

# Focus on Trabectedin in Ovarian Cancer: What Do We Still Need to Know?

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**Abstract:** In the era of single and combination maintenance therapies as well as platinum and Poly (ADP-ribose) polymerase inhibitors (PARPi) resistance, the choice of subsequent treatments following first-line platinum-based chemotherapy in recurrent ovarian cancer (ROC) patients has become increasingly complex. Within the ovarian cancer treatment algorithm, particularly in the emerging context of PARPi resistance, the role of trabectedin, in combination with pegylated liposomal doxorubicin (PLD) still preserves its significance. This paper offers valuable insights into the multifaceted role and mechanism of action of trabectedin in ROC. The main results of clinical trials and studies involving trabectedin/PLD, along with hints of Breast Cancer genes (BRCA)-mutated and BRCAness phenotype cases, are critically discussed. Moreover, this review provides and contextualizes potential scenarios of administering trabectedin in combination with PLD in ROC, according to established guidelines and beyond.

**Keywords:** ovarian cancer, trabectedin, platinum eligibility

## Introduction

Ovarian cancer is frequently diagnosed at advanced stages, and it often recurs despite an optimal initial treatment, which includes complete cytoreductive surgery and chemotherapy with platinum compounds followed by maintenance with Poly (ADP-ribose) polymerase inhibitors (PARPi) or bevacizumab.<sup>1–6</sup>

Recurrent ovarian cancer (ROC) is still a major challenge in the landscape of gynecologic oncology.<sup>7–9</sup> Indeed, ROC usually presents as a complex clinical scenario that requires a multidisciplinary approach.<sup>10</sup> Moreover, several key concepts need to be addressed before deciding treatment at recurrence, such as the timing from prior platinum therapy, the tumor's histology, the Breast Cancer (BRCA) mutational status, previous maintenance therapies, and side effects related to previous treatments.

Among the possible choices in the ROC setting, the association of trabectedin plus pegylated liposomal doxorubicin (PLD) is still the only non-platinum doublet approved to treat platinum-sensitive ROC, defined classically as disease recurrence after 6 months of platinum-based chemotherapy.<sup>11</sup> This approval comes from the results of the OVA-301,<sup>12</sup> a randomized clinical trial that showed the superiority of trabectedin plus PLD over PLD alone in ROC patients, particularly in those recurring after 6–12 months from the last platinum cycle. Subsequently, other randomized and observational studies have investigated the role of trabectedin in ROC, with discordant results.

Nowadays, the classical definition of platinum sensitivity has been revised and includes the concept of “platinum eligibility”: if there is a reasonable likelihood that patients might respond to platinum rechallenge— in case of absence of progression during platinum-based therapy or shortly thereafter and no contraindications to platinum— the patients may be considered as “platinum eligible” and therefore might receive platinum-based chemotherapy.<sup>13,14</sup> However, in the

current manuscript, we will use the classical definition of platinum sensitivity, given that several clinical trials were conducted using this earlier definition.

By a question-based approach, this work is dedicated to unraveling the role of trabectedin in treating ROC, analyzing both the pros and cons that have emerged in the various studies. Moreover, our aim is also to explore the role of trabectedin in the current times, in which PARPi-induced platinum resistance has emerged as a critical challenge in ovarian cancer treatment.

## Which is the Mechanism of Action?

Trabectedin manifests its multifaceted mechanism of action through two principal routes. Firstly, it exercises a targeted influence on DeoxyriboNucleic Acid (DNA) within malignant cells, causing cell cycle arrest and inducing apoptosis.<sup>15</sup>

Secondly, trabectedin displays a distinct mechanism of action related to its impact on the tumor microenvironment: the modulation of various elements within the tumor microenvironment has been noted, encompassing tumor-associated macrophages (TAMs) and vascular endothelial cells. These actions collectively impair the tumor's ability to sustain growth and evade immune surveillance, thereby augmenting the overall antitumor effect of trabectedin.

