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Emerging treatment strategies in recurrent platinum-sensitive ovarian cancer: Focus on trabectedin

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ABSTRACT

Ovarian cancer (OC) is the leading cause of death from gynecological malignancies. In spite of high response rates to the standard front-line treatment for advanced disease with cytoreductive surgical debulking, followed by platinum/taxane-based chemotherapy, most patients eventually relapse developing drug-resistant disease. Owing to the molecular heterogeneity, genetic instability and mutagenicity of OC, increases in survival might be achieved by translating recent insights at the morpho-molecular levels to individual therapeutic strategies. Several emerging treatments have been shown to be active in platinum-sensitive (PS) recurrent OC (ROC), but an optimal strategy still has not been established. Based on the recent results, it is likely that the introduction of novel non-platinum based chemotherapies and molecular targeted therapies will have a major impact on the management of ROC. Some current strategies are focused on the extension of platinum-free interval (PFI) in patients with PS, particularly in those with partially PS disease. Apparently, the PFI extension by an effective non-platinum intervention, such as trabectedin plus pegylated liposomal doxorubicin (PLD), may reduce cumulative platinum-induced toxicities leading to longer survival after the reintroduction of subsequent platinum. The introduction of novel therapies, such as the antiangiogenic monoclonal antibody bevacizumab, opens a new field of targeted therapies in this indication. In this review, we aim to outline the therapeutic potential of new emerging approaches, particularly the role of non-platinum therapy with trabectedin in combination with PLD in patients with PS ROC.

Introduction

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies, with 50% of all cases occurring in women over 65 years of age, and the fifth most frequent cause of death by cancer in women with approximately 125,000 deaths annually worldwide [1]. Approximately 75% of women with ovarian cancer (OC) present advanced stage of disease associated with poor outcome. Over the past two decades the standard first-line treatment paradigm for advanced epithelial OC has been maximal cyto-reductive surgical debulking followed by platinum-based chemotherapy with the prognosis of therapy closely related to the disease stage at diagnosis and the extent residual disease following surgery [2]. Yet, while the median survival has been extended to more than 4 years, overall survival (OS) has not changed over the last 30 years.

In spite of high response rates to primary therapy (70–80%) [2–5] only approximately 15% of women achieve cure [5]. The remaining patients have drug-resistant disease or ultimately develop incurable recurrent disease with an overall 5-year survival rate lower than 50% [5,6]. Therefore, identification of new drugs and emerging treatment strategies for recurrent OC (ROC) represents a clinical challenge.

Treatment of recurrent platinum-sensitive ovarian cancer

ROC is not a curable disease; thus, the principal objective of salvage treatments is to prolong survival in patients with platinum-

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sensitive (PS) disease, improve quality of life (QoL), particularly in patients with platinum-resistant (PR) disease, and alleviate cancer-related symptoms. Re-treatment with platinum-based chemotherapy is common practice in recurrent disease after relapse; however, its effectiveness is highly correlated with platinum-free interval (PFI) [7]. In 2010, the 4th Ovarian Cancer Consensus Conference of the Gynecological Cancer InterGroup meeting held in Vancouver established the definition of PFI as the interval from the last date of platinum dose until documented progressive disease [8]. The initial bipolar empiric categorization of patients with ROC on PR and PS patients, with a PFI of <6 months and ⩾6 months, respectively, did not sufficiently reflect the disease prognosis since PFI is a continuous variable rather than one dichotomized at 6 months [9–11]. Therefore, it was agreed that the PFI should be used to subcategorize patients into the following subgroups: platinum-refractory patients, with disease progression while receiving last line of platinum-based therapy or within four weeks of last platinum dose, PR (PFI <6 months), partially PS (PFI of 6–12 months) and fully PS (PFI >12 months) [8,12]. In addition to PFI, duration of response to previous therapy, disease stage at time of diagnosis, as well as patient's tolerability, performance status and preference of a particular treatment are the main criteria for selecting therapies for ROC and also the most important prognostic factors.

Patients with a fully PS relapse typically receive a salvage second-line therapy based on rechallenge with platinum-containing regimens with response rate ranging from 30% to 75% [13]. These patients generally undergo a series of salvage treatments, with each subsequent treatment associated with progressively shorter PFI during disease remission. Markman et al. have reported that the length of a prior response to platinum-based therapy seems to be highly predictive of the upper limit of the response duration of a subsequent platinum treatment, assuming the same or similar drug/s are used for subsequent treatment [14]. Nevertheless, patients treated with a regimen consisting of platinum plus an agent not administered during their prior treatment may have secondary responses of longer duration than the previous one [14].

Among PS patients, those patients with partially PS (PPS) disease after primary platinum-based therapy, obtain substantially lower response rate to platinum re-challenge (27–33%) [15]. Women with PPS disease represent ~20–40% [16–20] of all patients, for whom controversies and uncertainties still exist regarding the best post-progression treatment. It has been proposed that PFI extension through intercalation of a non-platinum therapy prior to subsequent platinum rechallenge may increase the likelihood of response of a later platinum re-treatment [21–27].

The treatment of ROC continues to evolve as new drugs with diverse mechanisms of action are introduced into the oncologist's armamentarium. The aim of this review is to identify the position of emerging treatment strategies in the treatment algorithm for ROC that fits with the potential of those drugs. Moreover, since there are women with ROC who could benefit from a delay in platinum re-treatment, who are not good candidates for platinum-based therapy or this agent is not the best treatment option for them, the selection of suitable patients who may largely benefit from non-platinum based therapy was also reviewed.

