ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

The systemic treatment of recurrent ovarian cancer revisited

T. Baert[1,2*], A. Ferrero[3], J. Sehouli[4], D. M. O'Donnell[5], A. González-Martín[6], F. Joly[7], J. van der Velden[8], P. Blecharz[9], D. S. P. Tan[10,11], D. Querleu[12], N. Colombo[13,14], A. du Bois[1†] & J. A. Ledermann[15†]

[1]Department of Gynecology and Gynecological Oncology, Kliniken Essen-Mitte, Essen, Germany; [2]Department of Oncology, KU Leuven, Leuven, Belgium; [3]Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, Mauriziano Hospital, Turin, Italy; [4]Department of Gynecology with Center for Oncological Surgery, Charité—University hospital Berlin, Berlin, Germany; [5]Department of Oncology, St. James's Hospital, Dublin, Ireland; [6]Medical Oncology Department, Clínica Universidad de Navarra University Hospital, Madrid, Spain; [7]Department of Oncology, Centre Francois Baclesse, Caen, France; [8]Department of Medical Oncology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands; [9]Department of Gynecologic Oncology, Center of Oncology, M. Sklodowska-Curie Institute, Krakow, Poland; [10]Department of Haematology-Oncology, National University Cancer Institute of Singapore; [11]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [12]Department of Surgical Oncology, Institut Bergonié, Bordeaux, France; [13]Department of Medicine and Surgery, European Institute of Oncology IRCCS, Milan; [14]Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; [15]Cancer Research UK and UCL Cancer Trials Centre, UCL Cancer Institute, London, UK

Available online 3 March 2021

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 (e.g. 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 inhibitor can be offered, regardless of the *BRCA* mutation status. Here we review contemporary decision-making processes in the systemic treatment of relapsed ovarian cancer.

Key words: recurrent ovarian cancer, platinum-based chemotherapy, platinum re-treatment, poly(ADP-ribose) polymerase (PARP) inhibitor

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 >6 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 <6 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 on 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]

*Correspondence to: Dr Thaïs Baert, Department of Gynecology and Gynecologic Oncology, Ev. Kliniken Essen-Mitte, Henricistraße 92, 45136 Essen, Germany. Tel: +49-201-1743-4521; Fax: +49-201-1743-4540
E-mail: thais.baert@gmail.com (T. Baert).

† Both authors contributed equally as senior authors.

In both studies, response rates were highest in patients with the longest treatment-free interval for platinum-based chemotherapy (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 4-12 months to define intermediate platinum-sensitive disease[7] and a 6-month cut-off for platinum sensitivity that has been in widespread use for the past 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 tumor 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 TFIp <6 MONTHS

Abandoning this strict definition of platinum resistance is important as patients with a TFIp <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 3-6 months (median OS 17.7 months after platinum-based chemotherapy versus 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 <6 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 >6 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 6 months, and combination therapy [pegylated liposomal doxorubicin (PLD)—trabectedin], which was studied in a broader population with an exploratory subgroup analysis of patients with a TFIp of 6-12 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 <6 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 6-12 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 versus 16.4 months, hazard ratio (HR) 1.41; 95%

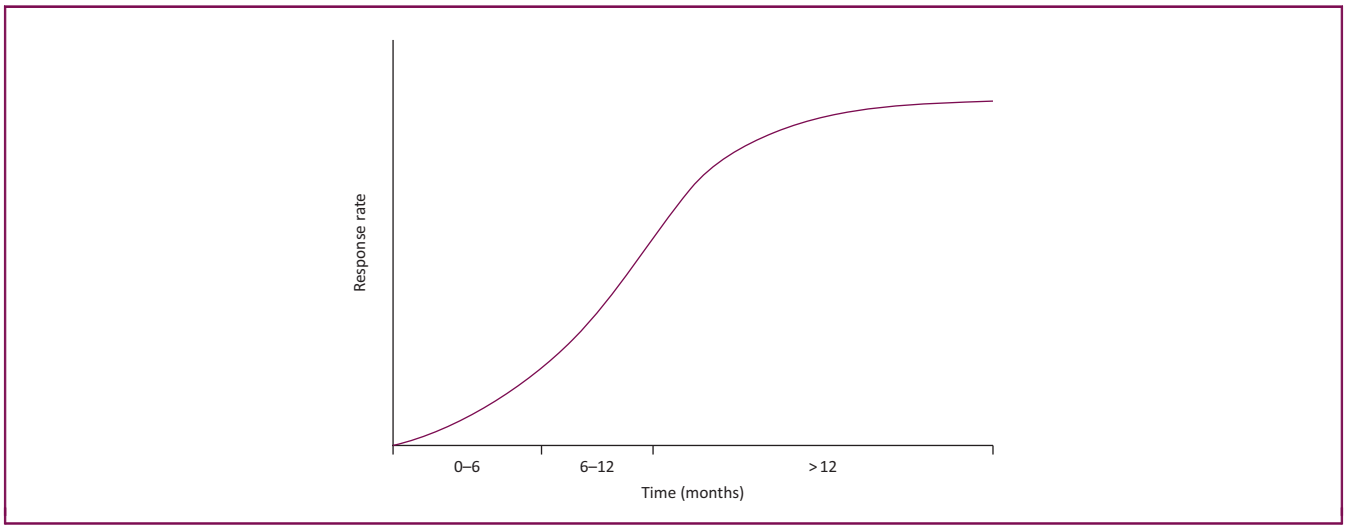

Figure 1. Schematic representation of response rate to platinum-based chemotherapy based on treatment-free interval for platinum (TFIp).

https://doi.org/10.1016/j.annonc.2021.02.015

Table 1. Overview of available phase II trials on platinum-based chemotherapy in ROC with a TFIp <6 months

Drug	Regimen	Phase	N	Inclusion	ORR	PFS	OS	Ref
Cisplatin—etoposide	Cisplatin 70 mg/m^2 infusions on days 1, 8, 15 and days 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—**g**emcitabine	Cisplatin 30 mg/m^2 plus gemcitabine (600-750 mg/m^2) 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/m^2 plus gemcitabine 750 mg/m^2 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, 28.0-59.1)	6 months (range 1-14 months)	12 months	17
	Cisplatin 30 mg/m^2 plus gemcitabine 600-750 mg/m^2 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/m^2 plus gemcitabine 1000 mg/m^2 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, 3.5-6.4)	13.2 months (95% CI, 10.2-16.2)	19
Carboplatin—**g**emcitabine	Carboplatin AUC 4 plus gemcitabine 1000 mg/m^2 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, 3.7-8.8)	11.7 months (95% CI, 9.0-18.4)	14
Carboplatin—**p**aclitaxel	Paclitaxel 80 mg/m^2 plus carboplatin AUC 2 on days 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/m^2 and carboplatin AUC 2.7, patients with clinical continued treatment with six maintenance cycles of paclitaxel 175 mg/m^2, 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, 6.7-9.9)	15 months (95% CI, 11.7-17.5)	21
	wP (paclitaxel 80 mg/m^2 on 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/m^2 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/m^2 and carboplatin at an AUC 2.7 in a weekly schedule, all patients received G-CSF (filgrastim) on day 5 (and if needed on day 6)	Non-randomized phase II	35 patients	ROC, TFIp <6 months	48%	7 months (95% CI, 6-8)	13 months (95% CI, 8-19)	13

CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; ROC, relapsed ovarian cancer; TFIp, treatment-free interval for platinum; wP, paclitaxel 80 mg/m^2 on 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/m^2 on days 1, 8 and 15 of a 28-day cycle.