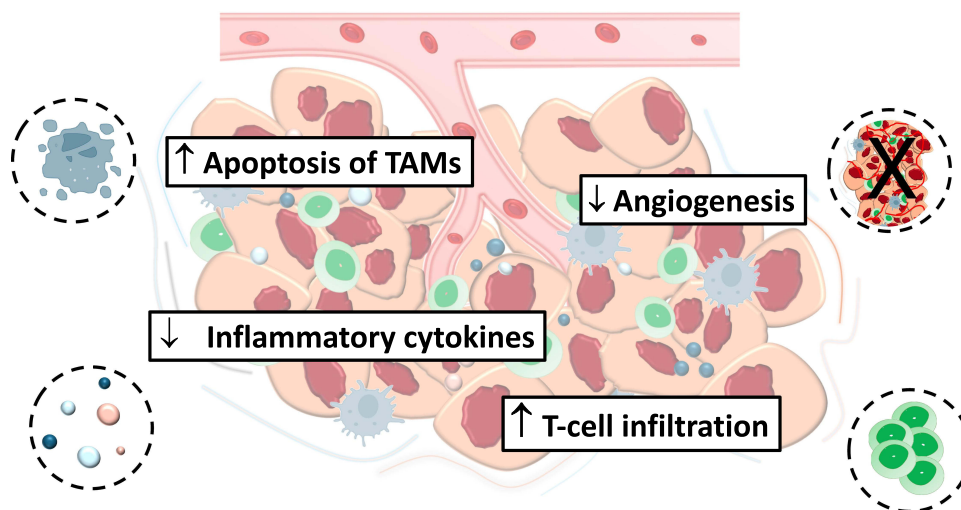
## DNA Binding

Trabectedin (Yondelis; ET-743) is a tetrahydroisoquinoline alkaloid originally discovered in the marine organism *Ecteinascidia turbinata* and is presently produced through synthetic procedures.<sup>16</sup> In contrast to other alkylating agents that typically interact with guanine at the N7 or O6 position within the major groove of DNA, trabectedin specifically binds to the exocyclic N2 amino group of guanines located in the minor groove of DNA, resulting in guanine residues' adducts.<sup>17</sup> These DNA adducts induce structural distortions in the DNA double helix,<sup>15</sup> ultimately blocking the binding of critical transcription factors to the DNA specific sequences.<sup>18</sup> This disruption in transcription factors' binding leads to the inhibition of activated genes transcriptional processes that are vital for cancer cell proliferation. Moreover, trabectedin extends its action beyond DNA binding, as it significantly interferes with the repair machinery of the DNA damage response. Notably, it disrupts TC-NER, a pivotal mechanism for correcting DNA lesions induced by various genotoxic insults.<sup>19–21</sup> By impairing NER, trabectedin fosters the accumulation of unrepaired DNA lesions, amplifying genomic instability within cancer cells. Differing from the response observed with other DNA-interacting drugs, such as platinum, which intensify their action against cells with defects in the nucleotide excision repair mechanism, trabectedin displays 2–10 times reduced sensitivity in TC-NER deficient cells,<sup>21</sup> while elevated levels of ERCC1 and XPG/ERCC5, indicative of proficient NER, seem to predict a more favorable response to trabectedin treatment.<sup>18,22–24</sup> The TC-NER pathway could potentially contribute to the buildup of unprocessed single-strand breaks and subsequently double-strand breaks (DSBs). Typically, the homologous recombination system (HRR) is involved in the repair of DSBs. However, in cells characterized by homologous recombination deficiency (HRD), the persistence of unrepaired DSBs leads to apoptosis, showing 100 times increased sensitivity to trabectedin,<sup>20</sup> since these HRD-positive cells are unable to enlist the machinery for DSBs' repairing. Data from the literature have suggested that the administration of trabectedin heightens the sensitivity to subsequent platinum-based chemotherapy.

Conversely, deficiencies in non-homologous end joining (NHEJ) appear to exert a marginal impact on the effectiveness of trabectedin.<sup>18,22,23,25</sup>

## Tumor Microenvironment

Beyond the direct effects on DNA, trabectedin modulates the tumor microenvironment, acting on monocytes and TAMs, directly involved in cancer cells' survival, proliferation, and invasion. The tumor microenvironment (TME), particularly tumor-associated macrophages (TAMs), has the capability to foster inflammation and neoangiogenesis through the production of growth factors, cytokines, and chemokines<sup>26</sup> (Figure 1). Trabectedin selectively activates the caspase-8 pathway, which results in monocytes/macrophages' apoptosis, but this effect is not observed in other leukocyte subsets, likely due to variations of functional tumor necrosis factor (TNF)-related apoptosis-inducing ligand receptors (TRAIL-Rs). At the same time, trabectedin promotes the infiltration and activation of CD8+ and CD4+ T-cells, enhancing the immune response against tumors.<sup>27</sup> Furthermore, thanks to its DNA-binding mechanism, trabectedin blocks the



**Figure 1** Mechanisms of action of trabectedin on the TME.

**Notes:** Trabectedin selectively induces apoptosis in TAMs and reduces the levels of specific inflammatory mediators (CCL2, IL-6, CXCL8). Additionally, trabectedin decreases neoangiogenesis and enhances T-cell infiltration.

**Abbreviations:** TAMs, Tumor-associated Macrophages; TME, Tumor Microenvironment.

transcription of CCL2, CXCL8, the vascular endothelial growth factor (VEGF) and interleukin (IL)-6,<sup>28</sup> as reported by Coward and Kulbe.<sup>29</sup> In gynecological malignancies, IL-6 assumes a key role by stimulating the proliferation, survival, migration, and invasion of tumor cells. Additionally, it is crucial in angiogenesis, as well as in the differentiation of TAMs and T-cells.<sup>17</sup> Furthermore, IL-6 emerges as a pivotal player in preparing the emergence of resistance to platinum agents (such as cisplatin) and taxanes (such as paclitaxel). This occurs through the upregulation of multidrug resistance-related genes (including MDR1 and GSTpi) and the suppression of pro-apoptotic proteins (such as Bcl-2 and Bcl-3).<sup>30</sup>

## Trabectedin in Recurrent Ovarian Cancer: Which are the Main Results? Phase III/IV Trials

**OVA-301 study** is a multicenter, open-label, randomized phase III trial that compared the efficacy and safety of PLD 30 mg/mq in combination with trabectedin 1.1 mg/mq every 3 weeks compared with PLD 50 mg/mq alone administered every 4 weeks.<sup>12</sup> In this study, 672 platinum-resistant and platinum-sensitive ovarian cancer patients were enrolled. One-third of these ( $n = 214$ , 32%) had a platinum treatment-free interval (TFIp) of 6–12 months. The primary endpoint was progression-free survival (PFS) while the secondary endpoints were overall response rate (ORR), overall survival (OS), and safety.

