BAROCCO Study

Best Approach in Resistant-Ovarian-Cancer with-Cediranib-Olaparib

Alessandra Baldoni | Reggio Emilia 22 June 2019

BAROCCO Study

An Italian multicenter randomized phase II study of weekly Paclitaxel vs. Cediranib-Olaparib with continuous schedule vs. Cediranib-Olaparib with intermittent schedule in patients with platinum resistant high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Sponsor: Istituto di Ricerche Farmacologiche Mario Negri – MaNGO Group
Study Lead Investigator: Prof. Nicoletta Colombo
Supporter: AstraZeneca

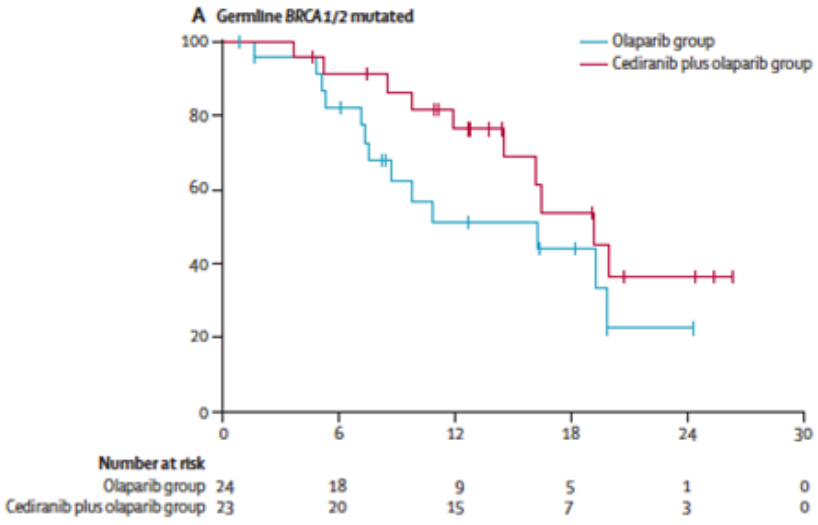
ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

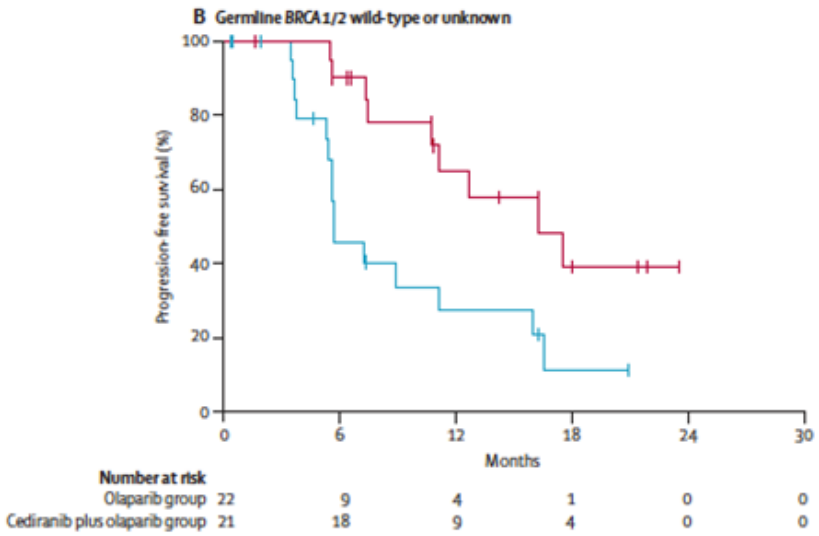
IEO Istituto Europeo di Oncologia

AstraZeneca

RATIONALE (I)

- Combination of Cediranib and Olaparib improves PFS in women with recurrent platinum sensitive ovarian cancer with respect to Olaparib (Liu JF, Lancet Oncol. 2014)
- Efficacy in terms of PFS of combination of Cediranib and Olaparib with respect to Olaparib in subpopulation of gBRCA1/2 wt or unknown (Liu JF, Lancet Oncol. 2014)



