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Results of a Phase II Trial Testing the Resensitization With Trabectedin in Platinum-resistant Ovarian Cancer

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Abstract. *Background/Aim: In patients with advanced platinum-resistant ovarian cancer we prospectively evaluated whether trabectedin could resensitize the tumor cells to platinum rechallenge. Patients and Methods: Upon progression to platinum-based chemotherapy, trabectedin was administered as a 3-hour infusion every three weeks and subsequently crossed over to carboplatin/carboplatin-based combinations. The primary endpoints comprised objective response rate (ORR) and time to progression after trabectedin (TTP Trab). Secondary endpoints included ORR following platinum post-trabectedin, the growth modulation index (GMI) assessed as the ratio of successive TTP to platinum, given after (TTP2) and before (TTP1) trabectedin, quality of life (QoL), and ancillary translational studies. Results: Ten patients with platinum-resistant ovarian cancer from a single institution were treated with trabectedin, one of whom achieved a partial response (PR) reaching the ORR of 10% and six had stable disease (SD) for a disease control rate (DCR) of 70%. After the treatment with platinum post-trabectedin, one patient achieved a PR and two had SD, attaining a rate of resensitization to platinum of 37.5%. The median TTP with trabectedin treatment was 15.0 weeks, while eight patients who received platinum post-trabectedin had the median TTP2 of 19.9 weeks. One patient reached the threshold of GMI >1 (12.5%) as indicator of clinical benefit. QoL of patients was not deteriorated with trabectedin. Predictive biomarkers of response to trabectedin and/or re-exposure to platinum could not be identified. Conclusion: Although trabectedin did not achieve a wide resensitization to platinum in this heavily pretreated platinum-resistant population, a significant number of patients attained disease control.*

Patients with ovarian carcinoma are initially responsive to platinum-based therapy, but eventually become resistant to treatment due to the development of platinum chemoresistance. Moreover, ovarian cancer with early relapse (*i.e.*, <6 months), classically called 'platinum-resistant', implies a substantial shortening of the life expectancy of those patients and constitutes a huge therapeutic challenge. Among patients with platinum-resistant disease, the probability of a response to a platinum-based chemotherapy is generally low and is associated with poor outcome. Thus, in patients with platinum-resistant disease, the principal objectives of salvage standard therapies are to improve quality of life (QoL) and alleviate cancer-related symptoms.

Trabectedin (Yondelis®) is a marine-derived compound with novel structure and mechanisms of action that differ from other chemotherapies in that it induces durable stabilizations and lowering of tumoral growth (1-5). Currently, trabectedin in combination with pegylated liposomal doxorubicin (PLD) has been approved in the European Union and in approximately 70 other countries around the globe for the treatment of patients with relapsed platinum-sensitive ovarian cancer based on the results of OVA-301 study (6). The capability of trabectedin to delay tumoral growth has been extensively studied in soft tissue sarcomas as well, proposing the growth modulation index (GMI) as one of the objectives

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to be considered at the time of evaluating trabectedin's efficacy (7). To date, three phase II studies have evaluated trabectedin monotherapy in patients diagnosed with platinum-resistant and platinum-sensitive ovarian cancer achieving an overall response rate (ORR) up to 43% (8-10). In addition, a phase III trial very recently reported efficacy data of single-agent trabectedin in patients with *BRCA* mutated or BRCAness phenotype with platinum-sensitive (57.4%) and platinum-resistant (42.6%) recurrent ovarian cancer (11). In that phase III trial, although trabectedin failed to improve OS compared to standard chemotherapy [hazard ratio (HR)=1.15, p=0.304], the drug reported significant activity in a heavily pretreated population with chemotherapy and poly(ADP-ribose) polymerase inhibitors (PARPi) (11). Retrospective data from our group suggested that sequential treatment with trabectedin might resensitize the tumor cells of patients and improve the efficacy of subsequent platinum-based chemotherapy (12). In addition, two prospective studies failed to clearly demonstrate this hypothesis, but both trials had a number of methodological issues, which precluded final conclusions (13, 14).

In addition to clinical data, there are some preclinical data to suggest potential mechanisms of reversing resistance to platinum compounds. Colmegna *et al*. found that trabectedin-resistant ovarian carcinoma and myxoid liposarcoma cell lines, with acquired resistance to trabectedin following repeated exposures to trabectedin, become much more sensitized to next platinum-based chemotherapy (1). In addition, mechanisms by which trabectedin restores tumor sensitivity to platinum include not only its interaction with components of the nucleotide excision repair machinery in tumor cells but also its inhibition of inflammatory mediators such as IL-6 in the tumor microenvironment (3, 15). *BRCA* mutations and associated homologous recombination repair deficiency may contribute to enhanced sensitivity to trabectedin observed in *BRCA*-mutated patients with ovarian cancer (15, 16). Nevertheless, platinum resistance seems to be a potentially reversible phenomenon. Despite the multiple mechanisms of resistance that have been described so far (17), it seems that non-platinum treatments may play a role in reverting platinum resistance and prolonging the platinum-free exposure, which (re) sensitize the tumor cells to further platinum (18).

The hypothesis of this study focuses on questioning whether trabectedin could reverse, at least in part, the resistance to platinum and (re) sensitize to further platinum treatment offering a greater clinical benefit compared to the currently approved standard therapies in platinum-resistant disease (monotherapy with or without bevacizumab) (19). This is the first prospective study, performed in women with platinum-resistant ovarian cancer that assesses whether intercalation with a non-platinum therapy such as trabectedin may resensitize tumor cells to a subsequent platinum rechallenge (EudraCT 2014-004020-21).