The median PFS was 7.3 months for the combination versus 5.8 months with PLD alone ( $P=0.019$ ) in the whole population, with the most significant benefit of the trabectedin/PLD observed in patients with TFIp of 6–12 months (7.4 vs 5.5 months Hazard ratio (HR) 0.65  $p=0.0152$ ) translated into a 35% reduction of tumor progression.

The ORR was 27.6% for trabectedin/PLD vs 18.8% for PLD ( $p=0.0080$ ) in the whole population and 35.3% vs 22.6% ( $p=0.0042$ ) in the platinum-sensitive setting.

Interestingly, in patients with TFIp of 6–12 months, the median OS of patients who have received the combination was 22.4 months versus 16.4 months in the PLD arm (HR: 0.64; 95% Confidence Interval (CI) 0.47–0.86;  $p=0.003$ ).

Remarkably, the preclinical hypothesis that trabectedin might enhance the sensitivity of subsequent platinum-based treatment was clinically assessed in two post hoc analyses of OS conducted in patients according to platinum sensitivity<sup>31</sup> and, separately, in patients with platinum-resistant disease<sup>32</sup> who were subsequently retreated with platinum salts. In all subsets of patients, treatment with trabectedin/PLD prior to subsequent third-line platinum retreatment showed an at least 6-month favorable trend toward longer OS compared with PLD alone. Significantly longer survival was registered in patients with a TFIp of 6–12 months, with an improvement of 9 months in median OS (median OS 27.7 vs 18.7 months;  $p < 0.0153$ ).<sup>12</sup>

Postponing platinum-based retreatment resulted in an extension of OS, suggesting that it could be due to an extension of PFS.

An exploratory subgroup analysis of the OVA-301 study evaluated the efficacy of the trabectedin/PLD combination according to BRCA mutation. Sixteen percent of patients (41 of 264) had a germline BRCA1 mutation, identified with DNA extraction from EDTA-preserved whole blood.

Among them, 17 patients were treated with PLD and 24 with the combination.

Better outcomes were observed in this subgroup of patients treated with trabectedin/PLD combination rather than PLD alone (median PFS 13.5 vs 5.5 months; HR 0.22; 95% confidence interval [CI] 0.09–0.52;  $p = 0.0002$ ; median OS 23.8 vs 12.5 months; HR 0.41; 95% CI 0.21–0.81;  $p = 0.0086$ , respectively).

Conversely, the outcomes of BRCA wild-type patients were not significantly different between the two groups of treatment (median PFS 6.0 versus 5.4 months,  $P = 0.2185$  and median OS 19.1 versus 19.3 months,  $P = 0.9377$  in the combination and PLD alone arms respectively).<sup>33</sup>

However, the small sample size of the trial did not allow confirmation of the increased benefit from the trabectedin/PLD combination in the BRCA mutated population.

The toxicity profile of trabectedin combined with PLD seems predictable and manageable, with transaminases elevations and neutropenia being the most common adverse events reported. However, neutropenic fever was reported in just 8% of cases and the transaminases increase was transient and generally decreased over subsequent cycles, with no significant clinical consequences such as liver failure.

The same safety profile was seen in elderly patients.<sup>34</sup>

Therefore, the acceptable safety profile and the almost complete absence of some inconvenient side effects, such as alopecia and hypersensitivity reactions, justify the use of the trabectedin/PLD combination in patients in which platinum-based therapy is not an option.

Based on the OVA-301 results, the **OVC-3006**, an open-label, randomized, active-controlled phase 3 trial was designed to evaluate the efficacy and safety of trabectedin/PLD combination as third-line chemotherapy in platinum-sensitive ROC patients who had received 2 previous lines of platinum-based chemotherapy.<sup>35</sup>

The patients were assigned 1:1 to receive either PLD 30 mg/mq followed by trabectedin 1.1 mg/mq every 3 weeks or PLD 50 mg/mq alone every 4 weeks, as to the OVA-301 study. Moreover, they were stratified according to the length of time to progression after first-line platinum-based chemotherapy (6 to 12 months, between 12 to 24 months and >24 months) and BRCA1/2 germline mutational status.

The primary endpoint was OS. The study was discontinued in 2018 after an interim analysis showed the futility threshold for OS was exceeded, and more toxicity was observed in the trabectedin/PLD arm.

However, although the termination, 576 patients were finally randomized (trabectedin/PLD,  $n = 289$ ; PLD,  $n = 287$ ) and the combination showed a significant increase in ORR compared to the PLD arm (46% vs 35.9%, respectively; odds ratio 1.52, 95% CI 1.07–2.16;  $p = 0.01$ ) despite the lack of PFS and OS benefit (median PFS 7.52 vs 7.26 months; HR:0.93, 95% CI:0.76–1.15;  $p = 0.52$  and median OS 23.8 vs 22.2 months; HR 0.92, 95% CI 0.73–1.18;  $p = 0.52$  in the trabectedin/PLD arm and PLD arm respectively).

