Individual patient data meta-analysis of randomized trials to assess the surrogacy of intermediate endpoints of overall survival in newly diagnosed advanced ovarian epithelial, fallopian tube and primary peritoneal cancer

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By the GCIG Meta-Analysis group

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Steering committee (in alphabetical order):

Secretariat:

Xavier Paoletti (Gustave Roussy, Villejuif, France)

xavier.paoletti@gustaveroussy.fr

Ros Glasspool (NHS Greater Glasgow and Clyde, Glasgow, UK)

Ros.Glasspool@ggc.scot.nhs.uk

GCIG **Consortium investigators:**

GCIG group representative for each trial contributed

Secretariat address:

Meta-Analysis platform

Service de Biostatistique et d'Epidémiologie

Gustave-Roussy Cancer Center

114, rue Edouard Vaillant

94805 Villejuif cedex

Phone: +33 1 42 11 65 64

Fax: +33 1 42 11 52 58

Advisory board: Marc Buyse, Tomasz Burzykowski, IDDI & Cluepoint, Hasselt University

RATIONALE AND BACKGROUND

In 2012, about 240 000 women were diagnosed with an advanced ovarian, epithelial, fallopian tube or primary peritoneal cancer (Ferlay 2015). Approximately 75 percent of women have stage III or stage IV disease at diagnosis. Initial management involves the combination of surgical cytoreduction and systemic chemotherapy. The combination of carboplatin–paclitaxel is the universal standard regimen in the management of ovarian cancer with the response rate of approximately 65%, median progression free survival (PFS) range between 16 and 21 months while median overall survival (OS) is 32–57 months (Ozols 2003). Although the majority of patients respond to first-line chemotherapy, most of them recur and require a salvage treatment. Thus, a very important priority for gynecologic oncology research is to improve the outcome of first-line treatment and numerous new agents are under development.

Currently, OS is the gold standard for the evaluation of treatment and is required by the regulatory agencies (Food and Drug Administration and the European Medical Agency). However, OS has a number of shortcomings as an endpoint. It is time consuming and costly to measure, and delays the development of subsequent trials. It suffers from the confounding effects of post study therapy and, where post progression survival is long, very large sample sizes are required to demonstrate an overall survival advantage following a modest improvement in PFS, (Broglio 2009). PFS gives an earlier assessment of anti-tumour activity, requires smaller sample sizes and is not affected by post progression therapy. However the clinical relevance is not clear. To be of valid clinical significance it must be a surrogate of OS or it must be associated with prolonged improvement or maintenance of quality of life. In response to this, the Gynecologic Cancer InterGroup, GCIG, recommended at the Tokyo 5th Ovarian Consensus Conference, that PFS can serve as a primary endpoint instead of OS, provided that secondary endpoints such as quality of life support the superiority of the investigated treatment (McGee 2017). They also recommended that various pathological, clinical covariates and biomarkers should be collected at baseline as they may modify the treatment effect. These statements are based on the extensive experience of the GCIG members in the conduct of clinical trials but there remains a lack of evidence for the validity of PFS as surrogate marker of OS in the modern era and with different treatment types.

In 2009, Buyse *et al* (2009) showed, that PFS was a good surrogate marker of OS in ovarian cancer but this study included a limited number of four trials which

investigated standard cytotoxic regimens (CP versus CAP). He found a correlation at the individual level measured by Kendall's tau of 0.84 (0.83, 0.85) and at the group level (Pearson squared correlation) of 0.95[0.82,0.99], in these trials, treatment effect on PFS predicted treatment effect on OS. Since then, novel targeted therapies have been introduced, many of which involve maintenance therapy. Post progression survival has also steadily increased. We therefore propose a quantitative assessment based on individual patient data in order to validate the use of PFS in specific treatment classes, indications.