Patients and Methods

Study design and patients. In this monocentric, open-label, and single-arm phase II study, the primary endpoints were to assess tumor response to trabectedin treatment defined as an ORR according to Response Evaluation Criteria in Solid Tumors Group (RECIST v.1.1) (20) and time to progression after trabectedin (TTP Trab). Secondary endpoints included ORR following the treatment with platinum post-trabectedin and the GMI assessed as the ratio of TTP after the rechallenge with platinum given after the treatment with trabectedin (TTP2) divided by the TTP following first treatment with platinum, given before trabectedin (TTP1). Quality of life (QoL) was tested during trabectedin administration, whereas ancillary translational studies were performed to identify biomarkers for further and wider clinical testing in this population of patients.

Eligible patients were adults (>18 years-old) with histologic or cytological diagnosis of epithelial ovarian cancer (excluding borderline and mesodermal tumors) and with platinum-resistant progression defined as tumor progression within one to six months after the last platinum dose. Eligible patients could be pretreated with up to four prior chemotherapy lines (maintenance treatment was not counted as a line) with a combination of either carboplatin plus paclitaxel, carboplatin plus gemcitabine or carboplatin plus PLD with or without prior antiangiogenic therapy; had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, measurable disease according to RECIST v.1.1 (20) or non-measurable disease by measuring the levels of the serum marker cancer antigen (CA)-125 according to the Gynecological Cancer Intergroup (GCIG) criteria (21), and had an adequate hematologic, cardiac, liver, and renal function. Exclusion criteria included the diagnosis of any other neoplasia diagnosed within five years prior inclusion in the study, excluding completely resected non-melanoma skin cancer or completely resected *in situ* cervical cancer, any medical, psychiatric, or any other condition that in the investigator's discretion would prevent the patient from entering the study, and documented brain or leptomeningeal disease.

All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments, the International Conference on Harmonization Guidance for Good Clinical Practice and approved by the National Health Authorities (AEMPS) and the Ethics Committee of the Hospital Clínico San Carlos (EudraCT code: EudraCT 2014-004020-21). Signed informed consents were obtained from all study participants included in the study.

Study treatments. Upon progression to carboplatin monotherapy or carboplatin-based combinations, the patients received trabectedin at the initial dose of 1.3 mg/m^2 body surface, given as a 3-hour intravenous infusion of every three weeks until progression, unacceptable toxicity, or consent withdrawal. Pretreatment with corticosteroids was considered mandatory for all patients receiving trabectedin. After the initial four cycles of trabectedin, patients with disease progression were rechallenged with either carboplatin or carboplatin-based combination, whereas those who were free from progressive disease continued with trabectedin treatment. Once trabectedin was discontinued, the election of post-trabectedin treatment with either carboplatin or carboplatin-based combination was done at the clinician's discretion depending on the patient's conditions and previous chemotherapy.

Study evaluations. Physical examination, pre-treatment evaluations, and the response evaluations measured either by RECIST v.1.1 (20) or CA-125 levels (21) were collected at baseline (within 28 days prior to the first trabectedin treatment cycle). Elevations in CA-125 levels were re-assessed at Day 1 of every cycle, whereas tumor hematology, blood chemistry (including creatinine, serum electrolytes, and coagulation tests), and liver function tests were performed weekly during the first two cycles and at days 1 and 15 thereafter. Response to treatment was evaluated every four cycles and at trabectedin discontinuation as per RECIST v.1.1 and/or according to serum concentrations of CA-125. All adverse events (AEs) were graded according to the National Cancer Institute-Common Terminology Criteria, v. 4.03. Quality of life was assessed at Day 1 of every cycle and at the end of treatment with trabectedin using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-OV28 questionnaires (22, 23).

Blood samples for translational studies were obtained before trabectedin treatment, 24 hours after administration, as well as on days 8 and 15 after infusion. Translational studies aimed to explore the correlation between genes involved in DNA repair mechanisms and trabectedin's mechanism of action and response. Monocyte subpopulation analyses was performed at the Hematology Department of Hospital Clínico San Carlos using flow cytometer to analyze classic monocytes (CD14++CD16–), intermedium monocytes (CD14++CD16+), and non-classic monocytes (CD14+CD16++) (24). Inflammatory cytokines (IL-4, IL-6, IL-8, IL-17A, MCP-1, TNFa, and VEGF) were analyzed with Milliplex analysis (HCYTOMAG-60K-07, Merck KGaA, Darmstadt, Germany). Tumor samples from the patients included in the study were also analyzed at PharmaMar's laboratories (Madrid, Spain) by using a PharmaMar tailored 206-gene panel to correlate the genomic aberrations using Ampliseq Designer tool (ThermoFisher Scientific, Waltham, MA, USA) found in genes with functions involved in DNA repair mechanisms or those related with trabectedin's mechanism of action (25).

