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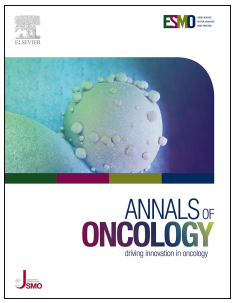

The Systemic Treatment of Recurrent Ovarian Cancer revisited

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The Systemic Treatment of Recurrent Ovarian Cancer revisited

Abstract

Treatment approaches for relapsed ovarian cancer have evolved over the past decade from a calendar-based decision tree to a patient-oriented biologically-driven algorithm. Nowadays, platinum-based chemotherapy should be offered to all patients with a reasonable chance of responding to this therapy. The treatment-free interval for platinum is only one of many factors affecting patients' eligibility for platinum re-treatment. Bevacizumab increases the response to chemotherapy irrespective of the cytotoxic regimen and can be valuable in patients with an urgent need for symptom relief (eg. pleural effusion, ascites). For patients with recurrent high grade ovarian cancer, which responds to platinum-based treatment maintenance therapy with a poly(ADP-ribose) polymerase (PARP) inhibitor can be offered, regardless of *BRCA* mutation status. Here we review contemporary decision-making processes in the systemic treatment of relapsed ovarian cancer.

Keywords:

- Recurrent ovarian cancer
- Platinum-based chemotherapy
- Platinum retreatment
- poly(ADP-ribose) polymerase (PARP) inhibitor

Highlights

Platinum-based chemotherapy remains the most active treatment for ovarian cancer.

Platinum should not be withheld after response to last platinum and a treatment-free interval of less than 6 months

We propose to move beyond the definition of platinum-resistance to a therapy-oriented definition of platinum eligibility

Platinum-non-eligible ovarian cancer (PNEOC) patients are those with progression on or immediately after their last platinum

Article

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Introduction

Platinum-based compounds are the most effective chemotherapy drugs for epithelial ovarian cancer. In relapsed epithelial ovarian cancer, the decision to use platinum-based chemotherapy has evolved into a restricted and somewhat arbitrary calendar-based method. Patients are considered eligible for further platinum-based chemotherapy and assumed to be 'platinum-sensitive' if relapse occurs more than six months after the end of the previous platinum-based treatment. They are classified as 'platinum-resistant' and deemed not eligible for platinum-based treatment if the interval is less than six months. In the latter situation they are usually offered non-platinum drug regimens. We review the history of these definitions and propose an alternative systemic treatment algorithm for relapsed ovarian cancer and therapy-oriented nomenclature based on discussions of the working group relapsed ovarian cancer during the 2018 ESMO-ESGO Consensus Conference on Ovarian Cancer.[1] The benefit of secondary cytoreductive surgery is increasingly recognised;[2] supporting evidence and patient selection for such surgery is beyond the scope of this review.

History of platinum re-treatment

The concept of re-challenge with platinum-based chemotherapy was introduced in the late 1980s, which was a time when few drugs were available for patients with recurrent ovarian cancer. A study by Blackledge *et al*. observed the highest response rates in patients who received combinations including cisplatin as a second-line chemotherapy.[3] In an exploratory multivariate analysis the treatment-free interval was the most important variable predicting response to second-line chemotherapy.[3] Retrospective observations from Gore *et al*. and Markman *et al*. described frequent secondary responses to platinum-based chemotherapy in patients previously treated with cisplatin or carboplatin.[4, 5] In both studies, response rates were highest in patients

with the longest treatment-free interval for platinum (TFIp).[4, 5] Later, Markman and Hoskins proposed that trials of new chemotherapy agents include a stratification according to the response to prior platinum-based chemotherapy. They proposed four categories: primary platinum-resistant, secondary platinum-resistant, potentially platinum-sensitive and indeterminate platinum-sensitive.[6] That definition underwent further changes, with variation in the 'cut-offs' of four to twelve months to define intermediate platinum-sensitive disease[7] and a six month cut-off for platinum-sensitivity that has been in widespread use for the last 30 years.[8] This was first questioned a decade ago at the 2010 Gynecologic Cancer InterGroup (GCIG) ovarian cancer consensus meeting. The use of a cut-off was criticized, as the tumour response to platinum-based chemotherapy increases gradually with TFIp in a non-categorical fashion (figure 1).[9] During the fifth GCIG consensus meeting in 2015, the terminology platinum-sensitive and platinum-resistant disease in clinical trials was abandoned. It was proposed that patients with relapsed ovarian cancer should be stratified in clinical trials using TFIp as a continuous variable among others such as histological subtype and prior therapies.[10]

Evidence for platinum re-treatment in patients with a treatment-free interval for platinum-based chemotherapy (TFIp) shorter than six months.

Abandoning this strict definition of platinum-resistance is important as patients with a TFIp shorter than 6 months still have a reasonable chance to respond to further platinum-based chemotherapy. A retrospective analysis of the Australian Ovarian Cancer Study reported an improved overall survival (OS) after platinum-based chemotherapy even in patients with a TFIp of only three to six months (median OS 17.7 months after platinum-based chemotherapy *vs* 10.6 months after a non-platinum regimen p=0.022).[11] In addition, Alsop et al. described the chances of response to therapy in patients experiencing first relapse. Platinum-based chemotherapy produced the highest response rates, both in *BRCA* mutation carriers and *BRCA* wild-type patients, irrespective of TFIp.[12] Clear evidence of the activity of platinum-based combination chemotherapy in patients with a TFIp of less than six months has been demonstrated in multiple (non-randomized) phase II trials with cisplatin-etoposide, cisplatin-gemcitabine, carboplatin-gemcitabine and carboplatin-paclitaxel.[13–22] Overall response rates varied between 16 and 58% as shown in table 1.[13–22] Conversely, a TFIp longer than six months does not guarantee a response to future platinum-based chemotherapy,[4, 5] although the proportion of patients who respond is higher.

