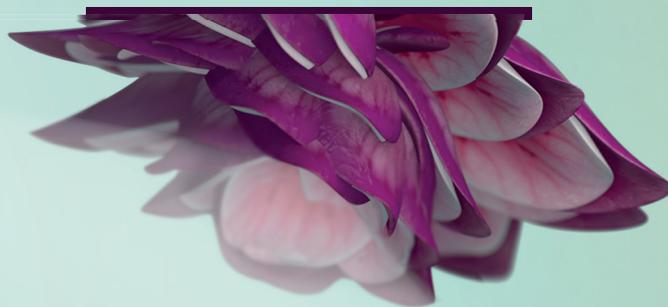


12th International Symposium
ADVANCED
**OVARIAN
CANCER**

Optimal Therapy. Update

Valencia, 22nd February 2019



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KEYNOTE LECTURE

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Biomarkers in Ovarian Cancer: To be or not to be

Michael Birrer, *O'Neal Comprehensive Cancer Center at UAB (AL), USA*.....7

SESSION 1 TRANSLATIONAL RESEARCH

Chairs:

Michael Birrer
O'Neal Comprehensive Cancer Center at UAB (AL), USA
Jose A López-Guerrero
Fundación Instituto Valenciano de Oncología, Valencia, Spain

Precision Medicine in epithelial ovarian cancer

Iain McNeish
Imperial College London, UK.....13

The potential role of liquid biopsies in ovarian cancer

Martin Widschwendter
University College London, UK.....17

TILs and PD-L1 expression in ovarian cancer: What to do with it?

George Coukos
University of Lausanne, Switzerland.....19

SESSION 2 TREATMENT OF PRIMARY DISEASE

Chairs:

Jonathan A. Ledermann
UCL Cancer Institute, University College, London, UK
Luis Chiva
Clínica Universidad de Navarra, Madrid, Spain

How to manage lymph nodes in ovarian cancer in 2019

Philipp Harter
Kliniken Essen-Mitte, Essen, Germany.....21

Can we predict who lives long with ovarian cancer?

Michael A. Bookman
Kaiser Permanente Northern California, USA.....25

Landscape of systemic therapy for ovarian cancer in 2019

Keiichi Fujiwara
Saitama Medical University International Medical Center, Saitama, Japan.....31

Does HIPEC improve survival in AOC?

Chairs:

Jan B. Vermorken
Antwerp University Hospital, Edegem, Belgium
Giovanni Scambia
Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy

PRO:

Gabe Sonke
Netherlands Cancer Institute, Amsterdam, the Netherlands.....35

CONS:

Ignace Vergote
University Hospitals Leuven, European Union.....39

SESSION 3 TREATMENT OF RECURRENT DISEASE

Chairs:

Eric Pujade-Lauraine
Hôpital Hotel-Dieu, Paris, France
Ana Oaknin
Vall d'Hebron University Hospital. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Who needs surgery?

Jalid Sehouli
Charité University of Medicine, Berlin, Germany.....43

Do all patients need systemic therapy?

Michael Friedlander
Royal Hospital for Women and Nelune Cancer Center, Sydney, Australia.....47

Landscape of systemic therapy for recurrent ovarian cancer in 2019

Sandro Pignata
National Cancer Institute, Naples, Italy.....53

SESSION 4 NEW DEVELOPMENTS

Chairs:

Mansoor Mirza
Copenhagen University Hospital, Copenhagen, Denmark
Andrés Redondo
Hospital Universitario La Paz, Madrid, Spain

Immunotherapy in Ovarian Cancer: Still promising?

Antonio González
Clínica Universidad de Navarra, Madrid, Spain.....57

New Strategies in Ovarian Cancer Treatment

Elise C. Kohn
National Cancer Institute, Bethesda (MD), USA.....61

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 22nd February 2019 its twelfth edition will be held. This symposium is organized every other year by GEICO (*Grupo Español de Investigación de Cáncer de Ovario*, Spanish Ovarian Research Group), and, since 2009, together with ESMO (European Society for Medical Oncology).

GEICO (www.grupogeico.org) was founded in June, 1999 and from its beginning has developed its own studies. GEICO is also collaborating within the framework of the EORTC (the European Organization for the Research and Treatment of Cancer), ENGOT (the European Network for Gynecological Oncological Trials) and the GCIG (the Gynecologic Cancer InterGroup). GEICO members are medical oncologists, gynecologists, radiation oncologists and molecular biologists especially interested in the study and research of gynecological tumors.

The meeting is held under the auspices of the Spanish Society of Medical Oncology (SEOM), GCIG, and the European Society for Medical Oncology (ESMO), and its Educational Committee for Medical Oncology Recertification Approval (ESMO/MORA).

One hundred and fifty people attended the symposium in its first edition, held in 1996. Since then, the interest in this meeting has increased. During the last edition in 2017, more than four hundred colleagues from different parts of the world (Europe, North and Latin America, Asia and Australia) were present at the symposium.

Because of GEICO's strong commitment to international collaboration, most of the other important international cooperative groups, working in the field of gynecologic oncology will be present again at this 2019 symposium, such as GOG-F, NCIC, AGO, EORTC-GCG, ANZGOG, GINECO, JGOG, GOTIC, MRC, MITO, MANGO, NCI, NOGGO, NSGO.

From the 2nd edition (1999) onwards, conference proceedings have been published as full papers in the "International Journal of Gynecological Cancer" (Blackwell 2000, vol 10 (suppl 1); 2001, vol 11 (suppl 1); 2003, vol 13 (suppl 2); 2005, vol 15 (suppl 3); 2008, vol 18 (suppl 1); Wolters Kluwer Lippincott Williams & Wilkins 2009, vol 19 (suppl 2); and "Annals of Oncology" (Oxford University Press 2011, vol 22, (suppl 8); 2013, vol 24 (suppl 10); 2016, vol 27 (suppl 1); 2017, vol 28 (suppl 8).

Our meeting has the category of a classic educational activity where many people come to teach, to learn, and also to discuss the value of how standard as well as new approaches are being incorporated into the management of ovarian cancer. In this symposium, held on one day, we cover most relevant hot topics concerning diagnosis, biology and therapy of ovarian cancer.

WELCOME!

Andrés Poveda and Jan B. Vermorken

Directors



KEYNOTE LECTURE

Biomarkers in Ovarian Cancer: To be or not to be

Michael Birrer

O'Neal Comprehensive Cancer Center at UAB (AL), USA

Rebecca Arend, Alba Martinez, Tomasz Szul, and Michael J. Birrer*

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In 2019, there are estimated 22,530 new cases and 13,980 deaths (ratio of 1.5:1) in the US¹. Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 78. Her lifetime chance of dying from ovarian cancer is about 1 in 108. Patients with early-stage high grade disease (stage I and II) are associated with an excellent 5-year survival rate after surgery and adjuvant chemotherapy². Unfortunately, the majority of epithelial ovarian cancer (EOC) patients present with extensive peritoneal spread beyond the pelvic cavity (FIGO Stage III/IV) that ascribes a considerably worse prognosis. 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. 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. The emergence of detailed genomic analysis, cutting edge characterization of tumor stroma, and the rise of effective targeted therapies such as bevacizumab and Poly (ADP-ribose) polymerase (PARP) inhibitors has created the opportunity to stratify ovarian cancer patients to provide optimal therapy. This paper will review the present state of the science with regard to ovarian cancer biomarkers and how they can be used to clinically manage these patients.

EARLY STAGE OVARIAN CANCER

Approximately 25% of ovarian cancer is limited to the ovarian or the pelvis (early stage). High grade ovarian cancers are treated with complete resection and most if not all are treated with adjuvant chemotherapy. It is well recognized that this group of patients is overtreated and a better understanding of the molecular features of their tumors will help stratify patients. An international consortium has undertaken a complete genomic/proteomic/immunologic characterization of high grade serous and endometrioid early stage ovarian cancer^{3,4}. Initial results demonstrates unique genomic features between endometrioid and serous tumors, copy number variation (CNV) which in part reflects advanced stage disease, and unique patterns of infiltrating immune cells. Integrated analysis has developed several signatures with the ability to predict those patients who will recur.

ADVANCED STAGE DISEASE

Optimizing the surgical approach

Primary debulking surgery remains a pivotal part in the current management of epithelial ovarian cancer. Patients who have substantial residual disease after debulking surgery have not benefitted from the procedure. With the establishment of the fact that neoadjuvant chemotherapy with interval debulking surgery (NACT-IDS) is equivalent to primary debulking, stratifying patients to undergo primary surgery has become a critical issue^{5,6}. A meta-analysis of the transcriptional profiles from more than 1,250 primary debulked EOCs 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- β pathway underlying the overexpression of genes that render oncogenic modulation of both tumor and the tumor microenvironment, including epithelial-mesenchymal transition, metastasis, chemoresistance, desmoplastic stroma activation and angiogenesis. Despite the requirement of independent validation using prospective clinical specimens, identification of TGF- β signaling which underlies the difficulty of optimal cytoreduction may warrant the triage of patients through diagnostic laparoscopy specimens⁷. Such findings would further support the test of TGF- β inhibition as a potential approach for post-operative management of suboptimally debulked tumors, or in the neoadjuvant setting to increase the efficacy of NACT-IDS and maximize the optimal cytoreduction rate. Inhibition of TGF- β signaling not only will decrease disseminated growth of tumor lesions, but will also sensitize these tumors to chemotherapy or recently emerged immunotherapies.

