FINAL STUDY REPORT

Title:

Retrospective multicenter study of elderly patients with ovarian cancer treated with trabectedin and PLD according to SmPC

Study Number: **GEICO 105-O**

Retrospective, non-interventional (observational) study

Report Version**:** V1 of 14 December 2022

Sponsor**:** Grupo Español de Investigación en Cáncer de Ovario (GEICO)

Clinical Coordinating Investigator:
Dr. María Jesús Rubio – Hospital Universitario Reina Sofía (Córdoba)

Funding entity:
PharmaMar

Study Information

Title	Retrospective multicenter study of elderly patients with ovarian cancer treated with trabectedin and PLD according to SmPC
Sponsor	Grupo Español de Investigación en Cáncer de Ovario (GEICO)
Version identifier of the final study report	V1 of 14 December 2022
Date of last version of the final study report	14 December 2022
Active substance(s)	Two drugs under observation: • Trabectedin • Doxorubicin hydrochloride
Medicinal product(s)	Two drugs under observation: • Trabectedin • Pegylated liposomal doxorubicin
Marketing authorization holder	• PharmaMar (Trabectedin) • Pegylated liposomal doxorubicin (various manufacturers)
Research question and objectives	Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for platinum-sensitive relapsed ovarian cancer and is an option for those patients in whom platinum is not the best option. There are some studies with trabectedin in combination with PLD in which some patients with this profile have been included, although not exclusively. Therefore, it is of interest to study the safety and efficacy profile of this treatment in elderly patients. The general objective of the study is to describe the real-life use of trabectedin + PLD in elderly patients diagnosed with platinum-sensitive relapsed ovarian cancer treated according to the Summary of Product Characteristics (SmPC). The specific objective is to evaluate real-world data about: • Safety profile • Progression-free survival (PFS) • Overall response rate (ORR) (CR+PR) according to RECIST 1.1 criteria • Disease control rate (DCR) (CR+PR+SD) • Overall survival (OS) • Trabectedin + PLD treatment information • Previous and subsequent treatments to trabectedin + PLD • Patient characteristics and medical history
Country of study	Spain

Author	Patricio Ledesma Head of Clinical Operations Sofpromed Investigación Clínica, SL CRO appointed by the Sponsor (GEICO)

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1. Abstract

Title

Retrospective multicenter study of elderly patients with ovarian cancer treated with trabectedin and PLD according to SmPC

Keywords

Trabectedin, pegylated liposomal doxorubicin, ovarian cancer

Rationale and background

The median age at which ovarian cancer is diagnosed is 63 years (50-75). This is still a significant adverse factor for survival results. Seventy years can be considered the lower limit for the elderly term, since most of age-related changes occur later. Because of this, this group of patients is often not included in clinical trials and sometimes they do not receive adequate treatment. Little information is available on chemotherapy treatments in elderly patients. Data on the use of first-line chemotherapy in this population (EWOC-1) have recently been published [4].

Trabectedin in combination with PLD is indicated for platinum-sensitive relapsed ovarian cancer and is an option for those patients in whom platinum is not the best option. There are some studies with trabectedin in combination with PLD in which some patients with this profile have been included, although not exclusively. Therefore, it is of interest to study the safety and efficacy profile of this treatment in elderly patients. With this information we will be able to know its real use in routine clinical practice at the national level in Spain in this population for which not much information is available.

Safety and efficacy data (e.g., PFS, ORR, OS) will be collected retrospectively in order to draw conclusions about the combination of trabectedin + PLD, as a treatment option in this patient profile.

Research question and objectives

Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for platinum-sensitive relapsed ovarian cancer and is an option for those patients in whom platinum is not the best option. There are some studies with trabectedin in combination with PLD in which some patients with this profile have been included, although not exclusively. Therefore, it is of interest to study the safety and efficacy profile of this treatment in elderly patients.

The general objective of the study is to describe the real-life use of trabectedin + PLD in elderly patients diagnosed with platinum-sensitive relapsed ovarian cancer treated according to the Summary of Product Characteristics (SmPC).

The specific objective is to evaluate real-world data about:

- Safety profile
- Progression-free survival (PFS)
- Overall response rate (ORR) (CR+PR) according to RECIST 1.1 criteria
- Disease control rate (DCR) (CR+PR+SD)
- Overall survival (OS)

- Trabectedin + PLD treatment information
- Previous and subsequent treatments to trabectedin + PLD
- Patient characteristics and medical history

Study design and setting

The study consists of a retrospective observational, multicenter study in which the fundamental exposure factor being investigated is a drug (trabectedin and PLD). The study was developed at national level with 15 sites in Spain, during a data collection period of 5 months, including patients treated with trabectedin and PLD according to the SmPC.

The main treatment observed in this study was trabectedin in combination with PLD in elderly patients with platinum-sensitive relapsed ovarian cancer according to the SmPC. The recommended dose of trabectedin plus PLD is administered every three weeks by infusion over 3 hours at a dose of 1.1 mg/m^2 immediately after 30 mg/m^2 of PLD.

Subjects, study size, and inclusion/exclusion criteria

The sample size was determined by all patients diagnosed with platinum-sensitive relapsed ovarian cancer treated with trabectedin and PLD between January 1st 2015 and December 31st 2019.

This retrospective clinical study was planned to include approximately 45-50 patients with the referred characteristics (no formal sample size was calculated due to the observational nature of the study).

Given that the study was a multicenter study at national level in Spain, considering a percentage of failures in the collection or analysis of the samples (missing or unevaluable data) of around 10%, a sample size of 40-45 patients with evaluable data was estimated.

The study recruited women according to the following criteria:

Inclusion criteria:

1. Written informed consent must be signed by all patients participating in the study who can be interviewed in the hospital (accessible, alive patients) or absence of consent sheet must be signed by the investigator. Informed consent may not be required from inaccessible patients (dead, lost, etc.) according to ethics committee permissions and applicable law for retrospective studies in Spain.
2. Adult women (≥70 years at the time of treatment initiation with trabectedin and PLD).
3. Histological diagnosis of platinum-sensitive relapsed ovarian cancer (PFI ≥ 6 months).
4. Treatment started with trabectedin and PLD (at least one cycle) as standard of care between January 1st 2015 and December 31st 2019.
5. Patients must have received at least one cycle of trabectedin + PLD.

Exclusion criteria:

1. Patients without medical record available (lost, empty or unretrievable clinical information).
2. Patients who explicitly refuse to participate in the study.

Variables and data sources

- Safety profile: All trabectedin + PLD-related hematological and non-hematological, serious and non-serious adverse events (grade, start date, end date, action taken with trabectedin and/or PLD, outcome) will be collected. In addition, adverse event treatments will be registered in the study database.
- Progression-free survival (PFS): Defined as the time in months since first trabectedin + PLD dose date until radiological progression (or death due to any cause) according to RECIST 1.1 criteria.
- Overall response rate (ORR): Defined as the number of patients having a best overall response (BOR) of complete response (CR) or partial response (PR), divided by the total number of response-evaluable patients (according to RECIST 1.1 criteria).
- Disease control rate (DCR): Defined as the percentage of patients having a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST 1.1 criteria.
- Overall survival (OS): Defined as the number of months since first trabectedin + PLD dose date until death due to any cause. OS will be censored at the last date the patient was known to be alive.
- Trabectedin + PLD treatment information (for both drugs): Line number in which trabectedin + PLD was given, starting dose, relative dose intensity (RDI), total dose, dose management (reductions, delays, omissions, interruptions, and their reasons), number of treatment discontinuations, reasons for discontinuations, duration of treatment, treatment status (ended or ongoing), and number of cycles.
- Previous and subsequent treatments to trabectedin + PLD: Number of previous/subsequent treatments, type, date, previous antiangiogenic agents, and clinical results of treatments before and after trabectedin + PLD.
- Patient characteristics and medical history: Sex, age, ECOG, platinum sensitivity, platinum-free interval (PFI), progression free survival (PFS), mutational status (*BRCA1*, *BRCA2*, and in other HRR genes [germline/somatic] and variant classification [pathogenic, probably pathogenic, or VOUS]), histology, tumor grade and number of previous relapses.

These data were obtained from the participating hospitals per local practice (clinical records, local reports).

Results

Between November 2021 and June 2022, 43 patients were recruited with median age 74 years (70-86). At initial diagnosis, most common FIGO stages were IIIC (51.2%), IVB (11.6%), and IIIB (7.0%). Before trabectedin+PLD (baseline), patients had ECOG performance status 0, 1, or 2 (34.1%, 41.5%, and 9.8%) and 81.4% had measurable disease. The median number of previous lines was 2 (1-6). The initial dose of trabectedin was 1.1 mg/m^2 in 76.7% of patients (16.3% with <1.1 and 4.7% with >1.1 mg/m^2) while 76.7% of patients had PLD at 30 mg (18.6% with <30 mg and 2.3% with >30 mg). The median of trabectedin+PLD cycles was 5 (1-21) and 53.5% of patients had at least one cycle delayed. All patients ended treatment for the following reasons: patient's decision (7.0%), doctor's decision (23.3%), disease progression (39.5%), toxicity (23.83%) and 7.0% due to other factors. Median PFS for the trabectedin+PLD combination was 7.7 months (95% CI 4.4-9.4) with best overall response rates of 4 CR (9.3%), 14 PR (32.6%), 13 SD (30.2%), and 5 PD (11.6%). Median overall survival (OS) was 19.5 months (95% CI 12.8-27.2). Overall, the most common G3-4 hematological events were neutropenia (23.3%), thrombocytopenia (7.0%), and anemia (2.3%),

being asthenia (11.6%), mucositis (4.7%), and transaminitis (4.7%) the most frequent G3 non-hematological toxicities.

Discussion

The safety profile of the trabectedin+PLD combination for elderly women in real-life setting is manageable and efficacy results are comparable to those of previous clinical trials.