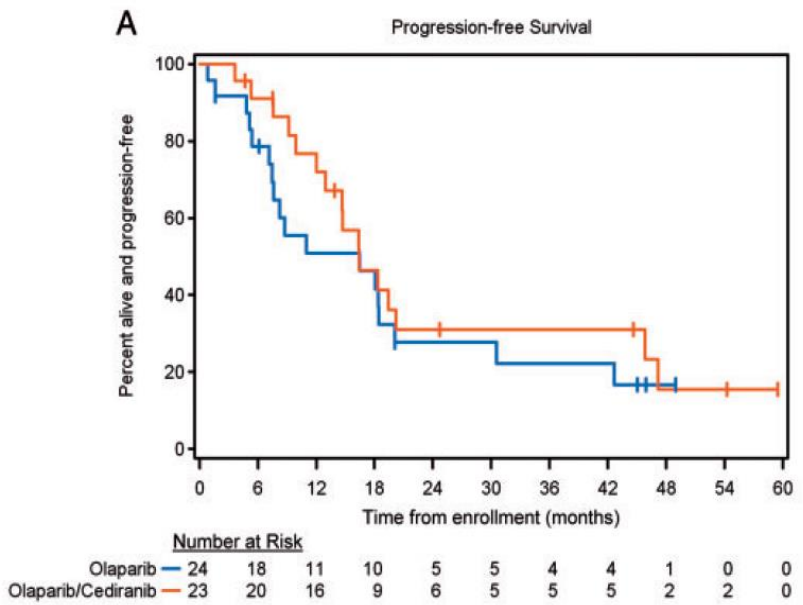


RATIONALE (II)

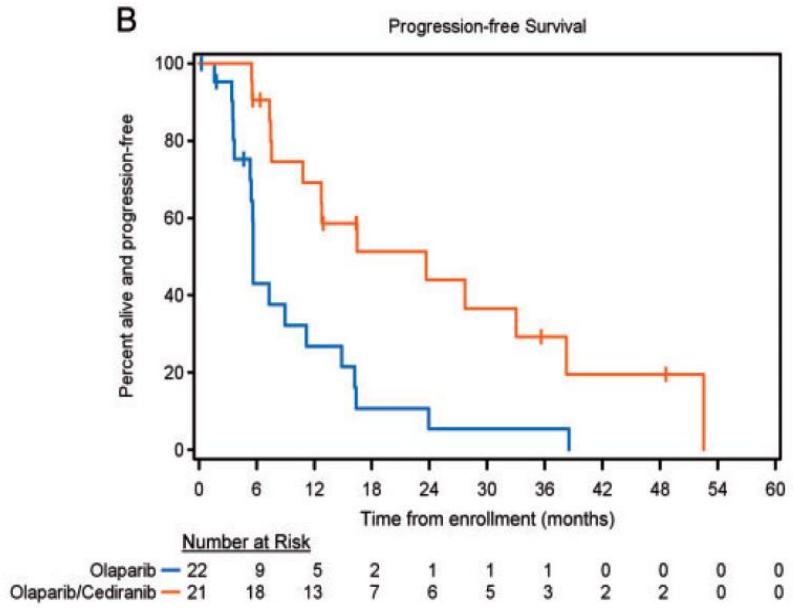
Update results (Liu JF, Annals of Oncology 2019):

- Confirmed efficacy in terms of PFS of Cediranib and Olaparib combination with respect to Olaparib in overall study population (Median PFS: **16.5** months vs. **8.2** months, HR: **0.50** (95% CI 0.30 – 0.83); p=0.006
- Confirmed efficacy also in **gBRCA wt or unknown** subpopulation (Median PFS : **23.7** months vs. **5.7** months, HR: **0.31** (95% CI 0.15 – 0.66); p=0.0013

gBRCA mutation carrier (n=47)

