study Design

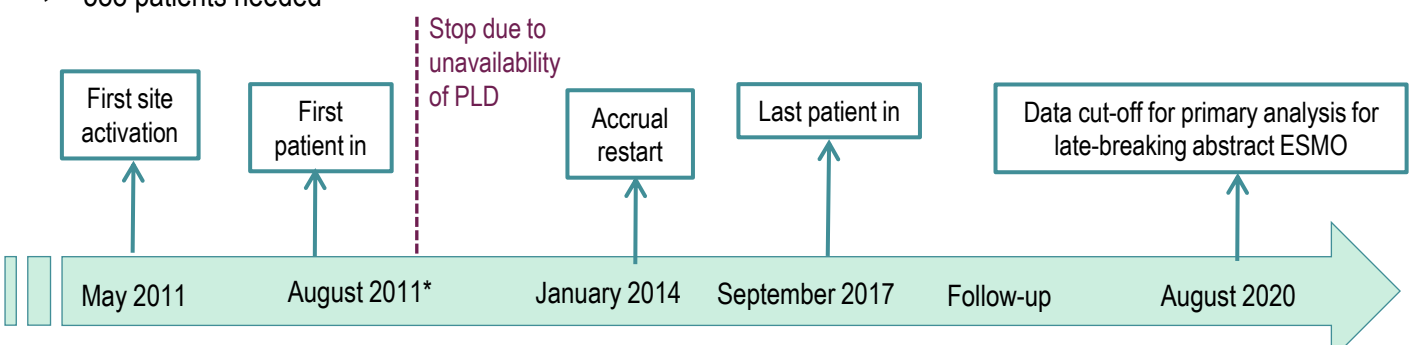


ENGOT European Network of Gynaecological Oncological Trial groups
GCIG GYNECOLOGIC CANCER INTERGROUP
MaNGO
BGOG
NOGGO
NSGO
DGOG
AGO AUSTRIA
SAKK
GEICO Grupo Español de Investigación en Cáncer de Ovario
NHS National Services Scotland

Statistical analysis plan

This study is designed to demonstrate the superiority of trabectedin/PLD over carboplatin/PLD in terms of OS:

- ✓ Median OS of 18-24 months for carboplatin/PLD arm
- ✓ HR: 0.75, 2.5% one-sided significance level and 85% power
- ✓ 442 events (deaths) are required
- ✓ planned accrual period of 42 months and 30 months follow-up (total duration 6 years)
- ✓ 588 patients needed



*the accrual after the first patient was stopped due to unavailability of PLD.

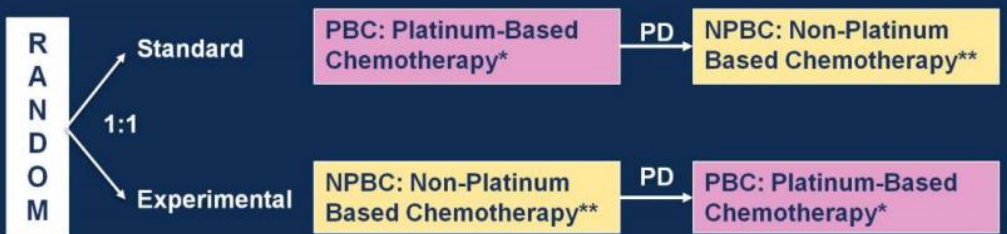
MITO-8 Results

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, Ciro Gallo, and Francesco Perrone

J Clin Oncol 35:3347-3353. © 2017

Study Design



***Pt-based Chemotherapy:**
- Carboplatin + Paclitaxel or
- Carboplatin + Gemcitabine
(in case of neurotoxicity at baseline)

****Non-Pt-Based Chemotherapy:**
- PLD or other approved single agents

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

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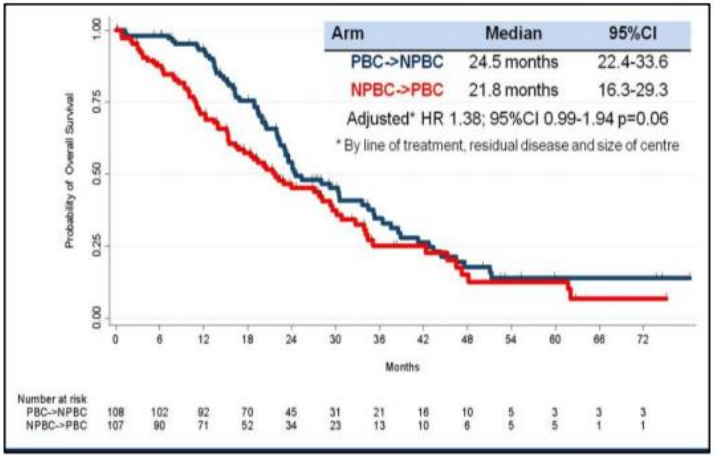
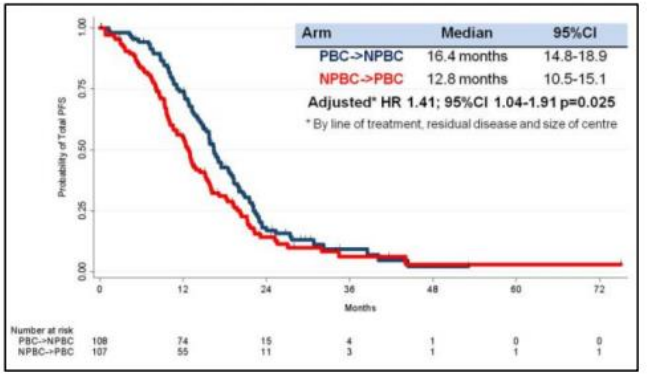
J Clin Oncol 35:3347-3353. © 2017

OS



PFS2



MITO-8 results

- Median OS was 24.5 months (95% CI, 22.4 to 33.6 months) in the standard arm and 21.8 months (95% CI, 16.3 to 29.3 months) in the experimental arm.
- 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.

