BAROCCO Trial

Best **A**pproach in **R**esistant-**O**varian-**C**ancer with-**C**ediranib-**O**laparib

Basket of fruit - Michelangelo Merisi - Caravaggio 1599

Ambrosian Library - Milano

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

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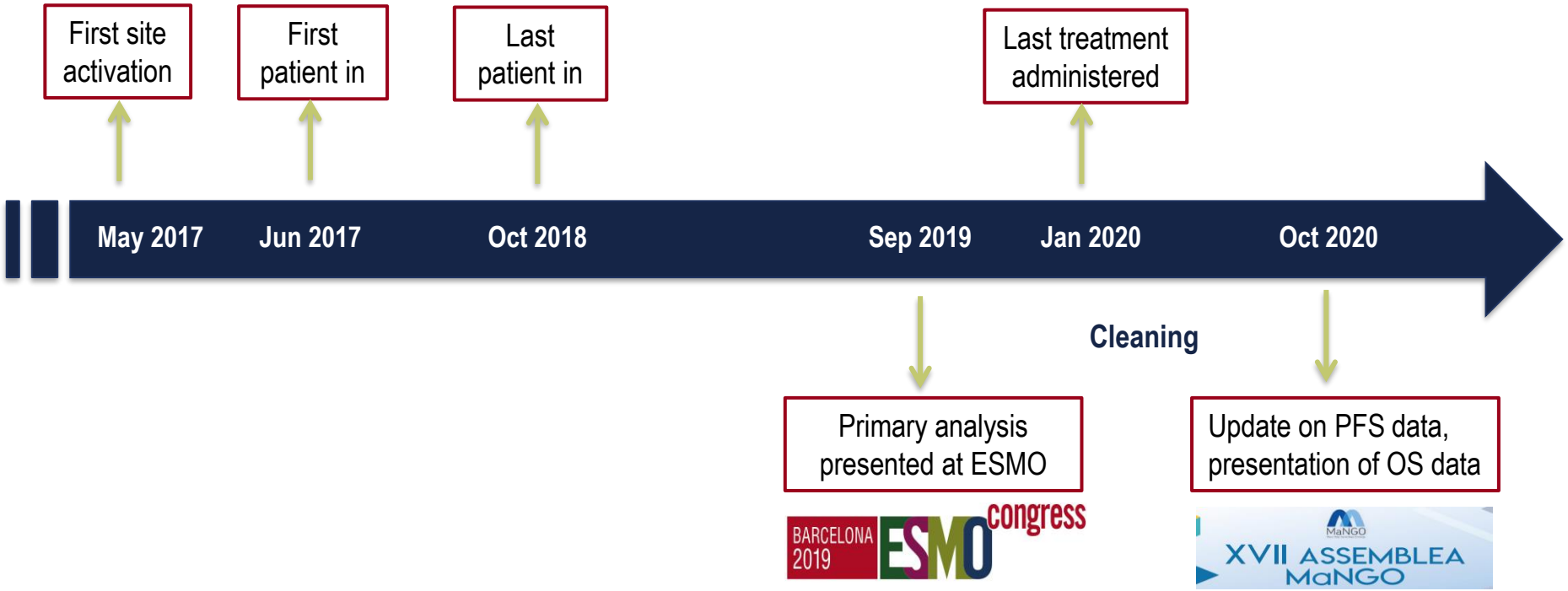
Sponsor: *MaNGO - Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan*
Supporter: *AstraZeneca*