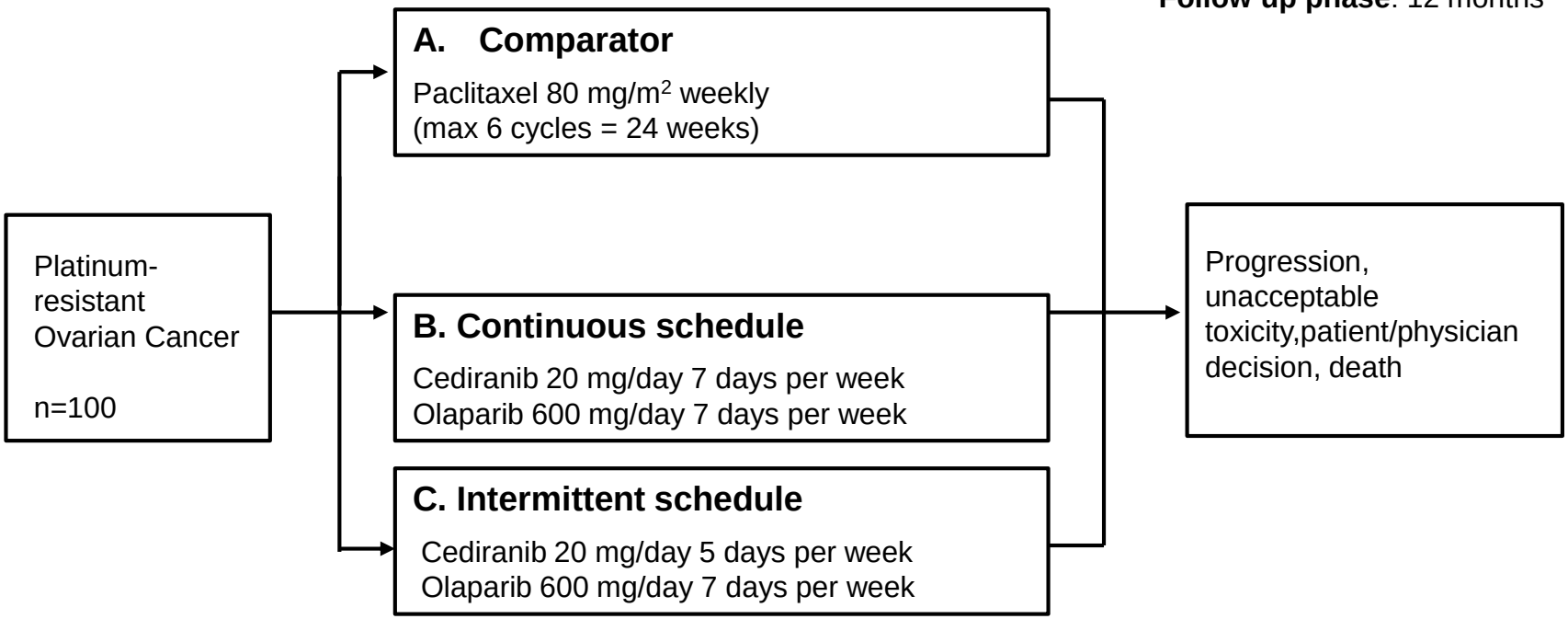


gBRCA non-carrier/status unknown (n=43)



STUDY DESIGN

Enrollment phase: 18 months
Follow up phase: 12 months



Randomization ratio 1:1:1

Stratification factors

- Number of previous chemotherapy lines (1-2 lines vs 3 or more lines)
- Germline mutational BRCA status (wild type vs mutated vs still unknown)
- Prior antiangiogenetic drugs (yes vs no)

PRIMARY OBJECTIVES

1. **Efficacy**

- Compare the efficacy of the combination of cediranib + olaparib vs pacliatxel in terms of **PFS**
- Two comparisons: i. continuous schedule vs control; ii. intermittend schedule vs control

2. **Safety**

- If both experimental arms are superior to comparator in efficacy: compare the safety of the combination of cediranib + olaparib administered according to continuous schedule vs intermittent schedule in terms of **mean no. of evacuations per day** over the first 4 weeks of treatment

SAMPLE SIZE

Efficacy

- Median PFS of 3.4 months for control arm (AURELIA trial, Pujade-Lauraine *et al*, 2014)
- Detection of a **HR of 0.51** (advantage in median PFS of 3.3 months)

5% one-sided significance level,
at least 80% power

→ **55 events**
(approximately 60 patients)
for each comparison

Considering the two comparisons (intermittent vs paclitaxel and continuous vs paclitaxel)