Marketing Authorization Holder

PharmaMar

Names and affiliations of principal investigators

1. María Jesús Rubio – Hospital Universitario Reina Sofía de Córdoba (Coordinating Investigator)
2. Blanca Hernando Fernández – Hospital Universitario de Burgos
3. Eva Guerra – Hospital Universitario Ramón y Cajal
4. Anna Carbó – Instituto Català d'Oncologia (ICO)
5. Luis Miguel de Sande – Hospital Universitario de León
6. Arancha Manzano – Hospital Clínico San Carlos
7. Alba González-Haba – Hospital Universitario de Badajoz
8. Alfonso Yubero-Esteban - Hospital Clínico Universitario Lozano Blesa
9. María del Mar Gordon – Hospital Universitario de Jerez de la Frontera
10. Diego Soto de Prado – Hospital Clínico de Valladolid
11. Ignacio Romero – Fundación Instituto Valenciano de Oncología
12. Purificación Estévez - Hospital Universitario Virgen del Rocío
13. Carlos E. Robles – Hospital Virgen de Valme
14. Jerónimo Martínez – Hospital Clínico Universitario Virgen de la Arrixaca
15. Miguel Corbellas – Hospital Universitario Dr. Peset

2. List of abbreviations

- AE: Adverse Event
- CM: Concomitant Medication
- CR: Complete Response
- CRO: Clinical Research Organization
- ECOG: Eastern Cooperative Oncology Group
- E-CRF: Electronic Case Report Form
- GEICO: Grupo Español de Investigación en Cáncer de Ovario
- ICF: Informed Consent Form
- KM: Kaplan-Meier
- MH: Medical History
- ORR: Overall Response Rate
- PFS: Progression-Free Survival
- PIS: Patient Information Sheet
- PR: Partial Response
- RECIST: Response Evaluation Criteria in Solid Tumors
- SD: Stable Disease

3. Investigators

1. María Jesús Rubio – Hospital Universitario Reina Sofía de Córdoba (Coordinating Investigator)
2. Blanca Hernando Fernández – Hospital Universitario de Burgos
3. Eva Guerra – Hospital Universitario Ramón y Cajal
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13. Carlos E. Robles – Hospital Virgen de Valme
14. Jerónimo Martínez – Hospital Clínico Universitario Virgen de la Arrixaca
15. Miguel Corbellas – Hospital Universitario Dr. Peset

4. Other responsible parties

The Sponsor of this study was the Grupo Español de Investigación en Cancer de Ovario (GEICO).

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	1 November 2021	29 November 2021	
End of data collection	31 March 2022	10 June 2022	Includes data cleaning period. Delay caused by the need of issuing additional queries.
Final report of study results	30 June 2022	14 December 2022	Delay caused by the need of issuing additional queries.

6. Rationale and background

Ovarian cancer is a devastating disease, being the fourth leading cause of cancer death in women. Its incidence increases at menopause, the mean age at diagnosis is 63 years. This is still a significant adverse factor for survival results, therefore better treatments are needed for older patients [1].

Aging is the progressive reduction of the functional reserve of multiple organ systems, as the result of spontaneous depletion and environmental influences. Seventy years of age can be considered the lower limit of senescence because most age-related changes occur after senescence.

Sabatier, Renaud, et al published a study "Prognostic factors for epithelial ovarian epithelial cancer in the elderly: a case-control study" in which they conclude that the prognosis of ovarian cancer is worse for older women, due to the fact that they are more frequently suboptimally tretated. In this study, no correlation could be observed between geriatric factors and the achievement of surgery or chemotherapy. Therefore, the treatment decision should be based on an objective geriatric evaluation to improve the outcome in this population [2].

GOG conducted an observational study (GOG 273) of chemotherapy toxicity in elderly patients with ovarian, primary peritoneal, or fallopian tube carcinoma. 290 patients were enrolled between August 2011 and Dec 2019. Patients receive chemotherapy comprising carboplatin, paclitaxel, and colony stimulating factors (regimen 1) or carboplatin alone (regimen 2) every 21 days for 4 cycles as chosen by their physicians and / or patients. Patients may undergo additional surgery and / or chemotherapy at the discretion of the treating physician. Baseline blood tests are drawn at 1, 6, and 24 hours of each cycle for pharmacokinetic studies. The quality of life of the patients is assessed using the FACT-O, FACT-Ntx, IADL questionnaires and the ability to complete the social activity questionnaires at the beginning of the study, before cycles 1 and 3, and after 3 to 6 weeks after completing treatment. Nutritional status, such as body mass index and weight loss, and comorbidity and hearing impairment are also assessed. They conclude that patients with a higher baseline IADL (instrumental activities of daily living) score (more independent) were more likely to complete 4 cycles of chemotherapy and less likely to experience grade 3 or higher toxicity [3].

The results of the EWOC-1 study, a randomized study to evaluate 3 regimens of 1st-line chemotherapy in vulnerable elderly patients diagnosed with ovarian cancer (A GCIG-ENGOT-GINECO study) have recently been published, concluding after comparing 3 chemotherapy regimens (two combinations of carboplatin + paclitaxel and the third with carboplatin alone), that monotherapy is less active and vulnerable patients have less survival than with combination regimens. Therefore, even elderly patients should be offered a carboplatin + paclitaxel regimen [4].

Currently, there are few studies that collect data on ovarian cancer in this population exclusively and in second or later lines.

In clinical trials, a part of the population affected by the disease (elderly) is not usually included. This patient profile is more common in daily clinical practice: older patients, with ECOG or PS 1-2, with comorbidities, polymedicated, etc. Around 23% of ovarian cancer patients are 70 years or older [5] and their prognosis so far tends to be worse overall, probably due to the misperception of the possibilities of optimal surgery and adequate systemic treatment.

Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with recurrent platinum-sensitive ovarian cancer following the results of study OVA-301 [6]. When choosing a therapy in recurrent disease, we must not only take into account the

platinum free interval, but also the morbidities, toxicities, number of previous platinum lines, response to the last line, *BRCA* mutational status, etc. [7]. The results of the real-life European NIMES-ROC study consistently support that trabectedin + PLD is active in patients with platinum-sensitive recurrent ovarian cancer with an acceptable and manageable safety profile. The overall findings appear to be consistent with those previously observed in a randomized controlled clinical phase III trial and further support the use of trabectedin + PLD for heavily pre-treated patients with platinum-sensitive recurrent ovarian cancer [8].

In the OVA-301 study [9] and the real-life study, NIMES ROC [8], some patients with these characteristics (62-86 years) were included, so it is considered that it would be of interest to collect retrospective data from safety and efficacy at the national level to have information on the use of trabectedin in combination with PLD in daily clinical practice in elderly patients, since this is not currently available in this population.

Currently the data that are available in the population of elderly women with recurrent ovarian cancer are through non-pre-planned sub-analyzes, that is, there is no study that specifically collects the data of this profile of patients.

Oza et al. (ROSiA study) explored the efficacy and safety of bevacizumab in patients older than 70 years compared to a young population with newly diagnosed ovarian cancer. 12% of the patients included were 70 years or older, had greater comorbidities than the young population (hypertension, stage IV, ECOG greater than 1). Older patients experienced a higher incidence of adverse effects of all grades compared to the younger profile. Regarding progression-free survival at two years, the results obtained are similar between the two populations despite having a worse prognosis [10].
In the platinum-resistant elderly population, there are data from the AURELIA study subanalysis, where 37% were 65 years or older. The median PFS and response rate were similar between those <65 and ≥65 years. Grade 2 and 3 hypertension were more common in the older than 65 age group [11].

Olaparib has been studied in this population after an analysis of 8 prospective studies. Data were collected from 398 patients (78 of them aged 65 years or older), the majority had received ≥ 5 prior lines of chemotherapy. Tolerability and toxicity of olaparib was similar between women ≥ 65 years and < 65 years of age treated for advanced recurrent ovarian cancer [12].

Regarding trabectedin, the data available are from the patients included in the phase III OVA-301 trial and in the real-life study NIMES ROC [8]. Although this population is not exclusively analyzed, patients older than 65 years and polytreated have been included [8,9]. Vergote et al., analyzed the safety profile in the population older than 65 years included in the OVA-301. There were no marked differences by age in the safety profile/tolerability of trabectedin + PLD, except for more fatigue in the older subset (≥ 65 years) compared with younger patients (< 65 years) [13]. Therefore, it would be of interest to collect data on the safety and efficacy of trabectedin in combination with PLD in elderly patients with advanced relapsed ovarian cancer to obtain information on daily clinical practice at the national level in this subgroup of patients.

7. Research questions and objectives

Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is indicated for platinum-sensitive relapsed ovarian cancer and is an option for those patients in whom platinum is not the best option. There are some studies with trabectedin in combination with PLD in which some patients with this profile have been included, although not exclusively. Therefore, it is of interest to study the safety and efficacy profile of this treatment in elderly patients.

The general objective of the study was to describe the real-life use of trabectedin + PLD in elderly patients diagnosed with platinum-sensitive relapsed ovarian cancer treated according to the Summary of Product Characteristics (SmPC).

The specific objective was to evaluate real-world data about:

- Safety profile
- Progression-free survival (PFS)
- Overall response rate (ORR) (CR+PR) according to RECIST 1.1 criteria
- Disease control rate (DCR) (CR+PR+SD)
- Overall survival (OS)
- Trabectedin + PLD treatment information
- Previous and subsequent treatments to trabectedin + PLD
- Patient characteristics and medical history

8. Amendments and updates

One amendment was performed to generate protocol version 2.0 of 27 October 2021, which included the following changes:

5.3 Population.

- Inclusion criteria 2: ≥70 years at the time of treatment initiation with trabectedin and PLD (not the time of initial diagnosis).
- Inclusion criteria 3 has been clarified in terms of platinum sensitivity, specifying that PFI must be ≥ 6 months.
- Exclusion criteria 3: Life expectancy < 3 months has been deleted as it is not applicable for a retrospective observational study.

PFI was clarified to "Platinum Free-Interval", and PFS as “Progression Free-Survival” in all corresponding sections.

9. Research methods

9.1 Study design and setting

The study consisted of a retrospective observational, multicenter study in which the fundamental exposure factor being investigated was a drug (trabectedin and PLD). The study was developed at national level with 15 sites in Spain, during a data collection period of 5 months, including patients treated with trabectedin and PLD according to the SmPC.

The main treatment observed in this study was trabectedin in combination with PLD in elderly patients with platinum-sensitive relapsed ovarian cancer according to the SmPC. The recommended dose of trabectedin plus PLD was administered every three weeks by infusion over 3 hours at a dose of 1.1 mg/m^2 immediately after 30 mg/m^2 of PLD.

9.2 Subjects

The study recruited women according to the following criteria:

Inclusion criteria:

1. Written informed consent must be signed by all patients participating in the study who can be interviewed in the hospital (accessible, alive patients) or absence of consent sheet must be signed by the investigator. Informed consent may not be required from inaccessible patients (dead, lost, etc.) according to ethics committee permissions and applicable law for retrospective studies in Spain.
2. Adult women (≥70 years at the time of treatment initiation with trabectedin and PLD).
3. Histological diagnosis of platinum-sensitive relapsed ovarian cancer (PFI ≥ 6 months).
4. Treatment started with trabectedin and PLD (at least one cycle) as standard of care between January 1st 2015 and December 31st 2019.
5. Patients must have received at least one cycle of trabectedin + PLD.