Statistical analysis. Patients who were platinum-resistant were subsequently switched off to a platinum after trabectedin treatment, potentially being a non-active treatment in this subset of patients. To reduce exposure to a possible non-active treatment, an exploratory Bayesian design assumed non-informative prior distribution. The null hypothesis, defined as a GMI ≥1 in <5% of patients was considered to support the hypothesis that the treatment was effective vs. the alternative hypothesis with a GMI ≥1 in >10% of patients. With these assumptions, the estimated number of patients to be enrolled was 10 patients. Frequency tables were generated for categorical variables, whereas a description of the study population used classical descriptive statistics (*i.e.*, numbers and percentages for categorical variables, and median and range for continuous data).

The analysis of ORR was defined as the percentage of patients with a complete response (CR) or partial response (PR), while disease control rate (DCR) was defined as the percentage of patients with an objective response and stable disease (SD). The response was analyzed using a Bayesian approach, with the Bayes quadratic loss estimator with its 95% confidence interval (CI). The statistical analysis was performed using the IBM SPSS Statistics v.21 statistical software (IBM Spain, S.A.).

Time-to-event endpoints (*e.g.*, TTP) and their fixed-time estimations were estimated according to the Kaplan-Meier method. The TTP after trabectedin (*i.e.*, TTP Trab) was defined as the time interval from the first administration of trabectedin to the earliest date of disease progression. TTP to platinum pre-trabectedin (TTP1) was calculated from the first cycle of platinum given prior trabectedin to the first evidence of disease progression; TTP to platinum post-trabectedin (TTP2) was calculated from the first platinum rechallenge following progression to trabectedin to the first evidence of disease progression. The GMI, an intra-patient comparison of successive TTP (GMI=TTPn/TTPn−1), was calculated as defined by Von Hoff (26) and expressed as the following ratio: GMI=TTP2/TTP1. Since successive TTPs tend to become shorter, a GMI ≥1 was considered as a threshold of activity (26).

Starting from the first application of trabectedin, all AEs and serious adverse events (SAEs) according to their relationship with study treatment were documented as well as analytical results, deaths, and the reason for treatment discontinuations, and delays and/or dose reductions. All AEs and SAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 18.0) and graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTCAE) v.4.03. The summary scores of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module 28 (EORTC QLQ-OV28) health-related questionnaire as well as their subscales and individual symptoms, and the mean change from the first to the third trabectedin cycle as per the EORTC QLQ-C30 and QLQ-OV28 questionnaires were used as patient-reported outcome (PRO) instruments for evaluation of QoL.

Results

Patient characteristics. Twelve patients signed the informed consent, 10 of whom were eligible for the study and were included in the analysis set (Figure 1). Two patients were excluded from the efficacy analysis set because of refractory disease and pretreatment with more than four prior lines. Two patients did not complete the study due to AEs not related with trabectedin (bronchoaspiration pneumonia and influenza B pneumonia, respectively); thus, eight out of 10 enrolled patients were rechallenged with platinum after the treatment failure with trabectedin.

Most patients had metastatic high-grade serous-papillary and poorly differentiated ovarian cancer at diagnosis (Table I). At the time of inclusion, 80% of patients did not present ascites despite peritoneal involvement in 70% and three patients had liver metastases. All patients underwent surgery and chemotherapy as previous treatments. The median prior number of lines was 3 (range=2-3) (Table I).

Efficacy. The median number of trabectedin cycles administered was 3.50 (interquartile range=3.00-5.75) with five patients receiving four or more cycles and up to a maximum of eight cycles of treatment. Regarding the overall trabectedin activity, one patient with serous/papillary carcinoma achieved PR reaching the ORR of 10% and six other patients had SD as a best result for a DCR of 70%.

Following platinum rechallenge after the treatment with trabectedin, one patient achieved a PR and two had SD,

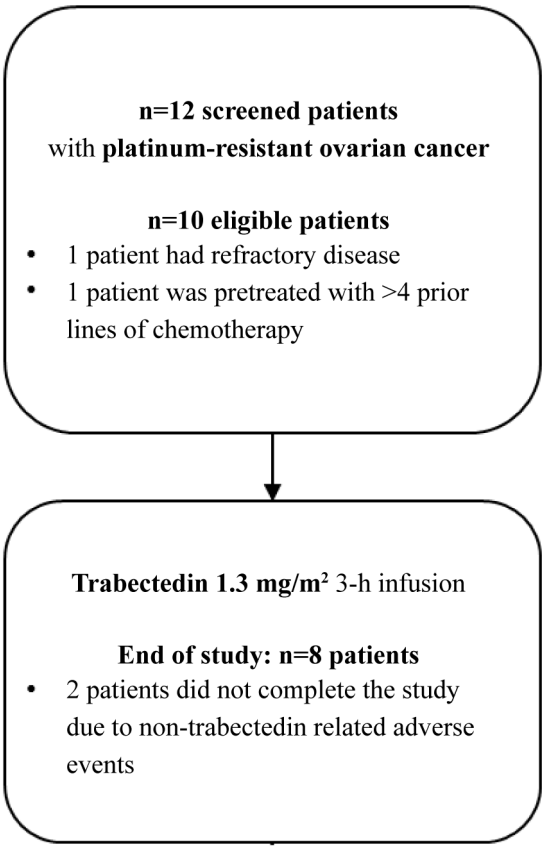


Figure 1. *Study design*.

Table I. *Patient and disease characteristics at baseline*.

