Supplementary Tables and Figures

Treatment line	Study	Treatment	Regimen	Patient sample	Platinum sensitive/ resistant	Median lines of prior treatment (range)	Measures/ endpoints	Key results	Author
Maintainance after 1st line	Prospective	Maintenance post CR with platinum Arm A: MC plus methotrexate Arm B: observation alone	MC=50mg daily, MTX=2.5mg daily	n=60	sensitive = 100%	n/a	PFS, toxicity	Arm A PFS=18m Arm B PFS=15.5m	El-Husseini et al, 2016.
Maintainance after recurrent disease	Prospective	Maintenance Bevacizumab plus MC post induction chemotherapy with cisplatin/epirubicincyclophosphamide/bevacizumab	Bev=15mg/kg every 21d plus MC=50mg daily 2weeks on/1week off	n=39	resistant= 20.5% sensitive= 79.5%	1 (1-2)	ORR/PFS/ OS	ORR=10% PFS=8.4m OS=22.7m	Petrioli et al, 2015.
Recurrent disease	Prospective	MC monotherapy	100mg daily 3weeks on/1 week off	n=14	n/a	3 (3-5)	ORR/PFS/ OS	ORR=7% PFS=3m OS=7m	Watanabe et al, 2010.
	Retrospective	MC monotherapy	50mg daily continuously	n=54	resistant = 37% sensitive = 63%	4 (1-9)	ORR/PFS/ OS	ORR=20.4% PFS=4m OS=13m	Ferrandina et al, 2014
	Retrospective	MC monotherapy	150mg daily 2weeks on/2weeks off	n=26	resistant = 45.4% sensitive = 54.6%	3 (1-6)	Ca125 response, PFS, OS	Ca125 response =44% PFS=4m OS=8m	Handolias et al, 2016.
	Retrospective	Bevacizumab plus MC	Bev=10mg/kg every 14d MC=50mg daily continuously	n=66	resistant =100%	6.5 (3-16)	ORR/PFS/ OS	ORR=42.4% PFS=3m OS=12m	Barber et al, 2013.
	Prospective	Bevacizumab plus MC	Bev=10mg/kg every 14d MC=50mg daily continuously	n=70	resistant= 40% sensitive= 60%	2 (1-3)	ORR/PFS/ OS	ORR=24% PFS=7.2m OS=16.9m	Garcia et al, 2008.
	Retrospective	Bevacizumab plus MC	Bev=10mg/kg every 14d MC=50mg daily continuously	n=15	resistant= 27% sensitive =73%	8 (5-15)	Ca125 response/O RR/PFS	Ca125 response =67% ORR=33% PFS=3.9m	Chura et al, 2007.
	Prospective	Sequential Bevacizumab and MC; MC added upon progression on Bevacizumab	Bev=15mg/kg every 21d followed by MC=50mg daily continuously	n=20	resistant= 70% sensitive =30%	1 (0-2)	ORR/PFS/ OS	ORR=10% PFS=8.4m OS=22.7m	Matulonis et al, 2012.
	Retrospective	Bevacizumab plus MC	Bev=10mg/kg every 14d MC=50mg daily continuously	n=38	resistant= 79% sensitive= 21%	4 (1-8)	ORR/PFS/ OS	ORR=40.5% PFS=4.5m OS=10.7m	Sánchez-Muñoz et al, 2010.
	Prospective phase I	MC plus pazopanib	MC=50mg daily plus pazopanib = 400-800mg daily continuously	n=16	resistant= 56% sensitive= 44%	2.5 (2-4)	ORR/PFS/ OS	ORR=44% PFS=8.3m OS=24.9m	Dinkic et al, 2017.
	Randomised phase II	MC +/- veliparib	Arm A: MC 50mg daily Arm B: MC 50mg plus veliparib 60mg daily continuously	n=75	n/a	4 (1-9)	ORR/PFS	Arm A: ORR=22% PFS=2.3m Arm B: ORR=18% PFS=2.1m	Kummar et al, 2015.

Table S1: Studies with metronomic cyclophosphamide in ovarian cancer

Abbreviations: MC=metronomic cyclophosphamide; ORR=overall response rate (CR+PR); PFS=progression-free survival; OS=overall survival; CR=complete response; PR=partial response.