Exclusion criteria:

1. Patients without medical record available (lost, empty or unretrievable clinical information).
2. Patients who explicitly refuse to participate in the study.

9.3 Variables

- Safety profile: All trabectedin + PLD-related hematological and non-hematological, serious and non-serious adverse events (grade, start date, end date, action taken with trabectedin and/or PLD, outcome) will be collected. In addition, adverse event treatments will be registered in the study database.
- Progression-free survival (PFS): Defined as the time in months since first trabectedin + PLD dose date until radiological progression (or death due to any cause) according to RECIST 1.1 criteria.
- Overall response rate (ORR): Defined as the number of patients having a best overall response (BOR) of complete response (CR) or partial response (PR), divided by the total number of response-evaluable patients (according to RECIST 1.1 criteria).

- Disease control rate (DCR): Defined as the percentage of patients having a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST 1.1 criteria.
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- Trabectedin + PLD treatment information (for both drugs): Line number in which trabectedin + PLD was given, starting dose, relative dose intensity (RDI), total dose, dose management (reductions, delays, omissions, interruptions, and their reasons), number of treatment discontinuations, reasons for discontinuations, duration of treatment, treatment status (ended or ongoing), and number of cycles.
- Previous and subsequent treatments to trabectedin + PLD: Number of previous/subsequent treatments, type, date, previous antiangiogenic agents, and clinical results of treatments before and after trabectedin + PLD.
- Patient characteristics and medical history: Sex, age, ECOG, platinum sensitivity, platinum-free interval (PFI), progression free survival (PFS), mutational status (*BRCA1*, *BRCA2*, and in other HRR genes [germline/somatic] and variant classification [pathogenic, probably pathogenic, or VOUS]), histology, tumor grade and number of previous relapses.

9.4 Data sources and measurement

The data collected in this study included family history characteristics, clinical-pathological features of the tumor, treatment approaches (including therapies before and after the main treatment under study), safety and efficacy information, and long-term outcomes. These data were obtained from the participating hospitals per local practice (clinical records, local reports).

9.5 Bias

Since this was a retrospective observational study, no sources of bias were identified.

9.6 Study size

The sample size was determined by all patients diagnosed with platinum-sensitive relapsed ovarian cancer treated with trabectedin and PLD between January 1st 2015 and December 31st 2019.

This retrospective clinical study was planned to include approximately 45-50 patients with the referred characteristics (no formal sample size was calculated due to the observational nature of the study).

Given that the study was a multicenter study at national level in Spain, considering a percentage of failures in the collection or analysis of the samples (missing or unevaluable data) of around 10%, a sample size of 40-45 patients with evaluable data was estimated.

9.7 Data transformation

Stratification Factors

No particular stratification factors were used.

Patients Characteristics

The information of patients such as age, sex, race and other baseline characteristics were summarized.

Exposure

All data collected that was not free text was reported: mean starting dose, number of dose reductions, reasons for reductions, number of treatment discontinuations, reasons for discontinuations, and duration of treatment.

Concomitant Medications (CMs) and Medical History (MH)

The CMs were presented in the summary using frequency counts and percentages. When summarizing the number and percentage of subjects with some concomitant medications, subjects with multiple occurrences of the same CM were counted only once.

In MH all data collected that was not free text was reported: number of previous relapses, number of previous chemotherapy regimens, types of treatments received (chemotherapy, targeted therapies), prior maintenance or with maintenance, treatment-free interval (platinum-based chemotherapy, non-platinum-based chemotherapy, targeted therapy).

Initial Ovarian Cancer Diagnosis

The information of initial diagnosis such as age, tumor histology, and FIGO stage was summarized.

Ovarian Cancer Treatments (Previous Surgeries)

All the data collected was summarized as the number of previous surgeries (categorically and numerically).

Ovarian Cancer Treatments (Previous Systemic Treatments)

All data collected other than free text was reported: total number of previous lines, total number of each type of treatment received per patient.

Progression-Free Survival (PFS)

PFS: Measured in months from the date of the first dose to the date of the first progression (PD) (whether radiological, clinical or biological) or to the date of death from any cause, whichever occurs first.

Objective Response Rate (ORR)

ORR: Confirmed best overall tumor response of CR or PR according to RECIST v1.1.

Adverse Events (AEs)

The AEs were presented in the summary using counts and frequency percentages. They were stratified by grade and event. The number of events and the number of patients and percentage who had that event was indicated.

Clinical Laboratory Evaluations

Laboratory raw variables collected in the baseline visit were summarized.

9.8 Statistical methods

9.8.1 Main summary measures

All variables will be summarized separately. Depending on the type of the variable, the following statistics were reported:

- Continuous variables: number of subjects (n), number of missings, mean, standard deviation (STD), median, standard error (SE, if needed), 25th and 75th percentiles, minimum, and maximum.
- Categorical variables: frequencies and percentages (calculated over the number of non-missing values).

In general, minimum and maximum were reported using the same number of decimal places as collected in the raw data. Mean, STD, median, 25th and 75th percentiles will be reported with one additional decimal place.

9.8.2 Main statistical methods

Time to event data was listed and summarized at every specified timepoint using the number patients at risk, number of patients censored, number of patients with the event, Kaplan Meier estimate (%), and the 95% confidence interval. In addition, 25th, 50% and 75th percentiles from Kaplan-Meier (KM) curves will be used.

9.8.3 Missing values

No imputation of missing data was performed.

9.8.4 Sensitivity analyses

Not applicable.

9.8.5 Amendments to the statistical analysis plan

No amendments were made to the initial statistical analysis plan.

9.9 Quality control

Each study site was subject to remote clinical monitoring and review by the ethics committees.

The study data was reviewed and cleaned by periodic inspection of the e-CRFs. Remote reviews were performed with enough frequency to ascertain the following:

- Integrity and accuracy of data:
- Informed consent (version, signature and date)

- Eligibility criteria
- e-CRF completion.
- Protocol deviations according GCPs and the applicable regulatory local requirements. Taking appropriate action to prevent recurrence to the detected deviations.
- Compliance with approved protocol and all approved amendments, if any.
- That the investigator receives all documents needed to conduct the study properly and to comply with the applicable regulations.
- That the investigator and local staff are adequately informed about the study through telephone initiation visits.

The study appointed CRO reviewed the e-CRFs for compliance with the protocol, and for inconsistent or missing data. When any missing data or data anomalies were found, queries were sent to the relevant center for resolution. Following the required reviews, the e-CRF data items were exported into the clinical study database for statistical analysis.

10. Results

10.1 Participants

The study recruited a total of 43 eligible participants.

10.2 Descriptive data

Table 1. Subject Disposition. Descriptive Statistics.
All Patients.

	Total (n=46)
Signed Informed Consent	
Yes	46 (100.0%)
No	0 (0.0%)
Way of signature	
Present	5 (10.9%)
Absent (definitive)	41 (89.1%)
Absent (temporal, by phone)	0 (0.0%)
Enrolled patients	
Yes	43 (93.5%)
No	3 (6.5%)
Wavers?	
Yes	0 (0.0%)
No	46 (100.0%)
Initial Dose of Trabectedin (mg/m2)	
N	43
N Miss	3 (6.5%)
Mean	1.1
Std Dev	0.1
Median	1.1
q1	1.1
q3	1.1
Minimum	0.8
Maximum	1.5
Trabectedin split	
Missing	1 (2.3%)
<1.1	7 (16.3%)
1.1	33 (76.7%)
>1.1	2 (4.7%)

*Trabectedin and PLD initial dose based on patient.

Table 1. Subject Disposition. Descriptive Statistics.
All Patients.

	Total (n=46)
Initial Dose of PLD (mg/m2)	
N	43
N Miss	3 (6.5%)
Mean	29.4
Std Dev	3.3
Median	30.0
q1	30.0
q3	30.0
Minimum	23
Maximum	46
PLD split	
Missing	1 (2.3%)
<30	8 (18.6%)
30	33 (76.7%)
>30	1 (2.3%)
End of treatment	
Yes	44 (100.0%)
No	0 (0.0%)
Reason of EoT	
Patient's decision	3 (6.8%)
Doctor's decision	10 (22.7%)
Progression	18 (40.9%)
Toxicity	10 (22.7%)
Other	3 (6.8%)
Last Status	
Alive with disease	7 (15.9%)
Alive without disease	1 (2.3%)
Lost to follow-up	0 (0.0%)
Dead	36 (81.8%)
Progression	
Yes	42 (95.5%)
No	2 (4.5%)
Death	
Yes	36 (83.7%)
No	7 (16.3%)

*Trabectedin and PLD initial dose based on patient.

Table 1. Subject Disposition. Descriptive Statistics.
All Patients.

	Total (n=46)
Reason of Death	
Ovarian cancer	35 (97.2%)
Toxicity	0 (0.0%)
Unknown	1 (2.8%)
Other	0 (0.0%)

*Trabectedin and PLD initial dose based on patient.

Table 2. Analysis Sets. Descriptive Statistics.
All Patients.