Response rates to a re-challenge with a platinum-based doublet chemotherapy vary between 47.2% and 66% (table 2).[4, 23–27] Non-platinum-based chemotherapy can be divided into monotherapy, which was tested in patients with a TFIp shorter than six months, and combination therapy (pegylated liposomal doxorubicin [PLD]-trabectedin), which was studied in a broader population with an exploratory subgroup analysis of patients with TFIp of six to twelve months.[22, 28–34] As described in table 3, response rates of non-platinum-based monotherapy vary between 16.3 and 35%.[22, 28–34] It should be noted that none of the drugs listed in table 3 and licensed for use in this definition of platinum-resistance were compared to platinum therapy in phase III trials. Figure 2 is a graphical representation of the available data on platinum and non-platinum-based chemotherapy in patients with a TFIp shorter than six months. Prolongation of the TFIp by the interposition of a non-platinum-based chemotherapy has been proposed as a possible strategy to improve the response to subsequent platinum-based therapy, but has so far not been proven to be beneficial. The MITO-8 study showed that treating patients with a TFIp of six to twelve months at first or second relapse with a non-platinum-based regimen before re-introducing platinum at the subsequent relapse did not

improve survival. In contrast, median progression-free survival (PFS) was significantly shorter in patients who were first treated with a non-platinum-based regimen (12.8 vs 16.4 months – HR 1.41 – 95% CI: 1.04 to 1.92 – p=0.025).[35] The INOVATYON trial comparing carboplatin/PLD with trabectedin/PLD followed by platinum-based therapy in patients relapsing with a TFIp six to twelve months showed no improvement in OS (HR 1.10 – 95% CI: 0.92 to 1.32 – p=0.284) and PFS was longer after treatment with carboplatin/PLD compared to trabectedin/PLD (9.0 vs 7.5 months - HR 1.26 – 95% CI: 1.07 to 1.49 – p=0.005).[36] The above data suggest that platinum-based chemotherapy should always be considered as a treatment option for patients with recurrent ovarian cancer, unless there is a clear contra-indication (figure 3).

Nomenclature

As we move beyond the definitions of platinum-resistance and platinum-sensitivity based on TFIp, an update of the nomenclature is required. Such definitions should avoid a mixture of observed ("real") platinum sensitivity in patients with a response to platinum re-challenge and expected ("potential") platinum sensitivity based on TFI. A more practical approach should be therapy-oriented and therefore classified as platinum-eligible or platinum-non-eligible. Platinum-non-eligible ovarian cancer (PNEOC) patients are those with progression on or immediately after their last line of platinum-based chemotherapy or who have contraindications for further platinum-based chemotherapy, such as severe platinum allergy which cannot be managed by a desensitization regimen.[37] All other cases of relapse should be considered as platinum-eligible ovarian cancer (PEOC). One should also clearly distinguish between expected and observed responses to platinum-based chemotherapy. Patients without evaluable disease after primary cytoreductive surgery to no residual disease, or who have relapsed following FIGO stage I disease should be considered platinum eligible, although they have not had an observed response to platinum-based chemotherapy. Patients who did not respond to platinum-re-challenge in second or later-line relapse should not be exposed to further platinum-based chemotherapy.

Considerations beyond TFIp

Factors other than TFIp and prior response to platinum-based chemotherapy need to be taken into account when considering the options for further systemic therapy and the possibility of platinum re-challenge (figure 4). These should include persistent toxicity, current symptoms and patient preference. Following second or later relapse, the number of prior lines of treatment, the response to those individual treatments and life expectancy should also be taken into account. A prognostic nomogram using six variables (TFIp, performance status, size of the largest tumour, CA-125, haemoglobin and the number of organ sites of metastasis) has been proposed to provide an objective method of predicting survival after platinum-based therapy.[38] Another important variable is tumour biology and histology, as knowledge of this will assist in assessing the chance of response to platinum-based chemotherapy. Response to platinum-based chemotherapy is lower in patients with low-grade serous, clear cell and mucinous ovarian cancers.[39–41] Alternative treatment strategies should be considered in patients with these histiotypes, specifically whether there is an option to evaluate the response to targeted agents.

Molecular changes in tumours, such as the presence of homologous recombination deficiency, also increase the likelihood of a response to platinum-based chemotherapy.[42] Genomic abnormalities, such as a deleterious mutation in *BRCA1 or BRCA2* are associated with a high probability of response to

platinum-based chemotherapy.[43] Other genetic alterations genes that play a role in homologous recombination, such as *ATM*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D* are also linked to a higher response to platinum-based chemotherapy.[44] In contrast, genetic alterations that lead to inactivation of *RB1*, *NF1*, *RAD51B* and *PTEN*, reversal of deleterious mutations in *BRCA1* and *BRCA2* or amplification of *MDR1, BRD4* or *CNNE1* are associated with a reduced likelihood of response to platinum-based chemotherapy.[45, 46] In addition, transcription factors such as RELA (NF- κB p65 - reticuloendotheliosis viral oncogene homolog A) and STAT5B (signal transducer and activator of transcription 5B) are overexpressed in platinum-resistant ovarian cancer.[47] These are considered as associations and there are currently no validated molecular predictive biomarkers that identify PNEOC. Therefore, biomarkers should be evaluated further as potential PNEOC predictors but so far, they cannot be used to withhold platinum-based chemotherapy from a patient with relapsed ovarian cancer.

Chemotherapy in relapsed ovarian cancer

There are several chemotherapy options with or without platinum-based drugs available for relapsed ovarian cancer. The most commonly used regimens are listed in table 2 and 3. [4, 22, 32–34, 23–26, 28–31]. The choice of chemotherapy should be based on the toxicity spectrum and patient preferences. For later line platinum-based chemotherapy, there is no level 1 evidence available to show a benefit of combination chemotherapy *vs* single agent carboplatin. However, a meta-analysis of individual patient data has shown a significant improvement in PFS and OS with platinum combination therapy in recurrent disease.[48] Response rates and PFS observed with platinum-based chemotherapy in clinical trials is shown in figure 1B and 1D respectively. Patients who are not eligible for further platinum-based chemotherapy (PNEOC) are typically offered single agent non-platinum-based chemotherapy such as paclitaxel weekly, PLD or topotecan.[49, 50] One exception to this may be patients who are unable to receive further platinum-based chemotherapy but have a TFIp longer than six months. One study supports the use of the combination of PLD and trabectedin in these patients. In an exploratory subgroup analysis of patients with a TFIp of 6-12 months in the OVA-301 trial, the PLD-trabectedin combination led to an improved overall survival (22.4 months;95% CI, 19.4 to 25.1) compared to PLD alone (19.5 months; 95% CI, 17.4 to 22.1).[28] Newer drugs such as lurbinectedin have not been shown to be superior. In a phase III trial comparing lurbinectedin to PLD or topotecan in patients with a TFIp < 6 months the median PFS for lurbinectedin was 3.5 months *vs* 3.6 months in the standard chemotherapy arm (HR 1.04 – 95%CI, 0.84 to 1.29).[51] Alternative non-platinum options for the PNEOC group include oral etoposide, tamoxifen, gemcitabine and treosulfan, though the expected benefit of these agents is small.[8, 52]