For advanced stage tumors which are predicted to be effectively debulked, the question remains as to whether we can improve on their treatment. It is clear that the amount of tumor left after surgery is directly related to patient survival. Improving the resection rate by removing smaller deposits of tumor should result in better patient outcomes and potentially increased cures. Single walled nano tubes (SWNTs) have demonstrated important physical properties which allows them to be used as novel imaging agents. Recent work has led to the development of a novel molecular imaging agent and device to detect sub-

KEYNOTE LECTURE

Biomarkers in Ovarian Cancer: To be or not to be

Michael Birrer

O'Neal Comprehensive Cancer Center at UAB (AL), USA

visible deposits of ovarian cancer cells. The contrast agent is an intra-peritoneal injectable nanomolecular probe, composed of SWNT, coupled to an engineered M13-bacteriophage carrying a modified peptide targeting secreted protein, acidic and rich in cysteine (SPARC), an extracellular protein overexpressed in ovarian cancer. The imaging system is capable of detecting SWNT fluorescence in the second near-infrared window (NIR-II) band. This agent has been applied to a validated orthotopic murine model of ovarian cancer where tumors spread intra-peritoneal and frequently produce ascites. The imaging system produced remarkable sensitivity and specificity for tumor detection, many of which were sub-visible⁸. This technology is ready to transition to the clinic and may usher in a new age of micro-debulking for ovarian cancer.

STRATIFICATION OF HIGH-GRADE SEROUS OVARIAN CANCER

Homologous recombination deficiency (HRD)

Approximately half of high grade serous carcinomas (HGSC) exhibit defective DNA repair through alterations in homologous recombination (HR) pathway genes; about fourteen percent of these are due to germline BRCA mutations and an additional six percent due to somatic BRCA mutations^{9,10}. In addition to BRCA, other mutations in the HR pathway can have a germline or a somatic mutation that leads to HR deficiency. Patients with "Homologous Recombination Deficiency" due to mutations in HR pathway genes cannot repair double-strand DNA breaks. Given that PARP is an enzyme that is necessary to repair single-strand DNA breaks, using a PARP Inhibitor prevents this, leading to an accumulation of double-strand breaks. Therefore, if a PARP inhibitor is used in a patient who cannot repair double-strand breaks (an HRD deficient patient) this leads to tumor cell death, which is the phenomenon called "synthetic lethality". The question then becomes: What is the best way to test for HRD? While germline testing uses an extremely accurate, reproducible, well-established technique, it will identify a smaller number of patients who may benefit from PARP inhibitor treatment than somatic Next Generation Sequencing (NGS) testing.

A study by Pennington, et al. looked at over 350 patients with 390 different ovarian carcinomas including primary and recurrent tumors¹¹. Approximately one-third of these patients had some form of HR Repair Pathway alterations: 22.6% were germline, 7.6% were somatic, and 1.1% were both germline and somatic. The most common germline mutation was BRCA1 (54%), then BRCA2 (21%), followed by 9 other genes (1-5%): BARD1, BRIP1, CHEK1, CHEK2, FAM175A, NBN, PALB2, RAD51D, and RAD51C. The somatic mutations included BRCA1 (54%), BRCA1 (17%), CHEK2 (9%), ATM (8%), BRIP1 (6%), MRE11A (3%), and RAD51C (3%). This paper confirmed the correlation between HR mutations and platinum sensitivity; approximately 80-90% of patients with either a germline or somatic HR mutation were also platinum sensitive; whereas almost 50% of the patients without an HR mutation were platinum resistant or refractory.

HR pathway defects leads to genomic instability, which can functionally be characterized measuring the frequency of copy number changes in each chromosome by either a gain or a loss of an allele of a specific gene (loss of heterozygosity; LOH), which has also been correlated with increased response to platinum-based chemotherapy. Genome-wide LOH can be measured by comprehensive tumor genomic profiling based on NGS. Thus, genomic instability caused by chromosomal alterations, nucleotide substitutions, insertions, and deletions that accumulate in the absence of DNA repair due to DNA repair gene mutations (germline and somatic) influence the patients' response to therapy (platinum and PARP inhibitors). Most patients with a germline or a somatic mutation in a DNA repair gene will have LOH due to the loss of a wild-type allele in the presence of a mutated gene allele¹². Although, there are additional patients that can be identified as having HRD due to other things beyond germline and somatic HR pathway gene mutations. In addition to using LOH as a surrogate biomarker for HRD, two other consequences of genomic instability can be measured by an allelic imbalance in the unequal contribution of maternal and paternal DNA sequences with or without changes in overall DNA copy number (Telomeric Allelic Imbalance - TAI) and measuring chromosomal breaks between adjacent regions of ≥ 10 megabases (Large-scale State Transitions -LST)¹³.

Currently the only Companion Diagnostic test (biomarker) are germline BRCA mutations for the usage of olaparib monotherapy after 3 lines of prior therapy and germline + somatic BRCA mutations for the usage of rucaparib monotherapy after 2 prior lines of therapy and olaparib maintenance therapy in the upfront setting. The additional biomarkers, such as germline and somatic mutations in other HR pathway genes, LOH status (high/low), or HRD status (positive/negative) based on LOH, TAI, and LST have been looked at in clinical trials and while there was a positive correlation between benefit from PARP inhibition and all of these additional biomarkers, none have been approved as Companion Diagnostic Tests^{14,15}. The reason for this is that the majority of the trials where these biomarkers were analyzed, were trials that only



included patients with platinum sensitive disease. Platinum sensitivity itself can be used as a surrogate biomarker for HRD; therefore, in platinum sensitive patients, PARP inhibitor maintenance was approved regardless of HRD status or other biomarkers. Although patients that are HRD positive or have LOH high status or the presence of germline or somatic mutations in other HR genes in addition to platinum sensitivity do have an even stronger benefit from PARP inhibitor maintenance than platinum sensitivity alone and therefore could be used in counseling patients. Additionally, the use of these other biomarkers - either in the upfront setting before you know the patients' platinum sensitivity status or in platinum resistant patients - may play a role in the near future in expanding the number of patients that will benefit from PARP inhibitor therapy.

ANTI-ANGIOGENESIS

The effectiveness of anti-angiogenesis agents for ovarian cancer is well known. Bevacizumab is now approved for both up front and recurrent disease (platinum sensitive and resistant) based upon multiple randomized phase III trials. Of great concern is identifying the precise patients who will benefit the most from this agent and suffer the least from its toxicity. Although there is no approved biomarker(s) to satisfy these needs, there has been a lot of work in this area. Recent characterization of GOG218 demonstrated that all of the bevacizumab benefit could be predicted by the CD31 expression of the tumor¹⁶. This finding makes biologic sense and will require validation. Further, there has been a lot of work on serum-based biomarkers and while a lot of it has been negative, serum IL6 levels seem to correlate with bevacizumab benefit. This too will require independent validation.

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

One of the challenges for the future management of ovarian cancer is its inherent genomic instability. Except for TP53 and BRCA1/2, actionable point mutations in well accepted oncogenes or tumor suppressive genes are relatively infrequent in HGSC¹⁰. Instead, a high-degree of chromosome instability prevails in HGSC and leads to extensive DNA gains and losses which activate oncogenes or inactivate tumor suppressors through gene amplification, deletion or translocation to drive early-stage tumorigenesis and the development of chemoresistance^{17,18,19}. The identification of novel "druggable" targets with high-frequency copy number variation remains challenging even after the completion of several comprehensive genomic studies²⁰. This will require careful biologic and laboratory based experiments to characterize the important drivers of this tumor and how they evolve during the natural history of the disease. This approach has already yielded the identification of important genes along with their therapeutic potential.

CONCLUSION

Despite the molecular complexities of epithelial ovarian cancer, intensive work by many different laboratories are beginning to fulfill the promise of personalized oncology. The extensive heterogeneity in molecular abnormalities implies there may not be a one-size fits all solution for the clinical management of EOC. The development of validated biomarkers and novel technologies are critical for the strategy. It is clear that stratification of patients at initial diagnosis along with the selection of patients who would benefit from adjuvant chemotherapy is close at hand. Better surgical approaches and the appropriate selection of patents for new therapies such as PARP inhibitors and anti-angiogenesis agents is at hand.

KEYNOTE LECTURE

Biomarkers in Ovarian Cancer: To be or not to be

Michael Birrer
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SESSION - 1

TRANSLATIONAL RESEARCH

Precision medicine in epithelial ovarian cancer

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Precision medicine for epithelial ovarian cancer (EOC) lags behind many other solid malignancies. In particular, high grade serous carcinoma (HGSC), the commonest histological type of ovarian cancer, remains a disease of severely unmet clinical need with little improvement in cure rates for the past twenty years¹, and an incidence: mortality ratio that is similar to that of pancreas, brain and lung cancers.

Unlike other solid malignancies, driver oncogenic mutations are rare in HGSC; rather, it is driven by copy number (CN) aberrations and is marked by universal TP53 mutation² and extreme genomic complexity³. Clinically, HGSC is characterized by a strong propensity to develop lethal, drug-resistant sub-clones that arise from on-going chromosomal instability (CIN), which drives evolutionary change⁴.

Precision medicine in HGSC is hindered by several key challenges. The majority of biological and clinical advances in HGSC have centred on defective homologous recombination (HRD), which identifies patients who strongly benefit from platinum-based chemotherapy and PARP inhibitor therapy⁵. However, current neoadjuvant chemotherapy trials indicate that nearly 40% of patients do not benefit from existing standard-of-care treatments⁶ and there has been no systematic approach to personalise therapy for these patients.