Among the tools to evaluate ovarian progression cancer and response to treatment, CA125 is an important marker in epithelial ovarian cancer (Söletormos 2016). CA125 is routinely used in follow up (Pignata 2011) however Rustin found that starting treatment at the time of asymptomatic rising CA125 offered no survival advantage and was associated with worse quality of life suggesting that use of PFS defined by CA125 has limited clinical relevance (Rustin 2011a). This was in line with an early work by J. Cruickshank and col. (1992) who found disappointing predictive ability on 81 patients.
The GCIG has integrated the elevation of CA125 with radiological RECIST criteria to give a combined definition of progression. In 2010 the GCIG recommended that GCIG CA125 criteria could be used to define progression but not for response in first line trials and be used for both progression and response in trials of relapsed disease. They recommended that further validation was required in trials of maintenance therapy and acknowledged that no validation had been performed in molecularly targeted therapy (Rustin 2011b). The combined criteria have never been investigated as a surrogate using the meta-analytic approach.
Lindemann et al. retrospectively analyzed the GCIG definition of progression in the Aurelia trial in relapsed setting and concluded that there was poor concordance between CA-125 at the time of progression and RECIST in platinum-resistant cancer, demonstrating the importance of further investigation of the validity of change in CA125 as a marker of progression (Lindemann 2016). However no such works have been done so far in first line treatment. Furthermore, the relationship between the dynamic evolution (time to increase, velocity of increase etc.) of CA-125 and response and progression by RECIST has not been investigated and these factors may influence the value of CA125 as a marker of progression and as a surrogate of PFS. Certainly differences in the method of assessing progression can affect the difference in the magnitude of effect between therapies (Burger 2011).
A last aspect we would like to investigate is the introduction of a new measure of

treatment efficacy in addition to the hazard ratio. The restricted mean survival time (RMST) has been proposed to quantify the treatment effect in several recent trials (Oza 2015). The difference in RMST between two treatment arms quantifies the additional life expectancy due to the investigational treatment. It is an alternative summary measure to median survival and it is not dependent upon the proportional hazard assumption (that is the assumption that treatment effect is constant in time). RMST can be computed for PFS as well as OS. To the best of our knowledge, their relationship has never been explored.

It is therefore timely to perform a meta-analysis in order to provide a more accurate assessment of the prognostic and predictive role of the CA-125 dynamic and assess the relationship between PFS defined by combined GCIG criteria or by RECIST and OS and between RMST for PFS and OS in different first line treatments.

Following the framework set up by Buyse et al. (2000) and Burzykowski et al (2006) surrogacy should be measured both at the individual level (does a patient with longer PFS have longer survival) and at the trial level (does a treatment effect on PFS predict a treatment effect on OS). Only a meta-analysis of several trials allows exploration of both levels. This approach was recently applied in other settings such as colon cancer (Shi 2015), Head and Neck cancer (Michiels 2009), lymphomas (Sargent 2015), gastric (Paoletti 2013), ovarian cancers (Buyse 2009) etc.

Using the same meta-analysis approach, our objectives are (i) to examine PFS using RECIST or GCIG definition of progression, using both HR and RMST, as candidate surrogate endpoints for OS in trials studying the effect of chemotherapy or chemotherapy with targeted agents in the first line treatment of advanced ovarian cancer and (ii) to explore the association between repeated measurements of CA-125 and PFS.

OBJECTIVES AND ENDPOINTS

Objectives

The primary objective of this project is to assess surrogate endpoints for OS when quantifying effect of systemic chemotherapy or the addition of targeted agents to standard regimens for newly diagnosed advanced ovarian cancer using data from randomized clinical trials. We will investigate

1) Progression free survival defined as per GCIG criteria and by RECIST alone as surrogate of OS
2) Restricted mean survival time (RMST) for PFS as a surrogate of RMST for OS
3) Best Overall response using RECIST or WHO criteria as surrogate of OS
4) CA-125 evolution (velocity of rise, time to rise etc.) as a surrogate endpoint of PFS in first-line advanced ovarian cancer.

For objectives 1 and 2, treatment effects on PFS after various follow-up times (12 months, 18 months 24 months) will be correlated to OS and 3-year survival.
The assessment of surrogacy will be further explored in sub-groups defined by histology, FIGO staging, type of regimen (cytotoxic versus targeted agents) and in maintenance treatments by timing of the randomization. The relationship with other prognostic factors such as age and cytoreductive status will also be explored. Finally, as a sensitivity analysis, we will look at the surrogacy on older versus more recent trials as the standard of care after progression has evolved in the last decade.

