GCIG Prague 2010

On behalf of the Gynecologic Cancer Intergroup (GCIG)

4th Ovarian Cancer Consensus Conference

Co-Chairs

Gavin CE Stuart & Henry C Kitchener,
4th Ovarian Cancer Consensus Conference

- 1st OCCC – 1993 Denmark
- 2nd OCCC – 1999 Netherlands
- 3rd OCCC – 2004 Germany
- 4th OCCC – June 24-28th 2010 Vancouver, Canada
4th Ovarian Cancer Consensus Conference

• Scientific Steering Committee
  – Henry Kitchener – Co-Chair
  – Gavin Stuart – Co-Chair
  – Monica Bacon - GCIG
  – Andreas duBois – AGO Germany
  – Michael Friedlander – ANZGOG
  – Jonathan Ledermann – MRC/NCRI (UK)
  – Christian Marth – AGO Austria
  – Tate Thigpen (GOG US)
  – Ted Trimble (NCI US)
4th Ovarian Cancer Consensus Conference

- 2008 – 13 Questions determined
- 2009 – Each member group identifies allocated number of delegates
- 2009 – Presenters and discussants identified
- 2010 – Draft presentations circulated to delegates
- 2010 – June 24-28th – Consensus meeting
4th Ovarian Cancer Consensus Conference

Identification of the 12 most important questions to be addressed (GCIG vote on „12 questions“ - 1st level of acceptance)

2 outlines (overview) per question from 24 representatives (sent to all participants/working group members)

Discussion of outlines among all groups (auditorium)

Discussion completion or modification of outlines within working group (with chairpersons coaching)

Working group refinement of statements

Working group discussion first draft of statements

Discussion of statements among all groups (auditorium)

Working group discussion first draft of statements

2nd refinement of statements by all groups (auditorium)

Discussion of statements among all groups (auditorium)

Voting on final statements
### Participating groups and delegates:

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### Guests:

Vermorken, Gotay, Wenzel, Beller

### Industry Partners:

TAIHO, Astra Zeneca, Lilly, Boehringer, Pharmamar, GSK, Amgen, OrthoBio
Countries represented in the Consensus Conference on Ovarian Cancer 2004 /2010
A1-1: What are the appropriate endpoints for different trials: (maintenance, upfront chemotherapy trials including molecular drugs)?

- Appropriate endpoints for clinical trials should reflect the achievement of clinical benefit which is defined as improvement of one or more of the following subjective and objective endpoints:
  - toxicity
  - time without symptoms
  - patient reported outcomes (PRO)
  - Progression-free survival (PFS)
  - Overall survival (OS)

- In addition, cost effectiveness should be evaluated when feasible.
A1-2: What are the appropriate endpoints for different trials: (maintenance, upfront chemotherapy trials including molecular drugs)?

- The recommended **primary** endpoints for future front line/maintenance clinical trials in ovarian cancer are:
  - **Phase II Screening for activity**
    - PFS, PFS at defined time point, or Response
  - **Phase III**
    - Early **ovarian cancer** - Recurrence free survival (note: recurrence = recurrent disease + deaths from any cause)
    - Advanced **ovarian cancer** - Both PFS and OS are important endpoints to understand the full impact of any new treatment. Although overall survival is an important endpoint, progression free survival is most often the preferred primary endpoint for trials because of the confounding effect of the post-recurrence/progression therapy on overall survival. Each protocol should specify if PFS or OS is the preferred endpoint. Regardless of which is selected, the study should be designed and powered for both PFS and OS when feasible.
  - **Maintenance trials**: These criteria should be applied to trials that include maintenance therapy.
A2: Are there any subgroups defined by tumor biology who need specific treatment options/trials?

- Histopathology remains the gold standard to classify epithelial ovarian cancer subgroups; however, there is emerging evidence to show different genetic and molecular profiles. Since there are different clinical behaviour patterns for some of the histopathological subgroups, it is advised that separate trials are developed for the subgroups listed below:
  - Clear cell carcinoma
  - Mucinous carcinoma
  - Low grade serous cancer

- When trials for the above are not available, patients within these subgroups should be entered into ongoing phase III studies.
A3: Is the 2004 GCIG recommend standard comparator arm still valid?

- The standard arm must contain a taxane and a platinum agent administered for six cycles. The recommended regimen is paclitaxel (175 mg/m²) and carboplatin (AUC 5-6) intravenously every 3 weeks.
- Acceptable additions or variations in dose, schedule, and route of delivery should be supported by at least one clinical trial demonstrating non-inferiority or superiority to a taxane/platinum.
A4: What is the role of modifying dose schedule, and delivery of chemotherapy?

• Optimizing dose, schedule, and route of delivery of available agents is under ongoing study. The results of these studies should clarify the eventual role of these approaches.

• Two specific approaches, the alteration of dose/schedule and the use of intraperitoneal therapy, have been shown to be superior in at least one trial*.
  • Dose-dense weekly paclitaxel plus every three week carboplatin (JGOG 3016)
  • Intraperitoneal chemotherapy as given in GOG 172

*see also QA5
A5: What role does surgery play today?

- Surgical staging should be mandatory and should be performed by a gynecologic oncologist.
- The ultimate goal is cytoreduction to microscopic disease. There is evidence that reduction to \( \leq 1 \) cm macroscopic disease is associated with some benefit. The term “optimal” cytoreduction should be reserved for those with no macroscopic residual disease.
- Documentation must be provided as to the level of cytoreduction (at least microscopic vs. macroscopic).
- Delayed primary surgery following neoadjuvant chemotherapy is an option for selected patients with stage IIIC and IV ovarian cancer as included in EORTC 55971.
B1 Molecular Prognostic and Predictive Factors: What should be the standards for clinical trials?