Antiangiogenic treatment in relapsed ovarian cancer

Angiogenesis is one of the hallmarks of cancer, and neo-angiogenesis is abundantly present in ovarian cancer.[53, 54] Enhancement of tumour responses has been seen when cytotoxic drugs are combined with bevacizumab, a widely used anti-angiogenic in ovarian cancer.[55, 56] Combining anti-angiogenic therapy with chemotherapy followed by maintenance post chemotherapy has consistently shown an improvement in response rates and PFS, cf. table 4.[55, 56, 65, 57–64] Currently, bevacizumab is the only one of these drugs approved for the treatment of ovarian cancer.[39] Recently, the AGO-OVAR 2.21 study showed that in recurrent ovarian cancer the combination of carboplatin AUC5 - PLD 30mg/m² q4w with bevacizumab 10 mg/kg q2w (CD-bev) is

superior to the combination of carboplatin AUC 4 – gemcitabine 1000mg/m² d1,d8 q3w with bevacizumab 15 mg/kg q3w [CG-bev]) used in the OCEANS trial at first relapse after platinum-based chemotherapy (TFIp > 6 months). Patients in the experimental arm (CD-bev) had a median PFS of 13.3 compared to 11.7 (HR 0.807; 95% CI, 0.681 to 0.956, p=0.01 in the control arm (CG-bev). CD-bev also induced an advantage in OS compared to CG-bev (HR 0.810; 95% CI, 0.668 to 0.983,p=0.03) and this advantage was shown in both patients with and without prior bevacizumab therapy.[66] The MITO16B trial investigated if patients who had relapsed during or after first-line treatment with bevacizumab (TFIp > 6 months) had a benefit from further treatment with bevacizumab in combination with second line platinum-based chemotherapy. The addition of bevacizumab led to a median improvement in PFS of 3 months (HR 0.51; 95% CI, 0.41 to 0.65 ,11.8 *vs* 8.8 months, p<0.01) in patients who were previously treated with bevacizumab.[67]

Poly(ADP-ribose) polymerase (PARP) inhibitor in relapsed ovarian cancer

PARP is a key enzyme involved in the repair of single-stranded breaks in DNA. Inhibition of PARP leads to the accumulation of double stranded DNA breaks, which are then repaired by homologous recombination. In the presence of homologous recombination deficiency, PARP inhibitors can lead to a process sometimes called synthetic lethality, through the generation of unrepaired double-stranded DNA breaks.[68, 69] Homologous recombination deficiency is common in ovarian cancer, especially in high-grade serous ovarian cancer (HGSOC), which accounts for the benefit of PARP inhibitor therapy in a large proportion of patients with ovarian cancer.[70] Currently, the European Medicines Agency (EMA) and Food and Drug Administration (FDA) have approved the use of three different PARP inhibitors in ovarian cancer: olaparib, niraparib and rucaparib.[71] PARP inhibitors are mainly used as maintenance therapy, which is initiated after a response to platinum-based chemotherapy has been documented. In this context, all three PARP inhibitors are effective in high grade ovarian cancers, irrespective of *BRCA* mutational status of the tumour and are approved as maintenance following a response to platinum-based therapy for recurrent disease (see table 5).[72–77] It is worth noting that although a TFIp of at least 6 months was an eligibility criteria for these trials, and as we move beyond the definitions of platinum-resistance and platinum-sensitivity based on TFIp, there are anecdotal data to suggest that patients with short TFIp recurrent disease who subsequently respond to platinum-based chemotherapy may also derive benefit from maintenance PARPi therapy.[78]

The effect of maintenance therapy with PARP inhibitors on PFS is most pronounced in patients with a deleterious *BRCA* mutation, followed by patients with HRD positive (based on Myriad Mychoice or Foundation LOH HRD score) tumours. [72–74, 76] Recently, the SOLO-2 trial of olaparib maintenance in this group of patients has shown as 12.9 month increase in median OS. The OS hazard ratio of 0.74, unadjusted for the 38% of placebo patients who received a PARP inhibitor at a later date was in favour of olaparib but was of borderline statistical significance. Importantly, 22% of patients remain on olaparib with continuing benefit for more than five years.[77] The EMA has approved rucaparib as monotherapy in patients with a deleterious BRCA mutation, who have received at least two prior lines of platinum-based chemotherapy and are unable to receive further platinum-based chemotherapy. Treatment with rucaparib led to an objective response rate of 54% (95% CI, 44 to 64) and a duration of response of 9.2 months (95% CI, 6.6 to 11.7 months) in patients with a deleterious BRCA1/2 mutation and at least two prior lines of chemotherapy in ARIEL2 and study 10.[79] Olaparib and niraparib have also been approved by the FDA based on phase II data.[80, 81] The benefit of monotherapy has been supported by the result of the SOLO-3 trial that included germline BRCA-mutated patients who relapsed after at least two prior lines of platinum-based chemotherapy and had a TFIp of more than six months. These patients were

randomized to either olaparib 300mg twice daily or single agent non-platinum chemotherapy (PLD, paclitaxel weekly, gemcitabine or topotecan). Overall response rate in the olaparib group was 72.2% *vs* 51.4% in the chemotherapy group (odds ratio 2.53; 95% CI,1.40 to 4.58; p=0.002).[82] The incidence of treatment- related side effects was similar in both treatment groups; serious adverse events were more common in the olaparib group (24% *vs* 18%), but did not lead to treatment discontinuation in most patients (7% in the olaparib group *vs* 20% in the chemotherapy group).[82] The available evidence for PARP inhibitor monotherapy derived from phase II and III trials is listed in table 6.[82–89]