→ **90 eligible patients**

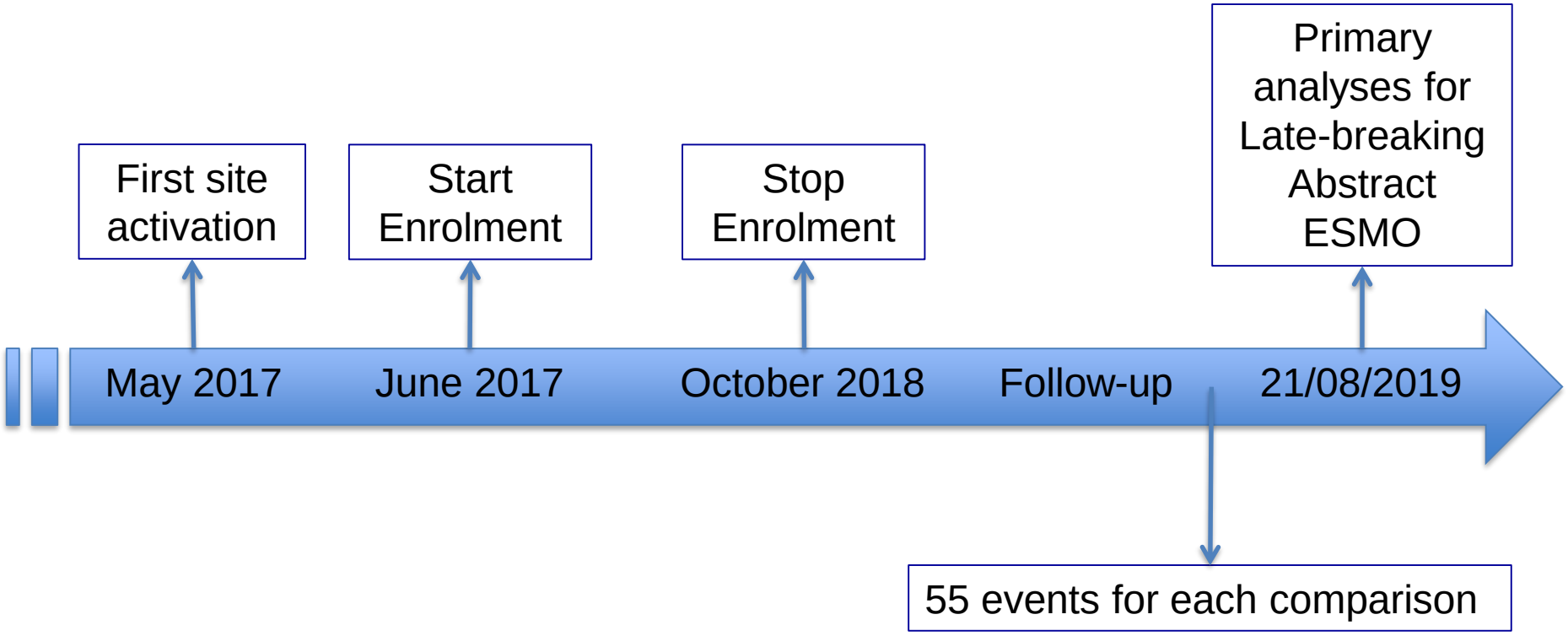
Considering a 10% of drop out

→ **total of 100 patients**

Safety

- No preliminar data about better safety profile for the intermittent schedule of Cediranib
- Mean reduction of **two evacuations per day** over the first cycle considered clinical relevant
- Detection with power greater than 90% and with one-sided 5% significance level

STUDY TIMELINES



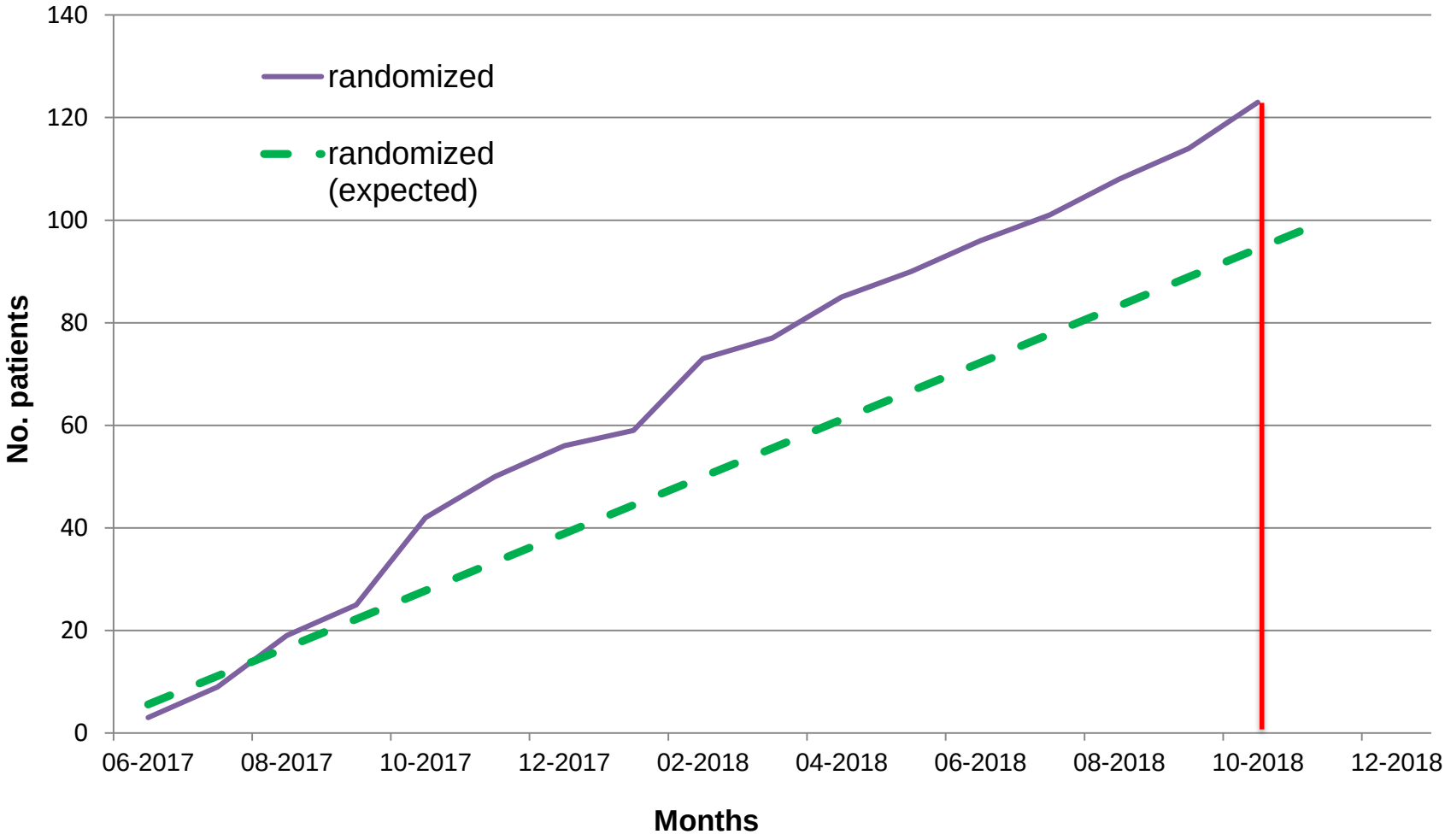
ENROLLMENT (I)