- Current prognostic and predictive markers are not adequately validated or useful.
- Histotype specific biomarkers are useful for subtype classification and should be included in histotype-specific clinical trials. Central pathology review should be encouraged for these trials.
- The design of clinical trials should include the collection of biological specimens to address important translational research questions.
- The collection of biological specimens at the time of relapse and subsequent progression should be encouraged in order to allow comparison with primary samples.
B-2 What are the promising targets for future therapeutic approaches?

- The most promising targets in clinical trials are angiogenesis and homologous recombination deficiency.
- To select patients for trials investigating these targets, predictive biomarkers are required. Understanding mechanisms of resistance is a priority.
- Other promising targets currently being studied based on ovarian cancer biology include:
  - PI3-Kinase and Ras/Raf pathways
  - Folate receptor
  - Immune targets/cytokines, Notch/hedgehog, IGF merit further investigation.
- Targeted agents should be studied both as single agents and in combination based on appropriate preclinical data.
B-3 Do We have Appropriate Methods for Evaluating Targeted Therapies?

• Currently there is no other validated method, than the standard methods, for evaluating targeted therapies.
• In order to evaluate targeted therapies, it is important to demonstrate an appropriate effect on the target in early phase studies.
• Patient selection for clinical trials should be based on the known biology of target action and appropriately validated.
• Criteria other than response (RECIST) are relevant and assessment of patient reported outcomes, quality of life, and measurement of the duration of stable disease may provide valuable information about efficacy.
• New trial designs such as randomized feasibility studies, or trials using a patient as their own control should be used to evaluate novel agents.
• Ca-125 and functional imaging should be validated for use with targeted agents.
B-4 Which Targeted Therapies could be regarded as part of a Control arm in Ovarian Cancer Clinical Trials

• Bevacizumab could be incorporated in the control arm of a randomized trial, as a consequence of the results of a trial with bevacizumab that met its primary endpoint.

• Future trials of targeted agents must include measures that better characterize meaningful outcomes for patients. Eg. cost effectiveness, clinical benefit which includes toxicity and quality of life.

(Note: Further discussion on this point will occur in October 2010)
C1: What is the role of cytoreductive surgery for recurrent ovarian cancer?

• Surgery may be appropriate in selected patients.
• As yet, there is no level I evidence which demonstrates a survival advantage associated with surgical cytoreduction for women with recurrent ovarian cancer.
• Randomized phase III trials evaluating the role of surgery in recurrent ovarian cancer are a priority.
• Cytoreductive surgery for women with recurrent ovarian cancer may be beneficial if it results in optimal cytoreduction as defined in A4.
C2: How to Define Distinct Patient Populations in need of specific therapeutic approaches?

Distinct patient populations for clinical trial enrolment may be considered by interval from last platinum therapy.

Each trial will need to specify how they define the date of progression (Ca-125 alone, radiological, symptomatic).

The following subgroups should be considered:

- Progression while receiving last line of platinum based therapy or within 4 weeks of last platinum dose
- Progression-free interval since last line of platinum of < 6 months
- Progression-free interval since last line of platinum of 6-12 months
- Progression-free interval since last line of platinum of > 12 months*

The PFI is defined from the last date of platinum dose until PD

Note: (Document whether patient had maintenance/consolidation therapy – which agent and for how long.)

(Document histological type, molecular markers (such as BRCA), and surgery for recurrent disease.)

* For this group, a platinum-based combination therapy should be the control arm for randomized trials.
C3: Should endpoints for trials with recurrent disease vary from those of first-line trials?

- Phase III trials for patients with recurrent epithelial ovarian cancer (progression-free interval since last line of platinum of >6 months from the last day of platinum dose until PD) should be large enough to detect clinically meaningful differences in both PFS and OS. Trial design should consider scheduled interim analyses to monitor for futility.

- In phase II trials for recurrent disease standard endpoints such as response rate (RECIST or GCIG-defined CA 125 response) and PFS are appropriate. Additional endpoints may include symptom benefit and clinical benefit.

- The choice of the primary endpoint needs to be fully justified with appropriate power calculations.
C3: Should endpoints for trials with recurrent disease vary from those of first-line trials?

• Symptom control/ Quality of life (for early relapse) and overall survival (for late relapse) may be the preferred primary endpoints although PFS should still be used in the assessment of new treatments.

• Future research should include the development and validation of primary and secondary endpoints such as clinical benefit which includes health-related quality of life, patient-reported outcomes of symptoms, time without symptoms or toxicity, and additionally cost-effectiveness.

• Note:

Early relapse = progression-free interval since last line of platinum of <6 months from the last day of platinum dose until PD.

Late relapse = progression-free interval since last line of platinum of >6 months from the last day of platinum dose until PD.
C4: Is CA 125 progression alone sufficient for entry/eligibility into clinical trials?

- Asymptomatic patients who meet GCIG definition of CA125 progression (without radiological or clinical evidence of recurrence) could be eligible for specific clinical trials.
- There is evidence that treating patients with asymptomatic CA-125 increase does not improve overall survival.
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- Final manuscripts to be published in the International Journal of Gynecologic Oncology in early 2011