Patient selection criteria:
Informed consent
Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2,
anticipated life expectancy ≥ 3 months
absolute neutrophil count (ANC) ≥ 1,500/mm^3
platelet count ≥ 100,000/mm^3
bilirubin and creatinine ≤ 1.5 times the upper limit of normal
radiological and/or clinical evidence of disease progression
For Ca125-based disease progression, at least two separate rising Ca125 results were required, at least 28 days apart, in combination with symptomatic progression

Table S2: Patient selection criteria for treatment with MC

		All patients
Patient demographics		**n=68**
Age	n (range)	69 (25-85)
Lines of prior treatment	median (range)	3 (1-10)
Baseline Ca125 (U/mL)	median (range)	656 (18-122,600)
Performance status		
percentage (%)	**0**	2 (3%)
	1	39 (57%)
	2	27 (40%)
Lines of prior platinum-based treatment		
number (%)	**1-2**	44 (65%)
	3-4	20 (29%)
	≥ 5	3 (4%)
Histology		
number (%)	**HGS**	n= 53 (78%)
	LGS	n= 1 (1%)
	Carcinosarcoma	n= 2 (3%)
	NOS	11 (16%)
Platinum resistant relapse		
number (%)	**Yes**	59 (87%)
	No	9 (13%)
	Yes- primary	18/59 (31%)
	Yes- acquired	41/59 (69%)
***gBRCA* status**		
number (%)	**Pathogenic mutation**	10 (15%)
	wild type	38 (56%)
	unknown	20 (29%)
Cycles of MC median (range)		3 (1-14)

Table S3: Patient characteristics. *gBRCA*: germline *BRCA* status. HGS=high-grade serous; LGS=low-grade serous; NOS=non-otherwise specified, MC=metronomic cyclophosphamide.

	Intention-To-Treat population					
Response rate criteria	**Combined[$]**	**n=68**	**Radiological[+]**	**n=68**	**Ca125 response**	**n=68**
	Complete response	0 (0%)	Complete response	0 (0%)		
	Partial response	16 (24%)	Partial response	3 (4%)	Response	17 (25%)
	Stable disease	8 (12%)	Stable disease	12 (18%)	Non-response/Non-PD	24 (35%)
	Progressive disease	26 (38%)	Progressive disease	28 (41%)	Progressive disease	6 (9%)

Table S4. Response rates in the ITT population. 18/68 patients did not fulfil the criteria to be evaluable, hence the percentages are not adding up to 100%. [$]at least 1 radiological tumour assessment and/or 2x Ca125 measurements. [+]At least 1 radiological tumour assessment.

Response rate criteria		**Platinum-sensitive**	**Platinum-resistant**	**p value**	**Acquired resistance**	**Primary resistance**	**p value**
Combined criteria[$]	**Evaluable patients**	**n=9**	**n=41**		**n=30**	**n=11**	
	Partial response	6 (67%)	10 (24%)	**p=0.02**	9 (30%)	1 (9%)	**p=0.005**
	Stable disease	1 (11%)	7 (17%)		6 (20%)	1 (9%)	
	Progressive disease	2 (22%)	24 (59%)	p=0.06	15 (50%)	9 (82%)	p=0.08

Table S5: Response rates in evaluable patients by combined criteria as per Gynaecologic Cancer Intergroup criteria 2005 (34). Comparisons were done using Chi-square test with Yate's correction when required. Partial responses (PR) were compared against non-responders (SD+PD) and progressive disease results were compared to CR+PR+SD results. Abbreviations: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). [$]at least 1 radiological tumour assessment and/or 2x Ca125 measurements.

Toxicity (n=56)	Grade 1-2	Grade 3
Neutropenia	10 (18%)	1 (2%)
Nausea	9 (16%)	0 (0%)
Anaemia	4 (7%)	0 (0%)
Diarrhoea	3 (5%)	0 (0%)
Mucositis	3 (5%)	0 (0%)
Fatigue	3 (5%)	0 (0%)
Cystitis	1 (2%)	0 (0%)
Influenza	1 (2%)	0 (0%)
Transaminitis	0 (0%)	1 (2%)

Table S6: Toxicity results. There were no grade 4/5 toxicities observed with MC treatment.

Univariate Analysis					
			95% CI for OR		
Combination criteria[$]		**OR for disease progression**	**lower**	**upper**	**p value**
	Age (>70yo)	1.83	0.51	6.57	0.352
	PS > 1	2.2	0.56	9.046	0.253
	gBRCA mutation	**0.06**	**0.006**	**0.51**	**0.011**
	Platinum resistance	5.2	0.91	30.2	0.06
	Prior lines of platinum ≥3	**0.1**	**0.02**	**0.44**	**0.002**
Radiological criteria[+]	Age (>70yo)	1.73	0.47	6.39	0.409
	PS > 1	4.87	0.92	25.8	0.06
	gBRCA mutation	**0.06**	**0.01**	**3.92**	**0.003**
	Platinum resistance	**8.66**	**1.47**	**50.9**	**0.017**
	Prior lines of platinum ≥3	**0.14**	**0.03**	**5.94**	**0.007**

Table S7: Univariate analysis.