Table 2. Overview of platinum-based chemotherapy in relapsed ovarian cancer

	ORR	PFS	Refs
Carboplatin monotherapy	29.6%-54.0%	7.3-10.0 months	4,23,25
Carboplatin—paclitaxel	66%	9.4-13.0 months	23,24
Carboplatin—gemcitabine	47.2%-62.5%	8.4-10.0 months	25,27
Carboplatin—PLD	63%	11.3 months	24,26

ORR, overall response rate; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

confidence interval (CI), 1.04-1.92; $P = 0.025$].[35] The INOVATYON trial comparing carboplatin/PLD with trabectedin/PLD followed by platinum-based therapy in patients relapsing with a TFIp of 6-12 months showed no improvement in OS (HR 1.10, 95% CI: 0.92-1.32, $P = 0.284$) and PFS was longer after treatment with carboplatin—PLD compared to trabectedin—PLD (9.0 versus 7.5 months; HR 1.26; 95% CI, 1.07-1.49; $P = 0.005$).[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 contraindication (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 International Federation of Gynecology and Obstetrics (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

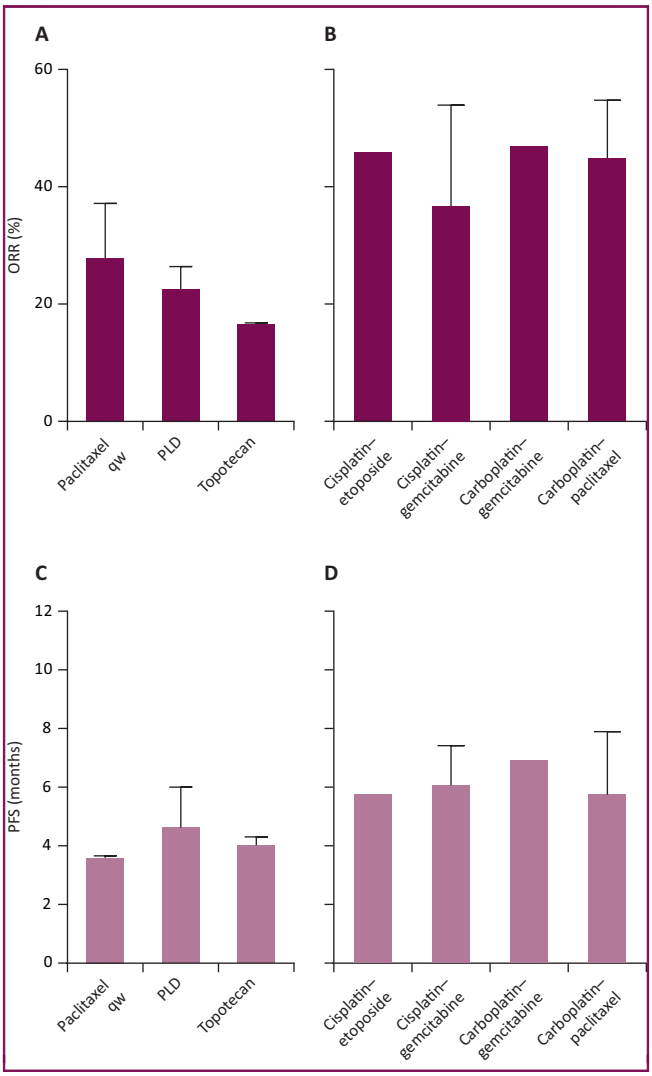

Figure 2. Graphical representation of the reported overall response rates (ORRs) and progression-free survival (PFS) for platinum-based and non-platinum-based chemotherapy in relapsed ovarian cancer with a treatment-free interval for platinum shorter than 6 months.[13-22,30-34] (A) ORR in % of non-platinum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

Table 3. Overview of non-platinum-based chemotherapy in relapsed ovarian cancer

	ORR	PFS	TFIp	Refs
Paclitaxel weekly	20.9%-35%	3.6-3.7 months	<6 months	22,30
PLD	19.7%-25.7%	3.7-5.7 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%-17%	3.9-4.3 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%	7.3-9.2 months	Poveda et al. 6-12 months Monk et al. 115 pt <6 months-218 ≥6 months	28,29

ORR, overall response rate; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; pt, patients; TFIp, treatment-free interval for platinum.