Clinical Site	Drop out rate in control arm >>10%	No. patients enrolled			
		Paclitaxel	Ced+Ola continuous	Ced+Ola intermittent	Total
IEO - Istituto Europeo di Oncologia		20	23	19	**62**
ROMA - Policlinico Umberto I		9	4	8	**21**
PADOVA - Istituto Oncologico Veneto		3	8	7	**18**
BRESCIA - Spedali civili		5	1	4	**10**
REGGIO EMILIA - Arcispedale S.M.Nuova		1	3	2	**6**
MONZA - Ospedale S. Gerardo		3	0	1	**4**
GENOVA - Ospedali Galliera		0	2	0	**2**
Total		**41**	**41**	**41**	**123**

Enrollment extension to include required 90 evaluable patients for primary analyses

ENROLLMENT (II)

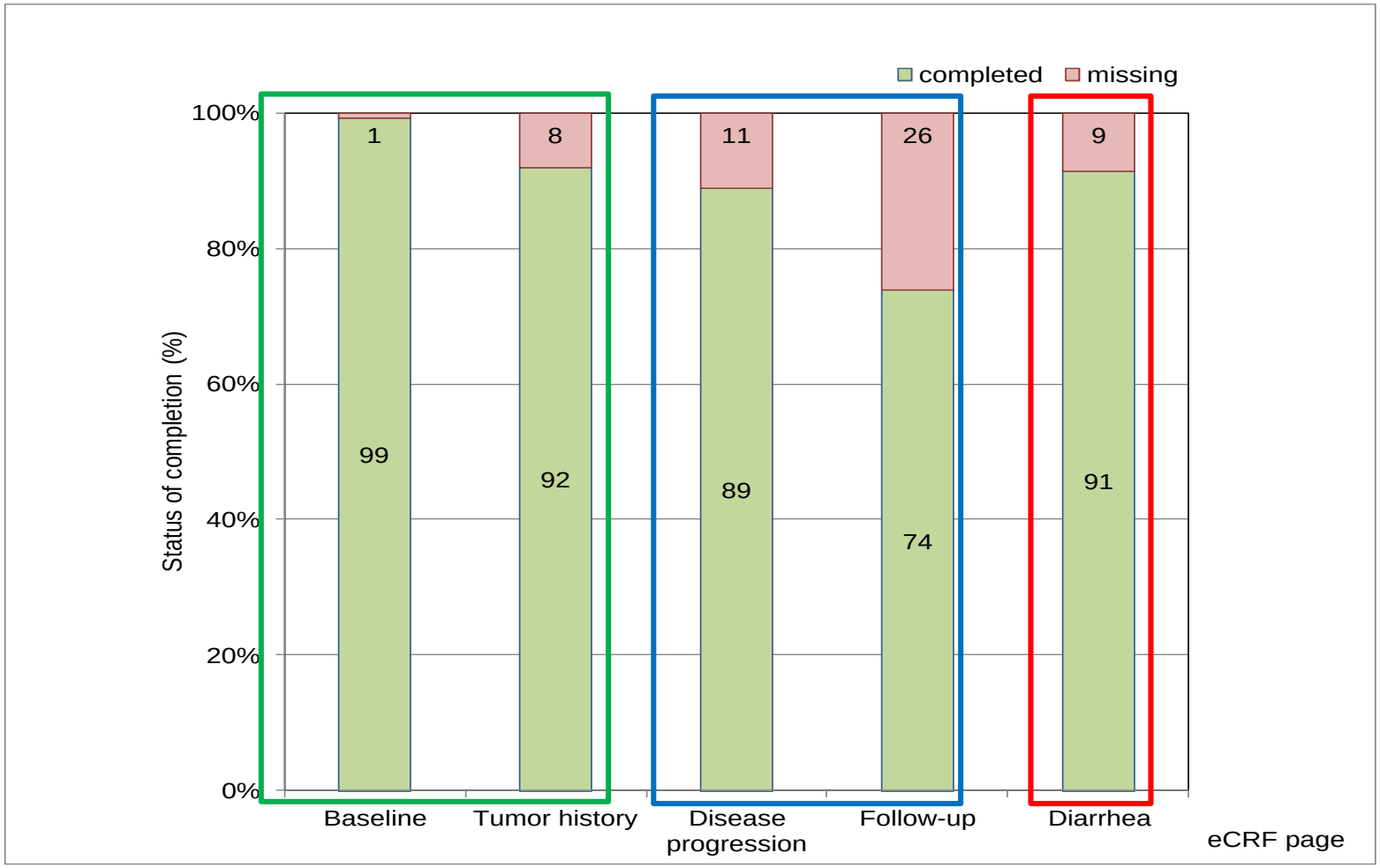
Mean accrual rate: 8 patients/month
Accrual stop: 17 October 2018