Anti-angiogenesis agents have some activity^{7,8} but predictive biomarkers are not available, and attempts to apply other broadly targeted therapies across HGSC patient populations (e.g. folate receptor antagonists, EGFR inhibitors) have met with little success^{9,10}. Response to immune checkpoint inhibition is only ~10% in HGSC^{11,12} and there is significant overlap between HRD and T cell infiltration¹³. Current first-line trials are largely targeting patients with response to standard-of-care treatment and therefore do not address important questions for non-HRD patients.

There is an urgent need for validated predictive biomarkers for women with HGSC that can be used at time of diagnosis to choose therapy and to develop new trials for non-HRD patients. Genomic signatures based on whole genome sequencing of tumours have the potential to address this challenge^{14, 15, 16, 17}. However, the signature of a mutational process will persist even if the process is turned off, for example by a revertant mutation. Current signature approaches based on bulk sequencing cannot distinguish between processes that are extinct (no longer present) and those that are active (present and driving tumour behaviour) and potentially targetable. New approaches are required to identify active processes as a key stepping stone to effective precision medicine in HGSC.

Non-HGSC (clear cell, endometrioid, mucinous) EOC presents separate challenges, not least the relative rarity of these tumours and the recognition that they are essentially separate diseases, with different cells of origin and driver mutations from HGSC. However, histotype-specific trials are open (e.g. NICCC in ovarian clear cell carcinoma) and our understanding of disease biology in non-HGSC histotypes has improved greatly in recent years.

In this talk, I will discuss strategies for driving precision medicine in ovarian cancer including the use of genomic biomarkers, focussing primarily on HGSC.

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SESSION - 1

TRANSLATIONAL RESEARCH

The potential role of liquid biopsies in ovarian cancer

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Despite a myriad of attempts in the last three decades to diagnose ovarian cancer (OC) earlier, this clinical aim still remains a significant challenge. Aberrant methylation patterns of linked CpGs analyzed in DNA fragments shed by cancers into the bloodstream (i.e. cell-free DNA) can provide highly specific signals indicating cancer presence.

We analyzed 699 cancerous and non-cancerous tissues using a methylation array or reduced representation bisulfite sequencing to discover the most specific OC methylation patterns. A three-DNA-methylation-serum-marker panel was developed using targeted ultra-high coverage bisulfite sequencing in 151 women and validated in 250 women with various conditions in particular those associated with high CA125 levels (endometriosis and other benign pelvic masses), serial samples from 25 patients undergoing neoadjuvant chemotherapy and a nested case control study of 172 UKCTOCS control arm participants which included serum samples up to two years prior to OC diagnosis.

The cell-free DNA amount and average fragment size in the serum samples was up to 10 times higher than average published values (based on samples that were immediately processed) due to leakage of DNA from white blood cells owing to delayed time to serum separation. Despite this, the marker panel discriminated high grade serous OC patients from healthy women or patients with a benign pelvic mass with specificity/sensitivity of 90.7% (95%Confidence Interval (CI) 84.3-94.8%) and 41.4% (95%CI 24.1-60.9%), respectively. Levels of all three markers plummeted after exposure to chemotherapy and correctly identified 78% and 86% responders and non-responders (Fisher's exact test $p=0.04$) respectively which was superior to a CA125 cut-off of 35IU/mL (20% and 75%). 57.9% (95%CI 34.0-78.9%) of women who developed OC within two years of sample collection were identified with a specificity of 88.1% (95%CI 77.3-94.3%). Sensitivity improved further (63.6%) when specifically analyzing CA125 negative samples only.

Our data suggests that DNA methylation (DName) patterns in cell-free DNA have the potential to detect a proportion of OCs up to two years in advance of diagnosis and may potentially guide personalized treatment. The prospective use of novel collection vials which stabilize blood cells and reduce background DNA contamination in serum/plasma samples, will facilitate clinical implementation of liquid biopsy analyses.

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SESSION - 1

TRANSLATIONAL RESEARCH

TILs and PD-L1 expression in ovarian cancer:
What to do with it?

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In epithelial ovarian cancer (EOC), intratumoral or intraepithelial TILs (ieTILs), i.e. T cells specifically infiltrating tumor islets, occur in approximately half of the patients and correlate with longer survival. As with many other solid tumors, despite promising results in mouse models, response of EOC to PD-1 blockade has been quite limited in the clinic, but the mechanisms underlying therapeutic failures in immunoreactive human tumors harboring TILs are not well understood. We sought to understand whether ovarian TILs are tumor-specific, and if so, whether the PD-1/PD-L1 pathway is relevant. Our work shows that there is indeed a spontaneous and tumor-specific T-cell response in a large proportion of EOC, accurately heralded by ieCD8+ TILs. Tumor specific antigens will be discussed. Our work also shows that the PD-1/PD-L1 is a central immune checkpoint pathway in these tumors. However, only a fraction of such tumors with ieTILs respond to PD-1. We dissected the mechanisms underlying response to PD-1 blockade and therapeutic approaches to enhance response to PD-1 in human and mouse preclinical models. Therapeutic approaches to achieve effective immunotherapy in ovarian cancer will be discussed, including combination checkpoint blockade, adoptive T cell therapy and new rational combinations.



SESSION - 2

TREATMENT OF PRIMARY DISEASE

How to manage lymph nodes in ovarian cancer in 2019

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Ovarian cancer is mostly diagnosed in an advanced stage with seedings in the peritoneal cavity and metastatic deposits in the lymph nodes, while distant metastases occur less frequently. Ovarian cancer can spread both in the pelvic and the para-aortic lymph nodes. Anatomic reports have shown that para-aortic lymph node metastases are the main localization¹. Whilst the reported rates of lymph node metastases in early ovarian cancer, macroscopically defined to the ovary (FIGO I) is about 13-20%^{2,3}, the rate increases to more than 50% in patients with advanced stages of the disease⁴, which shows also already peritoneal metastases. We have to differentiate patients into those in whom the tumor is limited to the genital tract versus those who have already distant tumor lesions

EARLY OVARIAN CANCER

The aim of surgery in patients with early ovarian cancer is not only the complete removal of the tumor, but also to confirm there is no distant microscopic disease. The final stage also influences the choice of chemotherapy. Whilst stage I disease needs usually only carboplatin single agent therapy⁵, a combination with paclitaxel is indicated in patients with advanced disease⁶. Already last decade a combined analysis of the EORTC/ACTION trials showed that surgical staging in patients with early ovarian cancer improves progression-free-survival (PFS) and overall survival (OS)⁷. This finding led to the recommendation in nearly all national and international guidelines^{8,9} to perform a surgical staging including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, cytology, peritoneal biopsies and pelvic and para-aortic lymphadenectomy (LNE). A randomized trial in whom patients with early ovarian cancer were randomized to systematic pelvic and para-aortic lymphadenectomy versus sampling of lymph nodes did not show a significant survival benefit for systematic lymphadenectomy¹⁰. As this trial was underpowered to show any meaningful differences, its results were not accepted universally. However, we have to keep in mind, that ovarian cancer is a heterogeneous disease including multiple different tumor types like high grade serous, low grade serous, low grade endometrioid, high grade endometrioid, clear cell, low grade mucinous (grade 1), high grade mucinous (grade 2, grade 3) tumors.

Have all tumor types the same potential for lymph node metastases?

The rate of positive lymph nodes in early ovarian cancer irrespective of histologic subtype and grade is reported to be about 13-20% as described above. However, the rates are varying between the histologic subtypes. Whilst the rate in high grade serous carcinoma and also in low grade serous carcinoma is above 10%¹¹, is the rate in patients with low grade endometrioid OC12 or low grade mucinous ovarian cancer < 2%^{13,14}. Therefore, lymph node staging is indicated in patients at risk for lymph node metastases, but not in patients with a very limited probability of positive nodes like in patients with low grade endometrioid and low grade mucinous tumors.

ADVANCED OVARIAN CANCER

The surgical aim in patients with advanced ovarian cancer is macroscopic complete resection¹⁵ and not the detection of subclinical microscopic disease.

However, retrospective data showed an impact on prognosis of systematic lymphadenectomy in patients with advanced ovarian cancer¹⁶, even if clinically negative nodes were resected¹⁷. Therefore, the LION trial has been initiated. In this trial, 640 patients with advanced ovarian cancer (FIGO IIB-IV), who had a macroscopic complete resection and clinically negative pelvic and para-aortic lymph nodes, were randomized to systematic pelvic and para-aortic lymphadenectomy versus no lymphadenectomy. The primary endpoint was overall survival. The lymphadenectomy arm showed a significantly higher rate of infections, relaparotomies and postoperative mortality and did not translate into a benefit in progression-free or overall survival¹⁸.

The LION trial has clearly shown, that in patients with advanced ovarian cancer the removal of negative nodes is not indicated and brings harm to the patients.

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SESSION - 2

TREATMENT OF PRIMARY DISEASE

Can we predict who lives long (and well)
with ovarian cancer?

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Our patients benefit from sophisticated cytoreductive surgery, combination chemotherapy, advanced imaging technologies, genetic risk assessment, and tumor molecular profiling. However, advanced ovarian cancer remains a highly lethal disease. Communication regarding goals and expectations can be challenging for patients and families during primary therapy, as they try to understand and cope with a life-threatening diagnosis. Patients establish their personal balance between detailed information-seeking behavior and information avoidance, which can evolve over time. Physicians tend to focus on interventions, rather than outcomes, hoping to minimize stress, anxiety, and depression. There is a risk of saying too much, or not saying enough, and it is not always easy to decipher the evolving needs of the patient.

When patients ask about their prognosis and survival, they are often seeking specific details beyond percentages, time spans, and Kaplan-Meier actuarial survival curves. Web-based resources, while often accurate, present aggregate statistical data, and it can be difficult for an individual patient to accept or understand the impact of ovarian cancer on a personal level. Answering these important questions requires us to appreciate the unique context for each patient, in terms of existing knowledge, age, family lifecycle events, comorbidities, social situation, and preconceived expectations.