Currently, olaparib is being used in first-line setting in patients with a known deleterious BRCA mutation, based on SOLO-1.[90] Recently, the FDA approved the use of niraparib maintenance therapy in all patients with advanced epithelial ovarian cancer without progression after platinum-based chemotherapy based on the results of PRIMA.[91] In addition, the FDA approved the combination of olaparib and bevacizumab in patients with HRD positive or BRCA-mutated advanced epithelial ovarian cancer.[92] No license is available for re-treatment with PARP inhibitors and it is currently unclear whether PARP inhibitor retreatment is beneficial, as PARP inhibitor retreatment was not allowed in most studies. Currently, the OReO study (NCT03106987) which is recruiting patients will help to answer this question.[93] This study is for patients who were previously successfully treated with a PARP inhibitor and who after disease progression responded to their most recent line of platinum-based chemotherapy.

The therapeutic effect of PARP inhibitor treatment might be enhanced through a combination with an anti-angiogenic drug, as hypoxia increases the sensitivity of cancer cells to PARP inhibitors due to downregulation of homologous recombination repair mechanism.[94] The combination of olaparib and cediranib is especially interesting. Cediranib impairs homologous recombination repair by induction of hypoxia and consequently suppresses the expression of homologous recombination repair genes, and also exerts a direct effect on DNA repair via platelet-derived growth factor receptor inhibition.[94] The combination of cediranib and olaparib has also clinically proven to be effective in a randomized phase II trial.[95] A retrospective subgroup analysis showed the improvement in efficacy of olaparib in combination with cediranib was most pronounced for patients without a deleterious germline *BRCA* mutation.[96] The recently published results of the NRG GY004 trial comparing the combination of cediranib and olaparib with chemotherapy or olaparib showed again that cediranib added to the effect of olaparib, and this was seen in both $gBRCA^{mut}$ and $BRCA^{wt}$ groups. However, the study was negative as the chemotherapy-free regimen was not superior to chemotherapy.[97] Additive effects were also seen in the AVANOVA2 study, evaluating the combination of niraparib and bevacizumab *vs* niraparib monotherapy.[98] Results of the BAROCCO and OCTOVA studies comparing weekly paclitaxel and the combination of olaparib and/or cediranib are awaited.[99, 100] Currently, a phase III trial (ICON9) is investigating the addition of cediranib to olaparib maintenance in patients who responded to platinum-based chemotherapy for relapsed ovarian cancer (NCT03278717).

Immune-oncology strategies in relapsed ovarian cancer

Immunotherapy is an emerging therapeutic field in ovarian cancer and there is significant interest in evaluating checkpoint inhibitors in this disease. The immune system is thought to play an important role in ovarian cancer, but the results of trials of immune checkpoint inhibitor monotherapy have shown little activity.[101–104] Combining PLD with the PD-L1 inhibitor, avelumab in the JAVELIN Ovarian 200 trial showed no added benefit to avelumab to PLD alone.[105] Similarly, in the first line setting the JAVELIN OVARIAN 100 trial adding avelumab to carboplatin and paclitaxel and continuing the drug as

maintenance failed to show any benefit compared to chemotherapy alone. The hazard ratio for PFS was 1.14 (95% CI, 0.832 to 1.565) in favour of chemotherapy.[106] Combining two immunomodulatory agents, such as anti-PD1 and anti-CTLA4 agents may be more active, but also more toxic.[107] An additional strategy is the combination of an immune checkpoint inhibitor with a PARP inhibitor; PARP inhibitors can activate STING (stimulator of interferon genes) pathway to increase T cell infiltration in the tumour.[108–110] Results of the TOPACIO (phase I-II) and MEDIOLA trials show that this combination is feasible and the response rates in these studies were encouraging.[111, 112] A subgroup analysis of TOPACIO suggested that the combination of niraparib and pembrolizumab was especially promising for patients without deleterious *BRCA* mutations or homologous recombination deficiency.[111] The current the ANITA/ENGOT ov-41/GEICO 69-O trial is comparing platinum-based chemotherapy for recurrent ovarian cancer followed by niraparib maintenance to platinum-based chemotherapy with atezolizumab followed by maintenance niraparib in combination with atezolizumab.[113] An alternative strategy, which has shown promising results in other cancer types, is the combination of an immune checkpoint inhibitor and an anti-angiogenic agent.[114, 115] Results from a phase I study in ovarian cancer show that the administration of both durvalumab and cediranib is feasible and can lead to a partial response in heavily pre-treated patients.[116] The AGO-OVAR 2.29 and ATALANTE studies combining chemotherapy, bevacizumab and atezolizumab in patients with relapsed ovarian cancer are ongoing.[117, 118] However, currently no immunotherapeutic agent has been approved for the treatment of recurrent ovarian cancer, nor included in any current treatment guideline.

Conclusion

A variety of therapeutic options are available for women with recurrent ovarian cancer. Survival can be prolonged by selective sequential use of these existing treatments. Platinum-based chemotherapy continues to be the backbone of chemotherapy; platinum is the most active chemotherapy drug and has established new standards of care, together with bevacizumab and PARP inhibitors. Maintenance therapy with PARP inhibitors after platinum should now be considered a standard approach after response to platinum, if the patient is not receiving bevacizumab and has not previously been treated with a PARP inhibitor. In addition to significant prolongation in median PFS, a proportion of patients are 'super responders' who experience disease control for many years. Olaparib maintenance prolongs OS in patients with and without a BRCA mutation.[77, 119] Therefore, using platinum-based therapy to its maximum effect allows patients to access maintenance treatment that can further extend disease control. In the absence of prospectively validated tests that can accurately predict response to platinum compounds, platinum-based chemotherapy should not be withheld simply based on a TFIp of less than 6 months. Currently, platinum resistance can only be diagnosed confidently in patients whose cancer progresses during platinum-based therapy, or in those with symptomatic relapse occurring very soon after finishing platinum. We propose the algorithm in figure 5 for the treatment of patients with recurrent epithelial ovarian cancer, based on the current available literature and therapeutic options.[1] In patients with significant symptoms, especially those presenting with pleural effusion and/ or ascites, the combination of platinum-based chemotherapy with bevacizumab has the highest probability of response and is therefore likely to control symptoms more quickly, thus improving quality of life, and prolong PFS.[56, 120] For patients not on bevacizumab, chemotherapy followed by a PARP inhibitor, irrespective of BRCA or HRD status[74, 76] is the treatment of choice. There is no evidence to support an order of sequencing platinum-combinations. The decision is often based on prior toxicity, patient choice and the anticipation of what drugs could be used later in the course of the disease. For platinum non-eligible ovarian cancer patients (PNEOC), monotherapy with a non-platinum-based drug

