



**11th**  
International  
Symposium  
**Advanced Ovarian Cancer  
Optimal Therapy. Update**

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# 11th International Symposium on Advanced Ovarian Cancer Optimal Therapy. Update

The International Symposium on Advanced Ovarian Cancer: Optimal Therapy. Update was founded by Dr. Andrés Poveda and Prof. Jan B. Vermorken and each edition has been directed by them.

On March, 3rd its eleventh edition is being held. This symposium is organized every other year by GEICO (Grupo Español de Investigación de Cáncer de Ovario, Spanish Ovarian Cancer Group), and, since 2009, together with ESMO (European Society for Medical Oncology).

GEICO (Grupo Español de Investigación de Cáncer de Ovario, Spanish Ovarian Cancer Group), was founded in June, 1999 and from its beginning has developed its own studies as well as collaborated with international groups involved in the Research on ovarian cancer such as EORTC, NSGO, NCIC; AGO, GINECO and others. GEICO members are medical oncologists, gynecologist and molecular biologists especially interested in the study and research of gynecological tumors. They belong to different hospitals all over Spain. GEICO is part of the GCIG (Gynecologic Cancer InterGroup). GEICO is also member of ENGOT (European Network of Gynaecological Oncological Trial Groups)

The meeting is held under the auspices of the Spanish Society of Medical Oncology (SEOM), the Gynecologic Cancer InterGroup (GCIG), and the European Society for Medical Oncology (ESMO), Educational Committee for its Medical Oncology Recertification Approval (ESMO/MORA) Program. It is also accredited by the European Accreditation Council for Continuing Medical Education (EACCME).

One hundred and fifty people attended the symposium's first edition, held in 1996. Since then, the interest in this meeting has increased. Last edition (2015), more than four hundred and fifty people coming not only from Spain but also from Europe, North and Latin America, Asia and Australia were present in the symposium. This is a great challenge for us.

Some important international cooperative groups, from Europe, America and Australia collaborate with this symposium such as GOG, NCIC, AGO, AGO-Austria, ANZGOG, GINECO, GEICO, GOTIC, JGOG, KGOG, MRC, MITO, MANGO, NCI, NOGGO, etc.

From the 2nd edition (1999) onwards, the entire papers have been published in the "International Journal of Gynecological Cancer" (Blackwell. 2000, vol. 10; supp. 1. 2001, vol. 11; supp. 1. 2003, vol. 13, supp. 2. 2005, vol. 15; supp. 3; 2008, vol. 18, supp. 1; Wolters Kluwer Lippincott Williams & Wilkins 2009, vol. 19, supp. 2), and "Annals of Oncology" (Oxford University Press 2011, vol. 22, supp. 8; 2013, vol. 24, supp. 10; 2015, vol. 27, supp. 1).

Our meeting has the category of a classic educational activity where many people come to teach, to learn and to discuss ways how to incorporate both standard and new approaches into clinical practice. In this one day symposium, we try to cover the most important and relevant aspects on diagnosis, biology and treatment in the daily management of patients with this disease.

WELCOME!

Andrés Poveda and Jan B. Vermorken  
Directors





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**Keynote lecture: Immunotherapy in ovarian cancer**  
Kunle Odunsi, *Roswell Park Cancer Institute, Buffalo (NY), USA*

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## INTRODUCTION AND BACKGROUND

Immunological destruction of tumors is a multistep, coordinated process that can be modulated or targeted at several critical points to elicit tumor rejection. These steps in the cancer immunity cycle include: (i) generation of sufficient numbers of effector T cells with high avidity recognition of tumor antigens *in vivo*; (ii) trafficking and infiltration into the tumor; (iii) overcoming inhibitory networks in the tumor microenvironment; (iv) direct recognition of tumor antigens and generation of an effector anti-tumor response; and (v) persistence of the anti-tumor T cells. In the past decade, several immune-based interventions have gained regulatory approval in many solid tumors and hematologic malignancies. These interventions include immune checkpoint blockade, cancer vaccines, and adoptive cell therapy. There are currently no approved immune therapies for ovarian cancer. In this presentation, the current understanding of the host immune response in ovarian cancer patients will be briefly reviewed, progress in immune therapies, and future directions for exploiting immune based strategies for long lasting durable cure.

In an effort to understand whether the immune system plays a role in controlling ovarian cancer, our group<sup>(1)</sup> and others demonstrated that the presence of tumor infiltrating lymphocytes (TILs) is associated with improved clinical outcome in ovarian cancer patients. Recently, we hypothesized that the quality of infiltrating T cells could also be a critical determinant of outcome in ovarian cancer patients. In this regard, we examined the TCR repertoire of a large number of ovarian cancer patients and observed for the first time that the correlation between TIL frequency and clinical outcome is dictated by T cell clonality. These data will be presented in the context of emerging understanding of how the tumor immune contexture could provide a guide to the selection of the most appropriate immunotherapy for each patient.

## IMMUNE SUPPRESSIVE NETWORKS IN OVARIAN CANCER

A major barrier to successful deployment of cancer immunotherapy for ovarian cancer patients is the immunosuppressive tumor microenvironment. Even if large numbers of tumor-specific T cells are generated in patients by active immunization or adoptive transfer, these T cells may not readily destroy tumor targets *in vivo*. Previous studies by our group have defined some of the dominant immune resistance mechanisms in ovarian cancer to include extrinsic suppression of CD8+ effector cells by regulatory T cells (Tregs)<sup>(1,2)</sup>; metabolic deregulation via tryptophan catabolism by the immunoregulatory enzyme indoleamine-2,3-dioxygenase (IDO)<sup>(3,4)</sup>; engagement of the inhibitory receptor PD-1 by the ligand PD-L1/B7-H1<sup>(5-7)</sup> and development of antigen loss variants<sup>(8)</sup>; myeloid derived suppressor cells<sup>(9)</sup>, and inhibitory cytokines such as TGF- $\beta$ . Collectively, this redundant immunosuppressive network facilitates tumor progression by actively restraining endogenous anti-tumor immunity and serves as an important obstacle that must be overcome in order to implement efficacious immunotherapeutic strategies.

Evidence in several cancer systems has shown that T cell expression of inhibitory immune checkpoint receptors is one mechanism by which tumors evade or dampen host immunity. Blockade of these inhibitory receptors with specific antibodies is designed to reinstate an existing anti-tumor response. This has been achieved through three general strategies: 1) the inhibition of immunosuppressive receptors expressed by activated T lymphocytes, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1); 2) the inhibition of the principal ligands of these receptors, such as the PD-1 ligand (PD-L1); and 3) the activation of co-stimulatory receptors expressed on the surface of immune effector cells such as tumor necrosis factor receptor superfamily, member 4 (TNFRSF4 or OX40), TNFRSF9 (CD137 or 4-1BB) and TNFRSF18 (GITR).

Although checkpoint blockade has shown significant promise in overcoming immune suppression and mediating tumor regression in melanoma and other solid tumors, the response rates in ovarian cancer have been modest. The first published data supporting checkpoint inhibitors as a potentially valuable therapeutic approach in ovarian cancer were observed in trials of the anti-PD-1 antibody nivolumab and the anti PD-L1 antibody BMS-93655. In the 20 patients treated with nivolumab in whom responses could be evaluated, the best overall response was 15% and the disease control rate in all 20 patients was 45%. Two additional immune checkpoint trials using the anti-PD-L1 antibody avelumab and the anti-PD-1 antibody pembrolizumab were presented at the 2015 ASCO annual meeting. Of 75 heavily pre-treated ovarian cancer patients that received avelumab, 8 patients experienced partial responses, 33 patients had stable disease, and there were no complete responses, with a disease control rate of 54.7%. In the KEYNOTE-028 Phase-1b study of pembrolizumab in 26 heavily pre-treated ovarian cancer patients with a PD-L1 expression level of  $\geq 1$  % of tumor cells, the results showed one complete response, two partial responses and six

## Keynote lecture: Immunotherapy in ovarian cancer

Kunle Odunsi

patients with stable disease, corresponding to a disease control rate of 34.6%. While these results are promising, the mechanisms of resistance to immune checkpoints in ovarian cancer are unclear. It is possible that redundant immune suppressive mechanisms (e.g. TGF- $\beta$ , IDO) counteract the beneficial effects of checkpoint blockade.

In our studies, we have demonstrated that multiple inhibitory receptors are often co-expressed on tumor-antigen specific CD8+ T cells<sup>(5)</sup>. In human ovarian cancer, tumor antigen-specific CD8+ TILs co-express PD-1 and LAG-3 and are impaired in IFN- $\gamma$  and TNF- $\alpha$  production compared with PD-1 or LAG-3 single positive cells. Simultaneous blockade of PD-1 and LAG-3 ex vivo restored effector function to a greater extent than single checkpoint blockade, thereby suggesting that monotherapy of checkpoint blockade may not be sufficient for eliciting robust anti-tumor responses. Importantly, we showed that blockade of PD-1, LAG-3, or CTLA-4 alone using genetic ablation or blocking antibodies conferred a compensatory upregulation of the other checkpoint pathways, potentiating their capacity for local T-cell suppression that, in turn, could be overcome through combinatorial blockade strategies<sup>(7)</sup>. Durable antitumor immunity was most strongly associated with increased numbers of CD8+ T cells, the frequency of cytokine-producing effector T cells, reduced frequency of Tregs and arginine-expressing monocytic myeloid-derived suppressor cells in the peritoneal TME. These data will be presented and provide a basis for combinatorial checkpoint blockade in clinical intervention for ovarian cancer.

### SHARED TUMOR ANTIGENS, NEOANTIGENS AND CANCER VACCINES IN OVARIAN CANCER

Interest in cancer vaccines has increased as one immunotherapeutic approach used to harness the immune system in extending remission rates and prevention of further malignant growth. The biological principle of cancer vaccines is to stimulate an immune response specifically directed against malignant cells. In this manner, cancer vaccines may be used prophylactically and therapeutically. For prophylactic vaccination, the goal is to mount an immune response that will recognize and eradicate cancer cells early enough to prevent malignant progression. As a complement to the prophylactic approach, cancer vaccines may also be used therapeutically to serve as a “booster” for pre-existing anti-tumor immune responses or activating anti-tumor immunotherapies that have been actively administered to the patient. The adaptable nature of cancer vaccines is partially governed by the nature of the tumor antigen and has been leveraged to elicit anti-cancer immune responses in a multitude of cancer immunotherapy applications.

Human tumor antigens defined to date can be classified into one or more of the following categories: 1) differentiation antigens that are restricted to very defined tissues; 2) mutational antigens; 3) amplification antigens; 4) splice variant antigens; 5) glycolipid antigens; 6) viral antigens; 7) cancer-testis (CT) antigens. CT antigens are a unique class of antigens that demonstrate high levels of expression in adult male germ cells but generally not in other normal adult tissues. Their aberrant expression in a variable proportion of a wide range of different cancer types makes them promising candidates for immunotherapy.

Among CT antigens, NY-ESO-1 is one of the most spontaneously immunogenic tumor antigens described. The NCI antigen prioritization panel has ranked NY-ESO-1 in the top 10 antigens for further development of immunotherapies. It has two characteristics that make it a viable candidate: 1) testis-restricted expression in normal tissues and 2) its immunogenicity. A combination of RT-PCR and IHC data indicates aberrant expression of NY-ESO-1 in up to 43% of ovarian cancer patients<sup>(10)</sup>. The antigen elicits both cellular and humoral immune responses in a high proportion of patients with NY-ESO-1-expressing tumors. Emerging evidence also suggest that NY-ESO-1 and some additional CT antigens, may be selectively expressed by cancer “stem cells.” Therefore, the development of strategies to target CT antigens in ovarian cancer could have potential therapeutic benefit. A number of NY-ESO-1 based clinical trials have been conducted in ovarian cancer patients, and additional trials are on-going. Details of some of these vaccine studies will be discussed during the seminar.

Recent developments in sequencing technologies offer a unique opportunity to generate truly personalized cancer vaccines. Mutational antigens or neoantigens, are tumor-specific as they are not present in normal cells. Moreover, these neoantigens are not subject to immune tolerance mechanisms. Personalized vaccines targeting neoantigens have significant theoretical advantages. Eliciting immune responses against neoantigens restricts immune recognition to the mutations that arise only in a patient’s own tumor cells and thereby minimizes the risk of inducing autoimmune responses. In addition, targeting neoantigens is potentially more effective as the induced T cell responses to neoantigens are high in affinity and are not limited by tolerance mechanisms. Finally, targeting neoantigens potentially limits antigen-loss, a common mechanism that tumor cells utilize to escape immune destruction. One of the hallmarks



of cancer is genome instability and one potential weakness of targeting a single tumor antigen is the potential for antigen-loss, thus targeting multiple neoantigens overcomes this concern. As several thousand mutations may be present in an individual cancer, algorithms are required to prioritize mutations for immune targeting. Although the use of neoantigen-based vaccines has not yet been reported in ovarian cancer clinical trials, it is anticipated that such clinical trials will be developed in the near future.

## **ADOPTIVE T CELL THERAPY**

Adoptive cell therapy (ACT) involves the ex vivo selection of antigen-specific T cells and their expansion to desired magnitude for achieving a targeted immune response. In contrast to vaccine strategies, ACT is free of the in vivo immune suppressive constraints that can limit the magnitude, duration, and phenotype of a desired anti-tumor immune response achieved by other passive immunotherapy approaches. T cells used for ACT can be derived from peripheral blood lymphocytes (PBL) or TILs. Upon modification and expansion ex vivo, the activated T cells are re-infused into patients usually after they have received a lymphodepleting pre-conditioning chemotherapy.

Initial studies demonstrating the potential of T cell immunotherapy to eradicate solid tumors came from the NCI in studies of adoptive transfer of in vitro selected TILs. Unfortunately, methods of isolating and manufacturing TILs are labor intensive and only successful in a subset of patients. In order to improve the therapeutic potential of transferred cells, investigators have recently focused on genetic modification of PBLs to exhibit tumor antigen specificity. ACT using genetically engineered PBLs to express anti-tumor receptors holds promise for extending the use of ACT to patients with epithelial cancers, such as ovarian cancer.

T cells can be genetically modified to express either 1) a tumor antigen-specific T cell receptor (TCR) encoding the  $\alpha$  and  $\beta$  chains with specificity for tumor-restricted peptide expressed on a given HLA molecule or 2) a “chimeric antigen receptor” (CAR) encoding a transmembrane protein comprising the tumor antigen-binding domain of an immunoglobulin linked to one or more T cell costimulatory molecules. CAR T cells have also demonstrated encouraging results of inducing complete response in 70% to 90% of patients with relapsed or refractory B-cell acute lymphoblastic leukemia. ACT using TCR-engineered T cells have resulted in objective responses in the majority of treated patients. In ovarian cancer, there are two on-going trials evaluating the efficacy of TILs (NCT02482090, NCT01883297). Phase I studies of engineered T cells targeting MUC16 (NCT02498912), mesothelin (NCT01583686), and NY-ESO-1 (NCT01567891, NCT02457650) are on-going. Although spectacular responses have been observed, the majority of clinical responses are short-lived with ultimate tumor relapse. A major explanation for this sub-optimal outcome is the relatively limited long-term survival and effector function due to suppression or exhaustion of infused engineered T cells.

Recent reports indicate that T cells that are expanded ex vivo to maintain more stem like T cell populations known as T stem cell memory (Tscm) cells, are capable of a more sustained response by replenishing effectors. A clear benefit of transferring less mature, more stem-like cells is likely due to increased persistence and replenishing capability of these cells in vivo. Conceptually, the regenerative nature of hematopoietic stem cells may provide a long-lasting, potentially life-long supply of effector T cells engineered against tumor antigens by TCR gene-modification of PBLs. This approach is currently being tested at Roswell Park Cancer Institute in a clinical trial in ovarian cancer patients.

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**The new WHO classification of ovarian, fallopian tube, and primary peritoneal  
cancer and its clinical implications**

Elise C. Kohn, *National Cancer Institute, Bethesda (MD), USA*

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*Out with the old and in with the new*— Both the histologic and staging classifications of malignant ovarian/tubal/peritoneal cancers have changed. Change can be embraced because it is perceived to be progress, growth, or success. However, change often brings along controversy. The new FIGO staging system for all ovarian cancers and the WHO histologic classification for epithelial ovarian cancers are no different. The purposes of histologic classification, grading, and staging of cancers are patient-oriented for diagnostic accuracy, prognostication, and treatment planning. They are also important tools for cross evaluation of demographic, epidemiologic, treatment, and outcomes data. Thus, the most consistent, simple to use, and long-standing system provides the most stability and reliability for patient care planning and data analysis. Herein lie the controversies.

The WHO histologic classification is in line with what is generally being done in patient care and, with its relative simplicity, allows retrospective classification rather readily so older “data” are not “lost”. The histologic differences between the major 5 types of epithelial ovarian cancer can be identified even by the non-gynecologic pathologist. Overall, the WHO classification codifies what has been in use in many countries for a decade or more, with a few additional twists. It incorporates many major scientific advances in our understanding of epithelial cancers of the ovary, fallopian tubes, and peritoneum. It recognizes probable precursor events, lineages, and molecular characteristics. Serous cancers are now divided by low and high grade in a simpler system, readily determined by architecture, potential involvement of a serous borderline component, lack of diffuse p53 immunostaining and/or mutation, and frequent BRAF/KRAS mutations. Micropapillary serous borderline variant is recognized for its higher risk of peritoneal implants, within which there is a 50% probability of serous low grade cancer at its base. How a “moderately well-differentiated” or grade 2 tumor should be classified has been addressed with more clarity. Such cancers should undergo p53 immunostaining and if positive should be considered high grade. The frequency of p53 loss of function mutations in HGSOC appears to range around 33% and can be determined by complete absence of p53 within the tumor, whereas lack of p53 mutation should be associated with sporadic nuclear p53 staining. High grade cancers of serous/endometrioid/transitional histology now come together under the HGSOC label, with common p53 mutation. The role of the precursor, such as endometriosis and serous tubal intraepithelial carcinoma (STIC) lesions is mentioned, but not fully integrated into reclassification of “ovarian” cancers. No significant changes were proposed for clear cell cancer, despite the frequent association with and transformation of underlying endometriosis. The codification of change that is in place in many institutions worldwide makes more clear the distinctions of the different types of ovarian/fallopian tube/peritoneal cancers and will allow more clear harmonization of data and understanding of disease.