Comments in relation to INOVATYON study

- the prolongation of PFI in the MITO-8 study had been performed using a monotherapy, that in most of the cases (90.7%) was PLD.
- the OVA-301 trial showed that the combination of trabectedin and PLD was superior to PLD alone in terms of OS in relapsed partially platinum sensitive ovarian cancer
- in the case of INOVATYON trial the expected increase in survival could be due not only to a prolongation of PFI - supposedly longer with trabectedin and PLD than with PLD alone - but also to the peculiar mechanism of action of trabectedin that could enhance the efficacy of subsequent platinum based therapies

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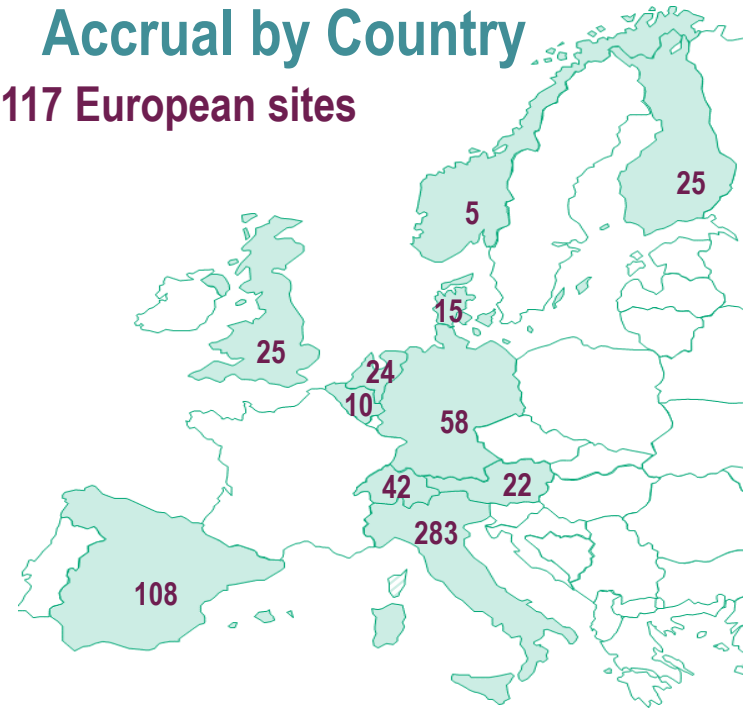
Accrual by Country