OR= Odds ratio. Univariate analysis with Ca125 response as dependent variable is not shown, as results were not statistically significant. 95% CI=95% confidence interval. [$]at least 1 radiological tumour assessment and/or 2xCa125 measurements. [+]At least 1 radiological tumour assessment.

Multivariate Analysis					
Response criteria			**95% CI for OR**		
Combination criteria		**OR for disease progression**	**lower**	**upper**	**p value**
	Age (>70yo)	2.12	0.34	13.00	0.41
	PS > 1	0.45	0.48	4.3	0.49
	gBRCA mutation	0.08	0.007	1.06	0.056
	Platinum resistance	4.92	0.54	55.5	0.19
	Prior lines of platinum ≥3	**0.11**	**0.016**	**0.81**	**0.03**
Radiological criteria	Age (>70yo)	4.81	0.64	35.9	0.12
	PS > 1	3.29	0.36	29.8	0.28
	gBRCA mutation	**0.075**	**0.008**	**0.671**	**0.02**
	Platinum resistance	6.64	0.62	70.2	0.11
	Prior lines of platinum ≥3	0.3	0.04	1.87	0.2

Table S8: Multivariate analysis including all variables.

OR=odds ratio. 95% CI=95% confidence interval. Analysis with Ca125 response as dependent variable not shown, as results were not statistically significant.

Multivariate Analysis					
			95% CI for OR		
Combination criteria[$]		**OR for disease progression**	**lower**	**upper**	**p value**
	Age (>70yo)	1.80	0.32	10.16	0.51
	PS > 1	0.70	0.09	5.53	0.73
	gBRCA mutation	**0.07**	**0.01**	**0.84**	**0.04**
	Prior lines of platinum ≥3	**0.14**	**0.02**	**0.87**	**0.04**
Radiological criteria[+]	Age (>70yo)	3.69	0.59	23.11	0.16
	PS > 1	5.46	0.66	45.41	0.12
	gBRCA mutation	**0.07**	**0.01**	**0.55**	**0.01**
	Prior lines of platinum ≥3	0.38	0.07	2.09	0.27
Combination criteria[$]		**OR for disease progression**	**lower**	**upper**	**p value**
	Age (>70yo)	3.12	0.60	16.30	0.18
	PS > 1	1.53	0.28	8.47	0.63
	gBRCA mutation	**0.07**	**0.01**	**0.68**	**0.02**
	Platinum resistance	3.34	0.40	28.19	0.27
Radiological criteria[+]	Age (>70yo)	5.24	0.75	36.54	0.10
	PS > 1	4.59	0.58	36.56	0.15
	gBRCA mutation	**0.05**	**0.01**	**0.44**	**0.01**
	Platinum resistance	5.50	0.56	53.65	0.14

Table S9: Multivariate analysis including excluding the variables of platinum resistance and prior lines of platinum treatment, sequentially.

OR= odds ratio. 95% CI=95% confidence interval. Analysis with Ca125 response as dependent variable not shown, as results were not statistically significant. [$]at least 1 tumour assessment and/or 2xCa125 measurements. [+]At least 1 radiological tumour assessment.

Multivariate Analysis					
			95% CI for OR		
Combination criteria[$]		**OR for disease progression**	**lower**	**upper**	**p value**
	Age (>70yo)	1.62	0.31	8.36	0.56
	PS > 1	0.59	0.08	4.54	0.61
	Platinum resistance	6.57	0.71	60.81	0.10
	Prior lines of platinum ≥3	**0.10**	**0.02**	**0.56**	**0.01**
Radiological criteria[+]	Age (>70yo)	2.40	0.47	12.38	0.30
	PS > 1	2.17	0.31	15.22	0.44
	Platinum resistance	7.94	0.96	65.82	0.06
	Prior lines of platinum ≥3	**0.18**	**0.04**	**0.91**	**0.04**

Table S10: Multivariate analysis.

Multivariate analysis excluding *gBRCA* as a variable. OR= odds ratio. 95% CI=95% confidence interval. Analysis with Ca125 response as dependent variable not shown, as results were not statistically significant. [$]at least 1 tumour assessment and/or 2xCa125 measurements. [+]At least 1 radiological tumour assessment.