Concerning BRCA status, an exploratory analysis was also performed to confirm the combination's efficacy according to mutational status.

The analysis involving 155 (26.9%) BRCA 1/2 mutated patients, 78 (27.0%) in the trabectedin/PLD group and 77 (26.8%) within the PLD alone and found that BRCA1/2 mutated patients had a median PFS of 10.1 months in the combination arm vs 7.6 months in patients treated with PLD alone (HR:0.72, 95% CI:0.48–1.08;  $p = 0.039$ ).

Moreover, the median OS in this subgroup was 34.2 months in the trabectedin/PLD arm compared with 20.9 months in the PLD arm (HR 0.54, 95% CI 0.33–0.90;  $p = 0.016$ ), with even longer benefit seen for patients with TFIp of 6 to 12 months (31.5 vs 14.9 months respectively; HR 0.37, 95% CI 0.17–0.82;  $p = 0.011$ ).

OVC-3006 and OVA-301 trials have some essential differences (primary endpoint, previous lines of platinum-based chemotherapy and stratification by platinum sensitivity). Thence, EMA's human medicines committee (CHMP) concluded that OVC-3006 results do not change the benefit–risk balance of trabectedin in the currently authorized indications. Moreover, a post hoc analysis showed that 42% of patients in OVC-3006 were platinum-resistant following

their last platinum-based treatment. In addition, the committee pointed out that due to the early discontinuation of the study, the results do not provide sufficient clinical evidence to question the OVA-301 results, whose primary endpoint was PFS.

The **INOVATYON** study is a randomized, open-label, phase 3 trial designed to demonstrate an improvement in OS for the trabectedin/PLD combination in ROC patients with disease progressing 6 to 12 months after their last platinum dose.

Differently from others, in this trial, the carboplatin/PLD doublet was compared with trabectedin plus PLD followed by platinum rechallenge at relapse in patients with ROC (up to two previous platinum-based lines), with a TFIp of 6–12 months.

The primary endpoint was OS, but it was not reached as it was similar between regimens, being 21.4 months for carboplatin/PLD and 21.9 months for trabectedin/PLD (HR 1.13; 95% CI 0.94–1.35;  $p = 0.197$ ). Moreover, as further confirmation, in the overall population, PFS was better with carboplatin/PLD (9.0 vs 7.5 months; HR 1.29; 95% CI 1.09–1.53;  $p = 0.003$ ).

Apparently, these data called into question the hypothesis that trabectedin/PLD given before platinum prolongs the survival in ROC patients who have a TFIp of 6–12 months, but although the PFS was longer in the carboplatin/PLD arm, the PFS after subsequent therapy (PFS-ST) was in favor of trabectedin/PLD arm, mainly when platinum was administered after this combination, even if not statistically significant (HR 0.87; 95% CI 0.72–1.06;  $p = 0.161$ ), showing a possible positive impact on outcomes of trabectedin/PLD doublet. Moreover, there was no difference in PFS between both arms in patients treated with two previous lines.

Regarding the safety profile, unlike previous studies, grade serious adverse events, including hematological, gastrointestinal, and hepatic treatment-related toxicities, were reported more in the trabectedin/PLD than in the carboplatin/PLD group.

Although the study did not meet its primary endpoint, some considerations must be made. Especially regarding the INOVATYON study, it should be underlined that the choice of OS, however clinically indisputable, is challenging to achieve in the context of OC, as it requires a considerable trial size, prolonged times for final analysis, and potential treatment effect biases resulting from active post-progressive therapies and supportive care.<sup>36</sup>

Moreover, all three of these phase III trials were mainly run in the pre-maintenance era (bevacizumab/PARPi), and the whole populations enrolled in these trials did not reflect the current population of patients treated in daily clinical practice. Finally, information regarding BRCA and HRD status was only partially available, preventing us from contextualizing the data according to current treatment strategies.

In conclusion, even though the study results suggest that a platinum doublet remains the standard of care for ROC patients with a TFIp between 6 and 12 months, the similar OS still indicates a possible role of trabectedin/PLD in patients treated with multiple prior lines of platinum, who show platinum hypersensitivity or may need a longer recovery time from platinum-related toxicities.

Finally, the non-interventional prospective **NIMES-ROC** phase IV trial evaluated trabectedin/PLD in real-life clinical practice in platinum-sensitive ROC patients.<sup>37</sup>

Trabectedin/PLD combination was given regardless of prior use of antiangiogenic treatment and could continue as long as the patient had clinical benefit.

The primary endpoint was to assess PFS, while the secondary endpoints were disease control rate (DCR), ORR and OS.

The median PFS was 9.46 months (95% CI 7.9–10.9), with around 40% of patients free from progression 12 months after treatment. The ORR and the DCR were 37.2% and 64.2%, respectively. The median OS was 23.5 months (95% CI 18.1–34.1).