617 patients from 117 European sites



ENGOT
European Network of Gynaecological Oncological Trial groups

GCIG
GYNECOLOGIC CANCER INTERGROUP

MaNGO
Mario Negri Gynecologic Oncology

BGOG

NOGGO

NSGO

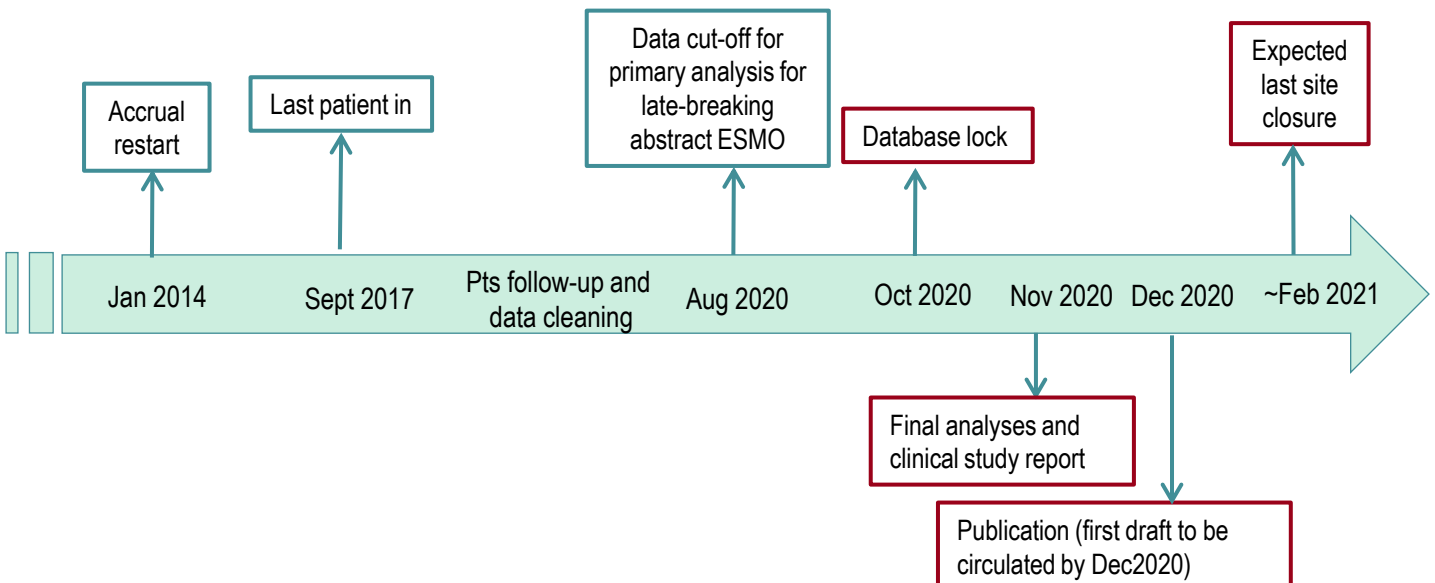
DGOG

AGO AUSTRIA

SAKK
THE DRIVE PROGRESS TO CANCER CARE

GEICO
Grupo Español de Investigación en Cáncer de Ovario

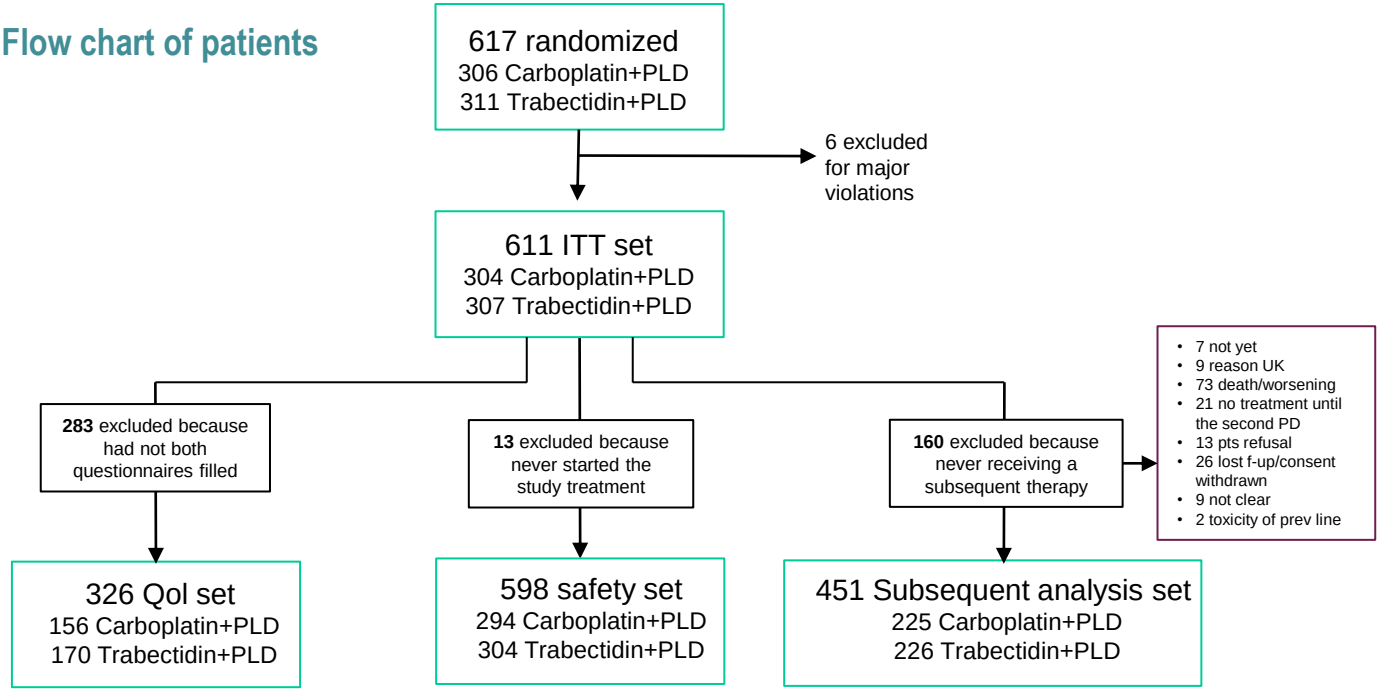
NHS National Services Scotland


Accrual restart
Last patient in
Data cut-off for primary analysis for late-breaking abstract ESMO
Database lock
Expected last site closure
Jan 2014
Sept 2017
Pts follow-up and data cleaning
Aug 2020
Oct 2020
Nov 2020
Dec 2020
~Feb 2021
Final analyses and clinical study report
Publication (first draft to be circulated by Dec2020)

RESULTS

As presented at ESMO 2020 with some additional information

Flow chart of patients



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Patient Baseline Characteristics

		Carboplatin+PLD (N=304)	Trabectedin+PLD (N=307)
Age - Median (Q1 - Q3)		64.0 (55.0-70.0)	63.0 (55.0-71.0)
Performance status - (%)	0	74.2	68.9
	1	24.1	28.5
	2	1.7	2.6
Histological type - (%).	Serous	83.2	86.0
	Endometroid	3.3	3.6
	Other	13.5	10.4
Measurable disease at study entry - (%)		72.4	72.3
Germline BRCA mutational status - (%).	Mutated	9.2	13.4
	Wild-type	46.7	40.1
	Unknown	44.1	46.6
Number of prior treatments* - (%).	1	69.7	69.7
	2	29.9	30.6
Previous anthracycline-based chemotherapy - n (%)		9.2	9.8
Last Platinum Free interval (months) - Median (Q1- Q3)		8.4 (6.9-9.9)	8.3 (7.0-9.9)

*1 patient in Carboplatin+PLD arm did not receive any prior treatment

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Treatment Compliance

	Carboplatin+PLD (N=304)	Trabectedin+PLD (N=307)
Never started - (%)	3.3	1.0
Treatment interrupted >=6 cycles - (%)	68.1	53.4
Treatment interrupted < 6 cycles - (%)	28.3	45.6
Reason: -n (%)		
Disease progression	55 (64.0)	70 (50.0)
Unacceptable toxicity	13 (15.1)	27 (19.3)
Patient refusal/Consent withdrawn	4 (4.6)	13 (12.8)
Physician decision	5 (5.8)	8 (5.7)
Death	5 (5.8)	6 (4.3)
Intercurrent illness of sufficient severity	1 (1.2)	8 (5.7)
Lost to follow-up	-	1 (0.7)
Screening failure	1 (1.2)	-
Other	2 (2.3)	2 (1.4)
Treatment ongoing - (%)	0.3	-

Treatment Compliance

	Carboplatin+PLD (N=304)	Trabectedin+PLD (N=307)
Never started - (%)	3.3	1.0
Treatment interrupted >=6 cycles - (%)	68.1	53.4
Treatment interrupted < 6 cycles - (%)	28.3	45.6
Reason: -n (%)		
Treatment completed	145 (70.0)	89 (54.3)
Disease progression	30 (14.5)	39 (23.8)
Physician decision	20 (9.7)	13 (7.9)
Unacceptable toxicity	7 (3.4)	12 (7.3)
Patient refusal	5 (2.4)	7 (4.3)
Intercurrent illness of sufficient severity	0 (0.0)	2 (1.2)
Consent withdrawn	0 (0.0)	1 (0.6)
Other	0 (0.0)	1 (0.6)
Treatment ongoing - (%)	0.3	-

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Treatment Compliance

Italy vs. other countries

	Carboplatin+PLD (N=304)	Trabectedin+PLD (N=307)
ITALY		
Never started - (%)	4 (2.7)	1 (0.8)
Treatment interrupted >=6 cycles - (%)	107 (72.8)	74 (56.9)
Treatment interrupted < 6 cycles - (%)	36 (24.5)	55 (42.3)
OTHER COUNTRIES		
Never started - (%)	6 (3.8)	2 (1.1)
Treatment interrupted >=6 cycles - (%)	100 (63.7)	90 (50.8)
Treatment interrupted < 6 cycles - (%)	50 (31.8)	85 (48.0)

