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Review

Multimodal Treatment of Primary Advanced Ovarian Cancer

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Abstract. *Epithelial ovarian cancer is the second most common malignancy of the female genital tract, with approximately 7,400 new cases annually in Germany. With 5,500 deaths per year, ovarian cancer is the leading gynecologic cause of death. Epithelial ovarian cancer is characterized by morphologic heterogeneity with 4 molecular biological subtypes (immunoreactive-like, differentiated-like, proliferative-like, mesenchymal-like) with different prognosis. Significantly improved survival is achieved by optimal debulking with no residual disease (R0). Systematic lymphonodectomy of clinical negative lymph nodes has no effect on overall survival in advanced ovarian cancer. Interval debulking in advanced ovarian cancer after three cycles of neoadjuvant chemotherapy with carboplatin/paclitaxel is controversial. Standard chemotherapy for advanced ovarian cancer consists of six cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2, in a three-week cycle. Intraperitoneal chemotherapy is not a standard therapy. Anti-hormonal therapy with an aromatase inhibitor plays a minor role in therapy of both low grade serous ovarian cancer (LGSOC) and high grade serous ovarian cancer (HGSOC). A major achievement in ovarian cancer therapy has been the results of the SOLO-1 trial, in which olaparib as a first line maintenance monotherapy resulted in an overall 70% lower risk of disease progression in patients with advanced Breast Cancer Gene (BRCA)-mutated ovarian cancer.*

Epithelial ovarian cancer is the second most common malignant disease of the female genital tract in Germany with approximately 7,400 new cases annually. Thus, one in 75 women will develop ovarian cancer during her lifetime. With 5,500 deaths annually, ovarian cancer is the leading gynecologic cause of death (1).

Over the past 15 years, the quality of treatment for ovarian cancer has been continuously improving. Median PFS has increased from 12.7 months in 2004 to 20.7 months in 2016 in FIGO stages III and IV. Treatment at an experienced center and an optimal tumor reduction during primary surgery is not least responsible for this (2).

Morphologic Heterogeneity of Ovarian Cancer

Epithelial ovarian cancer exhibits morphologic heterogeneity. Basically, five subtypes of epithelial ovarian cancer with different prognosis are differentiated: high grade serous (HGSOC, 80%), low grade serous (LGSOC, 7%), mucinous (3%), clear cell (5%), and endometrioid ovarian cancer (5%) (Figure 1). The mutations and molecular alterations associated with epithelial ovarian cancer differ depending on the histologic subtype (3). For example, Konecny *et al*. (4) defined four molecular subtypes (immunoreactive-like, differentiated-like, proliferative-like, mesenchymal-like) in high-grade serous ovarian cancer, which are associated with different prognosis and show different therapeutic response to bevacizumab therapy. For instance, in a retrospective review of data from the AGO Ovarian Cancer 11/ICON7 trial, Kommoss *et al*. (5) demonstrated that the proliferative subtype of HGSOC benefited from bevacizumab therapy with a statistically significant improvement in median overall survival of 17.2 months, whereas no statistically significant benefit in overall survival was seen in any of the other molecular biology subtypes (Figure 2).

Experience of Treatment Center

Treatment center experience plays a crucial role in ovarian cancer therapy. In 2014 Bristow *et al*. (6) proved that patients