Regarding BRCA mutational status, the study did not demonstrate a statistically significant difference in outcomes in terms of PFS and OS or platinum sensitivity during treatment with the combination of BRCA1/2 mutated and BRCA WT patients, even if around 38% of patients enrolled were not tested for BRCA status.

The overall outcomes data of NIMES-ROC are consistent with OVA-301 data despite the patients enrolled in the two clinical trials having different characteristics. In fact, unlike the other prospective clinical trials, the NIMES-ROC had

less restrictive eligibility criteria, so the patient population enrolled was heterogeneous and heavily pretreated (72.5% of patients received  $\geq 2$  prior chemotherapy lines in NIMES-ROC while only one previous line of treatment was allowed in the OVA-301 study).

The overall results support that the trabectedin/PLD combination has an antitumor activity even in heavily pretreated patients in real life, and this might be relevant considering that patients tend to develop progressive drug resistance over time.<sup>38</sup>

Regarding the toxicity profile, no new safety signals were reported in patients treated with trabectedin/PLD, compared to prior studies results, considering that around 60% of them received  $\geq 6$  cycles of therapy and that these patients obtained better response than those who received  $< 6$  cycles ( $p < 0.001$ ), supporting the use of the combination until disease progression.

Tables 1 and 2 summarize the characteristics, results, and safety profiles of the main clinical trials, respectively.

## What is the Role of Trabectedin in the Current Clinical Practice? Ineligibility for Platinum-Based Treatment

In recent years, the definitions of platinum resistance have been questioned and changed. According to the most recent guidelines,<sup>13</sup> ovarian cancer patients for which platinum is not an option are those progressing under platinum, those with early symptomatic progression, or those with platinum intolerance. Among the latter, when the relapse occurs  $> 6$  months from the previous platinum, the combination of trabectedin/PLD may be recommended.

On this regard, the issue of intolerance or hypersensitivity reactions to carboplatin is frequently observed, with reported frequencies reaching up to 33%.<sup>39–43</sup> Using the trabectedin/PLD combination can circumvent the risk of potentially life-threatening reactions to platinum-based chemotherapy for patients with a history of hypersensitivity reactions. Additionally, non-platinum regimens can serve as a preventive measure for the development of hypersensitivity reactions in at-risk patients, such as those with prior allergies or BRCA1/2 mutations, which are proved to independently increase the risk of hypersensitivity to carboplatin (odds ratio 13.1; 95% CI:2.6–65.4,  $p = 0.0017$ ).<sup>44</sup>

In addition to hypersensitivity issues, toxicity concerns must be thoroughly considered before contemplating platinum re-treatment. Indeed, platinum-based chemotherapy commonly gives rise to neurotoxicity, myelosuppression, renal toxicity, and ototoxicity, which can persist beyond the completion of treatment. Notably, even if neurological dysfunction is a less frequent side effect with carboplatin-based regimens compared to other platinum

**Table 1** Trabectedin/PLD in Platinum-Sensitive ROC

Trial Information	Study Design	Number Patients	Trabectedin/PLD Line of Treatment	PFS Months	OS Months	ORR %
<b>OVA-301</b> (NCT00113607) Monk et al, 2010 <sup>12</sup>	Randomized, controlled phase III trial	218	Second line in all pts	9.2	27	35.2
<b>OVC-3006</b> (NCT01846611) Monk et al, 2020 <sup>35</sup>	Randomized, controlled phase III trial	172	Third line in all patients	10	24.7	54.1
<b>INOVATYON</b> (NCT01379989) Colombo et al, 2023 <sup>36</sup>	Randomized, controlled phase III trial	227	Second line in 69.4% of pts Third line in 30.6% of pts	7.5	21.9	/
<b>NIMES-ROC</b> (NCT02825420) Pignata et al, 2021 <sup>37</sup>	Non-interventional prospective phase IV trial	218	$\geq$ third line in all pts	9.5	23.6	37.2

**Abbreviations:** ORR Overall Response Rate; OS, Overall Survival; PFS Progression-free Survival; PLD, Pegylated Liposomal Doxorubicin; pts, patients.

**Table 2** Grade 3 and 4 Adverse Events Trabectedin/PLD Related

TOXICITY	OVA-301 Monk et al, 2010 <sup>12</sup>				OVC-3006 Monk et al, 2020 <sup>35</sup>				INOATYON Colombo et al, 2023 <sup>36</sup>				NIMES-ROC Pignata et al, 2021 <sup>37</sup>			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
	Np	%	Np	%	Np	%	Np	%	Np	%	Np	%	Np	%	Np	%
Anemia	31	9.3	10	3.0	61	21.3	0	0	11	3.6	1	0.3	14	6.4	0	0
Leukopenia	82	24.6	28	8.4	32	11.2	9	3.1	14	4.6	8	2.6	7	3.2	2	0.9
Neutropenia	96	28.8	113	33.9	47	16.4	77	26.9	62	21.1	56	18.4	37	17	29	13.3
Thrombocytopenia	34	10.2	27	8.1	22	7.7	21	7.3	14	4.6	9	3.0	8	3.7	4	1.8
Nausea	29	8.7	0	0	21	7.3	0	0	27	8.9	1	0.3	NA	NA	NA	NA
Vomiting	33	9.9	1	0.3	18	6.3	0	0	20	6.6	0	0	8	3.7	0	0
Fatigue	19	5.7	1	0.3	31	10.8	0	0	0	0	0	0	11	5.0	0	0
Stomatitis	3	0.9	0	0	5	1.7	0	0	7	2.3	1	0.3	NA	NA	NA	NA
ALT increase	21	28.5	3	2.4	94	32.9	12	4.2	48	15.8	10	3.3	NA	NA	NA	NA
AST increase	95	6.3	8	0.9	23	8.0	5	1.7					NA	NA	NA	NA