ON-SITE MONITORING

- 21 site visits performed (Site Initiation Visits & Routine Site Visits)
- 7 site visits will be performed (Close-Out Visits)
- Patients monitored: 40/123 (32.5 %)
- Initial Informed Consent Forms (ICFs) monitored: 123/123 (100 %)
- ICF major critical issues:
  - Submission of erroneous version of ICFs
  - Absence of the ICF (one patient)

DATA COLLECTION



BASELINE CHARACTERISTICS

	Paclitaxel N=41	Ced+Ola continuous N=41	Ced+Ola Intermittent N=41	Total N=123
Age				
Mean (SD)	62.4 (8.3)	61.0 (11.4)	61.4 (9.4)	61.6 (9.7)
Performance status – n (%)				
0	32 (86.5)	36 (90.0)	29 (76.3)	97 (84.3)
1	5 (13.5)	4 (10.0)	9 (23.7)	18 (15.7)
Missing	4	1	3	8
Race - n (%)				
Asian	0 (0.0)	1 (2.6)	1 (2.6)	2 (1.7)
Black	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.9)
Caucasian	35 (87.5)	35 (89.7)	37 (97.4)	107 (91.5)
Other	4 (10.0)	3 (7.7)	0 (0.0)	7 (6.0)
Missing	1	2	3	6
CA-125 (U/mL)				
Mean (SD)	2361.2 (7528.1)	2304.3 (5123.4)	856.5 (1336.8)	1840.2 (5291.0)

TUMOUR CHARACTERISTICS

	Paclitaxel N=41	Ced+Ola continuous N=41	Ced+Ola Intermittent N=41	Total N=123
Time from diagnosis (years)				
Mean (SD)	2.5 (2.3)	3.5 (2.9)	3.2 (2.4)	3.1 (2.6)
Missing	10	1	2	13
Primary Site - n (%)				
Fallopian	4 (12.5)	2 (4.9)	0 (0.0)	6 (5.3)
Ovary	27 (84.4)	38 (92.7)	39 (97.5)	104 (92.0)
Peritoneal	1 (3.1)	1 (2.4)	1 (2.5)	3 (2.7)
Missing	9	0	1	10
F.I.G.O. Stage - n (%)				
IC	1 (4.0)	1 (2.7)	2 (5.6)	4 (4.1)
IIB	0 (0.0)	0 (0.0)	2 (5.6)	2 (2.0)
IIC	0 (0.0)	1 (2.7)	1 (2.8)	2 (2.0)
IIIA	2 (8.0)	0 (0.0)	0 (0.0)	2 (2.0)
IIIB	2 (8.0)	4 (10.8)	2 (5.6)	8 (8.2)
IIIC	15 (60.0)	19 (51.4)	19 (52.8)	53 (54.1)
IV	5 (20.0)	12 (32.4)	9 (25.0)	26 (26.5)
Unknown	0 (0.0)	0 (0.0)	1 (2.8)	1 (1.0)
Missing	16	4	5	25
Histological Type - n (%)				
Clear cell	3 (10.0)	2 (4.9)	4 (10.0)	9 (8.1)
Endometrioid	1 (3.3)	3 (7.3)	3 (7.5)	7 (6.3)
Mixed Epithelial	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.9)
Serous	26 (86.7)	34 (82.9)	33 (82.5)	93 (83.8)
Unknown	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.9)
Missing	11	0	1	12