The FIGO 2014 staging reclassification raises more questions. First, it is not selective to epithelial ovarian/tubal/peritoneal cancers, although it is to those it is targeted, but includes stromal and germ cell tumors as well. There was no consideration if this system was best for those other cancers in terms of the goal of staging of driving patient care and prognostication. However, even within the epithelial cancers, it is a one-size-fits-all classification. Second, most of the changes were made on nearly only retrospective case series of epithelial cancers. Such outcomes can be viewed with skepticism because of the great dependence upon the skill and aggressiveness (or not) of the debulking surgeon, and limited information based upon the extent of surgery. This also was dependent upon publications, biased by those institutions reporting their series. Issues arise, such as where there was no lymphadenectomy because the patient may have already been considered stage IIIC (FIGO 1988) or because the patient was felt to be a stage I, albeit without an adequate upper abdomen or lymph node assessment. Third is ongoing controversy regarding stage 2 and whether, like with a 2-level grading system, there should be a 3-level staging system, local/advanced/metastatic. This would obviate having to explain in teaching that the pelvis is identified by an invisible line between anterior iliac crests, and local can be clearly defined. The issue of pleural effusion can also be again wrapped into metastatic disease so that the positive pleural biopsies of the aggressive surgeons that now upstages to IVB will not be an issue, and not contribute to stage variability. Last, and concerning, is the issue for data harmonization, these changes were made in a fashion that make retrospective regrading difficult—any lymph node positive is now IIIA whereas those patients were IIIC previously causing stage migration. Therefore, there can be no comparison of clinical trial outcomes where the staging system differs, FIGO 1988 v FIGO 2014. That nullifies two decades of clinical trials and clinical progress, including many of the seminal studies of intraperitoneal therapy, taxane schedule studies, and more.

## The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications

Elise C. Kohn

The progress of the WHO epithelial ovarian/tubal/peritoneal cancer histologic classification is notable. It is a more simple and supportable system that incorporates histology, cytology, and invites use of time-honored and validated molecular classifications where questions arise. It can be applied retrospectively where tissue resources (slides, photomicrographs, etc) exist so adds value without losing history. The FIGO 2014 staging reclassification, done with the best of intentions, changes the landscape in a less transparent and harmonious way and needs to be applied and considered with caution.



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**Whole-genome characterization of systemic treatment resistance  
in ovarian cancer**

Elizabeth Christie, *Peter MacCallum Cancer Centre, Melbourne, Australia*

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## BACKGROUND

High-grade serous ovarian cancer (HGSC) accounts for approximately 50-60% of epithelial ovarian cancers. The five-year survival rate for women diagnosed with HGSC is between 35-40%, due to primary treatment resistance in 15-25% of patients and emergence of chemotherapy resistance in a majority of the remaining women<sup>(1-3)</sup>. A number of studies have previously identified primary and acquired chemotherapy resistance mechanisms<sup>(4-6)</sup>. We sought to further our understanding of mechanisms of chemotherapy resistance, using next generation sequencing<sup>(7)</sup>.

## PATIENTS AND METHODS

We utilised 114 tumour samples from 92 HGSC patients (FIGO stage III or IV) from the Australian Ovarian Cancer Study. All of the patients received platinum-based chemotherapy as part of primary treatment<sup>(7)</sup>. The patients were classified into 4 different treatment response groups:

- Refractory to primary treatment: 12 patients who progressed whilst on treatment, or within 1 month of the end of treatment.
- Primary resistant: 37 patients who progressed within 6 months of the end of primary therapy.
- Primary sensitive: 20 patients who showed no evidence of disease progression within 6 months of the end of treatment.
- Acquired resistant: 23 patients who were primary sensitive, but failed to respond to chemotherapy for relapsed disease.

For all patients a germline sample and at least one fresh frozen tumour sample was utilised. Where possible we analysed a primary tumour sample collected at surgery, for the acquired resistant cohort, the relapse samples analysed were tumour cells isolated from ascites or collected during rapid autopsy<sup>(8)</sup>.

For each sample we performed whole genome sequencing (WGS) and a single nucleotide polymorphism SNP array. For tumour samples we also performed RNA sequencing and a methylation array. In order to validate mechanisms of acquired chemoresistance, we utilised a validation cohort of 51 relapse ascites samples, performing "reverse transcription" PCR (RT-PCR) and real time quantitative PCR (qPCR)<sup>(7)</sup>.

## RESULTS

As expected, WGS identified TP53 mutations in the majority of primary HGSC samples. In addition, numerous structural variants (SVs), including disruption of the driver genes NF1 and RB1, were identified. Relapse samples from cases with paired primary tissue were found to have an increased mutational burden of single nucleotide variants (SNVs) and insertions and deletions (INDELs)<sup>(7)</sup>.

### Primary treatment resistance compared to a primary sensitive cohort

We observed that the mutational burden was significantly reduced in primary resistant and refractory patients compared to patients that were sensitive to primary treatment. As we had previously described, amplification of CCNE1 was associated with resistance to primary treatment<sup>(4,7)</sup>, and patients with homologous recombination repair defects, including germline BRCA1/2 mutations, were enriched in the primary sensitive cohort<sup>(7,9)</sup>. No other differences were observed between primary sensitive and primary resistant and refractory cases in WGS, RNAseq or array data.

# Whole-genome characterization of systemic treatment resistance in ovarian cancer

Elizabeth Christie

## Acquired chemotherapy resistance

In the acquired resistant cohort we identified 4 mechanisms that explained resistance in half of the cases in the cohort<sup>(7)</sup>.

In half of the acquired resistant cases with germline BRCA1/2 mutations, we observed secondary mutations in BRCA1/2 that restored the open reading frame leading to functional homologous recombination repair. Previous studies have shown that BRCA1/2 reversion mutations lead to chemoresistance to platinum-based chemotherapy and PARP inhibitors<sup>(10)</sup>. Notably, two patients had more than one reversion mutation, including a rapid autopsy patient in which 11 BRCA2 reversions were observed across the 17 sites sampled at autopsy<sup>(7)</sup>. More recently, we have found that BRCA1/2 reversion mutations can be identified in the circulating cell free DNA from matched plasma samples (Christie et al, Accepted JCO).

In the second autopsy case in the study no reversion mutations were evident, however the tumour samples were characterised by extensive desmoplastic stroma, which was not present in the primary sensitive tumour sample<sup>(7)</sup>. In pancreatic cancer, desmoplasia is associated with reduced chemotherapy uptake and subsequently increased resistance<sup>(11)</sup>.

We also observed one patient who had somatic methylation of the BRCA1 promoter in the primary sensitive tumour sample but not in the recurrent resistant sample, which had BRCA1 expression comparable to BRCA1 wild type samples. We hypothesize that restored BRCA1 expression in the recurrent sample would result in proficient homologous recombination repair and subsequently chemoresistance.

The final mechanism we identified involves SVs in the multidrug resistance gene ABCB1, resulting in fusion of the promoter and non-coding exon 1 of an upstream gene SLC25A40 to the coding exons of ABCB1 and subsequent high levels of ABCB1 expression. This fusion was observed in 4 patients of the acquired resistant cohort, and in a further 4 recurrent ascites that were part of the validation cohort, a total of ~8% of all recurrent samples tested. ABCB1 encodes P-glycoprotein, which is an efflux pump for a number of chemotherapies commonly used in the treatment of HGSC. All patients with an SLC25A40-ABCB1 fusion had been treated with at least one P-glycoprotein substrate prior to collection of the tumour sample with the fusion, and had shown resistance to that chemotherapy. Examination of further recurrent ascites samples has identified that additional fusion partners for ABCB1 occur, and ABCB1 fusions are present in ~15% of recurrent samples.

The BRCA1/2 reversions and the ABCB1 SVs were mostly found to be subclonal, i.e. present in only a subset of cells within the tumour, and in some patients multiple reversions and ABCB1 SVs have been identified.

## **CONCLUSION**

The mechanisms of acquired chemoresistance are heterogeneous, both within and between patients. If heterogeneity contributes to acquired resistance we will require diverse approaches and specific biomarkers in order to resensitize patients to standard chemotherapies. Further work remains to elucidate the mechanism(s) of acquired chemoresistance in all patients, and how resistance is conferred to neighbouring cells in patients whose resistance mechanisms are subclonal.



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# Advanced Ovarian Cancer Optimal Therapy. Update

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**How can molecular abnormalities influence our clinical approach**  
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In 2016, an estimated 22,400 new cases and 14,200 deaths (ratio of 1.5:1) in the US was reported for epithelial ovarian cancer (EOC)<sup>(1)</sup>. While patients with early-stage disease are associated with an excellent outcome, the majority of EOC patients present with extensive peritoneal spread beyond the pelvic cavity (FIGO Stage III/IV) that ascribes a considerably worse prognosis<sup>(1)</sup>. For women diagnosed with advanced stage EOC, only 30% may survive more than 5 years, even after the most intensive care based on current clinical practices. Despite the emergence of targeted therapies such as bevacizumab based anti-angiogenesis therapy, most newly diagnosed EOC patients are universally subjected to a treatment paradigm consisting of aggressive cytoreductive (debulking) surgery followed by platinum and paclitaxel based adjuvant chemotherapy. However, there is a broad spectrum of survival in women with EOC, including those women who cannot be surgically debulked and have a poor prognosis, to women who well respond to chemotherapy but die of recurrent disease and a small subset of patients who are long term survivors. Given the new discoveries in the molecular biology of ovarian cancer, the stratification and more effective treatment of ovarian cancer patients is needed.

## **EARLY DETECTION OF OVARIAN CANCER**

Unfortunately, diagnosis of EOC at its asymptomatic early-stage (FIGO Stage I/II) has proven difficult through routine clinical screening. The value of widespread screening using serum CA125 and transvaginal ultrasound has not been clearly demonstrated by the recently finalized UKCTOCS trial employing more than 200,000 eligible subjects<sup>(2)</sup>. Global proteomic analysis has identified and validated multiple potential protein biomarkers which are increased in the plasma from EOC patients compared to control patients with benign cysts<sup>(3)</sup>. In parallel with this effort, high-throughput sequencing of cervical-vaginal fluid samples from ovarian cancer patients seeks to identify tumor specific mutated DNA<sup>(4,5)</sup>. Nevertheless, the ultimate sensitivity and specificity of these technologies still need optimization to warrant clinical applicability.

## **PREOPERATIVE STRATIFICATION TO MAXIMIZE THE BENEFIT OF CYTOREDUCTION**

Primary debulking surgery remains a pivotal part in the current management of epithelial ovarian cancer<sup>(6)</sup>. However, EOC patients who have macroscopic (> 1cm) residual disease do not appear to benefit from primary cytoreduction. Conversely, universally applying neoadjuvant chemotherapy with interval debulking surgery (NACT-IDS) has been demonstrated not a superior alternative<sup>(7,8)</sup>. The development of biomarkers that can reliably predict surgical outcome therefore becomes an unmet clinical need to stratify patients in advance for surgical options. While optimal cytoreduction is influenced by various factors including the tumor anatomical locations, surgical skills and the fitness of the patients, the intrinsic tumor biology has been suggested equally important and profoundly influential to optimal cytoreduction-associated prognosis improvement, as reflected by the decreased potentials of dissemination and/or chemo-resistance. A meta-analysis of more than 1,250 EOC transcriptional profiles has revealed a robust genomic signature with distinctive biological features dictating suboptimally debulked tumors. Subsequent biological annotation of the “debulking signature” has implicated hyperactivation of TGF- $\beta$  pathway underlying the overexpression of genes rendering enhanced epithelial-mesenchymal transition, metastasis, chemoresistance, desmoplastic stroma activation and angiogenesis<sup>(9)</sup>. Despite the requirement of independent validation using prospective clinical specimens, the “debulking signature” may warrant the triage of patients through diagnostic laparoscopy specimens<sup>(10)</sup>. It would further

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support the test of TGF- $\beta$  inhibition as a potential approach of post-operative management for suboptimally debulked tumors, or in the neoadjuvant setting to increase the efficacy of NACT-IDS and maximize the optimal cytoreduction rate.

### STRATIFICATION OF PATIENTS BY TUMOR HISTOLOGY

In line with pathological and clinical observations, recent genomic studies have demonstrated that different EOC histotypes have distinct molecular features and should be considered unique diseases<sup>(11)</sup>. High-grade serous (HGSC), the most common histotype accounting for 60-65% of EOCs has somatic TP53 mutations and a high degree of genomic instability<sup>(11,12)</sup>. Extensive genomic gain and loss, rapid growth and aggressive dissemination are generally associated with HGSC of which the epithelial cells lining fallopian tube fimbria are likely the primary precursors<sup>(13)</sup>. Importantly, low-grade serous tumors (LGSC), comprising approximately 10% of the EOC, significantly differs in genomics and expression profiles over its high-grade serous counterparts<sup>(14,15)</sup>. Approximately 70% of LGSC have activating mutations in KRAS or BRAF, and consequential preponderance of the constitutively activated RAS/RAF/MAPK signaling pathway<sup>(14,16)</sup>. Similarly, 75% of the rare mucinous tumors also present activating KRAS mutation and related transcriptional network<sup>(17,18)</sup>. Endometrioid and clear cell ovarian cancer comprising 15-20% of the EOC cases frequently develop from endometriosis or retrograde menstruation and are commonly characterized with frequent hyper-activation of PI3K/Akt pathway due to activating mutations of PI3KCA or deletion of PTEN in more than 50% of tumors<sup>(19)</sup>. Specifically, endometrioid carcinomas are marked with activating mutations of CTNNB1 and constitutive, ligand-independent activation of oncogenic Wnt/ $\beta$ -catenin pathway<sup>(20)</sup>, while clear cell carcinomas are characterized by somatic inactivating mutations of the tumor suppressor ARID1A associated with chromatin remodeling<sup>(21)</sup>.

Such molecular diversity among different EOC histotypes would strongly discourage the treatment of EOC as a single disease entity without the stratification of different histological or molecular subtypes<sup>(22,23)</sup>. In addition, the recognition of the unique biology and molecular features of tumor with different histotype and grade has given rise to tumor specific trials. Therapeutic targeting of hyperactivated Ras/Raf/MEK/Erk pathway has been proposed as a novel approach to target LGSCs. The recent phase II clinical trial using selumetinib (AZD6244), an oral non-ATP competitive small molecule inhibitor of MEK1/2, has demonstrated significant benefit with increased objective response rate and decreased toxicity compared with conventional cytotoxic agents (GOG-239)<sup>(24)</sup>. Hyperactivation of PI3K/Akt/mTOR pathway has been utilized as the basis of a phase II trial specifically targeting ovarian clear cell carcinoma (GOG-0268) examining temsirolimus, a strong inhibitor against mTOR1/2 as a first-line therapy to consolidate carboplatin/paclitaxel chemotherapy. In addition to genomic aberrance, transcriptomic analyses revealed a network dominated by IL6/STAT3 signaling to augment the response to hypoxia and metabolic stress (by HIF-1 $\alpha$ , HIF-2 $\alpha$ /EPAS1 and ENO-1) and generate a highly angiogenic phenotype<sup>(25,26)</sup>. These data informed the design of a currently ongoing phase II clinical trial using Sunitinib (GOG-0254), a pan receptor tyrosine kinases inhibitor primarily targeting tumor microvasculature through the inhibition of angiogenic signals from VEGF, PDGF, and c-kit<sup>(26)</sup>. The initial report suggested the utility of Sunitinib as a second- or third-line treatment of patients with persistent or recurrent clear cell ovarian carcinoma<sup>(27)</sup>.

### STRATIFICATION OF HIGH-GRADE SEROUS OVARIAN CANCER WITH HRD

Genomic studies have reinforced the centrality of inactivating TP53 mutations and disruption of homologous recombination directed DNA repair in high-grade serous ovarian cancers (HGSC)<sup>(12)</sup>. Approximately 50% of HGSC exhibit homologous recombination deficiency (HRD), which can be attributed by various mechanisms including germline mutation, somatic mutation or epigenetic silencing of BRCA1, BRCA2<sup>(28)</sup> and other Fanconi anemia pathway components (such as BRIP1, BARD1, RAD51B and RAD51C)<sup>(12,29-31)</sup>. HRD determines increased platinum sensitivity



and provides the rationale for the use of PARP inhibitors to introduce synthetic lethality against HGSCs<sup>(32-34)</sup>. Olaparib, an oral inhibitor of PARP1/2 has recently been approved by FDA for the treatment of BRCA-mutated ovarian cancer. Olaparib monotherapy has generated promising results from several phase I/II clinical trials for the treatment of recurrent ovarian cancer, including used as maintenance treatment for platinum sensitive HGSCs<sup>(32,35)</sup>. Reliable prediction of therapeutic indication is currently under active development, including measuring the genome-wide consequence of HRD or genomic scarring to stratify patients who will mostly likely respond to PARP inhibitors<sup>(36,37)</sup>.

## **CHALLENGES AND THE FUTURE PERSPECTIVE FOR HIGH-GRADE SEROUS OVARIAN CANCER**

Except for TP53 and BRCA1/2, actionable point mutations in well accepted oncogenes or tumor suppressive genes are relatively infrequent in HGSC<sup>(12)</sup>. Instead, a high-degree of chromosome instability prevails in HGSC and leads to extensive DNA gains and losses rendering activation of oncogenes or inactivation of tumor suppressors through gene amplification, deletion or translocation to drive early-stage tumorigenesis and the development of chemoresistance<sup>(38-40)</sup>. Even so, identification of novel “druggable” targets with high-frequency copy number variation remains challenging. Moreover, high-degree genomic instability induces extensive yet different DNA copy number variations (clonal diversity) within the same treatment naïve tumor, which provide molecular background for chemoresistance, a hallmark of HGSC which ultimately determines the poor patient outcome<sup>(41,42)</sup>.

Despite the chaotic genomics in HGSC, the recent effort of genomic analyses, in particular The Cancer Genome Atlas (TCGA)<sup>(12)</sup>, has suggested the power of integrative analyses of genomic data from different platforms, such as the exome, methylome and transcriptome to provide biomarkers for new modality of ovarian cancer treatment. One of such genes we have previously identified is FGF18, which is amplified and overexpressed to mediate the poor outcome in a subset of HGSCs<sup>(43)</sup>. Subsequent biological validation has suggested FGF18 confers a proinflammatory phenotype through NF-κB dependent upregulation of cytokine production to manifest oncogenic impacts. Furthermore, HGSC cancer cells with elevated FGF18 foster a tumor microenvironment characterized by enhanced angiogenesis and augmented tumor-associated macrophage infiltration and M2 polarization, which reciprocally augment the proinflammatory status of HGSC cells to form a positive feedback loop. In addition to FGF18, the critical role of FGF signaling in the tumorigenesis of HGSC can also be suggested by the amplification and overexpression of other pathway components, including FGFR4, one of the FGF18 receptors residing at the same amplicon<sup>(44)</sup> as well as FRS2, which confers signaling from all four FGF receptors<sup>(12,45)</sup>. The availability of effective FGF signaling inhibitory approaches<sup>(46)</sup> may provide a novel targeted therapy for a subset of HGSC patients with specific hyperactivation in this pathway.