	Total (n=46)
Patients with signed ICF	
Yes	46 (100.0%)
No	0 (0.0%)
Intent-to-Treat	
Yes	43 (93.5%)
No	3 (6.5%)
Safety Analysis Set	
Yes	43 (93.5%)
No	3 (6.5%)
Full Analysis Set	
Yes	43 (93.5%)
No	3 (6.5%)
Per Protocol	
Yes	43 (93.5%)
No	3 (6.5%)

Table 3. Patients Characteristics. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Age (at trabectedin+PLD treatment initiation according to SmPC)	
N	43
N Miss	0 (0.0%)
Mean	74.7
Std Dev	3.5
Median	74.0
q1	72.0
q3	77.0
Minimum	70
Maximum	86
Age	
Missing	0 (0.0%)
<70	0 (0.0%)
[70-75]	30 (69.8%)
>75	13 (30.2%)
Race	
White	41 (95.3%)
Black or African American	0 (0.0%)
Asian	0 (0.0%)
American Indian or Alaska Native	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
Unknown	2 (4.7%)
Existence of measurable disease	
Yes	35 (83.3%)
No	7 (16.7%)
Existence of bulky disease	
Yes	12 (29.3%)
No	29 (70.7%)

Table 3. Patients Characteristics. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Weight	
N	37
N Miss	6 (14.0%)
Mean	69.5
Std Dev	12.2
Median	69.0
q1	59.0
q3	79.0
Minimum	49
Maximum	94
Weight (Kg)	
Missing	6 (14.0%)
<58	7 (16.3%)
[58-77]	18 (41.9%)
>77	12 (27.9%)
ECOG	
0	14 (34.1%)
1	17 (41.5%)
2	4 (9.8%)
3	0 (0.0%)
4	0 (0.0%)
Unknown	6 (14.6%)
Platelet count (cells/uL)	
Missing	6 (14.0%)
<150000	3 (7.0%)
>=150000	34 (79.1%)
Leukocytes count (10^9/L)	
Missing	6 (14.0%)
<4500	37 (86.0%)
>=4500	0 (0.0%)
Neutrophils count (cells/uL)	
Missing	6 (14.0%)
<1500	0 (0.0%)
>=1500	37 (86.0%)

Table 3. Patients Characteristics. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Hemoglobin count (g/dL)	
Missing	4 (9.3%)
<11.6	14 (32.6%)
>=11.6	25 (58.1%)
CA 125 (U/mL)	
Missing	6 (14.0%)
<=46	5 (11.6%)
[46-500]	22 (51.2%)
[500-1000]	7 (16.3%)
>1000	3 (7.0%)

Table 4. Exposure. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Initial Dose of Trabectedin (mg/m2)	
N	42
N Miss	1 (2.3%)
Mean	1.1
Std Dev	0.1
Median	1.1
q1	1.1
q3	1.1
Minimum	0.8
Maximum	1.5
Trabectedin split	
Missing	1 (2.3%)
<1.1	7 (16.3%)
1.1	33 (76.7%)
>1.1	2 (4.7%)
Total dose Trabectedin	
N	35
N Miss	8 (18.6%)
Mean	2.5
Std Dev	4.4
Median	1.8
q1	1.5
q3	1.9
Minimum	1
Maximum	28
Initial Dose of PLD (mg/m2)	
N	42
N Miss	1 (2.3%)
Mean	29.4
Std Dev	3.3
Median	30.0
q1	30.0
q3	30.0
Minimum	23
Maximum	46

Table 4. Exposure. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
PLD split	
Missing	1 (2.3%)
<30	8 (18.6%)
30	33 (76.7%)
>30	1 (2.3%)
Total dose PLD	
N	35
N Miss	8 (18.6%)
Mean	71.4
Std Dev	138.2
Median	49.5
q1	42.4
q3	53.0
Minimum	34
Maximum	865
Duration of treatment (months)	
N	43
N Miss	0 (0.0%)
Mean	4.2
Std Dev	3.5
Median	4.0
q1	2.0
q3	6.0
Minimum	0
Maximum	21
Number of cycles	
N	43
N Miss	0 (0.0%)
Mean	5.4
Std Dev	3.6
Median	5.0
q1	3.0
q3	6.0
Minimum	1
Maximum	21

Table 4. Exposure. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Number of Cycles	
0	0 (0.0%)
1	2 (4.7%)
2	8 (18.6%)
3	6 (14.0%)
4	3 (7.0%)
5	3 (7.0%)
6	11 (25.6%)
7	1 (2.3%)
8	3 (7.0%)
9	1 (2.3%)
>9	5 (11.6%)
Line of treatment	
2	15 (34.9%)
3	16 (37.2%)
4	8 (18.6%)
5	3 (7.0%)
6	1 (2.3%)
Number of Interruptions	
N	42
N Miss	1 (2.3%)
Mean	0.0
Std Dev	0.2
Median	0.0
q1	0.0
q3	0.0
Minimum	0
Maximum	1
Interruptions	
0	42 (97.7%)
1	1 (2.3%)
>1	0 (0.0%)

Table 4. Exposure. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Total days of Interruptions	
N	42
N Miss	1 (2.3%)
Mean	0.0
Std Dev	0.0
Median	0.0
q1	0.0
q3	0.0
Minimum	0
Maximum	0
Number of Delayed	
N	42
N Miss	1 (2.3%)
Mean	1.3
Std Dev	1.5
Median	1.0
q1	0.0
q3	2.0
Minimum	0
Maximum	7
Delays	
0	20 (46.5%)
1	7 (16.3%)
2-4	15 (34.9%)
5	0 (0.0%)
6	0 (0.0%)
7	1 (2.3%)
>7	0 (0.0%)
Total days delated	
N	42
N Miss	1 (2.3%)
Mean	12.3
Std Dev	15.5
Median	6.5
q1	0.0
q3	22.0
Minimum	0
Maximum	54

Table 4. Exposure. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
End of treatment	
Yes	43 (100.0%)
No	0 (0.0%)
Reason of EoT	
Patient's decision	3 (7.0%)
Doctor's decision	10 (23.3%)
Progression	17 (39.5%)
Toxicity	10 (23.3%)
Other	3 (7.0%)
Specify other reason	
Infection	1 (33.3%)
Knee prothesis infection	1 (33.3%)
Unknown	1 (33.3%)

Listing 1. Duration of Trabectedin + PLD Treatment. Intention to Treat.

Subjid	Site	EoT	Interruptions	Reductions	Drugs Exposure
01-001	HUB	Yes	0	1	3.50
01-002	HUB	Yes	0	1	6.13
02-001	HRYC	Yes	0	1	0.97
02-002	HRYC	Yes	0	2	3.43
03-001	ICOG	Yes	0	2	3.63
03-002	ICOG	Yes	0	2	3.90
04-001	HLEO	Yes	1	1	7.00
04-002	HLEO	Yes	0	0	8.23
04-003	HLEO	Yes	0	0	8.70
04-004	HLEO	Yes	0	2	4.47
04-005	HLEO	Yes	0	0	2.50
04-006	HLEO	Yes	0	1	1.20
04-007	HLEO	Yes	0	0	1.50
04-008	HLEO	Yes	0	2	9.60
05-002	HURS	Yes	0	0	0.73
05-003	HURS	Yes	0	0	4.70
05-004	HURS	Yes	0	0	3.10
05-006	HURS	Yes	0	0	4.27
06-001	HCSC	Yes	0	0	0.03
06-002	HCSC	Yes	0	0	2.13
06-003	HCSC	Yes	0	0	1.43
06-004	HCSC	Yes	0	1	4.23
06-005	HCSC	Yes	0	0	0.77
06-006	HCSC	Yes	0	1	5.87
06-007	HCSC	Yes	0	0	7.47
06-009	HCSC	Yes	0	2	4.37
07-001	HUBA	Yes	0	0	1.90
09-001	HUJF	Yes	0	0	4.60
09-002	HUJF	Yes	0	0	4.00
09-003	HUJF	Yes	0	0	1.20
10-001	HVAL	Yes	0	1	2.63
10-002	HVAL	Yes	0	0	0.03
10-003	HVAL	Yes	0	0	7.40
11-001	IVOG	Yes	0	0	1.13
11-002	IVOG	Yes	0	1	5.67
12-001	HUVR	Yes	0	1	1.50
12-002	HUVR	Yes	0	1	5.27
12-003	HUVR	Yes	0	1	5.00
12-004	HUVR	Yes	0	1	0.73
13-001	HVVA	Yes	0	1	20.93
14-001	HCVA	Yes	0	2	4.23
15-001	HUDP	Yes	0	1	1.77

Exposure to Trabectedin+PDL in months
Only patients who have finished treatment (n = 43)

Listing 1. Duration of Trabectedin + PLD Treatment. Intention to Treat.

Subjid	Site	EoT	Interruptions	Reductions	Drugs Exposure
15-002	HUDP	Yes	0	1	1.43

Exposure to Trabectedin+PDL in months
Only patients who have finished treatment (n = 43)

Table 5. Baseline Laboratory. Descriptive Statistics.
Safety Analysis Set.

	Total (n=43)
Platinum sensitivity	
Yes	43 (100.0%)
No	0 (0.0%)
Platinum-Free Interval (PFI)	
N	43
N Miss	0 (0.0%)
Mean	11.0
Std Dev	7.2
Median	9.0
q1	7.0
q3	11.0
Minimum	6
Maximum	42
PFI	
Missing	0 (0.0%)
0-10	30 (69.8%)
11-20	11 (25.6%)
More than 30	2 (4.7%)
Number of previous relapses	
N	43
N Miss	0 (0.0%)
Mean	1.6
Std Dev	1.0
Median	1.0
q1	1.0
q3	2.0
Minimum	1
Maximum	5
Previous relapses	
Missing	0 (0.0%)
1	30 (69.8%)
2-3	10 (23.3%)
More than 4	3 (7.0%)

Table 5. Baseline Laboratory. Descriptive Statistics.
Safety Analysis Set.

	Total (n=43)
Progression-Free Survival (PFS)	
N	43
N Miss	0 (0.0%)
Mean	8.3
Std Dev	8.0
Median	8.0
q1	3.0
q3	10.0
Minimum	0
Maximum	47
PFS	
Missing	0 (0.0%)
0-6 Months	18 (41.9%)
7-12 Months	18 (41.9%)
13-18 Months	4 (9.3%)
19-24 Months	2 (4.7%)
2 Years	0 (0.0%)
3 Years	1 (2.3%)
More than 5 Years	0 (0.0%)
Weight	
N	37
N Miss	6 (14.0%)
Mean	69.5
Std Dev	12.2
Median	69.0
q1	59.0
q3	79.0
Minimum	49
Maximum	94
Weight	
Missing	6 (14.0%)
Less than 40Kg	0 (0.0%)
40-70 Kg	19 (44.2%)
70-100 Kg	18 (41.9%)
More than 100Kg	0 (0.0%)
Existence of measurable disease	
Yes	35 (81.4%)
No	7 (16.3%)
Missing	1 (2.3%)

Table 5. Baseline Laboratory. Descriptive Statistics.
Safety Analysis Set.