**Abbreviations:** ALT, alanine amino transferase; AST aspartate amino transferase; NA; not available; Np, number patients.

compounds, it could manifest in 4–6% of patients.<sup>45</sup> This percentage increases when carboplatin is administered in combination with other agents, such as taxanes, up to 54%.<sup>46</sup> Among patients experiencing neurotoxicity, the likelihood of persistence was 15% at 6 months post-chemotherapy, 14% at 1 year post-chemotherapy, and 11% at 2 years post-chemotherapy.<sup>46</sup> This emphasizes the necessity for alternative therapeutic options, among whom trabectedin plus PLD represents a suitable strategy.

## Expected Inefficacy of Subsequent Platinum-Based Chemotherapy

In recent times, not only platinum resistance but also PARPi resistance has been a challenge in treating advanced-stage ovarian carcinoma, given their extensive use as maintenance in the first-line setting over the relapsed ones. Additionally, there is a notable overlap between mechanisms of resistance to platinum compounds and PARPi, regardless of BRCA mutational status.

Several data support this issue; in the post-hoc analysis of the SOLO2 trial, the interval until the second progression was extended in the placebo group compared to the olaparib group, especially in those treated with platinum-based treatment after PARPi progression (HR: 2.89, 95% CI 1.73–4.82) but also, at a less extent, in those receiving non-platinum-based regimens (HR: 1.58, 95% CI 0.86–2.90).<sup>47</sup>

Besides, more recently, data from a post-hoc exploratory analysis of the PAOLA1 have been presented and showed that efficacy of subsequent chemotherapy is lower if recurrence occurred during olaparib maintenance (during the first 24 months of PARPi maintenance) (HR: 0.65, 95% CI 0.50–0.84; P=0.0011 in favor of the recurrence that occurred after the end of olaparib administration).<sup>48</sup>

Several trials are underway to overcome this issue, but nowadays, results are unsatisfying, and the need to overcome PARPi and platinum resistance is urgent in everyday clinical practice. At present, after the progression on PARPi, there are no standard approaches to be proposed, and clearly, the hypothesis that trabectedin/PLD can restore platinum sensitivity regains importance, as also suggested by the authors of the INOVATYON trial.<sup>36</sup>

Few data are available on this issue. From one side, preliminary outcomes of the MITO 39 trial suggested that previous exposure to PARPi could also decrease the efficacy of the trabectedin/PLD regimen compared with naïve patients.<sup>49</sup> However, in a recent case–control study including patients progressing under PARPi, patients subsequently

treated with trabectedin/PLD (experimental group) were compared with a series of patients who received platinum-based treatment (control group) instead. This study suggests that a combination of trabectedin/PLD might be as effective as a platinum-based, both in terms of PFS and OS, with acceptable toxicity profiles on both sides.<sup>50</sup>

Therefore, in a sequence strategy, trabectedin/PLD might be a reasonable choice after a PARP inhibitor progression to restore platinum sensitivity, mainly but not limited to patients with multiple prior lines of platinum, who may need a stronger recovery from platinum toxicities. Contrarily, the combination would be completely missing (in the entire history of the disease) if we prefer to administer platinum after a PARPi progression because patients are expected to recur briefly, often before 6 months.

Interestingly, the combination of lurbinectedin, an analogue of trabectedin, plus paclitaxel, will be evaluated in ROC patients who have carried out 2 or 3 previous lines of chemotherapy (at least one combination with platinum and paclitaxel) and both maintenance therapies, bevacizumab, and PARPi, in the LUPPA-1/ENGOT-ov73 trial. The findings further clarify whether non-platinum-containing agents are more effective than platinum compound in patients progressing after PARPi, even in platinum-eligible patients, and overcome cross-resistance, improving response to subsequent platinum-based treatment.

## Possible Scenarios of Trabectedin + PLD Administration

In this context, we reported below some common scenarios in which the trabectedin/PLD combination might find indications.

### Scenario a) No Maintenance After First Line Chemotherapy

If the patient did not carry out any maintenance in the first-line setting, at first recurrence with a > 6-month TFIp in absence of contraindications to platinum (platinum eligibility), platinum-based chemotherapy is recommended to allow maintenance with bevacizumab (if no contraindications) or PARPi (Figure 2. 1°ROC TFIp >6 mo – Platinum Eligibility).

At second recurrence with a > 6-month TFIp and platinum eligibility, platinum-based chemotherapy with subsequent PARPi maintenance (if not previously administered) or trabectedin/PLD could be considered. Bevacizumab may not be allowed after first recurrence in some countries according to local regulations (Figure 2. 2°ROC TFIp >6 mo - Platinum Eligibility).