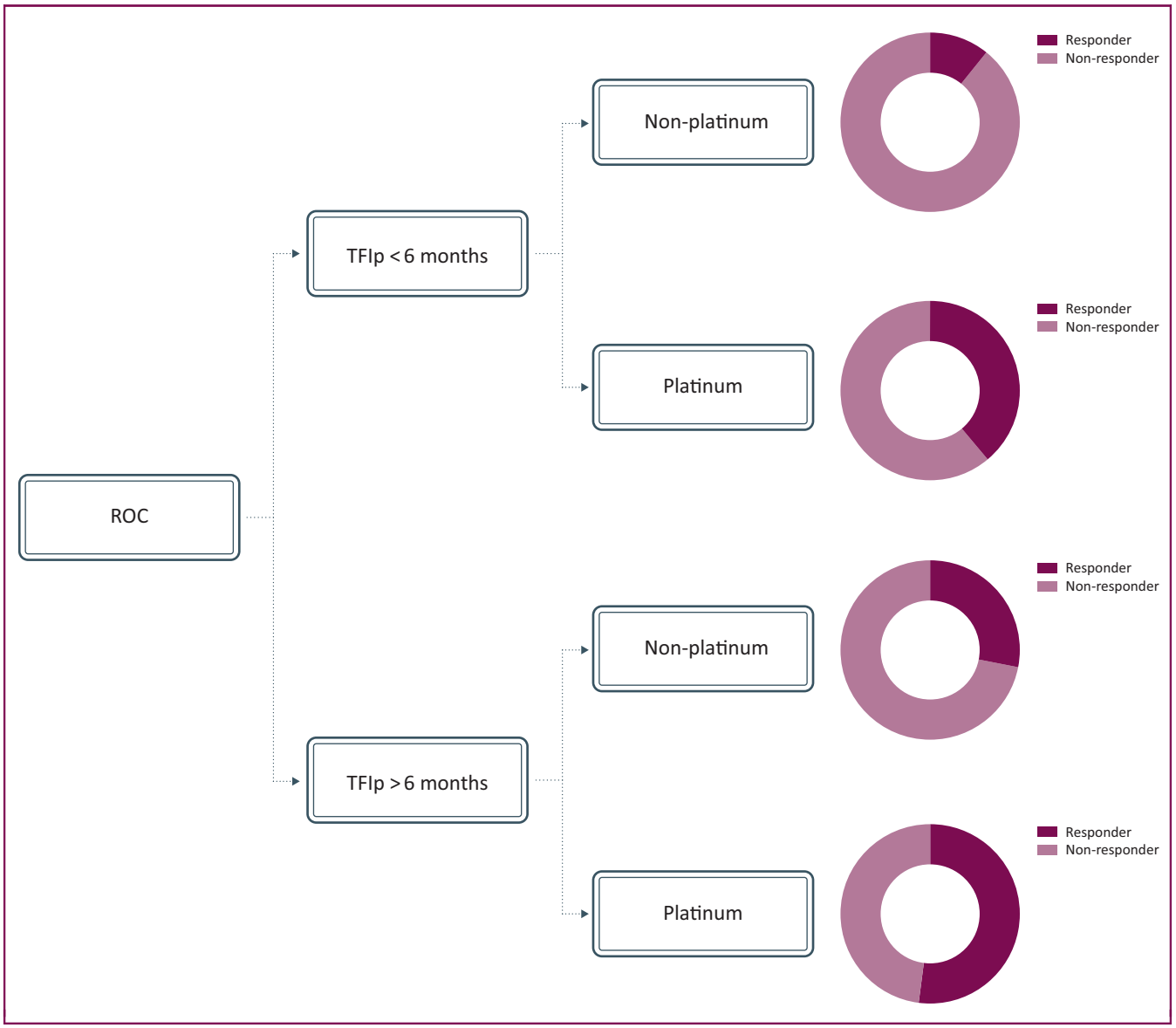

Figure 3. Schematic overview of representing the responders and non-responders to platinum- and non-platinum-based chemotherapy categorized by treatment free-interval for platinum (TFIp) shorter or longer than 6 months.[13-22,28-34]
ROC, recurrent epithelial ovarian cancer.

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 tumor, cancer antigen-125, hemoglobin 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 tumor 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 tumors, 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 alteration genes that play a role in homologous recombination, such as *ATM*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*,

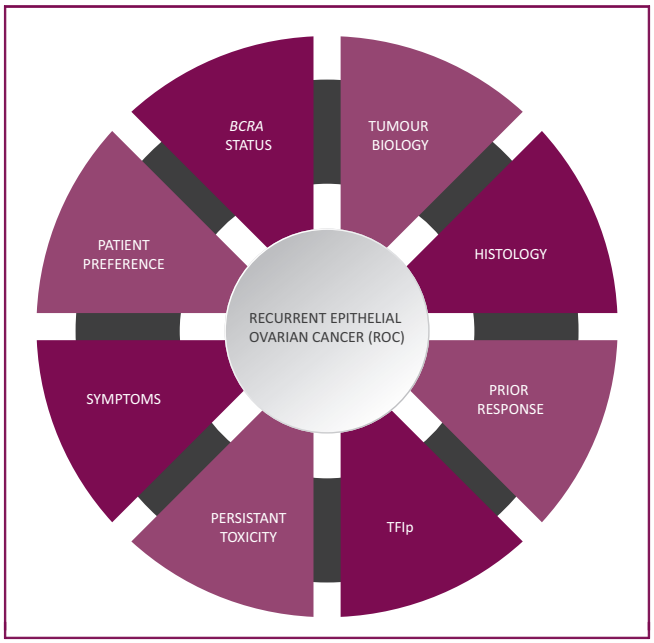

Figure 4. Important variables for the treatment of recurrent ovarian cancer. ROC, recurrent epithelial ovarian cancer; TFIp, treatment-free interval for platinum-based chemotherapy.

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 Tables 2 and 3.[4,22-26,28,31-34] 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 versus 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 are shown in Figure 2B and D, 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 >6 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 OS (22.4 months; 95% CI, 19.4-25.1) compared to PLD alone (19.5 months; 95% CI, 17.4-22.1).[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 versus 3.6 months in the standard chemotherapy arm (HR 1.04; 95% CI, 0.84-1.29).[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]

ANTI-ANGIOGENIC TREATMENT IN RELAPSED OVARIAN CANCER

Angiogenesis is one of the hallmarks of cancer, and neoangiogenesis is abundantly present in ovarian cancer.[53,54] Enhancement of tumor 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).[55-65] Currently, bevacizumab is the only one of these drugs approved for the treatment of ovarian cancer.[39] Recently, the AGO-OVAR 2.21/ENGOT-ov 18 study showed that in recurrent ovarian cancer the combination of carboplatin area under the curve (AUC) 5—PLD 30 mg/m^2 q4w with bevacizumab 10 mg/kg q2w (CD-bev) is superior to the combination of carboplatin AUC 4—gemcitabine 1000 mg/m^2 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, 0.681-0.956; $P = 0.01$ in the control arm) (CG-bev). CD-bev also induced an advantage in OS compared to CG-bev (HR 0.810; 95% CI, 0.668-0.983; $P = 0.03$) and this advantage was shown in both patients with and without prior bevacizumab therapy.[66] The MITO16B/MANGO-OV2b/ENGOT Ov-17 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-

https://doi.org/10.1016/j.annonc.2021.02.015

Table 4. Overview of studies on anti-angiogenic drugs in relapsed ovarian cancer

Anti-angiogenic 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/m^2, 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, 0.388-0.605) $P < 0.0001$—12.3 versus 8.6 months	HR 0.952 (95% CI, 0.771-1.176)—ns −32.9 versus 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/m^2) 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, 0.534-0.739) $P < 0.0001$—13.8 versus 10.4 months	HR 0.829 (95% CI, 0.683-1.005) $P = 0.056$—42.4 versus 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, 0.38-0.60) $P < 0.001$—6.7 versus 3.4 months	HR 0.85 (95% CI, 0.66-1.08) $P < 0.174$—16.6 versus 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. three prior lines)	Topotecan 1.25 mg/m^2 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, 0.43-0.83) $P = 0.0018$—6.7 versus 4.4 months	HR 0.65 (95% CI, 0.45-0.93) $P = 0.017$—17.1 versus 10.1 months	58
		Pazopanib	MITO-11	74	Recurrence <6 months after last platinum-based therapy (max. two prior lines)	Paclitaxel 80 mg/m^2 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, 0.25-0.69) $P = 0.0002$—6.35 versus 3.49 months	HR 0.60 (95% CI, 0.32-1.13) $P = 0.056$—19.1 versus 13.7 months	59
			Richardson et al. *JAMA Oncol* 2018	106	Recurrence <6 months after last platinum-based therapy (max. three prior lines (one non-platinum line)	Paclitaxel 80 mg/m^2 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, 0.57-1.22) $P = 0.20$—7.5 versus 6.2 months	HR 1.04 (90% CI, 0.60-1.79) $P = 0.90$—20.7 versus 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 immediately preceding the chemotherapy	BIBF 1120 250 mg/placebo twice daily maintenance starting 4-8 weeks after completion of chemotherapy	HR 0.65 (95% CI, 0.42-1.02) $P = 0.06$—36-week PFS rate 16.3% versus 5.0%	HR 0.84 (95% CI, 0.51-1.39) $P = 0.51$	64
	VEGF-R	Cediranib	ICON6	456	Recurrence ≥6 months after front-line platinum-based therapy	In arm A (reference) patients received six cycles of platinum-based chemotherapy plus once-daily oral placebo tablets during the chemotherapy phase, and then received placebo alone during the maintenance phase; in arm B	HR 0.56 (95% CI, 0.44-0.72) $P < 0.0001$—11.0 versus 8.7 months (arm C versus arm A). Arm B PFS 9.9 months (95% CI, 9.4-10.5)	Immature HR 0.77 (95% CI, 0.55-1.07) $P = 0.11$—26.3 versus 21 months (arm C versus arm A)	61