	Total (n=43)
Existence of bulky disease	
Yes	12 (27.9%)
No	29 (67.4%)
Missing	2 (4.7%)
Brain metastasis	
Yes	0 (0.0%)
No	43 (100.0%)
Platelet count (cells/nL)	
N	37
N Miss	6 (14.0%)
Mean	251892
Std Dev	81702
Median	241000
q1	189000
q3	296000
Minimum	12E4
Maximum	42E4
Platelet count (cells/nL)	
Missing	6 (14.0%)
Less than 150000	3 (7.0%)
150000-450000	34 (79.1%)
More than 450000	0 (0.0%)
Leukocytes count (10^9/L)	
N	37
N Miss	6 (14.0%)
Mean	6.8
Std Dev	2.3
Median	6.5
q1	4.9
q3	7.7
Minimum	4
Maximum	14
Leukocytes count (10^9/L)	
Missing	6 (14.0%)
Less than 4.5	4 (9.3%)
4.5-11.0	33 (76.7%)
More than 11.0	0 (0.0%)

Table 5. Baseline Laboratory. Descriptive Statistics.
Safety Analysis Set.

	Total (n=43)
Absolute Neutrophils (cells/nL)	
N	37
N Miss	6 (14.0%)
Mean	4148.9
Std Dev	1812.0
Median	3820.0
q1	3000.0
q3	4970.0
Minimum	1830
Maximum	8880
Absolute Neutrophils (cells/nL)	
Missing	6 (14.0%)
Less than 1500	0 (0.0%)
1500-8000	0 (0.0%)
More than 8000	0 (0.0%)
1500-80	35 (81.4%)
More th	2 (4.7%)
Hemoglobin (g/dL)	
N	39
N Miss	4 (9.3%)
Mean	12.0
Std Dev	1.5
Median	12.1
q1	11.0
q3	13.4
Minimum	8
Maximum	15
Hemoglobin (g/dL)	
Missing	4 (9.3%)
Less than 11.6	14 (32.6%)
11.6-15.0	25 (58.1%)
More than 15.0	0 (0.0%)

Table 5. Baseline Laboratory. Descriptive Statistics.
Safety Analysis Set.

	Total (n=43)
CA125 (U/mL)	
N	37
N Miss	6 (14.0%)
Mean	452.1
Std Dev	780.4
Median	174.9
q1	67.0
q3	540.0
Minimum	0
Maximum	4389
CA125 (U/mL)	
Missing	6 (14.0%)
Less than 46.0	5 (11.6%)
46.0-200.0	16 (37.2%)
More than 200.0	16 (37.2%)

Table 6. Concomitant Medication. Descriptive Statistics.
Intention to Treat.

		Total
Stage Trabectidin+PLD		
Type		
Reason		
Before		
Antiacid		
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Anticoagulant		
Medical history comorbidities	SUBJECTS	1 (2.3%)
	EPISODES	1
Antidepressant		
Medical history comorbidities	SUBJECTS	1 (2.3%)
	EPISODES	1
Antiemetic		
Prophylaxis	SUBJECTS	2 (4.7%)
	EPISODES	2
Antihypertensive		
Medical history comorbidities	SUBJECTS	2 (4.7%)
	EPISODES	3
Colony-stimulating factor		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Diuretic		
Other	SUBJECTS	1 (2.3%)
	EPISODES	1
Magnesium (supplement)		
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Proton-pump inhibitor		
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Transfusion		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Vitamin B12 (supplement)		
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Other		
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
During		
Antibiotic		

Patients n = 43

Table 6. Concomitant Medication. Descriptive Statistics.
Intention to Treat.

		Total
Stage Trabectidin+PLD		
Type		
Reason		
Adverse event	SUBJECTS	2 (4.7%)
	EPISODES	2
Antidiarrheal medication		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Antiemetic		
Adverse event	SUBJECTS	2 (4.7%)
	EPISODES	2
Antifungal		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Apetite stimulant		
Other	SUBJECTS	1 (2.3%)
	EPISODES	1
Colony-stimulating factor		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Corticosteroid		
Adverse event	SUBJECTS	2 (4.7%)
	EPISODES	2
Potassium chloride (supplement)		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Transfusion		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Other		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Before and During		
Analgesic		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Other	SUBJECTS	1 (2.3%)
	EPISODES	2
Prophylaxis	SUBJECTS	3 (7.0%)
	EPISODES	3
Antiacid		
Prophylaxis	SUBJECTS	4 (9.3%)
	EPISODES	4

Patients n = 43

Table 6. Concomitant Medication. Descriptive Statistics.
Intention to Treat.

Stage Trabectidin+PLD Type Reason		Total
Antibiotic		
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Antidepressant		
Medical history comorbidities	SUBJECTS	4 (9.3%)
	EPISODES	4
Prophylaxis	SUBJECTS	2 (4.7%)
	EPISODES	2
Antidiabetic medication		
Medical history comorbidities	SUBJECTS	2 (4.7%)
	EPISODES	2
Antiemetic		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Antihistamine		
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Antihypertensive		
Medical history comorbidities	SUBJECTS	5 (11.6%)
	EPISODES	5
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Antiplatelet drug (antiaggregant)		
Medical history comorbidities	SUBJECTS	2 (4.7%)
	EPISODES	2
Benzodiazepines		
Medical history comorbidities	SUBJECTS	2 (4.7%)
	EPISODES	2
Prophylaxis	SUBJECTS	3 (7.0%)
	EPISODES	3
Colony-stimulating factor		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Corticosteroid		
Other	SUBJECTS	1 (2.3%)
	EPISODES	1
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1

Patients n = 43

Table 6. Concomitant Medication. Descriptive Statistics.
Intention to Treat.

Stage Trabectidin+PLD / Type / Reason		Total
Diuretic		
Medical history comorbidities	SUBJECTS	1 (2.3%)
	EPISODES	1
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Laxative		
Medical history comorbidities	SUBJECTS	1 (2.3%)
	EPISODES	1
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Magnesium (supplement)		
Medical history comorbidities	SUBJECTS	1 (2.3%)
	EPISODES	1
Iron sulfate (supplement)		
Medical history comorbidities	SUBJECTS	1 (2.3%)
	EPISODES	1
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Proton-pump inhibitor		
Other	SUBJECTS	1 (2.3%)
	EPISODES	1
Prophylaxis	SUBJECTS	2 (4.7%)
	EPISODES	2
Statins		
Medical history comorbidities	SUBJECTS	5 (11.6%)
	EPISODES	5
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1
Other		
Adverse event	SUBJECTS	1 (2.3%)
	EPISODES	1
Medical history comorbidities	SUBJECTS	4 (9.3%)
	EPISODES	5
Other	SUBJECTS	2 (4.7%)
	EPISODES	3
Prophylaxis	SUBJECTS	1 (2.3%)
	EPISODES	1

Patients n = 43

Listing 2. Concomitant Medication. Intention to Treat.

Subjid	Site	Stage**	Type Med/Therapy*	Reason*
01-001	HUB	BT	Antidepressant	MHC: Paroxetina
		BDT	Antidiabetic Medication	MHC: Sitagliptina
		DT	Antidiarrheal Medication	AE: Movicol
		BT	Antiemetic	Prophylaxis
		BDT	Statins	MHC: Atorvastatina
01-002	HUB	DT	Antifungal	AE: Mycostatin
		BT	Antihypertensive	MHC: Enalapril
		BT	Antihypertensive	MHC: Sutril
		BT	Magnesium (Supp)	Prophylaxis
		BT	O: Orfidal	Prophylaxis
		BT	Proton-Pump Inhibitor	Prophylaxis
02-002	HRYC	BT	Antiacid	Prophylaxis
		BDT	Antihypertensive	MHC: Hypertension
		DT	Colony-Stimulating Factor	AE: Neutropenia
		BT	Diuretic	O: Hepatotoxicity
03-001	ICOG	DT	Antibiotic	AE: Urinary Tract Infection
		BDT	Colony-Stimulating Factor	AE: Neutrophil Count Decrease
03-002	ICOG	DT	Antibiotic	AE: Urinary Tract Infection
04-001	HLEO	BDT	Analgesic	Prophylaxis
		BDT	Antidepressant	MHC: Depression
		BDT	O: Morphine	O: Pain Disease
		BDT	Statins	MHC: Dislipemia
04-002	HLEO	BDT	Analgesic	Prophylaxis
		BDT	Antiacid	Prophylaxis
		BDT	Antihypertensive	MHC: Arterial Hypertension
		BDT	Iron Sulfate (Supp)	Prophylaxis
		BDT	Statins	MHC: Dislipemia
04-003	HLEO	BDT	Antiacid	Prophylaxis
		BDT	Antiemetic	Prophylaxis
04-004	HLEO	DT	O: Neupogen	AE: Neutropenia
04-005	HLEO	BDT	Antidiabetic Medication	MHC: Diabetes Mellitus
		BDT	Benzodiazepines	Prophylaxis
04-006	HLEO	BDT	Antidepressant	Prophylaxis
		BDT	Antihistamine	Prophylaxis
		BDT	Antihypertensive	MHC: Arterial Hipertension
		BDT	Statins	MHC: Dislipemia
04-007	HLEO	BDT	Antihypertensive	MHC: Arterial Hipertension
		BDT	Benzodiazepines	Prophylaxis
		BDT	Laxative	MHC: Constipation
		BT	Vitamin B12 (Supp)	Prophylaxis
04-008	HLEO	BDT	Analgesic	Prophylaxis

**BT - Before Treatment, DT - During Treatment, BDT - Before and During treatment
*O - Other, MHC - Medical history comorbidities
*supp = Supplement, AA = Antiaggregant, AE = Adverse Event

Listing 2. Concomitant Medication. Intention to Treat.