End-points

The end-points will be

- Overall survival (OS) defined from the date of randomization to the date of death whatever the cause is. Patients alive at the cut-off point will censored at the last date they were known to be alive
- Progression-free survival (PFS) defined as the time from randomization to progression using radiological and clinical criteria (RECIST for instance)
- PFS defined from the date of randomization to progression as per GCIG criteria
- Time to second subsequent therapy or death (TSST)
- Biological markers (CA-125)
- Response rate by RECIST (best overall response and response at six cycles of treatment will be assessed)
- Restricted mean survival (RMST) for both PFS and OS that defined as the mean difference between the two PFS (respectively OS) treatment curves up to a 5- and 10-year horizon.

Prognostic factors

Data on major prognostic factors will also be collected for all trials included in the meta-analyses. A particular interest will be given to:

- Primary treatment modality (Surgery vs NACT)
- The maximal residual lesion size (e.g. <1cm or 1 – 2cm or no residual) status after surgery
- Patient's age at diagnosis
- Performance status
- Histologic subtype (including grade) (data on whether pathological review was performed or not for the trial will also be collected)
- Blood count at baseline (Neutrophils, lymphocytes and platelets etc.)
- FIGO stage
- Germline mutation (BRACA1/2) status

These data will be used to investigate variations in surrogacy assessment.

METHODS

Trials selection

Inclusion criteria

All trials included in the meta-analysis must satisfy the following criteria:

- Randomized clinical trials in epithelial ovarian cancer (including fallopian tube, primary peritoneal cancers)
- That collected overall survival and progression free survival
- That compared investigational treatment to standard treatment
- Trials published after 2004 and completed accrual before 31th December 2014.

Exclusion criteria

- Trials that evaluated
  - radiotherapy or surgery as primary objective
  - immunotherapy
  - intra-peritoneal trials
- Trials that randomized less than 60 patients

For trials reported multiple times, we will use the most recent data.

Trial Search

Data from all published and published randomized trials in ovarian cancer are sought using electronic database searching (GCIG, Pubmed, Scopus, Wos, Embase, ClinicalTrials, Centerwatch, National Cancer Institute NIH, Cochrane) and searching (meeting proceedings, review, articles). Other sources of clinical data such as clinicaltrials.gov have been consulted.

Description of the targeted trials

The eligible trials are described in Appendix B. In total, 37 randomized phase II or phase III trials for a total of 28,473 patients will be requested for the meta-analysis for the primary endpoints.

- **Appendix B.1** describes trials evaluating the added value of additional systemic treatment (no maintenance) to standard treatment; 15 trials (N=14,571) will be useable. Only one trial investigated targeted agent (MTA) and 14 (13,634 pts) investigated cytotoxic agents.
- **Appendix B.2** describes trials evaluating intensification regimen of various schedules (no maintenance) (5 trials, N=2,854).
- **Appendix B.3** describes trials evaluating maintenance treatments (18 trials, N=11,048 pts) including 7 trials of MTA.

Data collection

Individual patient data are requested. Whenever possible, updated follow-up will be asked. The data needed for each patient are presented below. Template for data transfer is proposed. The full database of the trial can be provided if this proves to be less time consuming for the contributors.
The individual data needed to carry out the meta-analysis should be sent to the secretariat:

SEND TO
Xavier Paoletti *Biostatistitics and Epidemiology dpt* *Meta-analysis platform* Gustave Roussy Cancer Center 114 rue Edouard Vaillant 94805 Villejuif Cedex, France Email: xavier.paoletti@gustaveroussy.fr Tel: +33 1 42 11 65 64

Data should be sent preferably in computerized form (Compact Disk, USB stick, or through electronic web-transfer). A secured server will be set up to serve as a drop box. MS-DOS or Macintosh format can be used. The tape or listing should contain individual data for EVERY randomized patient, whether eligible or not and whether properly followed up or not. Possible codes are suggested, but others may be used.
Example of requested data is summarized in the Appendix A.

Data Storage:

All anonymized data will be secured at the Gustave Roussy Data Center, meta-analysis platform.
The Data Center is part of the hospital and then benefits from the hospital firewalls and protections. All databases will be declared at the French national agency for data and privacy protection (CNIL). Data will be backed up on the hospital file system.