Owing to the complex genomics in HGSC, targeting genomically intact cellular components comprising tumor microenvironment have recently come into the spotlight. Anti-angiogenesis therapy using a humanized VEGFA neutralizing antibody bevacizumab in a first line setting with platinum/paclitaxel has demonstrated improvement in progression-free survival from two independent Phase III clinical trials GOG-0218 and ICON7<sup>(47,48)</sup>. The benefit of bevacizumab in platinum-resistant recurrent ovarian cancer has also been suggested by the AURELIA trial<sup>(49)</sup>. However, the benefit of universal bevacizumab administration tends to be modest in the above trials, making it an urgent need to identify biomarkers predictive of bevacizumab response<sup>(50,51)</sup>. Alternatively, combinations of anti-angiogenesis with other targeted treatments may also be considered, as demonstrated by the recent phase II clinical trial using the VEGFR inhibitor cedarinib and the PARP inhibitor olaparib<sup>(52)</sup>.

Recently, immune therapy including therapeutic vaccines, CAR-T cells or immune checkpoint inhibition has become another promising area for the management of HGSCs<sup>(53,54)</sup>. Numerous studies have confirmed the prognostic significance of intraepithelial CD8+ T-cells<sup>(55)</sup>, which recognizes both shared tumor antigens (such as Her2, CTAG1B,

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mesothelin and hTERT) and neoantigens from aberrant genomic alteration. One of the major obstacles lies in the immunosuppressive phenotype frequently presented in HGSC. Interestingly, transcriptomic profiling studies have revealed an immunoreactive molecular subtype in a subset of HGSC, which is associated with relatively better outcome<sup>(40,56)</sup>. Such signature thus provides potentials to stratify patients to appropriate immune therapy options. Another potential consideration is HGSC only has an intermediate global mutation load which may affect the abundance of neoantigens<sup>(57)</sup>. In this regard, enhanced immune response may be expected in tumors defective of DNA repair pathway, such as those with mutated BRCA1<sup>(55)</sup>.

### CONCLUSION

Accumulating knowledge has suggested a highly complex genomic landscape in epithelial ovarian cancer. The extensive heterogeneity in molecular abnormalities implies there may not be a one-size fits all solution for the clinical management of EOC. Anti-neoplastic treatment can significantly benefit from comprehensive genomic studies by providing a better understanding of the genomic aberrance and consequential molecular dysregulation underlying tumorigenesis and chemoresistance. While large-scale genomic studies have presented opportunities for identification of novel therapeutic biomarkers to warrant personalized treatment with improved outcomes, comprehensive validation at both bioinformatical and biological levels as well as clinical studies are essential to translate the findings from genomic profiling studies. Furthermore, appropriate integration of genomic profiles with large-scale studies of metabolome, proteome and immune repertoire<sup>(55,58-60)</sup> would generate valuable information to delineate the biological consequences of an identified molecular abnormality to warrant its clinical potential as a novel therapeutic target.



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**Surgery: The European perspective**

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Ovarian cancer is one of the most challenging diseases in gynecology due to the late stage presentation at time of primary diagnosis. Surgery and platinum-based chemotherapy are the cornerstones of the multimodal treatment. Nevertheless, the postoperative residual tumor mass is the most relevant clinical factor. Therefore all activities should be supported which assess the quality of surgery. In this context several societies including the European Society of Gynaecological Oncology has defined quality criteria for surgery. In the presentation we discussed the need and the importance of surgical quality due to the fact that overall survival depends on quality of surgery and medical interventions. Despite the undisputable role of surgery in the primary disease setting, the surgical management of recurrent disease has remained subject to an emotional international discussion. Only few prospective studies exist about the effect of surgery in relapsed ovarian cancer. Most of them are retrospective and reported that complete cytoreduction was associated with a better prognosis. Nevertheless, the selection of patients eligible for surgery in recurrent situation is essential but there are different definitions in the various publications. The implementation of predictive factors for complete tumor resection and defining the patient group with recurrent disease who might profit from this approach are crucial.

The prospective German DESKTOP II trial has validated the so called AGO Score in 516 patients, among whom 51% were classified as score-positive. The rate of complete macroscopic cytoreduction achieved was 76%, and the mortality rate of surgery was 0.8%. The "AGO Score" has been further evaluated retrospectively in 209 patients who underwent secondary surgery. Of these patients, 70 women had at least one negative criterion in regard to AGO Score. A total of 127 women in the "AGO Score"-positive group received complete cytoreduction. Overall, 48.5% of patients with one negative criterion also underwent surgery with no residual disease. The PFS was 22 months in the AGO-positive patients who were tumor free and 21 months in the AGO-negative patients with complete resection. The randomized phase III part of the DESKTOP trial will be presented at ASCO 2017.

The ESGO quality criteria have been recently finalized and are recommended for incorporation in institutional or governmental quality assurance programs in European countries. Furthermore they would serve as a basis in certification processes of the gynecological centers. The quality indicators have been identified according to scientific evidence and/or experts' consensus. A four-step evaluation process revealed ten structural, process or outcome indicators crucial for the quality assurance in gynecology centers. Perioperative management, minimal requirements for surgical and pathology reports and postoperative complications reporting were described as quality indicators (QI). Furthermore each QI was associated with a score and a self-assessment was defined. Among those, rate of complete surgical resection, number of surgical procedures performed annually, clinical trials participation and others were listed. The quality indicators and corresponding targets provide a quantitative basis for improving care in the surgical management of advanced ovarian cancer.

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**Surgery: The American perspective**

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# 11th International Symposium Advanced Ovarian Cancer Optimal Therapy. Update

Historically, the concept of surgical cytoreduction of ovarian cancer was first described by Joseph V. Meigs in 1934, in his textbook, *Tumors of the Female Pelvic Organs*<sup>(1)</sup>. Although the routine use of cytotoxic chemotherapy would not happen for many years, the concept of surgical cytoreduction aiding adjuvant treatment, at that time radiation therapy, was the fundamental basis of this strategy. Support of aggressive surgical cytoreduction would gain momentum with the publication of Griffith's seminal paper in 1975<sup>(2)</sup>. In addition, two publications by Hoskins, et al. based on Gynecologic Oncology Group (GOG) protocols, further supported the role of aggressive surgical cytoreduction and confirmed the inverse relationship of the amount of residual disease at primary surgery and survival outcomes<sup>(3,4)</sup>. Aided by the concurrent development and routine use of cisplatin chemotherapy, the concept of aggressive surgical cytoreduction followed by cytotoxic chemotherapy became the standard of care for ovarian cancer for nearly two decades.

Biologically, the rationale behind the benefit of surgical cytoreduction is not definitive. Theoretically, surgical removal of ovarian cancer stem cells, chemo-resistant cell populations and the supportive tumor microenvironment would enhance chemotherapy efficacy<sup>(5,6)</sup>. The counter argument to this biologic rationale has been that the bulk of disease in a patient that has an "optimal" surgical cytoreduction is more chemosensitive than a patient whose surgical cytoreduction is "suboptimal" and yields the improved outcome seen in prospective clinical trials.

In addition, critics of the concept reference the subjective variability of surgical cytoreduction and its outcome<sup>(7,8)</sup>. The terms "optimal" and "suboptimal" are based on the individual surgeon's assessment of the largest residual tumor site at the end of the operation. This is often based on a visual impression and is not an objective measurement in most cases. In addition, achievement of an "optimal" surgical cytoreduction is dependent on the skills of the surgeon, availability of intensive care unit support, and in the cases of resection of disease outside the peritoneal cavity, additional surgeons of differing disciplines. In the United States, many women with ovarian cancer have their first encounter with surgical cytoreduction outside of this paradigm of high volume, tertiary care facilities.

Amidst the background of concerns about surgical morbidity, the unresectable nature of disease outside of the peritoneal cavity or in the parenchyma of solid organs and with questions about the impact of tumor biology on outcome as opposed to resectability, the EORTC-NCIC trial of primary surgical debulking versus neoadjuvant chemotherapy (NACT) followed by interval cytoreduction was undertaken. The oft quoted results of this trial, demonstrating no improvement of progression free or overall survival for either strategy were reported by Vergote in 2008, and published in 2010<sup>(9)</sup>. The CHORUS trial, published by Kehoe, et al, in 2015, yielded a similar lack of difference in the two strategies<sup>(10)</sup>. Uptake of this strategy of neoadjuvant chemotherapy has been on the rise, with reports in the United Kingdom of 37.4% in an article by Barton, et al, in 2013<sup>(11)</sup>. In the United States, the rate of NACT increased from 8.6% to 22.6% of women diagnosed with ovarian cancer from 2004 to 2013, with a likely further increase since then<sup>(12)</sup>.

Criticisms of these trials include the lack of better prognosis stage 3 patients, heterogeneity of surgical effort, differences in chemotherapy regimens between the two arms, and an overall survival rate equivalent to "suboptimal" debulked patients in GOG trials. In addition, dramatically enhanced overall survival rates in ovarian cancer patients undergoing resection to no gross residual disease followed by intraperitoneal chemotherapy were published by Landrum, et al, in 2013<sup>(13)</sup>. In her manuscript, patients who underwent resection to no gross residual disease followed by intraperitoneal chemotherapy on GOG 114 and GOG 172 demonstrated median progression free and overall survival of 43 and 110 months respectively.

Given this, research in ovarian cancer surgical cytoreduction has turned to methods to effectively identify those patients whose surgery may result in a cytoreduction to "optimal" or no gross residual disease versus those likely to benefit from a NACT strategy. This generally consists of the combination of radiologic imaging to rule out stage IV disease (in most cases, although aggressive pleural resections are undertaken in a few centers in the US) along with laparoscopic assessment of the feasibility of resection. Rutten, et al, published the results of a prospective randomized trial of primary cytoreductive surgery (PCS) followed by adjuvant chemotherapy versus laparoscopic assessment<sup>(14)</sup>. In this intent to treat study, the patients randomized to laparoscopic assessment were then categorized as feasible for PCS or not. The primary outcome was futile laparotomy, which occurred in 10% of those patients randomized to the laparoscopy arm versus 39% of patients in the PCS arm. Of note, 62% of those randomized to laparoscopy underwent PCS. Therefore, in those patients randomized to laparoscopy that underwent PCS, the rate of futile laparotomy was 10/63 or 16%.

## Surgery: The American perspective

Paul A. DiSilvestro

One particular advantage of NACT as a primary approach to ovarian cancer treatment is the ability to more rapidly assess the efficacy of newer targeted therapies, comparing biomarker expression in pretreated specimens as compared to tissue obtained after initial chemotherapy and targeted therapeutic intervention. Changes in predictive biomarker expression may yield faster methods of obtaining drug approvals if this expression correlates with disease status at the time of interval cytoreduction. The surgical endpoint at the time of interval cytoreduction could be analogous to breast cancer treatment with the goal of pathologic complete response (pCR). How pCR is best determined remains to be defined<sup>(15)</sup>.

In summary, the role of surgery in the treatment of ovarian cancer is an ever-changing paradigm. Accurately identifying patients that will undergo “optimal” PCS and sparing those who will not from unnecessary surgical morbidity is critical. The strategy of NACT has the additional benefit of an expedited pathway for new drug development.



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**Surgery: The Australian perspective**

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## HOW AND WHY WE SHOULD ASSESS QUALITY OF CARE

Assessment of surgical outcomes and quality of care is important, especially in this era of limited resources and increasing demand. All those involved in the provision of health care, no matter at what level, want to know whether they are indeed providing the care they think they are, and whether it is being delivered to a standard that is expected or required. From a whole population point of view, it is also important to know whether all patients are receiving quality care with easy access, regardless of their financial, geographic or socio-demographic circumstances. Assessment of quality of care is important to establish baseline information, set standards of care, enable benchmarking against peers, set priorities, and to inform quality improvement. It takes time, effort and resources.

In order to assess quality of care, one must first define what quality care is. Whilst morbidity and mortality are often used as markers of quality of care, they are quite crude measures and certainly are non specific. Ultimately quality of care is a value judgment, reflecting the values and goals of the health care system and society at large<sup>(1)</sup>.

## THE AUSTRALIAN HEALTH SYSTEM

Australia has a publically funded universal health care system in which public hospital treatment is provided free of charge to everyone. However, private health insurance is also available so that insured people can choose to have treatment provided in private facilities by private specialist doctors. Health care delivery is the responsibility of both state and federal governments, with state governments funding all aspects of public hospital care and the federal government funding outpatient care (i.e.: general practitioner and specialists visits, as well as outpatient pharmaceuticals). Additionally, there are a myriad of government agencies involved in cancer care including Cancer Australia (national), Cancer Councils (state based), Cancer Institutes (state based) and the Agency for Clinical Innovation (state based). All agree, in principle, that assessment of quality of care is essential but none can agree on how it should be done, who should do it, and, most importantly, who should fund it. The Australian Institute of Health and Welfare published a report in 2009 listing 55 national indicators of safety and quality in health care, but implementation has been slow<sup>(2)</sup>. Of the 31 hospital and specialised health service-specific indicators, only two are being reported nationally<sup>(3)</sup>.

Australia has eight state-and territory-based Cancer Registries and Australian law requires that all hospitals, pathology laboratories, radiotherapy centres and death registries report all cancer cases and deaths to one of these.

Surgical gynaecological cancer care is provided by certified gynaecological oncologists (CGO) who undergo 3 years of additional training after their initial specialist qualification in Obstetrics and Gynaecology, including and oral and written examination and a thesis. Only CGO's are permitted to advertise themselves as gynaecological oncologists. In almost all cases, the gynaecological oncologists act as the team leader for the multidisciplinary care of the patient.

## WHAT DO WE KNOW ABOUT CURRENT QUALITY OF OVARIAN CANCER CARE IN AUSTRALIA?

Knowledge about the quality of ovarian cancer care, and especially surgical care, is piecemeal and derived from several sources. Most centres have databases which record, to various degrees, morbidity, mortality, extent of surgery and sometimes outcomes. There is no ability to compare data between centres. Several centres distribute annual or 5 yearly reports.

National data regarding ovarian cancer care is derived mostly from surveys and from the Australian Ovarian Cancer Study. A survey of Australian gynaecological oncologists in 2008 showed that there was substantial variation in the rate of optimal debulking surgery and the extent of surgery performed<sup>(4)</sup>. Another survey assessed the use of intraperitoneal chemotherapy for optimally debulked patients and found that only half of Australian centres were offering IP chemotherapy to eligible patients<sup>(5)</sup>. The survey also reported the use of neo-adjuvant chemotherapy and interval debulking varied substantially between centres from 10 to 40% (unpublished data).

The Australian Ovarian Cancer Study (AOCS) is a national population based study of approximately 1800 patients with epithelial ovarian cancer from all states in Australia. Patients were recruited between 2002 and 2006, with clinical data collected at the time of diagnosis and then every 6 months for a minimum of 5 years. Over 200 papers on all aspects of ovarian cancer care have been published as a result of this study.

## Surgery: The Australian perspective

Alison Brand

Data from AOCS has shown that there is significant variation in those patients who receive standard adjuvant treatment consisting of combination chemotherapy<sup>(6)</sup>. Women aged greater than 70 were less likely to start chemotherapy and were more likely to receive single agent carboplatin. Only 68% of women received combination carboplatin-paclitaxel and only half completed six cycles without treatment modification or delay.

Extent of lymph node dissection in early epithelial cancer was examined in the AOCS cohort. Lymph node sampling was performed in only 68% of women who had apparent early stage disease. Overall survival was improved in those who had lymph node sampling<sup>(7)</sup>.

Data from AOCS has also revealed that regional or remote residence, co-morbidities and relative socioeconomic disadvantage is associated with poorer survival<sup>(8)</sup>. Others have also reported that increased distance of residence from a gynaecological oncology service was an important determinant of access to a gynaecological oncologist, and consequently survival<sup>(9)</sup>. For a country the size of Australia, this inequity of access is of concern.

### THE WAY FORWARD

It is known that outcomes for ovarian cancer can be improved in many ways, including several that have nothing to do with expensive new drugs, ultraradical surgery or even robots. Examples include: ensuring surgery is performed by suitably trained gynaecological oncologists, ensuring correct diagnosis, optimising chemotherapy, encouraging access to clinical trials, optimising supportive care and engaging in risk reduction strategies. It is also known that suboptimal care exists and that variation in outcomes also exist<sup>(6,8,10,11)</sup>.

A pilot study of a clinical quality registry (CQR) for ovarian cancer is about to begin in Australia. A CQR collects a defined minimum dataset to measure performance of an individual or centre against a range of clinical quality indicators (CQIs)<sup>(3)</sup>. It then provides risk-adjusted, benchmarked data to participating institutions. This will allow health service providers to improve their systems and processes, with the expectation that this will lead to improved patient care and outcomes.

The proposed ovarian cancer pilot is based on a previously successfully implemented CQR for prostate cancer which was able to demonstrate an improvement in timeliness of treatment, reductions in percentage of patients with positive margins and reduction in unnecessary surgery for low risk disease for men with prostate cancer<sup>(12)</sup>.

In setting performance indicators, it is essential that targets are SMART; ie specific, measurable, achievable, relevant and timely<sup>(13)</sup>. Indicators should be evidence based and should be determined by extensive discussion with experts and stakeholders to ensure appropriateness and buy-in.

The proposed clinical quality indicators for the pilot have been developed by a working group of the Australian Society of Gynaecological Oncologists led by Associate Professor R Rome (personal communication). A survey of all gynaecological oncologists was undertaken in 2015 to determine the relevant and agreed CQI's and these were cross-referenced to quality indicators from other international groups including the Scottish Cancer Taskforce and the European Society of Gynaecological Oncology<sup>(14,15)</sup>. Currently six centres across Victoria and New South Wales are involved in the pilot which is anticipated to run for 2 years. The proposed indicators include: thoroughness of staging, use of a multidisciplinary team, pathological diagnosis before treatment, appropriateness of chemotherapy agent, thoroughness of primary debulking surgery, thoroughness of interval debulking surgery, rate of intra-operative and post-operative complications, and adequacy of documentation.

### CONCLUSION

Like many countries, Australia does not currently have a registry capable of benchmarking ovarian cancer care, or ovarian cancer surgical outcomes. The Ovarian Cancer CQR will be an important first step in rectifying this. Clinical registries can play an important role as a stimulus for quality improvement by providing high quality and relevant data. The words of John Rustin are as true now, as they were in the 1800's: *"Quality is never an accident; it is always the result of intelligent effort"*.