with or without bevacizumab should be used. This review is based on the ESMO-ESGO Ovarian Cancer Consensus Conference (2018)[1] and updated with the most recent published data. It provides a detailed discussion of a rapidly changing field that will continue to evolve as the results of new major trials appear. However, platinum-based chemotherapy remains the cornerstone of systemic treatment in ovarian cancer and should be used in all patients until disease progression or intolerable adverse events such severe allergy to platinum are observed.

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Legend

Figure 1. Schematic representation of response rate to platinum-based chemotherapy based on treatment-free interval for platinum (TFIp)

Figure 2. Graphical representation of the reported overall response rates (ORR) and progression-free survival (PFS) for platinum-based and non-platinum-based chemotherapy in relapsed ovarian cancer with a treatment-free interval for platinum shorter than 6 months.[13, 14, 30–34, 15–22] Care should be taken in the interpretation of these figures as cross-trial comparison is not appropriate. PLD: pegylated liposomal doxorubicin.

Figure 3. Schematic overview of representing the responders and non-responders to platinum and non-platinum-based chemotherapy categorized by treatment free-interval for platinum (TFIp) shorter or longer than 6 months. [13, 14, 28–34, 15–22] ROC: recurrent epithelial ovarian cancer

Figure 4. Important variables for the treatment of recurrent ovarian cancer.
TFIp: treatment free interval for platinum-based chemotherapy – ROC: recurrent epithelial ovarian cancer

Figure 5. Decision-tree for relapsed epithelial ovarian cancer (EOC).[1] First evaluate if the patient is fit and willing to undergo further treatment. The different variables important in the decision-making process, such as tumor biology, histology, number of prior lines, treatment free interval for platinum-based chemotherapy (TFIp), persistent toxicity, patient´s symptoms and preferences should be taken into account. In patients with first relapse the option of surgery should be considered and discussed with the patient. Next, the main question should be answered: is platinum-based chemotherapy an option for the patient. Dependent on the answer to this question the patient can be treated in accordance to this flow-chart. Adapted with permission from Colombo N, Sessa C, du Bois A et al. ESMO – ESGO consensus conference recommendations on ovarian cancer : pathology and molecular biology , early and advanced stages, borderline tumours and recurrent disease. Ann. Oncol. 2019; 30(May):672–705. PEOC: platinum-eligible ovarian cancer - PNEOC: platinum-non-eligible ovarian cancer PLD: pegylated liposomal doxorubicin – PARP: Poly(ADP-ribose) polymerase – BRCAmut: pathogenic BRCA mutation – BRCAwt: absence of a pathogenic BRCA mutation.

Drug	Regimen	Phase	*N*	Inclusion	ORR	PFS	OS	Ref
Cisplatin-Etoposide	cisplatin 70mg/m² infusions on day 1, 8, 15 and day 29, 36, 43, combined with daily oral etoposide 50 mg on days 1–15 and days 29–43 of each 6-week cycle	non-randomized phase II	28 patients (TFIp < 4 months)	ROC	46%	5 months	13 months	[15]
Cisplatin-Gemcitabine	cisplatin 30 mg/m² plus gemcitabine (600–750 mg/m²) on days 1 and 8 of each 21-day cycle	non-randomized phase II	14 patients (TFIp < 6 months)	ROC, no prior cisplatin - gemcitabine combination therapy	57%	8 months (range 3-16 months)	NA	[16]
	cisplatin 30 mg/m² plus gemcitabine 750 mg/m² on days 1 and 8 of each 21-day cycle	non-randomized phase II	36 patients	ROC, platinum and paclitaxel resistant	42.9% (95% CI, 28.0 to 59.1)	6 months (range 1-14 months)	12 months	[17]
	cisplatin 30 mg/m² plus gemcitabine 600–750 mg/m² on days 1 and 8 of each 21-day cycle	non-randomized phase II	57 patients	ROC, TFIp < 6 months	16% (+ 54% stable disease)	5.4 months	14.9 months	[18]
	cisplatin 40 mg/m² plus gemcitabine 1000 mg/m² on days 1 and 15 of each 28-day cycle	non-randomized phase II	50 patients	ROC, TFIp < 6 months, prior paclitaxel treatment	31.5%	4.9 months (95% CI, 3.5 to 6.4)	13.2 months (95% CI, 10.2 to 16.2)	[19]

Carboplatin-Gemcitabine	carboplatin AUC 4 plus gemcitabine 1000mg/m² on day 1, followed by a second dose of gemcitabine on day 8 of each 21-day cycle	non-randomized phase II	40 patients	ROC, TFIp < 6 months	47%	6.9 months (95% CI, 3.7 to 8.8)	11.7 months (95% CI 9.0 to 18.4)	[14]
Carboplatin-Paclitaxel	paclitaxel 80 mg/m² plus carboplatin AUC 2 on day 1,8 and 15 of each 28-day cycle	non-randomized phase II	8 patients (TFIp < 6 months)	ROC	37.5%	3.2 months	11.4 months	[20]
	six weekly induction cycles paclitaxel 90 mg/m² and carboplatin AUC 2.7, patients with clinical continued treatment with six maintenance cycles paclitaxel 175 mg/m², and carboplatin AUC 6 on day 1 of each 21-day cycle	non-randomized phase II	43 patients (TFIp < 6 months)	ROC and prior treatment with paclitaxel and carboplatin	51% (induction phase) - 58% best response	8 months (95% CI, 6.7 to 9.9)	15 months (95% CI, 11.7 to 17.5)	[21]
	wP (paclitaxel 80 mg/m² days 1, 8, and 15 of a 28-day cycle) or wP + C (wP plus carboplatin AUC 5 on day 1 of a 28-day cycle) or wP + wT (wP plus topotecan 3 mg/m² days 1, 8, and 15 of a 28-day cycle) for six to nine cycles or until progression.	randomized phase II	51 patients treated with wP + C	ROC, TFIp < 6 months, prior treatment with paclitaxel and carboplatin	37%	4.8 months	15.2 months	[22]

