

## General Report

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### Actualities in Ovarian Cancer in the Perspective of 2015 (ASCO and ECCO)

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#### Rezumat

#### *Actualităţi în cancerul ovarian, perspectiva anului 2015 (ASCO și ECCO)*

Cancerul de ovar reprezintă a-4-a cauză de deces prin cancer la femei, majoritatea pacientelor fiind diagnosticate în stadii avansate ale bolii (III-IV). Cancerul ovarian local avansat ar trebui considerat o boala cronică cu multiple recăderi evolutive, terapia adjuvantă fiind obligatorie. Tratamentul afecţiunii este unul multidisciplinar, oncologul reprezentând pilonul central.

**Cuvinte cheie:** cancer ovarian, Bevacizumab, BRCA-1, BRCA-2, Olaparib, studii clinice

**Key words:** ovarian cancer, Bevacizumab, BRCA-1, BRCA-2, Olaparib, Clinical trials

#### Introduction

Ovarian cancer represents the 4-th reason of cancer related death in women, the majority of patients being diagnosed in advanced stages of the disease, (III-IV), with just 70% one year survival. At the molecular level, ovarian cancers are considered to be genomic instable. Another characteristic of the disease is the hereditary etiology 10-15% of patients. Of these, 90% have mutations of the BRCA1 and BRCA 2 oncogenes. The treatment of the disease is multidisciplinary, with a dedicated team (which involves a gynecologist surgeon, an oncologist, a pathologist, a radiologist and a psychologist), where the oncologist is the centerpiece and the cytoreductive surgery is considered to be the first therapeutic maneuver that can establish the prognostic of the disease.

The loco-regional advanced ovarian cancer should be considered a chronic disease, with multiple evolutionary relapses and where the adjuvant treatment is mandatory and the treatment of the relapses varies with disease free interval from initial response to platinum salt treatment. If the association of Paclitaxel - Cisplatin represents the therapeutic standard according to GOG 111 (1), OV10(2), Dutch-Danish, AGO, GOG 158 (3) studies from 2010, the association of the anti-angiogenic treatment to the standard therapy pointed out a new therapeutic standard.

Two clinical studies - GOG 0218 (4) and ICON 7 (4) define the role of the treatment with Bevacizumab associated

#### Abstract

Ovarian cancer represents the 4-th reason of cancer related death in women, the majority of patients being diagnosed in advanced stages of the disease, (III-IV). The loco-regional advanced ovarian cancer should be considered a chronic disease, with multiple evolutionary relapses and where the adjuvant treatment is mandatory. The treatment of the disease is multidisciplinary and the oncologist is the centerpiece.

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with Paclitaxel and Carboplatin chemotherapy. Both studies included patients with epithelial tumors. The GOG 0218 study included patients with stage III (optimal or suboptimal surgery) and stage IV and ICON7 also included patients with stage I and II with G3 or clear cells carcinoma. Unlike the ICON 7 study, where the dose for Bevacizumab is 7,5 mg/kg every 3 weeks, for 12 months, the Bevacizumab dose is different in the GOG 0218 study - 15 mg/kg, every 3 weeks and its administration is concurrent with the 6 series of chemotherapy, followed by maintenance with the same dose of Bevacizumab for 15 months.

## Discussions

The novelty of ICON 7 study is defining of high risk categories - inoperable or suboptimal operated >1 cm and stage IV disease. Disease free survival data updated in 2013 at ECCO establish a difference of 9, 4 months in favor of maintenance treatment with Bevacizumab for high risk patients with suboptimal surgery. (30, 3 months versus 39, 7 months for high risk patients) 2015 points out- through the ROSIA study (5) presented at ECCO Vienna - a higher PFS with safety conditions met at the end point and the efficacy of the prolonged duration of the maintenance treatment with Bevacizumab. The design of the study resembles to the GOG 0218 and ICON7 studies, mentioning that this study included patients with neoadjuvant treatment and so the treatment sequence allowed the investigator to choose the method of administration, either weekly administration of Paclitaxel versus 3weeks administration and the dose of Bevacizumab 15 mg/kg or 7,5mg/kg, for a period of 2 years or more than 36 cycles or till the the disease progression or unacceptable toxicity.