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**Surgery: The Asian perspective**

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Recent strategies for treating ovarian cancer mainly focus on the new targeted or immune-therapy combined with chemotherapy for decreasing drug-resistant cancer cells. Thus, the role of surgery is relatively getting smaller because it cannot overcome biologic characteristics of ovarian cancer. However, surgical treatment is still very important in terms of two aspects. First, it is the only prognostic factor, which can be controlled by surgeons. Second, the maximal reduction of tumor burdens can improve the effect of adjuvant drugs. However, the scope of cytoreduction is very different depending on surgeons. For this reason, we performed the survey for evaluating the quality of surgery for ovarian cancer in Asia from December 2016 and February 2017. This survey included 38 questions about general, training and procedure information (Table 1).

Table 1. The survey for the Asian perspective on the quality of surgery for ovarian cancer.

<b>GENERAL INFORMATION</b>	
Q1	Where is your hospital or center located
Q2	How many patients with advanced ovarian cancer do you operate annually?
Q3	What is your definition of optimal cytoreduction?
Q4	What are your barriers to optimal cytoreduction?
Q5	What are your surgical findings precluding optimal cytoreduction for advanced ovarian cancer?
Q6	Do the barriers or surgical findings precluding optimal cytoreduction affect your decision for selecting the first treatment between upfront debulking surgery and neoadjuvant chemotherapy in advanced ovarian cancer?
Q7	Can you determine preoperatively whether patients can receive optimal cytoreduction?
Q8	How can you predict optimal cytoreduction before debulking surgery?
<b>TRAINING INFORMATION</b>	
Q9	Is there any fellowship program for gynecologic oncology in your hospital or center?
Q10	How long are physicians in your hospital or center trained in the fellowship program?
Q11	Is there any surgical protocol of debulking surgery for advanced ovarian cancer?
Q12	Are there additional training courses outside of the fellowship program for gynecologic oncology in your hospital or center?
Q13	Where do physicians in your hospital or center have a chance to receive additional training courses?
Q14	How long does a physician receive additional training courses in your hospital or center?
Q15	What is the criteria for completing the whole training course in your hospital or center?

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### PROCEDURE INFORMATION

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- Q16 What percentage of your advanced ovarian cancer patients receive neoadjuvant chemotherapy?
- Q17 After neoadjuvant chemotherapy, what percentage of them receive optimal cytoreduction?
- Q18 What is your mean time for interval debulking surgery after neoadjuvant chemotherapy?
- Q19 After upfront debulking surgery, what percentage of them receive optimal cytoreduction?
- Q20 What is your mean time for upfront debulking surgery?
- Q21 When do you usually perform appendectomy in advanced ovarian cancer?
- Q22 Do you perform en bloc resection of the uterus, rectosigmoid colon and peritoneum?
- Q23 Do you perform ablation of peritoneal implants?
- Q24 Do you perform omentectomy?
- Q25 Do you perform lymphadenectomy?
- Q26 Do you perform small bowel surgery?
- Q27 Do you perform large bowel surgery?
- Q28 Do you perform diaphragmatic stripping?
- Q29 Do you perform diaphragmatic resection and reconstruction?
- Q30 Do you perform superficial liver mass resection?
- Q31 Do you perform parenchymal liver mass resection?
- Q32 Do you perform cholecystectomy?
- Q33 Do you perform portal triad stripping?
- Q34 Do you perform splenectomy?
- Q35 Do you perform distal pancreatectomy?
- Q36 Do you perform bladder surgery?
- Q37 Do you perform ureter surgery?
- Q38 Do you perform cardiophrenic lymph node dissection?
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More than 200 gynecologic oncologists from six countries (Republic of Korea, Japan, China, Taiwan, Malaysia and Indonesia) participated in this surgery. The final results will be shown in “the 11th Advanced Ovarian Cancer Optimal Therapy; Update”.





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**How far should we go in optimal cytoreductive surgery in ovarian cancer?\***  
Jonathan S. Berek, *Stanford University, Stanford (CA), USA*

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Cytoreductive surgery for patients with advanced epithelial ovarian cancer has been practiced for over four decades. The preoperative extent of metastatic disease and the achievement of complete postoperative cytoreduction have prognostic significance. Patients with advanced epithelial ovarian cancer should be referred to high volume cancer units, and managed by multidisciplinary teams. There has been increasing use of neoadjuvant chemotherapy and interval cytoreductive surgery. In patients with poor performance status, which is usually due to large volume ascites or large pleural effusions, neoadjuvant chemotherapy reduces the postoperative morbidity, although if the tumor responds well to the chemotherapy, the inflammatory response can make the surgery more challenging. Postoperative morbidity is generally tolerable, but increases in older patients, and in those having multiple, aggressive surgical procedures, such as bowel resection or diaphragmatic stripping. Primary cytoreductive surgery should be regarded as the gold standard for most patients<sup>(1-4)</sup>.

### **AGGRESSIVENESS OF THE SURGEON**

A 2006 study from the Mayo Clinic retrospectively examined 194 consecutive patients with stage IIIC ovarian cancer who underwent primary surgical exploration between 1994 and 1998, in order to correlate the rate of optimal cytoreduction, defined as residual disease less than 1 cm, with clinicopathologic variables and the aggressiveness of the surgeon<sup>(5)</sup>. They reported that the only independent variables were the American Society of Anesthesiology (ASA) score, the presence of carcinomatosis, and the aggressiveness of the surgeon. Factors that were not significant included the age of the patient, the CA125 level, the presence of ascites, and the presence of diaphragmatic or mesenteric involvement. A subsequent analysis of the same group of patients demonstrated that disease-specific survival was markedly improved for patients with carcinomatosis if they were operated on by surgeons who most frequently used radical procedures compared to those least likely to use radical procedures (5-year disease-specific survival rates of 44% versus 17%, respectively;  $p < 0.001$ )<sup>(6)</sup>.

### **ROLE OF LYMPHADENECTOMY**

The only randomized, prospective trial to investigate the role of lymphadenectomy in patients with advanced ovarian cancer was a multicenter study reported by Benedetti-Panici in 2005<sup>(7)</sup>. Patients who had residual intraperitoneal nodules  $\leq 1$  cm were randomized to either systematic pelvic and paraaortic lymphadenectomy ( $n = 216$ ) versus resection of bulky nodes only ( $n = 211$ ). Both arms were well matched for clinical variables, and to be eligible for the study, patients in the lymphadenectomy arm had to have a minimum of 15 nodes removed from the pelvis and 10 nodes from the paraaortic area. With a median follow-up of 68.4 months, there was a 6-month benefit in terms of progression-free interval ( $p = 0.02$ ), but no benefit in terms of overall survival. Systematic lymphadenectomy increased the median operating time by 90 minutes, the transfusion rate by 12%, and increased the incidence of lymphocysts and lower limb lymphedema.

### **CYTOREDUCTIVE SURGERY IN PATIENTS WITH STAGE IV DISEASE**

The data on complete surgical resection of all metastatic disease is based on patients with stage III ovarian cancer. The data on patients with stage IV disease is less clear, because most studies are heterogeneous and retrospective, and the exact extent of any residual disease in the thorax is not usually known. Several studies have nevertheless shown a significant survival advantage when optimal residual disease status could be achieved in the pelvis and abdomen<sup>(8,9)</sup>. A recent study evaluated the prognostic impact of residual disease after intra-abdominal cytoreduction in 326 consecutive patients with stage IV ovarian cancer treated at Essen, Germany, from 2000 to 2014<sup>(10)</sup>, in which primary cytoreductive surgery was performed in 286 patients (87.7%). Median survivals for patients with no residual disease, 1-10 mm and  $>10$  mm were 50, 25 and 16 months respectively ( $p = 0.001$ ). Abdominal wall and splenic metastases can usually be resected at the time of primary cytoreduction. Splenic metastases are usually related to hematogenous dissemination and detected on CT scan, but they may occasionally be related to direct infiltration from a large omental "cake"<sup>(11)</sup>. Unlike earlier studies<sup>(12)</sup>, the authors were unable to show any impact on overall

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survival, as long as these masses could be completely resected. Parenchymal liver metastases have traditionally been considered an indication for neoadjuvant chemotherapy; however, Lim et al. reported 16 patients who had parenchymal liver metastases with advanced ovarian cancer<sup>(13)</sup>, and 14 (87.5%) had parenchymal invasion from peritoneal seeding, and were able to undergo complete resection. These patients, who were officially FIGO stage IV, had the same survival as patients with Stage IIIC disease. Patients such as this often require diaphragmatic stripping or resection at the time of liver resection.

### NEOADJUVANT CHEMOTHERAPY

In 2010, Vergote et al. published the results of the European Organization for Research and Treatment of Cancer (EORTC) – National Cancer Institute of Canada (NCIC) randomized trial of primary debulking surgery (PDS) followed by platinum-based chemotherapy or platinum-based neoadjuvant chemotherapy (NACT) followed by debulking surgery if there was no disease progression for patients with stage IIIC or IV ovarian, fallopian tube, or peritoneal carcinoma<sup>(14)</sup>. Between 1998 and 2006, 718 patients were enrolled in the study but 48 were excluded, leaving 670 for randomization from 59 different institutions (median accrual per institution, 5 patients). The baseline characteristics of the two groups were well balanced. Optimal cytoreduction, defined as largest residual tumor  $\leq 1$  cm, was achieved in 41.6% of patients after primary debulking and 80.6% of patient after interval debulking. Postoperative death within 28 days of surgery occurred in 2.5% of patients in the primary surgical group and 0.7% in the NACT group. Grade 3 or 4 hemorrhage occurred in 7.4% of patients after primary surgery and 4.1% after interval debulking, infection in 8.1% and 1.7% respectively, and venous thrombosis in 2.6% and 0%, respectively. The median overall survival was 29 months in the PDS (primary debulking surgical) group and 30 months in the NACT group, while the median progression-free survival in each group was 12 months. Complete resection of all macroscopic disease was the single most important prognostic factor in both groups. The authors did note that the occurrence of fibrosis after chemotherapy might make interval debulking more difficult. No residual disease status is easier to attain after neoadjuvant chemotherapy, because if the disease is chemosensitive, small metastatic nodules, such as commonly occur on the diaphragm, bowel or its mesentery, will usually disappear macroscopically. Therefore, patients whose disease was debulked to no residual disease status after PDS have a much better overall and progression-free survival than those who attain this status after NACT<sup>(15,16)</sup>.

A similar outcome was shown in the CHORUS study – a randomized trial of primary surgery (n=276) versus primary chemotherapy and interval debulking (n=274) for advanced ovarian cancer, which was carried out in 87 hospitals in the UK and New Zealand, and reported in 2015<sup>(17)</sup>. The study found that survival outcome was similar in the two arms, with less morbidity and mortality in the neoadjuvant chemotherapy arm. As in the EORTC-NCIC study, the rate of optimal cytoreduction was low in the primary surgical arm-- only 41% of patients were cytoreduced to  $\leq 1$  cm-- and the median overall 3-year survival in each group was only 22-24 months. The comparable survival and lower morbidity and mortality in the NACT group has led some in the gynecologic oncology community, particularly in Europe, to conclude that NACT should be regarded as the treatment of choice<sup>(18,19)</sup>. However, the studies have been criticized, particularly on the basis that most of the patients received poor standard surgery, and that the progression-free (PFS) and overall survivals (OS) were substantially shorter than expected. In a combined analysis of the EORTC-NCIC and CHORUS studies of 1220 selected patients with Stage IIIC-IV ovarian and fallopian tube cancer with long-term follow-up (7 years), it is confirmed that NACT results in similar survival compared with PDS<sup>(20)</sup>. The authors recommend that preferably only patients with biopsy-proven stage IIIC or IV are candidates for neoadjuvant chemotherapy and that interval debulking should be planned after 3 courses of chemotherapy. However, the authors furthermore concluded that patients with stage IIIC and metastases  $\leq 5$  cm are generally better treated with primary debulking, depending on good general condition, and for example, no extensive spread on the bowel, or tumor on inoperable sites such as around the superior mesenteric artery. They recommended that patients with Stage IV disease are generally better treated with neoadjuvant chemotherapy, except for easily resectable Stage IV disease, e.g. in the inguinal lymph nodes and the spleen.

Chi et al. reported a large group of patients treated at Memorial Sloan-Kettering with primary debulking surgery during an identical time period as the EORTC-NCIC trial<sup>(21)</sup>. They concluded that PDS should continue to be the initial treatment for patients with advanced ovarian cancer, with NACT reserved for those patients who were not fit for the surgery. An updated report of the Memorial Sloan Kettering experience on 586 patients with advanced ovarian cancer treated from 2008 to 2013 was published in 2016<sup>(22)</sup>, and the PDS group had a median overall survival of 71.7 months, compared with 42.9 months for the NACT group. The authors concluded that selection criteria for NACT require



further definition and should take institutional surgical strategy into account. The EORTC-NCIC trial was also heavily criticized by the German and Austrian Gynecologic Oncology Groups, who recommended that primary surgery, with the objective of complete surgical resection, should remain the standard of care for patients with advanced ovarian cancer, with neoadjuvant chemotherapy restricted to selected patients with surgical contraindications<sup>(23)</sup>.

A British study reported that if optimal residual disease status could not be achieved after NACT, the patients did not attain a better overall survival than that after chemotherapy alone<sup>(24)</sup>. A 2012 multicenter French study evaluated the outcome of maximal cytoreductive surgery in 572 patients with stages IIIC to IV (pleural effusion only) ovarian, fallopian tube or peritoneal cancer, treated between 2003 and 2007<sup>(25)</sup>. Patients undergoing primary (190; 36%) and interval debulking were included. Complete cytoreduction was achieved in 65% of patients having primary surgery and 74% of those having an interval operation. Experienced operators performed all the surgeries, and large bowel resection was performed in 38%, pelvic and paraaortic lymphadenectomy in over 75%, and diaphragmatic stripping in 47% of patients. Complete cytoreduction was significantly associated with improved median disease-free (19.5 versus 14.7 months) and overall survival (72.6 versus 36.9 months), compared to patients with any residual disease in univariate analysis ( $p < 0.0001$ ). In multivariate analysis, significantly better disease-free ( $p = 0.0067$ ) but not overall survival ( $p = 0.0748$ ) was found for patients having primary surgery. They concluded that primary surgery should remain the treatment of choice, but conceded that the will and skill of the surgeon was an important variable.

One key feature of these trials and analyses is that the performance status of women tended to be poorer than those women who may not have been entered on the trials as evidenced by the considerably longer median survivals in randomized trials of chemotherapy in women whose disease had been optimally resected. Women entered on these randomized trials tend to have a poorer status and shorter median survivals than those patients who were entered on many of the randomized trials for chemotherapy (e.g., IV vs. IP) after primary cytoreductive surgery. Thus, the potential benefit of PDS might be missed.

Rauh-Hain and colleagues presented an analysis of patients with epithelial ovarian cancer in the US National Cancer Database<sup>(26)</sup>. The retrospective cohort study was of 22,962 women who had stage IIIC and IV disease who were treated at hospitals across the United States between 2003 and 2011 that reported to the database. The analysis focussed on patients 70 years or younger, who had a Charlson comorbidity index of 0 and were likely candidates for either treatment. Of these women, 19,863 (86.4%) received primary cytoreductive surgery (PCS) and 3,126 (13.6%) underwent neoadjuvant chemotherapy (NACT). Among propensity-score matched groups, the median overall survival was 37.3 (95% CI, 35.2-38.7) months in the PCS group compared to 32.1 (95% CI, 30.8-34.1) in the NACT group. Therefore, there was a significantly longer survival in the primary cytoreductive surgery group than in the neoadjuvant chemotherapy group. However, if the NACT group had a higher proportion of women with performance statuses of 1 to 2 compared with those who underwent PCS (60% vs. 50%), the association of PCS and improved survival would not be statistically significant. The lower survival in women who received NACT was likely explained by a higher prevalence of limited performance status in women undergoing NACT. The authors concluded that primary cytoreductive surgery was associated with improved survival compared with neoadjuvant chemotherapy in otherwise healthy women 70 years or younger with advanced-stage epithelial ovarian cancer. The Society of Gynecologic Oncology and the American Society of Clinical Oncology published their clinical-practice guideline for the management of these patients and these recommendations support that primary cytoreductive surgery should be the approach of choice for most stage III patients who are medically fit<sup>(27)</sup>.

## **PATIENT SELECTION FOR PRIMARY SURGERY**

Selecting patients who are most appropriate for primary surgery or NACT is an important challenge, in order to decrease postoperative morbidity and mortality, maximize patient outcomes, and provide cost-effective treatment. The National Surgical Quality Improvement Program (NSQIP) database was used to identify women who underwent primary surgery for ovarian cancer from 2005 to 2012, to determine if there was a group of patients who may be better treated with NACT<sup>(28)</sup>. The perioperative complication rate increased from 9.5% in women younger than 50 years to 14.6% in women  $\geq 70$  years. In a series of multivariable models, the number of extended cytoreductive procedures performed and the preoperative serum albumen level were the factors most consistently associated with morbidity. These factors were more important than age, and this study highlights the fact that “biological age” is much more important than “chronological age” in determining the patient’s suitability for major surgery. The authors concluded that women might benefit from NACT if they are likely to require extended cytoreduction, and have a poor performance status and low serum albumen levels.

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Because the best outcomes are obtained in patients with no residual disease at the end of cytoreduction, numerous attempts have been made to try to predict these patients in advance, so that there is a better selection of patients for NACT vs. PDS. These efforts have included utilization of serum biomarkers, such as pre-operative CA125 levels<sup>(29-31)</sup>, use of imaging, including CT, MRI and PET-CT<sup>(32)</sup>, and more recently the incorporation of laparoscopy in the selection of candidates to undergo primary debulking. Fagotti et al. reported their single institution outcomes comparing staging laparoscopic surgery and clinical-radiological evaluation to assess patient suitability for primary debulking surgery or neoadjuvant chemotherapy<sup>(33)</sup>. In their study of 65 patients, they found that the overall accuracy rate of laparoscopy in predicting optimal cytoreduction was 90%. The negative predictive value of clinic-radiological evaluation was 73%, whereas the negative predictive value of laparoscopy was 100%. They subsequently have published a scoring system, the Predictive Index Value (PIV), and in a prospective study of 113 patients found that at a PIV of  $\geq 8$ , the probability of optimal cytoreduction (residual tumor  $\leq 1$ cm) at laparotomy was 0<sup>(34)</sup>. This has since been prospectively validated<sup>(35)</sup>.