XVII Assemblea MaNGO - Milano 16 Ottobre 2020 | Francesca Tettamanzi

Study timeline



Background

- Platinum-resistant ovarian cancer (PROC) still represents a high unmet need. Median PFS is 3-4 months even after weekly paclitaxel, which is recognized as the most effective chemotherapy regimen. New therapeutic options in this setting would be of great clinical interest.
- Single-agent olaparib was approved by the FDA in **gBRCAm** relapsed ovarian cancer ($\geq$ 3 lines). However, the efficacy of Poly(ADP-ribose) polymerase inhibitors (PARPi) therapy in **BRCA wt PROC** patients is very limited. CLIO[1] : 13% ORR and PFS 2.9 months. Quadra[2] : 3% ORR.
- Olaparib activity was observed beyond BRCAm tumours in platinum-sensitive relapsed ovarian cancer and was increased when combined with an antiangiogenic agent:
  - The combination of **cedirabib-olaparib compared to olaparib** led to a median PFS 23.7 vs. 5.7 months, HR: 0.31 (95% CI 0.15 – 0.66); p=0.0013 in gBRCA wt patients[3]
  - The combination of **bevacizumab and niraparib compared to niraparib** led to a median PFS 11.3 vs 4.2 months; p= 0.0001 in gBRCA wt patients[4]
- Combination of cediranib and olaparib may have a **synergistic effect** due to potentiation of olaparib effect by cediranib which induces down regulation of genes involved in Homologous Recombination (HR), thus producing a sort of functional BRCAness that favors the selective activity of the PARP inhibitor[3,5]

1.Vanderstichele A et al. ASCO 2019; 2. Moore KN et al, Lancet Oncol 2019; 3.Liu et al. AnnOncol 2019;
4. Mirza M et al, Lancet Oncol 2019; 5. Kaplan AR, Sci Transl Med, May 2019

Study Objectives and Design

To investigate the efficacy and toxicity of cediranib and olaparib in the PROC population

90 evaluable patients:

- Platinum-Resistant Ovarian Cancer
- Any **gBRCA status**
- **Any line of treatment and any last line**

Stratification factors

- Previous lines:1-2 vs ≥3
- gBRCA status: wild type vs mutated vs still uknown
- Prior antiangiogenetic: yes vs no

R
1:1:1

Paclitaxel (up to 24 infusions)
Paclitaxel 80 mg/m^2 weekly

Continuous schedule (up to PD)
Cediranib 20 mg/day 7 days per week
Olaparib tablets 300 mg x 2/day 7 days/week

Intermittent schedule (up to PD)
Cediranib 20 mg/day 5 days per week
Olaparib tablets 300 mg x 2/day 7 days/ week

RECIST tumor evaluation every 8 weeks

Two independent primary efficacy comparisons.
Endpoint: **PFS**

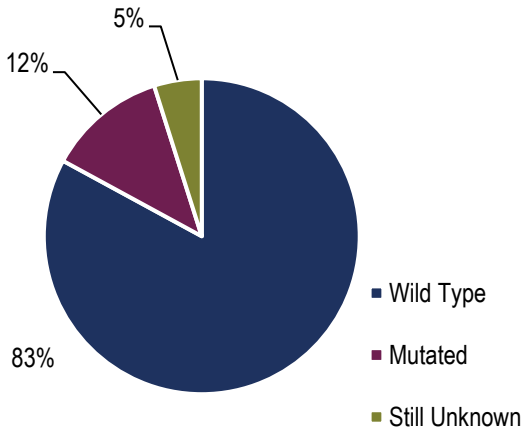
If both schedules superior in efficacy, then safety comparison.
Endpoint: **diarrhoea severity**

Patient Baseline Characteristics

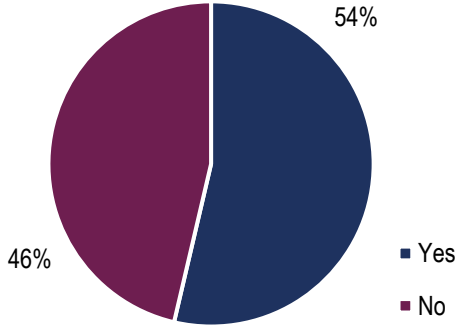
		Paclitaxel N=41	Continuous N=41	Intermittent N=41
Mean age		62.6	61.0	61.4
PS	0	85 %	90 %	77 %
	1	15 %	10 %	23 %
Mean Years from diagnosis		2.6	3.8	3.1
F.I.G.O. Stage	I-II	3 %	5 %	13 %
	III-IV	87 %	92 %	87 %
	Unknown	10 %	3 %	3 %
Histological Type	Serous	88 %	83 %	83 %
	Clear cell	9 %	5 %	10 %
	Endometrioid	3 %	7 %	7 %
	Mixed Epithelial	0	2 %	0
	Unknown	0	2 %	0
Median Platinum Free interval (mos)		3.0	2.2	1.5
Months from last line to first dose (median)		2.6	3.0	2.0