Data access will be restricted to selected members of the data center under the responsibility of Xavier Paoletti.

Statistical methods

Data check:

The individual patient data of each database sent by the investigators are verified by checking:

- the randomization process,
- the extent of follow-up,
- and the number of patients excluded after randomization.

The randomization process is verified by

- comparing the number of patients and the distribution of their initial characteristics between the two treatment groups
- checking the regularity of the inclusion process in the trial (distribution of days of enrollment for instance)
- Comparing follow-up between treatment groups.

Each trial will be re-analyzed. All descriptive results will be compared to the publications. In case of discrepancies, queries will be emitted to the sponsor. The process includes assessing

- the design of the trial,
- the nature of the treatments being compared,
- the population of patients included,

This process is essential to assess the characteristics, quality and the availability of the data.

Data analysis:

All analyses will be carried out on all randomized patients according to their allocated treatment arm, irrespective of the received treatment ("Intent to treat analyses"). Patients for whom individual data are not available will be excluded. If there are many such patients in a given trial, consideration will be given to exclude this trial from the meta-analysis.

The validity of PFS as surrogates for survival will be investigated through measures of

association between the endpoints, and through a joint model to estimate trial specific treatment effects on these endpoints. The model will be adjusted for prognostic factors, if appropriate data are available.

Individual level surrogacy

First, correlation will be assessed at the individual level. The association between distributions of OS and the candidate surrogate endpoint will be evaluated by a bivariate survival model. Both models based on Hougaard and on Clayton copulas will be fitted. The best model according to the Akaike's criterion will be selected. An estimated correlation coefficient ρ close to 1 will indicate a strong correlation between OS and the candidate surrogate at the patient level.

Trial level surrogacy

Then, correlation at the trial level will be assessed. Correlation between treatment effect on candidate surrogate and treatment effect on OS will be quantified through a linear regression model. Treatment effects will be estimated by log hazard ratios. The linear regression model will be weighted by the trial size. The coefficient of correlation R estimated by this model will reflect the trial-level surrogacy.

In order to enhance interpretation for the clinician's point of view, the correlation between effect of treatment on 1 and 2-year PFS and 3-year OS will also be regarded. The event rates over time will be evaluated in order to explore whether other cut-off points are more appropriate.

Surrogate threshold effect

One objective of a surrogate endpoint is to predict the treatment effect on OS observing treatment effect on the surrogate endpoint. In this way, the Surrogate Threshold Effect (STE) will be calculated. STE is defined as the minimum treatment effect that is necessary on the surrogate to be able to predict a non-zero effect on overall survival in a trial of infinite size. Its calculation is based on the linear regression used for the determination of trial level surrogacy. Graphically this value is situated at the vertical of the intersection of the line hazard ratio of OS=1 and the confidence interval of the regression line.

Validation strategy

A leave-one-out cross-validation will be used to validate the results obtained. It consists in re-estimating the linear model on all trials except one. The fitted model will be used

in the left trial to predict the treatment effect on OS based on the observed treatment effect on the candidate surrogate. Predicted hazard ratio and actual hazard ratio will be compared for each trial.