	Total (n=10)	
	n	%
Age (years)		
Mean (standard deviation)	64 (8.55)	
Median (interquartile range)	68 (54.38-70.64)	
Race		
Caucasian	10	100
Histological subtype		
Serous/papillary	7	70
Clear cell	1	10
Mucinous	0	0
Endometroid	1	10
Other	1	10
Histological grade		
Well differentiated	1	10
Poorly differentiated	8	80
Dedifferentiated	1	10
Stage at study enrollment		
Locally advanced	1	10
Metastatic	9	90
Number of prior lines (includes neo/adjuvant setting)		
1	0	0
>1	10	100
Median	3.00 (2.00-3.00)	
Time from diagnosis to study enrollment (weeks)		
Mean (standard deviation)	148.86 (61.76)	
Median (interquartile range)	137.57 (116.57-155.57)	
Time from last platinum progression to study enrollment (weeks)		
Mean (standard deviation)	21.14 (17.17)	
Median (interquartile range)	17.36 (11.54-23.56)	

attaining a rate of re-sensitization to platinum of 37.5% (*i.e.*, three out of eight patients). The patient who achieved a PR previously obtained a SD as a best response following the treatment with trabectedin. Characteristics of responding patients to trabectedin and platinum re-challenge are described in Table II.

The treatment with trabectedin achieved a median TTP of ~3.4 months (15.0 weeks; 95%CI=2.82-27.17) and the treatment with platinum after trabectedin a median of ~4.6 months (TTP2: 19.85 weeks; 95%CI=1.98-37.73). A GMI >1 was reached by one patient (12.50%). Individual data of TTP1, TTP during the treatment with trabectedin (TTP Trab), and TTP2 are described in Table III.

Toxicity. All patients were assessable for toxicity and all experienced AEs of any grade. Grade 3/4 trabectedin-related AEs were reported in seven patients, whereas no deaths attributed to treatment-related AEs or unexpected AEs occurred during the study. No new safety concerns were observed during the treatment with trabectedin. Most frequent AEs seen with trabectedin were gastrointestinal disorders, experienced by seven patients, two of whom had grade 3 nausea. Moreover, grade 3 asthenia was reported in two patients. Most common clinically significant laboratory tests were grade 3 alanine aminotransferase increase; grade 3 neutropenia and grade 3 febrile neutropenia observed in one patient each.

Among patients who were rechallenged with carboplatin or carboplatin-based combinations, all toxicities were expected and manageable. No grade 3/4 platinum related AEs were reported and only a grade 2 asthenia was observed in one patient.

Quality of life. The adherence to both questionnaires was adequate. Although this analysis was carried out in this series with a very limited number of patients, no significant changes in relation to baseline were detected in QLQ-C30 (data not sown) and EORTC QLQ-OV28 questionnaires (Figure 2).

Translational research. The data of the human blood monocytes and pro-inflammatory cytokines (and somatic

Table II. *Characteristics of responding patients to trabectedin and platinum rechallenge.*

Trabectedin treatment						
Patient no.	Age	Histologic type	Sites of disease	Best response	TTP Trab (weeks)	OS*
1	53	Serous/papillary	Lymphatic/Peritoneum/Bone	PR	21.85	Alive
3	71	Adenocarcinoma	Lymphatic	SD	30.00	Alive
4	71	Endometroid	Liver/Lymphatic/Peritoneum	SD	19.71	Alive
6	61	Serous/papillary	Lung/Lymphatic/Peritoneum	SD	18.86	Alive
8	52	Serous/papillary	Lungs/Peritoneum	SD	15.00	Alive
10	66	Serous/papillary	Liver/Peritoneum	SD	20.29	Alive
11	75	Serous/papillary	Lung/Peritoneum/Bone/Pancreas	SD	9.00	Alive
Platinum rechallenge						
Patient no.	Age	Histologic type	Sites of disease	Best response***	TTP 2 (weeks)	OS**
4	71	Serous/papillary	Liver/Lymphatic/Peritoneum/Bone	PR	32.86	Alive
5	70	Serous/papillary	Lymphatic/Peritoneum/Pleura	SD	18.57	Alive
10	66	Serous/papillary	Lung/Peritoneum/Bone/Pancreas	SD	49.00	Alive

*Overall survival at the end of treatment with trabectedin. **Overall survival at the end of treatment with carboplatin or its combinations. ***Eight patients were rechallenged with platinum after trabectedin treatment: three patients obtained response; two were not evaluable for response; and three patients progressed. PR: Partial response; SD: stable response; TTP Trab: time to progression after the treatment with trabectedin; TTP2: time to progression after rechallenge with platinum post-trabectedin.

gene alterations) did not reveal any parameter predictive of trabectedin response or predictive of platinum re-sensitization. Of note, the results of IL-6 were not significant as in most samples it was below the threshold of detection. Only the patient who achieved a PR to trabectedin obtained an increase in cytokine plasma levels at 24 h after the first trabectedin administration with exception of the anti-inflammatory cytokine IL-4.

Three deleterious *BRCA1/2* mutations were detected in the tumor tissue of three patients, two of them with SD with trabectedin treatment, but again not significantly related with response to trabectedin. Nevertheless, these findings are only exploratory as it is a retrospective analysis in a small sample of patients included in this study.

Discussion

To the best of our knowledge, this study is a unique prospective study in patients with resistant ovarian cancer where the hypothesis of resensitization to platinum with a non-platinum agent trabectedin was tested. Although a GMI ≥1 with the next subsequent platinum line was not reached in most patients, 12.5% of them rejected the null hypothesis, which might justify a greater study of this strategy in this population of patients with a dismal prognosis.