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Treatment Compliance

Italy vs. other countries

	Carboplatin+PLD (N=304)	Trabectedin+PLD (N=307)
ITALY		
Never started - (%)	4 (2.7)	1 (0.8)
Treatment interrupted >=6 cycles - (%)	107 (72.8)	74 (56.9)
Treatment interrupted < 6 cycles - (%)	36 (24.5)	55 (42.3)
Reason: Treatment completed	63 (58.9)	30 (40.5)
OTHER COUNTRIES		
Never started - (%)	6 (3.8)	2 (1.1)
Treatment interrupted >=6 cycles - (%)	100 (63.7)	90 (50.8)
Treatment interrupted < 6 cycles - (%)	50 (31.8)	85 (48.0)
Reason: Treatment completed	82 (82.0)	59 (65.6)

Number of completed cycles in subjects who have discontinued the treatment after at least 6 cycles

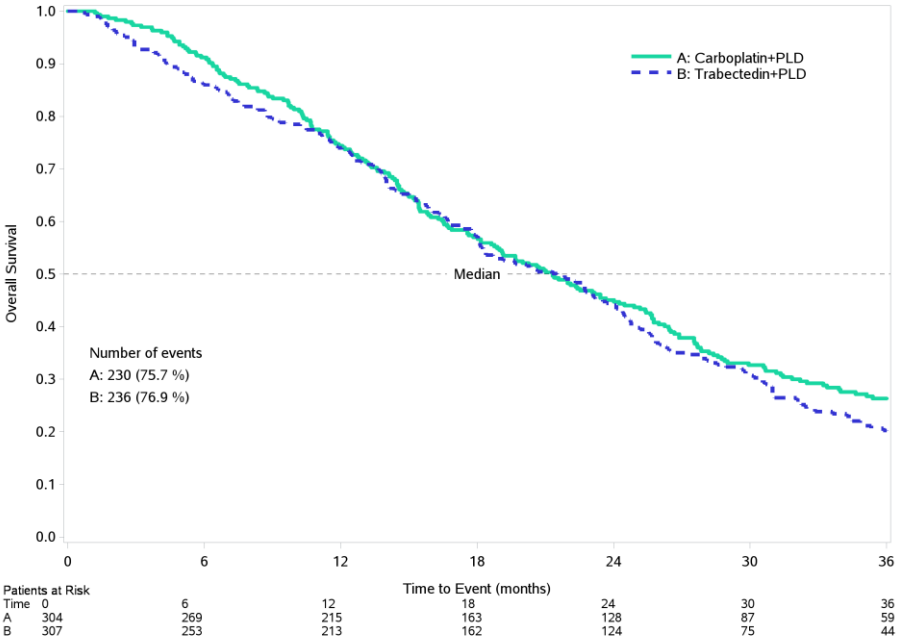
	Carboplatin+PLD N=86	Trabectidin+PLD N=140	OVERALL N=226
Number of cycles			
Mean (SD)	7.0 (1.9)	7.9 (3.7)	7.4 (2.9)
Median (Q1 - Q3)	6.0 (6.0-7.0)	6.0 (6.0-8.5)	6.0 (6.0-8.0)
Min - Max	6.0 - 16.0	6.0 - 29.0	6.0 - 29.0
Number of cycles - n(%)			
≥6	207 (100)	164 (100)	371 (100)
≥7	60 (29.0)	68 (41.5)	128 (34.5)
≥8	51 (24.6)	60 (36.6)	111 (29.9)
≥9	35 (16.9)	41 (25.0)	76 (20.5)

Number of completed cycles in subjects who have discontinued the treatment after at least 6 cycles

Italy vs. other countries

	Carboplatin+PLD N=86	Trabectidin+PLD N=140	OVERALL N=226
ITALY			
Number of cycles - n(%)			
Mean (SD)	7.5 (2.3)	9.5 (4.8)	8.3 (3.6)
Median (Q1 - Q3)	6.0 (6.0-9.0)	8.0 (6.0-11.0)	7.0 (6.0-9.0)
Min - Max	6.0 - 16.0	6.0 - 29.0	6.0 - 29.0
OTHER COUNTRIES			
Number of cycles - n(%)			
Mean (SD)	6.4 (1.3)	6.7 (1.5)	6.5 (1.4)
Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
Min - Max	6.0 - 15.0	6.0 - 14.0	6.0 - 15.0

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

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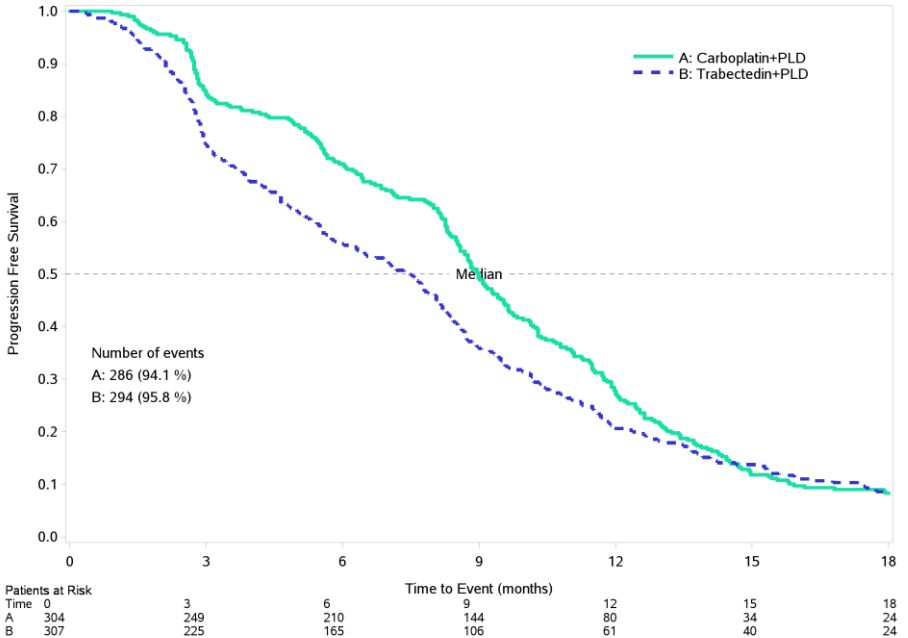
Secondary Endpoint: Progression free survival