Predictive models offer the promise of a tailored assessment, integrating individual patient data with larger statistical datasets. However, existing models and nomograms are often limited to common clinical and pathologic data elements, without addressing the more complex issues confronted by an individual patient with ovarian cancer. In addition to serving as a tool to facilitate difficult conversations, predictive models could also be utilized to guide clinical decisions related to surgery and chemotherapy. Contemporary databases could provide enhanced benchmarks for clinical trials, interrogating a repository of historical data to create a virtual reference population to support non-randomized prospective studies.

We await enhanced models that integrate molecular data, clinical data, and functional imaging, while incorporating newer treatment practices and recognizing changes in individual outcomes over time. It is also important to extend beyond estimates of PFS and OS, to address quality of life and the evolution of treatment-related toxicity. This presentation will review different predictive models, with attention to strengths, weaknesses, hypotheses to be tested, and future directions.

WHAT ARE THE OPPORTUNITIES FOR PREDICTIVE MODELS?

- Inform patients and families regarding a range of expected outcomes (response, remission duration, survival), tailored according to their individual clinical scenario.
- Refine expected outcomes over time, as new information becomes available (progression-free interval, response to treatment, BRCA status).
- Provide a matched virtual reference arm for non-randomized clinical trials, such as phase IV post-marketing studies.
- Establish a tailored statistical threshold to screen new interventions for clinical activity based on actual characteristics of the enrolled population.
- In a highly-lethal disease, predictive models could extend beyond survival percentages, and contribute to the assessment of quality-adjusted survival, or time without symptoms or toxicity.
- Identify potential clinical-pathologic risk factors with a meaningful impact on long-term outcomes, such as obesity, chemotherapy-induced neutropenia, relative dose intensity, and physical activity.

WHAT ARE THE LIMITATIONS OF PREDICTIVE MODELS?

- Treatments continuously evolve, and historical databases could become outmoded in terms of predicting progression-free survival (PFS) or overall survival (OS). For example, most models pre-date neoadjuvant chemotherapy (NACT), maintenance therapy, genetic risk assessment, and molecular profiling.
- Models are weighted toward patients with “average” clinical characteristics, with reduced precision among outliers (positive and negative).

- Ovarian cancer is characterized by clinical and molecular heterogeneity. However, the most heavily weighted prognostic factors (stage, residual disease, histology) have less heterogeneity, limiting individual predictive value for a typical patient.
- Stage is closely linked to histology, with a predominance of non-serous tumors in women with early-stage disease, limiting clinical relevance in high-grade serous carcinoma (HGSC), where risk is greater.
- Older studies incorporate grade as a continuous variable, rather than recognizing distinct cancer entities (low-grade serous carcinoma and HGSC), differentiated by molecular and clinical characteristics.
- Large databases may omit important clinical variables (such as BMI, grade, comorbidities).
- Models could be restricted to specific subpopulations and selection bias (such as tertiary care, global region).
- Models are not yet sufficiently robust to guide treatment decisions (such as triage to NACT or different chemotherapy regimens).
- Retrospective models are hypothesis-generating, and not capable of directly establishing cause and effect, limiting the impact on clinical practice without prospective validation.
- Treatment selection based on predictive models may fail to provide an advantage in PFS or OS, due to limited differences between treatment regimens (such as NACT with interval cytoreductive surgery vs primary cytoreductive surgery).



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SESSION - 2 TREATMENT OF PRIMARY DISEASE

Can we predict who lives long (and well) with ovarian cancer?

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SESSION - 2

TREATMENT OF PRIMARY DISEASE

Landscape of systemic therapy for ovarian cancer in 2019

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INTRODUCTION

According to the 5th Ovarian Cancer Consensus Conference statement in 2015, intravenous 3-weekly carboplatin and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced stage ovarian cancer. Acceptable alternative schedules, and routes of delivery include 1) weekly intravenous paclitaxel in combination with 3-weekly intravenous carboplatin, 2) the addition of bevacizumab to the standard chemotherapy drugs after primary surgery, 3) intraperitoneal platinum-based chemotherapy after primary surgery with <1 cm residual disease¹.

A number of evidences have been published since then and the landscape of systemic chemotherapy is now changing dramatically. In this presentation, we will discuss current standard systemic therapy and future possibilities.

WEEKLY PACLITAXEL

The role of weekly administration of paclitaxel is now very controversial. Although the Japanese GOG study has shown a clear overall survival (OS) benefit by changing the administration schedule of paclitaxel from every 3-weekly to a weekly dose-dense manner², MITO-7³, GOG268⁴, and ICON-8 studies failed to reproduce the results. It is not clear whether the JGOG study results were based on ethnic difference.

BEVACIZUMAB

Since the GOG218⁵ and ICON-7⁶ trials have shown benefit of progression-free survival (PFS), the addition of bevacizumab to carboplatin and paclitaxel became one of the standard treatments for advanced ovarian cancer patients. However, it is still controversial because none of the studies demonstrated OS benefit, so it may imply that bevacizumab can be preserved after recurrence, which showed OS benefit⁷.

POLY (ADENOSINE DIPHOSPHATE-RIBOSE) POLYMERASE (PARP) INHIBITORS

The result of the SOLO-1 trial was published in 2018⁸. This was an international, randomized, double-blind, phase 3 trial to evaluate the efficacy of one of the PARP inhibitors, as maintenance therapy in patients with newly diagnosed stage III or IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy. The patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. The primary efficacy outcome was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The trial demonstrated a statistically significant improvement in investigator-assessed PFS for olaparib compared to placebo. Estimated median PFS was not reached in the olaparib arm and was 13.8 months in the placebo arm (HR 0.30; 95% CI: 0.23-0.41; p<0.0001). At the time of the analysis of PFS, OS data were not mature. Most common (≥10%) adverse reactions of any grade occurring in patients who received olaparib in SOLO-1 were nausea, fatigue, abdominal pain, vomiting, anemia, diarrhea, upper respiratory tract infection/influenza/nasopharyngitis/bronchitis, constipation, dysgeusia, decreased appetite, dizziness, neutropenia, dyspepsia, dyspnea, urinary tract infection (UTI), leukopenia, thrombocytopenia, and stomatitis.

Based on the results, FDA US approved olaparib for germline BRCA mutated (gBRCAm) or somatic BRCA mutated (sBRCAm) ovarian cancer. FDA also approved the BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.) to identify patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are eligible for olaparib. The effectiveness of the BRACAnalysis CDx test was based on the SOLO-1 trial population for whom deleterious or suspected deleterious gBRCAm status was confirmed with either prospective or retrospective testing with the BRACAnalysis CDx test. (<https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm628876.htm>)

It will be obvious that olaparib is to be incorporated as a standard maintenance therapy after effective first line chemotherapy for gBRCAm or sBRCAm advanced ovarian cancer patients.

Future Directions of PARP inhibitor in Primary Therapy for Ovarian Cancer

COMBINATION OF PARP INHIBITOR WITH OTHER AGENTS

With Antiangiogenics

In the PAOLA-1 study maintenance therapy of olaparib in combination with bevacizumab was compared with current standard bevacizumab maintenance therapy alone in patients with advanced high grade serous ovarian cancer. In this study, tumor BRCA mutation status was a stratification factor, but all the patients who responded to the first line chemotherapy were included. The result will be available Q3 2019.

With Immune Checkpoint Inhibitor

Currently, multiple studies have just started to evaluate the combined efficacy of PARP inhibitors and immune checkpoint inhibitors (ICI) in primary chemotherapy. The use of PARP inhibitors are for maintenance, but the use of ICIs varies, in combination with chemotherapy and/or maintenance only.

INTRAPERITONEAL CHEMOTHERAPY

Intraperitoneal (IP) chemotherapy has been one of the most important research questions. Although three randomized trials using cisplatin showed survival benefit of IP chemotherapy for optimally debulked stage III ovarian cancer patients⁹, it has not been accepted as standard therapy mainly because it has not been shown that IP administration of carboplatin is more efficacious than IV administration. Although the OV21 randomized phase II study showed significant improvement of progression-free rate at 9 month¹⁰, large scale randomized phase III GOG252 study failed to show the survival benefit of IP carboplatin when bevacizumab was integrated in the IP arm¹¹. At this time, there is one randomized trial (iPocc Trial) that is waiting for the survival data maturation to evaluate the efficacy of IP carboplatin¹². If this trial data is positive, there will be further discussion how to best incorporate IP chemotherapy in the primary treatment of advanced ovarian cancer.

Another approach for IP chemotherapy is a hyperthermic intraperitoneal chemotherapy (HIPEC)¹³. This will be extensively discussed in a separate session of this symposium.

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SESSION - 2

TREATMENT OF PRIMARY DISEASE Does HIPEC improve survival in AOC? PRO:

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INTRODUCTION

Long-term survival for patients with epithelial ovarian cancer has not improved over the past decades.¹ New treatment approaches are therefore eagerly awaited. A recent randomized clinical trial evaluating the role of hyperthermic intraperitoneal chemotherapy (HIPEC) represents such a new treatment approach that may benefit a selection of patients with stage III ovarian cancer.² The study showed an increase in recurrence-free survival (RFS) of 3.5 months and an increase in overall survival (OS) of almost 12 months with the addition of HIPEC to interval cytoreductive surgery (ICS) following neo-adjuvant chemotherapy.