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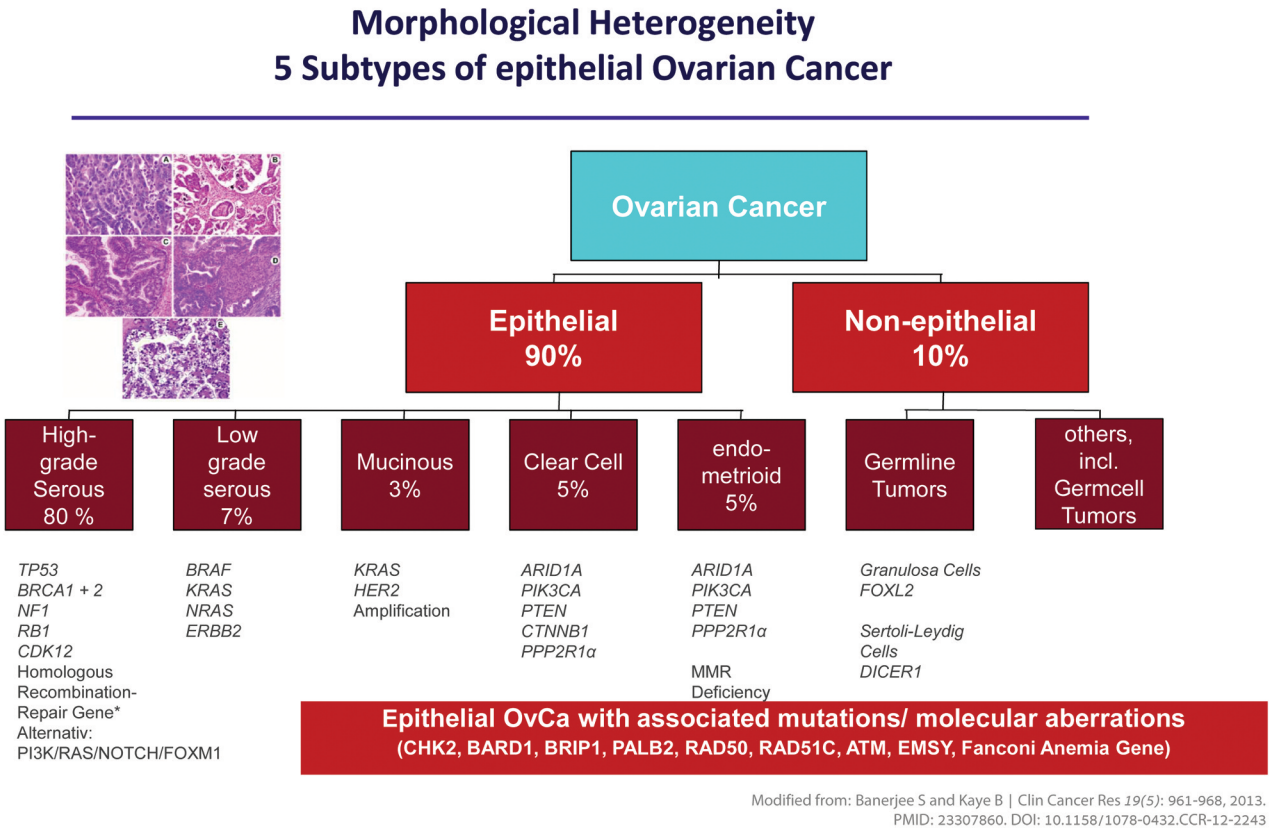


Figure 1. *Morphologic heterogeneity.*

treated in a high-volume hospital (more than 20 cases per year) and by a high-volume surgeon (more than ten cases per year) have a significantly improved survival. This is due to the improved R0 resection rate. DuBois *et al*. (7), reviewing the AGO study data, showed that overall survival is worsened by a factor of 2.7 when a tumor remnant of 1-10 mm remains compared with R0 resection. Even if macroscopic tumor remission cannot be achieved, patients benefit from maximal tumor reduction. Thus, patients with a tumor remnant of 1-10 mm have a survival advantage of almost seven months compared to patients with a tumor remnant of more than 1 cm. Compatible with this, Keyver-Paik *et al*. (8) showed an R0 resection rate in advanced ovarian cancer (FIGO stage IIB-IV) of more than 60% in an evaluation of more than 1000 ovarian cancers from 3 centers.