Median PFS (Q1-Q3):

Carboplatin+PLD: 9.0 mos (5.5-12.4)

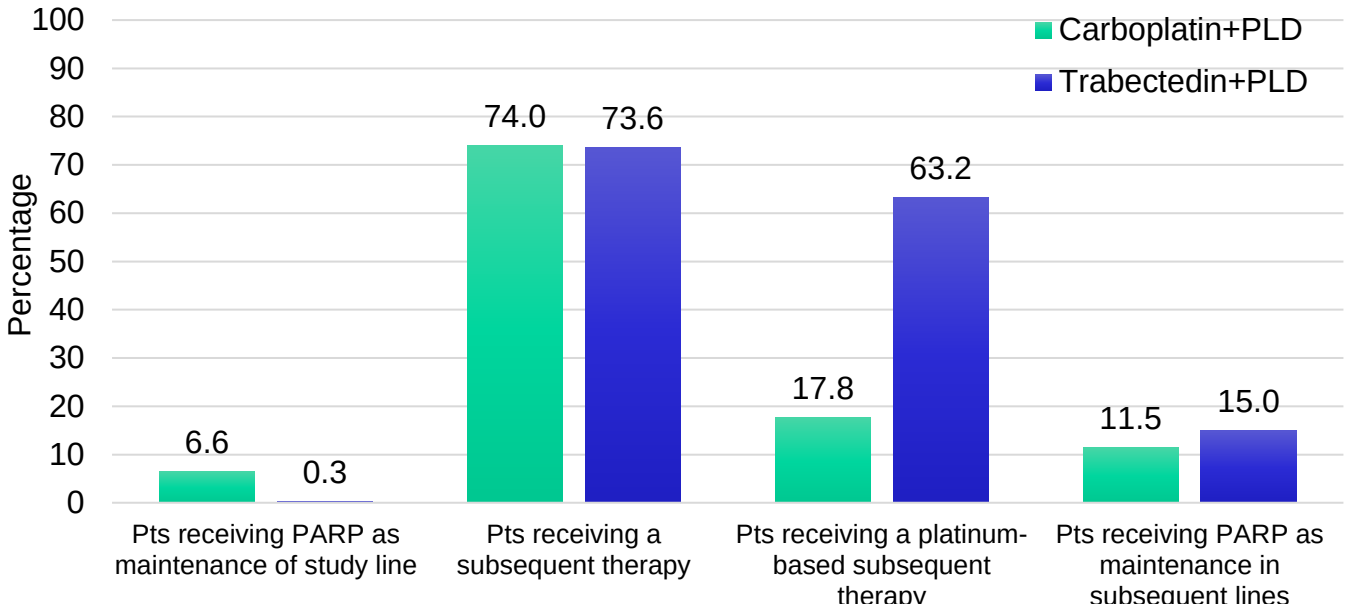
Trabectedin+PLD: 7.5 mos (3.0-11.5)

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

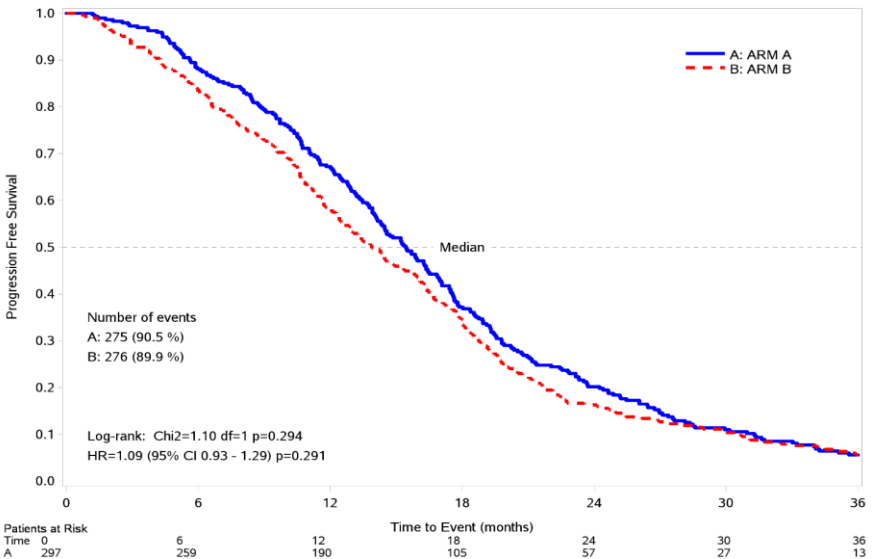
Trabectedin+PLD vs. Carboplatin+PLD

1.26 [1.07-1.49]; 0.005

Subsequent therapies (ST)



Secondary Endpoint: Progression free survival 2*



Median PFS (Q1-Q3):

Carboplatin+PLD: 15.3 mos (10.2-21.3)

Trabectedin+PLD: 13.5 mos (7.8-19.8)

