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Trabectedin plus pegylated liposomal doxorubicin in the treatment of patients with partially platinum-sensitive ovarian cancer: current evidence and future perspectives

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The effectiveness of platinum re-treatment in relapsed ovarian cancer depends on relapse-free/treatment-free intervals. Platinum agents can be effectively readministered to platinum-sensitive patients (relapsing >12 months after platinum), but efficacy is lower in partially platinum-sensitive (PPS) disease (relapsing 6–12 months after platinum). There is no clear standard treatment challenging PPS patients. Survival data in this subset with chemotherapy combinations such as pegylated liposomal doxorubicin (PLD) plus carboplatin or gemcitabine plus PLD are available from phase II trials ranging from 16 to 21 months. Recent results from OVA-301 phase III randomized trial evaluating trabectedin plus PLD showed the longest median overall survival ever reported in PPS patients (23 months). Subsequent chemotherapy (including platinum-based regimens) was administered later and survival in patients receiving third-line platinum was longer in patients treated with trabectedin plus PLD compared with those treated with PLD alone. These results suggest that prolonging platinum-free interval (PFI) with an effective non-platinum regimen improves outcome with subsequent third-line platinum treatment. An ongoing phase III trial (INOVATYON) aims to demonstrate if the results observed with trabectedin plus PLD in PPS patients are due to PFI extension, and if PFI extension with non-platinum combination prolongs response to subsequent platinum and survival in this population.
Key words: ovarian cancer, platinum-free interval, recurrence, trabectedin

introduction

Platinum-containing regimens are currently the mainstay of initial treatment of ovarian cancer and platinum-sensitive relapsed disease. In relapsed ovarian cancer, the effectiveness of platinum re-treatment depends on the relapse-free/treatment-free intervals (Table 1). Platinum agents can be effectively readministered to patients with disease relapsing >12 months after completion of a platinum regimen (i.e. patients with platinum-sensitive disease), with response rates ranging from 30% to 60%, but ovarian cancer that relapses 6–12 months after platinum treatment has lower response to platinum rechallenge (25%–30%) [3–6] and is considered partially platinum sensitive (PPS).

These categories are based on empirical observations made ~20 years ago. Ovarian cancer relapsing in the 6–12 months time frame has also been defined as 'intermediate platinum sensitive' or simply as 'chemotherapy sensitive' because new non-platinum agents and combinations are being identified as active in this setting [7, 8]. The use of non-platinum agents in relapsed ovarian cancer to prolong platinum-free interval (PFI) has gained interest recently, as the likelihood of response to platinum reinduction at next relapse may increase [9]. The acquired resistance to platinum is an unstable phenotype over time [10]. Thus, *in vitro* studies [11] have shown platinum resistance as an unstable, inducible, and perhaps reversible phenomenon. *In vitro* [11] and clinical data [9, 12, 13] suggest that PFI extension in patients with relapsed PPS ovarian cancer through intercalation of a non-platinum therapy before platinum-based regimens at further progression could be beneficial from a clinical point of view. It has been hypothesized that platinum (or chemotherapy) sensitivity could be restored using a PFI prolongation strategy [6, 7]. Furthermore, most patients with recurrent ovarian cancer will die due to tumor progression; therefore, the definition of the best therapeutic index for these patients including not only tumor and symptom control but also the toxicity profile is one of the most challenging topics in gynecologic oncology. Rechallenge with platinum-based combinations is not only associated with risk

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of development of severe allergy [1] but also polyneuropathy and alopecia [14].

Based on these considerations, both from the clinical and the scientific perspective, the use of platinum as the first treatment option in patients with PPS relapse may be questioned. Limited information exists in this regard as most clinical trials with newer agents have been either nonrandomized phase II studies or phase III randomized studies conducted in a heterogeneous population of women, sometimes even including patients with platinum-resistant disease. Unfortunately, phase III studies of combination regimens compared with platinum monotherapy and others comparing various non-platinum single agents usually have not reported separate data for the PPS subset. Therefore, interpretation of the activity of the newer agents in the PPS population is often difficult, and this may affect decision making in clinical practice [5].

results of clinical trials evaluating combination regimens and including patients with PPS ovarian cancer