### CONCLUSIONS

Determining the optimal management of patients with advanced ovarian cancer is a significant challenge, and is best accomplished if these patients are centrally referred to a multidisciplinary team in a tertiary referral center that is seeing a large volume of such cases. This team should include not only a team of surgeons with the experience and willingness to undertake the appropriate operation, but also anaesthesiologists, internists and oncologic nurses who are experienced in the intraoperative and postoperative care of such patients. All options should be discussed with the patient, and informed consent obtained for whatever course of action is felt to be most appropriate. The prognosis for these patients is predetermined by the extent of their metastatic disease at presentation. The only thing that can optimize the prognosis is to primarily resect all of the metastatic disease. Neoadjuvant chemotherapy cannot improve the prognosis, but may make the surgery less morbid in selected patients. For patients with stage III disease, primary surgery will usually be the treatment of choice, unless the patient has a poor performance status, or comorbidities that can be improved with more time. The poor performance will usually be associated with gross ascites and low serum albumin levels, and 2-3 cycles of neoadjuvant chemotherapy will usually get these patients into a more fit state for surgery. Such patients often have carcinomatosis, and the ascites will dry up and small nodules on the visceral and parietal peritoneum will disappear if the disease is chemosensitive. Although this will improve the likelihood of complete cytoreduction and decrease the postoperative morbidity, it will not improve the prognosis for the patient. Several attempts have been made to predict patients preoperatively who will not be optimally cytoreduced, but the only preoperative investigation that would convince the treating physicians to definitely initiate neoadjuvant chemotherapy would be one that predicted platinum resistance. For patients with stage IV disease, consideration should usually be given to the use of neoadjuvant chemotherapy, particularly if the patient has a large pleural effusion. This is particularly true for the elderly and the grossly obese. If parenchymal lung or liver disease is present, the possibility of another primary cancer must be considered, particularly of the gastrointestinal tract or the breast. If this has been excluded, consultation with a thoracic or liver surgeon should be sought to determine the feasibility of undertaking primary resection of these metastases at the time of abdominal cytoreduction. Patients at high risk for postoperative morbidity are those with a poor performance status, low serum albumin level, or significant comorbidity, particularly if they are elderly or obese. With the evidence presently available, primary cytoreductive surgery should be considered the standard of care for patients with advanced ovarian cancer, with selective use of neoadjuvant chemotherapy for patients at high risk for postoperative morbidity.

\*Redacted and edited with permission from the author from Hacker NF, Rao A. Surgery for advanced ovarian cancer. In Epithelial Ovarian Cancer. Ed. Hacker NF: Best practices and research in obstetrics and gynaecology. Monograph to be published April 2017.



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**11th**  
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# Advanced Ovarian Cancer Optimal Therapy. Update

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**Harmonizing clinical trials within GCIg: Consensus and unmet needs from OCCG-5**  
Michael A. Bookman, *Arizona Oncology and US Oncology Research, Tucson (AZ), USA*

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The Gynecologic Cancer InterGroup (GCIG) 5th Ovarian Cancer Consensus Conference (OCCC) was held in Tokyo, Japan, from 7-9 November 2015, with the mission to provide an “International Consensus for Designing Better Clinical Trials”, distinct from conventional treatment guidelines or standard-of-care recommendations. Consensus methodology was based on the collective experience from 4 prior meetings, including Elsinore, Denmark (1993)<sup>(1)</sup>, Bergen aan Zee, the Netherlands (1998)<sup>(2)</sup>, Baden-Baden, Germany (2004)<sup>(3)</sup> and Vancouver, Canada (2010)<sup>(4)</sup>.

A Scientific Planning Committee (SPC) was convened in 2013 to frame key topics and questions, which included (A) Individualized Therapy and Patient Factors, (B) First-Line Intervention, (C) Rare Tumors, (D) Recurrent Disease, and a plenary session “Incorporating Patient-Reported Outcomes (PROs)/Quality of Life (QoL) in GCIG Trials”. All twenty-nine GCIG clinical trial groups participated in OCCC-5, with representation distributed among the topic groups.

A total of 12 key questions and 3 associated subtopics were presented for discussion and refinement in working groups, followed by final consensus voting. After the meeting, each Group developed a manuscript to foster harmonization of the consensus recommendations within the context of international collaborative clinical research.

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### OCCC-5: KEY CONSENSUS QUESTIONS

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#### Group A: Individualized Therapy and Patient Factors

- A1: What are the most important factors to be evaluated prior to initial therapy (1. Clinical, 2. Pathology, 3. Biomarkers)?
- A2: What are the most important factors to be evaluated in recurrent disease?
- A3: Are there specific considerations for special patient subpopulations (1. Race/Ethnicity, 2. Frail/Elderly)?

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#### Group B: First Line Intervention

- B1: What defines the clinical subgroups that should be used for comparator studies?
- B2: What different control arms could be considered for trials of first-line therapy?
- B3: What should be the endpoints for first-line trials?

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#### Group C: Rare Tumors

- C1: Research issues/needs unique to rare ovarian tumor types
- C2: What should be investigated in rare epithelial ovarian cancer (eOC), germ cell tumors (GCTs) and sex-cord stromal tumors (SCSTs)?
- C3: Are randomised trials possible?

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#### Group D: Recurrent Disease

- D1: What are the subgroups for clinical trials in recurrent ovarian cancer?
  - D2: What are the control arms for clinical trials in recurrent ovarian cancer?
  - D3: What are the endpoints for clinical trials in recurrent ovarian cancer?
- 

In addition to these key questions, each Group identified areas of unmet need, to promote integration with the design of future clinical trials.

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### OCCC-5: POTENTIAL AREAS OF UNMET NEED

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- Potential role of intra-operative scoring and/or post-operative imaging to document the extent of residual disease
- Universal staging criteria in the context of NACT with interval cytoreductive surgery
- Chemotherapy response scores following NACT that can be utilized as a surrogate endpoint
- Standards for immunologic assessment, including lymphocyte infiltration scores, T cell subsets, PD-1/PD-L1, etc.
- International harmonization regarding the definition and categorization of race/ethnicity

## Harmonizing clinical trials within GCIG: Consensus and unmet needs from OCCC-5

Michael A. Bookman

- Specific trials for elderly or frail patients were recognized as an important unmet need. More efforts should be devoted to developing validated and harmonized criteria for defining frailty, age being one component, together with comorbidities and capacity for autonomy
- Increased utilization of NACT provides an opportunity for short-term trials to evaluate novel treatments prior to surgery; translational endpoints in these ‘window of opportunity’ studies need to be better defined and validated.
- This lack of high level evidence regarding the management of rare ovarian tumors makes it difficult to define control arms for randomized studies, but identifies areas of unmet need that should be the subject of investigations.
- Patients who have received multiple lines of therapy should not be excluded from clinical trials but would benefit from trials specifically designed for this heavily pretreated population, including the possibility that a control arm would not be necessary in selected populations where patient outcomes are particularly poor, such as progression during chemotherapy.
- Well-designed trials of targeted interventions, such as immune checkpoint blockade, in patients with low tumor burden (including asymptomatic elevation of CA-125) remains an area of interest
- It is important to recognize the increasing monetary and non-monetary costs of clinical research. For example, the frequency and analysis of radiological assessments in trials often exceeds standard-of-care, contributing to the costs of drug development, as well as “out-of-pocket” expenses, and is increasingly recognized as a burden of research.
- Development of clinical trials for implementation in resource-poor settings will require innovation in selection of endpoints, goals of treatment, and monitoring of outcomes.

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The GCIG OCCC provides a structured process for definition and vetting of international criteria to promote harmonization in clinical research. Attention to these criteria will hopefully foster collaboration on research prioritization, trial design, enrollment, and analysis of data. In addition, the recognition of important unmet needs offers a framework for important questions that can be incorporated within planned trials as primary or secondary endpoints.



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**Front line therapy: Standard treatment**

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Surgery is an essential part of the treatment of advanced ovarian cancer. The main objective of primary surgery is to obtain a complete resection of all macroscopically visible disease. Since the majority of patients despite complete resection will recur, chemotherapy is necessary to improve outcome.

The combination of paclitaxel 175 mg/m<sup>2</sup> and carboplatin area under the curve (AUC) 5 or 6 mg/ml/min administered intravenously every 3 weeks has been the standard of care in frontline therapy of EOC during the last 15 years<sup>(1)</sup>. In the mid 1990s, two large, randomized clinical trials demonstrated that the combination of paclitaxel and cisplatin was superior to the regimen of cisplatin and cyclophosphamide<sup>(2,3)</sup>. Later on, three other randomized clinical trials confirmed that the substitution of cisplatin by carboplatin in combination with paclitaxel had the same efficacy but a better safety profile and convenience of administration<sup>(4)</sup>. Unfortunately, median time to progression is not fully satisfactory, with a range of 12–18 months depending on the residual disease after surgery, and a 5-year OS of <35%.

Since the end of the 1990s, several chemotherapy-based strategies have tried to improve the outcome of patients with advanced ovarian cancer. However, neither the substitution of paclitaxel by another drug, such as docetaxel or pegylated liposomal doxorubicin (PLD)<sup>(5)</sup>, nor the addition of a third drug to the paclitaxel-carboplatin doublet in the form of triplet or sequential doublets, were able to obtain better results<sup>(6)</sup>.

Two different strategies consisting of a change in the route of administration of platinum by intraperitoneal delivery, or the schedule of administration of paclitaxel in a dose-dense regimen of weekly administration, have shown to improve the outcome of patients with advanced ovarian cancer. However, the results of both strategies are still controversial and have not been widely adopted as standard therapy. Intraperitoneal therapy will be discussed in a separate presentation.

Dose-dense chemotherapy consists of more frequent administration of some or all of the drugs of the regimen, usually in a weekly or every other week schedule, sometimes obtaining a higher cumulative dose. This strategy was adopted in a randomized clinical trial called “NOVEL” launched by the Japanese Gynecologic Oncology Group<sup>(7)</sup>. Patients with stage IIB–IV ovarian cancer were randomized to a standard schedule of paclitaxel 180 mg/m<sup>2</sup> and carboplatin AUC 6 mg/ml/min administered every 3 weeks, or the administration of weekly paclitaxel 80 mg/m<sup>2</sup> and carboplatin AUC 6 mg/ml/min every 3 weeks. The dose-dense regimen obtained a longer time to progression (28.1 vs. 17.5 months; hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.62–0.91; p=0.0037) and also OS (5-year OS was 58.7 vs. 51.1%; HR 0.79; 95% CI 0.63–0.99; p=0.0448). Despite the results of this trial, dose-dense regimen has not been widely adopted due to the toxicity reported with this regimen and the potential pharmacogenetic differences between the Japanese and the Caucasian populations. Three large, randomized clinical trials are assessing the dose-dense issue in the Western population— MITO-7, GOG-262 and ICON8. The first two could not confirm the value of dose-dense therapy. The results of ICON8 are awaited with great interest.

In summary, the combination of paclitaxel and carboplatin administered every 3 weeks is still the most accepted backbone chemotherapy for advanced ovarian cancer.

Maintenance therapy has been explored as a strategy to prolong the progression-free interval (PFI) and OS of patients with advanced ovarian cancer. Unfortunately, all but one trial including conventional chemotherapy failed to show some impact in the outcome of patients.

Anti-angiogenic therapy was identified as one of the most promising targeted therapies in ovarian cancer. Neoangiogenesis is a necessary step for tumour proliferation and invasion, as a result of an imbalance between pro-angiogenic and anti-angiogenic factors in favour of the former. One of the most important pathways implicated in the initiation of tumour angiogenesis is the interaction of vascular endothelial growth factor (VEGF) with its receptors (VEGFR-1, -2, and -3). In fact, VEGF overexpression has been demonstrated to be an adverse prognostic factor in

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ovarian carcinoma as it has been associated with tumour progression and shortened OS. Additionally, other factors and pathways such as platelet-derived growth factor (PDGF) or fibroblast growth factor (FGF) have been implicated in ovarian cancer progression, prognosis and resistance to anti-VEGF therapy.

Bevacizumab (Genentech, South San Francisco, CA, USA) is a humanized monoclonal antibody against VEGF-A. It was the first anti-angiogenic therapy used in the clinic and the most extensively studied anti-angiogenic agent in ovarian cancer.

Two large, prospective, randomized clinical trials have included bevacizumab in the frontline therapy of ovarian, primary peritoneal or fallopian tube cancer in combination with standard chemotherapy followed by a maintenance period with bevacizumab<sup>(8,9)</sup>.

The GOG-218 trial was a double-blind, randomized clinical trial that included patients with ovarian cancer, fallopian tube cancer or primary peritoneal carcinomatosis with suboptimal or optimal cytoreduction (<1cm) but with residual macroscopic tumour after frontline debulking surgery<sup>(8)</sup>. A total of 1,873 patients were included. All patients received standard chemotherapy with intravenous paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC 6 mg/ml/min administered every 3 weeks for six cycles, and were randomized to one of the following three arms: the control arm consisted of the administration of intravenous placebo in cycles 2 through 22; the second group, also called the 'bevacizumab initiation group', consisted of the administration of bevacizumab 15 mg/kg every 3 weeks in cycles 2 through 6 concurrently with chemotherapy followed by placebo from cycles 7–22; and the bevacizumab-throughout group was chemotherapy with bevacizumab 15 mg/kg added in cycles 2 through 6 followed by a period of maintenance from cycles 7–22 (approximately 15 months in total). The main endpoint of the GOG trial was PFS determined by CA-125 GCIG progression criteria or radiological progression according to RECIST criteria. The bevacizumab initiation group did not obtain any significant benefit in outcome over the control group. However, the bevacizumab-throughout group had a significantly longer PFS than the control group (14.1 vs. 10.3 months; HR 0.71; 95% CI 0.625–0.824; p<0.001). The maximal separation of the PFS curves for the bevacizumab-throughout group and the control group occurred at 15 months, with convergence approximately 9 months later.

In the ICON7 trial, a total of 1,528 patients with EOC, fallopian tube cancer or primary peritoneal carcinomatosis with FIGO (International Federation of Gynecology and Obstetrics) stage I of high risk (defined as grade 3 or clear cell histology) to stage IV were randomized to one of the following arms: the standard arm was intravenous paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC of 6 mg/ml/min every 3 weeks, and the experimental arm was the same chemotherapy regimen to which bevacizumab 7.5 mg/kg every 3 weeks added from cycles 1–18 (a total of 12 months)<sup>(9)</sup>. Patients were stratified according to the extension of the disease and debulking (stage I–III with optimal debulking <1 cm vs. stage I–III with suboptimal debulking >1 cm vs. inoperable stage III and stage IV), timing of treatment initiation (<4 weeks vs. >4 weeks) and GCIG group. The primary endpoint in this trial was also the PFS, but in this case progression was defined by RECIST criteria only. The median PFS was 17.3 months in the standard therapy group and 19.0 months in the bevacizumab group. A comparison of Kaplan–Meier curves for PFS showed a significant difference between the two groups (estimated HR for progression or death in the bevacizumab group, 0.81; 95% CI 0.70–0.94; p = 0.004). The effect of bevacizumab was maximal at 12 months, with an improvement in PFS at this time of 15.1 % compared with the standard arm. No significant differences in OS have been found in GOG-218 or ICON7. Regarding safety, the most common side effect associated with the administration of bevacizumab was the development of grade >2 hypertension (22.9% in GOG-218 and 18.9% in ICON7). In GOG-218, there were no significant differences among the three groups in the rates of other adverse events, including gastrointestinal perforation (GIP) or fistula, proteinuria of grade 3 or greater, neutropenia of grade 4 or greater or febrile neutropenia, venous or arterial thrombosis, and wound disruption. Similar conclusions were obtained in ICON7, except for grade >3 thromboembolic events, which were 7% with bevacizumab versus 3% with standard therapy. Finally, the rate of GIP was observed in only 1% of patients in ICON7 and less than 2% in the GOG-218 trial.



The differences in patient population between the two studies could have influenced the magnitude of the impact of the intervention. Ten percent of patients included in ICON7 had stage I or IIA disease, and the rate of patients with optimal debulking (defined as residual disease <1cm) after primary surgery was much higher in ICON7 than in the GOG-218 trial (74 vs. 35%, respectively). Moreover, in the ICON7 trial there was a heterogeneous mix of patients with different stages and residual disease after surgery, which means differences in prognosis. In fact, the test for interaction suggests that the size of the effect of bevacizumab differed between patients at high risk for progression and the rest of the study population ( $p=0.06$ ), showing a benefit for the high-risk group. A subanalysis of patients at high risk of progression (defined as stage IV or stage III and suboptimal cytoreduction with residual disease >1cm) showed that the estimated median PFS was 10.5 months with standard therapy compared with 16 months with bevacizumab (HR for progression or death in the bevacizumab group, 0.73; 95% CI 0.60–0.93;  $p=0.002$ ), and that OS increased from 28.8 months in the standard-therapy group to 36.6 months in the bevacizumab group (HR for death in the bevacizumab group, 0.64; 95% CI 0.48–0.85;  $p=0.002$ ).

Trebananib (AMG-386; Amgen, Thousand Oaks, CA, USA) is a first-in-class investigational peptide-Fc fusion protein peptibody that neutralizes the interaction between the Tie2 receptor and angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2). The angiopoietin axis promotes vascularization in ovarian cancer by a different pathway than the VEGF–VEGFR interaction. Trebananib has entered an extensive programme for clinical development, known as “TRINOVA”, which includes three different studies. However, inclusion of trebananib into the upfront therapy (ENGOT-ov6/TRINOVA-3) failed to meet the primary endpoint.

Pazopanib (Votrient™; GlaxoSmithKline, London UK) is an oral small-molecule angiogenesis inhibitor targeting VEGF receptors (VEGFR-1, -2 and -3), PDGF receptors (PDGFR- $\alpha$  and  $\beta$ ), FGF receptors (FGFR-1 and -3) and c-Kit. Based on the antitumour activity shown in patients with recurrent and small-volume disease, pazopanib was investigated as maintenance therapy in frontline therapy in an international cooperative AGO-OVAR-16 trial led by the AGO group (Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovar). In this study, patients without progression after first-line therapy based on platinum/taxanes and a tumour of less than 2cm in basal evaluation were randomized to maintenance with placebo or pazopanib. Results demonstrated that pazopanib as maintenance therapy had a statistically significant PFS benefit (HR 0.766; 95% CI 0.64–0.91;  $p=0.0021$ ; median 17.9 vs. 12.3 months, respectively), but no effect on OS.

Nintedanib (BIBF 1120; Boehringer Ingelheim, Ingelheim, Germany), a 6-methoxycarbonyl-substituted indolinone, is a potent inhibitor of VEGFR-1, -2 and -3, as well as PDGF receptors (PDGFR- $\alpha$  and  $\beta$ ) and FGF receptors (FGFR-1, -2 and -3). Additionally, it inhibits Src and fms-like tyrosine kinase 3 (FLT-3). Nintedanib was studied in the international cooperative phase III trial AGO-OVAR 12/LUME-OVAR-1. This trial included patients with an initial diagnosis of ovarian, primary peritoneal or fallopian tube cancer stage IIB–IV after initial debulking surgery, or with only biopsy for patients with stage IV in whom surgery was not considered an option. 1,366 patients were randomized to paclitaxel/carboplatin every 3weeks with placebo or nintedanib for six cycles followed by maintenance therapy with placebo or nintedanib for 120 weeks (including the period of concurrence with chemotherapy) if no progression or intolerance was detected. Nintedanib added to paclitaxel and carboplatin chemotherapy significantly increased PFS (HR 0.84; 95% CI 0.72–0.98;  $p=0.0239$ ). OS data have not been reported yet.