MECHANISM OF ACTION

The peritoneal surface is the primary site of disease recurrence in epithelial ovarian cancer. HIPEC specifically targets the peritoneal surface by increasing the exposure to cytotoxic chemotherapy in order to prevent recurrences. Intraperitoneal chemotherapy increases dose intensity in the peritoneum compared with intravenous delivery. In addition, intra-operative treatment using HIPEC is not hampered by post-operative adhesions. Lastly, hyperthermia induces a BRCA-like phenotype (homologous recombination deficiency) thereby sensitizing tumor cells to DNA damaging agents.³ Hyperthermia may also denature proteins, induce heatshock proteins that serve as receptors for natural killer-cells, induce apoptosis, and inhibit angiogenesis.^{4,5,6,7}

TRIAL DESIGN

OVHIPEC-1 was a nationwide, randomized, phase-3 trial performed in eight hospitals experienced in HIPEC in the Netherlands. Eligible patients had newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer and were referred for neoadjuvant chemotherapy because their abdominal disease was too extensive for primary cytoreductive surgery (PCS). Patients had responded to three cycles of neo-adjuvant carboplatin/paclitaxel and were randomized (1:1) to ICS with or without HIPEC (90 minutes using cisplatin 100 mg/m²). Randomization was performed during surgery, only if the surgeon anticipated complete or optimal cytoreduction. Sodium thiosulphate was administered intravenously to prevent nephrotoxicity. Patients received an additional three cycles of carboplatin and paclitaxel after surgery. During follow-up, physical examination and measurement of serum CA-125 level were repeated every 3 months for 2 years and then every 6 months. CT-scans were performed at 1, 6, 12, and 24 months after the last cycle of chemotherapy. The primary endpoint was RFS; OS and quality of life were key secondary endpoints. 245 patients with sufficient follow-up were required to detect a hazard ratio of 0.67.

OUTCOME

In the intention-to-treat analysis, the hazard ratio (HR) for disease recurrence or death was 0.66 (95% CI, 0.50 to 0.87; P=0.003). The median RFS was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. The median OS was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group (HR = 0.67; 95% CI, 0.48 to 0.94; P=0.02). The percentage of patients with grade 3-4 adverse events in the two arms of the study was similar (P=0.76).

CONCLUSION

The addition of HIPEC to ICS represents a viable treatment option in those patients with stage III epithelial ovarian cancer who are not candidates for PCS. HIPEC results in longer RFS and OS than surgery alone and does not increase side effects.

DISCUSSION

While providing a very welcome new treatment option for a group of patients with ovarian cancer with dismal prognosis, the publication of the randomized OVHIPEC trial has raised a storm of critique.

One of the concerns raised is the choice of RFS rather than OS as primary endpoint. However, RFS was internationally advocated as primary endpoint by du Bois and colleagues at the 3rd Ovarian Cancer Consensus Meeting to prevent that treatment for recurrent disease would dilute the effect of the experimental treatment.⁸ The OVHIPEC trial showed almost identical Hazard Ratios for RFS and OS, reinforcing the validity of RFS as a surrogate endpoint. Given the lower rate of events for OS than for RFS, the same HR automatically translates into a larger absolute OS than RFS benefit.

Another concern that some authors raised relates to possible imbalances in prognostic factors between the treatment arms. This critique is rather surprising when discussing a randomized trial as it ignores the general principle that randomization ensures equality of prognosis on the basis of all known and unknown prognostic factors combined. Therefore, small and by definition random imbalances in baseline characteristics have no impact on the overall validity of the study results.

Some authors suggested that heterogeneity in the effect of HIPEC across participating centers is a leading source of bias that is responsible for the overall positive results of the study. However, the appropriate statistical method for assessing the heterogeneity of treatment effects among the levels of a baseline variable begins with a statistical test for interaction.⁹ The OVHIPEC trial results were consistent across the levels of prespecified stratification factors (including center) and post hoc subgroups, without any test for interaction being statistically significant.

It has also been suggested that the OVHIPEC trial 'significantly underreported perioperative and long term toxicity' because the study used the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) classification rather than the Clavien-Dindo method. However, Alyami and colleagues showed in over 800 patients that in fact the Clavien-Dindo method underestimates toxicity in patients undergoing cytoreductive surgery with HIPEC compared to CTCAE.¹⁰ Finally, several authors noted that the results of the OVHIPEC study represent a minority of stage III patients who are not candidate for PCS. This is a valid point that is well acknowledged in the original publication. A subsequent study is now set-up to study the effect of HIPEC after primary cytoreductive surgery.

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SESSION - 2

TREATMENT OF PRIMARY DISEASE Does HIPEC improve survival in AOC? CONS:

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Hyperthermic intraperitoneal chemotherapy (HIPEC) became a treatment option in patients with colon cancer after positive results of a randomized trial comparing surgery and HIPEC versus palliative treatment alone¹. This concept for treatment of peritoneal metastases was in the subsequent years generalized to many other tumors with peritoneal carcinomatosis. Subsequently, numerous academic groups published statements warning the international community to remain scientific and avoid implementing potentially morbid methods without any evidence^{2,3}. The main criticism of the above mentioned trial in colon cancer was the missing comparison of versus surgery alone. Quenet et al. presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2018 the results of a prospective randomized trial of 265 patients with peritoneal carcinomatosis of colorectal origin which were randomized to cytoreductive surgery + HIPEC versus cytoreductive surgery alone⁴. The addition of HIPEC failed to show any benefit neither for the progression-free (PFS) nor for overall survival (OS). In addition, the HIPEC arm was significantly more morbid with a 60 days post-OP grade 3-5 complications of 24.1% vs 13.6% in the control arm (p=0.030). Despite widely used there was no evidence of the use of HIPEC in ovarian cancer. In 2015, a trial investigating the role of HIPEC in recurrent ovarian cancer was published⁵. However, this study showed multiple weakness and raised more questions than answers regarding methodology and numerous other issues, which are still not answered by the authors⁶.

Recently, van Driel et al. reported a benefit in both PFS (14.2 vs 10.7 months, p=0.003) and OS (45.7 vs 33.9 months, p=0.02) gained by the use of HIPEC at interval debulking, whilst another trial presented by Lim et al. that patients with primary and interval debulking failed to show any benefit of HIPEC^{7,8}.

In addition to these contradictory results, there were many further aspects which were criticized. The selection of patients for IDS or primary debulking of the participating centers was not reported. As only patients after neoadjuvant chemotherapy were eligible and a surprisingly high rate of patients were eligible after 3 cycles of chemotherapy for randomization (only 10 patients showed insufficient response to neoadjuvant chemotherapy, any patients with primary progressive disease were not reported). It is unclear, if there was in the participating centers a general strategy to favor interval surgery in all patients with advanced OC (and therefore the results have to be discussed in the context of data of centers favoring upfront surgery?). There is also an imbalance regarding the randomized patients. Three patients in the HIPEC arm were excluded for intra-operative finding of PD, whilst this scenario did not occur in the standard arm. A main critical point is the heterogeneity of the results showing the largest effect in the smaller centers, in which randomization was done in particular already before open surgery. Furthermore, it is questionable, if the adverse events are reported completely. From time of randomization (day of surgery) until 6 weeks after last cycle of chemo were only 6% and 4% of any grade of anemia, less than 10% with any grade and less than 2 patients with any grade 3 or 4 adverse event regarding leukopenia, neutropenia, or thrombocytopenia. There were only 16% and 19% with an alopecia. Specific data for post-operative complications like re-laparotomies were not reported.

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SESSION - 3

TREATMENT OF RECURRENT DISEASE

Relapsed Ovarian cancer: Who needs surgery?

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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 in the primary setting. Despite this undisputable role of surgery in primary ovarian cancer, the surgical management of recurrent disease has remained subject to an emotional international discussion.

In principle, the different goals of surgery in relapsed ovarian cancer have to be defined as a prerequisite for a structured dialogue. In this context, palliative surgery with the goal of symptom control (eg. in case of bowel obstruction) and cytoreductive surgery with the goal of prolonging the progression free survival and overall survival should be differentiated.

Several studies demonstrate the feasibility and good clinical outcome for patients who underwent surgery with the aim of maximal cytoreduction. Most of these studies are retrospective and have been performed by a single center.

Furthermore, the selection criteria of patients eligible for salvage surgery is essential but there are different definitions in the various publications. Only few prospective studies exist about the effect of surgery in relapsed ovarian cancer.

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" was 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. Overall, 127 women in the "AGO score"-positive group achieved a 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.

Recent monocenter analysis demonstrated also that despite a negative AGO-score patients can achieve in a trained gynecological center a complete resection with a good clinical outcome (Muallem et al, Harter et al).

An interim analysis of the randomized DESKTOP phase III study was presented at ASCO 2017.

Overall, 407 pts have been randomized. The median PFS was 14 months without and 19.6 months in the surgery arm (HR: 0.66, 95%CI 0.52-0.83, p<0.001). The median time until the first subsequent therapy (TFST) was 21 vs 13.9 months in favor of the surgery arm (HR 0.61, 95%CI 0.48-0.77, p<0.001). Also the PFS-2 results favour the surgical arm. Analysis of the primary endpoint was immature.

The 60-days mortality rates were 0 and 0.5% in the surgery and no-surgery arm, and the rate of re-laparotomies were 3.5%.

At ASCO 2018 the GOG presented the results of their randomized trial in patients with relapsed ovarian cancer without any benefit in progression free and overall survival. In this trial 485 women were randomized without applying a structured score of patient's selection. The HR for death was 1.28 (95%CI: 0.92-1.79) corresponding to a median overall survival of 53.6 months vs. 65.7 months, respectively. The median progression-free survival was 18.2 months in the surgery arm vs. 16.5 months in the control arm (HR: 0.88 (95% CI: 0.70 - 1.11). No new safety signals have been observed.