Patient Baseline Characteristics: Stratification Factors

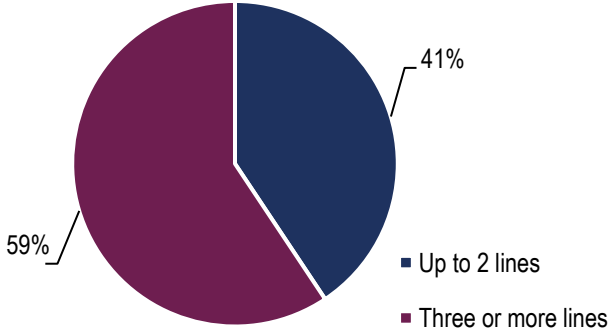
By BRCA status (n=123)



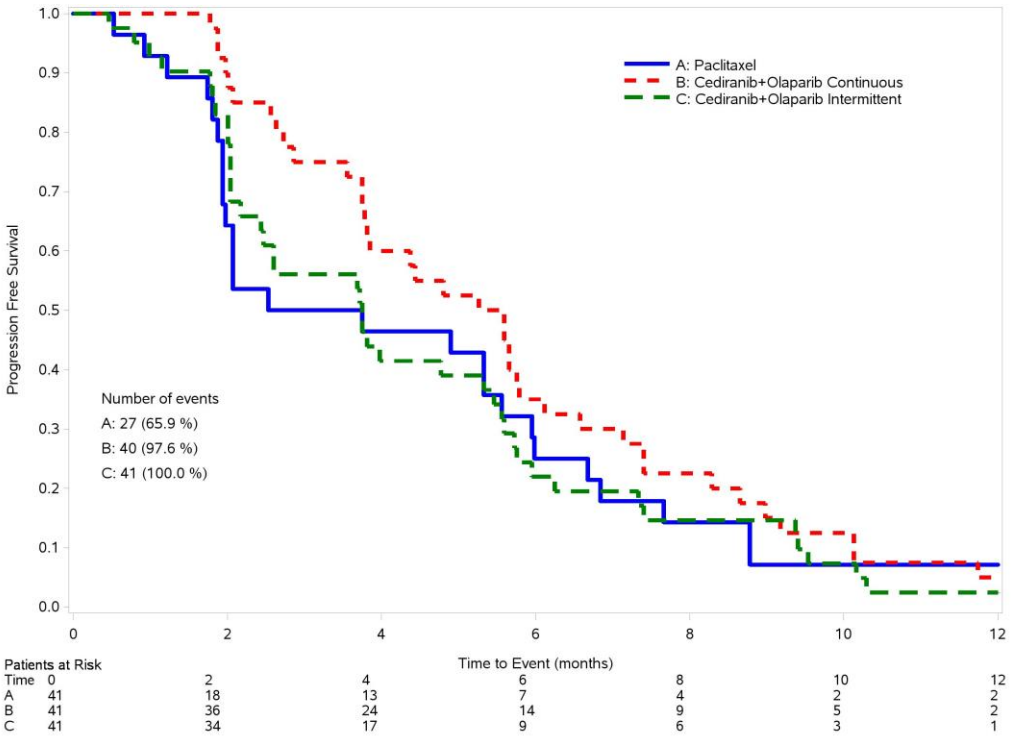
By previous anti-angiogenetic treatment (n=123)



By no. of previous chemotherapy (n=123)



Primary Endpoint: Progression-free Survival (by Investigator Assessment)



Median PFS (Q1 - Q3):

Paclitaxel 3.1 (1.9 – 6.3) months

Continuous 5.4 (3.2 – 7.4) months

Intermittent 3.8 (2.0 – 5.8) months

HR PFS [90% CI]; p-value Log-rank:

Paclitaxel vs Continuous 0.79 [0.52-1.19]; 0.34

Paclitaxel vs Intermittent 1.03 [0.68-1.55]; 0.90

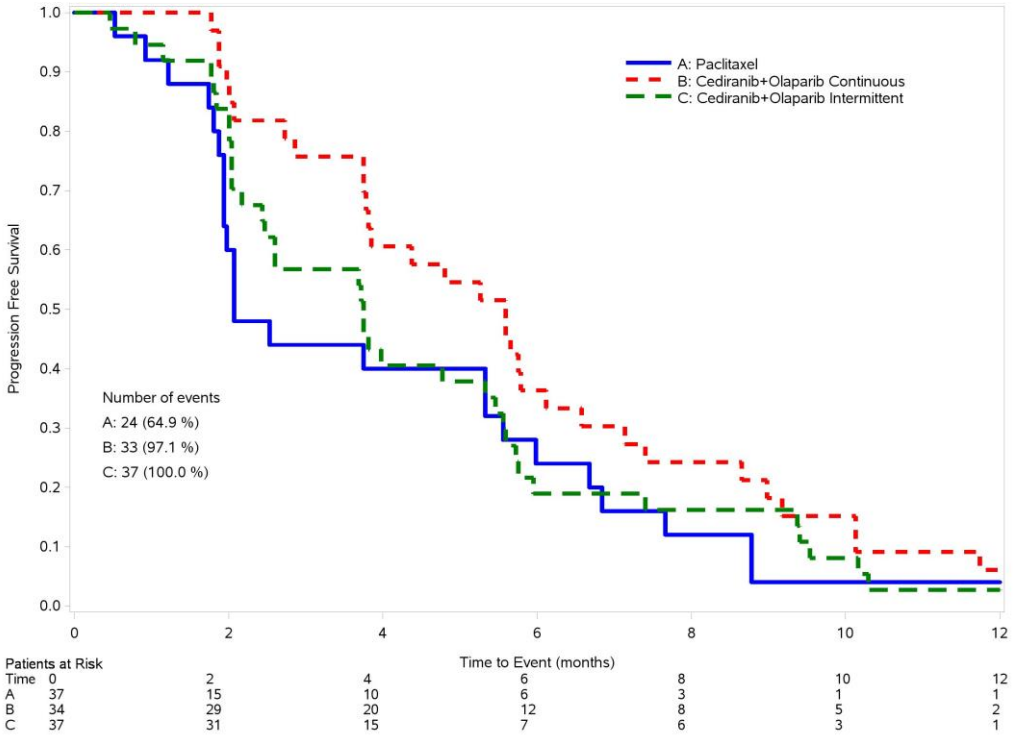
Test for proportional hazard:

Paclitaxel vs Continuous **p=0.015 - Not proportional**

Difference of area under the PFS curves:

1.13 months (95% CI: -0.41 to 2.69; p=0.15) in favor of Continuous

PFS In BRCA WT Or Still Unknown Patients



Median PFS (Q1 - Q3):