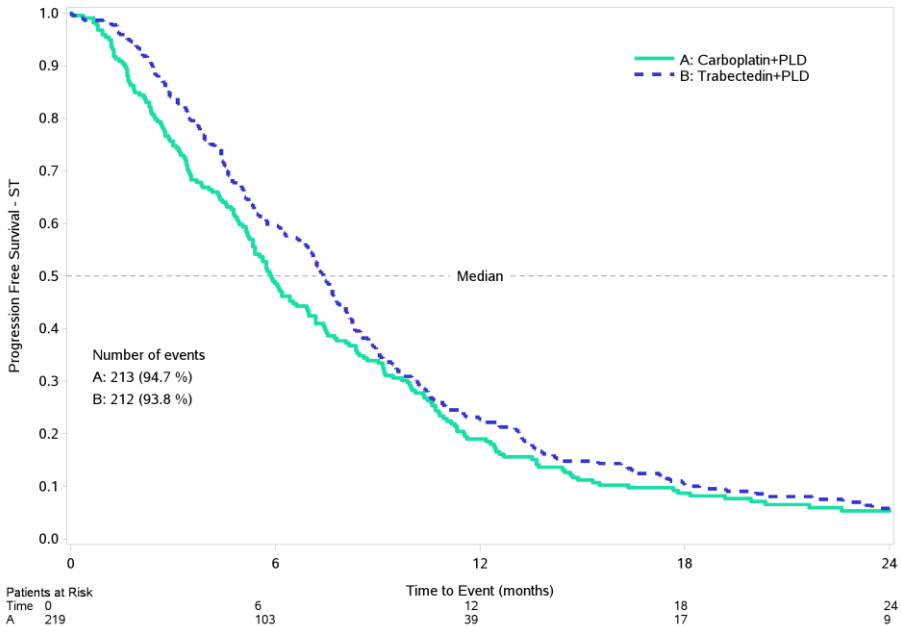
HR PFS [95% CI]; p-value :

Trabectedin+PLD vs. Carboplatin+PLD

1.09 [0.93-1.29]; 0.291

*From randomization to second progression

Secondary Endpoint: Progression free survival after ST *



Median PFS - ST (Q1-Q3):

Carboplatin+PLD: 5.7 mos (2.9-10.5)

Trabectedin+PLD: 7.4 mos (4.1-10.9)

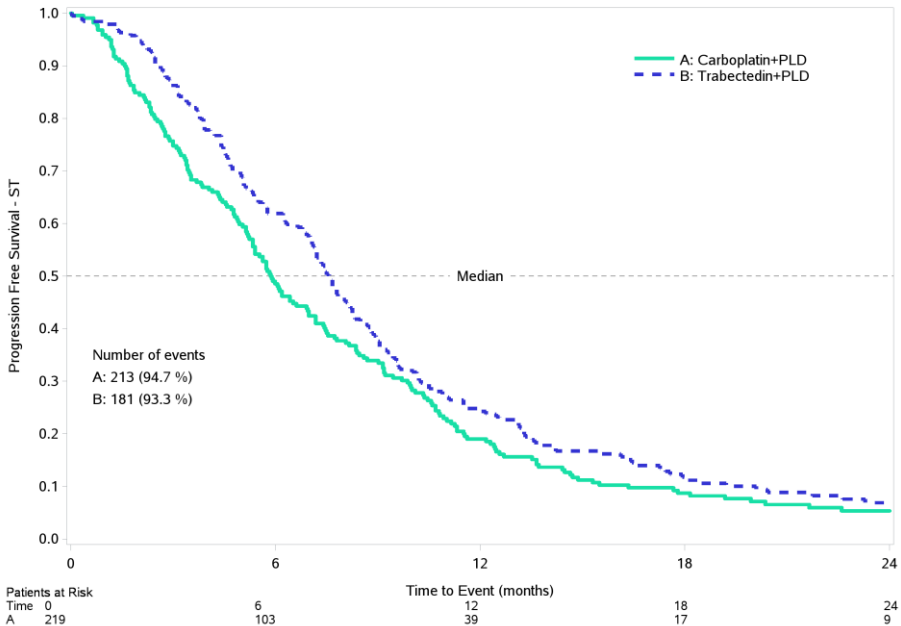
HR PFS - ST [95% CI]; p-value :

Trabectedin+PLD vs. Carboplatin+PLD

0.84 [0.70-1.02]; 0.086

*Calculated from the start of subsequent therapy

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 :

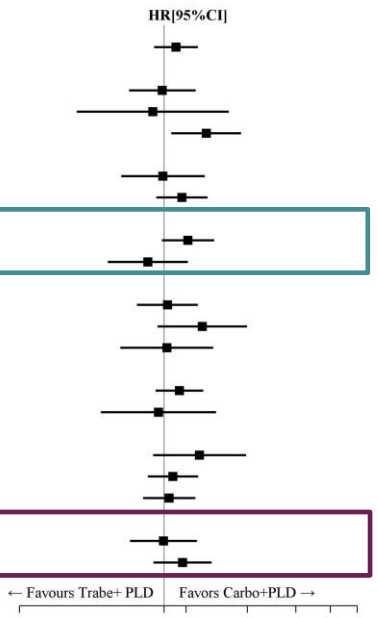
Trabectedin+PLD vs. Carboplatin+PLD

0.80 [0.65-0.98]; 0.028

*Calculated from the start of subsequent therapy

OS subgroup analysis

Variable	Events/n (%)	HR [95%CI]
OVERALL	466/611 (76.27)	1.10 [0.92-1.33]
BRCA		0.069*
Wild-type	203/265 (76.6)	0.99 [0.75-1.30]
Mutated	39/69 (56.52)	0.91 [0.48-1.72]
Unknown	187/228 (82.02)	1.42 [1.06-1.90]
Presence of misurable disease at study entry		0.43*
No	129/169 (76.33)	0.99 [0.70-1.40]
Yes	337/442 (76.24)	1.16 [0.94-1.44]
Number of prior treatments		0.098*
1	326/425 (76.71)	1.22 [0.98-1.52]
2	139/185 (75.14)	0.87 [0.63-1.22]
Size of residual disease after initial surgery		0.742*
<=1 cm	239/316 (75.63)	1.03 [0.80-1.33]
>1 cm	112/146 (76.71)	1.38 [0.95-2.00]
Unknown	104/136 (76.47)	1.02 [0.69-1.51]
Hystology		0.498*
Serous	398/516 (77.13)	1.14 [0.93-1.38]
Not serous	67/94 (71.28)	0.95 [0.59-1.54]
Patients receiving a subsequent therapy		0.383*
No	104/129 (80.62)	1.34 [0.91-1.98]
Yes	352/451 (78.05)	1.08 [0.87-1.33]
-Yes – platinum therapy arm B	326/419 (77.8)	1.04 [0.84-1.30]
Country		0.414*
Italy	200/277 (72.2)	0.99 [0.75-1.31]
Other	266/334 (79.64)	1.17 [0.91-1.49]