Continued

Table 4. Continued

Anti-angiogenic mechanism	Drug	Clinical trial name	*N*	Inclusion criteria	Regimen	PFS	OS	Ref
					(concurrent), patients received six cycles of platinum-based chemotherapy plus once-daily oral cediranib 20 mg, and 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			
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 three prior lines of chemotherapy, including at least one platinum-based regimen	Paclitaxel 80 mg/m^2 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, 0.52-1.12) $P = 0.165$ (arm A + B versus arm C) 7.2 (arm A) versus 5.7 (arm B) versus 4.6 months (arm C)	HR 0.60 (95% CI, 0.34-1.06) $P = 0.081-22.5$ versus 20.9 months (arm A versus arm C)	[63]
		TRINOVA-1	919	Recurrence ≤12 months after last platinum-based therapy (max. three prior lines)	Paclitaxel 80 mg/m^2 once weekly (3 weeks on/1 week off) plus either intravenous trebananib 15 mg/kg or placebo once weekly	HR 0.70 (95% CI, 0.61-0.80) $P < 0.001-7.4$ versus 5.4 months	HR 0.95 (95% CI, 0.81-1.11) $P = 0.52-19.3$ versus 18.3 months	[62]

ANG, angiopoietin; AUC, area under the curve; BV, bevacizumab; C, carboplatin; CI, confidence interval; FGF-R, fibroblast growth factor receptor; G, gemcitabine; HR, hazard ratio; ns, non-significant; PD, progressive disease; PDGF-R, platelet-derived growth factor receptor; QW, weekly; TIE, tyrosine kinase with immunoglobulin-like and endothelial growth factor-like domain; TFI, treatment-free interval; VEGF-A, vascular endothelial growth factor A; VEGF-R, vascular endothelial growth factor receptor.

0.65; 11.8 versus 8.8 months; $P < 0.01$) in patients who were previously treated with bevacizumab.[67]

POLY(ADP-RIBOSE) POLYMERASE INHIBITOR IN RELAPSED OVARIAN CANCER

Poly(ADP-ribose) polymerase (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 (PARPis) 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, which accounts for the benefit of PARPi 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 PARPis in ovarian cancer: olaparib, niraparib and rucaparib.[71] PARPis are mainly used as maintenance therapy, which is initiated after a response to platinum-based chemotherapy has been documented. In this context, all three PARPis are effective in high-grade ovarian cancers, irrespective of the *BRCA* mutational status of the tumor, 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 criterion 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 PARPis on PFS is most pronounced in patients with a deleterious *BRCA* mutation, followed by patients with homologous recombination deficiency (HRD)-positive (based on Myriad myChoice or Foundation loss-of-heterozygosity HRD score) tumors.[72-74,76] Recently, the SOLO-2/ENGOT-Ov21 trial of olaparib maintenance in this group of patients has shown a 12.9-month increase in median OS. The OS HR of 0.74, unadjusted for the 38% of placebo patients who received a PARPi at a later date, was in favor of olaparib but was of borderline statistical significance. Importantly, 22% of patients remain on olaparib with continuing benefit for >5 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, 44-64) and a duration of response of 9.2 months (95% CI, 6.6-11.7 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

Table 5. Overview of studies on poly(ADP-ribose) polymerase (PARP) inhibitor maintenance therapy in relapsed ovarian cancer

Drug	Trial	N	Inclusion	Regimen	PFS overall	PFS *BRCA*mut	PFS *BRCA*wt	OS overall	Refs
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 400 mg twice daily versus placebo	8.4 versus 4.8 months; HR* 0.35 (95% CI, 0.25-0.49) $P < 0.001$	11.2 versus 4.3 months; HR 0.18 (95% CI, 0.10-0.31) $P < 0.0001$	7.4 versus 5.5 months; HR 0.54 (95% CI, 0.34-0.85) $P = 0.0075$	NS; HR 0.88 (95% CI, 0.64-1.21) $P = 0.44$	72,75
	SOLO-2/ENGOT-Ov21	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 300 mg twice daily versus placebo	NA	19.1 versus 5.5 months; HR* 0.30 (95% CI, 0.22-0.41) $P < 0.0001$	NA	51.7 versus 38.8 months; HR 0.74 (95% CI, 0.54-1.00) $P = 0.0537$ - Myriad gBRCA subset 52.4 versus 37.4 months; HR 0.71 (95% CI, 0.5-0.97) $P = 0.0306$	73,77
Niraparib	NOVA/ENGOT-OV16	553	Maintenance treatment in platinum-sensitive (>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 300 mg once daily versus placebo	NA	21 versus 5.5 months; HR 0.27 (95% CI, 0.173-0.410) $P < 0.0001$	9.3 versus 3.9 months; HR 0.45 (95% CI 0.338-0.607) $P < 0.0001$	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 600 mg twice daily versus placebo	13.7 versus 5.4 months; HR 0.35 (95% CI, 0.28-0.45) $P < 0.0001$	16.6 versus 5.4 months; HR 0.23 (95% CI, 0.16-0.34) $P < 0.0001$	High LOH 9.7 versus 5.4 months; HR 0.44 (95% CI, 0.29-0.66) $P < 0.0001$-low LOH 6.7 versus 5.4 months; HR 0.58 (95% CI, 0.40-0.85) $P = 0.0049$	NA	74

*BRCA*mut, pathogenic BRCA mutation; *BRCA*wt, BRCA wild type; CI, confidence interval; gBRCA, germline pathogenic BRCA mutation; HR, hazard ratio; HR*, for progression or death; LOH, loss of heterozygosity; NA, not available; NS, non-significant.

Table 6. Overview of studies on poly(ADP-ribose) polymerase (PARP) inhibitor treatment in relapsed ovarian cancer

Drug	Trial	N	Inclusion	Regimen	PFS overall	PFS BRCAmut	PFS BRCAwt	OS overall	Refs
Olaparib	SOLO-3/NRG GY004	266	Single-agent olaparib versus 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 two prior lines of platinum-based chemotherapy	Olaparib 300 mg twice daily versus single-agent physician's choice chemotherapy	NA	13.4 versus 9.2 months; HR[a] 0.62 (95% CI, 0.43-0.91) $P = 0.013$	NA	NA	[82]
	CLIO	160	Single-agent olaparib versus 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/m^2 q4w or carboplatin AUC 4 d1 gemcitabine 1000 mg/m^2 days 1 and 8 q3w if TFIp >6 months and BRCAwt, $n = 60$)	Olaparib 300 mg twice daily versus physician's choice chemotherapy	TFIp <6 months: NS-2.9 versus 3.4 months TFIp >6 months: 6.4 versus 8.5 months	TFIp <6 months: ORR 38%	TFIp <6 months: ORR 13%	TFIp >6 months: 23.9 versus 27.7-HR 1.01 (95% CI, 0.40-2.51), 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 400 mg twice daily	NA	7.03 months (IQR: 3.65-11.24)	NA	16.62 months (IQR: 9.43-NA[b])	[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 chemotherapy	Niraparib 300 mg once daily	NA	NA	NA	12.2 months (IQR 3.7-22.1)-BRCAmut 19.0 months (IQR: 14.5-24.6)	[85]
Rucaparib	Study 10	42	Single-agent rucaparib in gBRCA-mutated high-grade serous ovarian cancer patients, with two to four previous lines of chemotherapy, who had progressed 6 months or more after their most recent platinum-based treatment	Rucaparib 600 mg twice daily	NA	Median DOR 6.6 months (95% CI, 5.1-11.3)	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 600 mg twice daily	Median DOR 5.7 months (IQR: 2.8-10.1)	12.8 months (95% CI, 9.0-14.7)	High LOH 5.7 months (95% CI, 5.3-7.6)-Low LOH 5.2 months (95% CI, 3.6-5.5)	NA	[87]
Veliparib	GOG-280	52	Single-agent veliparib in gBRCA-mutated platinum-resistant or -sensitive (not refractory) ovarian cancer patients, who had received one to three prior chemotherapy regiments	Veliparib 400 mg twice daily	NA	8.18 months	NA	NA	[88]

AUC, area under the curve; BRCAmut, pathogenic BRCA mutation; CI, confidence interval; DOR, duration of response; gBRCA, pathogenic germline BRCA mutation; HR, hazard ratio; IQR, interquartile range; LOH, loss of heterozygosity; NA, not available; ORR, overall response rate.