Based on the available evidence and until the final overall survival data of DESKTOP-III and an additional pooled meta-analysis will definitively define the role of secondary cytoreductive surgery salvage surgery followed by subsequent chemotherapy should be discussed with the patients as a valuable option.

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SESSION - 3

TREATMENT OF RECURRENT DISEASE

Do all patients need systemic therapy?

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The simple answer to this broad and provocative question is No! Clearly not all patients with recurrent ovarian cancer need or should be offered systemic therapy. However, I will expand on my response to this open-ended question and focus on the 3 common clinical scenarios where the benefit of systemic therapy is uncertain and which are most applicable to the subtext of the question. These include 1. Patients with a very poor prognosis and low likelihood of benefit from systemic therapy 2. Patients with specific histological subtypes of recurrent ovarian cancer including clear cell, mucinous and low grade serous cancers where response rates to systemic therapy are low and 3. Asymptomatic patients with CA125 progression following 1st line chemotherapy for advanced stage ovarian cancer where early initiation of chemotherapy is currently not recommended.

1. PATIENTS WITH A POOR PROGNOSIS AND LOW LIKELIHOOD OF BENEFIT FROM SYSTEMIC THERAPY

Leaving aside the frail elderly patients as well as patients with multiple comorbidities with recurrent ovarian cancer where systemic therapy may not be clinically appropriate, the majority of patients who fall into this subgroup have “platinum resistant” recurrent ovarian cancer (PR-ROC). However, the definition of PR-ROC is broad and overly simplistic which does not do justice to the complexity and the heterogeneity of the patients included under the umbrella term, and does not necessarily help identify which patients will /will not derive benefit from systemic therapies. “Platinum resistant” ovarian cancer was arbitrarily defined as disease recurrence/progression within 6 months of completion of first-line platinum-based chemotherapy and was associated with a low response rates to platinum based chemotherapy and a short survival. Progression was predominantly based on clinical, symptomatic or radiological evidence of recurrence. The patients included those with all histological subtypes of ovarian cancer with measurable disease who were entered onto phase 2 trials following progression after 1st line chemotherapy. However, this label is now more loosely applied to also include asymptomatic patients with CA125 /PET scan evidence of progression within 6 months following any line of chemotherapy and also includes patients with small volume disease on a CT scan¹. Most trials of patients with PR-ROC do not take these factors into account or distinguish between patients with primary and secondary platinum resistance. The variable objective response rates, progression free survival and overall survival reported in a large number of clinical trials underscores the heterogeneity of patients with PR-ROC² and limitations with the definition. Many patients have a good performance status and may benefit from either standard systemic therapies and should also be considered for participation in clinical trials if available. These are not the patients with PR-ROC who should not be offered systemic therapy.

There are however a subset of women with PR-ROC who have a very short survival and administering chemotherapy/systemic therapies to patients in the final weeks of life is not appropriate and should be discouraged. This principle is broadly applicable to patients with almost all cancers and has been the subject of several studies which have consistently reported that between 20-50% of patients with incurable cancers received chemotherapy within 30 days of death which is hard to defend given the lack of benefit^{3,4}. ASCO identified that chemotherapy at end of life as one of the top 5 practices that could improve patient care and reduce costs if addressed appropriately⁵. Nevertheless, the administration of systemic treatment towards the end of life is still all too common. For example, in a recent prospective study of 386 patients with metastatic cancer refractory to at least 1 chemotherapy regimen who were considered terminally ill and subsequently died, 56% were still receiving chemotherapy at enrolment a few months before death⁶. These patients were more likely to have cardiopulmonary resuscitation, mechanical ventilation and to die in an intensive care unit and not be referred to palliative care. There was no difference in survival between patients who did not receive chemotherapy compared to those that did but this was not a randomised trial⁶.

There are many reasons why we continue to prescribe treatment even when there is little chance in making any difference to either improving symptom control or survival. Multiple factors influence the decision to recommend further chemotherapy as well as why some patients want to continue receiving treatment until the very end even though the likelihood of prolonging life is minimal⁷. Hope is an important motivation, but it is well documented that expectations of clinicians and patients are commonly very optimistic, and the benefits of systemic therapy are overestimated and the limited survival not appreciated. It's unclear whether this reflects inadequate doctor -patient communication and /or failure to recognise the limitations of systemic therapy in patients in the terminal disease trajectory.⁸ It is likely that patient acceptance of ongoing treatment would be lower if there was a better appreciation of the limited impact of chemotherapy on survival in patients with end stage recurrent ovarian cancer and in the end this comes down to good communication

about prognosis and treatment goals. Most patients with advanced cancer do want information regarding prognosis, but are afraid to ask and we as clinicians need to start the conversation. Survival estimates from clinical trials provide a basis for providing information regarding likely prognosis and there is evidence to suggest that estimating and discussing 3 scenarios -worst case -typical and best case is preferred by most patients with advanced cancers as opposed to median survival⁹.

The provocative title of the talk reflects the uncertainty regarding the cost benefit of systemic therapy in a subset of patients with recurrent ovarian cancer specifically the human costs of futile treatments although the financial costs cannot be ignored. However, it is challenging to identify the patients who have a particularly poor prognosis and short survival. In the Symptom Benefit Study (SBS), almost 20% of the 570 patients with PRROC who were considered suitable candidates for palliative chemotherapy, stopped treatment within 8 weeks of starting chemotherapy due to rapid disease progression, death, or patient preference. Their median progression free survival (PFS) was 1.2 months and median overall survival (OS) 2.9 months¹⁰. It is worth noting that the majority of those who stopped treatment within 8 weeks were rated as having a good performance status (PS) of 0-1 at baseline which underscores the limitations of clinical assessment of performance status. There are a number of adverse prognostic factors associated with a poor survival and include patient reported outcome measures (PROMS) as well as tumour related factors which are often interdependent and closely related. The modified Glasgow Prognostic Score (mGPS) which is based on markers of inflammation including CRP and serum albumin is a simple scoring system and has been validated as an independent predictor of OS in patients with ROC after adjusting for performance status and platinum sensitivity¹¹. In the SBS, a higher mGPS was associated with worse Health-related Quality of Life (HRQOL) including symptoms such as nausea/vomiting, pain, dyspnoea, appetite loss, even though most patients had a good PS of 0-1. PROMS are also very helpful in assessing the impact of the cancer in patients with recurrent ovarian cancer and baseline measures of (HRQOL) prior to treatment showed that low Global health status (GHS), role function (RF), physical function (PF) and high abdominal/gastrointestinal symptoms were all significantly associated with stopping chemotherapy within 8 weeks and a poor survival¹². These measures can be used to counsel patients and their families regarding prognosis and may help to moderate expectations. The provision of more accurate prognostic information could help avoid futile treatment and aggressive care at end of life.

2. PATIENTS WITH RECURRENT OVARIAN CANCER WITH SPECIFIC HISTOLOGICAL SUBTYPES INCLUDING CLEAR CELL, MUCINOUS AND LOW GRADE SEROUS CANCERS

The response rates to systemic therapy are very low in patients with recurrent/metastatic clear cell and mucinous ovarian cancers and their overall prognosis is poor. The response rates to platinum and taxane based chemotherapy in the first line setting in patients with clear cell cancer with measureable disease ranges from 11-27% and response rates of < 10% have been reported with a wide range of systemic therapies in patients with recurrent clear cell cancer^{13,14}. It is important to be confident of the histological diagnosis of clear cell as it can be confused with high grade serous cancer and mixed histology clear cell/serous cancers are more likely to respond to conventional systemic therapies. Patients with a good performance status with recurrent clear cell cancer should be considered for clinical trials given the low response rates with chemotherapy while supportive care alone is more appropriate in those with large volume disease and who are symptomatic and have a low performance status given the poor prognosis. Recurrent mucinous ovarian cancers are rare, but have even lower response rates to chemotherapy than clear cell cancers and the same treatment principles mentioned above apply¹⁵.

In contrast, recurrent low grade serous cancers are commonly resistant to chemotherapy with a 2- 5% objective response rate reported to a range of systemic therapies but these patients have a better prognosis than clear cell and mucinous cancers¹⁶. Outside clinical trials it is hard to make a strong case for systemic treatment in these patients. Patients with low grade serous cancers have much longer survival prospects than those with clear cell /mucinous cancer which should also be communicated to the patients even though systemic treatments have a limited role.

3. ASYMPTOMATIC PATIENTS WHO HAVE COMPLETED 1ST LINE CHEMOTHERAPY WITH CA125 PROGRESSION WITH EITHER NO OR ONLY SMALL VOLUME DISEASE ON IMAGING

The MRC OV05/EORTC55955 trial of early vs delayed chemotherapy found that there was no survival advantage or quality of life benefit associated with early commencement of chemotherapy in patients with CA125 progression following complete radiological and biochemical remission after 1st line treatment¹⁷. Briefly, women randomized to early treatment started chemotherapy 4.8 months (95% CI 3.6-5.3) earlier than those allocated to delayed treatment. Following second line treatment 67% of patients assigned to early and 54% assigned to delayed treatment started 3rd line chemotherapy. The median time with good quality of life was 7.2 months in those assigned to early treatment and 9.2 months in those who had delayed chemotherapy. The median overall survival in both arms from randomization was just over 2 years. Based on the results of this trial, systemic treatment is not recommended in asymptomatic patients with CA125 progression and /small volume disease in most management guidelines¹⁸.