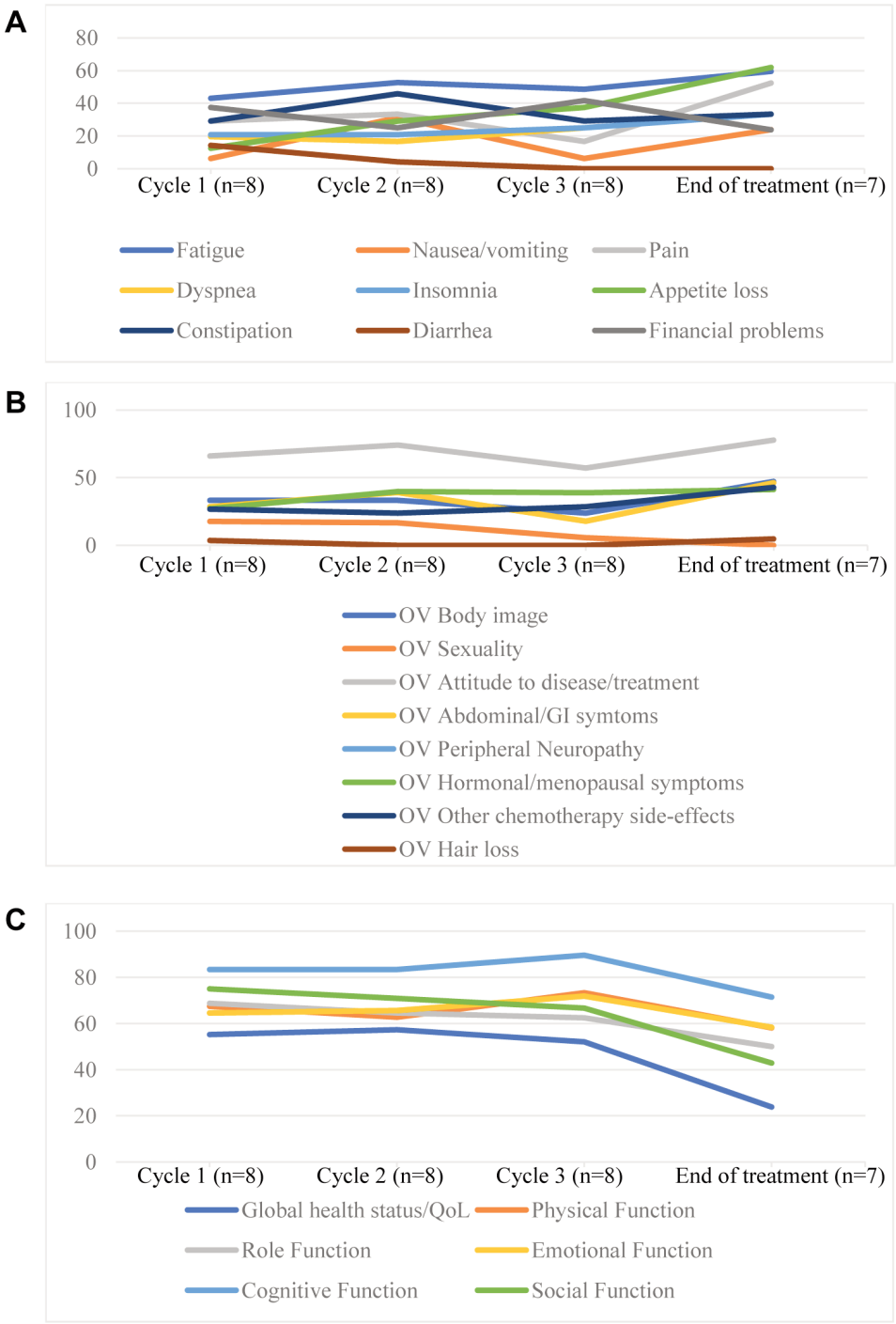
Herein, the treatment with trabectedin given after platinum failure in 10 patients with platinum-resistant relapse reached a DCR of 70% (1 PR and 6 SD). Upon progression to trabectedin, eight patients were crossed to platinum

Table III. *Growth modulation index (GMI).*

Growth modulation index (GMI)	n=8	Percentage %
GMI TTP2/TTP1		
<1	7	87.50
1	0	0.00
>1	1	12.50
GMI TTP Trab/TTP1		
<1	7	87.50
1	0	0.00
>1	1	12.50
GMI TTP2/TTP Trab		
<1	6	75.00
1	0	0.00
>1	2	25.00

Patient no.	GMI TTP2/ TTP1	GMI TTP Trab/ TTP1	GMI TTP2/ TTP Trab
1	0.30	0.66	0.45
3	0.42	1.29	0.32
4	0.60	0.64	0.94
5	1.48	0.61	2.44
6	0.33	0.43	0.75
7	0.12	0.15	0.80
9	0.6	0.23	2.63
10	0.16	0.41	0.39

TTP Trab: Time to progression after the treatment with trabectedin; TTP1: time to progression after the treatment with platinum pre-trabectedin; TTP2: time to progression after rechallenge with platinum post-trabectedin.



A: QLQ-OV28 Questionnaire, Symptom scales sintomas.
B: QLQ-OV28 Questionnaire, Global health status
C: QLQ-OV28 Questionnaire, Functional scales
Higher scores (range: 0–100) indicate better outcomes on global quality of life/health.