[a] HR in accordance with blinded independent central review.

[b] Not enough data to calculate upper limit of IQR.

https://doi.org/10.1016/j.annonc.2021.02.015

by the FDA based on phase II data.[80,81] The benefit of monotherapy has been supported by the result of the SOLO-3/NRG GY004 trial that included germline *BRCA*-mutated patients who relapsed after at least two prior lines of platinum-based chemotherapy and had a TFIp of >6 months. These patients were randomized to receive either olaparib 300 mg twice daily or single-agent non-platinum chemotherapy (PLD, paclitaxel weekly, gemcitabine or topotecan). The overall response rate in the olaparib group was 72.2% versus 51.4% in the chemotherapy group (odds ratio 2.53; 95% CI, 1.40-4.58; $P = 0.002$).[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% versus 18%), but did not lead to treatment discontinuation in most patients (7% in the olaparib group versus 20% in the chemotherapy group).[82] The available evidence for PARPi monotherapy derived from phase II and III trials is listed in Table 6.[82-89]

Currently, olaparib is being used in the 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/ENGOT-OV26/GOG-3012.[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 PARPis and it is currently unclear whether PARPi re-treatment is beneficial, as PARPi re-treatment was not allowed in most studies. Currently, the OReO/ENGOT Ov-38 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 PARPi and who after disease progression responded to their most recent line of platinum-based chemotherapy.

The therapeutic effect of PARPi treatment might be enhanced through a combination with an anti-angiogenic drug, as hypoxia increases the sensitivity of cancer cells to PARPis due to reduced efficacy 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 that 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 NSGO-AVANOVA2/ENGOT-ov24 study, evaluating the combination of niraparib and bevacizumab versus 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 programmed death-ligand 1 inhibitor avelumab in the JAVELIN Ovarian 200 trial showed no added benefit of addition of avelumab to PLD alone.[105] Similarly, in the first-line setting in 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 HR for PFS was 1.14 (95% CI, 0.832-1.565) in favor of chemotherapy.[106] Combining two immunomodulatory agents, such as anti-programmed cell death protein 1 and anti-cytotoxic T-lymphocyte-associated protein 4 agents may be more active, but also more toxic.[107] An additional strategy is the combination of an immune checkpoint inhibitor with a PARPi; PARPis can activate STING (stimulator of interferon genes) pathway to increase T-cell infiltration in the tumor.[108-110] Results of the TOPACIO/KEYNOTE-162 (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/KEYNOTE-162 suggested that the combination of niraparib and pembrolizumab was especially promising for patients without deleterious *BRCA* mutations or homologous recombination deficiency.[111] The current 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 pretreated patients.[116] The AGO-OVAR 2.29/ENGOT OV-34 and ATALANTE/ENGOT OV-29 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.

CONCLUSIONS

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 PARPis. Maintenance therapy with PARPis 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 PARPi. 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 <6 months. Currently, platinum resistance can only be diagnosed confidently in

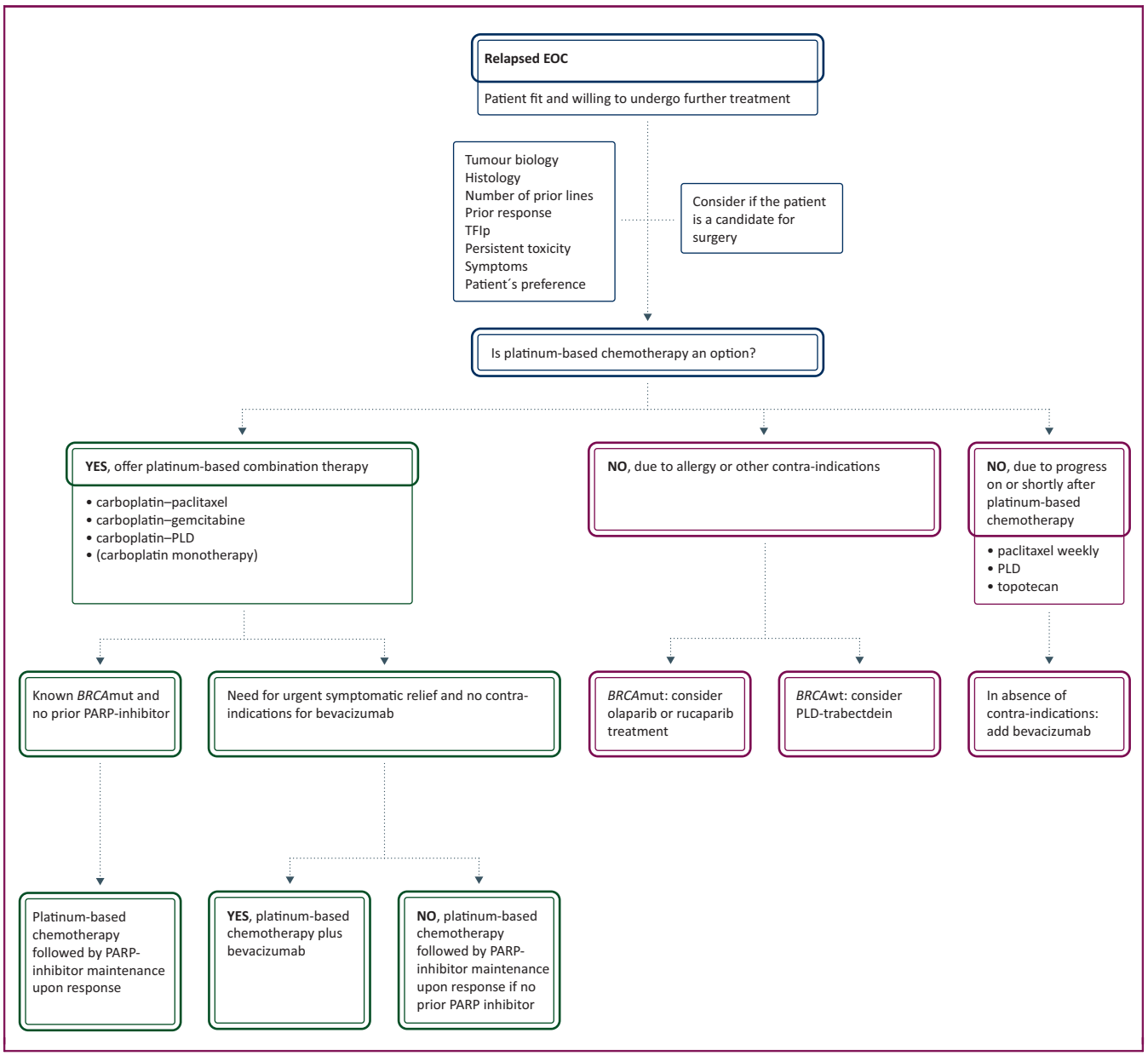

Figure 5. Decision-tree for relapsed epithelial ovarian cancer (EOC).[1]
First evaluate if the patient is fit and willing to undergo further treatment. The different variables important in the decision-making process, such as tumor biology, histology, number of prior lines, treatment-free interval for 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. Depending on the answer to this question, the patient can be treated in accordance with this flow chart. Adapted with permission from Colombo et al.[1] *BRCA*mut, pathogenic *BRCA* mutation; *BRCA*wt, absence of a pathogenic *BRCA* mutation; PARP, poly(ADP-ribose) polymerase; PEOC, platinum-eligible ovarian cancer; PLD, pegylated liposomal doxorubicin; PNEOC, platinum-non-eligible ovarian cancer.