Frontline chemotherapy for EOC has not changed in the last decade and the combination of paclitaxel and carboplatin administered every 3weeks has remained the standard of care<sup>(10)</sup>. Alternative schedules, such as, for instance, intraperitoneal administration of chemotherapy or dose-dense regimen, are still controversial and have not been adopted widely in clinical practice. This scenario has recently changed due to the introduction of targeted agents, especially anti-angiogenic agents. Data from two large, randomized clinical trials have shown that adding bevacizumab, a monoclonal antibody against VEGF, to the chemotherapy regimen followed by a maintenance period of bevacizumab prolongs the PFS, mainly in patients considered at high risk of relapse. The results of the clinical trials with bevacizumab have been considered the proof of concept of the value of anti-angiogenic therapy in the frontline therapy of ovarian cancer. The addition of bevacizumab to paclitaxel and carboplatin can be considered as standard of care at least in patients with FIGO stage IIIb or higher. However, several questions have risen about the optimal setting, dose and duration of bevacizumab. Additionally, we already have positive results of other phase III trials with anti-angiogenic agents, in frontline (pazopanib and nintedanib) therapy. The great challenge for the near future will be the selection of patients with advanced ovarian cancer obtaining more benefit from these different options in frontline therapy and in recurrent disease setting.

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**Update intraperitoneal therapy**

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The role of intraperitoneal (IP) chemotherapy in treating newly diagnosed advanced epithelial ovarian cancer (EOC) has been a subject of controversy for almost three decades. Three large appropriately powered intergroup trials have demonstrated the survival benefit associated with IP over intravenous (IV) therapy in advanced, low-volume EOC<sup>(1,2,3)</sup>. Despite the positive clinical trial results and a subsequent National Cancer Institute alert, IP treatment has not been widely accepted as the standard of care in the United States and is infrequently used in Europe<sup>(4,5)</sup>. The hesitancy of clinicians to use IP therapy is likely attributed to higher toxicity, inconvenience, catheter complications, flaws in clinical trial design and uncertain long-term benefits. More recently, a fourth randomized phase 3 trial of 1,560 subjects has reported negative results<sup>(6)</sup>. How do we integrate the seemingly contradictory results of these four studies (Table 1)?

The most frequently cited rationale for IP therapy has been the pharmacologic advantage of direct contact between tumor implants and chemotherapy containing peritoneal fluid. This creates higher chemotherapy concentrations within the tumor microenvironment and an inherent dose-intensity compared to intravenous (IV) administration. However, platinum dose-intensity has been extensively evaluated in multiple randomized trials without any evidence of improved outcomes yet clearly associated with increased patient toxicity. More importantly, simple measurements of area under the concentration-time curve in peritoneal fluid have failed to document actual tumor drug penetration. Indeed, ascites complicates the peritoneal space and develops from disordered capillary architecture, leaky blood vessels, high interstitial pressure, and absent lymphatics. Together with postoperative fibrosis and adhesions, there are substantial barriers to direct drug penetration, and it is not surprising that many studies have documented limited influx, amounting to only a few cell layers<sup>(7,8)</sup>. In fact, cisplatin and many other compounds are absorbed rapidly from the peritoneal space, and macroscopic tumors may receive higher cumulative drug dosing from systemic recirculation compared with direct tumor penetration.

Despite many years of research, it appears that we have collectively failed to describe the key biologic targets of IP therapy in terms of direct tumor cytotoxicity, alterations in the peritoneal stromal microenvironment (such as a reduction in angiogenesis or growth factors), or enhancement of the host immune response. It is clear that each of these pathways are potential mechanisms of clinical benefit for IP cytotoxic chemotherapy, yet all are unproven.

## COMBINED RESULTS OF TWO POSITIVE STUDIES

Recently, Devansu Tewari et al. retrospectively analyzed the data from two phase III Gynecologic Oncology Group (GOG) trials that compared IP to IV therapy among 876 patients in the taxane era<sup>(9)</sup>. The authors made three primary conclusions from the combined analysis of GOG protocol 114 and 172: Demonstration of an advantage in overall survival (OS) beyond 10 years (Figure 1A); Demonstration that IP therapy is effective in patients with macroscopic (gross) residual disease < 1 cm (Figure 1B); and description of a causative relationship between OS and the number of IP cycles delivered (Figure 1C).

## A SEEMINGLY DEFINITIVE NEGATIVE STUDY

Walker et al reported at the 2016 Annual Meeting of the Society of Gynecologic Oncologists the long awaited results of GOG-0252 (NCT00951496; Bevacizumab and Intravenous or Intraperitoneal Chemotherapy in Treating Patients With Stage II-III Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer)<sup>(6)</sup>.

Among, 1,560 trial participants, the median age was 58 years. 84% had Stage III disease, 72% had high-grade serous histology, and 57% had no visible residual disease following optimal cytoreduction. Completion rates by treatment arm varied between 59-65%. Cross-over to the IV only therapy occurred in 16% randomized to the IP carboplatin arm and 28% randomized to IP cisplatin arm.

Fifteen deaths possibly due to toxicity were relatively evenly distributed among treatment arms. Similarly, intestinal perforations/fistula/leak occurred in all three arms (range, 3.7% - 5.3%). While nearly 30% of patients in each arm reported grade 2+ peripheral neuropathy, treatment-induced hypertension (20.5%) and grade 3/4 nausea and vomiting (11.2%) were observed more often in the IP cisplatin arm. IP therapy did not confer a significant improvement in progression-free survival (PFS) over IV only, with the median PFS by intent-to-treat being 24.9 (IV), 27.3 (IP carboplatin), and 26.0 months (IP cisplatin). Median PFS for Stage II/III patients with 1 cm or less visible tumor was 26.8 (IV), 28.7 (IP carboplatin), and 27.8 months (IP cisplatin). Median PFS for stage III patients with no visible residual disease was 31.3, 31.8, and 33.8 months respectively. Neurotoxicity was a major problem in all arms. Survival data is not yet mature but is unlikely to show an OS advantage to any of the three treatment arms.

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### FLAWED CLINICAL TRIAL DESIGNS

None of these four trials completely defines the role of IP chemotherapy in newly diagnosed advanced ovarian cancer. GOG protocol 104 used cyclophosphamide and the assessment of PFS was not recorded. Gynecologic Oncology Group protocol 114 used an induction cycle of high dose chemotherapy and GOG protocol 172 used a weekly and dose intense regimen in the IP arm making it impossible to attribute the entire clinical benefit to the IP route of administration. Additionally, the doses used in GOG protocol 172 are seemingly too toxic and impractical. Finally, GOG protocol 252 integrated bevacizumab into all three treatment arms. However, this is the only trial that isolated the effect of IP administration and compared IP cisplatin to IP carboplatin.

### FUTURE STUDIES

Future large randomized trials are unlikely. However, the Japanese iPocc trial is eagerly anticipated. (NCT01506856; Intraperitoneal Therapy For Ovarian Cancer With Carboplatin Trial).

### WHY HAS INTRAPERITONEAL CHEMOTHERAPY NOT BEEN ADOPTED?

The clinical benefits of IP chemotherapy have not been clearly demonstrated. The hesitancy of clinicians to use IP therapy is also related to higher toxicity, inconvenience, catheter complications, as well as flaws in clinical trial design. Clearly, administration of IP chemotherapy requires increased resources in terms of both space and time to deliver compared with therapy administered IV. As yet, we have not arrived at the optimal IP chemotherapy regimen, which balances efficacy with toxicity and quality of life.

**Table 1**

Agents, doses, schedules and routes of administration for four pivotal IV versus IP chemotherapy phase 3 trials.

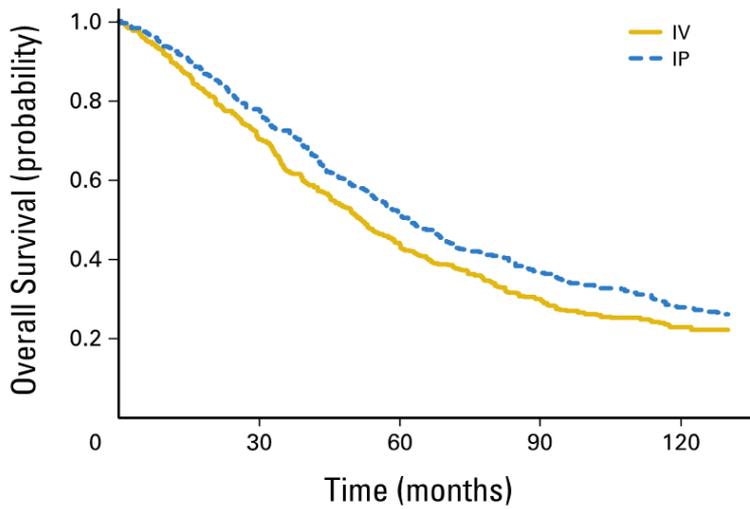
Study	Control Arm (IV)	Experimental Arm (IP)	Median Survival IP	Median Survival IV
GOG 104 <sup>(1)</sup>	Cisplatin 100 mg/m <sup>2</sup> IV; cyclophosphamide 600 mg/m <sup>2</sup> IV, Every 3 weeks x 6	Cisplatin 100 mg/m <sup>2</sup> IP; cyclophosphamide 600 mg/m <sup>2</sup> IV, Every 3 weeks x 6	OS 49 Months	OS 41 Months P = 0.02
GOG 114 <sup>(2)</sup>	Cisplatin 75 mg/m <sup>2</sup> IV; paclitaxel 135 mg/m <sup>2</sup> (24-hr) IV, Every 3 weeks x 6	Carboplatin (AUC 9) IV every 28 days x 2; cisplatin 100 mg/m <sup>2</sup> IP; paclitaxel 135 mg/m <sup>2</sup> (24-hr) IV, Every 3 weeks x 6	OS 62 Months	OS 53 Months P=0.05
GOG 172 <sup>(3)</sup>	Cisplatin 75 mg/m <sup>2</sup> IV; paclitaxel 135 mg/m <sup>2</sup> (24-hr) IV, Every 3 weeks x 6	Paclitaxel 135 mg/m <sup>2</sup> (24-hr) IV; cisplatin 100 mg/m <sup>2</sup> IP; paclitaxel 60 mg/m <sup>2</sup> IP on day 8, Every 3 weeks x 6	OS 65 Months	OS 49 Months P=0.03
GOG 252 <sup>(6)</sup>	Paclitaxel 80 mg/m <sup>2</sup> weekly IV; carboplatin AUC 6 IV; bevacizumab 15 mg/kg IV, bevacizumab every 3 weeks maintenance	1) Paclitaxel 80 mg/m <sup>2</sup> weekly IV; carboplatin AUC 6 IP; bevacizumab 15 mg/kg IV, bevacizumab every 3 weeks maintenance  2) Paclitaxel 135 mg/m <sup>2</sup> day 1 IV (24-hr); cisplatin 75 mg/m <sup>2</sup> day 2 IP; paclitaxel 60 mg/m <sup>2</sup> day 8 IP; bevacizumab 15 mg/kg IV, bevacizumab every 3 weeks maintenance	PFS  1) 27.3 Months  2) 26.0 Months	PFS 24.9 Months  P = NS

OS = overall survival, PFS = Progression-free survival, IP = Intraperitoneal, IV = Intravenous, NS = Non-significant



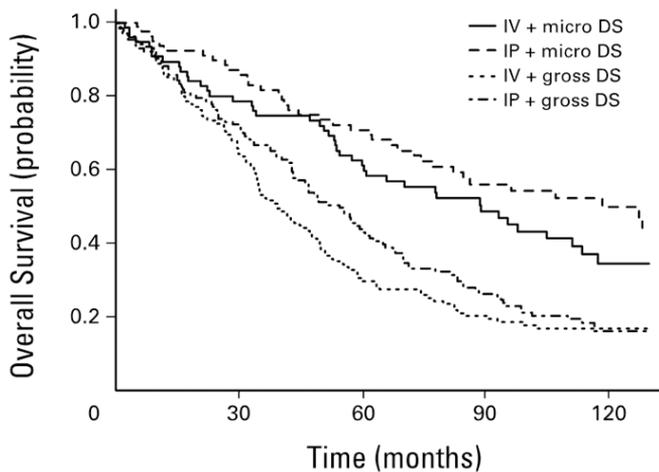
**Figure 1**

**A.** Long-term overall survival of patients treated with IV versus IP chemotherapy in Gynecologic Oncology Group (GOG) protocols 114 and 172 (P = .04).



No. at risk					
IV	436	303	184	110	68
IP	440	337	217	140	85

**B.** Long-term overall survival of patients treated with IV versus intraperitoneal IP chemotherapy based on extent of residual disease in GOG protocols 114 and 172 (DS; P < .001). NOTE. Gross residual defined as ≤ 1 cm; micro residual defined as no visible disease.

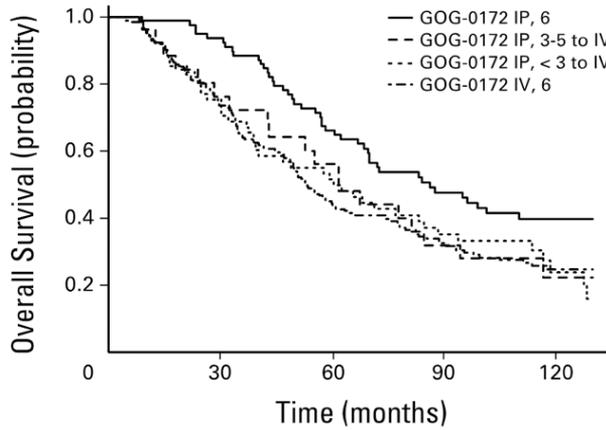


No. at risk					
IV + micro DS	75	59	45	27	14
IP + micro DS	78	66	52	34	20
IV + gross DS	135	86	40	24	12
IP + gross DS	126	91	53	31	13

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**C.** Long-term overall survival based on number of cycles of IP therapy ( $P = .03$ ). Analysis restricted to patients in GOG protocol 172 who completed all six cycles of chemotherapy (both IP and IV arms).



No. at risk	0	30	60	90	120
GOG-0172 IP, 6	78	73	50	31	19
GOG-0172 IP, 3-5 to IV	26	19	14	8	4
GOG-0172 IP, < 3 to IV	61	46	30	18	7
GOG-0172 IV, 6	182	133	79	47	25

IP = Intraperitoneal IV = Intravenous



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**Front line therapy: New approaches**

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Surgery and chemotherapy, with carboplatin and paclitaxel are the backbone of first-line therapy. The completeness of surgery is prognostic and this has led increasingly to the development of specialization and centralization. There are data to show that these two factors contribute to improved outcome, probably augmented by specialized multidisciplinary care; these benefits are reflected in an improvement one-year survival and progression-free survival (PFS), but the extent to which surgery alone has improved overall survival (OS) is less clear.

The 5th Ovarian Cancer consensus conference accepted that PFS is a useful endpoint for the evaluation of new therapies, but additional endpoints, such as PFS2 (time to second progression) and OS should be included in the evaluation of new therapies<sup>(1)</sup>. Two decades of clinical trials with additional cytotoxic drugs failed to demonstrate any benefit, but an improvement in PFS and OS with weekly paclitaxel, first described 7 years ago appeared to be a long-awaited breakthrough<sup>(2)</sup>. It is an accepted standard of care, but subsequent trials (MITO-7; GOG 262) have not confirmed the benefit of weekly paclitaxel<sup>(3,4)</sup>. The results of the large ICON8 trial is eagerly awaited. Conflicting data and interpretation of intraperitoneal therapy trials persists; impressive long-term follow-up data of GOG 172<sup>(5)</sup> have not been matched by the recent results of GOG252; the results of the recently completed Japanese trial, iPocc may hold the key to the further use or abandonment of intraperitoneal therapy.

Current research strategies are now almost exclusively directed towards the incorporation of molecular therapies. Bevacizumab was the first agent to be extensively tested with two trials demonstrating an improvement in PFS. The absence of an overall OS benefit has led to different interpretation of the value of bevacizumab on the two sides of the Atlantic. A subgroup analysis of the ICON7 trial showed that PFS and OS is improved only in a higher risk group using half the licensed dose<sup>(6)</sup>. There has been an extensive search for predictive factors, so far without a clear outcome. Use of bevacizumab varies in clinical practice and in clinical trials; thus, an evolution of new studies with molecular therapy is emerging with very different control arms. For example, in Europe the 'Boost' Trial is examining prolonged maintenance therapy with bevacizumab (15 versus 30 months) and PAOLA-1 is evaluating the addition of the PARP inhibitor olaparib to bevacizumab maintenance therapy. In contrast, there are at least two major front-line studies that do not use bevacizumab. One incorporates the PARP inhibitor veliparib, and the other, JAVELIN 100 is evaluating the PDL-1 inhibitor avelumab as maintenance or with chemotherapy followed by maintenance therapy. If the pure first-line maintenance trial, SOLO-1 investigating olaparib in patients with a BRCA mutation is positive, it may be possible avoid the complexities of bevacizumab use, provided that BRCA testing is performed at diagnosis.

The 5th Ovarian Cancer Consensus Conference on Ovarian cancer has drawn together a global consensus for the acceptance of standard therapies for trials and directions for research but as investigation of new molecularly targeted therapies moves forwards, it does so using different standard treatments that could lead to a wider divergence in global practice. This could be brought together again if one or more of these new treatments results in a significantly large increase in outcome, particularly overall survival.