Genomic heterogeneity of ovarian cancer: toward patient-tailored therapy

OC is a broad term for different heterogeneous cancers that are derived from different, often non-ovarian tissues, resulting in the different OC histotypes (i.e., mucinous, endometrioid, clear cell and serous, high grade and low grade serous). Therefore, OC is a misleading term for a series of genomically and etiologically heterogenic diseases that often do not arise from ovarian tissue and simply share an anatomical location [6,28]. Given the complexity of OC, the current single approach to treatment of OC as a single disease has to move toward patient-tailored therapy based on molecular and histotype-driven treatments. Recently, the Cancer Genome Atlas Research Network (TCGA) has described the genomic and epigenomic abnormalities of 489 patients with advanced-stage, high-grade serous OC, with the aim to identify molecular abnormalities that influence pathophysiology, outcomes, and constitute therapeutic targets [29]. The integrated analysis performed by TCGA has definitely demonstrated the low mutation rate of high grade OC except for TP53 and BRCA1/2 genes which were affected in 96% and 22% of OC, respectively, but without a clear correlation between the expression and methylation patterns of those genes and clinical outcomes. In contrast, extensive focal and broad DNA losses and gains were seen through the genome of OC with DNA deletions and amplification in many genes. Yet again, the patterns of methylation and gene expression across the samples did not strongly correlate with clinical outcomes. Therefore, it has been proposed that serous OC might not be targeted with drugs, challenging if our understandings of the plethora of genomic data will translate into clinically useful approaches (Birrer MJ, Genomic Analysis. Keynote Lecture, 9th Advanced Ovarian Cancer Symposium, Valencia, Spain. March 2013; unpublished results). Regarding the association of BRCA1/2 mutation with survival and sensitivity to platinum-based chemotherapy, this and other genomic analyses of OC have confirmed improved OS and overall response rate (ORR) in patients with germline BRCA mutations as compared non-carriers [29–32]. Indeed, deficiencies of the homologous recombination pathway in DNA repair can impair DNA cross-links repair introduced by platinum-based chemotherapy and result in higher survival rates due to an improved response in BRCA-deficient patients. Furthermore, these homologous recombination defects sensitize tumors for targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors [33]. Therefore, in a variety of malignancies including OC, enhanced expression of the DNA repair proteins, such as BRCA1/2 and excision repair cross complementation group 1 (ERCC1), have correlated with resistance to both platinum and PARP inhibitors [31,34–38]. Additionally, preclinical models and *ex-vivo* results also demonstrated that the tumor microenvironment has become an important focus of attention as an adjunct to molecular therapeutics and chemotherapy in ovarian cancer. Therefore, drugs ability to modulate the tumor microenvironment might be largely responsible for the antitumor effects by decreasing the factors potentially relevant for tumor growth, progression, and metastatic spread [39].

Treatment endpoints in recurrent ovarian cancer

The optimal treatment for women with epithelial ROC is rapidly evolving in parallel with our understanding of the pathways and networks controlling cell signaling, proliferation, and cell death. However, decision-making strategies for optimal treatment of ROC are complex as many active cytotoxic drugs and an increasing number of biological agents are becoming available [40]. This represents challenges in defining the endpoints, optimal timing and sequencing of most drugs or treatment regimen, such as monotherapy or in combination, particularly in the development of new clinical trials. The most controversial issue of the ROC treatment surrounds the lack of an OS advantage observed with the number of investigational regimens and compounds, often being associated with increased toxicity and no improvements in patients QoL [17,18,20,41,42]. Therefore, the selection of clinically-meaningful scientific objectives and standardized study endpoints is critical [7]. In contrast with first-line therapy, where an excellent correlation has been observed between progression-free

survival (PFS) and OS, for recurrent disease, this correlation is less clear. There was consensus that phase III trials for patients with ROC should be large enough to detect clinically meaningful differences in both PFS and OS [7,8]. Though OS is an important endpoint, PFS is considered as the preferred primary endpoint for phase III trials, since after disease progression patients often crossover to receive other study drug or different regimens. The extent of clinically meaningful improvement in PFS as an early surrogate for OS has been questioned since dissociations between PFS and OS outcomes are commonly observed after trial completion, suggesting that for many treatment settings an improvement in PFS does not result in an improved OS [43,44]. The hazard of death is likely to change after disease progression; thus, for clinical trials with a PFS benefit, lack of statistical significance in OS does not necessarily imply lack of improvement in survival, especially if post-progression survival is long ($\geqslant$12 months) [43,44]. It is important to acknowledge that the impact of subsequent post-trial treatments on a particular study's outcome is likely to be unknown. Therefore, it is still controversial what evidence of benefit and how much of improvement would be clinically meaningful for approval of a new treatment or regimen in ROC [44–46]. Thus far, no data have supported that routine treatment of women who only have asymptomatic cancer antigen (CA)-125 increase may improve OS in the recurrent setting [7]. Future research should also consider some new endpoints such as clinical or symptom benefit, which includes health-related QoL, patient-reported outcomes regarding symptoms, and time without symptoms or toxicity.

Chemotherapy use in platinum-sensitive disease

To date, just a few phase III randomized trials have demonstrated a statistically significant improvement in OS with an investigation drug/regimen in women with ROC. In some of those studies no detailed or separate data for the PPS subgroup is reported, essentially because until relatively recently the patients with PPS recurrence were not recognized as a separate group. In 2003, the International Collaborative Ovarian Neoplasm 4 (ICON-4) trial that evaluated 802 women with PS OC was the first to show that a combination of platinum and paclitaxel was more effective than single-agent platinum compounds [16]. This study reported that a combination of carboplatin and paclitaxel provided superior PFS by a median of 3 months (12.0 *vs.* 9.0 months; $p = 0.0004$) and OS by 5 months (29.0 *vs.* 24.0 months; $p = 0.02$) when compared with treatment with carboplatin alone. In the study by Pfisterer et al., a combination of gemcitabine and carboplatin in patients with PS ROC was associated with a median improvement in PFS of 2.8 months (8.6 *vs.* 5.8 months; $p = 0.0031$), but with greater toxicity and no improvement in OS (18.0 *vs.* 17.3 months) and QoL when compared with carboplatin alone [17]. The large phase III CALYPSO trial, carried out in 976 patients with PS ROC, reported that a combination of carboplatin and pegylated liposomal doxorubicin (PLD) was associated with a 1.9- and 0.6-months improvement in PFS in patients with PS (11.3 *vs.* 9.4; $p = 0.005$) and PPS (9.4 *vs.* 8.8 months; $p = 0.004$) disease, respectively, compared with the standard therapy of carboplatin and paclitaxel [18,42,47]. Although improvement in median PFS was modest, the combination of PLD and carboplatin was non-inferior and a less toxic alternative to the standard regimen of carboplatin and paclitaxel. However, no statistically significant difference was observed between arms in OS (30.7 *vs.* 33.0 months; $p = 0.94$), and in the PPS subset, the final survival data are not presented.