Paclitaxel 2.1 (1.9, 6.0) months

Continuous 5.6 (3.8, 7.4) months

Intermittent 3.8 (2.0, 5.7) months

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

Paclitaxel vs Continuous 0.67 [0.40 – 1.15]; 0.15

Paclitaxel vs Intermittent 0.90 [0.53 – 1.51]; 0.68

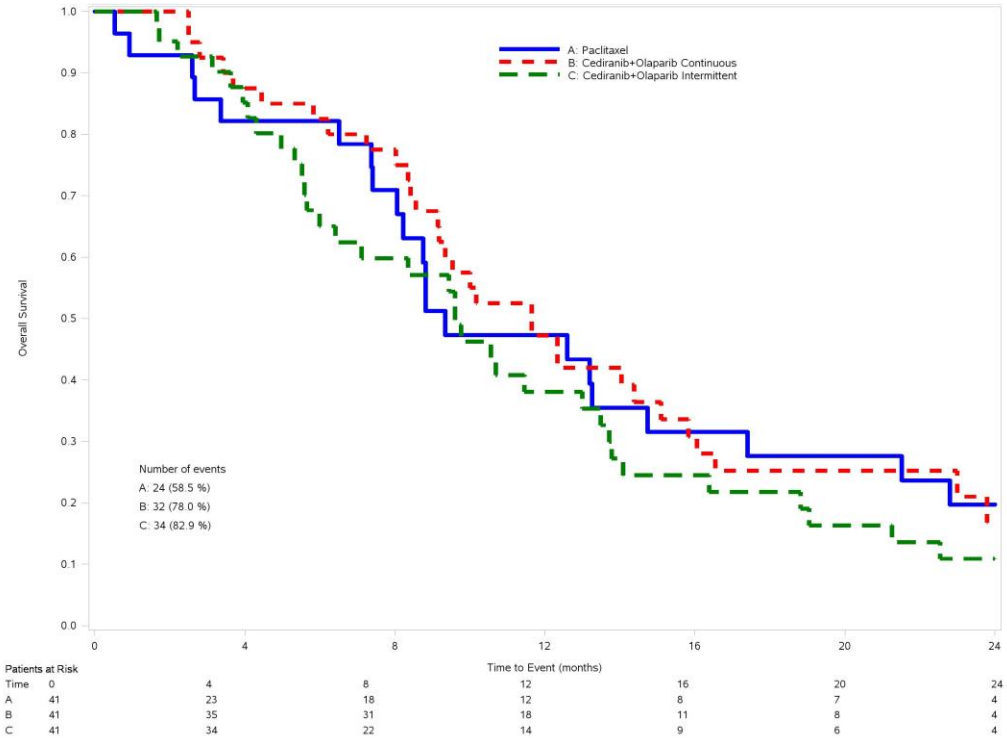
Test for proportional hazard:

Paclitaxel vs Continuous **p= 0.004 - Not proportional**

Difference of area under the PFS curves:

1.41 months (95% CI: -0.69 to 2.77; p= 0.04)
in favor of Continuous

Secondary Endpoint: Overall Survival



Median OS (Q1 - Q3):