STRATIFICATION FACTORS

	Paclitaxel N=41	Ced+Ola continuous N=41	Ced+Ola Intermittent N=41	Total N=123
BRCA status - n (%)				
Both BRCA1-2 Wild Type	33 (82.5)	30 (73.2)	31 (75.6)	94 (77.0)
Only BRCA1 Mutated	3 (7.5)	5 (12.2)	2 (4.9)	10 (8.2)
Only BRCA2 Mutated	1 (2.5)	1 (2.4)	1 (2.4)	3 (2.5)
Both BRCA1-2 Mutated	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.8)
Both BRCA1-2 Still Unknown	4 (9.8)	4 (9.8)	7 (17.1)	15 (12.2)
Previous treatment with antiangiogenic drugs - n (%)				
No	19 (46.3)	19 (46.3)	20 (48.8)	58 (47.2)
Yes	22 (53.7)	22 (53.7)	21 (51.2)	65 (52.8)
Previous chemotherapy lines - n (%)				
Up to 2 lines	17 (41.5)	15 (36.6)	16 (39.0)	48 (39.0)
Three or more lines	24 (58.5)	26 (63.4)	25 (61.0)	75 (61.0)
Total previous chemotherapy line - n (%)				
1	7 (21.9)	7 (17.1)	7 (17.5)	21 (18.6)
2	8 (25.0)	8 (19.5)	8 (20.0)	24 (21.2)
3	12 (37.5)	9 (22.0)	12 (30.0)	33 (29.2)
4	3 (9.4)	12 (29.3)	10 (25.0)	25 (22.1)
5	1 (3.1)	3 (7.3)	2 (5.0)	6 (5.3)
6	1 (3.1)	1 (2.4)	1 (2.5)	3 (2.7)
7	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.9)
Missing	9	0	1	10

ADVERSE EVENTS (AEs)

	Paclitaxel N=26	Ced+Ola Cont. N=40	Ced+Ola int. N=39	Overall N=105
Subjects with at least one AE – n (%)	17 (65.4)	33 (82.5)	26 (66.7)	76 (72.3)
Subjects with at least one ADR – n (%)	14 (53.8)	30 (75)	24 (61.5)	68 (64.8)

ADVERSE DRUG REACTIONS (ADRs)

	Paclitaxel N=14	Ced+Ola Cont. N=30	Ced+Ola int. N=24	Overall N=68
Patients with G3-G4-G5 ADRs – n (%)	**2 (14.3)**	**15 (50)**	**12 (50)**	**29 (42.6)**
Blood and lymphatic system disorders - n (%)	-	4 (13.3)	5 (20.8)	9 (13.2)
Anemia	-	4 (13.3)	4 (16.7)	8 (11.8)
Febrile neutropenia	-	-	1 (4.2)	1 (1.5)
Gastrointestinal disorders - n (%) without Diarrhea	-	5 (16.7)	4 (16.7)	9 (13.2)
Gastric fistula	-	1 (3.3)	-	1 (1.5)
Mucositis oral	-	1 (3.3)	-	1 (1.5)
Nausea	-	1 (3.3)	3 (12.5)	4 (5.9)
Vomiting	-	-	2 (8.3)	2 (2.9)
General disorders and administration site conditions - n (%)	-	4 (13.3)	2 (8.3)	6 (8.8)
Fatigue	-	4 (13.3)	2 (8.3)	6 (8.8)
Infections and Infestations – n (%)	1 (7.1)	-	-	1 (1.5)
Sepsis	1 (7.1)	-	-	1 (1.5)
Investigations - n (%)	2 (14.3)	2 (6.7)	1 (4.2)	5 (7.4)
Neutrophil count decreased	2 (14.3)	1 (3.3)	1 (4.2)	4 (5.9)
Platelet count decreased	-	1 (3.3)	-	1 (1.5)
White blood cell decreased	1 (7.1)	-	-	1 (1.5)
Metabolism and nutrition disorders - n (%)	-	1 (3.3)	-	1 (1.5)
Anorexia	-	1 (3.3)	-	1 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - n (%)	-	1 (3.3)	-	1 (1.5)
Myelodysplastic syndrome	-	1 (3.3)	-	1 (1.5)
Skin and subcutaneous tissue disorders - n (%)	-	1 (3.3)	-	1 (1.5)
Palmar-plantar erythrodysesthesia syndrome	-	1 (3.3)	-	1 (1.5)
Vascular disorders - n (%)	-	5 (16.7)	3 (12.5)	8 (11.8)
Hypertension	-	5 (16.7)	2 (8.3)	7 (10.3)
Thromboembolic event	-	-	1 (4.2)	1 (1.5)