	18 cycles of paclitaxel 60 mg/m² and carboplatin at an AUC 2.7 in a weekly schedule, all patients received G-CSF (filgastrim) on day 5 (and if needed on day 6)	non-randomized phase II	35 patients	ROC, TFIp < 6 months	48%	7 months (95% CI, 6 to 8)	13 months (95% CI 8 to 19)	[13]

Table 1 ***Overview of available phase II trials on platinum-based in relapsed ovarian cancer (ROC) with a treatment-free interval for platinum (TFIp) shorter than 6 months****. NA: not available - ORR: overall response rate – Ref: reference - PFS: progression-free survival – OS: overall survival – G-CSF: granulocyte colony-stimulating factor – wP: paclitaxel 80 mg/m² days 1, 8, and 15 of a 28-day cycle - wP + C: wP plus carboplatin AUC 5 on day 1 of a 4-week cycle - wP + wT: wP plus topotecan 3 mg/m² days 1, 8, and 15 of a 28-day cycle .*

	ORR	PFS	Ref
Carboplatin monotherapy	29.6% to 54%	7.3 to 10 months	[4, 23, 25]
Carboplatin-Paclitaxel	66%	9.4 to 13 months	[23, 24]
Carboplatin-Gemcitabine	47.2% to 62.5%	8.4 to 10 months	[25, 27]
Carboplatin-PLD	63%	11.3 months	[24, 26]

Table 2 ***Overview of platinum-based chemotherapy in relapsed ovarian cancer****. ORR: overall response rate – PFS: progression-free survival – Ref: reference PLD: pegylated liposomal doxorubicin.*

	ORR	PFS	TFIp	Ref
Paclitaxel weekly	20.9 to 35%	3.6 to 3.7 months	<6 months	[22, 30]
PLD	19.7% to 25.7%	3.7 to 5.7 months	Muggia et al. 29 pt < 6 months – 6 ≥ 6 months Gordon et al. 130 pt < 6 months – 109 ≥ 6 months	[31, 32]
Topotecan	16.3% to 17%	3.9 to 4.3 months	Gordon et al. 124 pt < 6 months – 111 ≥ 6 months Creemers et al. 62 pt < 6 months – 30 ≥ 6 months Ten Bokkel Huinink et al. 60 pt < 6 months – 52 ≥ 6 months	[32–34]
PLD-trabectedin	27.6%	7.3 to 9.2 months	Poveda et al. 6-12 months Monk et al. 115 pt < 6 months – 218 ≥ 6 months	[28, 29]

Table 3 ***Overview of non-platinum-based chemotherapy in relapsed ovarian cancer****. ORR: overall response rate – PFS: progression-free survival – Ref: reference - PLD: pegylated liposomal doxorubicin – pt: patients.*

Antiangiogenic mechanism	Drug	Clinical trial name	*N*	Inclusion criteria	Regimen	PFS	OS	Ref
Inhibition of VEGF-A	bevacizumab	OCEANS	484	recurrence ≥ 6 months after front-line platinum-based therapy	Carboplatin-Gemcitabine (G [1000 mg/m2, days 1 and 8] and C [AUC 4, day 1], q 21 days for 6–10 cycles) + concurrent placebo or bevacizumab (BV 15 mg/kg q 21 days), followed by BV until progression or unacceptable toxicity.	HR 0.484 (95% CI, 0.388 to 0.605) p<0.0001 - 12.3 *vs* 8.6 months	HR 0.952 (95% CI, 0.771–1.176) - ns - 32.9 *vs* 33.6 months	[55, 65]
		GOG-213	674	recurrence ≥ 6 months after front-line platinum-based therapy	six 3-weekly cycles of paclitaxel [175 mg/m²] and carboplatin [AUC5]) +/- bevacizumab (15 mg/kg of bodyweight) every 3 weeks and continued as maintenance every 3 weeks until progression or unacceptable toxicity.	HR 0.628 (95% CI, 0.534 to 0.739) p<0.0001 - 13.8 *vs* 10.4 months	HR 0.829 (95% CI, 0.683 to 1.005) p=0.056 - 42.4 *vs* 37.3 months	[57]
		AURELIA	361	first and second recurrence < 6 months after last platinum-based therapy	pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan as single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity, or consent withdrawal.	HR 0.48 (95% CI, 0.38 to 0.60) p<0.001 - 6.7 *vs* 3.4 months	HR 0.85 (95% CI, 0.66 to 1.08) p<0.174 - 16.6 *vs* 13.3 months	[56]