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 PARPi, irrespective of the *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 PNEOC patients, 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 as severe allergy to platinum are observed.

FUNDING

None declared.

DISCLOSURE

TB has been an advisor for Tesaro and received research grant from Amgen and non-financial support from Amgen, MSD, Roche and Tesaro, outside the submitted work. JS has reported advisory boards and lectures for PharmaMar, AstraZeneca, Clovis, Roche and Tesaro. AG-M has received consulting fees, lecture fees or travel support from Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK/TESARO, ImmunoGen, Mersana, Merck Sharp & Dohme, Novartis, Oncoinvent, Pfizer/Merck, PharmaMar, Roche and Sotio. FJ reports expertise, board fees and travel support from AZ, GSK, BMS, Clovis, Pfizer, Astellas, Merck, MSD, Ipsen, Novartis, Sanofi and Baxter. PB has received consultancy, travel and lecture fees and honoraria from AstraZeneca, Roche and GSK and has received research funding from AstraZeneca. DSPT is funded by the Singapore Ministry of Health's National Medical Research Council under the Clinician Scientist Award (NMRC/CSA—INV/0016/2017) and has received consultancy fees and honoraria from AstraZeneca, Bayer, Eisai, Genmab, Merck, MSD, Roche and Tessa; and has received research funding from AstraZeneca, Bayer and Karyopharm. NC has reported advisory roles for Roche, PharmaMar, AstraZeneca, Clovis, Tesaro, Pfizer, Takeda and Biocad and speaker's honoraria from Roche, PharmaMar, AstraZeneca and Tesaro. AdB has received grants and personal fees from Roche, Astra Zeneca, Tesaro, Clovis, Pfizer, Biocad, Genmab/Seattle Genetics and MSD, outside the submitted work. JAL reports advisory boards and/or lecture fees from AstraZeneca, GSK, Artios Pharma, Clovis Oncology, MSD/Merck, Amgen, Pfizer and Eisai. Grant funding: AstraZeneca, MSD/Merck. IDMC fees: Regeneron. All other authors have declared no conflicts of interest.

REFERENCES

1. 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.
2. du Bois A, Sehouli J, Vergote I, et al. Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: final analysis of AGO DESKTOP III/ENGOT-ov20. *J Clin Oncol* 2020;38(suppl 15). Abstr. 6000.
3. Blackledge G, Lawton F, Redman C, Kelly K. Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. *Br J Cancer* 1989;59(4):650-3.
4. Gore ME, Fryatt I, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. *J Clin Oncol* 1990;36(2):207-11.
5. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991;9(3):389-93.
6. Markman M, Hoskins W. Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated population. *J Clin Oncol* 1992;10(4):513-4.
7. Berek JS, Bertelsen K, Brady MF, et al. Advanced epithelial ovarian cancer: 1998 consensus statements. *Ann Oncol* 1998;10(suppl 1):87-92.
8. Markman M, Bookman MA. Second-line treatment of ovarian cancer. *Oncologist* 2000;5(1):26-35.
9. Stuart GCE, Kitchener H, Bacon M, et al. 2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the fourth ovarian cancer consensus conference. *Int J Gynecol Cancer* 2011;21(4):750-5.
10. Mcgee J, Bookman M, Harter P, et al. Fifth Ovarian Cancer Consensus Conference: individualized therapy and patient factors. *Ann Oncol* 2017;28(4):702-10.
11. Lindemann K, Gao B, Mapagu C, et al. Response rates to second-line platinum-based therapy in ovarian cancer patients challenge the clinical definition of platinum resistance. *Gynecol Oncol* 2018;150(2):239-46.
12. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian ovarian cancer study group. *J Clin Oncol* 2012;30(21):2654-63.
13. Vergote I, Debruyne P, Kridelka F, et al. Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: a study in 108 patients by the Belgian Gynaecological Oncology Group. *Gynecol Oncol* 2015;138(2):278-84.
14. Ledermann JA, Gabra H, Jayson GC, et al. Inhibition of carboplatin-induced DNA interstrand cross-link repair by gemcitabine in patients receiving these drugs for platinum-resistant ovarian cancer. *Clin Cancer Res* 2010;16(19):4899-905.
15. van der Burg MEL, de Wit R, van Putten WLJ, et al. Weekly cisplatin and daily oral etoposide is highly effective in platinum pretreated ovarian cancer. *Br J Cancer* 2002;86(1):19-25.
16. Nagourney RA, Brewer CA, Radecki S, et al. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol* 2003;88(1):35-9.