Outcomes for the PPS population in phase II trials evaluating combined chemotherapy regimens are shown in Table 2. The combination regimen most extensively evaluated in the PPS subset of patients has been pegylated liposomal doxorubicin (PLD) plus carboplatin [15–18]. While the combination was active in patients with platinum-sensitive ovarian cancer, antitumor efficacy was consistently lower in PPS patients. Thus, Ferrero *et al.* [15] found lower median progression-free survival (PFS) and median overall survival (OS) for the PPS population (7.9 and 21 months) compared with the platinum-sensitive population (11.4 and 36 months; $P = 0.001$ and $P = 0.006$, respectively). Rapoport *et al.* [17] also found lower median

Table 1. Relapsed ovarian cancer: population characteristics according to initial response to platinum-containing chemotherapy and treatment outcomes and options

	Initial response to platinum-containing chemotherapy	Platinum-free interval (months)	Response rate to second-line platinum (%)	Treatment options
Platinum refractory	No	NA	NA	PLD, topotecan, paclitaxel
Platinum resistant	Yes	<6	10	PLD, topotecan, paclitaxel
Partially platinum sensitive	Yes	6–12	25%–30%	PLD, topotecan, paclitaxel + platinum, gemcitabine + platinum, PLD + platinum, trabectedin + PLD
Platinum sensitive	Yes	>12	30%–60%	Paclitaxel + platinum, gemcitabine + platinum, PLD + platinum, trabectedin + PLD

Based on Gadducci *et al.* [1] and Monk [2].
NA, not applicable; PLD, pegylated liposomal doxorubicin.

Table 2. Phase II clinical trials evaluating combination regimens for second-line therapy of partially platinum-sensitive relapsed ovarian cancer

Treatment	PLD + carboplatin								Gemcitabine + PLD	
Reference	Ferrero *et al.* [15]		Power *et al.* [16]		Rapoport *et al.* [17]		Weber *et al.* [18]		Mirza *et al.* [19]	
n	104		58		40		81		79	
Prior taxane (%)	100		100		85		NA		NA	
% PPS patients	41		100		48		40		33	
Primary end point	ORR		ORR		ORR		ORR		PFS	
	All patients	PPS patients	All patients	PPS patients	All patients	PPS patients	All patients[a]	PPS patients	All patients[a]	PPS patients
PFS, median (months)	9.5	7.9	10.0[b]	10.0[b]	15.1[b]	9.7[b]	13.6	8.8	6.4	7.4
OS, median (months)	32	21	19	19	35	21	39	NA	13	16

Another phase II study evaluated the gemcitabine plus vinorelbine combination [20], but no PFS or OS data were provided. This study showed a lower ORR in PFS patients (23% versus 62% in patients with platinum-free interval >12 months).
[a]No patients with platinum-free interval >12 months.
[b]Time to progression.
NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PPS, partially platinum sensitive.

time to progression (TTP; 15.1 versus 9.7 months) and median OS (35 versus 21 months) in the PPS subset of patients. Similar results were found by Weber *et al.* [18], with a lower PFS in the PPS subset compared with patients with PFI >12 months (8.8 versus 13.6 months). Power *et al.* [16] evaluated PLD plus carboplatin exclusively in PPS patients and found similar figures: median TTP was 10 months and median OS 19 months.

A phase II trial by Mirza *et al.* [19] evaluated gemcitabine plus PLD. Median PFS was 7.4 months and median OS 16.2 months in the PPS subset. This study did not include a subset with PFI >12 months.

Few data from phase III randomized trials are available on the PPS population (Table 3). In an exploratory analysis of the gynecologic cancer intergroup trial (AGO-OVAR 2.5 trial), Pfisterer *et al.* [21, 26] found that PFS was longer in the PPS population treated with gemcitabine/carboplatin compared with carboplatin alone (7.9 versus 5.2 months), but the benefit in this subgroup of patients was inferior than that obtained in patients with platinum-sensitive disease (9.3 versus 6.7 months).