If both PARPi and bevacizumab have already been administered and/or are not allowed, at a new recurrence with TFIp >6 months, even if platinum rechallenge is a possible option, trabectedin/PLD could be considered (Figure 2. 3° ROC TFIp >6 mo – Platinum Eligibility).

In cases of platinum ineligibility, among no-platinum strategies, guidelines suggest trabectedin/PLD in case of TFIp >6 months (Figure 2. 1°ROC TFIp >6 mo, 2°ROC TFIp >6 mo and 3° ROC TFIp >6 mo - Platinum Ineligibility).

### Scenario b-c) PARPi or Bev Maintenance After First Line Chemotherapy

If the patient received the PARPi (or bevacizumab) in the upfront treatment, platinum should be administered at first recurrence after >6 months from last platinum in platinum-eligible cases, to allow maintenance with bevacizumab (if no contraindications) (or PARPi) (Figure 2. 1°ROC TFIp >6 mo - Platinum Eligibility).

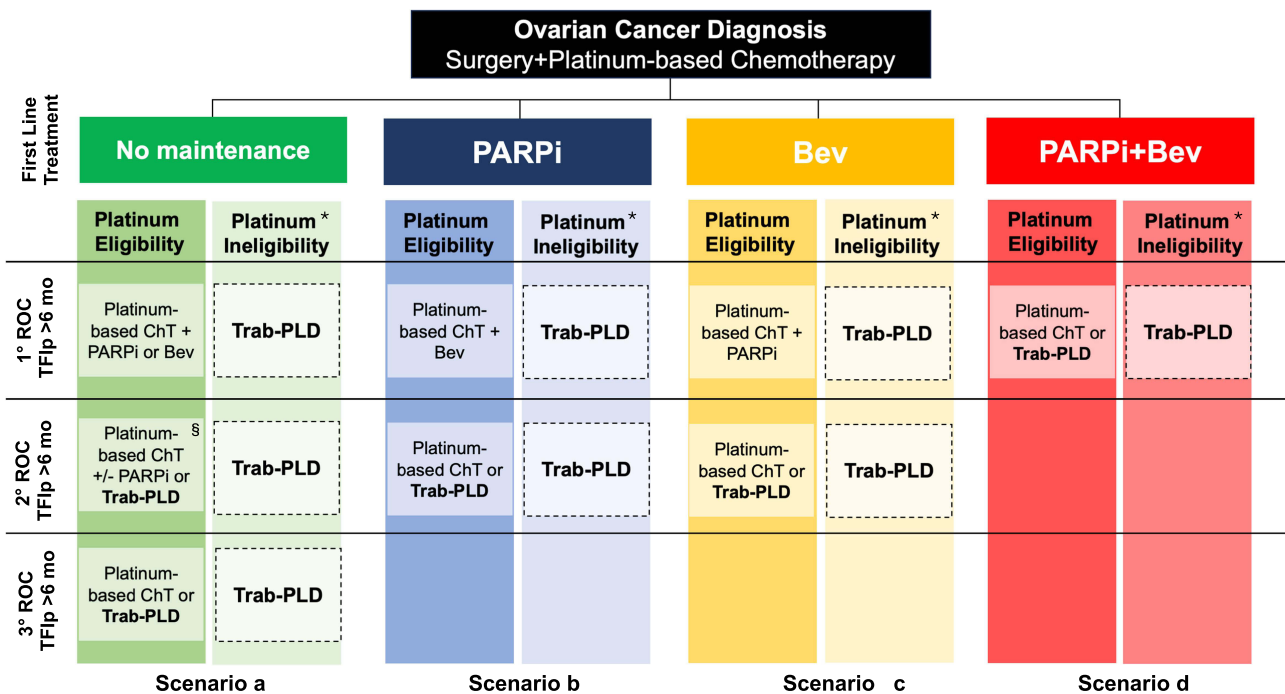
After both PARPi and bevacizumab treatment, at a new recurrence with TFIp>6 months, platinum rechallenge is possible, but trabectedin/PLD could be considered (Figure 2. 2° ROC TFIp >6 mo - Platinum Eligibility).

If the patient is not susceptible to platinum therapy for the reasons indicated above (platinum-ineligibility), among no-platinum strategies, the combination trabectedin/PLD is in indication according to recent guidelines (Figure 2. 1°ROC TFIp >6 mo, 2°ROC TFIp >6mo - Platinum Ineligibility).

### Scenario d) PARPi + Bev Maintenance After First Line Chemotherapy

If the patient has undergone therapy with concomitant maintenance PARPi and bevacizumab in the first-line setting, at the first relapse platinum-eligible, a new platinum doublet therapy could be considered, but trabectedin/PLD represents a valid alternative (Figure 2. 1°ROC TFIp >6 mo - Platinum Eligibility).





**Figure 2** Possible scenarios of treatment with trabectedin/PLD for ROC.

**Notes:** For practicality and clarity, the figure depicts the first, second, or third relapses. However, trabectedin/PLD may be administered at any relapse with TFIp >6 months, provided that the combination has not been previously employed. \*Due to contraindications to platinum-based treatment (hypersensitivity and/or residual toxicity).  
<sup>§</sup>Bevacizumab may not be allowed after first recurrence in some countries according to local regulations.