Primary Debulking Surgery and Interval Debulking Surgery

Surgery includes complete assessment of intra-abdominal tumor spread *via* median longitudinal laparotomy and careful exploration of the entire abdominal cavity, including inspection and palpation of the diaphragmatic domes, liver, omental bursa, paracolic gutters, small and large intestines, omentum majus and minus and retroperitoneal and para-aortic lymphatic ducts. Obtaining an aspiration cytology for cytologic examination is standard. The aim of surgery is to remove all visible tumor metastases. Limits of operability are given in case of extensive involvement of the small intestinal serosa, the small intestinal mesentery at the transition to the serosa, involvement of the mesenteric root or the truncus coeliacus and in case of diffuse infiltration of the stomach or pancreas.

If the postoperative tumor remnant is estimated to be larger than 1 cm, the absolute radicality of the procedure should be discarded. Due to the lower chemosensitivity of low grade serous ovarian cancers, upfront debulking surgery has great importance especially in this situation. According to Harter *et al*. (9), 85.1% of patients received primary surgery with optimal cytoreduction followed by chemotherapy in Germany in 2016. Interval surgery after neoadjuvant chemotherapy was performed in 9.7%, while only 5.2% of patients did not receive surgery. According to current data, systematic lymphonodectomy of clinical negative lymph nodes has no effect on overall survival in advanced ovarian cancer and should therefore no longer be

Moleculargenetic Heterogeneity

Significant Improvement of OAS with Bevacizumab in the proliferative Subtype of the EOC (AGO-Ovar 11/ICON7)

Benefit Bevacizumab + Standard Therapy vs. Standard Therapy

Subtype	Proliferative (n=96)	Non-proliferative		
		Differentiated (n=73)	Mesenchymal (n=68)	Immunreactive (n=121)
Progression-free Survival				
ΔPFS, median Improvement	10.2 Months	3.76 Months	8.23 Months	3.8 Months
HR (95% KI) *p*	0.48 (0.3-0.76) *p*=0.002	0.86 (0.48-1.54) *p*=0.615	0.67 (0.39-1.14) *p*=0.138	0,88 (0.57-1.35) *p*=0.546
Overall Survival				
ΔOS, median Improvement	17.2 Months	23.03 Months	11.77 Months	1.5 Months
HR (95% KI) *p*	0.54 (0.32-0.91) *p*=0.021	0.69 (0.34-1.38) *p*=0.294	0.75 (0.40-1.41) *p*=0.37	1.01 (0.6-1.7) *p*=0.965

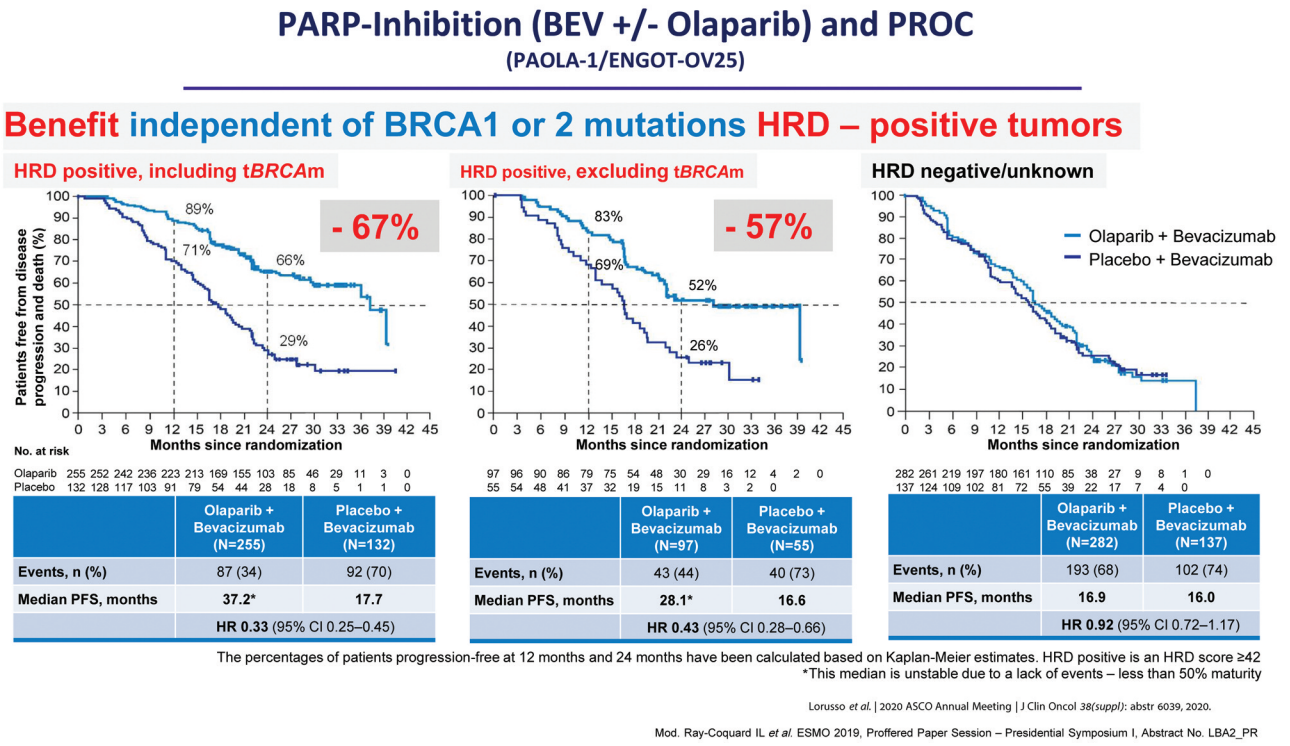
Kommoss S *et al.* | J Clin Oncol *36(suppl)*: Abstract 5520, 2018.