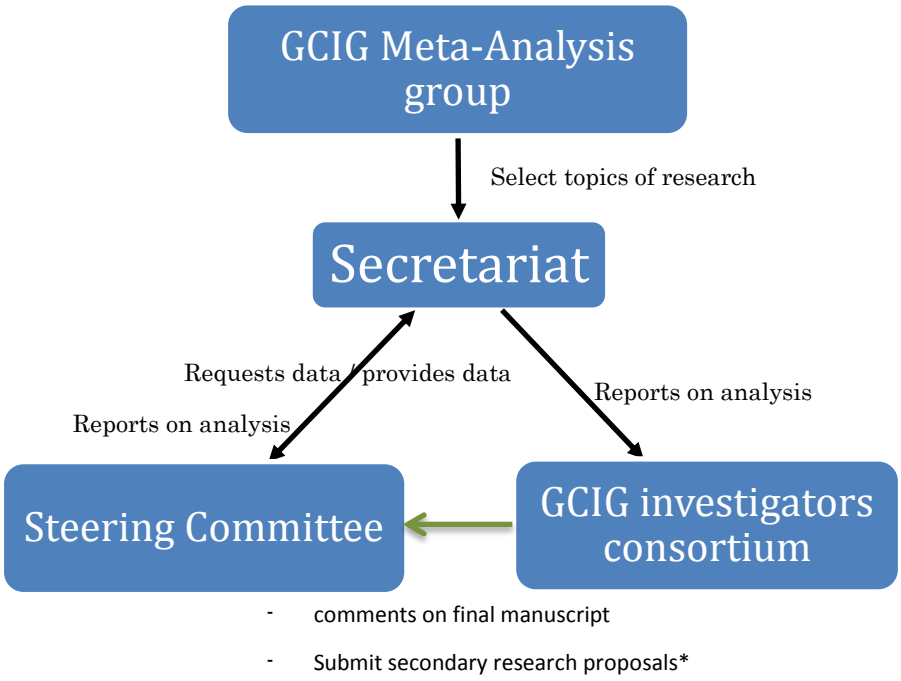
Project management

The GCIG meta-analysis initiative is supervised by the GCIG meta-analysis group. For each database that is created (for instance surrogacy in first line ovarian cancer randomized trials), there will be

- **a Steering Committee** made up of a representative from each GCIG group that agrees to contribute data to meta-analysis and the IPC/senior statistician and medical advisor. They will be responsible for
    - overseeing the project,
    - agreeing the final protocol,
    - reviewing and discussing the results and writing the manuscript.
    - Reviewing, agreeing on and hierarchizing all secondary research proposals on the collected database

  Groups will be responsible for nominating their steering committee member.
- The Secretariat made up of the senior statistician/IPC, medical advisor and a junior statistician. They will be responsible for
    - the protocol development, trial selection
    - data collection, cleaning, safe storage –
    - the analysis
    - statistical reports for each research question and material for presentations
- A project consortium made up of a representative for every trial that is contributed to the project. They will
    - share responsibility for reviewing and agreeing the results of the analysis and approving the manuscript with the project steering committee. If not one of the authors selected by their groups, they will be listed as collaborators in the manuscripts.

- Have the possibility to submit secondary research proposals on the collected database



*All three groups may submit secondary research questions to the steering committee

GUIDELINES FOR AUTHORSHIP

See attached document

APPENDIX:

Appendix A: Requested Data

To be completed based on the protocol

TRIAL DATA

Trial name	character
Name of the principal investigator	character

Note: the following coding is purely indicative. Any format will be welcome and the secretariat will do standardization.

For each patient is needed:

RANDOMIZATION

Unique patient identification	character
Cooperative group (or country) in case of intergroup	Character
Allocated treatment arm at randomization	
Post-operative standard regimen	1
Post operative investigational agent	2
…	…
Date of randomization	dd/mm/yyyy
Excluded from published analysis	
Yes	1
No	2
If yes, please specify the reasons	character

BASELINE PATIENT CHARACTERISTICS

Date of birth (or age at entry)	dd/mm/yyyy
Unknown	99
Performance Status: code as convenient but supply details of the Performance status scale used. Suggested coding if WHO/ECOG coding used:	
ECOG 0	0
ECOG 1	1
ECOG 2	2
ECOG 3	3
ECOG 4	4
Unknown	99
Karnofsky	0-100%
Stratification factors	

DISEASE CHARACTERISTICS AT PATIENT ENTRY

FIGO Stage at patient entry (specify version)	
Stage IA	1
Stage IB	2
Stage IC (1,2 or 3)	3
Stage IIA	4
Stage IIB	5
Stage IIIA (1 or 2)	6
Stage IIIB	7
Stage IIIC	8
Stage IVA	9
Stage IVB	10
Unclassifiable	11
Unknown	99

Histological subtype (provide classification used)	
Serous carcinoma	1
Endometrioid	2
Mucinous	3
Mixed clear cell	4
Pure clear cell	5
Other	6
unknown	99
Histological grade (provide classification used)	
1	1
2	2
3	3
Or	
Low grade	1
High grade	2
Blood count at baseline	
Neutrophils	Number
Lymphocytes	Number
Platelets	Number