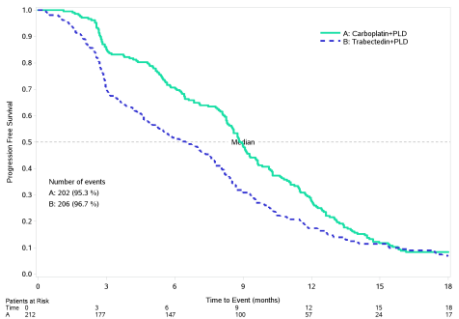
* interaction test

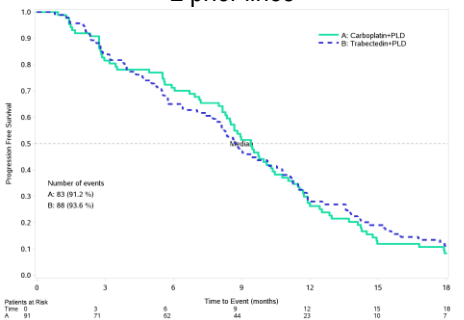
Subgroup according to number of prior lines

1 prior line

2 prior lines

PFS





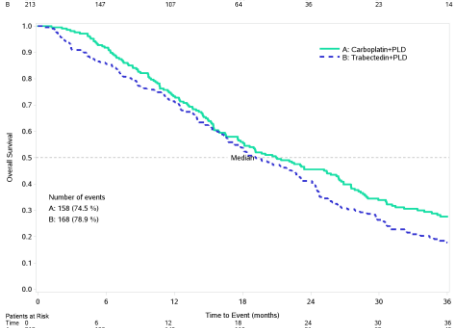
HR PFS [95% CI]; p-value :

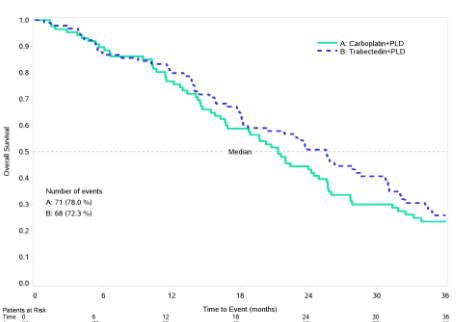
1 prior line: 1.42 [1.17-1.73]; <0.001

2 prior lines: 1.03 [0.76-1.39]; 0.863

Interaction test: 0.080

OS





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

1 prior line: 1.22 [0.98-1.52]; 0.073

2 prior lines: 0.87 [0.63-1.22]; 0.426

Interaction test: 0.098

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Drug related Adverse Events

	Carboplatin+PLD (n=294)		Trabectedin+PLD (n=304)		P-value
	Any grade	≥G3	Any grade	≥G3	(G0-2 / ≥G3)
Subjects with at least one drug related adverse event	80%	36%	89%	69%	<0.001
Drug related Adverse Events (≥ 10% of patients)					
Hematological	51%	28%	62%	45%**	<0.001
Thrombocytopenia	24%	11%	13%	8%	0.323
Neutropenia	38%	22%	51%	39%°°	<0.001
Gastrointestinal	50%	7%	62%	18%	<0.001
Hepatotoxicity*	5%	1%	27%	18%	<0.001§
Neurotoxicity°	18%	6%#	18%	5%#	0.650
Peripheral neuropathy	9%	0.3%#	8%	0.2%#	0.169
Asthenia	17%	0.3%	21%	3%	0.011§
Palmar-plantar erythrodysaesthesia syndrome	8%	0.3%	11%	2%	0.217§
Drug related Adverse Events of clinical interest					
Hypersensitivity	4%	1 pt G3	2%	-	
Deaths related to treatment (or for which the relationship with treatment can not be excluded)					
Myelodysplastic syndrome		1 pt			
Pulmonary oedema				1 pt	
Unknown cause of death		1 pt			

include AE> G2 ; § fisher exact test; **1pt G5 pancytopenia; °° 1 pt G5 sepsis

* includes Gamma-glutamyltransferase increase, Liver function test abnormal, Alanine aminotransferase increase, Aspartate aminotransferase increase, Transaminases increase, Liver disorder;

° includes: includes Dizziness, Vertigo, Presyncope, Syncope, Dysgeusia, Headache, Insomnia, Memory impairment and Neuropathy (neuropathy includes Peripheral sensory, Hypoaesthesia, Paraesthesia)

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Drug related Adverse Events

Italy vs. other countries

	ITALY				Other countries			
	Carboplatin+PLD (n=143)		Trabectedin+PLD (n=129)		Carboplatin+PLD (n=151)		Trabectedin+PLD (n=175)	
	Any grade	≥G3	Any grade	≥G3	Any grade	≥G3	Any grade	≥G3
Hematological	55%	26%	64%	47%	48%	30%	60%	43%
Thrombocytopenia	25%	10%	11%	8%	23%	11%	15%	7%
Neutropenia	40%	20%	55%	41%	36%	25%	48%	37%
Gastrointestinal	41%	4%	55%	15%	59%	10%	67%	20%
Hepatotoxicity*	5%	0%	31%	19%	6%	1%	25%	18%
Neurotoxicity°	6%	2%	7%	2%	25%	10%	23%	8%
Peripheral neuropathy	4%	1%	2%	1%	13%	5%	11%	2%
Asthenia	21%	1%	22%	5%	13%	0%	20%	2%