Paclitaxel 9.3 (7.4 – 21.5) months

Continuous 11.6 (8.2 – 23.0) months

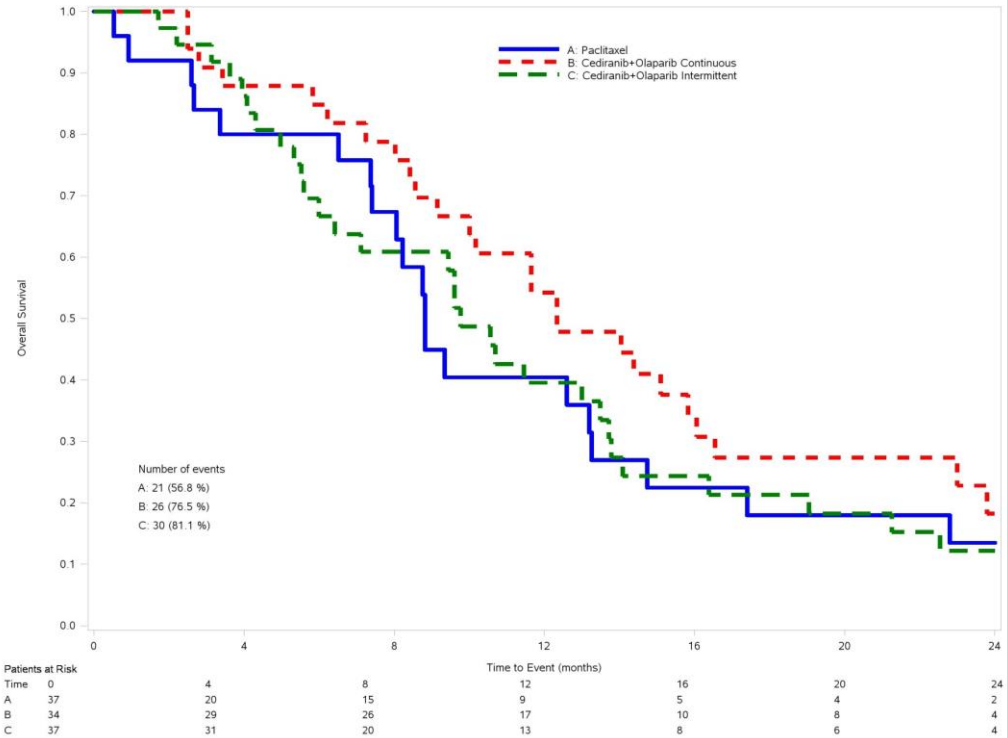
Intermittent 9.6 (5.5 – 14.1) months

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

Paclitaxel vs Continuous 0.89 [0.52-1.51]; 0.66

Paclitaxel vs Intermittent 1.13 [0.67-1.92]; 0.64

OS In BRCA WT Or Still Unknown Patients



Median OS (Q1 - Q3):

Paclitaxel 8.8 (7.4 –14.7) months

Continuous 12.3 (8.4 – 23.0) months

Intermittent 9.8 (5.5 – 14.1) months

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

Paclitaxel vs Continuous 0.68 [0.38-1.22]; 0.197

Paclitaxel vs Intermittent 0.94 [0.54-1.64]; 0.819

Patients' Compliance

	Paclitaxel N=28	Continuous N=41	Intermittent N=41
Administered dose as mg/week, mean (SD)			
Paclitaxel	76 (28)	-	-
Cediranib	-	118 (16)	81 (25)
Olaparib	-	3210 (850)	3305 (1099)
Dose intensity (administered /expected* weekly dose), %			
Paclitaxel	95%	-	-
Cediranib	-	84%	81%
Olaparib	-	76%	79%
Number of administered cycles, median (Q1-Q3)	4 (2-6)	5 (3-8)	5 (3-7)

*Expected weekly dose:

- Paclitaxel: 80 mg/m2
- Olaparib: 4.200 mg
- Cediranib continuous: 140 mg
- Cediranib intermittent: 100 mg

Drug related Adverse Events (AEs)

	Paclitaxel N=28		Continuous N=41		Intermittent N=40	
Subjects with at least one drug related AE	70%		78%		78%	
Drug related AEs (≥10% of patients)	Any grade	≥G3	Any grade	≥G3	Any grade	≥G3
Anemia	18%	-	17%	10%	23%	15%
Neutrophil count decreased	11%	7%	7%	2%	5%	3%
Diarrhoea	4%	-	51%	5%	58%	3%
Mucositis oral	7%	-	12%	2%	-	-
Nausea	18%	-	56%	2%	50%	8%
Vomiting	-	-	42%	-	38%	5%
Peripheral sensory neuropathy	14%	-	-	-	-	-
Peripheral motor neuropathy	11%	4%				
Fatigue	23%	-	51%	10%	43%	13%
Alopecia	18%	-	-	-	-	-
Rash maculo-papular	11%	-	5%	-	5%	-
Hypertension	-	-	29%	12%	18%	13%
Asthenia	-	-	-	-	3%	3%
Myelodysplastic syndrome	-	-	2% (1)	**2%* (1) G5**	-	-
Pneumonitis	-	-	2% (1)	2%* (1)	-	-
Sepsis	4% (1)	**4%* (1) G5**	-	-	-	-

SADR (1pts, Intermittent)