Figure 2. *Mixed-model repeated-measures analyses for the QLQ-O28 questionnaire throughout the study period. A) QLQ-OV28 Questionnaire, Symptom scales. B) QLQ-OV28 Questionnaire, Global health status. C) QLQ-OV28 Questionnaire, Functional scales. Higher scores (range=0-100) indicate better outcomes on global quality of life/health.*

retreatment and achieved a DCR of 37.5% (1 PR and 2 SD), suggesting that trabectedin induces a re-sensitization to platinum treatment only in some patients. Only one out of eight patients re-exposed to platinum achieved a GMI >1, which is considered as a sign of activity in this phase II trial. Nevertheless, given the low number of participants (some of them with incomplete samples), it is difficult to draw conclusions from the results reported in this study. In prior retrospective studies, taxanes were tested as a non-platinum therapy to increase progression-free interval (PFI). Those studies included far more population [*i.e.*, 82 patients in study of Markman *et al*. (27) and 33 patients in study of Kavanagh *et al*. (18)] and concluded that a prolonged PFI with a non-platinum agent such as taxanes had a value in the platinum-resistant ovarian cancer population. In a prior trabectedin publication including 30 platinum-resistant ovarian cancer patients, two out of 28 evaluable patients (7%) for response according to RECIST criteria, achieved a PR with a TTP of 4 and 4.6 months, respectively, and eight (29%) other patients achieved SD as best response (8).

Only scant data are available concerning the efficacy and toxicity of trabectedin in patients with advanced ovarian cancer refractory to or experiencing disease relapse after platinum/taxane-based chemotherapy (8). In a prior publication of our group, patients with platinum-resistant/refractory or partially platinum-sensitive recurrent ovarian cancer and treated with trabectedin obtained an ORR of 18.2% and a median OS of 21.3 months despite representing a heavy pre-treated population with more than five lines prior to trabectedin exposure (12). The results of that retrospective publication suggested that a sequential treatment with trabectedin followed by platinum could re-sensitize tumoral cells to platinum and was an additional rationale for this prospective study. Trabectedin dose of 1.3 mg/m^2 is inferior of the doses used in prior studies (28). Yet, the study of Del Campo *et al*. reported no-inferiority of this lower dose in terms of efficacy and tolerance as compared to 1.5 mg/m^2 (10). As a result, the dose of trabectedin used in this study was considered adequate to answer the study's hypothesis.

Upon progression to trabectedin, eight out of 10 patients continued with platinum treatment. Platinum doses were not pre-specified in this study as, for instance, in Kavanagh's study in which carboplatin dose was pre-specified as 300 mg/m^2 in 28-day cycles after failure to non-platinum treatment (18). The low number of patients included in our study and the heterogeneity of treatments following trabectedin progression could explain the results obtained in terms of radiological responses in more than two third of patients. Of note, two patients received more than four cycles of trabectedin, but this did not translate this treatment into a major benefit at the time of carboplatin re-introduction as these patients received only 2 and 3 cycles of carboplatin, respectively.

Trabectedin was generally well-tolerated with toxicities in line with extensive prior experience and reports reflecting the transient and non-cumulative myelosuppression and transaminase increases. No new safety signals were reported following the treatment with carboplatin in monotherapy or carboplatin combinations as well. In addition, although limited by the number of patients, the results in terms of QoL obtained during trabectedin treatment confirmed no significant deterioration in QoL among the treated patients. In addition, our translational studies did not show any predictor of response. The patient achieving a PR to trabectedin was the only one in whom pro-inflammatory cytokines decreased during the treatment with trabectedin.

In conclusion, the results of our study do not support the routine use of trabectedin as a method to resensitize ovarian cancer cells to platinum. Still, the fact that a significant number of patients attained a meaningful DCR (*i.e.*, 70%) with trabectedin therapy and with subsequent carboplatin, warrants further studies in a greater patient population.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Gloria Marquina and Antonio Casado conceived the study and performed analysis and interpretation of date; all Authors performed literature review, wrote, and revised the manuscript and agreed to the published version of the manuscript.

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References

1 Colmegna B, Uboldi S, Frapolli R, Licandro SA, Panini N, Galmarini CM, Badri N, Spanswick VJ, Bingham JP, Kiakos K, Erba E, Hartley JA and D'Incalci M: Increased sensitivity to platinum drugs of cancer cells with acquired resistance to trabectedin. Br J Cancer *113(12)*: 1687-1693, 2015. PMID: 26633559. DOI: 10.1038/bjc.2015.407

2 Larsen AK, Galmarini CM and D'Incalci M: Unique features of trabectedin mechanism of action. Cancer Chemother Pharmacol *77(4)*: 663-671, 2016. PMID: 26666647. DOI: 10.1007/s00280-015-2918-1

3 Germano G, Frapolli R, Simone M, Tavecchio M, Erba E, Pesce S, Pasqualini F, Grosso F, Sanfilippo R, Casali PG, Gronchi A,

Virdis E, Tarantino E, Pilotti S, Greco A, Nebuloni M, Galmarini CM, Tercero JC, Mantovani A, D'Incalci M and Allavena P: Antitumor and anti-inflammatory effects of trabectedin on human myxoid liposarcoma cells. Cancer Res *70(6)*: 2235-2244, 2010. PMID: 20215499. DOI: 10.1158/0008-5472.CAN-09-2335