Surgical procedure if any	
Primary complete resection	1
Delayed surgery	2
No surgery	3
….	
Unknown	99
Date of surgical procedure	dd/mm/yyyy
Maximal residual disease	
< 1cm	0
1 – 2 cm	1
> 2cm	2
Unknown	99

TREATMENT

Date start of treatment	dd/mm/yyyy
Date end of treatment	dd/mm/yyyy
Number of cycles	Numeric value

CA-125

CA125 (specify unit)	
At entry	Numeric value
At each follow-up viit	Numeric value
At progression	Numeric value
Unknown	99

FOLLOW-UP

Date of last follow-up (Date of death or date of last visit, updated if possible)	dd/mm/yyyy
Status at last follow-up (updated if possible)	
Alive	0
Dead	1
Cause of death, if applicable	
Clearly disease related	1
Clearly toxicity related	2
Non disease, non-toxicity	3
Unknown	9
First progression (progression of cancer, all second cancers)	
No	
Yes	1
Unknown	2
	99
Type of first progression	
pelvic and intra-abdominal	1
supra diaphragmatic	2
visceral metastasis	3
distant nodes	4
second cancer	5
other	6
unknown	99
Assessment of progression	
CT-scan	1
MRI	2
CA-125	3
other	4
unknown	99
Date of first progression	dd/mm/yyyy
Date of first biological progression (CA125, …)	dd/mm/yyyy
Reason of treatment discontinuation	
Disease relapse	1
Adverse event including toxic death	2

Other reason	3
Unknown	99

Date of next treatment initiation	dd/mm/yyyy

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Appendix B: Description of trials

B1- Trials of first line cytotoxic chemotherapy or targeted agent (**no maintenance**) (15 trials, N=14,571 pts)

1st Author	Year	Group (Sponsor)	Trt A	Trt B	nb of pts	OS	PFS	CA125
Lindemann K	2012	GCIG (NSGO)	paclitaxel/carbo + epirubicin	paclitaxel/carbo.	887	Y	Y	Y
Pignata S	2011	MITO2	paclitaxel/carbo + doxorubicin	paclitaxel/carbo.	820	Y	Y	Y
Burger RA[+]	2011	GOG	CT + beva (arm B)	CT	937	Y	Y	Y
Hoskins P	2010	NCIC	paclitaxel/carbo + cicplatin/topotecan	paclitaxel/carbo.	819	Y	Y	Y
du Bois A	2010	AGO-OVAR	paclitaxel/carbo + gemcitabine	paclitaxel/carbo.	1742	Y	Y	N
Bolis G	2010	University of Milan	paclitaxel/carbo + topotecan	paclitaxel/carbo.	326	Y	Y	N
Okamoto A	2014	JGOG - 3017	irinotecan / cisplatin	paclitaxel/carbo.	667	Y	Y	Y
Bookman MA[*]	2009	GCIG (GOG)	Tri-therapy	paclitaxel/carbo.	4312	Y	Y	N
Aravantinos G	2008	HeCOG	paclitaxel cisplatin + doxorubicin	paclitaxel/carbo.	451	Y	Y	?
Lhommé C	2008	Novartis	paclitaxel/carbo + valspodar	paclitaxel/carbo.	762	Y	Y	Y
Fruscio R	2008		cisplatin/paclitaxel + ifosfamide	cisplatin/paclitaxel + epirubicin	208	Y	Y	Y
Mouratidou D	2007		cisplatin + cyclophosphamide	cisplatin/paclitaxel	120	Y	Y	Y
Nicoletto MO	2007	Goccne Group	non platinum CT	platinum CT	161	Y	Y	Y
du Bois A	2006	GCIG (AGO)	paclitaxel/carbo + epirubicin	paclitaxel/carbo.	1282	Y	Y	N
Vasey PA	2004	SGTG	Docetaxel/carboplatin	paclitaxel/carbo.	1077	Y	Y	Y

+ *Only MTA*. In this GOG trial (3 arms), one arm investigated bevacuzimab administered for 6 cycles. The total number of patients is 625 + 625/2 (the pbo group is split)

++ Data on OS not available.