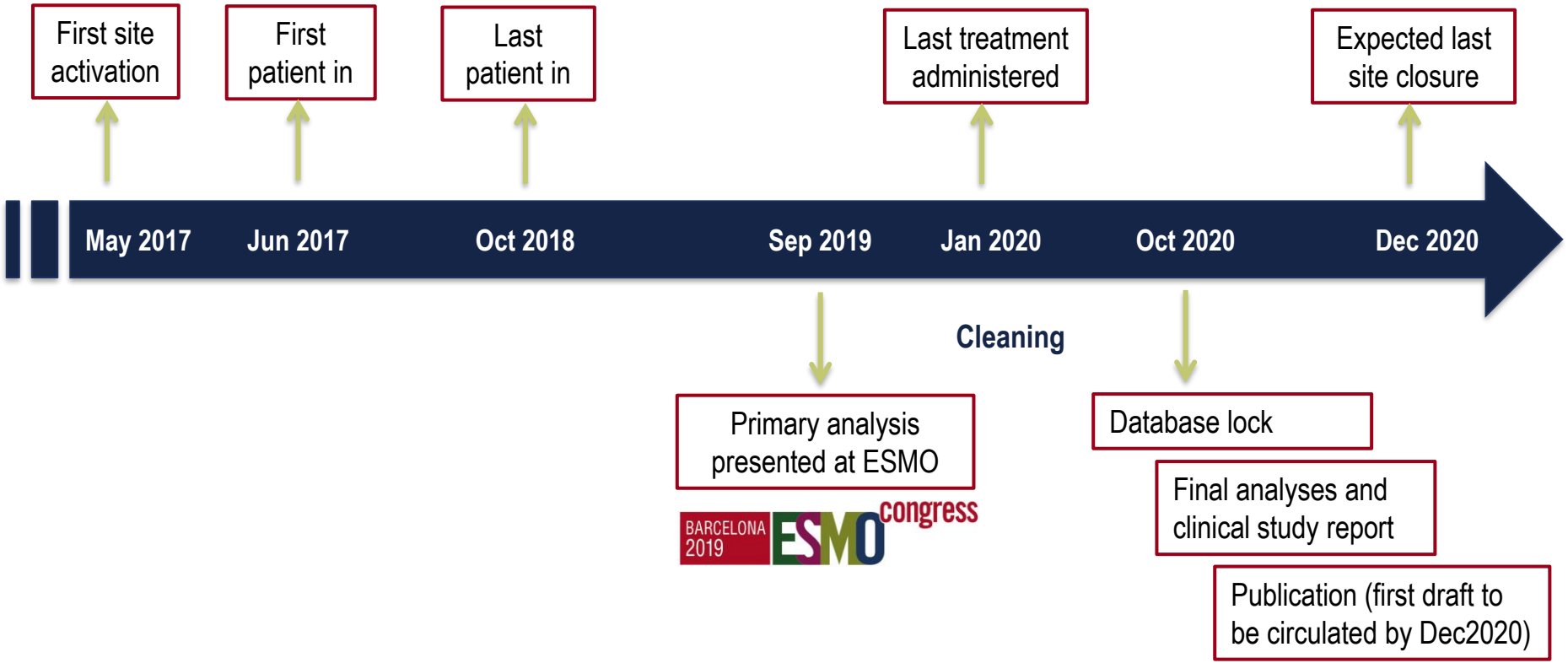
SADR

SUSAR

Conclusions

- ✓ BAROCCO included a difficult-to-treat population with a high unmet need:
  - 59% patients received three or more lines
  - Median Platinum Free Interval : 1.93 months (IQR 0.7-4.3)
- ✓ First trial with the combination cediranib-olaparib in PROC with a control arm
- ✓ Although not statistically significant, the continuous administration shows a promising trend for improved progression free survival, particularly in gBRCAwt population with HR for PFS Continuous vs Paclitaxel 0.67 [0.40 – 1.15]; 0.15
- ✓ The same trend is observed with respect to overall survival, with HR for OS Continuous vs Paclitaxel 0.68 [0.38-1.22]; 0.197 in gBRCAwt population
- ✓ The regimen of cediranib 20 mg daily and olaparib 300 mg tablets twice daily was well tolerated with few severe side effects: severe diarrhoea occurred only in 5% of patients with the continuous administration
- ✓ The interruption of cediranib administration for two days may have a detrimental effect on PFS and OS with no benefit on toxicity; intermittent schedule does not prevent cediranib dose suspensions/reductions leading to the administration of 81% of the expected dose
- ✓ The combination of cediranib and olaparib represents an active, feasible, oral regimen, which deserves further investigation. These results support ongoing trials investigating the same combination in PROC patients (NRG GY005, NCT02502266, CONCERTO, NCT02889900)

What next?


First site activation
First patient in
Last patient in
Last treatment administered
Expected last site closure
May 2017
Jun 2017
Oct 2018
Sep 2019
Jan 2020
Oct 2020
Dec 2020
Cleaning
Primary analysis presented at ESMO
BARCELONA 2019 ESMO congress
Database lock
Final analyses and clinical study report
Publication (first draft to be circulated by Dec2020)

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