Current treatment options for patients with ROC are frequently guided by safety considerations and convenience. Regardless of the regimen, rechallenge with platinum-based chemotherapy is commonly limited by the risk of cumulative long-term toxicities. Overall, clinically significant sequelae such as chemotherapy-induced hypersensitivity reactions (~20% of OC patients) [48], neurotoxicity including residual neuropathy (~23%) [49] and severe cumulative myelosuppression [50] are commonly caused by platinum-based chemotherapy. This issue should be carefully taken into account before considering platinum re-treatment as the platinum-associated cumulative and irreversible toxicities may jeopardize its long-term interventions on subsequent relapses [50]. Consideration of platinum-induced cumulative toxicity takes on greater significance as the number of salvage regimens increase, as it could be given only to those patients of whom the toxicities would be acceptable, underscoring the need for an efficacious non-platinum regimen associated with an acceptable toxicity profile.

Two randomized phase III studies have represented an important step in the transition from platinum doublets to non-platinum drugs, changing the paradigm in the treatment algorithm of patients with PS and PR ROC. Ten Bokkel Huinink et al. evaluated topotecan and paclitaxel in relapsed disease and suggested that topotecan had efficacy at least equivalent to that of paclitaxel, resulting in a higher response rate and median durations of response in both PS and PR patients and significantly longer time to progression (23 *vs.* 14 weeks; $p = 0.002$) [41]. In the study by Gordon et al. the efficacy and safety of PLD and topotecan were tested in 474 patients with ROC, 220 of whom had PS disease. They reported that treatment with PLD significantly prolonged survival compared with topotecan (median OS: 14.4 *vs.* 13.7 months; $p = 0.05$) [51,52]. Noteworthy, data analyzed in PS patients demonstrated a far more pronounced statistically significant benefit of PLD for PFS (median PFS: 6.7 *vs.* 5.4 months; $p = 0.037$) and OS (median OS: 24.8 *vs.* 16.1 months; $p = 0.017$), with longer OS by a median of 8.7 months. Further analysis demonstrated that the survival benefit was more prominent in the PPS subgroup ($n = 122$; hazard ratio [HR] = 1.58; $p = 0.021$) than in patients with a PFI of >12 months ($n = 97$; HR = 1.15; p = 0.057) [15]. PLD and topotecan have separately confirmed to be feasible intervening non-platinum agents for extending the PFI, resulting in acceptable toxicities and response rates during platinum re-treatment in the setting of PS disease [53,54]. These results lead to the regulatory approval of PLD and topotecan by the Food and Drug Administration (FDA) as single agents in the treatment of both PS and PR ROC. Moreover, based on these studies the UK National Institute for Clinical Excellence (NICE) recommends PLD as a single agent (or a platinum-taxane combination) for the treatment of PPS ROC.

Trabectedin

Trabectedin (Yondelis®) is a tetrahydroisoquinoline alkaloid, originally isolated from the marine tunicate *Ecteinascidia turbinata* and currently produced synthetically. The trabectedin phase I program documented responses in patients with ovarian carcinoma [55]. Subsequently, three phase II studies reported promising activity of trabectedin as a single-agent, especially in patients with PS disease, with a manageable and non-cumulative toxicity profile [56–58]. Trabectedin was the first anticancer marine-derived drug to be approved in the European Union in 2007 for the treatment of patients with soft tissue sarcoma after failure of anthracyclines and ifosfamide, or for those patients who are unsuitable to receive these agents. Based on the results of a large phase III study OVA-301, in 2009 the European Commission granted a marketing authorization for the non-platinum combination of trabectedin with PLD for the treatment of patients with PS ROC.

Trabectedin has a unique mechanism of action based on interaction with the minor groove of the DNA double helix, which triggers a cascade of events that interfere with several transcription factors, DNA binding proteins and DNA repair pathways, resulting in G2-M cell cycle arrest and ultimately apoptosis (Fig. 1A) [59].

Trabectedin cytotoxicity is determined by the functional nucleotide excision repair (NER) and a deficient homologous recombination repair (HRR) machinery [60]. Consequently, trabectedin shows decreased activity (from 2- to 8-fold) in NER-deficient cell lines, while cells deficient in HRR are approximately 100 times more sensitive to the drug, indicating that trabectedin causes DNA double-strand breaks [60–64].

Emerging evidence indicates that trabectedin has dual effects, since in addition to induce direct growth inhibition, cell death and differentiation of malignant cells it affects the tumor microenvironment by reducing the production of key inflammatory mediators [39,59,65]. At therapeutic concentrations trabectedin has selective anti-inflammatory and immunomodulatory properties on monocytes and tumor associated macrophages (TAMs) and inhibits the production of factors potentially relevant for tumor growth, progression, and the inhibition of tumor-promoted angiogenesis (Fig. 1B). In patients treated with trabectedin, a strong dose-dependent and selective reduction of the production of protumoral inflammatory cytokines by monocytes, macrophages, TAMs and freshly isolated ovarian tumor cells was observed [39,65–67]. The markedly reduced production of those proinflammatory mediators, in particular CCL2, interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), may underlie the strong association between chronic inflammation and cancer progression. Thus, trabectedin also targets inflammatory cells of the tumor microenvironment reducing an angiogenic and pro-inflammatory effect mediated by cytokines and leading to a delayed response with a prolonged stabilization (i.e. tumor dormancy). Overall, trabectedin is probably more than a cytotoxic drug, given that the antitumor activity of trabectedin arises from a different combination of more than one mechanism, providing a consolidated therapeutic approach as a multitarget drug with far more multifaceted activity than initially formulated. Through these mechanisms trabectedin is likely to impact relevant biological pathways involved in cancer, which may influence disease outcome.