Figure 2. *Molecular-genetic heterogeneity and response to bevacizumab.*

performed from FIGO stage IIB onwards. The results of the LION trial showed no significant difference in both, overall survival [65.5 months with lymphonodectomy (LNE) *versus* 67.2 months without LNE] and PFS. In contrast, lymphonodectomy was primarily associated with increased morbidity (infections, relaparotomies) and mortality.

Approximately 23% of ovarian cancers are diagnosed in women over the age of 75. In addition, older patients are more likely to be classified in an advanced stage disease (FIGO III and IV) at initial diagnosis. Median overall survival in elderly patients is significantly worse at 30 vs. 64 months in a study by Trillsch *et al*. (10). This is due both to the significantly reduced rate of macroscopic tumor reduction during primary surgery and to the limited options for optimal platinum-based combination chemotherapy, which are significantly reduced to 40.4% *versus* 70.1%. Thus, treatment decisions such as the indication for primary debulking surgery and optimal combination chemotherapy should be made individually based on the patient's general condition using, for example, the HADS score and not only based on age (11-14).

Interval debulking (IDS) in advanced ovarian cancer after three cycles of neoadjuvant chemotherapy with carboplatin/paclitaxel is controversial. Arguments in favor of IDS are a lower rate of postoperative complications, a lower surgical complexity with reduced procedure time, a lower blood loss and a shorter hospital stay. The value of neoadjuvant chemotherapy with three cycles of carboplatin and paclitaxel followed by interval debulking surgery has been evaluated in four prospective randomized phase III-trials, whose validity is questioned because of deficiencies in study design and quality of surgical therapy (15-20). These deficiencies include: Bias with increased inclusion of patients with a poor prognosis; Significantly lower complete resection rates of only 16-19% compared to >50%; Median duration of the operation is only 120 and 165 minutes, which is significantly lower than the expected operating time for a radical debulking operation. Nevertheless, IDS is a reasonable perspective especially for fragile patients or patients who cannot undergo radical surgery, for example due to pulmonary embolism at the time of diagnosis.



	Olaparib + Bevacizumab (N=255)	Placebo + Bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	**37.2***	**17.7**
	HR 0.33 (95% CI 0.25–0.45)	

	Olaparib + Bevacizumab (N=97)	Placebo + Bevacizumab (N=55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	**28.1***	**16.6**
	HR 0.43 (95% CI 0.28–0.66)	

	Olaparib + Bevacizumab (N=282)	Placebo + Bevacizumab (N=137)
Events, n (%)	193 (68)	102 (74)
Median PFS, months	**16.9**	**16.0**
	HR 0.92 (95% CI 0.72–1.17)	

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42
*This median is unstable due to a lack of events – less than 50% maturity

Lorusso *et al.* | 2020 ASCO Annual Meeting | J Clin Oncol *38(suppl)*: abstr 6039, 2020.