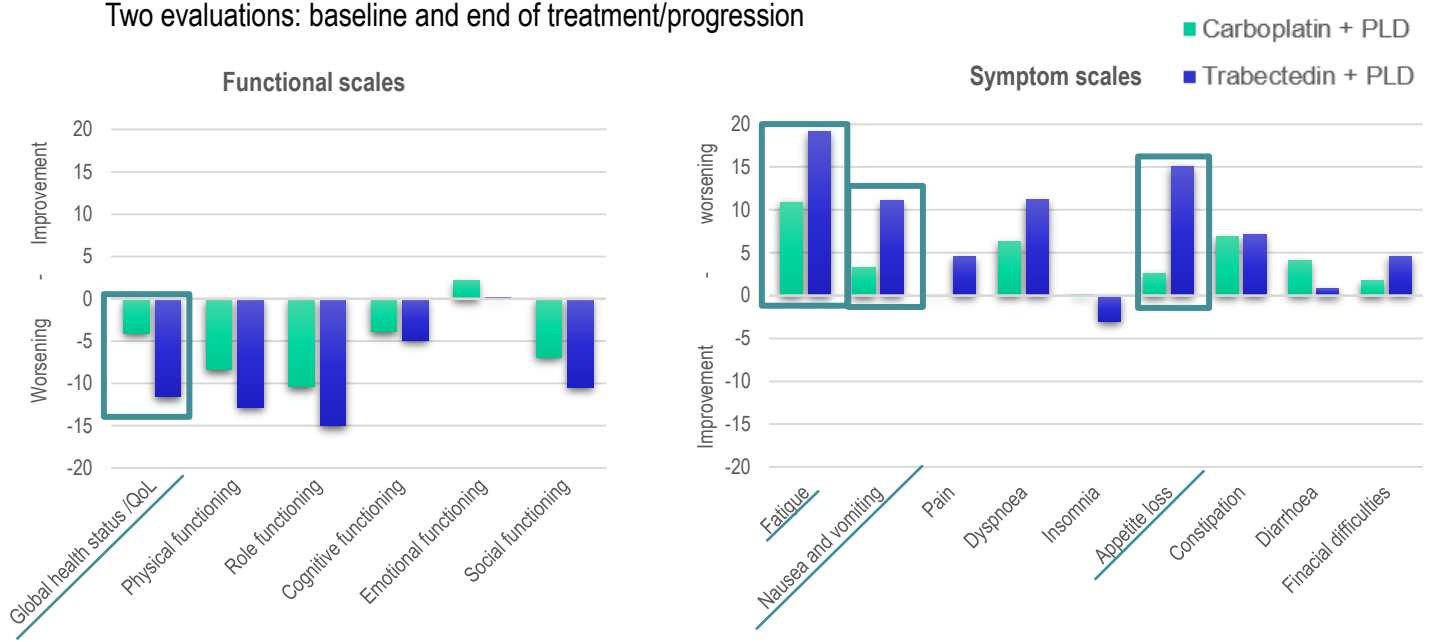
include AE> G2 ; § fisher exact test; **1pt G5 pancytopenia; °° 1 pt G5 sepsis

* includes Gamma-glutamyltransferase increase, Liver function test abnormal, Alanine aminotransferase increase, Aspartate aminotransferase increase, Transaminases increase, Liver disorder;

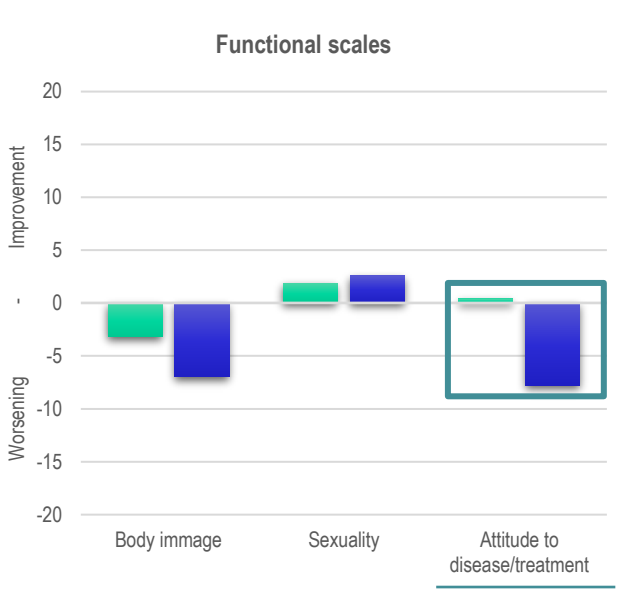
° includes: includes Dizziness, Vertigo, Presyncope, Syncope, Dysgeusia, Headache, Insomnia, Memory impairment and Neuropathy (neuropathy includes Peripheral sensory, Hypoaesthesia, Paraesthesia)

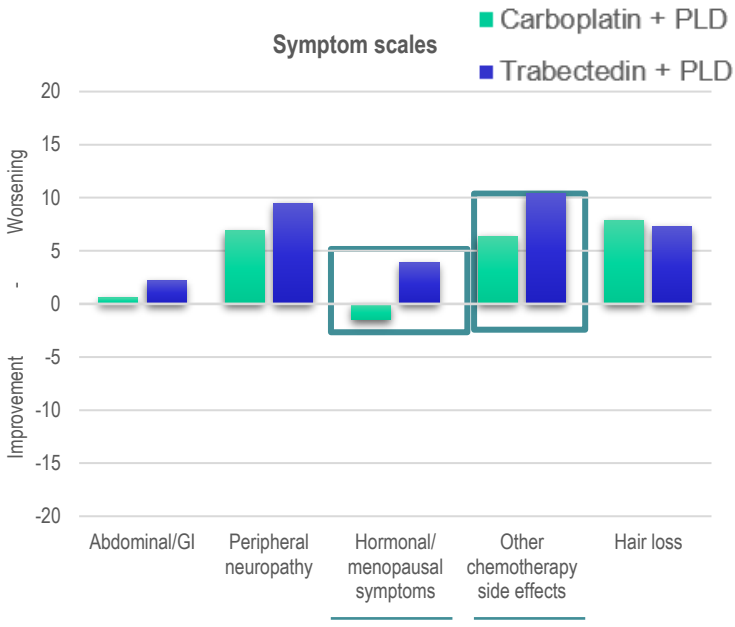
Secondary Endpoint: Quality of life (EORTC - QLQ-C30)

Two evaluations: baseline and end of treatment/progression



Secondary Endpoint: Quality of life (EORTC - QLQ-OV28)





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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.

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