The phase III OVA-301 study

The results from the randomized phase III OVA-301 trial, which compared PLD (Doxil®/Caelyx®) with a combination of trabectedin plus PLD, is gaining attention in the treatment of ROC, especially in the subset of PPS relapse [19]. The pivotal OVA-301 trial ($n = 672$), included both patients with PR (PFI <6 months) and PS disease (PFI $\geqslant$6 months). The OVA-301 study differed from previous trials in the same setting (e.g. CALYPSO and OCEAN trials) as it included only the patients who were not expected to benefit from or who were ineligible for or who were not willing to receive re-treatment with platinum-based chemotherapy. The eligible patients had received one prior platinum-based chemotherapy and experienced either persistence, recurrence or disease progression, and were required to have measurable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST) and an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant$2. The major exclusion criteria were refractory disease and isolated rise in CA-125 without documented radiological evidence of disease progression. The primary endpoint was PFS by blinded independent radiology review. The results of OVA-301 in the whole population showed that trabectedin plus PLD obtains significant benefits over PLD in terms of PFS (median PFS: 7.3 months *vs.* 5.8 months; $p = 0.019$), ORR (27.6% *vs.* 18.8%; $p = 0.008$) and a positive trend in OS over PLD alone. The toxicity related to trabectedin plus PLD was acceptable. Benefits appeared more evident in the PS subset PFS (median PFS: 9.2 months *vs.* 7.5 months; $p = 0.0170$) and even more pronounced in patients with PPS disease with a PFI of 6–12 months PFS (median PFS: 7.4 months *vs.* 5.5 months; $p = 0.0015$) [19,27,68,69]. It was the first positive randomized phase III trial in ROC that included a non-platinum and non-taxane combination. The final analyses of patient-reported outcomes have shown little or no decrement in patient-reported functional status and symptoms in patients who received trabectedin plus PLD as compared with PLD alone [70–72].

The study was designed to be sufficiently powered to consider both PFS and OS results. Recently, the protocol-defined analysis of final survival data in the overall population showed a 14% decrease in the risk of death for patients randomized to receive the combination of trabectedin plus PLD (HR = 0.86; $p = 0.0835$; unstratified log-rank test) [73]. The median OS was 22.2 months for trabectedin plus PLD, and 18.9 months for the PLD arm (Table 1). Despite study stratification that resulted in well-balanced arms in terms of the two platinum-sensitivity categories, i.e., PR and PS, an unanticipated but significant overall imbalance in the PFI between the two arms favoring the PLD arm was observed (mean PFI: trabectedin plus PLD = 10.6 months *vs.* PLD = 13.3 months; $p = 0.009$) [73]. Because the log rank analysis stratified by the dichotomous categorization into platinum resistant (i.e., PFI <6 months) and platinum sensitive (i.e., PFI $\geqslant$6 months) could not account for the imbalance in PFI between both arms, a multivariate analysis based on the Cox regression was performed following the statistical analysis plan of the study to provide an appropriate and reliable estimate for treatment effect. The Cox proportional hazard model considered several prespecified prognostic factors as covariates, including PFI as a continuous variable. This analysis in the overall population resulted in a relevant and significant improvement in OS with a 18% decrease in the risk of death in patients treated with trabectedin plus PLD compared with PLD (HR = 0.82; 22.6 *vs.* 19.4 months; $p = 0.0285$) (Fig. 2A)]. According to the log-rank Kaplan–Meier test in patients with PS disease the treatment with trabectedin plus PLD resulted in a 17% decrease in the risk of death as compared with PLD alone (HR = 0.83; $p = 0.1056$) (Table 1) [74]. However, the results of the Cox regression showed that trabectedin plus PLD resulted in a significant 22% decrease in the risk of death compared with the PLD arm (median OS: 28.4 *vs.* 24.1; HR = 0.78;

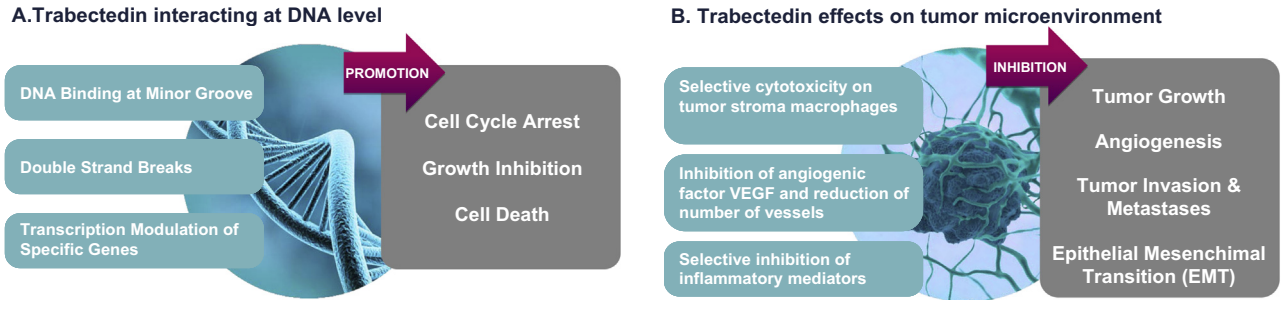

Fig. 1. Mechanism of action of trabectedin.

Table 1
Final analysis of overall survival (OVA-301 study).

Final overall survival analysis Cut-off date: 12 November 2010	Median OS (months) (95%CI)		Kaplan–Meier unstratified log-rank analysis	
	Trabectedin plus PLD	PLD	Hazard ratio[a] Median (95% CI)	*p* Value
All population (*N* = 672; 522 events/150 censored)	22.2 (19.3–25.0)	18.9 (17.1–21.5)	0.86 (0.72–1.02)	0.0835
Resistant (PFI <6 months) (*N* = 242; 206 events/36 censored)	14.2 (11.1–16.8)	12.4 (10.6–14.8)	0.92 (0.70–1.21)	0.5452
Sensitive[b] (PFI ⩾6 months) (*N* = 430; 316 events/114 censored)	27.0 (24.1–31.4)	24.1 (20.9–25.9)	0.83 (0.67–1.04)	0.1056
PPS[c] (PFI 6–12 months) (*N* = 214; 177 events/37 censored)	22.4 (20.3–27.7)	16.4 (14.1–19.4)	0.64 (0.47–0.86)	0.0027
Very sensitive[c] (PFI ⩾12 months) (*N* = 217; 140 events/77 censored)	36.5 (26.3–42.3)	31.7 (25.9–39.7)	0.83 (0.59–1.16)	0.2750