Pujade-Lauraine *et al.* [22] reported a median PFS of 9.4 months in the subset of patients with PPS disease treated with PLD plus carboplatin (CALYPSO trial); this PFS value was shorter than the 11.3 months found in the overall population, although the risk reduction of disease progression (PD) or death was higher (27% versus 18% in the overall population). Survival data were still immature in the latest report issued for this recent phase III clinical trial [22], although the available information of this regimen from phase II studies showed OS figures of 19–21 months [15–17].

Based on these and other published studies, the National Comprehensive Cancer Network (NCCN) (http://www.nccn.org) and the UK National Institute for Clinical Excellence (NICE) (http://www.nice.org.uk) classify patients into three categories according to their time to relapse: 0–6 months, 6–12 months, and >12 months. NCCN recommends using similar treatment regimens (platinum based) for patients whose disease recurs after >6 months (platinum-sensitive patients); PLD is also recommended as an acceptable recurrence modality. A platinum–taxane combination or single-agent PLD is recommended for the treatment of patients with PPS ovarian cancer by the NICE.

The NOGGO-AGO intergroup study HECTOR (hycamtin and carboplatin versus established regimens for the treatment of ovarian cancer relapse) for platinum-sensitive patients, which is assessing topotecan plus carboplatin in a 3-day schedule in comparison with the current standard, has been closed [27]. In this study, choice of the control arm was between paclitaxel plus carboplatin or gemcitabine plus carboplatin or carboplatin plus PLD, based on late toxicity (e.g. polyneuropathy) and patients' preferences (e.g. alopecia). The planned interim safety report of this trial conducted on the first 200 patients showed that most patients preferred a therapy without alopecia and polyneuropathy [27]. This underlines the need to incorporate the patient's expectations and preference into daily clinical practice. Previously, a phase III trial had shown that non-platinum topotecan combinations do not provide a survival advantage over topotecan monotherapy in patients with relapsed ovarian cancer [28] and, therefore, in this trial topotecan monotherapy offered the best therapeutic index.

role of trabectedin plus PLD in PPS ovarian cancer

Trabectedin (Yondelis®) is a marine-derived antineoplastic agent, initially isolated from the tunicate *Ecteinascidia turbinata*

Table 3. Phase III clinical trials evaluating combination regimens for second-line therapy of partially platinum-sensitive relapsed ovarian cancer

Treatment	Gemcitabine/carboplatin versus carboplatin (AGO-OVAR 2.5)		PLD/carboplatin versus carboplatin/ paclitaxel (CALYPSO)		PLD/trabectedin versus PLD (OVA-301)	
Reference	Pfisterer *et al.* [21]		Pujade-Lauraine *et al.* [22] and Vasey *et al.* [23]		Monk *et al.* [24] and Poveda *et al.* [25]	
n[a]	178		466		337[b]	
Prior taxane (%)	71		100		80	
% PPS patients	40		35		37[c]	
Primary end point	PFS		PFS		PFS	
	All patients	PPS patients	All patients	PPS patients	All patients	PPS patients
PFS, median (months)	8.6	7.9	11.3	9.4	7.3	7.4
Risk reduction of PD or death (%)	28	NA	18	27	21	35
OS, median (months)	18	NA	NA	NA	22	23
Risk reduction of death (%)	4	NA	NA	NA	15	41

[a]Number of patients in the combination arm. Results shown here are only those obtained with the combined treatment.

[b]123 patients with PPS disease (PFI 6–12 months).

[c]OVA-301 included 35% of patients with platinum-resistant disease (PFI <6 months).

NA, not available; OS, overall survival; PD, disease progression; PFI, platinum-free interval; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PPS, partially platinum sensitive.

and currently produced synthetically, that was first approved in 2007 as a single agent in the European Union for the treatment of patients with soft tissue sarcoma (STS) after failure of standard-of-care chemotherapy, namely anthracyclines or ifosfamide (or who were unsuited to receive them), and in combination with PLD received approval in 2009 for the treatment of patients with relapsed, platinum-sensitive ovarian cancer. Early phase II trials showed encouraging activity as a single agent in relapsed ovarian cancer [29–31] and a randomized phase III trial (OVA-301) confirmed that trabectedin plus PLD (Doxil®/Caelyx®) improved PFS over PLD alone [24]. A further analysis in patients with PPS disease [25] showed that, according to an independent radiology review, benefit in terms of PFS was improved with respect to PLD alone, with a 35% risk reduction of PD or death compared with 21% for the overall relapsed population [24]. The risk reduction of PD or death reached 46% when data were evaluated according to an independent oncology review, which involved both clinical and imaging data in the assessment of PD.