17. Rose PG, Mossbruger K, Fusco N, Smrekar M, Eaton S, Rodriguez M. Gemcitabine reverses cisplatin resistance: demonstration of activity in platinum- and multidrug-resistant ovarian and peritoneal carcinoma. *Gynecol Oncol* 2003;88(1):17-21.
18. Brewer CA, Blessing JA, Nagourney RA, et al. Cisplatin plus gemcitabine in platinum-refractory ovarian or primary peritoneal cancer: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol* 2006;103(2):446-50.
19. Bozas G, Bamias A, Koutsoukou V, et al. Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pretreated, ovarian and peritoneal carcinoma. *Gynecol Oncol* 2007;104(3):580-5.
20. Havrilesky LJ, Alvarez AA, Sayer RA, et al. Weekly low-dose carboplatin and paclitaxel in the treatment of recurrent ovarian and peritoneal cancer. *Gynecol Oncol* 2003;88(1):51-7.
21. van der Burg MEL, Vergote I, Onstenk W, et al. Long-term results of weekly paclitaxel carboplatin induction therapy: an effective and well-tolerated treatment in patients with platinum-resistant ovarian cancer. *Eur J Cancer* 2013;49(6):1254-63.
22. Lortholary A, Largillier R, Weber B, et al. Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomized phase II trial from Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO). *Ann Oncol* 2012;23(2):346-52.
23. Parmar M, Ledermann J, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;361(9375):2099-106.
24. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol* 2010;28(20):3323-9.
25. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006;24(29):4699-707.
26. Ferrero J, Weber B, Geay J, et al. Second-line chemotherapy with pegylated liposomal doxorubicin and carboplatin is highly effective in patients with advanced ovarian cancer in late relapse: a GINECO phase II trial. *Ann Oncol* 2007;18(2):263-8.
27. du Bois A, Lück HJ, Pfisterer J, et al. Second-line carboplatin and gemcitabine in platinum sensitive ovarian cancer—a dose-finding study by the Arbeitsgemeinschaft Gynakologische Onkologie (AGO) Ovarian Cancer Study Group. *Ann Oncol* 2001;12(8):1115-20.
28. Poveda A, Vergote I, Tjulandin S, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6—12 months) subpopulation of OVA-301 phase III randomized trial. *Ann Oncol* 2011;22(1):39-48.
29. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. *J Clin Oncol* 2010;28(19):3107-14.
30. Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;101(3):436-40.
31. Muggia BFM, Hainsworth JD, Jeffers S, et al. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997;15(3):987-93.
32. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;19(14):3312-22.
33. Creemers BGJ, Bolis G, Gore M, et al. Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European phase II study. *J Clin Oncol* 1996;14(12):3056-61.
34. ten Bokkel Huinink W, Lane SR, Ross GA. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. *Ann Oncol* 2004;15(1):100-3.
35. Pignata S, Scambia G, Bologna A, et al. Randomized controlled trial testing the efficacy of platinum-free interval prolongation in advanced ovarian cancer: the MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study. *J Clin Oncol* 2017;35(29):3347-53.
36. Colombo N, Gadducci A, Sehouli J, et al. INOVATYON study: randomized phase III international study comparing trabectedin/PLD followed by platinum at progression vs carboplatin/PLD in patients with recurrent ovarian cancer progressing within 6-12 months after last platinum line. *Ann Oncol* 2020;31(suppl 4). S245-S1216 (LBA30).
37. Gomez R, Harter P, Lück H, et al. Carboplatin hypersensitivity does introduction of skin test and desensitization reliably predict and avoid the problem? A prospective single-center study. *Int J Gynecol Cancer* 2009;19(7):1284-7.
38. Lee CK, Simes RJ, Brown C, et al. A prognostic nomogram to predict overall survival in patients with platinum-sensitive recurrent ovarian cancer. *Ann Oncol* 2013;24(4):937-43.
39. Kamura T, Kigawa J, Terakawa N, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. *Cancer* 2000;88(11):2584-9.
40. Pauly N, Ehmann S, Ricciardi E, et al. Low-grade serous tumors: are we making progress? *Curr Oncol Rep* 2020;22(1):8.
41. Bamias A, Sotiropoulou M, Zagouri F, et al. Prognostic evaluation of tumour type and other histopathological characteristics in advanced epithelial ovarian cancer, treated with surgery and paclitaxel/carboplatin chemotherapy: cell type is the most useful prognostic factor. *Eur J Cancer* 2011;48(10):1476-83.
42. Mukhopadhyay A, Plummer ER, Elattar A, et al. Clinicopathological features of homologous recombination—deficient epithelial ovarian cancers: sensitivity to PARP inhibitors, platinum, and survival. *Cancer Res* 2012;72(22):5675-83.
43. Tan DSP, Rothermundt C, Thomas K, et al. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. *J Clin Oncol* 2008;26(34):5530-6.
44. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res* 2014;20(3):764-75.
45. Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer. *Nature* 2015;521(7553):489-94.
46. Petersen S, Wilson AJ, Hirst J, et al. CCNE1 and BRD4 co-amplification in high-grade serous ovarian cancer is associated with poor clinical outcomes. *Gynecol Oncol* 2020;157(2):405-10.
47. Jinawath N, Vasoontara C, Jinawath A, et al. Oncoproteomic analysis reveals co-upregulation of RELA and STAT5 in carboplatin resistant ovarian carcinoma. *PLoS One* 2010;5(6):e11198.
48. Raja FA, Counsell N, Colombo N, et al. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. *Ann Oncol* 2013;24(12):3028-34.
49. Sehouli J, Stengel D, Oskay-Oezcelik G, et al. Nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer: results of a phase III study of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol* 2008;26(19):3176-82.
50. Sehouli J, Stengel D, Harter P, et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *J Clin Oncol* 2011;29(2):242-8.
51. Gaillard S, Oaknin A, Ray-Coquard IL, et al. Phase III trial of lurbinectedin versus PLD or topotecan in platinum-resistant ovarian cancer patients: results of CORAIL trial. *Ann Oncol* 2018;29(suppl 8):932O.
52. Pujade-Lauraine E, Banerjee S, Pignata S. Management of platinum-resistant, relapsed epithelial ovarian cancer and new drug perspectives. *J Clin Oncol* 2019;37(27):2437-48.

53. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144(5):646-74.
54. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000;407(6801):249-57.
55. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012;30(17):2039-45.
56. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol* 2014;32(13):1302-8.
57. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel—carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18(6):779-91.
58. Chekerov R, Hilpert F, Mahner S, et al. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2018;19(9):1247-58.
59. Pignata S, Lorusso D, Scambia G, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2015;16(5):561-8.
60. Richardson DL, Sill MW, Coleman RL, et al. Paclitaxel with and without pazopanib for persistent or recurrent ovarian cancer: a randomized clinical trial. *JAMA Oncol* 2018;4(2):196-202.
61. Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;387(10023):1066-74.
62. Monk BJ, Poveda A, Vergote I, et al. Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): long-term survival, impact of ascites, and progression-free survival-2. *Gynecol Oncol* 2016;143(1):27-34.
63. Karlan BY, Oza AM, Richardson GE, et al. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer. *J Clin Oncol* 2012;30(4):362-71.
64. Ledermann JA, Hackshaw A, Kaye S, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. *J Clin Oncol* 2011;29(28):3798-804.
65. Aghajanian C, Goff B, Nycum L, et al. Final analysis of overall survival in OCEANS, a randomized phase III trial of gemcitabine, carboplatin, and bevacizumab followed by bevacizumab until disease progression in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol* 2014;133. Abstr. 137.
66. Pfisterer J. Comment: Platinum-sensitive ovarian cancer: liminal advances. *Lancet Oncol* 2020;2045(20):9-10.
67. Pignata S, Lorusso D, Joly F, et al. Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: the randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17. *J Clin Oncol* 2018;36(suppl). abstr 5506.
68. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly (ADP-ribose) polymerase. *Nature* 2005;434(7035):913-8.
69. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005;434(7035):236-9.
70. Lord CJ, Ashworth A. BRCAness revisited. *Nat Rev Cancer* 2016;16(2):110-20.
71. Gourley C, Balmaña J, Ledermann JA, et al. Moving from poly (ADP-Ribose) polymerase inhibition to targeting DNA repair and DNA damage response in cancer therapy. *J Clin Oncol* 2019;37(25):2257-69.
72. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366(15):1382-92.
73. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017;18(9):1274-84.
74. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;390(10106):1949-61.
75. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol* 2014;15(8):852-61.
76. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016;375(22):2154-64.
77. Poveda A, Floquet A, Ledermann JA, et al. Final overall survival (OS) results from SOLO2/ENGOT-ov21: a phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation. *J Clin Oncol* 2020;38(suppl 15). Abstr. 6002.
78. Ngoi NYL, Tay D, Heong V, et al. Reversal of bowel obstruction with platinum-based chemotherapy and olaparib in recurrent, short platinum-free interval, RAD51C germline mutation—associated ovarian cancer. *JCO Precis Oncol* 2018;(2):1-8.
79. Balasubramaniam S, Beaver JA, Horton S, et al. FDA approval summary: rucaparib for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer. *Clin Cancer Res* 2017;23(23):7165-71.
80. Kim G, Ison G, McKee AE, et al. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. *Clin Cancer Res* 2015;21(19):4257-61.
81. Wolford JE, Bai J, Moore KN, Kristeleit R, Monk BJ, Tewari KS. Cost-effectiveness of niraparib, rucaparib, and olaparib for treatment of platinum-resistant, recurrent ovarian carcinoma. *Gynecol Oncol* 2020;157(2):500-7.
82. Penson RT, Valencia RV, Cibula D, et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. *J Clin Oncol* 2020;38(11):1164-74.
83. Vanderstichele A, Van Nieuwenhuysen E, Han S, et al. Randomized phase II CLIO study on olaparib monotherapy versus chemotherapy in platinum-resistant ovarian cancer. *J Clin Oncol* 2019;37(suppl no. 15):5507.
84. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015;33(3):244-50.
85. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2019;20(5):636-48.
86. Shapira-frommer R, Oza AM, Domchek SM, et al. A phase 2 open-label, multicenter study of single-agent rucaparib in the treatment of patients with relapsed ovarian cancer and a deleterious BRCA mutation. *Eur J Cancer* 2015;51(suppl 3):S545.
87. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017;18(1):75-87.
88. Coleman RL, Sill MW, Bell-McGuinn K, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation—an NRG. *Gynecol. Oncol* 2015;137(3):386-91.