[a] Over PLD alone.
[b] Sensitive population: PFI ⩾6 months as determined at randomization by the study investigators.
[c] PFI categories are based on PFI data calculated from case report form. CI, confidence interval; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PPS, partially platinum-sensitive; OS, overall survival.

p = 0.0319) (Fig. 2B). In patients with PPS disease, the PFI imbalance was less pronounced between treatment arms and not statistically significant. Therefore, both the results of a log-rank Kaplan–Meier test (HR = 0.64; 22.4 months *vs.* 16.4 months; *p* = 0.0027), with an outstanding 36% decrease in the risk of death (Table 1), and the results of a Cox regression analysis, with a 35% decrease in the risk of death (HR = 0.65; 21.0 *vs.* 17.2 months;*p* = 0.0056) (Fig. 2C), showed a significant improvement in OS in patients treated with trabectedin plus PLD over PLD alone. Finally, the median OS in very sensitive patients with a PFI >12 months with trabectedin plus PLD (36.5 months) was in the range of that obtained with platinum combinations (Table 1). There results in combination with a manageable safety profile of trabectedin plus PLD makes this combination a valuable alternative for PS patients with ROC.

Subsequent treatments following OVA-301

Additional benefits with trabectedin plus PLD in 214 patients (32%) with PPS disease were observed upon administration of subsequent therapies. Previously the results of a *post hoc* exploratory analysis provided a detailed assessment of subsequent therapies and reported no major differences in post-progression therapies between arms [27,69]. Subsequent platinum-based treatment as any further line of chemotherapy was given to 121 patients with PPS disease. In this patients subset, trabectedin plus PLD induced a 6-months longer median OS with a significant 36% decrease in the risk of death compared with PLD alone (22.4 *vs.* 16.4 months; HR = 0.64; *p* = 0.0027), most likely as a result of an extension of the PFI (9.8 *vs.* 7.9 months; HR = 0.64; *p* = 0.0167) coupled with longer survival after the start of subsequent platinum-based chemotherapy (13.3 *vs.* 9.8 months; HR = 0.63; *p* = 0.0357) [69].

Differences were especially larger in patients who received platinum as first subsequent third-line therapy after discontinuation of OVA-301 (*n* = 94). Trabectedin plus PLD treatment resulted in an exceptional reduction of 42% in the risk of death compared with PLD (HR = 0.58; *p* = 0.0153) (Fig. 3). Median OS for trabectedin plus PLD was 27.7 months and 18.7 months for PLD alone with a notable improvement of 9-month in median OS. In this subpopulation, patients treated with trabectedin plus PLD received subsequent platinum later than those treated with PLD alone, with a median prolongation of the PFI of 4 months (11.5 *vs.* 7.5 months; HR = 0.61; *p* = 0.0203) [27]. The delay in subsequent platinum treatment was largely translated into an OS extension from first platinum by a median of 8.9 months (18.8 *vs.* 9.9 months; HR = 0.64; *p* = 0.0513) with respect to PLD alone, suggesting that extension in the PFI may improve the response to subsequent reintroduction of platinum [27].

OVA-301: current evidences

Overall, in OVA-301 benefits in PFS and OS were demonstrated in the PS subset of patients, and especially in patients with PPS disease, confirming the importance of the PFI as a key predictor of outcome in ROC: a longer PFI predicts a longer OS [73–75]. OC behaves as a chronic disease benefiting from multiple lines of platinum-based therapy. However, a maximum of three lines of subsequent relapse treatment seems to be beneficial for patients with ROC [76]. In contrast, the treatment with trabectedin as a single-agent evidenced no differences in response rate according to prior chemotherapy, given that patients with >1 line of previous chemotherapy (range: 2–4 lines) had response rates comparable

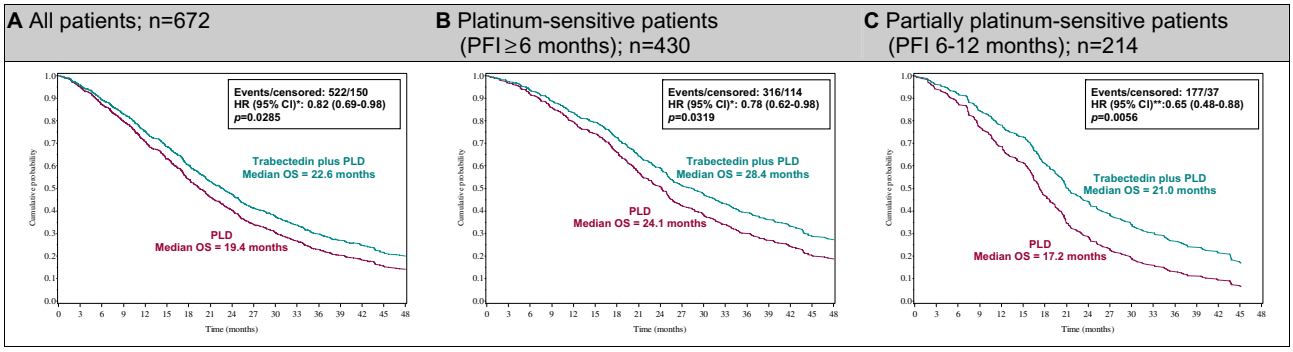

Fig. 2. Final analysis of overall survival in all randomized patients and patient subgroups according to platinum-sensitivity according to the Cox regression proportional hazard model. HR and *p* value for treatment comparison (over PLD alone) based on Cox regression analysis after adjustment for key prognostic factors: ECOG performance status, PFI as a continuous variable, race, baseline CA-125, age, baseline liver/lungs involvement and prior taxane. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; OS, overall survival.