* 5 arms investigated the adjunction of gemcitabine, methoxypolyethylene glycosylated, liposomal doxorubicin, or topotecan

** Enrolled fragile and stopped prematurely for superiority of carboplatin

B2- Trials of first line treatments of **intensification therapy or different schedules** (no maintenance) (5 trials, N=2854 pts)

1st Author	Year	Group (Sponsor)	Trt A	Trt B	nb of pts	OS	PFS	CA125
van der Burg ME*	2014	Erasmus MC Cancer Institute	weekly paclitaxel/platinum induction + weekly paclitaxel/platinum	weekly paclitaxel/platinum induction + 6 cycles weekly paclitaxel/platinum	267	Y	Y	Y
Pignata S	2014	GCIG / NCI Napoli (MITO7)	weekly paclitaxel/carbo	3-weekly paclitaxel/carbo	822	Y	Y	Y
Banerjee S	2013	SGCTG (SCOTROC4)	flat dosing carboplatin	intrapatient dose escalation carboplatin	964	Y	Y	Y
Katsumata N	2013	JGOG - 3016	dose-dense paclitaxel + carboplatin	Norm. Paclitaxel + carboplatin	637	Y	Y	Y
Ray-Coquard I	2007	GINECO	intensified cyclophosphamide + GCSF	normal cyclophosphamide + platinum	164	Y	Y	Y

B3- Description of trials of first line **maintenance treatments** (18 trials, N=11,048 pts)

1st Author	Year	Group (Sponsor)	Trt A	Trt B	nb of pts	OS	PFS	CA125
Du Bois A	2016	Boehringer Ingelheim (AGO-OVAR12)	paclitaxel/carbo + nintedanib	paclitaxel/carbo + pbo	1366	Y	Y	Y
Oza AM	2015	ICON7 (MRC)	CT + beva	CT	1528	Y	Y	Y
du Bois A	2014	AGO (GSK)	pazopanib maintenance	Std	940	Y	Y	Y
Vergote IB	2014	EORTC-GCIG	Erlotinib	observation	835	Y	Y	Y
Hainsworth JD	2015	Sarah Cannon Research Inst.	Paclitaxel/carbo + sorafenib	paclitaxel/carbo	85	Y	Y	Y
Herzog TJ	2013	Bayer	sorafenib	pbo	246	Y	Y	Y
Vergote IB+	2013	Eli Lilly	enzastaurin	pbo	142	N	Y	Y
Sabbatini P	2013	AGO OVAR, COGI, GINECO,	Abagovomab (maintenance	pbo	888	Y	Y	Y

		GEICO	therapy)					
Meier W*	2012	AGO-OVAR1	paclitaxel/carbo + lonafarnib	paclitaxel/carbo	105	Y	Y	N
Reyners AK**	2012	DoCaCel	docetaxel/carboplatin + celecoxib	docetaxel/carboplatin	196	Y	Y	Y
Burger RA++	2011	GOG	CT + beva (arm C)	CT	936	Y	Y	Y
Mannel RS	2011	GOG	paclitaxel/carbo + paclitaxel	paclitaxel/carbo	542	Y	Y	Y
Gordon AN	2011	Eli Lilly	paclitaxel/carbo + gemcitabine	paclitaxel/carbo	919	Y	Y	?
Pecorelli S	2009	After-6 Proto1	paclitaxel	obs	200	Y	Y	Y
Markman M	2009	SWOG -9701 / GOG-178	12 cycles Paclitaxel at CR	3 cycles Paclitaxel at CR	296	Y	Y	Y
Pfisterer J	2006	GINECO-AGO	paclitaxel/carbo + topotecan	paclitaxel + pbo	1308	Y	Y	N
Hirte H	2006	NCIC	paclitaxel/platinum + tanomastat	paclitaxel/platinum	243	Y	Y	Y
De Placido S	2004	MITO-01	Topotecan in CR	Observation in CR	273	Y	Y	Y

CR stands for patients in complete response after induction

+ The publication of the trial on Enzastaurin does not report any results on OS, suggesting there were no long follow-up.

* A Bayesian design was used to conduct the trial

** Early stopping due to excessive toxicity

++ In the GOG trial (3 arms), one arm investigated bevacuzimab throughout. The total number of patients is 623 + 625/2=936 (the pbo group is split)

Seven trials focused on MTA. They may be investigated separately.