This study has had a significant impact on clinical practice. However, it is probably time to challenge a management paradigm that was based on a trial that opened to recruitment over 20 years ago in 1997 when ovarian cancer was considered to be a single disease entity, the importance of BRCA mutations and homologous recombination deficiency was not appreciated and treatment options for recurrent disease were very limited. Although there are well recognized problems and pitfalls with cross study comparisons, most would agree that a median OS of 26 months in patients with Stage 3 and 4 ovarian cancer who have responded to chemotherapy as in the MRC OV05/EORTC55955 trial is far lower than what would be expected for a comparable population of patients today. For example, the median overall survival in a similar population of patients enrolled 12 years later in the OVAR 16 trial of maintenance pazopanib vs placebo following response to 1st line treatment was 5 years in both arms despite an almost 6 month increase in PFS with maintenance pazopanib¹⁹. Similarly, the median overall survival for all patients in ICON7 was 58 months in both arms (chemotherapy alone or with bevacizumab) which suggests improvement in overall survival over time and this is probably related to more lines of treatment for recurrent disease²⁰. It is likely that median OS of patients diagnosed with advanced stage ovarian cancer in 2019 will be even appreciably longer given the large PFS benefits with maintenance olaparib in the BRCA population and the potential impact of both PARP inhibitors and immune checkpoint inhibitors which are being trialed in other molecular subsets. It is questionable whether median OS is the best endpoint for 1st line / 2nd line trials given the fact that many patients have multiple lines of treatment after recurrence which impact on survival.

Although this may seem heretical to some, it is time to reconsider the role and timing of systemic therapy in asymptomatic patients with CA125 progression following the completion of 1st line chemotherapy. There is now a much stronger case to be made for early treatment in selected patients with CA125 progression and they should be enrolled in clinical trials although it would be hard to repeat the MRC/EORTC trial.

CONCLUSIONS

It is self-evident that not all patients with recurrent ovarian cancer need or should be offered systemic therapy. There is growing acceptance of the importance of personalized approach to treatment in patients with recurrent ovarian cancer and recognition of the complex interplay between patient and tumour associated factors which impact on likelihood of response to systemic therapies and prognosis. Despite the advances in the management of patients with advanced stage ovarian cancer and an ever increasing number of systemic treatment and clinical trial options, the majority of women who are diagnosed with recurrent ovarian cancer will ultimately die due to treatment refractory disease. Continuing treatment in the last weeks or months of life is not in the best interest of the patient or her family and in addition costly with direct and indirect costs to health care systems and should be avoided. It is possible to identify patients with a particularly poor prognosis prior to their nth line of treatment using simple measures including PROMs, prognostic scores and clinical factors. This should be the catalyst to discuss prognosis and goals of treatment. Not offering systemic therapy does not mean that the patient will be abandoned and she needs to be reassured that the focus will be on providing optimal supportive care which is critically important. At the other end of the treatment continuum, it is also time to challenge the no treatment paradigm for all asymptomatic patients with CA125 progression following response to 1st line treatment.

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SESSION - 3

TREATMENT OF RECURRENT DISEASE

Landscape of systemic therapy for recurrent
ovarian cancer in 2019

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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 (ie, 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. The concept of treatment free interval has replaced the traditional platinum free interval to include all these characteristics. So, the concept of Platinum Free Interval is not still applicable today. In the last consensus (5th Ovarian Carcinoma Consensus Conference) conference of Tokyo 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 not candidate for platinum therapy. Patients relapsed during first line treatment (refractory) or in the few following months (resistant) represent a very heterogeneous group of various biological tumor behaviours. 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). Regarding molecular targeted therapy, interesting data have been obtained in this setting with antiangiogenic compounds. In the AURELIA randomized phase III trial⁴, 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. Immunotherapy as single agent and in combination with chemotherapy failed to show clinically meaningful results, with both the Keynote 100 with Pembrolizumab and the Javelin 200 with Avelumab showing low response rate and no additional PFS benefit.

Relapses candidate for platinum rechallenge. Platinum based doublets are standard of care, 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 PARP inhibitors, including olaparib, niraparib and rucaparib. 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. MITO 16 B has shown that this effect is also evident in patients previously treated with bevacizumab.

Olaparib, Niraparib, rucaparib have been shown in 3 different phase 3 trials to prolong PFS when given as maintenance after chemo. A significant proportion of patients remain on treatment for a long time, with some patients treated for years. The effect of PARPi is higher in patients with BRCA mutation, both at germline or somatic level, but the PFS gain is also evident in patients without mutation

RESEARCH ONGOING

Several strategies are under investigation. In early recurrences drugs affecting the cell cycle check points or antibody drug conjugates targeting folate receptors appear the more promising therapies in trials. In patients candidate to receive a platinum doublets the combination of immunotherapy with bevacizumab or with PARP inhibitors is currently under investigation.

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SESSION - 4

NEW DEVELOPMENTS

**Immunotherapy in epithelial Ovarian Cancer:
Sill promising?**

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RATIONAL FOR IMMUNOTHERAPY IN OVARIAN CANCER

The role of tumor-infiltrating lymphocytes (TILs)

In 2003, Coukos and colleagues first reported that CD3+ TILs are associated with a ~8-fold improvement in 5-year survival rate (38% vs 4.5%) in ovarian cancer (Zhang et al., 2003)¹. In a recent meta-analysis, CD8+ TILs were associated with a 2.2-fold survival advantage (Hwang et al., 2012)². Prognosis is most strongly linked to intraepithelial TIL (i.e., T cells found within malignant tumor epithelium) as opposed to stromal T cells, suggesting that CD8+ TIL mediate their anti-tumor effects through direct contact with tumor cells. This effect is enhanced by CD4+ and CD20+ TIL and diminished by Tregs (deLeeuw RJ et al., 2014 and Nielsen JS et al., 2012)^{3,4}.

Role of PD-L1 expression in ovarian cancer.

The ligands for programmed cell death 1 (PD-1), an immuno-inhibitory receptor belonging to CD28/cytotoxic T lymphocyte antigen 4 family, are PD-1 ligand 1 and 2 (PD-Ls). It has been proposed that the aberrant expression of PD-Ls on tumor cells impairs antitumor immunity, resulting in the immune evasion of the tumor cells.

Hamanishi et al.,⁵ reported in 2007 a 68% rate of PD-L1 expression in 70 patients with ovarian cancer. Patients with higher expression of PD-L1 had a significantly poorer prognosis than patients with lower expression. The 5-year survival rate for patients with high- versus low-expressing PD-L1 tumors was 52.6 ± 7.7% versus 80.2 ± 8.9%, p = 0.016, respectively.

A significant inverse correlation was observed between PD-L1 expression and the intraepithelial CD8+ T lymphocyte count, suggesting that PD-L1 on tumor cells directly suppresses antitumor CD8+ T cells. Multivariate analysis showed the expression of PD-L1 on tumor cells and intraepithelial CD8+ T lymphocyte counts are independent prognostic factors.

However, the most current data on the role of PD-L1 as prognostic factor in ovarian cancer have been contradictory. Although some authors have confirmed the observation by Hamanishi (Chatterjee et al., 2017)⁶ others have shown exactly the opposite (Silvia Darb-Esfahani et al., 2016, Stefanie Aust et al., 2017, Webb et al., 2016)^{7,8,9}. These controversial results have raised several questions including the method of determination, which types of cells should be scored for surface PD-L1 expression (tumor cell vs immune infiltrate vs both) and the best cut-off percentage of scored cells to determine PD-L1 positivity.

ANTI PD-1/ PD-L1 THERAPY IN EPITHELIAL OVARIAN CANCER

PD-1/PD-L1 blockade was proposed as a potential strategy for restoring antitumor immunity in ovarian cancer.

Several antibodies directed against PD-1 and PD-L1 have been developed and were tested clinically in patients with ovarian cancer. Data of activity in early phase I/II trials with nivolumab, pembrolizumab, avelumab and atezolizumab have been reported. Nivolumab (anti-PD1) showed 3 responses (2 CR + 1 PR) in 20 patients with platinum-resistant disease. Of note, two of the responses were long lasting and there was no relationship between response and PD-L1 expression (Hamanishi J et al., 2015)¹⁰. Pembrolizumab (anti-PD1) achieved 3 responses (1 CR + 2 PR) in 26 patients included in the Keynote-028 trial that were not candidate for standard therapy, and which tumor expressed PD-L1 in 1%. Response duration was > 24 weeks (Varga A et al., 2015)¹¹. Avelumab (anti-PD-L1) was associated to a 9.7% overall response rate in 124 patients with refractory or recurrent OC (progression within 6 months, or after 2nd/3rd line. Responses were observed in PD-L1 positive (12.3%) and in PD-L1 negative (5.9%) tumors based on ≥1% threshold (Disis et al., 2016)¹². Finally, atezolizumab (anti PD-L1) demonstrated a response in 2 out of 8 heavily pretreated patients (Infante et al., 2016)¹³.

The largest trial communicated so far with check-point inhibitors in monotherapy for ovarian cancer patients is the KEYNOTE-100 trial. This study included 376 recurrent non-mucinous ovarian cancer patients that were treated with pembrolizumab 200 mg iv every 3 weeks in 2 different cohorts. In cohort A (285 patients) patients had 1-3 prior lines and a treatment-free interval (TFI) of 3-12 months. In cohort B (91 patients) 4-6 prior lines and a TFI > 3 months were allowed. The primary endpoint was overall response rate (ORR), being 7.4% in cohort A and 9.9% in cohort B. Median duration of response was 8.2 months in cohort A and was not reached in cohort B (Matulonis et al., 2018)¹⁴.