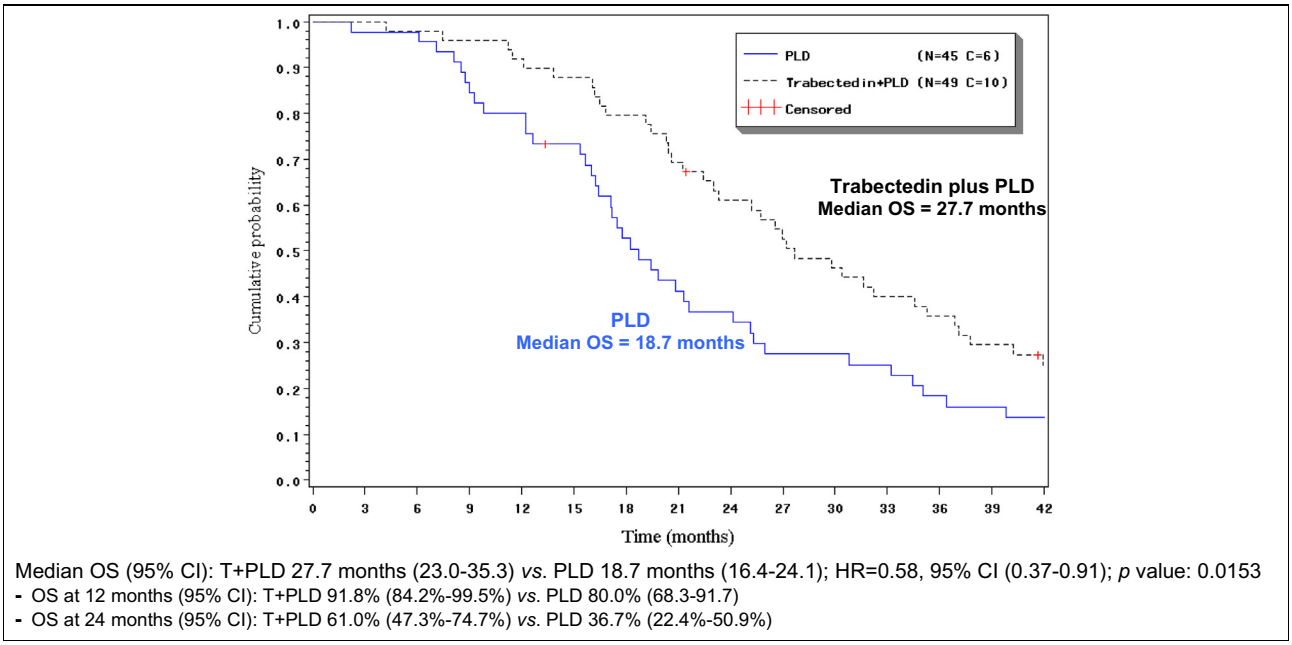

Fig. 3. Final analysis of overall survival in patients with partially platinum-sensitive disease (PFI of 6–12 months) from OVA-301 receiving platinum as first subsequent third-line chemotherapy (unstratified log-rank test according to Kaplan–Meier analysis). C, number of censored patients; CI, confidence interval; PFI, platinum-free interval; HR, hazard ratio; PLD, pegylated liposomal doxorubicin; OS, overall survival; T, trabectedin.

to those observed in patients pretreated with only one prior line of chemotherapy [58,77]. Moreover, in PS patients who did not achieve a complete response after first-line platinum-based treatment before OVA-301 an enhanced benefit with trabectedin plus PLD in terms of PFS and response rate was also observed [78]. Rechallenge with platinum and taxanes drugs has been limited by the risk of residual toxicity or hypersensitivity reactions [48–50]. Therefore, the PFI extension by trabectedin plus PLD may represent an additional benefit for patients with PS disease by giving them some extra time to recover from toxic effects of their prior platinum-based therapy, and thus allowing future treatment options. The data from OVA-301 additionally support that PFI can be prolonged by an effective non-platinum intervention between platinum regimens resulting both in survival advantage when re-introducing the subsequent platinum and recovery from previous platinum-induced toxic effects [23–25].

In contrast to results observed with many other drugs/regimens, the enhanced benefit in PFS seen in all patient populations treated with trabectedin plus PLD has translated into survival benefit, suggesting the role of PFS as an early surrogate for OS in ROC. Particularly exciting results were those observed in patients with PPS disease, where a 35% risk reduction of disease progression or death was translated into a 36% reduction in the risk of death and a 6.0-month improvement in median OS favoring the trabectedin plus PLD combination [68,73]. The exploratory analyses have previously underlined that the superiority of trabectedin plus PLD over single-agent PLD cannot be explained by the differences in the extent or nature of subsequent therapies, which were similar between the two treatment arms [27]. Instead, the longer survival with subsequent platinum is more likely to be due to a longer PFI leading to a significant delay of the rechallenge with subsequent platinum therapy and ultimately to longer survival.

Targeted therapies in the treatment of ROC

Although different "targeted therapeutic approaches" are currently being explored, with the important exception of antiangiogenic agents, such as bevacizumab, cediranib and pazopanib, and PARP inhibitor, olaparib, limited biological and clinical activity have been demonstrated in treating ROC.

Bevacizumab

Bevacizumab (Avastin®), a humanized recombinant monoclonal VEGF-A-neutralizing antibody, has been the most studied antiangiogenic agent. The results of phase II feasibility studies of bevacizumab as monotherapy or in combination supported the addition of bevacizumab to platinum-based regimens and provided the rationale for designing phase III trials for testing bevacizumab both as first- and second-line treatment of patients with OC [79–82]. To date, two randomized phase III trials have evaluated the addition of bevacizumab to front-line chemotherapy and as maintenance therapy for OC (GOG-0218 and ICON-7/AGO-OVAR-11) [83,84]. While both trials met their primary endpoints (superior PFS as compared to standard chemotherapy), the advantage appeared to be derived primarily from the maintenance therapy, with convergence of the PFS curves shortly after bevacizumab treatment discontinuation, with no significant difference in OS and QoL scores across treatment groups. Only among the women at high-risk for progression subgroup (FIGO stage IV) enrolled in the ICON-7/AGO-OVAR-11 study, statistical significance in favor of the bevacizumab arm was reached for median OS (bevacizumab arm: 36.6 months *vs.* standard-therapy arm: 28.8 months; HR = 0.64; $p = 0.002$) [86]. Nevertheless, surprisingly no such OS differences were observed in GOG 0218, in which only high-risk patients were enrolled. The hypothesis, whether the benefit in term of PFS after the addition of bevacizumab to front-line chemotherapy may further modulates the clinical outcome after the start of subsequent therapies, still remains speculative. Recently, a cost-effectiveness analysis of bevacizumab based on the results of GOG-0218 indicated that the addition of bevacizumab as maintenance therapy to standard chemotherapy is not cost-effective [85].