The survival obtained with trabectedin plus PLD in this subset of patients was remarkable [25]. Although no survival data are available from other phase III trials, the median OS value of 23 months (i.e. a 41% reduction in the risk of death compared with PLD alone) compares favorably with the 16–21 months range of survival found in phase II trials with other combination chemotherapies, such as PLD plus carboplatin or gemcitabine plus PLD (Table 2), and is the longest ever reported in the PPS setting (Figure 1).

Additional benefits with the trabectedin plus PLD combination included that subsequent administration of platinum at relapse was delayed by 1.9 months with respect to PLD alone (median of 9.8 versus 7.9 months) and, importantly, that patients treated with trabectedin plus PLD had a greater survival advantage (median OS prolongation of 3.5 months) counted from the beginning of subsequent platinum-based therapy: 13.3 versus 9.8 months [25]. This survival benefit was obtained when patients received further therapy, which included not only platinum but also other agents as the first subsequent treatment. Of note, the survival advantage was enhanced, with a median OS prolongation of 8.7 months (18.6 versus 9.9 months), in patients who only received platinum as first subsequent therapy [32]. The fact that survival with subsequent therapy was prolonged when only platinum was administered seems to indicate that the greater survival benefit could be related to an extension of platinum-free interval in these patients. Another hypothesis is that trabectedin could induce molecular alterations or changes in the tumor cells that could increase sensitivity to a subsequent platinum-based re-treatment.

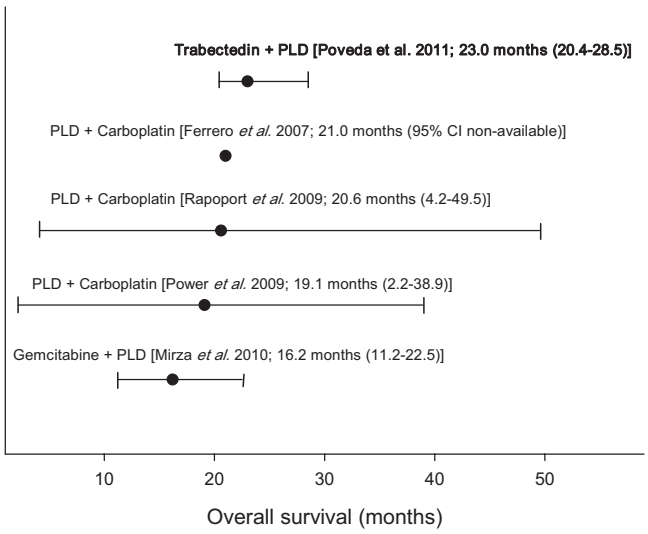

Figure 1. Summary of overall survival data found with combined chemotherapies in clinical trials conducted on patients with partially platinum sensitive ovarian cancer. Only data from trabectedin + PLD was obtained in a phase III randomized trial. CI, confidence interval; PLD, pegylated liposomal doxorubicin. Data shown are median (95% CI).

Furthermore, clinically significant toxic effects such as hypersensitivity reactions or residual neurotoxicity are common and may hamper readministration of platinum-based chemotherapy, therefore underscoring the need for an efficacious non-platinum regimen [8, 33], particularly in the PPS population [3, 26]. The safety profile found for trabectedin plus PLD in patients with PPS disease was similar to that found in the overall ovarian cancer population [25]. Unlike established platinum- and taxane-based regimens, trabectedin/PLD was associated with a greatly diminished incidence of neuropathy and alopecia, as well as with a lack of end-organ cumulative toxic effects. Hence, use of this non-platinum-based combination may allow the treatment of patients who still have not recovered from previous platinum toxicity.

perspectives

PFI extension with a non-platinum combination

The PFI, defined by clinical and radiological Gynecologic Oncology Group criteria, is the most critical predictor of sensitivity to platinum rechallenge. Extending the PFI with intervening non-platinum therapy has been proposed to increase the efficacy of a subsequent re-treatment with platinum in patients with platinum-sensitive recurrent ovarian cancer [9, 12, 13]. This hypothesis is based on data from small series, and although not validated prospectively, this strategy has in fact entered daily clinical practice in many countries [33]. The 'PFI extension strategy' provides an alternate sequence plan, with a greater recognition of the chronic nature of relapsed ovarian cancer [34].