The primary end point was the safety of treatment and secondary end point were progression free survival (PFS), response rate (RR), response interval and overall survival.

The study results are similar with those of ICON7 study even if there were inconsistencies (caveats) regarding patients included in the study and the manner of assessing response to treatment. This is the largest PFS for first line treatment and maintenance treatment with Bevacizumab (for 25.5 months, 18.3 months for "high risk" subgroup and 21.6 months for stage III and IV).

The safety profile was similar to that of ICON7 and GOG0218, excepting proteinuria and hypertension which were common, although only few patients have discontinued treatment due to them.

The study concludes that increased duration of Bevacizumab maintenance treatment would also increase PFS without compromising safety of the treatment. This has to be confirmed by final results, probably in 2017 and phase III studies like BOOST (NCT01462890).

Another topic brought up the value of CA125 marker sensitivity compared with standard CT scan in detecting disease progression in patients with ovarian cancer. This was presented in a post-hoc analysis of the AURELIA study presented by Dr. Ignacio Romero on behalf of Dr. Kristina

Lindemann.

This topic was discussed in 2014 as a result of a study published by G. Rustin in Lancet in 2010 (6). The post hoc analysis aimed to define the consistency of disease progression evaluated by using RECIST criteria system (CT) and CA125 using the GCIC criteria.

Results of the analysis determined that only half of patients with radiologically progressive disease were consistent with CA125 criteria and only a third of patients with early progression detected on CT scan have an increased value of CA125. The authors conclude that this issue should be viewed with caution and criticism before becoming adopted. The main criticism is that the study represents only a post-hoc analysis and not one of the GCIC.

Another important study was the 19 study (randomised trial of maintenance treatment with Olaparib in platinum sensitive relapsed ovarian cancer) published by Lederman (7). The results showed the decrease of disease progression or death by 82 % in patients treated with Olaparib. 51.3% of patients in the study had BRCA germline or somatic mutation detected; the study led to registration of Olaparib by EMA for maintenance treatment in patients with high grade ovarian cancer, with germinal or somatic BRCA mutation detected and partial or complete response to platinum-based chemotherapy in 2015.

Also for this type of high grade ovarian cancer patients, the phase II prospective study ARIEL2 (A Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARIEL2) presented both at ASCO and ECCO 2015, allowed the validation of a new method for identifying ovarian cancer patients responsive to Rucaparib. This is another PARP inhibitor with increased activity and high response rate in patients with BRCA mutation.

The first part of the study identified the molecular signature of high grade ovarian cancer patient, being the predictive value method for clinical response to Rucaparib treatment.

The methodology uses the Medicine Foundation's NGS technique in defining categories of patients with BRCA mutation (mBRCA) or BRCA-like (wild form) that respond to Rucaparib. The method allows to define categories of BRCA silent and BRCA - like patients and biomarker negative upon LOH genomic and cut-off for high and low genomic LOH category.

Having identified this method and the high response rate to treatment (75% for BRCA patients and PFS of 0.67 in BRCA-like tumors versus negative biomarker) in April 2015 US FDA allowed the breakthrough registration (breakthrough therapy designation) of the molecule, that will subsequently be evaluated in future studies like ARIEL2 for maintenance or ARIEL3(A Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients With Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer (ARIEL3) ) for treatment.

ECCO 2015 also completes the role of therapy without platinum salts in patients sensitive or partial sensitive to

platinum, allowing lower toxicity and the recovery of distant neuropathy, decreased hypersensitivity reactions and especially prolongation of platinum free survival and increased response to subsequent platinum therapy.

Translational studies published by Lorusso D in *Annals of Oncology* (8) regarding ORR (52.2%) and OS (83%) in patients with BRCA mutant and BRCA-ness phenotype to Trabectedin treatment, the MITO-15 study and Monk (9) (about the status of BRCA and the OVA-301 study about the increased response to Trabectedin and pegylated doxorubicin confirm the importance and place of platinum-free chemotherapy in platinum salt responsive patients and especially for those patients with of platinum free survival of 6-12 months.

## Conclusions

After nearly 20 years with no significant results achieved recently molecular studies allowed the definition of high grade serous ovarian cancer category and have lead to promising results regarding the use of antiangiogenic treatments and PARP inhibitors.

**Conflicts of interest:** none declared.

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