89. Loverix L, Vanderstichele A, Olbrecht S, et al. Randomized phase II CLIO study on olaparib monotherapy versus chemotherapy in platinum-sensitive recurrent ovarian cancer. *Soc Gynecol Oncol* 2020. Abstr. 30.
90. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018;379(26):2495-505.
91. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2019;381(25):2391-402.
92. Coquard IR, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med* 2019;381(25): 2416-28.
93. Pujade-lauraine E, Colombo N, Glasspool R, et al. OREO/ENGOT OV-38: a phase IIIB trial of olaparib maintenance retreatment in patients with epithelial ovarian cancer. *Ann Oncol* 2017;28(suppl 5). Abstr. 2242.
94. Kaplan AR, Gueble SE, Liu Y, et al. Cediranib suppresses homology-directed DNA repair through down-regulation of BRCA1/2 and RAD51. *Sci Transl Med* 2019;11(492):eaav4508.
95. Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol* 2014;15(11):1207-14.
96. Liu JF, Barry WT, Birrer M, et al. Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. *Ann Oncol* 2019;30(4):551-7.
97. Liu JF, Brady MF, Matulonis UA, et al. A phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in recurrent platinum-sensitive ovarian cancer. *J Clin Oncol* 2020;38(suppl 15). Abstr. 6003.
98. Vergote I, du Bois A, Floquet A, et al. Overall survival results of AGO-OVAR16: a phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer. *Gynecol Oncol* 2019;155(2):186-91.
99. Colombo N, Nicoletto O, Benedetti Panici P, et al. BAROCCO: a randomized phase II study of weekly paclitaxel vs cediranib-olaparib with continuous schedule vs cediranib-olaparib with intermittent schedule in advanced platinum resistant ovarian cancer. *Ann Oncol* 2018;29(suppl 8). Abstr. 1002TiP.
100. Nicum S, Strauss VY, McGregor N, et al. OCTOVA: a randomised phase II trial of olaparib, chemotherapy, or olaparib and cediranib in patients with BRCA-mutated platinum-resistant ovarian cancer. *Ann Oncol* 2017;28(suppl 5). Abstr. 3047.
101. Turner TB, Buchsbaum DJ, Straughn JM, et al. Ovarian cancer and the immune system—the role of targeted therapies. *Gynecol Oncol* 2016;142(2):349-56.
102. Baert T, Vergote I, Coosemans A. Ovarian cancer and the immune system. *Gynecol Oncol Rep* 2017;19:57-8.
103. Disis ML, Taylor MH, Kelly K, et al. Efficacy and safety of avelumab for patients with recurrent or refractory ovarian cancer: phase 1b results from the JAVELIN Solid Tumor Trial. *JAMA Oncol* 2019;5(3):393-401.
104. Matulonis UA, Shapira-Frommer R, Santin AD, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol* 2019;30(7):1080-7.
105. Coosemans A, Vankerckhoven A, Baert T, et al. Combining conventional therapy with immunotherapy: a risky business? *Eur J Cancer* 2019;113:41-4.
106. Ledermann JA, Colombo N, Oza AM, et al. Avelumab in combination with and/or following chemotherapy vs chemotherapy alone in patients with previously untreated epithelial ovarian cancer: results from the phase 3 JAVELIN ovarian 100 trial. *Soc Gynecol Oncol* 2020: LBA25.
107. Zamarin D, Burger RA, Sill MW, et al. Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG oncology study. *J Clin Oncol* 2020;38(16):1814-23.
108. Wang Z, Sun K, Xiao Y, et al. Niraparib activates interferon signaling and potentiates anti-PD-1 antibody efficacy in tumor models. *Sci Rep* 2019;9(1):1853.
109. Brown JS, Sundar R, Lopez J. Combining DNA damaging therapeutics with immunotherapy: more haste, less speed. *Br J Cancer* 2018;118(3):312-24.
110. Ding L, Kim HJ, Wang Q, et al. PARP inhibition elicits STING-dependent antitumor immunity in Brca1-deficient ovarian cancer. *Cell Rep* 2018;25(11):2972-2980.e5.
111. Konstantinopoulos PA, Waggoner S, Vidal GA, et al. Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma. *JAMA Oncol* 2019;5(8):1141-9.
112. Drew Y, Kaufman B, Banerjee S, et al. Phase II study of olaparib + durvalumab (MEDIOLA): updated results in germline BRCA-mutated platinum-sensitive relapsed (PSR) ovarian cancer (OC). *Ann Oncol* 2019;30(suppl 5). Abstr. 1190PD.
113. González-Martín A, Colombo N, Heitz F, et al. ENGOT-Ov41/GEICO-69-O/ANITA trial: a phase III randomized, double-blinded trial of platinum-based chemotherapy (CT) with or without atezolizumab (ATZ) followed by niraparib maintenance with or without ATZ in patients with recurrent ovarian, tubal or perit. *J Clin Oncol* 2019;37(suppl 15). Abstr. TPS5599.
114. Martin JD, Fukumura D, Duda DG, et al. Reengineering the tumor microenvironment heterogeneity to alleviate hypoxia and overcome cancer heterogneity. *Cold Spring Harb Perspect Biol* 2016;6(12): a027094.
115. Chen DS, Hurwitz H. Combinations of bevacizumab with cancer immunotherapy. *Cancer J* 2018;24(4):193-204.
116. Lee J, Cimino-Mathews A, Peer CJ, et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women's cancers: a dose-esc. *J Clin Oncol* 2017;35(19): 2193-202.
117. Marmé F, Pautier P, Van Nieuwenhuysen E, et al. AGO-OVAR 2.29 (ENGOT-ov34): atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy in recurrent ovarian cancer (ROC). *J Clin Oncol* 2019;37(suppl 15). Abstr. TPS5601.
118. Kurtz J-E, Marth C, Oaknin A, et al. ATALANTE (ENGOT-ov29): a randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab. *J Clin Oncol* 2018;36(suppl 15). Abstr. TPS5607.
119. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer* 2018;119(9):1075-85.
120. Stockler MR, Hilpert F, Friedlander M, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. *J Clin Oncol* 2014;32(13):1309-16.