Inhibition of the VEGF-R tyrosine kinase	multi-target	sorafenib	TRIAS	174	recurrence < 6 months after last platinum-based therapy (max. 3 prior lines)	topotecan 1.25 mg/m² on days 1–5 followed by either oral sorafenib 400 mg or placebo twice daily on days 6–15, repeated every 21 days for up to six cycles. After completing six cycles patients could continue allocated study therapy (sorafenib or placebo) for up to 1 year or until disease progression, unacceptable toxicity, or consent withdrawal	HR 0.60 (95% CI, 0.43 to 0.83) p=0.0018 - 6.7 *vs* 4.4 months	HR 0.65 (95% CI, 0.45 to 0.93) p=0.017 - 17.1 *vs* 10.1 months	[58]
		pazopanib	MITO-11	74	recurrence < 6 months after last platinum-based therapy (max. 2 prior lines)	paclitaxel 80 mg/m² on days 1, 8, and 15 in a 28-day cycle plus pazopanib 800 mg/placebo given daily until disease progression, patient withdrawal, or prolonged or unacceptable toxic effects.	HR 0.42 (95% CI, 0.25 to 0.69) p=0.0002 - 6.35 *vs* 3.49 months	HR 0.60 (95% CI, 0.32 to 1.13) p=0.056 - 19.1 *vs* 13.7 months	[59]
			Richardson et al. JAMA Oncol 2018	106	recurrence < 6 months after last platinum-based therapy (max. 3 prior lines (1 non-platinum line))	paclitaxel 80 mg/m² on days 1, 8, and 15 in a 28-day cycle plus pazopanib 800 mg/placebo given daily until disease progression, patient withdrawal, or prolonged or unacceptable toxic effects.	HR 0.84 (90% CI, 0.57 to 1.22) p=0.20 - 7.5 *vs* 6.2 months	HR 1.04 (90% CI, 0.60 to 1.79) p=0.90 - 20.7 *vs* 23.3 months	[60]
	VEGF-R, FGF-R and PDGF-R	Nintedanib BIBF 1120	Ledermann et al. JCO 2011	83	partial or complete remission after last line of chemotherapy for relapsed serous ovarian cancer, with a TFI of ≤ 12 months	BIBF 1120 250 mg/placebo twice daily maintenance starting 4-8 weeks after completion of chemotherapy	HR 0.65 (95% CI, 0.42 to 1.02) p=0.06 - 36-week PFS rate 16.3% *vs* 5.0%	HR 0.84 (95% CI, 0.51 to 1.39) p=0.51	[64]

					immediately preceding the chemotherapy.				
	VEGF-R	cediranib	ICON6	456	recurrence ≥ 6 months after front-line platinum-based therapy	In arm A (reference) patients received 6 cycles of platinum-based chemotherapy plus once-daily oral placebo tablets during the chemotherapy phase, then received placebo alone during the maintenance phase; in arm B (concurrent), patients received 6 cycles of platinum-based chemotherapy plus once-daily oral cediranib 20 mg, then switched to placebo during the maintenance phase; in arm C (concurrent plus maintenance), patients received once-daily oral cediranib 20 mg during both phases.	HR 0.56 (95% CI, 0.44 to 0.72) p<0.0001 - 11.0 *vs* 8.7 months (arm C *vs* arm A). Arm B PFS 9.9 months (95% CI, 9.4 to 10.5)	immature HR 0.77 (95% CI, 0.55 to 1.07) p=0.11 - 26.3 *vs* 21 months (arm C *vs* arm A)	[61]
Inhibition of the interaction of ANG-1 and ANG-2 to the TIE2-receptor		trebananib AMG 386	Karlan et al. JCO 2012	161	recurrent ovarian cancer with maximum 3 prior lines of chemotherapy, including at least 1 platinum-based regimen	paclitaxel 80 mg/m² QW (3 weeks on/1 week off) and were randomly assigned 1:1:1 to also receive intravenous AMG 386 10 mg/kg (arm A), AMG 386 3 mg/kg (arm B) QW, or placebo QW (arm C) until progression, unacceptable toxicity, or withdrawal of consent.	HR 0.76 (95% CI, 0.52 to 1.12) p=0.165 (arm A + B *vs* arm C) 7.2 (arm A) *vs* 5.7 (arm B) *vs* 4.6 months (arm C)	HR 0.60 (95% CI, 0.34 to 1.06) p=0.081 - 22.5 *vs* 20.9 months (arm A *vs* arm C)	[63]

		TRINOVA-1	919	recurrence ≤ 12 months after last platinum-based therapy (max. 3 prior lines)	paclitaxel 80 mg/m² once weekly (3 weeks on/1 week off) plus either intravenous trebananib 15mg/kg or placebo once weekly	HR 0.70 (95% CI, 0.61 to 0.80) p<0.001 - 7.4 *vs* 5.4 months	HR 0.95 (95% CI, 0.81 to 1.11) p=0.52 - 19.3 *vs* 18.3 months	[62]

Table 4 ***Overview of studies on antiangiogenic drugs in relapsed ovarian cancer****. VEGF-A: vascular endothelial growth factor A – VEGF-R: vascular endothelial growth factor receptor – FGF-R: fibroblast growth factor receptor – PDGF-R: platelet-derived growth factor receptor – ANG: angiopoietin – TIE: tyrosine kinase with immunoglobulin-like and EGF-like domain – G: gemcitabine – C: carboplatin – BV: bevacizumab - QW: weekly - AUC: area under the curve – BV: bevacizumab – PD: progressive disease – HR: hazard ratio – TFI: treatment-free interval – ns: non-sginficant.*

Drug	Trial	*N*	Inclusion	Regimen	PFS overall	PFS BRCAmut	PFS BRCAwt	OS overall	Ref
Olaparib	Study 19	265	maintenance treatment in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had a partial or complete response to their most recent platinum-based regimen	Olaparib capsules 400mg twice daily *vs* placebo	8.4 *vs* 4.8 months; HR* 0.35 (95% CI, 0.25 to 0.49) P<0.001	11.2 *vs* 4.3 months; HR 0.18 (95% CI, 0.10 to 0.31) p<0.0001	7.4 *vs* 5.5 months; HR 0.54 (95% CI, 0.34 to 0.85) p=0.0075	NS; HR 0.88 (95% CI, 0.64 to 1.21) p=0.44	[72, 75]
	SOLO-2	295	maintenance treatment in platinum-sensitive, relapsed high-grade serous ovarian cancer or high-grade endometrioid ovarian cancer patients with a BRCA1/2 mutation who had received at least two lines of previous chemotherapy and had a partial or complete response to their most recent platinum-based regimen	Olaparib tablets 300mg twice daily *vs* placebo	/	19.1 *vs* 5.5 months; HR* 0.30 (95% CI, 0.22 to 0.41) p<0.0001	/	51.7 *vs* 38.8 months; HR 0.74 (95% CI, 0.54 to 1.00) p=0.0537 - Myriad gBRCA subset 52.4 *vs* 37.4 months; HR 0.71 (95% CI, 0.5 to 0.97) p=0.0306	[73, 77]
Niraparib	NOVA	553	maintenance treatment in platinum-sensitive (more than 6 months between penultimate platinum regimen and progression of disease), relapsed high-grade serous ovarian cancer who had received at least two lines of previous platinum-based chemotherapy and had a partial or complete response to their most recent platinum-based regimen	Niraparib 300mg once daily *vs* placebo	NA	21 *vs* 5.5 months; HR 0.27 (95% CI, 0.173 to 0.410) p<0.0001	9.3 *vs* 3.9 months; HR 0.45 (95% CI 0.338 to 0.607) p<0.0001	NA	[76]