SESSION - 4 NEW DEVELOPMENTS

Immunotherapy in epithelial Ovarian Cancer: Sill promising

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The second co-primary endpoint was ORR by PD-L1 expression measured as combined positive score (CPS). The CPS is the rate of total number of PD-L1+ cells (Tumor, lymphocytes, Macrophages) per total number of cells. In the confirmation set, ORR was 4.1% for CPS<1, 5.7% CPS ≥1, and 10.0% for CPS ≥10.

FUTURE DIRECTIONS WITH ANTI-PD-1/ANTI-PD-L1 INHIBITORS

The activity of check point inhibitors as monotherapy in patients with pretreated ovarian cancer is low, however the combination of anti-PD-1 or anti-PD-L1 with antiangiogenic therapy or PARP inhibitors has generated more interest and expectation.

Combinations of check-point inhibitors with antiangiogenic therapy

VEGF (vascular endothelial growth factor) has been shown to have immunosuppressive properties including, inhibition of dendritic cells differentiation, induction of PD-L1 expression, activation of Tregs and reduction of Tcell endothelial adhesion and intratumoral migration. Based on this background, the blockade of VEGF has been proposed as a way to potentiate the activity of checkpoint inhibitors.

A phase II trial presented in ESMO 2018 with the combination of Nivolumab 240 mg flat dose and bevacizumab 10mg/kg every 2 weeks until progression included 38 recurrent ovarian cancer patients (Liu et al., 2018)¹⁵. In 20 platinum-sensitive patients the ORR was 40% and in 18 platinum-resistant the ORR was 16.7%. Durable responses or prolonged stable disease were seen, even in platinum-resistant patients. The median progression-free survival was 8.1 months in the whole study population (9.4 months in PS and 5.3 months in PR).

Two ongoing randomized clinical trials are assessing the role of atezolizumab plus bevacizumab in ovarian cancer in two different settings: The GOG 3015 /ENGOT OV39/Imagyn 050 in front line, and the ENGOT ov29 /ATALANTE trial in the first platinum-sensitive relapse.

Combinations of check-point inhibitors and PARP inhibitors

The rationale for the combination of PARP inhibitors with check point inhibitors is based on the upregulation of PD-L1 in preclinical models after the exposition to PARPi (Jiao et al., 2017)¹⁶.

This biological observation has been tested clinically in 3 phase II studies. The MEDIOLA trial included 32 gBRCA mutant and platinum-sensitive patients that were treated with durvalumab and olaparib achieving a significant ORR of 63% (19% complete) for a chemo-free regimen (Drew et al., 2018)¹⁷. The same combination in a population of 32 patients with majority of platinum-resistant (83%) achieved a ORR of 14% (Lee et al., 2018)¹⁸. On the other hand, the TOPACIO trial included 60 pretreated patients of whom 50% were platinum-resistant, 29% platinum refractory and 29% not eligible for further platinum. Majority were tBRCA wild-type (77%). The ORR was 25% and responses were observed in platinum-resistant (23%) and platinum-refractory (24%) patients. The median duration of response was 9.3 months (Kostantinopoulos et al., 2018)¹⁹.

The combination of PARP inhibitors and check point inhibitors is considered as promising and is being explored in the upfront setting (DUO-O / ENGOT Ov46; ENGOT Ov43; FIRST / ENGOT Ov44 and ATHENA /GOG3020 / ENGOT Ov45), and in the 1st or 2nd platinum-sensitive recurrences (ENGOT-OV41/GEICO 69-O/ANITA).

IMMUNOTHERAPY IN OVARIAN CANCER BEYOND CHECK-POINT INHIBITORS

Other strategies of immunotherapy under clinical trial in ovarian cancer, including but not limited to dendritic cell vaccines, antibody-drug conjugates and adoptive immunotherapy, will be briefly reviewed during the presentation.

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SESSION - 4

NEW DEVELOPMENTS

New Strategies in Ovarian Cancer Treatment

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Progress in the treatment of ovarian cancer (OvCa) has been exponential over the last decade with a flurry of approvals, and many new agents and targets in development. Similarly, we are looking at current agents and approaches and asking if they are being deployed optimally in the current era. This has led to new questions, some controversy, and much optimism.

Many new strategies have emerged that may enhance, inform, and improve treatment for women with OvCa. These need to be examined and validated with thoughtful clinical trial design. First, as shown in the table below, is the recognition that OvCa is not a single disease, but comprised of several morpho-molecular types for which potential interventions may be more selective¹. The frequent mutations in BRAF and KRAS seen in low grade serous ovarian cancer (LGSOC) has led to several trials of MEK inhibitors, not all of which have yet reported. These mutations have not been proven to be drivers of LGSOC and the results of GOG-0239, a study of selumetinib, suggest that benefit was not dependent upon mutations in either BRAF or KRAS². They also are seen rarely and are non-driver events in HGSOC³.

Table 1. Strategies for optimizing ovarian cancer treatment.

Strategy	Example
Targeting morpho-molecular OvCa type	Differential therapy for LGSOC v HGSOC (GOG-0281, results pending)
New designs	Window of opportunity with short turnaround endpoint to inform next steps
New agents	e.g. prexasertib (CHK1/2 inhibitor); AZD6738 (ATR inhibitor); CB389 (glutaminase inhibitor)
Novel combinations	PARPi + anti-angiogenesis +/- immune checkpoint inhibitor to leverage hypoxic effects on tumor microenvironment (TME) and DNA damage
Targeting the TME not just the tumor	e.g. effects of bevacizumab, cediranib, possibly immune inhibitory agents
Improved therapeutic delivery	e.g. mirvetuximab soravtansine, antibody-directed conjugate bringing microtubular toxins to tumor cells via folate receptor targeting

Other new strategies are more directly interventional. New designs are useful approaches especially when such designs optimize information gathering to inform subsequent directions. The biggest advance and obstacle to date is the proliferation of new agents that may be of use for women with OvCa. Decisions of how and when to apply new agents should require compelling preclinical evidence, and especially for combinations, given the factorial number of opportunities that could be envisioned. Because of the massive number of potential combinations, designs such as window of opportunity and platform studies may allow investigation of several directions concomitantly leading to more rapid focus into successful directions. The NSGO-led OV-UMB1 study is an example of concomitant examination of immune checkpoint inhibitor-containing combinations. This design is an international academic collaboration yielding rapid evaluation of multiple doublets against standard of care and currently examines an inhibitor of CD73 and antiPD-L1, ATR inhibition with antiPD-L1, and a third randomization testing that doublet with the addition of olaparib.

The field of OvCa learned early that any of the diseases under the OvCa banner are not cured with single agent therapy, that combination therapy yields greater activity of longer duration, and that disease recurs with potentially new resistance mechanisms. That, coupled with intratumoral heterogeneity, has led to several directions. First, and associated with numerous approvals worldwide, is the recognition that treating the tumor microenvironment (TME) may be an important element. The addition of bevacizumab has led to incremental benefits in primary therapy (ICON7, GOG-0218), first recurrence platinum-sensitive disease (OCEANS, GOG-0213), and most notably in platinum-resistant OvCa (AURELIA). The most striking benefit of bevacizumab comes when one separates the balanced backbones of the AURELIA results, showing an improvement from PFS of 3.9 to 10.4 months (HR 0.46) with the addition of bevacizumab to weekly paclitaxel. Similar strong results were observed with the addition of the VEGF receptor inhibitor, cediranib, to olaparib for women with platinum-sensitive disease⁴; the definitive phase 3 trial NRG GY004 is maturing and results are expected this year.

The other TME target is the immune microenvironment. Single agent studies in OvCa to date have been disappointing. Some benefit may be seen with the combination of ipilimumab (ipi) and nivolumab⁵, where the single agent nivolumab response rate of 12% (PFS 2.0 months) increased to 33% (PFS 3.9 months) with the addition of ipi for the first 4 cycles. Note that the PFS was inferior compared to historical controls (approximately 4 months), especially when toxicity is considered. Numerous immune-oncology (IO) combinations with IO, anti-angiogenesis, PARPi, and chemotherapy, are under study across all stages of the tumor lifecycle. Observations suggest that perhaps targeting the vascular microenvironment may have the greatest impact in later recurrences where more classical chemotherapies are less effective, and that targeting the immune microenvironment may require earlier intervention, perhaps before the immune system is exhausted. These observations need to be examined in hypothesis-testing trials.

New agents and new approaches to therapeutic delivery are also on the horizon. A series of G2/M inhibitors are under development or already in clinical testing. These include the CHK1/2 inhibitor prexasertib, ATR inhibitors, and the WEE1 kinase inhibitor, adavosertib (AZD1775). Prexasertib has been reported to have ~33% response rate in variably pretreated platinum-resistant BRCA wild type HGSOC with exploratory results suggesting a possible susceptibility for those women whose tumors have upregulation of cyclin E⁶. Additional trials are ongoing to replicate those results and move this agent forward. The G2/M inhibitors may also have greater success in combination approaches. Adavosertib and PARP inhibition has been shown in numerous preclinical models to have greater benefit than either alone and may be due to the induction of replication stress on the background of DNA repair dysfunction (for example,⁷). Focused targeting of agents has been successful in several venues, most notably the antibody-directed conjugate TDM-1 targeting a microtubule toxin by anti-HER2 antibody. Progress has been made with the anti-folate receptor ADC, mirvetuximab soravtansine, in the treatment of platinum-resistant disease that has moderate or high expression of folate receptor (⁸, and studies ongoing).

There is cause to be optimistic and for every patient to be able to be offered a clinical trial. The new opportunities are legion and new strategies are being used to optimize our ability to move nimbly in this era of potential therapeutic riches.





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