Bevacizumab in the treatment of ROC

In ROC, two phase III studies with bevacizumab (15 mg/kg; given every 3 weeks) concomitantly administered with chemotherapy and pursued in maintenance until progression have been launched in sensitive relapse: GOG-213 and OCEANS [20,86]. The non-registration GOG-213 trial exploring the addition of bevacizumab to carboplatin plus paclitaxel chemotherapy in patients with PS disease is still in progress.

In the phase III registration-quality OCEANS protocol 484 women with PS ROC (PFI $\geqslant$6 months after front-line platinum-based therapy) were randomly assigned to receive 6–10 cycles of carboplatin (AUC 4) plus gemcitabine (1 g/m^2) chemotherapy with either bevacizumab (15 mg/kg) or placebo followed by bevacizumab or placebo, respectively, as maintenance therapy until disease progression [20]. All patients were required to have measurable disease according to RECIST v.1.0 and an ECOG performance status of 0 or 1. The patients were stratified by time from last platinum treatment to recurrence (PFI 6–12 *vs.* >12 months) and secondary cytoreductive surgery for ROC (yes *vs.* no). The bevacizumab arm significantly increased PFS compared with chemotherapy alone with the median PFS of 12.4 months for bevacizumab arm *vs.* 8.4 months for chemotherapy group (HR = 0.484; $p < 0.0001$). Noteworthy, median PFS in the chemotherapy arm (8.4 months) was almost identical to median PFS (8.6 months) observed in the carboplatin-gemcitabine arm in AGO OVAR trial [17]. As for ICON-7, the addition of bevacizumab significantly increased the ORR by 20% (78.5% *vs.* 57.4%; $p < 0.0001$) and the median duration of response (10.4 *vs.* 7.4 months; HR = 0.534; 95% CI: 0.408–0.698). Although the OS data from OCEANS are not sufficiently mature to draw clear conclusions, the results of the third interim analysis, based on 286 deaths (59% of patients), showed an unfavorable trend in survival in the bevacizumab arm compared with results obtained with the chemotherapy control group [87]. With a median follow-up of 42 months, median OS was 33.7 months in the chemotherapy arm and 33.4 months in the bevacizumab arm (HR: 0.96; CI 95%: 0.760–1.214; log-rank $p = 0.736$). The third interim analysis also evidenced that 89.3% (control arm) and 85.5% (bevacizumab arm) of patients received subsequent anticancer therapy, including bevacizumab as a single agent in 39.4% (control arm) and 22.2% (bevacizumab arm) of patients. Unfortunately, in OCEANS no data regarding patients' QoL were collected. Grade $\geqslant$3 hypertension (0.4% *vs.* 17.4%) and proteinuria (0.9% *vs.* 8.5%), and non-central nervous system bleeding of any grade (0.9% *vs.* 5.7%) occurred more frequently in the bevacizumab arm, but no more than expected according to data from other studies. Based on the recently reported results of OCEANS study, in September 2012 the European Commission granted marketing authorization for bevacizumab in combination with carboplatin and gemcitabine as a treatment for women with first recurrence of PS OC who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Although there is evidence that bevacizumab prolongs disease control in PS ROC, the improvement in PFS in any of phase III trials with bevacizumab did not translate into an OS advantage. Crossover, post-progression survival and development of resistance are probably reasons to explain the lack of OS benefit as well as the limited power of the sample. Several groups have evaluated the dynamics of tumor re-growth and survival, particularly regarding the appearance of a more aggressive and invasive disease following discontinuation of bevacizumab treatment. They demonstrated that radiographic regression of different tumor types can be sustained under continuous bevacizumab application; however, after withdrawal of bevacizumab a rapid tumor re-growth and "rebound" phenomenon with accelerated clinical decline was observed [88–90]. Additional results, expected to arrive in 2013, and future trials will provide important answers regarding the exact place of bevacizumab therapy in the recurrent setting, particularly regarding its optimal dose, treatment duration, and regimen. Furthermore, the optimal patients' selection to be treated with bevacizumab based on predictive biomarkers as well as factors including the drug's cost and potentially serious side effects with bevacizumab require serious consideration.

Other biological drugs

Other promising agents in various phases of investigation include multitargeted antiangiogenic tyrosine kinase inhibitors, such as cediranib and pazopanib, and the oral PARP inhibitor, olaparib.

Cediranib (AZD2171) is a potent oral tyrosine kinase inhibitor of all three VEGF receptors. Currently ICON-6, the three-stage, double-blind, placebo-controlled study, is the most advanced randomized phase III study that has evaluated cediranib plus chemotherapy in women with PS recurrence in first relapse [91]. Patients were randomized (2:3:3) to receive either six cycles of standard chemotherapy (paclitaxel 175 mg/m^2 and carboplatin AUC 5–6) concurrent with placebo; standard chemotherapy with cediranib-initiation (20 mg/day) treatment followed by placebo, or the same cediranib-initiation treatment followed by cediranib maintenance for 18 months or until disease progression. The results of the blinded first-stage analysis performed in 60 patients confirmed the safety of carboplatin and paclitaxel in combination with cediranib and recommended to expand ICON-6 to next stage [91].

Pazopanib (GW786034) is an oral antiangiogenic tyrosine kinase inhibitor associated with the VEGF, PDGF and KIT receptors. The results from the AGO-OVAR-16 study recently announced that pazopanib as maintenance therapy in women with advanced OC who have not progressed after front-line chemotherapy significantly extends time without recurrence (median PFS: 17.9 *vs.* 12.3 months; HR: 0.77; 95% CI: 0.64–0.91; $p = 0.0021$). The OS data (20% maturity) from this study are not mature [92].