Subjid	Site	Stage**	Type Med/Therapy*	Reason*
		BDT	Antiacid	Prophylaxis
		BDT	Benzodiazepines	Prophylaxis
		BDT	Statins	MHC: Dislipemia
05-002	HURS	DT	Corticosteroid	AE: Nausea And Vomiting
05-003	HURS	BT	Antihypertensive	MHC: Hypertension
		BDT	O: Potassium	AE: Hypokalemia
		DT	Potassium Chloride (Supp)	AE: Hypokalemia
09-003	HUJF	DT	Antiemetic	AE: Nausea And Vomiting
		BDT	Diuretic	MHC: Ascites
10-001	HVAL	BDT	Antiplatelet Drug (Aa)	MHC: Unknown
		BDT	Benzodiazepines	MHC: Anxiety
		BDT	O: Lipid-Lowering	MHC: Hyperclesterolemia
11-001	IVOG	BDT	Antihypertensive	MHC: Amlodipino 10mg
		BDT	Antihypertensive	MHC: Bisoprolol 5mg
		BDT	Antihypertensive	MHC: Hidroclorotiazida 12.5mg
		BDT	Antihypertensive	MHC: Valsartán 160mg
11-002	IVOG	BT	Anticoagulant	MHC: Hibor 10000 Ui
12-002	HUVR	BDT	O: Levotiroxine	MHC: Hypothyrodism
		BDT	Proton-Pump Inhibitor	Prophylaxis
12-003	HUVR	BDT	Antidepressant	MHC: Depression
		BDT	Antiemetic	AE: Nausea
		BT	Antiemetic	Prophylaxis
		BDT	Benzodiazepines	MHC: Depression
		BT	Colony-Stimulating Factor	AE: Neutropenia
		BDT	Corticosteroid	O: Intestinal Suboclusion Bt
		BDT	Laxative	Prophylaxis
		BDT	O: Fentanyl (Patch)	O: Intestinal Suboclusion Bt
		BDT	O: Morphine	O: Intestinal Suboclusion Bt
		BDT	Proton-Pump Inhibitor	O: Intestinal Suboclusion Bt
		BT	Transfusion	AE: Anemia
12-004	HUVR	BDT	Analgesic	O: Cancer-Related Pain
		BDT	Analgesic	O: Cancer-Related Pain
		BDT	Antibiotic	Prophylaxis
		BDT	Antidepressant	MHC: Depression
		DT	Antiemetic	AE: Nausea And Vomiting
		BDT	Antiplatelet Drug (Aa)	MHC: Chronic Leg Ischemya
		DT	Apetite Stimulant	O: Cancer-Related Hyporexia
		DT	Corticosteroid	AE: Asthenia
		BDT	Iron Sulfate (Supp)	MHC: Renal Failure
		BDT	Magnesium (Supp)	MHC: Renal Failure
		BDT	O: Ciclosporine	MHC: Renal Trasplant

**BT - Before Treatment, DT - During Treatment, BDT - Before and During treatment
*O - Other, MHC - Medical history comorbidities
*supp = Supplement, AA = Antiaggregant, AE = Adverse Event

Listing 2. Concomitant Medication. Intention to Treat.

Subjid	Site	Stage**	Type Med/Therapy*	Reason*
		BDT	O: Levotiroxine	MHC: Hypothyroidism
		BDT	Proton-Pump Inhibitor	Prophylaxis
		DT	Transfusion	AE: Anemia G2
13-001	HVVA	BDT	Antidepressant	Prophylaxis
		BDT	O: Anxiolytic	Prophylaxis
14-001	HCVA	BDT	Antidepressant	MHC: Depression
		BDT	Antihypertensive	Prophylaxis
		BDT	Diuretic	Prophylaxis
		BDT	Statins	Prophylaxis
15-001	HUDP	BDT	Analgesic	AE: Abdominal Pain
15-002	HUDP	BDT	Antiacid	Prophylaxis
		BDT	Corticosteroid	Prophylaxis
		BDT	O: Thyroideal Hormones	MHC: Total Thyroidectomy In 1982 Fo

**BT - Before Treatment, DT - During Treatment, BDT - Before and During treatment
*O - Other, MHC - Medical history comorbidities
*supp = Supplement, AA = Antiaggregant, AE = Adverse Event

Table 7. Medical History. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Relevant Comorbidities	
Yes	33 (76.7%)
No	10 (23.3%)
Other Previous Cancers	
Yes	6 (14.0%)
No	37 (86.0%)
Family history of Cancers	
Yes	30 (69.8%)
No	13 (30.2%)

Table 7.1. Medical History. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Family history of Cancers	
Yes	30 (69.8%)
No	13 (30.2%)
Familiars with cancer	
Aunt	6 (10.0%)
Brother	11 (18.3%)
Cousin	7 (11.7%)
Daughter	1 (1.7%)
Father	9 (15.0%)
Grandchild	1 (1.7%)
Grandfather	1 (1.7%)
Grandmother	2 (3.3%)
Mother	7 (11.7%)
Niece	1 (1.7%)
None	1 (1.7%)
Sister	9 (15.0%)
Uncle	4 (6.7%)
Types of cancer	
Bile Ducts	1 (1.7%)
Bladder	1 (1.7%)
Breast	14 (23.3%)
Colon	7 (11.7%)
Esophagus	1 (1.7%)
Gallbladder	1 (1.7%)
Gastric	6 (10.0%)
Hepatocarcinoma	1 (1.7%)
Kaposi Sarcoma	1 (1.7%)
Liver	3 (5.0%)
Lung	3 (5.0%)
None	1 (1.7%)
Ovarian	2 (3.3%)
Pancreas	6 (10.0%)
Parotide	1 (1.7%)
Prostate	4 (6.7%)
Renal	1 (1.7%)
Testicles	1 (1.7%)
Unknown	3 (5.0%)
Uterine	2 (3.3%)

Listing 3. Medical History. Family History of Cancers. Intention to Treat. Intention to Treat.

Subjid	Site	Cancer in Family	Member	Type
01-001	HUB	Yes	Brother	Lung
			Cousin	Gastric
01-002	HUB	Yes	Mother	Breast
			Brother	Gastric
02-001	HRYC	No		
02-002	HRYC	Yes	Mother	Pancreas
			Brother	O: Bile Ducts
			Uncle	Gastric
			Cousin	Breast
			Aunt	Pancreas
03-001	ICOG	No		
03-002	ICOG	Yes	Brother	Prostate
			Brother	Unknown
04-001	HLEO	Yes	O: Grandchild	Testicles
			Brother	Colon
04-002	HLEO	Yes	Sister	Breast
			Sister	Colon
			Brother	O: Renal
04-003	HLEO	No		
04-004	HLEO	Yes	Grandmother	Unknown
04-005	HLEO	No		
04-006	HLEO	Yes	Brother	Liver
			Brother	Liver
04-007	HLEO	Yes	Sister	Breast
			Father	Pancreas
			O: Niece	Breast
04-008	HLEO	Yes	O: Daughter	Ovarian
05-002	HURS	Yes	Mother	Breast
			Aunt	Breast
			Cousin	Breast
05-003	HURS	No		
05-004	HURS	No		
05-006	HURS	No		
06-001	HCSC	Yes	Brother	Colon
06-002	HCSC	Yes	Father	Prostate
			Uncle	Prostate
			Uncle	Prostate
			Uncle	O: Hepatocarcin
06-003	HCSC	No		
06-004	HCSC	No		

*O - Other

Listing 3. Medical History. Family History of Cancers. Intention to Treat. Intention to Treat.

Subjid	Site	Cancer in Family	Member	Type
06-005	HCSC	Yes	Father	Colon
			Aunt	O: Pancreas
			Grandmother	O: Pancreas
			Aunt	Breast
			Aunt	Colon
			Cousin	Breast
06-006	HCSC	Yes	Father	Colon
			Aunt	Breast
			Mother	O: Kaposi Sarco
06-007	HCSC	Yes	Grandfather	O: Parotide
			Cousin	Uterine
			Cousin	O: Bladder
06-009	HCSC	Yes	Father	O: Esophagus
07-001	HUBA	Yes	Sister	Colon
09-001	HUJF	Yes	Mother	Liver
			Father	Unknown
			Sister	Uterine
09-002	HUJF	Yes	Brother	Lung
09-003	HUJF	No		
10-001	HVAL	Yes	Sister	Breast
10-002	HVAL	Yes	Cousin	Breast
10-003	HVAL	Yes	Sister	Ovarian
11-001	IVOG	No		
11-002	IVOG	No		
12-001	HUVR	Yes	Mother	O: Gallbladder
			Father	Lung
12-002	HUVR	Yes	Father	Gastric
12-003	HUVR	Yes	Father	Gastric
12-004	HUVR	No		
13-001	HVVA	Yes	Sister	Breast
14-001	HCVA	Yes	Sister	Gastric
15-001	HUDP	Yes	Mother	Pancreas
15-002	HUDP	Yes	O: None	O: None

*O - Other

Table 7.2. Medical History. Other Previous Cancers. Descriptive Statistics. Intention to Treat.

	Total (n=43)
Previous Cancers	
Yes	6 (14.0%)
No	37 (86.0%)
Cancer Type	
Breast	3 (50.0%)
Carcinoid Tumor in Appendix	1 (16.7%)
Peritoneal Carcinomatosis	1 (16.7%)
Thyroideal Cancer	1 (16.7%)

Listing 4. Medical History. Family History of Cancers.

Subjid	Site	Previous Cancer	Cancer type
01-001	HUB	No	
01-002	HUB	Yes	Breast
02-001	HRYC	No	
02-002	HRYC	No	
03-001	ICOG	No	
03-002	ICOG	No	
04-001	HLEO	Yes	O: Peritoneal Carcinomatosis
04-002	HLEO	No	
04-003	HLEO	No	
04-004	HLEO	Yes	Carcinoid Tumor in Appendix
04-005	HLEO	No	
04-006	HLEO	No	
04-007	HLEO	No	
04-008	HLEO	Yes	Breast
05-002	HURS	No	
05-003	HURS	No	
05-004	HURS	No	
05-006	HURS	No	
06-001	HCSC	No	
06-002	HCSC	No	
06-003	HCSC	No	
06-004	HCSC	No	
06-005	HCSC	No	
06-006	HCSC	No	
06-007	HCSC	No	
06-009	HCSC	No	
07-001	HUBA	No	
09-001	HUJF	No	
09-002	HUJF	No	
09-003	HUJF	Yes	Breast
10-001	HVAL	No	
10-002	HVAL	No	
10-003	HVAL	No	
11-001	IVOG	No	
11-002	IVOG	No	
12-001	HUVR	No	
12-002	HUVR	No	
12-003	HUVR	No	
12-004	HUVR	No	
13-001	HVVA	No	

*O - Other

Listing 4. Medical History. Family History of Cancers.

Subjid	Site	Previous Cancer	Cancer type
14-001	HCVA	No	
15-001	HUDP	No	
15-002	HUDP	Yes	O: Thyroideal Cancer

*O - Other

Table 7.3. Medical History. Relevant Comorbidities. Descriptive Statistics.

	Total (n=43)
Relevant Comorbidities	
No	10 (23.3%)
Yes	33 (76.7%)
Time point	
Baseline	7 (8.3%)
Medical History	77 (91.7%)
Relevant comorbidities	
Anxiety	1 (1.2%)
Arterial hypertension	18 (21.4%)
Arthrosis	1 (1.2%)
COPD	1 (1.2%)
Cerebrovascular disease	1 (1.2%)
Depression	8 (9.5%)
Diabetes mellitus	4 (4.8%)
Dyslipemia	13 (15.5%)
Hypothiroidism	3 (3.6%)
Obesity	1 (1.2%)
Other relevant (Specify)	33 (39.3%)

Table 7.3. Medical History. Relevant Comorbidities. Descriptive Statistics.