Three large-size randomized phase III trials (CALYPSO, OVA-301, and MITO-8/ENGOT-ov-1) have been completed or are ongoing, and are evaluating different treatments in the PPS setting: carboplatin plus PLD versus carboplatin plus paclitaxel (CALYPSO), PLD versus trabectedin plus PLD (OVA-301), and PLD versus carboplatin plus paclitaxel (MITO-8/ENGOT-ov-1) [22, 23, 24, 25, 35]. The CALYPSO trial showed superiority of carboplatin plus PLD over standard carboplatin plus paclitaxel in the overall platinum-sensitive population [22] and in the PPS subpopulation [23], and survival data were still immature in the last report available for this trial [22]. The OVA-301 trial showed superiority of trabectedin plus PLD over PLD alone in the overall population of patients with relapsed ovarian cancer, with a large, statistically significant survival advantage in the PPS subset [24, 25]. In fact, subsequent chemotherapy

(including platinum-based regimens) was given later, and survival in patients who received third-line treatment with platinum was longer in those treated with trabectedin plus PLD compared with those treated with PLD alone. The MITO-8/ENGOT-ov-1 trial is still ongoing, with 88 of the required 253 patients recruited up to February 2011. The MITO-8/ENGOT-ov-1 trial has a design that allows receiving the opposite treatment after PD, and this would allow checking if the PFI prolongation strategy with a non-platinum monotherapy (PLD) can restore sensitivity to platinum in patients with ovarian cancer.

Trabectedin plus PLD is a new and effective therapy available in Europe and several other countries for patients with relapsed platinum-sensitive ovarian cancer. The benefits with this combination appeared to be particularly enhanced in the PPS subpopulation and therefore should be considered as a valuable treatment option in this challenging subset of patients. As no data are available on the comparison of trabectedin plus PLD with a platinum-based regimen, and based on data from OVA-301 and CALYPSO, a large, randomized phase III trial (INOVATYON) led by the Mario Negri Gynecologic Oncology group is currently about to start. This trial will compare PLD plus carboplatin (therapy evaluated in CALYPSO) with the non-platinum trabectedin plus PLD combination (therapy evaluated in OVA-301) in PPS patients. The primary objective is to demonstrate that trabectedin plus PLD prolongs OS over carboplatin plus PLD, but the study design allows rechallenge with the platinum-based therapy in the non-platinum arm after PD. This would allow the prospective evaluation of the effect of PFI extension with a non-platinum combination on response to subsequent platinum and survival in patients with relapsed PPS ovarian cancer. If this effect on third-line therapy is confirmed, such a novel treatment strategy would fulfill the requirement for a much needed alternative treatment in this patient population.

activity of trabectedin and effect of DNA repair mechanisms

Trabectedin interacts with the minor groove of the DNA and alkylates the N2 amino group of a guanine, with preference for alkylation at RC-rich sequences, and bends DNA toward the major groove [36]. Trabectedin cytotoxicity is determined by the synergistic action of two DNA repair mechanisms: an efficient nucleotide excision repair (NER) and a deficient homologous recombination repair (HRR) machinery. Consequently, trabectedin shows decreased activity (from two- to eightfold) in NER-deficient cell lines, while cells deficient in HRR are extremely sensitive to the drug, indicating that trabectedin causes DNA double-strand breaks. Preliminary data obtained in human STS [37, 38] and metastatic breast cancer [39] suggest that there is a higher probability of response to trabectedin when the tumor expresses high levels of XPG, a key component of NER, and low levels of BRCA1, a key component of HRR. Combination of trabectedin with novel targeted therapies [e.g. poly (ADP-ribose) polymerase (PARP) inhibitors] may be of interest in recurrent ovarian cancer, as some preclinical studies have shown that loss of PARP may confer a higher sensitivity to trabectedin [40] and recent studies have shown interesting results for PARP inhibitors in patients with ovarian cancer and BRCA1 or BRAC2 mutations [41]. Furthermore, as inflammation appears to be relevant for ovarian cancer growth, the ability of trabectedin to modulate inflammatory factors [42, 43] might also have a therapeutic role [44].