Olaparib (AZD2281) is a novel and the most studied orally active PARP inhibitor, which has shown antitumor activity in patients with ROC with BRCA germline mutations, a phenotype referred to as "BRCAness", and in lower extent in BRCAness-negative patients with a dysfunction of the homologous recombination DNA repair mechanism [93,94]. In a randomized phase II proof-of-concept trial the encouraging rate of responses have been observed in both PS (38%) and PR (30%) BRCA mutation carriers treated with olaparib 400 mg twice daily [95]. The results of phase II randomized, placebo-controlled study with olaparib, given as maintenance in PS ROC, showed that olaparib was associated with a significantly longer PFS (8.4 months) than in the placebo group (4.8 months), irrespective of BRCA status [96]. However, the interim analysis of this study evidenced that longer PFS did not translate into an improvement in OS. Recently, the results of a preplanned subgroup analysis from this study in 136 (51%) patients with a proved BRCA mutation (BRCAm) status confirmed that olaparib maintenance therapy prolonged PFS compared with placebo (median PFS: 11.2 *vs.* 4.3 months; HR: 0.19; 95% CI: 0.11–0.31; $p < 0.0001$). A second interim analysis of OS (58% maturity) fail again to demonstrate a statistical significant difference between the two arms (median OS: 29.8 *vs.* 27.8 months; HR: 0.88; 95% CI: 0.64–1.21) [97]. Finally, the comparative assessment of olaparib (400 and 200 mg twice daily) and PLD (50 mg/m^2) in patients with BRCA 1 or BRCA2 mutations and ROC in a phase II randomized study resulted in no statistically significant differences in PFS and ORR between both treatments [98].

Concluding remarks

A number of questions remain regarding the optimal treatment of PS ROC. Although platinum-based drugs are regularly used in patients with PS disease, uncertainties abound in the treatment of women with PPS relapse and women unsuited for platinum rechallenge. Considering the histological heterogeneity, distinct genetic abnormalities and treatment responses of ovarian cancers, the individualized patient selection is essential for the successful targeted treatment of specific groups of patients. Moreover, an effective consolidation or maintenance treatment with new drugs with acceptable non-cumulative toxicity to reduce the risk of recurrence after a clinical response and improve survival probably will have a great impact in ROC.

The responses seen with bevacizumab combined with chemotherapy in ROC evoke potential for future therapeutic strategies. Yet, several strategic questions need to be addressed before bevacizumab and other angiogenesis inhibitors become a part of standard therapy: the optimal use of these agents in first- or second-line regimens; should it be given as single-agent or in combination, in which dose/schedule and for how long, throughout treatment or as a maintenance therapy only; how to avoid/overcome the acquired resistant to those agents, and, finally, which are the best biomarkers for patient selection to predict tolerability and response? Regarding the latter question, for bevacizumab a range of predictive biomarkers have been proposed but none have proved to be robust [99]. The development of predictive biomarkers is an urgent and crucial step for selecting patients likely to derive benefit from these therapies, which will ultimately help us to move from an organ-specific approach towards a target and personalized treatment strategy of OC. In summary, based on the absence of data indicating bevacizumab improves OS when delivered with platinum-based chemotherapy in the setting of PS recurrent disease, a far stronger clinical and cost-effectiveness argument has to be made to support the administration of this novel drug.

The OVA-301 study demonstrated the superiority of trabectedin plus PLD over PLD alone in the overall population of patients, with striking differences in outcomes in patients with PS disease and the subset of patients with PFI 6–12 months who achieved a significant improvement of 6-months in median OS. Although definitive comparisons of trabectedin plus PLD to cytotoxic combinations are still lacking, the clinical activity of this combination has documented comparable activity to platinum combinations among PS patients. The results from OVA-301 have called into question the paradigm of platinum plus/minus taxane as mainstay treatment for patients with PS ROC, since those results support the hypothesis that the "artificial" prolongation of the PFI by intercalation with an effective non-platinum regimen improves the outcome with subsequent platinum treatment ultimately leading to longer survival [19,27,68,69]. In addition, extending the PFI would decrease cumulative long-term toxicities caused by platinum-based chemotherapy that increase with the number of treatments and can preclude their use on subsequent relapses, and provide some extra time for patients to recover from platinum-induced toxic effects allowing future treatment options. Therefore, the combination of trabectedin plus PLD now may represent an acceptable non-platinum/non-taxane alternative in treating patients with PS relapse, particularly for patients with PPS disease who can benefit from a delay in platinum re-treatment, patients with PS relapse suffering from platinum-induced toxicities or hypersensitivity or for patients who had received more than one platinum-based chemotherapy. Nevertheless, in the absence of randomized trials it is impossible to demonstrate the superiority of trabectedin plus PLD over standard platinum-based chemotherapy (±bevacizumab) in the setting of PS recurrent disease. Therefore, further randomized trials are needed to confirm the hypothesis of the "PFI extension strategy" with this combination. Notably, the ongoing academic phase III INOVATYON (refers to: INternational OVArian cancer patients Treated with YONdelis) trial is aimed to demonstrate that the combination of trabectedin plus PLD prolongs OS over carboplatin plus PLD (the regimen evaluated in the CALYPSO trial) in patients with PPS ROC.

Although we are currently experiencing a shift toward molecular targeted anticancer treatments, chemotherapies either alone or in combination with other diverse biological treatment will continue to be a mainstay of treatment for patients with ROC. Treatment of patients with ROC will possibly benefit most from the careful alignment of new cytotoxic chemotherapies and regiments, new trial designs and the addition of therapies targeting critical pathways responsible for tumor progression.

Conflict of interest

Dr. Andrés Poveda was compensated as consultant and received honoraria from PharmaMar, Roche, Janssen and Merck. Dr. Nicoleta Colombo received consulting fees and honoraria from PharmaMar, Roche, Amgen, GlaxoSmithKline and Merck. Dr. Isabelle Ray-Coquard received honoraria from Roche, PharmaMar and Amgen. All remaining authors have no conflicts of interests to declare.

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