	Total (n=43)
Specify	
Allergy To Clavulanic Acid	1 (3.0%)
Anal Fissure	1 (3.0%)
Appendectomy	1 (3.0%)
Ascites	1 (3.0%)
Atrial Fibrillation	1 (3.0%)
Carpal Tunnel Surgery	1 (3.0%)
Chronic Leg Ischemya	1 (3.0%)
Chronic Renal Disease	2 (6.1%)
Colecistectomy	1 (3.0%)
Constipation	1 (3.0%)
Cured Hepatitis B	1 (3.0%)
Curettage	1 (3.0%)
Deep Vein Thrombosis	1 (3.0%)
Finger Amputation	1 (3.0%)
Goitre	1 (3.0%)
Hernia	4 (12.1%)
Internal Hemorrhoids	1 (3.0%)
Lichen Planus	1 (3.0%)
Lipoma Surgery In Left Arm	1 (3.0%)
Osteoporosis	3 (9.1%)
Parietotemporal Hematoma Surgery	1 (3.0%)
Peripheral Neuropathy	1 (3.0%)
Polymyalgia Rheumatica	1 (3.0%)
Tendinopathy	1 (3.0%)
Tibial Plateau Fracture	1 (3.0%)
Varicose Veins	1 (3.0%)
Vertiginous Syndrome	1 (3.0%)

Listing 5. Medical History. Relevant Comorbidities.
Intention to Treat.

Subjid	Site	Comorbidities	Time point	Type
01-001	HUB	Yes	MH	Dyslipemia
			MH	Depression
			BL	Diabetes Mellitus
01-002	HUB	Yes	MH	Arterial Hypertension
			MH	O: Bocio
			MH	O: Osteoporosis
02-001	HRYC	No		
02-002	HRYC	Yes	MH	Arterial Hypertension
			MH	Copd
			MH	O: Osteoporosis
			MH	O: Internal Hemorrhoids
03-001	ICOG	Yes	MH	Arterial Hypertension
03-002	ICOG	Yes	MH	Arterial Hypertension
			MH	Depression
			MH	Hypothiroidism
04-001	HLEO	Yes	MH	O: Allergy To Clavulanic Acid
			MH	Dyslipemia
			MH	O: Peripheral Neuropathy
			MH	Depression
			MH	O: Carpal Tunnel Surgery
04-002	HLEO	Yes	MH	Arterial Hypertension
			MH	Dyslipemia
04-003	HLEO	Yes	MH	O: Hernia
			MH	Arterial Hypertension
04-004	HLEO	Yes	MH	Dyslipemia
			MH	O: Tibial Plateau Fracture
			MH	Depression
			MH	O: Finger Amputation
04-005	HLEO	Yes	MH	Diabetes Mellitus
04-006	HLEO	Yes	MH	Arterial Hypertension
			MH	Dyslipemia
04-007	HLEO	Yes	MH	O: Vertiginous Syndrome
			MH	O: Constipation
			MH	Arterial Hypertension
			MH	O: Hernia
			MH	O: Hernia
			MH	O: Lipoma Surgery In Left Arm
			MH	O: Curettage
04-008	HLEO	Yes	MH	Diabetes Mellitus
			MH	Dyslipemia

*O - Other
*MH - Medical History, BL - Baseline

Listing 5. Medical History. Relevant Comorbidities.
Intention to Treat.

Subjid	Site	Comorbidities	Time point	Type
05-002	HURS	Yes	MH	Diabetes Mellitus
			MH	Dyslipemia
05-003	HURS	Yes	MH	Arterial Hypertension
			MH	O: Hernia
			MH	O: Anal Fissure
			MH	O: Colecistectomy
			MH	O: Appendectomy
			MH	O: Tendonitis
05-004	HURS	No		
05-006	HURS	No		
06-001	HCSC	No		
06-002	HCSC	No		
06-003	HCSC	Yes	MH	O: Cured Hepatitis B
06-004	HCSC	No		
06-005	HCSC	No		
06-006	HCSC	No		
06-007	HCSC	Yes	MH	Cerebrovascular Disease
06-009	HCSC	No		
07-001	HUBA	Yes	MH	Arterial Hypertension
09-001	HUJF	Yes	BL	Arterial Hypertension
09-002	HUJF	Yes	MH	Arterial Hypertension
			MH	O: Atrial Fibrillation
09-003	HUJF	Yes	MH	Depression
			BL	O: Ascites
10-001	HVAL	Yes	BL	Arterial Hypertension
			BL	Dyslipemia
			BL	Anxiety
10-002	HVAL	Yes	MH	Arthrosis
			MH	O: Polimialgia Reumatica
			MH	O: Lichen Planus
			MH	O: Varicose Veins
10-003	HVAL	Yes	BL	Arterial Hypertension
11-001	IVOG	Yes	MH	Arterial Hypertension
11-002	IVOG	Yes	MH	Dyslipemia
			MH	O: Trombosis Venosa Profunda
12-001	HUVR	No		
12-002	HUVR	Yes	MH	Hypothiroidism
			MH	Dyslipemia
12-003	HUVR	Yes	MH	Obesity
			MH	Depression

*O - Other
*MH - Medical History, BL - Baseline

Listing 5. Medical History. Relevant Comorbidities.
Intention to Treat.

Subjid	Site	Comorbidities	Time point	Type
12-004	HUVR	Yes	MH	O: Chronic Renal Disease
			MH	Depression
			MH	O: Chronic Leg Ischemya
			MH	Hypothiroidism
			MH	O: Chronic Renal Disease
13-001	HVVA	Yes	MH	Arterial Hypertension
14-001	HCVA	Yes	MH	Dyslipemia
			MH	O: Parietotemporal Hematoma Su
			MH	Depression
15-001	HUDP	Yes	MH	Arterial Hypertension
			MH	Dyslipemia
15-002	HUDP	Yes	MH	Arterial Hypertension
			MH	Dyslipemia
			MH	O: Osteoporosis

*O - Other
*MH - Medical History, BL - Baseline

Table 8. Initial Ovarian Cancer Diagnosis History. Descriptive Statistics. Intention to Treat.

	Total (n=43)
Age at ovarian cancer diagnosis	
N	43
N Miss	0 (0.0%)
Mean	71.4
Std Dev	4.5
Median	71.0
q1	69.0
q3	74.0
Minimum	62
Maximum	85
Age	
Missing	0 (0.0%)
Less than 70 Years	12 (27.9%)
70-80 Years	29 (67.4%)
More than 80 Years	2 (4.7%)
Weight	
N	32
N Miss	11 (25.6%)
Mean	65.1
Std Dev	10.9
Median	64.5
q1	56.5
q3	72.0
Minimum	42
Maximum	94
Weight	
Missing	11 (25.6%)
Less than 70Kg	21 (48.8%)
70 - 75 Kg	6 (14.0%)
75 - 80 Kg	2 (4.7%)
More than 80Kg	3 (7.0%)
ECOG	
Missing	8 (18.6%)
0	14 (32.6%)
1	8 (18.6%)
2	4 (9.3%)
3	0 (0.0%)
4	0 (0.0%)
Unknown	9 (20.9%)

Table 8. Initial Ovarian Cancer Diagnosis History. Descriptive Statistics. Intention to Treat.

	Total (n=43)
Existence of measurable disease	
Missing	1 (2.3%)
Yes	35 (81.4%)
No	7 (16.3%)
Existence of bulky disease	
Missing	1 (2.3%)
Yes	23 (53.5%)
No	19 (44.2%)
Tumor histology	
Missing	1 (2.3%)
High grade serous ovarian cancer	40 (93.0%)
High grade fallopian tube cancer	1 (2.3%)
High grade primary peritoneal cancer	1 (2.3%)
FIGO Stage	
Missing	3 (7.0%)
IA	2 (4.7%)
IB	0 (0.0%)
IC1	1 (2.3%)
IC2	0 (0.0%)
IC3	0 (0.0%)
IIA	0 (0.0%)
IIB	0 (0.0%)
IIIA1	2 (4.7%)
IIIA2	1 (2.3%)
IIIB	3 (7.0%)
IIIC	22 (51.2%)
IVA	0 (0.0%)
IVB	5 (11.6%)
Unknown	4 (9.3%)
Other (Specify)	0 (0.0%)
Brain metastasis	
Missing	0 (0.0%)
Yes	0 (0.0%)
No	43 (100.0%)
Homologous recombination genes deficiencies	
No	42 (97.7%)
Yes	1 (2.3%)

Table 8. Initial Ovarian Cancer Diagnosis History. Descriptive Statistics. Intention to Treat.

	Total (n=43)
Existence of measurable disease	
Missing	1 (2.3%)
Yes	35 (81.4%)
No	7 (16.3%)
Existence of bulky disease	
Missing	1 (2.3%)
Yes	23 (53.5%)
No	19 (44.2%)
Tumor histology	
Missing	1 (2.3%)
High grade serous ovarian cancer	40 (93.0%)
High grade fallopian tube cancer	1 (2.3%)
High grade primary peritoneal cancer	1 (2.3%)
FIGO Stage	
Missing	3 (7.0%)
IA	2 (4.7%)
IB	0 (0.0%)
IC1	1 (2.3%)
IC2	0 (0.0%)
IC3	0 (0.0%)
IIA	0 (0.0%)
IIB	0 (0.0%)
IIIA1	2 (4.7%)
IIIA2	1 (2.3%)
IIIB	3 (7.0%)
IIIC	22 (51.2%)
IVA	0 (0.0%)
IVB	5 (11.6%)
Unknown	4 (9.3%)
Other (Specify)	0 (0.0%)
Brain metastasis	
Missing	0 (0.0%)
Yes	0 (0.0%)
No	43 (100.0%)
Homologous recombination genes deficiencies	
No	42 (97.7%)
Yes	1 (2.3%)

Table 9. Laboratory Initial Ovarian Cancer Diagnosis. Descriptive Statistics. Intention to Treat.