treatment of elderly population

Ovarian cancer is largely a disease of elderly postmenopausal women, with 43% of cases diagnosed in patients >65 years. Unfortunately, although ovarian cancer is so common in older women, these patients are often underrepresented in clinical studies. There is a small number of studies focusing on the elderly population, but these studies have suggested that these patients are less likely to be treated with standard therapy [45, 46] and to tolerate treatments [47]. A pooled analysis of data from five phase II trials assessed the effects of age on the efficacy and safety of trabectedin in 350 patients with STS [48]. No major differences were found in the safety profile of a subset of patients aged ≥70 years, with no evidence of cumulative or end-organ toxic effects. Thus, trabectedin appeared to be better tolerated than agents commonly used in STS therapy such as doxorubicin or ifosfamide, which are more likely to cause dose-limiting cardiac and renal toxicity in older patients, and may also offer a therapeutic alternative to elderly patients with ovarian cancer. In support of this, a low cardiac risk profile has been found in an extensive safety analysis of trabectedin in phase I, II, and III clinical trials conducted to date, either as a single agent or in combination with anthracyclines (doxorubicin and PLD), as well as in the postmarketing experience after its approval in Europe [49]. Additionally, a subset analysis on patients >65 years in the OVA-301 study showed no significant differences by age in the safety profile of trabectedin plus PLD, except for more fatigue in the older subset compared with younger patients (14% versus 7%, respectively). Moreover, no significant differences were observed in supportive treatment measures by age-group. Finally, and what is more relevant, older age was not associated with a detriment in PFS in patients receiving the combination of trabectedin and PLD when compared with younger patients [50].

conclusions

In summary, the evidence obtained to date supports trabectedin as an important addition to the existing patient care in the clinical setting of relapsed ovarian cancer, an incurable disease that remains the first cause of gynecologic cancer-related mortality. Survival data obtained in patients with PPS disease with the combination of trabectedin and PLD are encouraging as they are the longest published to date. Therefore, this non-platinum-based combination should be considered a new valuable treatment option for patients with advanced ovarian cancer after failure of platinum-based chemotherapy, particularly for those with a PFI between 6 and 12 months.

disclosure

JS has given lectures for PharmaMar-sponsored symposiums and has participated in advisory boards, VA is a PharmaMar employee, and AG-M has given lectures for PharmaMar-sponsored symposiums and has participated in advisory boards.