SERIOUS ADVERSE EVENTS (SAEs)

	Paclitaxel N=26	Ced+Ola Cont. N=40	Ced+Ola int. N=39	Overall N=105
SAEs - n	4	11	9	24
Subjects with at least one SAE – n (%)	3 (11.5)	10 (25)	8 (21.9)	21 (20)
Subjects with at least one SADRs – n (%)	1 (3.8)	2 (5)	2 (4.8)	5 (4.7)
Subjects with at least one SUSARs - n (%)	-	2 (5)	-	2 (19)
SADRs by Preferred Term (PT)	1	2	2	5
Anaemia	-	-	1 (2.4)	1 (0.9)
Asthenia	-	-	1 (2.4)	1 (0.9)
Sepsis	1 (3.8)	Fatal Outcome	-	1 (0.9)
Pneumonitis	-	1 (2.5)	-	1 (0.9)
Myelodysplastic syndrome	-	1 (2.5)	-	1 (0.9)

SUSAR, Resolved with sequaele

SUSAR, Fatal Outcome

Thanks to all collaborators of the project

Thank you for the attention

POPULATION - Inclusion Criteria

1. Confirmed **high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer**
2. Relapsed/progressive disease within 6 months from last platinum-based chemotherapy (**platinum resistant/refractory disease**)
3. **Any line of treatment after the first**
4. **Any "last" chemotherapy line including Paclitaxel** (Paclitaxel that should have been administered at least 6 months before the study beginning)
5. Women ≥ 18 years of age
6. Normal organ and bone marrow function measured within 28 days prior to administration of study treatment
7. ECOG performance status 0-1
8. Life expectancy ≥ 16 weeks
9. Evidence of non-childbearing status for women of childbearing potential or postmenopausal status
10. Willingness and ability to comply with the protocol
11. **At least one lesion (measurable as defined by RECIST 1.1)** that can be accurately assessed by CT scan or MRI with Chest X-ray at baseline and follow up visits
12. **BRCA1-2 mutation status known** or willingness to provide information about BRCA status within the end-of the study treatment
13. Provision of informed consent

POPULATION - Exclusion Criteria

1. Any **previous treatment with a PARP inhibitor**, including Olaparib
2. **Prior treatment with Cediranib** (previous **bevacizumab or other antiangiogenic drug allowed)**
3. **Previous progression to weekly Paclitaxel**
4. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥ 5 years.
5. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment. Bisphosphonates for bone metastases are allowed during the study
6. Concomitant use of known strong or moderate **CYP3A inhibitors**
7. Concomitant use of known strong or moderate **CYP3A inducers**
8. Persistent toxicities: >= CTCAE grade 2 (exception of alopecia)
9. Resting ECG with QTc > 470msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
10. Greater than +1 **proteinuria** on two consecutive dipsticks taken no less than 1 week apart unless urinary protein < 1.5g in a 24 hr period or urine protein/creatinine ratio < 1.5
11. History of **poorly controlled hypertension** or resting blood pressure >150/100 mmHg in the presence or absence of a stable regimen of anti-hypertensive therapy
12. Blood transfusions within 1 month prior to study start

POPULATION - Exclusion Criteria

13. Features suggestive of **MDS or AML** on peripheral blood smear
14. Patients with symptomatic uncontrolled brain metastases.
15. **Major surgery within 4 weeks** of starting study treatment and recovery from any effects of any major surgery
16. Inability to swallow medications and gastrointestinal disorders interfering with absorption of the study medication
17. Breast feeding women
18. Immunocompromised patients (e.g. patients serologically positive for human immunodeficiency virus (HIV) and receiving antiviral therapy)
19. Known active hepatic disease (i.e., Hepatitis B or C).
20. Known hypersensitivity to Olaparib, Cediranib or any of the excipients of the product.
21. Poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection
22. Known hypersensitivity to Paclitaxel
23. Uncontrolled seizures
24. History of **abdominal fistula or gastrointestinal perforation**
25. **Prior gastrectomy**