Rucaparib	ARIEL-3	564	maintenance treatment in platinum-sensitive, relapsed high-grade serous ovarian cancer or high-grade endometrioid ovarian cancer patients who had received at least two lines of previous chemotherapy and had a radiological partial or complete response and a serological complete response to their most recent platinum-based regimen	Rucaparib 600mg twice daily *vs* placebo	13.7 *vs* 5.4 months; HR 0.35 (95% CI, 0.28 to 0.45) p<0.0001	16.6 *vs* 5.4 months; HR 0.23 (95% CI, 0.16 to 0.34) p<0.0001	high-LOH 9.7 *vs* 5.4 months; HR 0.44 (95% CI, 0.29 to 0.66) p<0.0001 - low-LOH 6.7 *vs* 5.4 months; HR 0.58 (95% CI, 0.40 to 0.85) p=0.0049	NA	[74]

Table 5 ***Overview of studies on Poly(ADP-ribose) polymerase (PARP) inhibitor maintenance therapy in relapsed ovarian cancer****. HR: hazard ratio – Ref: reference - NS: non-significant – HR* for progression or death - NA: not available – LOH: loss of heterozygosity – BRCAmut: pathogenic BRCA mutation – BRCAwt: BRCA wild type – gBRCA: germ-line pathogenic BRCA mutation.*

Drug	Trial	*N*	Inclusion	Regimen	PFS overall	PFS BRCAmut	PFS BRCAwt	OS overall	Ref
Olaparib	SOLO-3	266	single agent olaparib *vs* standard of care, based on physician's choice of single agent chemotherapy (i.e paclitaxel, or topotecan, or pegylated liposomal doxorubicin, or gemcitabine) in platinum sensitive or partially platinum sensitive relapsed ovarian cancer patients who carry germline deleterious or suspected deleterious BRCA mutation and who have received at least 2 prior lines of platinum based chemotherapy.	Olaparib 300mg twice daily *vs* single agent physician´s choice chemotherapy	NA	13.4 *vs* 9.2 months; HR§ 0.62 (95% CI, 0.43 to 0.91) p=0.013	NA	NA	[82]
	CLIO	160	single agent olaparib *vs* standard of care (i.e paclitaxel, or topotecan, or pegylated liposomal doxorubicin, or gemcitabine if TFIp<6 months, n=100, or carboplatin AUC 5 pegylated liposomal doxorubicin 30 mg/m2 q4w or carboplatin AUC 4 d1 gemcitabine 1,000 mg/m2 d1 d8 q3w if TFIp > 6 months and BRCAwt, n=60)	Olaparib 300mg twice daily *vs* physician´s choice chemotherapy	TFIp < 6 months: NS - 2.9 *vs* 3.4 months TFIp>6 months: 6.4 *vs* 8.5 months	TFIp < 6 months: ORR 38%	TFIp < 6 months: ORR 13% -	TFIp > 6 months: 23.9 *vs* 27.7 – HR 1.01 (95% CI, 0.40 to 2.51), NS	[83, 89]
	Study 42	193	single agent olaparib in platinum resistant (recurrence within 6 months after last platinum) relapsed ovarian cancer patients who carry germline deleterious or suspected deleterious BRCA mutation	Olaparib capsules 400mg twice daily	NA	7.03 months (IQR: 3.65 to 11.24)	NA	16.62 months (IQR: 9.43 to NA#)	[84]
Niraparib	QUADRA	463	single agent Niraparib in patients with relapsed high-grade serous ovarian cancer who had been treated with three or more previous lines of	Niraparib 300mg once daily	NA	NA	NA	12.2 months (IQR 3.7 to 22.1) - BRCAmut	[85]

			chemotherapy					19.0 months (IQR: 14.5 to 24.6)	
Rucaparib	Study 10	42	Single agent Rucaparib in gBRCA mutated high-grade serous ovarian cancer patients, with 2-4 previous lines of chemotherapy, who had progressed 6 months or more after their most recent platinum-based treatment	Rucaparib 600mg twice daily	NA	Median DOR 6.6 moths (95% CI, 5.1 to 11.3)	NA	NA	[86]
	ARIEL-2, Part 1	206	Single agent Rucaparib in patients who had progressed 6 months or more after their most recent platinum-based treatment	Rucaparib 600mg twice daily	Median DOR 5.7 months (IQR: 2.8 to 10.1)	12.8 months (95% CI, 9.0 to 14.7)	LOH high 5.7 months (95% CI, 5.3 to 7.6) - LOH low 5.2 months (95% CI, 3.6 to 5.5)	NA	[87]
Veliparib	GOG-280	52	Single agent Veliparib in gBRCA mutated platinum resistant or sensitive (not refractory) ovarian cancer patients, who had received 1-3 prior chemotherapy regiments.	Veliparib 400mg twice daily	NA	8.18 months	NA	NA	[88]

Table 6 ***Overview of studies on Poly(ADP-ribose) polymerase (PARP) inhibitor treatment in relapsed ovarian cancer****. HR: hazard ratio – ORR: overall response rate – gBRCA: pathogenic germline BRCA mutation – BRCAmut: pathogenic BRCA mutation - LOH: loss of heterozygosity - DOR: duration of response – IQR: inter-quartal range – N/A: not available - §: HR in accordance to blinded independent central review - # Not enough data to calculate upper limit of IQR.*