references

1. Gadducci A, Tana R, Teti G et al. Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer. Int J Gynecol Cancer 2008; 18: 615–620.
2. Monk BJ. Recurrent ovarian cancer Exploring options for patients who relapse 6 to 12 months after chemotherapy. Oncology Biotech & News (HCP Beta Live) 2010. Priority report: 1–6.
3. Kaye S. Management of partially platinum-sensitive relapsed ovarian cancer. Eur J Cancer Suppl 2008; 6: 16–21.
4. 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: 650–653.
5. Ledermann JA, Raja F. Management strategies for partially platinum-sensitive ovarian cancer. Am J Cancer 2006; 5: 341–354.
6. Pujade-Lauraine E, Vergote I, Pignata S, Kristensen G. Optimizing management of recurrent epithelial ovarian cancer with non–platinum-based chemotherapy. Clin Ovarian Cancer 2008; 1: 139–140.
7. Colombo N, Gore M. Treatment of recurrent ovarian cancer relapsing 6-12 months post platinum-based chemotherapy. Crit Rev Oncol Hematol 2007; 64: 129–138.
8. Monk BJ, Coleman RL. Changing the paradigm in the treatment of platinum-sensitive recurrent ovarian cancer: from platinum doublets to nonplatinum doublets and adding antiangiogenesis compounds. Int J Gynecol Cancer 2009; 19 (Suppl 2): S63–S67.
9. Bookman MA. Extending the platinum-free interval in recurrent ovarian cancer: the role of topotecan in second-line chemotherapy. Oncologist 1999; 4: 87–94.
10. McClelland SE, Burrell RA, Swanton C. Chromosomal instability: a composite phenotype that influences sensitivity to chemotherapy. Cell Cycle 2009; 8: 3262–3266.
11. Horowitz NS, Hua J, Gibb RK et al. The role of topotecan for extending the platinum-free interval in recurrent ovarian cancer: an in vitro model. Gynecol Oncol 2004; 94: 67–73.
12. See HT, Freedman RS, Kudelka AP et al. Retrospective review: re-treatment of patients with ovarian cancer with carboplatin after platinum resistance. Int J Gynecol Cancer 2005; 15: 209–216.
13. Kavanagh J, Tresukosol D, Edwards C et al. Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer. J Clin Oncol 1995; 13: 1584–1588.
14. Pignata S, De Placido S, Biamonte R et al. Residual neurotoxicity in ovarian cancer patients in clinical remission after first-line chemotherapy with carboplatin and paclitaxel: the Multicenter Italian Trial in Ovarian cancer (MITO-4) retrospective study. BMC Cancer 2006; 6: 5.
15. Ferrero JM, Weber B, Geay JF 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: 263–268.
16. Power P, Stuart G, Oza A et al. Efficacy of pegylated liposomal doxorubicin (PLD) plus carboplatin in ovarian cancer patients who recur within six to twelve months: a phase II study. Gynecol Oncol 2009; 114: 410–414.
17. Rapoport BL, Vorobiof DA, Slabber C et al. Phase II study of pegylated liposomal doxorubicin and carboplatin in patients with platinum-sensitive and partially platinum-sensitive metastatic ovarian cancer. Int J Gynecol Cancer 2009; 19: 1137–1141.
18. Weber B, Lortholary A, Mayer F et al. Pegylated liposomal doxorubicin and carboplatin in late-relapsing ovarian cancer: a GINECO group phase II trial. Anticancer Res 2009; 29: 4195–4200.
19. Mirza MR, Lund B, Lindegaard JC et al. A phase II study of combination chemotherapy in early relapsed epithelial ovarian cancer using gemcitabine and pegylated liposomal doxorubicin. Gynecol Oncol 2010; 119: 26–31.
20. Ferrero A, Logrippo V, Spanu PG et al. Gemcitabine and vinorelbine combination in platinum-sensitive recurrent ovarian cancer. Int J Gynecol Cancer 2009; 19: 1529–1534.
21. 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: 4699–4707.
22. 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: 3323–3329.
23. Vasey P, Largillier R, Gropp M et al. 18LBA. A GCIG randomized phase III study of carboplatin (C) & pegylated liposomal doxorubicin (PLD) (C-D) vs carboplatin (C) & paclitaxel (P) (C-P): CALYPSO results in partially platinum-sensitive ovarian cancer (OC) patients. Eur J Cancer Suppl 2009; 7: 11.
24. Monk BJ, Herzog TJ, Kaye SB et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010; 28: 3107–3114.
25. 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: 39–48.
26. Pfisterer J, Ledermann JA. Management of platinum-sensitive recurrent ovarian cancer. Semin Oncol 2006; 33: S12–S16.
27. Meier W, Lichtenegger W, Marth C et al. Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or carboplatin plus pegylated doxorubicin (PLDC): a planed 200-pt interim safety analysis of the NOGGO-AGO-Germany-AGO Austria and GEICO-GCIG Intergroup Study (HECTOR). J Clin Oncol 2010; 28: (Abstr 5071).
28. 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: 3176–3182.
29. Sessa C, De Braud F, Perotti A et al. Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails. J Clin Oncol 2005; 23: 1867–1874.
30. Krasner CN, McMeekin DS, Chan S et al. A phase II study of trabectedin single agent in patients with recurrent ovarian cancer previously treated with platinum-based regimens. Br J Cancer 2007; 97: 1618–1624.
31. Del Campo JM, Roszak A, Bidzinski M et al. Phase II randomized study of trabectedin given as two different every 3 weeks dose schedules (1.5 mg/m^2 24 h or 1.3 mg/m^2 3 h) to patients with relapsed, platinum-sensitive, advanced ovarian cancer. Ann Oncol 2009; 20: 1794–1802.
32. Kaye SB, Colombo N, Monk BJ et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer delays third-line chemotherapy and prolongs the platinum-free interval. Ann Oncol 2011; 22: 49–58.
33. Pignata S, Ferrandina G, Scarfone G et al. Extending the platinum-free interval with a non-platinum therapy in platinum-sensitive recurrent ovarian cancer. Results from the SOCRATES Retrospective Study. Oncology 2006; 71: 320–326.
34. Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. Oncologist 2002; 7 (Suppl 5): 20–28.
35. Pignata S, Pujade-Lauraine E, du Bois A, Pisano C. Pegylated liposomal doxorubicin combined with carboplatin: a rational treatment choice for advanced ovarian cancer. Crit Rev Oncol Hematol 2010; 73: 23–30.
36. D'Incalci M, Galmarini CM. A review of trabectedin (ET-743): a unique mechanism of action. Mol Cancer Ther 2010; 9: 2157–2163.
37. Schoffski P, Taron M, Jimeno J et al. Predictive impact of DNA repair functionality on clinical outcome of advanced sarcoma patients treated with trabectedin. Eur J Cancer 2011; 47: 1006–1012.
38. Schöffski P, Casali PG, Taron M et al. DNA repair functionality modulates the clinical outcome of patients with advanced sarcoma treated with trabectedin (ET-743). Proc Am Soc Clin Oncol 2006;; 2006. ASCO Annual Meeting Proceedings Part I, vol. 24, no. 18S (June 20 Supplement): 9522.
39. Tedesco KL, Blum JL, Goncalves A et al. A phase II trial of trabectedin (T) in patients (pts) with HER2-positive and BRCA1/2 germ-line mutated metastatic breast cancer (MBC). J Clin Oncol 2010; 28: 123. (Abstr 1038).
40. Mandola MV, Kolb EA, Scotto KW. Poly (ADP-ribose) polymerase (PARP) contributes to cellular sensitivity to trabectedin (Yondelis™). Proc Am Assoc Cancer Res 2005; 46: 972. (Abstr 4122).
41. Audeh MW, Carmichael J, Penson RT et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010; 376: 245–251.