4 Germano G, Frapolli R, Belgiovine C, Anselmo A, Pesce S, Liguori M, Erba E, Uboldi S, Zucchetti M, Pasqualini F, Nebuloni M, van Rooijen N, Mortarini R, Beltrame L, Marchini S, Fuso Nerini I, Sanfilippo R, Casali PG, Pilotti S, Galmarini CM, Anichini A, Mantovani A, D'Incalci M and Allavena P: Role of macrophage targeting in the antitumor activity of trabectedin. Cancer Cell *23(2)*: 249-262, 2013. PMID: 23410977. DOI: 10.1016/j.ccr.2013.01.008

5 Tomao F, D'Incalci M, Biagioli E, Peccatori FA and Colombo N: Restoring platinum sensitivity in recurrent ovarian cancer by extending the platinum-free interval: Myth or reality? Cancer *123(18)*: 3450-3459, 2017. PMID: 28678350. DOI: 10.1002/cncr.30830

6 Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia FM, Pujade-Lauraine E, Lisyanskaya AS, Makhson AN, Rolski J, Gorbounova VA, Ghatage P, Bidzinski M, Shen K, Ngan HY, Vergote IB, Nam JH, Park YC, Lebedinsky CA and Poveda AM: Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. J Clin Oncol *28(19)*: 3107-3114, 2010. PMID: 20516432. DOI: 10.1200/JCO.2009.25.4037

7 Penel N, Demetri GD, Blay JY, Cousin S, Maki RG, Chawla SP, Judson I, von Mehren M, Schöffski P, Verweij J, Casali P, Rodenhuis S, Schütte HJ, Cassar A, Gomez J, Nieto A, Zintl P, Pontes MJ and Le Cesne A: Growth modulation index as metric of clinical benefit assessment among advanced soft tissue sarcoma patients receiving trabectedin as a salvage therapy. Ann Oncol *24(2)*: 537-542, 2013. PMID: 23117071. DOI: 10.1093/annonc/mds470

8 Sessa C, De Braud F, Perotti A, Bauer J, Curigliano G, Noberasco C, Zanaboni F, Gianni L, Marsoni S, Jimeno J, D'Incalci M, Dall'ó E and Colombo N: Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails. J Clin Oncol *23(9)*: 1867-1874, 2005. PMID: 15774779. DOI: 10.1200/JCO.2005.09.032

9 Krasner CN, McMeekin DS, Chan S, Braly PS, Renshaw FG, Kaye S, Provencher DM, Campos S and Gore ME: A Phase II study of trabectedin single agent in patients with recurrent ovarian cancer previously treated with platinum-based regimens. Br J Cancer *97(12)*: 1618-1624, 2007. PMID: 18000504. DOI: 10.1038/sj.bjc.6604088

10 Del Campo JM, Roszak A, Bidzinski M, Ciuleanu TE, Hogberg T, Wojtukiewicz MZ, Poveda A, Boman K, Westermann AM, Lebedinsky C and Yondelis Ovarian Cancer Group: 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 *20(11)*: 1794-1802, 2009. PMID: 19556318. DOI: 10.1093/annonc/mdp198

11 Scambia G, Raspagliesi F, Valabrega G, Colombo N, Pisano C, Cassani C, Tognon G, Tamberi S, Mangili G, Mammoliti S, De Giorgi U, Greco F, Mosconi AM, Breda E, Artioli G, Andreetta C, Casanova C, Ceccherini R, Frassoldati A and Lorusso D: Randomized phase III trial on trabectedin (ET-743) single agent versus clinician's choice chemotherapy in recurrent ovarian, primary peritoneal, or fallopian tube cancers of BRCA-mutated or BRCAness phenotype patients (MITO23). Journal of Clinical Oncology *40(17_suppl)*: LBA5504-LBA5504, 2022. DOI: 10.1200/JCO.2022.40.17_suppl.LBA5504

12 Casado A, Callata HR, Manzano A, Marquina G, Alonso T, Gajate P, Sotelo M, Cabezas S, Fernández C and Díaz-Rubio E: Trabectedin for reversing platinum resistance and resensitization to platinum in patients with recurrent ovarian cancer. Future Oncol *15(3)*: 271-280, 2019. PMID: 30465613. DOI: 10.2217/fon-2018-0554

13 Pignata S, Scambia G, Bologna A, Signoriello S, Vergote IB, Wagner U, Lorusso D, Murgia V, Sorio R, Ferrandina G, Sacco C, Cormio G, Breda E, Cinieri S, Natale D, Mangili G, Pisano C, Cecere SC, Di Napoli M, Salutari V, Raspagliesi F, Arenare L, Bergamini A, Bryce J, Daniele G, Piccirillo MC, Gallo C and Perrone F: Randomized controlled trial testing the efficacy of platinum-free interval prolongation in advanced ovarian cancer: The MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG study. J Clin Oncol *35(29)*: 3347-3353, 2017. PMID: 28825853. DOI: 10.1200/JCO.2017.73.4293