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**Treatment for recurrent disease: Standard treatment**  
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Despite optimal surgery and appropriate first-line chemotherapy, approximately 80% of patients with epithelial ovarian cancer (OC) will develop at different times a disease recurrence. The likelihood for relapse depends on many factors, including distribution of disease at initial presentation, success of initial surgical cytoreduction (i.e., the presence of any residual disease), rapidity of CA125 resolution, and treatment response after primary therapy. OC relapse can be detected biochemically (rising of Ca125), clinically or radiologically. Subsequent sequential treatment strategies maximize quality and length of life but are not curative. Prognosis at relapse is mainly dominated by chemosensitivity of the tumor. The choice of second-line chemotherapy depends on several factors such as platinum-free interval (PFI), persistent side effects of prior treatments, schedules and toxicity profiles of next therapies and patient preferences, but according to the rising knowledge on OC biology, also histologic subtype, BRCA1/2 mutation status, previous first line treatment with Bevacizumab, should influence the clinician's therapeutic algorithm. Retreatment with chemotherapy should not be routinely started in asymptomatic patients with CA125 progression alone. Some literature data demonstrated that early initiation of chemotherapy is not associated to any survival advantage and impact negatively on the QOL<sup>(1)</sup>. Until now, the PFI has been considered as the main prognostic factor that guides the treatment choice at the recurrence. Therefore, time from last platinum injection to recurrence drives treatment strategy that is based on non-platinum chemotherapy if PFI is shorter than 6 months (platinum-resistant), and on platinum-containing doublets if PFI is longer than 12 months (platinum-sensitive). When the PFI is between 6 and 12 months (partially platinum-sensitive) there is uncertainty, due to unsatisfactory results with platinum-containing doublets. Although these definitions have been used to identify some populations of interest in a number of clinical trials, these categories are somewhat arbitrary, because they are related to results from retrospective assessments of literature data. The resistance to platinum-based treatment is not a categorical variable and therefore in the real-world practice the distinction between resistant and sensitive disease is considerably less rigid and not only linked to the PFI. However, the emergence of a maintenance approach scrambles this initial definition in terms of the time to progression. So, the concept of Platinum Free Interval is not still applicable today. In the last consensus (5th Ovarian Carcinoma Consensus Conference) conference of Tokyo<sup>(2)</sup> the PFI paradigm has been partially revisited in the light of the introduction in the trials and in clinical practice of new targeted agents. In particular, this arbitrary distinction collides with the increasing knowledge of the heterogeneity of the tumor histologies, but more transversely, the different molecular abnormalities that underlie individual histologic subtypes. The best treatment to be proposed to our patients would be more reasonable thinking to the probability of response to platinum as a continuum rather than related to arbitrary time points, probably linked to tumor biology, and/or to the genomic profile of a specific time of ovarian cancer natural history. Also resistance to treatment is often not absolute and may be partially overcome. It seems that we may consider only early and delayed relapses as a reflection of tumor ability to respond to subsequent medical treatments.

### Early relapse

Patients relapsed during first line treatment (refractory) or in the few following months (resistant) represent a very heterogeneous group of various biological tumor behaviors. This condition is linked to unfavourable prognosis, so the main objective of treatment is to palliate symptoms and preserve quality of life. Monotherapy with non-platinum chemotherapy has showed to be equally effective and less toxic compared to combinations. A Cochrane systematic review of trials in platinum resistant EOC found that paclitaxel, PLD and topotecan offer similar objective response rates (10-20%), median PFS (3-4months), and overall survival, OS (around 12 months) with different toxicity profiles<sup>(3)</sup>. Regarding molecular targeted therapy, interesting data have been obtained in this setting with antiangiogenic compounds. In the AURELIA randomized phase III trial<sup>(4)</sup>, bevacizumab in combination with standard chemotherapy (PLD, weekly paclitaxel, or topotecan) and as single agent maintenance until progression demonstrated to prolong PFS (6.7 vs 3.4 months HR 0.48; 95% CI 0.38-0.60; P<0.001), but not the overall survival (OS) compared to standard chemotherapy. In a sub-group analysis, there was a significant OS benefit for bevacizumab in the weekly paclitaxel group (median 22 vs 13 months). According to those results, bevacizumab was licensed in this setting.

### Relapse after 6 months

This subgroup refers to platinum sensitive and partially sensitive patients, that are generally more responsive to chemotherapy. Chemosensitivity to platinum compounds is supposed to increase with longer interval from the initial therapy. The hypothesis that a benefit could derive from the artificial extension of PFI has been largely used in clinical practice and in the development of new drugs for more than 15 years, without any prospective confirmation of its

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validity. While for patients with PFI >12 months the use of platinum based combinations (carboplatin/PLD; carboplatin/paclitaxel and carboplatin/gemcitabine) is associated to a better outcome (PFS, OS) compared to non platinum or platinum single agent treatments<sup>(5,6)</sup>; in patients with a PFI between 6 and 12 months (partially platinum-sensitive) the efficacy of platinum doublets has been unsatisfactory. Some studies aimed to confirm this hypothesis (MITO8, INOVATYON). One of them, the MITO 8, a strategy based phase III trial that compared the sequence of platinum based chemotherapy (PBC) followed by a non platinum based chemo (NPBC), recently demonstrated that use of NPBC to artificially prolong the PFI is not beneficial for partially sensitive relapsed OC patients<sup>(7)</sup>. This evidence confirm that platinum-based treatment should be the first choice in this population, also because it increases the chance to have another therapeutic opportunity in case of response (olaparib or bevacizumab). A non-platinum-containing doublet (trabectedin plus PLD) has been recently introduced in the treatment of patients with platinum sensitive recurrent ovarian cancer based on PFS (but not OS) prolongation in the OVA-301 randomized trial<sup>(8)</sup>; a subgroup analysis suggested an OS prolongation in the same population of the MITO 8 trial. Interestingly, the combination of trabectedin/PLD demonstrated to prolong OS in those patients that received platinum after progression. For women who are unable to tolerate platinum chemotherapy because of hypersensitivity or other previous toxicity, single-agent chemotherapy may be used. Response rates of approximately 30% have been described with a number of agents, including PLD, gemcitabine, weekly paclitaxel, topotecan and oral etoposide. There are two established maintenance therapies for women affected by platinum-sensitive recurrent OC: bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor, and olaparib, an inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARPi). The activity of bevacizumab in platinum sensitive relapsed EOC has been demonstrated in the OCEANS trial, which randomized 484 women with platinum-sensitive recurrent OC to carboplatin and gemcitabine plus either bevacizumab or placebo. The bevacizumab-containing combination was associated with a better objective response rate (ORR, 78.5% vs 57.4% with the non-bevacizumab containing combination), and a longer PFS (12.4 vs 8.4 months), however, with no difference in OS, probably due to crossover<sup>(9)</sup>. Olaparib is the first-in-class to be licensed for the treatment of recurrent ovarian cancer harbouring deleterious BRCA mutations. The activity of olaparib as maintenance after response to platinum based chemotherapy was showed in the randomized trial “study 19” in the platinum-sensitive high grade serous relapsed ovarian, fallopian tube or peritoneal cancer. Olaparib maintenance significantly prolonged PFS with 6.9 months, (from 4.3 to 11.2 months [HR = 0.18; 95% CI (0.10, 0.31); P < 0.00001] compared to placebo. A smaller but significant benefit was also seen in BRCA wild-type patients [HR = 0.54; 95% CI (0.34, 0.85); P = 0.0075]<sup>(10)</sup> BRCA mutation constitute the first predictive marker for the treatment of ovarian cancer. Two different indications for use in the United States and Europe underline the complexity of clinical trial approvals, but also the versatility of this type of drug. Several other PARP inhibitors are undergoing clinical trials in the maintenance setting, in combination with chemotherapy, and with other molecular targeted therapies. Results are expected during the next 2–5 years and will most likely extend the opportunities for treatment of ovarian cancer. Olaparib is actually the treatment of choice as second-line option in patients with platinum-sensitive recurrent OC who carry a somatic or germline BRCA mutation. In contrast, bevacizumab, in combination with carboplatin and gemcitabine, can be considered for patients with platinum-sensitive recurrent OC who do not carry BRCA mutations. Testing for BRCA mutations now needs to be incorporated into everyday clinical practice, so that patients have the opportunity of benefiting from this new personalized therapy.

### TREATMENT ACCORDING TO TUMOR BIOLOGY

Historically, most of all clinical trials in ovarian cancer grouped all histologic subtypes together. However, there are 5 different histologic types of OC with a different genomic landscape, natural histories and patterns of response to therapy. Therefore, the inclusion in these trials of patients with biologically so different malignancies has undoubtedly led to some biases that confounded studies results. The existing treatment strategies based on PFI in OC has been largely driven, probably, by activity in high-grade serous (high-grade serous OC [HGSOC]) and endometrioid (high-grade serous endometrioid cancer [HGSEC]) histologies. Both type of tumors, particularly HGSOC are extremely chemosensitive, associated with prolonged treatment free interval and better response rates compared to the others. This condition is related to the fact that about 50% of tumors are characterized by DNA repair mechanism defects, not only linked to BRCA genes alterations, which makes those tumors sensitive to DNA damaging agents compounds. Loss-of-function mutations of genes of the homologous recombination pathway, especially BRCA1 and BRCA2, predicts higher rates of platinum sensitivity, better overall survival (OS), and better response to PARPi in women with OC. Some retrospective studies demonstrated that in HGSOC platinum based chemotherapy at relapse is associated to objective response rates of 65 -100%. PLD is another interesting drug in this setting of patients. Three studies (2 retrospective) showed a higher efficacy of PLD in BRCA mutated compared to unselected cases



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(RR of 7-25%, median PFS of 4 to 5 months), probably due to the mechanism of action of this drug (topoisomerase II inhibition in HRD cells, immuno-modulatory effects, particularly in BRCA1 mutated tumors)<sup>(11)</sup>. Also trabectedin (a minor groove DNA binder derived from marine organism) has been associated with high response rates and prolonged PFS when used both as a single agent and in combination with PLD<sup>(12,13)</sup>. In the recurrent disease setting, the first option in BRCA mutated platinum sensitive patients should be that of carboplatin combinations, and one of the preferred partners could be PLD or gemcitabine. There are, actually, no conclusive evidences about the impact of BRCA mutations on response to paclitaxel. For platinum resistant disease the first option in BRCA mutated OC (BMOC) patients should be PLD for patient that did not already receive it. It is important to not exclude the option of repeat platinum combination therapy at subsequent relapse. Clear cell, mucinous and serous low-grade tumors are the subtypes associated to a poor response to chemotherapy in general, and to platinum-based chemotherapy. So, at relapse, the option of a clinical trial with targeted therapy may also be appropriate in these populations (such as mitogen-activated protein kinase (MEK) inhibitors in low grade serous OC). In the 5th Ovarian Carcinoma Consensus Conference a greater clarity has been “imposed” in designing clinical trials, with special attention to rare histologies that have different prognosis and biological behavior<sup>(14)</sup>.

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**Secondary cytoreductive surgery**

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Epithelial ovarian cancer is an aggressive malignancy and it is most frequently diagnosed in an advanced disease stage<sup>(1)</sup>. The mainstay of primary treatment is surgery with the goal of complete resection<sup>(2)</sup>. Even if no complete resection is feasible to obtain, patients still have some benefit of surgery, if tumor reduction to residual disease less than 1 cm is achieved<sup>(3)</sup>. The introduction of bevacizumab to the standard chemotherapy with platinum/taxane and maintenance therapy up to 15 months have improved PFS<sup>(4,5)</sup>. Despite that, approximately 23% of patients relapse during or within 6 months after end of primary chemotherapy and 60% relapse after 6 months<sup>(3)</sup>. The standard approach for treating recurrent ovarian cancer is chemotherapy and surgery remains – so far – an option for individual patients who should be carefully selected.

Until now, there are no prospective data available showing that there is a survival benefit for patients undergoing surgery for recurrent ovarian cancer followed by chemotherapy compared to patients receiving chemotherapy alone. A comprehensive review of all published retrospective series to this topic was published in 2005<sup>(6)</sup>. This review was limited to series with more than 100 pts and mainly cytoreductive surgery for platinum sensitive recurrent ovarian cancer, as most of the identified series were rather small or had mixed patient cohorts. Eight series could be identified which reported prognostic factors for survival after cytoreductive surgery in recurrent ovarian cancer<sup>(7-14)</sup>. Primary FIGO-stage, histological subtype, localization and outcome of primary surgery were never reported to be of prognostic significance in the recurrent disease setting. Two series identified pre-operative chemotherapy as a negative prognostic factor. All series reported surgical outcome as independent prognostic factor for survival. The multicenter Descriptive Evaluation of preoperative Selection Criteria for Operability in recurrent Ovarian cancer I (DESKTOP I OVAR) by the AGO Study Group reported only complete resection as beneficial with an OS of 45.2 months. There were no differences between minimal residuals of 1-10 mm or >10 mm (19.7 vs 19.6 months). There were two series describing a benefit of cytoreduction to 1-20 mm compared to >20 mm<sup>(12)</sup> and 0.1-10 mm compared to >10 mm<sup>(13)</sup>. However, very heterogeneous patients cohorts and missing additional chemotherapy after surgery, in a substantial frequency of patients, limited the value of these analyses. In contrast, the largest single center series published by Sehouli et al. in 2010 confirmed the findings that only complete resection is beneficial. Moreover, a large international collaborative multicenter analysis including 1,100 patients showed that complete resection was strongly associated with the improvement of survival, with a median survival of 57.7 months, compared with 27.0 months in those patients with residual disease of 0.1-1 cm and 15.6 months in those with residual disease of >1 cm, respectively ( $P < 0.0001$ )<sup>(15)</sup>. In addition to complete resection, which was the strongest prognostic factor for further survival (HR: 2.94), the DESKTOP I series identified absence of ascites (HR: 2.30) and post-operative platinum based chemotherapy (HR: 1.82) as further prognostic factors.

In the past, it was difficult to identify suitable patients in whom complete resection was feasible. Therefore, the reported rates of complete resection varied between about 20 to 80%<sup>(16)</sup>. The AGO DESKTOP I evaluated 3 predictive factors for complete resection: Good performance status ECOG 0, complete resection at first surgery (alternatively, FIGO I/II in patients with unknown residual disease after primary surgery), and absence of ascites. Patients, in whom all these factors were present, a complete resection was feasible in 79% of patients (AGO-score positive). In the subsequent AGO DESKTOP II study this score was validated prospectively. The study was planned to show that a positive AGO Score reaches a positive predictive value for complete resection of > 66% (2 of 3 pts) with 95% probability and a significance level of  $p < 0.05$ . 516 patients with platinum-sensitive relapse were screened within 19 months. 32% of the patients with first relapse were operated on. One-hundred twenty-nine patients had a positive score. In patients with a positive score a complete resection could be achieved in 76%, resulting in a positive validation of the AGO-score<sup>(17)</sup>. Since the publication of the DESKTOP II study, the AGO-score has been validated by several other groups<sup>(18-22)</sup> (table 1). Complete resection rates in patients with positive AGO-score ranged between 67.0 and 89.3%, indicating that the AGO score is able to predict operability with complete resection with a high reliability. On the other hand, the AGO-score was not intended to give any information about inoperability. DESKTOP II already reported complete resection

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rates of 63.5% in AGO-score negative patients and in the consecutive analyses by other groups revealed complete resection rates ranging between 48.5 and 68.5%.

Primary surgery for advanced ovarian cancer bears a curative opportunity for affected patients. Therefore, it seems to be appropriate to accept an elevated morbidity and even low rates of mortality. Due to the fact, that the impact on survival of surgery for recurrent ovarian cancer is still not validated prospectively, and that the current understanding of treatment of recurrent ovarian cancer is survival prolongation and not cure, morbidity and mortality are of highest importance. Perioperative complications have been prospectively documented in DESKTOP II. 44% of patients had to receive packed blood cells, and 33% of patients had at least one perioperative complication. 24% of patients received an antibiotic treatment and 11% had to undergo a re-laparotomy. In a meta-analyses the weighted mean morbidity rate was a of 19.2%<sup>(23)</sup>. The 30-day mortality in DESKTOP II was reported to be 0.8%<sup>(17)</sup>, in a meta-analyses 1.2%<sup>(23)</sup> and up to 7.8% in single institutions<sup>(14)</sup>.

Despite numerous publications regarding the role of cytoreductive surgery for recurrent ovarian cancer, a prospectively randomized controlled study is still missing. The AGO DESKTOP III trial: "A prospective randomized trial comparing surgery and chemotherapy versus chemotherapy alone in recurrent ovarian cancer" (NCT01166737) is closed but the results are still pending. Another ongoing study investigating the role of cytoreductive surgery for platinum sensitive recurrent ovarian cancer is performed by the Gynecologic Oncology Group (GOG) (GOG 213; NCT00565851).

	AGO Score positive			AGO Score negative		
	Pts.	Complete resection (%)	Median OS (Months)	Pts.	Complete resection (%)	Median OS (Months)
Harter P et al. DESKTOP II <sup>(17)</sup>	129	76.0	n.a.	63	63,5	n.a.
Harter P et al. <sup>(18)</sup>	112	89.3	57,3	105	66,7	33.5
Janco J et al. <sup>(19)</sup>	102	84.3	n.a.	90	64,4	n.a.
Van der Laar R et al. <sup>(20)</sup>	111	82.0	n.a.	162	68,5	n.a.
Laas E et al. <sup>(21)</sup>	33	81.8	n.a.	32	65,6	n.a.
Muallem MZ et al. <sup>(22)</sup>	139	67.0	54,0	70	48,5	21.7

Table 1: Overview of published series evaluating the *Arbeitsgemeinschaft Gynäkologische Onkologie* (AGO)- DESKTOP Score; n.a. not reported



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**Treatment for recurrent disease: New treatments**  
Eric Pujade-Lauraine, *Hôpital Hotel-Dieu, Paris, France*

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## NEW DRUGS

Eric Pujade-Lauraine. Hôpital Hôtel-Dieu, AP-HP. Université Paris Descartes

Epithelial ovarian cancer (OC) patient outcome is on the way to be transformed by the PARP inhibitor class led by olaparib, which is also challenged by many others competitive molecules whose mechanism of action are close. DNA damage repair (DDR) targeted drugs, however, are not limited to PARPi which target the homologous recombination repair (HRR) pathway. Modulators of the cell cycle are aimed at preventing cycle arrest required for DNA repair and have recently open the door in ovarian cancer. Among the main other drugs of potential interest, let's list those which target mutant p53, the folate receptor alpha, the inhibitors of apoptose proteins (IAPs) and lurbinedetin. The list would not be complete if immunotherapy was not pointed out as one of the most promising field for the future progress in OC.

## DNA DAMAGE REPAIR TARGETED DRUGS

DNA repair targeted therapies exploit DNA repair defects in cancer cells to generate synthetic lethality (for example, cancer cells defective in one DNA repair pathway rely on alternate repair pathways; inhibition of a second repair pathway then results in cell death), an effect which selectively targets repair-deficient cancer cells.

### PARP inhibitors

Approximately 50% of ovarian carcinomas (OC) exhibit dysfunctional HRR. HRR deficiency confers sensitivity to inhibitors of the PARP enzyme, which is vital to several DNA repair pathways, including base excision repair (BER) and nonhomologous end-joining (NHEJ) pathways.