42. Allavena P, Signorelli M, Chieppa M et al. Anti-inflammatory properties of the novel antitumor agent yondelis (trabectedin): inhibition of macrophage differentiation and cytokine production. Cancer Res 2005; 65: 2964–2971.
43. Germano G, Frapolli R, Simone M et al. Antitumor and anti-inflammatory effects of trabectedin on human myxoid liposarcoma cells. Cancer Res 2010; 70: 2235–2244.
44. Sessa C, D'Incalci M. Trabectedin in ovarian cancer: could we expect more? Ann Oncol 2011; 22: 7–8.
45. Uyar D, Frasure HE, Markman M, von Gruenigen VE. Treatment patterns by decade of life in elderly women (> or =70 years of age) with ovarian cancer. Gynecol Oncol 2005; 98: 403–408.
46. Markman M, Lewis JL Jr, Saigo P et al. Epithelial ovarian cancer in the elderly. The Memorial Sloan-Kettering Cancer Center experience. Cancer 1993; 71: 634–637.
47. Moore KN, Reid MS, Fong DN et al. Ovarian cancer in the octogenarian: does the paradigm of aggressive cytoreductive surgery and chemotherapy still apply? Gynecol Oncol 2008; 110: 133–139.
48. Demetri G, Blay JY, Yovine A et al. Efficacy and safety of trabectedin in soft tissue sarcoma (STS) are independent of patient age. Ann Oncol 2009; 7: 590–591; (Abstr O9402).
49. Lebedinsky C, Gómez J, Park YC et al. Trabectedin has a low cardiac risk profile: a comprehensive safety analysis. Ann Oncol 2010; 21 (Suppl 28): 21. viii308 (Abstr 984P).
50. Vergote I, Vermorken J, Pujade Lauraine E et al. Safety analysis of trabectedin in combination with pegylated liposomal doxorubicin (PLD) vs PLD alone in ovarian cancer patients 65 years of age and older. Eur J Caner Suppl 2009; 7: 458. (Abstr P8028).