14 Colombo N, Gadducci A, Sehouli J, Rulli E, Mäenpää J, Sessa C, Montes A, Ottevanger NB, Berger R, Vergote I, D'Incalci M, Churruca Galaz C, Chekerov R, Nyvang GB, Riniker S, Herbertson R, Fossati R, Barretina-Ginesta MP, Deryal M, Mirza MR, Biagioli E, Iglesias M, Funari G, Romeo M, Tasca G, Pardo B, Tognon G, Rubio-Pérez MJ, DeCensi A, De Giorgi U, Zola P, Benedetti Panici P, Aglietta M, Arcangeli V, Zamagni C, Bologna A, Westermann A, Heinzelmann-Schwarz V, Tsibulak I, Wimberger P, Poveda A and INOVATYON study group: INOVATYON/ENGOT-ov5 study: Randomized phase III international study comparing trabectedin/pegylated liposomal doxorubicin (PLD) followed by platinum at progression vs carboplatin/PLD in patients with recurrent ovarian cancer progressing within 6-12 months after last platinum line. Br J Cancer *128(8)*: 1503-1513, 2023. PMID: 36759720. DOI: 10.1038/s41416-022-02108-7

15 Ray-Coquard I: Trabectedin mechanism of action and platinum resistance: molecular rationale. Future Oncol *13(23s)*: 17-21, 2017. PMID: 29020822. DOI: 10.2217/fon-2017-0318

16 Lorusso D, Scambia G, Pignata S, Sorio R, Amadio G, Lepori S, Mosconi A, Pisano C, Mangili G, Maltese G, Sabbatini R, Artioli G, Gamucci T, Di Napoli M, Capoluongo E, Ludovini V, Raspagliesi F and Ferrandina G: Prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients: the MITO 15 trial. Ann Oncol *27(3)*: 487-493, 2016. PMID: 26681678. DOI: 10.1093/annonc/mdv608

17 Cohen S, Bruchim I, Graiver D, Evron Z, Oron-Karni V, Pasmanik-Chor M, Eitan R, Bernheim J, Levavi H, Fishman A and Flescher E: Platinum-resistance in ovarian cancer cells is mediated by IL-6 secretion via the increased expression of its target cIAP-2. J Mol Med (Berl) *91(3)*: 357-368, 2013. PMID: 23052480. DOI: 10.1007/s00109-012-0946-4

18 Kavanagh J, Tresukosol D, Edwards C, Freedman R, Gonzalez de Leon C, Fishman A, Mante R, Hord M and Kudelka A: Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer. J Clin Oncol *13(7)*: 1584-1588, 1995. PMID: 7602347. DOI: 10.1200/JCO.1995.13.7.1584

19 Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D and Ray-Coquard I: Bevacizumab combined with chemotherapy for

platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol *32(13)*: 1302-1308, 2014. PMID: 24637997. DOI: 10.1200/JCO.2013.51.4489

20 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

21 Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, du Bois A, Kristensen G, Jakobsen A, Sagae S, Greven K, Parmar M, Friedlander M, Cervantes A, Vermorken J and Gynecological Cancer Intergroup: Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer *21(2)*: 419-423, 2011. PMID: 21270624. DOI: 10.1097/IGC.0b013e3182070f17

22 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB and de Haes JC: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst *85(5)*: 365-376, 1993. PMID: 8433390. DOI: 10.1093/jnci/85.5.365

23 Greimel E, Bottomley A, Cull A, Waldenstrom AC, Arraras J, Chauvenet L, Holzner B, Kuljanic K, Lebrec J, D'haese S and EORTC Quality of Life Group and the Quality of Life Unit: An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer *39(10)*: 1402-1408, 2003. PMID: 12826043. DOI: 10.1016/s0959-8049(03)00307-1

24 Ziegler-Heitbrock L, Ancuta P, Crowe S, Dalod M, Grau V, Hart DN, Leenen PJ, Liu YJ, MacPherson G, Randolph GJ, Scherberich J, Schmitz J, Shortman K, Sozzani S, Strobl H, Zembala M, Austyn JM and Lutz MB: Nomenclature of monocytes and dendritic cells in blood. Blood *116(16)*: e74-e80, 2010. PMID: 20628149. DOI: 10.1182/blood-2010-02-258558

25 Gaillard S, Oaknin A, Ray-Coquard I, Vergote I, Scambia G, Colombo N, Fernandez C, Alfaro V, Kahatt C, Nieto A, Zeaiter A, Aracil M, Vidal L, Pardo-Burdalo B, Papai Z, Kristeleit R, O'Malley DM, Benjamin I, Pautier P and Lorusso D: Lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum-resistant ovarian cancer: A multicenter, randomized, controlled, open-label phase 3 study (CORAIL). Gynecol Oncol *163(2)*: 237-245, 2021. PMID: 34521554. DOI: 10.1016/j.ygyno.2021.08.032

26 Von Hoff DD: There are no bad anticancer agents, only bad clinical trial designs – twenty-first Richard and Hinda Rosenthal Foundation Award Lecture. Clin Cancer Res *4(5)*: 1079-1086, 1998. PMID: 9607564.

27 Gynecologic Oncology Group, Markman M, Blessing J, Rubin SC, Connor J, Hanjani P and Waggoner S: Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol *101(3)*: 436-440, 2006. PMID: 16325893. DOI: 10.1016/j.ygyno.2005.10.036

28 Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, Hande KR, Keohan ML, Samuels BL, Schuetze S, Lebedinsky C, Elsayed YA, Izquierdo MA, Gómez J, Park YC and Le Cesne A: Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol *27(25)*: 4188-4196, 2009. PMID: 19652065. DOI: 10.1200/JCO.2008.21.0088

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