Mod. Ray-Coquard IL *et al.* ESMO 2019, Proffered Paper Session – Presidential Symposium I, Abstract No. LBA2_PR

Figure 3. *Results of the PAOLA-1/AGO-OVAR-20/ENGOT-OV25-Trial.*

Standard Chemotherapy

Standard chemotherapy for advanced ovarian cancer consists of six cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2, in a three-week cycle. Studies investigating the efficacy of chemotherapy by adding additional chemotherapeutic agents in terms of triplets failed to improve prognosis. Even dose-dense chemotherapy regimens (JGOG 3016, GOG 262, GOG 252, ICON 8, MITO-7), which for example lead to an improvement in prognosis in breast cancer, showed no significant improvement of overall survival (OAS) and (PFS) in ovarian cancer except in a Japanese study (JGOG 3016: med; OAS 100.5 months *versus* 62.2 months; HR=0.79; p=0.039) and in a subgroup of patients in the GOG 262 trial who did not receive bevacizumab therapy (PFS: 14.2 months *versus* 10.3 months; HR=0.62; p=0.03) (21-25).

Intraperitoneal Chemotherapy and Hyperthermic Intraperitoneal Chemotherapy

According to guidelines, intraperitoneal chemotherapy is not a standard therapy and should only be used in trials. Here, a distinction must be made between postoperative application as part of routine chemotherapy, *e.g.*, intraperitoneal chemotherapy administration *via* a Tenkoff catheter, and intraoperative hyperthermic chemotherapy (HIPEC). A Cochrane meta-analysis (26) showed that postoperative intraperitoneal administration may be associated with 19% improved overall survival with significantly increased side effects and reduced dose intensity of systemic chemotherapy.

During HIPEC, after achieving R0 resection, the abdominal cavity is lavaged with chemotherapy for 1 h at a temperature of approximately 40˚C during surgery. The possible advantage of this therapy could be due to additive cytotoxic effects from chemotherapy, for example with cisplatin, and hyperthermia at the cellular and tissue level. Increased cytotoxicity with intensified "DNA crosslinking" and improved peritoneal tumor penetration of the chemotherapeutic agent is also conceivable (27-29). In the first line situation, only one prospective randomized phase III trial in advanced ovarian cancer, which investigated the value of HIPEC with 100 mg cisplatin in the setting of IDS, has found a significant improvement in overall survival with 48 months *versus* 34 months (30). Many questions such as the type of intraperitoneal chemotherapy to be used (mono- *versus* combination-chemotherapy), the duration of intraperitoneal irrigation and the possible complications and side effects remain open, so that this form of chemotherapy should only be evaluated in trials.

Maintenance Therapy

Anti-hormonal therapy with an aromatase inhibitor plays a minor role in therapy. Nevertheless, studies with small case numbers in both LGSOC and HGSOC have shown a survival benefit in advanced ovarian cancer (31).

A significant development for the concept of maintenance therapy in advanced primary ovarian cancer has been achieved with two phase III trials in Europe and the USA with bevacizumab. In the GOG 218 trial, maintenance therapy with bevacizumab for 16 cycles after completion of chemotherapy showed a 3.8-month significant increase in PFS (14.1 months *versus* 10.3 months; HR=0.72) compared with the standard therapy at that time (carboplatin/paclitaxel). The AGO-OVAR 11 (ICON 7) trial showed comparable results with a significantly prolonged PFS of 2.4 months (16.9 months *versus* 19.3 months; HR=0.81; p=0.004). Patients at high risk of recurrence (FIGO III with tumor residue greater than 1 cm, FIGO IV) benefited in this study with an increase in overall survival of 7.8 months (36.6 *versus* 28.8 months; HR=0.64; p=0.002). In contrast, the GOG 218 study showed an increase in recurrence rate after completion of bevacizumab maintenance therapy. Therefore, an extension of bevacizumab maintenance therapy over a period of more than one year is being evaluated. In the AGO-OVAR17 trial, a doubling of bevacizumab therapy time from 22 to 44 cycles is being investigated (32, 33).