Olaparib is the first approved PARPi in OC. In EU, olaparib is approved in platinum-sensitive relapse as a maintenance treatment after responding to platinum-based chemotherapy in patients with germline and/or somatic BRCA mutation after study 19 showed benefit in OC in patients particularly those with germline BRCA1/2 mutations<sup>(1)</sup>. Olaparib is approved in the United States for patients with recurrent OC who have a germline BRCA1/2 mutation and in whom at least 3 lines of therapy have failed.

The first results of a phase III PARPi trial (niraparib) were disclosed with the NOVA trial. In maintenance after response to platinum chemotherapy in late relapse, they confirmed the results of the randomized phase II study 19, with a tolerable toxicity profile despite an increased rate of bone marrow toxicity. In addition, the NOVA trial has confirmed the activity of PARPi beyond BRCA mutation. The HRD test used in this study (MyChoice from MYRIAD) was able to enrich the BRCA wild type population in patients sensitive to niraparib, but a significant proportion of patients with negative HRD test could still benefit from the drug in terms of progression-free survival (PFS)<sup>(2)</sup>.

Rucaparib has benefited recently in US from an accelerated approval in patients with BRCA mutation treated with at least 2 lines of therapy whatever the free interval. In the large phase II trial ARIEL2, the HRD test from Foundation Medecine was also able to separate the HRD positive from the HRD negative population in terms of response rate and PFS<sup>(3)</sup>.

A better view of the PARPi scene in relapse will come this year with the results of the SOLO2 and ARIEL 3 phase III trials and with the labels obtained by these 3 compounds.

Where are the PARPi going to in OC?

## New treatments

Eric Pujade-Lauraine

Combinations are explored while the PARPi are currently moving in first-line. Preliminary efficacy results of the combination of olaparib and cediranib, a VEGF TKI, in late relapse were highly encouraging<sup>(4)</sup> and have justified the evaluation of the combination both in early and late relapse in phase III trials despite significant toxicity. More easily tolerable is the combination of olaparib and bevacizumab tested in first-line in the PAOLA-1 phase III trial. Niraparib has also started a phase III trial in maintenance of first-line (PRIMA trial) while SOLO1 trial is a phase III restricted to patient with BRCA mutation. Interestingly, veliparib has taken advantage of its weakness in being loosely trapped by DNA to be combined with chemotherapy in different settings of relapse, but also in first-line through a large phase III trial. Finally, PARPi and immunotherapy associations are actively explored.

### Modulators of the cell cycle

AZD1775 is a highly selective, potent, ATP competitive, small molecule inhibitor of WEE1 kinase. In vitro, AZD1775 inhibits WEE1 activity and induces DNA damage as well as G2 checkpoint escape in cell based assays. AZD1775 increases cytotoxicity when used in combination with DNA damaging agents, such as gemcitabine, cisplatin, carboplatin and topotecan, in p53-deficient cell lines. The combination of AZD1775 orally twice a day during 2.5 days every 21 day cycle with carboplatin (AUC5) achieved an impressive 43% overall response rate with a median PFS of 5.3 months in 21 evaluable patients with p53 mutant OC in relapse less than 3 months after the last dose of platinum. The most frequent grade 3 or 4 adverse events were thrombocytopenia (48%) and neutropenia (37%)<sup>(5)</sup>.

Prexasertib (LY2606368 monomesylate monohydrate) is a small molecule that in vitro preferentially binds to and inhibits CHK1 and, to a lesser extent, inhibits CHK2, thus inducing DNA double-strand breaks, a loss in checkpoint function, increased replication stress, and cell death. In phase II, prexasertib achieves a 35% response rate (n=20) in heavily pre-treated patients without gBRCA mutation<sup>(6)</sup>. Hematologic toxicity is also predominant.

## TARGETING p53

### APR-246

APR-246 is a methylated derivative and structural analog of PRIMA-1 (p53 re-activation and induction of massive apoptosis), with potential antineoplastic activity. Upon administration, PRIMA-1 analogue APR-246 covalently modifies the core domain of mutated forms of cellular tumor antigen p53 (p53) through the alkylation of thiol groups. These modifications restore both the wild-type conformation and function of mutant p53, which reconstitutes endogenous p53 activity, leading to cell cycle arrest and apoptosis in tumor cells. This agent has been shown in vitro to work synergistically with other antineoplastic agents. A randomized phase II trial is on-going combining APR-246 with carboplatin and PLD versus carboplatin and PLD in late relapse of patients with p53 mutant OC (PIsARRO trial).

### Ganetespib

Ganetespib exhibits its function by competitively inhibiting the ATPase activity of the Hsp90 core protein. Due to their aberrant conformation mutp53 proteins depend on permanent folding support by the multi-component Hsp90 chaperone machinery and that it is this stable interaction between mutp53 and Hsp90 that is largely responsible for mutp53 accumulation specifically in tumour cells. Hsp90 inhibition mediates effective destabilization and degradation of mutp53 in human tumour cells, acutely withdrawing an oncoprotein these cells depend on for survival. In vivo, ganetespib inhibits the growth of human tumor cell lines in mouse xenograft models.

Ganetespib is currently evaluated in combination with weekly paclitaxel in women with high-grade OC through a randomized phase II trial (GANNET trial).



## TARGETING FOLATE RECEPTOR

Despite the setbacks of previous experiences such as those of farletuzumab and vintafolide, targeting folate receptor alpha (FR) remains an active field in OC. IMGN853 consists of a humanized anti-FR monoclonal antibody attached via a disulfide containing linker to the cytotoxic maytansinoid, DM4. Preliminary results from a Phase 1 study indicate that IMGN853 elicits an overall response rate (ORR) of 53% in heavily pretreated patients with platinum resistant, FR-positive EOC. The majority of adverse events were Grade 1 or 2 in severity and included diarrhea (59%), blurred vision (50%), nausea (41%), vomiting (32%), fatigue (32%). FORWARD1 is currently evaluating the safety and efficacy of Mirvetuximab Soravtansine (IMGN853) versus investigator's choice of chemotherapy in adults with FR-positive EOC.

### Targeting apoptosis

Abnormal expression of anti apoptotic molecules is one of the most frequent mechanisms resulting in apoptosis resistance, making current anticancer therapies less effective or ineffective. Therefore, reactivation of cancer cell death programs in cancer is a promising strategy to overcome treatment resistance. Inhibitor of apoptosis (IAP) proteins comprise a family of anti apoptotic proteins that promote pro survival signalling pathways and prevent activation of the effector phase of apoptosis by interfering with the activation of caspase. Drugs targeting and inhibiting IAP proteins could be useful to induce cell death by themselves or by lowering the threshold for cell death induction when combined with other anticancer therapies like chemotherapy, targeted agents, or radiation therapy.

The small molecule Debio 1143 is a potent orally active IAP antagonist able to promote apoptosis in tumor cells by restoring caspase activity and modulating NF  $\kappa$ B signalling and TNF $\alpha$  effects. This molecule is currently tested in a randomized phase II trial of neoadjuvant carboplatin and paclitaxel, with or without Debio 1143 in patients with newly diagnosed advanced epithelial ovarian cancer.

### Lurbinectedin

Lurbinectedin is a synthetic tetrahydropyrrolo [4, 3, 2-de]quinolin-8(1H)-one alkaloid analogue and is an inhibitor of RNA polymerase II which is essential for the transcription process that is overactivated in tumors with transcription addiction. Lurbinectedin covalently binds to residues lying in the minor groove of DNA, which may result in delayed progression through S phase, cell cycle arrest in the G2/M phase and cell death.

In a two-stage controlled phase II study in 81 patients with resistant/refractory disease, lurbinectedin achieved a 22% response rate whereas no response was observed in patients treated with topotecan. The CORAIL randomized phase III is currently evaluating lurbinectedin compared with PLD or topotecan in platinum-resistant disease.

### Immunotherapy

Table 1 shows a sum-up of the molecules targeting the PD-L1/PD1 pathway. They have been tested in heavily pretreated OC patients. Despite a high expression of PD-L1 in OC (at least on archival biopsies), the response rate remains modest around 15%. As in other tumor types, these responses are long lasting in most of the cases.

The future of immunotherapy in OC holds in the combination of PD1/PD-L1 inhibitors with chemotherapy and/or targeted therapy. The JAVELIN200 compares in 550 patients with early relapse Avelumab alone versus PLD alone versus the combination of PLD+Avelumab. ATALANTE explores the combination of chemotherapy + bevacizumab

## New treatments

Eric Pujade-Lauraine

with Atezolizumab in a randomized trial of 405 patients in late relapse. JAVELIN100 is currently testing Avelumab in a large randomized trial for first-line in all comers.

	Nivolumab	Pembrolizumab	Avelumab	Atezolizumab	Durvalumab
No	20	26	124	12	20*
Previous line (No)	≥ 4 in 55% of cases	≥ 5 in 38.5%	≥ 3 In 65.3%	≥ 6 In 58%	4* Median:
PD-L1+ prevalence	80% (IC 2/3)	100% (≥ 1% TC)	77% (≥ 1% TC)	83% (IC 2/3)	73% (>5% TC)
Response rate	15%	11.5%	9.7%	25%	Not reported

Table 1: Drugs interacting with PD-L1/PD1 pathway in ovarian cancer (from Pujade-Lauraine, ESGO 2016)

## CONCLUSION

The brilliant story of the PARPi is just starting and several trials are exploring their role beyond BRCA and in early phase of the disease. Modulators of the cycle and immunotherapy are very attractive and have to confirm their role in the near future. Several others candidates have entered in randomized trial and hopefully some of them will be the drugs of the next future.



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**Keynote lecture: The real world evidence in the treatment of ovarian cancer**  
Elizabeth Eisenhauer, *Queen's University, Kingston (Ontario), Canada*

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## INTRODUCTION

Randomized clinical trial (RCT) evidence leads to regulatory approval and incorporation of novel treatments and technologies into practice. “Real world evidence (RWE)” refers to information on the utilization and outcome of new therapies and technologies in clinical practice. RWE is a broad term that may include data from single institution cohort studies, population based health services studies, and (inter)national data on survival and mortality. Such studies can provide information about the uptake of new treatments, their safety and effectiveness in clinical practice or explore trends in overall outcomes between groups or points in time.

As the costs of new cancer interventions have risen, and the bar for their marketing approval has fallen, there has been increasing attention paid to whether such new therapeutics “deliver” improved outcomes (“effectiveness”) in the real world of practice. Such information may affect ongoing reimbursement and illuminate the benefits of treatments in the more generalized populations to which new therapies may be applied (e.g. clinical trials may restrict patient entry to those with good performance status, no brain metastases etc., and in practice, a broader range of patients will be treated).

RWE also examines different patterns of care within populations by geography or over time and may be used to make inferences about the impact of those care patterns on patient and disease outcomes – perhaps helping forge policy or guideline change when RCTs are not feasible. For example, the work of Booth et al. in demonstrating a population level impact of peri-operative chemotherapy (neoadjuvant and adjuvant) in muscle invasive bladder cancer in Ontario has led to a renewed discussion on the place of adjuvant chemotherapy in this patient group<sup>(1)</sup>.

It is important to understand the strengths/weaknesses of RWE in interpreting their results: *when comparisons are made in particular, it is important to note that biases are inevitable* – particularly when contemporaneous treatments are compared in a single institution since patients are selected to undergo different treatments. More weight may be given to population based datasets with comparisons before/after a critical date (e.g. when a new drug or technique becomes available) or between jurisdictions/centres and in examining trends over time.

In ovarian cancer, RWE studies focussed on specific treatments are infrequent. Some identified are summarized below. In addition, trends in population mortality and incidence information, from which the impact of treatment can be inferred are also summarized:

### **RWE STUDIES OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY DEBULKING VERSUS PRIMARY DEBULKING**

The practice of NACT has risen since the publication of the EORTC<sup>(2)</sup> and CHORUS<sup>(3)</sup> randomized trials that concluded NACT was non-inferior to primary debulking strategy in management of patients who were fit for either procedure. But controversy remains, largely fueled by concerns about the reported survival in the two RCTs, the long history of primary debulking surgical practice and some smaller cohort studies suggesting worse outcomes in patients elected to receive NACT vs. primary debulking<sup>(4)</sup>. Since patients in cohort analyses are not randomly assigned – and since those with adverse prognostic indicators (e.g. poor performance status, greater disease burden, co-morbidities) may be preferentially offered NACT, it is to be expected that without careful correction for those factors, NACT outcomes will appear worse. One recent large study has attempted to address these shortcomings so by undertaking a propensity score matched analysis in a population dataset. The study by Rauh-Hain et al. used the US National Cancer Database and compared the outcomes of 2935 patients planned to receive NACT followed by surgery with 2935 patients planned to receive primary debulking followed by chemotherapy matched for age, stage, grade, histology<sup>(5)</sup>. Interestingly: in the NACT group, only 74% received surgery and in the primary debulking group,

# Keynote lecture: The real world evidence in the treatment of ovarian cancer

Elizabeth Eisenhauer

only 85% received post-op chemo. Median survival was shorter for NACT patients (32.1 vs 37.3 months) but the authors also showed that a fairly minor maldistribution of performance status 1-2 (not matched for in the data) of 60% in NACT and 50% in upfront surgery groups would have obscured the survival difference. This type of study underscores the complexity of using RWE to draw comparisons when *non-random prognostic associated factors lead to different treatment assignments*.

## IV/IP VERSUS IV CHEMOTHERAPY

One of the great controversies in the field of ovarian cancer treatment is that surrounding the use of IV/IP chemotherapy in optimal ovarian cancer. Three RCTs showed superiority in overall survival yet each was greeted with criticism and scepticism regarding the design, the treatment and control arm composition and more. These factors, coupled with concern over toxicity and inconvenience of IP administration, have led to limited uptake of IV/IP treatment in many regions. A recent “real world” study documented the changing trends of use of IV/IP treatment in some centres in the USA, and also attempted to review the impact on outcomes<sup>(6)</sup>. In this study, authors compiled treatment data from a prospective cohort of stage III, optimally debulked ovarian cancer patients treated in six National Comprehensive Cancer Centre network centres in the USA. Between 2003 and 2008, use of IV/IP based chemotherapy increased as a treatment policy with its use rising from 0% up to 50% of patients in this time frame, before plateauing. In a propensity score matched sample of cases from 2006-2012, IV/IP treatment was associated with significantly improved 3-year survival (HR 0.68, CI 0.47-0.99) compared to IV only treated patients. IV/IP regimens were not standardized and toxicity was higher in the IV/IP group. These data are supportive of the earlier clinical trials findings but also could not be controlled for all the variables that may have led to the selection of one treatment over the other. On the other hand, in this example, the use of IV/IP treatment was largely determined by policy change, since its use changed over time, not individual patient selection.

## INFERENCES ABOUT THE REAL WORLD IMPACT OF TREATMENT – TRENDS IN SURVIVAL AND MORTALITY RATES

The goal of prevention, early diagnosis/screening and treatment of cancer is to reduce incidence rates and improve survival and mortality rates (the burden of disease) in the population. The cumulative impact of new treatments should therefore, be reflected in improved population survival rates and reduced mortality from disease.

Changes in population survival rates (changes over time in the likelihood of surviving a diagnosis of cancer) are complex to use for this purpose since they may include lead time bias (trends to earlier diagnosis may give the impression of longer survival) and corrections must take place to ensure deaths from other causes are not incorrectly attributed to malignant disease. Mortality rates (deaths per 100,000 age-standardized population) may be a better approach to investigate if treatments are having a desirable effect, but it is important to note that age-standardized mortality rates are also subject to the influence of factors other than treatment, notably changes in incidence rates. While not all interventions that cause a rise in incidence rate result in a rise in mortality rate, some do. On the other hand, in general, factors/interventions leading to a decline in incidence rates normally lead to a decline in mortality rates. The most convincing evidence of the impact of treatment comes when incidence rates remain unchanged yet mortality rates fall.

## OVARIAN CANCER INCIDENCE, MORTALITY AND SURVIVAL TRENDS

What can be inferred about “real world” effectiveness of ovarian cancer treatments (surgery, chemotherapy etc.) through mortality trends? The situation is complicated because over the last 3 decades incidence rates have been falling. Some of this fall is attributed to the widespread use of protective oral contraceptive drugs and of decreased



use of post-menopausal hormone supplementation. Not surprisingly, mortality rates have also been falling. One approach to assess the impact of treatment on mortality, over and above that of change in incidence, is to evaluate whether mortality rates have been falling to a greater degree than incidence rates. And some data suggests that is the case.

In the US, modeling of SEER data show that 2004-2013 incidence rates for new ovarian cancer cases have been falling on average 1.9% each year over the last 10 years. Mortality rates have been falling on average 2.2% each year over this period<sup>(7)</sup>. Looking further back (1975-2013) incidence rates have fallen from between 1975 and 2013 from 16.3 to 11.4 per 100,000 and death rates from 9.8 to 7.2 per 100,000. Over a similar period (1975-2008), relative 5-year survival has increased from 33.7% to 46.2%.<sup>(6)</sup>

In France between 1980 and 2012, incidence rates have fallen by 0.6% per year and mortality rates by 1.2% per year<sup>(8)</sup>.

Trends in ovarian cancer mortality rates across most European countries and globally have also recently been reported<sup>(9)</sup> – these show declines in mortality rates from 2002-2012 with an EU mortality rate of 5.2 per 100,000 in 2012. The degree of fall, and the absolute mortality rate varies across EU countries and the globe. The authors attribute the majority of the effect on mortality to changes in incidence rates through oral contraceptive use and, beginning about 10 years ago, declines in menopausal hormone use. In their view, the impact of treatment was not as substantial as changes in incidence rates which were believed to play the major role in the fall in mortality.

Population data such as these are complex to analyse – and the relative impact of changes in incidence rates (which have been notable) and the effects of treatment are difficult to disentangle. Nonetheless, the data are consistent with an impact of treatment on mortality rates – though perhaps less marked than that of falling incidence rates. The population data showing increases in relative survival rates also support a treatment effect at the population level, although as discussed above other factors may influence this besides treatment effect.

## **SUMMARY**

Real world data on treatment impact is important to collect if the goal of clinical research is to reduce the overall burden of disease. Prospective (and to some degree retrospective) cohort data as well as population level data can illuminate the uptake of new treatments, provide supplemental information on their safety, and effectiveness. Comparative analyses are challenging however since non-randomized comparisons carry inherent biases. Trends in outcome over time may also offer evidence of the impact of new treatments, though these analyses also have limitations. Some have suggested that prospective assessment of real world evidence should be built into the reimbursement process for new drugs, especially those of high cost and marginal benefit, with their continued approval being conditional upon observations of supporting safety and effectiveness within the population in which they will be prescribed in practice. RWE including population based studies will never replace randomized clinical trials – but they offer complementary information for practitioners, patients and policy makers and are thus “partners in the evolution of medical science”<sup>(10)</sup>. More such studies in ovarian cancer are needed.

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