**Abbreviations:** Bev, Bevacizumab; ChT, Chemotherapy; PARPi, Poly (ADP-ribose) polymerase inhibitors; PLD, Pegylated Liposomal Doxorubicin; ROC, Recurrent Ovarian Cancer; TFIp, Treatment-Free Interval from last Platinum; trab, Trabectedin.

Even in this scenario, ineligibility to platinum requires the administration of a no-platinum strategy such as trabectedin/PLD (Figure 2. 1°ROC TFIp >6 mo - Platinum Ineligibility).

## Conclusion

To sum up, the introduction of maintenance therapies has prolonged the survival of patients with ovarian cancer. BRCA genes and HRD status are helpful in predicting the benefit from PARPi, even if they fail to identify the subgroup of patients who derive no benefit from these agents.

In addition, there are other controversies, both in the first line and the relapse, which currently make the management of ovarian cancer more challenging.

Throughout the disease's history, patients are repeatedly exposed to platinum-based treatments. However, it has been observed that repeated treatments, along with maintenance using PARPi, can lead to resistance to subsequent therapies. Therefore, it is crucial to identify treatment strategies to overcome platinum resistance.

In recent years, there have been changes and questions regarding the definition of platinum resistance and the traditional definition, based on a cut-off of 6 months for the TFIp, has been revised.

Currently, patients should be considered for treatment with platinum at relapse if there is a reasonable chance that they might benefit from platinum rechallenge, thus if there was no disease progression during previous platinum-based therapy or shortly after that. In such cases, the preferred course of action is administering platinum-based therapy to allow potential maintenance with PARPi or bevacizumab if not previously used.

However, not all patients are eligible for platinum therapy due to contraindications, such as hypersensitivity or residual toxicity. In such cases, the last European guidelines recommend using the trabectedin/PLD combination, considering its manageable side effects and possible long-term exposure mainly when used alongside common supportive therapies.

After PARPi treatment, platinum re-challenge provides less benefit, but to date, there is no sufficient data to establish whether other therapies may be more effective in this setting.

The MITO-8 trial showed the superiority of platinum-based therapy over non-platinum monotherapy in ROC patients with a pTFI of 6–12 months.<sup>51</sup> However, this population was not pretreated with PARPi. The INOVATYON trial also failed to demonstrate the superiority of a non-platinum regimen in patients with a pTFI of 6–12 months and a maximum 2 previous platinum-based lines, but there was no difference in PFS between platinum-based therapy and trabectedin/PLD combination in patients who had received 2 prior lines. Furthermore, also these patients were not pretreated with PARPi.<sup>36</sup> Hence, when the expected platinum therapy response is not optimal, albeit with TFIp >6 months, as seen in recurrences after PARPi ± bevacizumab, especially in patients who have received 2 previous lines of platinum and PARPi, trabectedin/PLD may be a reasonable choice, also to restore platinum sensitivity.

Considering that most of these assumptions are based on retrospective reports, there is a pressing need for new forthcoming trials that enroll patients who have undergone prior maintenance therapy to elucidate the impact of the combination in today's ROC population. Besides, data regarding the selection of patients who can benefit the most from the combination, including BRCA status, are still limited. Therefore, in the pursuit of providing more personalized treatment in the era of precision medicine, studies, prospective or from the real-life, testing trabectedin/PLD with stratification based on the molecular profile (including BRCA and HRD status) are required. In this context, the ongoing REPRAB study (MITO 36) aims to demonstrate that rechallenge with PLD with the combination of trabectedin is effective in terms of objective response rate, in ROC patients who have progressed within 6–12 months after the end of last platinum or after 12 months in patients not able to receive or not willing to receive other platinum treatments. This trial adds the translational endpoint to define the correlation between genetic assessment, including BRCA1/2 genes, and prognosis and to investigate the evolution over treatments of the genetic pattern.

In conclusion, the combination of trabectedin and PLD, even with some limits uncovered from randomized trials, still offers a reasonable and manageable therapeutic option for ROC patients with TFIp >6 months who are ineligible for therapy with platinum or in challenging and demanding scenarios.

Further evidence is needed to strengthen these assertions, but so far, this combination appears to align aptly with the evolving landscape of ovarian cancer treatment.

## Disclosure

SMB reports honoraria from GSK and Pharmamar.

CMS reports honoraria from GSK, AstraZeneca.

LV reports honoraria from GSK, Pharmamar, AstraZeneca.

AF reports commercial interests with AstraZeneca, MSD, Johnson & Johnson and Pharmamar, was a speaker for Fondazione Internazionale Menarini and GlaxoSmithKline.

GS reports research support from AstraZeneca and MSD and honoraria from Clovis Oncology, and is a consultant for GSK, Tesaro and Johnson & Johnson.

CM is on the consultant/advisory board for Clovis, Pharmamar, GSK, AstraZeneca and MSD, and received travel accommodation from Pharmamar and Roche.

The authors report no other conflicts of interest in this work.

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