BRCA mutations play an important role in ovarian cancer. It is currently estimated that approximately 35% of *BRCA* mutation carriers have no family history of *BRCA* mutation. More than one-third of platinum-sensitive recurrences have BRCA mutations. Approximately 6% of ovarian cancers have a somatic *BRCA* mutation without a germline mutation. Somatic and germline mutations in the *BRCA1* and *2* genes lead to loss of *BRCA* function. This results in impairment of homologous recombination repair of DNA and thus an increase in platinum sensitivity. The DNA repair enzyme PARP plays a crucial role in the occurrence of DNA double-strand breaks. In cancer cells lacking other components of DNA repair due to tumor genetic characteristics (BRCA1 and 2 or HRD), inhibition of the PARP enzyme prevents adequate repair of the DNA damage, which subsequently leads to increased genomic instability of the tumor cells and even to their cell death. Thus, PARP inhibition plays a therapeutic role in the treatment of ovarian cancer (34).

A major achievement in ovarian cancer treatment is the results of the SOLO-1 study, which evaluated olaparib first line maintenance monotherapy for 24 months in patients with advanced *BRCA* mutated ovarian cancer. In that study, olaparib therapy showed an overall 70% lower risk of disease progression (HR=0.30 (95%CI=0.23-0.41), p<0.001). With a median PFS of 56 months with 25 months of olaparib therapy, the beneficial effect persists beyond olaparib therapy, so there is also reasonable hope for improvement in OAS (35, 36).

In three additional first line phase III maintenance therapy trials (37) with the PARP inhibitor niraparib after response to platinum-containing chemotherapy, there was a significant improvement in PFS of 13.8 months *versus* 8.2 months in the placebo group (HR=0.62; 95%CI=0.50-0.76), regardless of *BRCA* mutation status. In patients whose tumor was HR-deficient, therapy with niraparib resulted in a significant improvement in PFS and a reduction in the risk of progression of 57%. Even in HR-competent tumors, niraparib therapy resulted in a 32% reduced risk of progression compared to placebo therapy [HR=0.68; (95%CI=0.49-0.94); p=0.02]. It should be mentioned that in this study patients in the standard arm did not receive bevacizumab therapy and patients with R0 resection during primary surgery for FIGO III stage have been excluded.

For a long time, it was unclear when bevacizumab therapy or PARP inhibition should be used in the first line situation. In the PAOLA-1/AGO-OVAR-20 trial (38, 39), the efficacy of combination maintenance therapy with olaparib and bevacizumab was investigated for the first time in patients with advanced ovarian cancer regardless of *BRCA* mutation status. This showed a benefit in PFS in HRD-positive patients independently of *BRCA* mutation status (Figure 3).

Furthermore, a significant improvement in PFS was shown even after first progression regardless of *BRCA* mutation status with HRD positivity in the context of combination maintenance therapy of olaparib and bevacizumab. Although overall survival data are currently pending, an improvement in OAS is likely.

PARP inhibitors are nowadays the new standard in the first line therapy of advanced ovarian cancer. BRCA and HRD testing are essential for choosing the right therapy. Even in BRCAwt/HR-deficient tumors, patients benefit from PARP inhibition. Thus, HRD testing should be performed in BRCA negative patients to provide access to effective PARP inhibition therapy. In patients without evidence of HRD, consideration must be given to whether therapy with niraparib or bevacizumab is preferred. This comparison is still pending from the studies to date.

Conflicts of Interest

All Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

MF and DF wrote the paper in the German language, CR performed the translation in English and CK checked the English spelling as a native speaker. All Authors contributed to editorial changes in the manuscript. All Authors read and approved the final manuscript.

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