	Total (n=43)
Absolute Neutrophils (cells/nL)	
N	36
N Miss	7 (16.3%)
Mean	4853.9
Std Dev	2210.2
Median	4610.0
q1	3175.0
q3	6075.0
Minimum	1300
Maximum	11E3
Absolute Neutrophils (cells/nL)	
Missing	7 (16.3%)
Less than 1500	1 (2.3%)
1500-8000	31 (72.1%)
More than 8000	4 (9.3%)
Hemoglobin (g/dL)	
N	37
N Miss	6 (14.0%)
Mean	12.0
Std Dev	1.3
Median	12.1
q1	11.1
q3	12.7
Minimum	9
Maximum	15
Hemoglobin (g/dL)	
Missing	6 (14.0%)
Less than 11.6	12 (27.9%)
11.6-15.0	24 (55.8%)
More than 15.0	1 (2.3%)

Table 9. Laboratory Initial Ovarian Cancer Diagnosis. Descriptive Statistics. Intention to Treat.

	Total (n=43)
CA125 (U/mL)	
N	35
N Miss	8 (18.6%)
Mean	959.0
Std Dev	1228.2
Median	469.8
q1	185.6
q3	1242.7
Minimum	8
Maximum	5879
CA125 (U/mL)	
Missing	8 (18.6%)
Less than 46.0	4 (9.3%)
46.0-200.0	6 (14.0%)
46.0-1000.0	15 (34.9%)
More than 1000.0	10 (23.3%)
Deficiencis in other genes	
Missing	0 (0.0%)
Yes	1 (2.3%)
No	42 (97.7%)
Variant classification	
Missing	1 (2.3%)
Pathogenic	3 (7.0%)
Probably pathogenic	0 (0.0%)
Variant of uncertain significant (VOUS)	2 (4.7%)
Unknown	37 (86.0%)

Listing 6. Initial Ovarian Cancer Diagnosis History.
Intention to Treat.

Subjid	Site	Age	ECOG	Measurable	Histology	FIGO
01-001	HUB	74	1	Yes	HG serous ovarian cancer	Unknown
01-002	HUB	73	1	No	HG serous ovarian cancer	IIIC
02-001	HRYC	72	Missing	Yes	HG primary peritoneal cancer	IIIC
02-002	HRYC	81	0	Yes	HG serous ovarian cancer	IIIC
03-001	ICOG	62	0	Yes	HG serous ovarian cancer	IA
03-002	ICOG	71	Unknown	Yes	HG serous ovarian cancer	IIIC
04-001	HLEO	75	Unknown	Yes	HG serous ovarian cancer	Missing
04-002	HLEO	71	Unknown	Yes	HG serous ovarian cancer	IIIB
04-003	HLEO	71	Missing	Yes	HG serous ovarian cancer	IIIC
04-004	HLEO	72	Unknown	Yes	HG serous ovarian cancer	IC1
04-005	HLEO	71	Missing	No	HG serous ovarian cancer	Unknown
04-006	HLEO	85	Missing	Missing	HG serous ovarian cancer	Missing
04-007	HLEO	75	2	Yes	HG serous ovarian cancer	Missing
04-008	HLEO	70	Missing	Yes	HG serous ovarian cancer	IIIB
05-002	HURS	77	Missing	Yes	HG serous ovarian cancer	IIIC
05-003	HURS	70	Unknown	Yes	HG serous ovarian cancer	IIIC
05-004	HURS	71	Unknown	Yes	HG serous ovarian cancer	Unknown
05-006	HURS	68	Missing	Yes	HG serous ovarian cancer	Unknown
06-001	HCSC	74	0	Yes	HG serous ovarian cancer	IVB
06-002	HCSC	69	0	Yes	HG serous ovarian cancer	IIIA1
06-003	HCSC	67	0	Yes	HG fallopian tube cancer	IIIC
06-004	HCSC	65	0	Yes	HG serous ovarian cancer	IIIC
06-005	HCSC	66	Unknown	Yes	HG serous ovarian cancer	IIIC
06-006	HCSC	67	0	Yes	HG serous ovarian cancer	IIIC
06-007	HCSC	79	Missing	Yes	HG serous ovarian cancer	IVB
06-009	HCSC	73	1	No	HG serous ovarian cancer	IIIC
07-001	HUBA	71	0	Yes	HG serous ovarian cancer	IVB
09-001	HUJF	72	0	Yes	HG serous ovarian cancer	IIIC
09-002	HUJF	74	1	Yes	HG serous ovarian cancer	IIIC
09-003	HUJF	74	0	Yes	HG serous ovarian cancer	IIIA2
10-001	HVAL	71	2	Yes	HG serous ovarian cancer	IIIC
10-002	HVAL	76	2	Yes	HG serous ovarian cancer	IIIC
10-003	HVAL	62	0	No	HG serous ovarian cancer	IA
11-001	IVOG	65	0	No	HG serous ovarian cancer	IIIC
11-002	IVOG	66	0	No	Missing	IIIA1
12-001	HUVR	70	Unknown	Yes	HG serous ovarian cancer	IVB
12-002	HUVR	70	0	Yes	HG serous ovarian cancer	IIIC
12-003	HUVR	69	2	Yes	HG serous ovarian cancer	IIIC
12-004	HUVR	75	1	Yes	HG serous ovarian cancer	IIIC
13-001	HVVA	69	1	Yes	HG serous ovarian cancer	IIIB
14-001	HCVA	73	Unknown	No	HG serous ovarian cancer	IIIC

*MG - High Grade

Listing 6. Initial Ovarian Cancer Diagnosis History.
Intention to Treat.

Subjid	Site	Age	ECOG	Measurable	Histology	FIGO
15-001	HUDP	73	1	Yes	HG serous ovarian cancer	IIIC
15-002	HUDP	71	1	Yes	HG serous ovarian cancer	IVB

*MG - High Grade

Table 10. Ovarian Cancer Treatments. Previous Surgery. Descriptive Statistics.
Intention to Treat.

	Total (n=43)
Surgeries	
N	38
N Miss	5 (11.6%)
Mean	1.2
Std Dev	0.4
Median	1.0
q1	1.0
q3	1.0
Minimum	1
Maximum	2
Number of Surgeries per Patient	
0	5 (11.6%)
1	29 (67.4%)
2	9 (20.9%)
more than 3	0 (0.0%)
When was surgery performed?	
Before relapse (primary)	41 (87.2%)
At relapse	6 (12.8%)
Surgery type	
Missing	2 (4.3%)
Primary Debulking Surgery	23 (48.9%)
Interval Debulking Surgery	15 (31.9%)
Secondary Cytoreduction	7 (14.9%)
Surgery outcome	
Missing	1 (2.1%)
R0	20 (42.6%)
R>0	10 (21.3%)
Unknown	16 (34.0%)

Table 11. Ovarian Cancer. Previous Systemic Treatments.

	Total (n=43)
N. of Prev. Treatments Lines per Patient	
N	43
N Miss	0 (0.0%)
Mean	2.6
Std Dev	1.3
Median	2.0
q1	2.0
q3	4.0
Minimum	1
Maximum	6
Prev. Treatments Lines per Patient	
0	0 (0.0%)
1 or 2 Lines	25 (58.1%)
3 or 4 Lines	15 (34.9%)
5 or more Lines	3 (7.0%)
Setting	
Before relapse	71 (64.0%)
At relapse	40 (36.0%)
Line	
Maintenance	23 (20.7%)
First	43 (38.7%)
Second	28 (25.2%)
Third	12 (10.8%)
Fourth	4 (3.6%)
Fifth	1 (0.9%)
Sixth	0 (0.0%)
Seventh	0 (0.0%)
Eighth	0 (0.0%)
Ninth	0 (0.0%)
Tenth	0 (0.0%)

*(CL) - Clinical Trial

Table 11. Ovarian Cancer. Previous Systemic Treatments.

	Total (n=43)
Treatment type	
Amg386 (Trinova Trial)	1 (0.9%)
Atezolizumab-Niraparib-Cobimetinib (CT)	1 (0.9%)
Bevacizumab	16 (14.4%)
Carboplatin	2 (1.8%)
Carboplatin-Bevacizumab-Paclitaxel	6 (5.4%)
Carboplatin-Caelyx	14 (12.6%)
Carboplatin-Gemcitabine	9 (8.1%)
Carboplatin-Gemcitabine-Bevacizumab	3 (2.7%)
Carboplatin-Paclitaxel	47 (42.3%)
Carboplatin-Paclitaxel-Veliparib/Placebo (CT)	1 (0.9%)
Docetaxel-Ciclofosfamide	1 (0.9%)
Farletuzumab-Pld-Carboplatin	1 (0.9%)
Gexmab 25201 (CT)	1 (0.9%)
Niraparib	2 (1.8%)
Olaparib	2 (1.8%)
Pankomab (CT)	1 (0.9%)
Pembrolizumab (CT)	2 (1.8%)
Rucaparib/Placebo (Ariel Trial)	1 (0.9%)
Reason end of treatment	
Toxicity	10 (9.0%)
Doctor's decision	9 (8.1%)
Patient's decision	1 (0.9%)
Progression	28 (25.2%)
Treatment completed	59 (53.2%)
Medium Cytoreductive Laparotomy	1 (0.9%)
Microondas Hepatic	1 (0.9%)
Unknown	2 (1.8%)
Best Radiological Response (RECIST)	
Complete Response (CR)	34 (30.6%)
Partial Response (PR)	32 (28.8%)
Stable Disease (SD)	32 (28.8%)
Progressive Disease (PD)	6 (5.4%)
Not assessable	7 (6.3%)
Treatment free interval	
<6 months	39 (35.1%)
6-12 months	38 (34.2%)
>12 months	34 (30.6%)

*(CL) - Clinical Trial

Table 11. Ovarian Cancer. Previous Systemic Treatments.

	Total (n=43)
Previous Platin treatment	
Yes	56 (50.5%)
No	6 (5.4%)
Not applicable (no previous treatment)	49 (44.1%)

*(CL) - Clinical Trial

Table 12. Ovarian Cancer. Subsequent Treatments.

	Total (n=43)
N. of Post. Treatments Lines per Patient	
N	32
N Miss	11 (25.6%)
Mean	2.4
Std Dev	1.2
Median	2.0
q1	1.0
q3	3.0
Minimum	1
Maximum	5
Post. Treatments Lines per Patient	
0 Lines	11 (25.6%)
1 or 2 Lines	17 (39.5%)
3 or 4 Lines	13 (30.2%)
5 or more Lines	2 (4.7%)
Best response	
Complete Response (CR)	1 (1.4%)
Partial Response (PR)	21 (28.4%)
Stable Disease (SD)	27 (36.5%)
Progression (PD)	14 (18.9%)
Progressive Disease (PD)	0 (0.0%)
Not assessable	11 (14.9%)

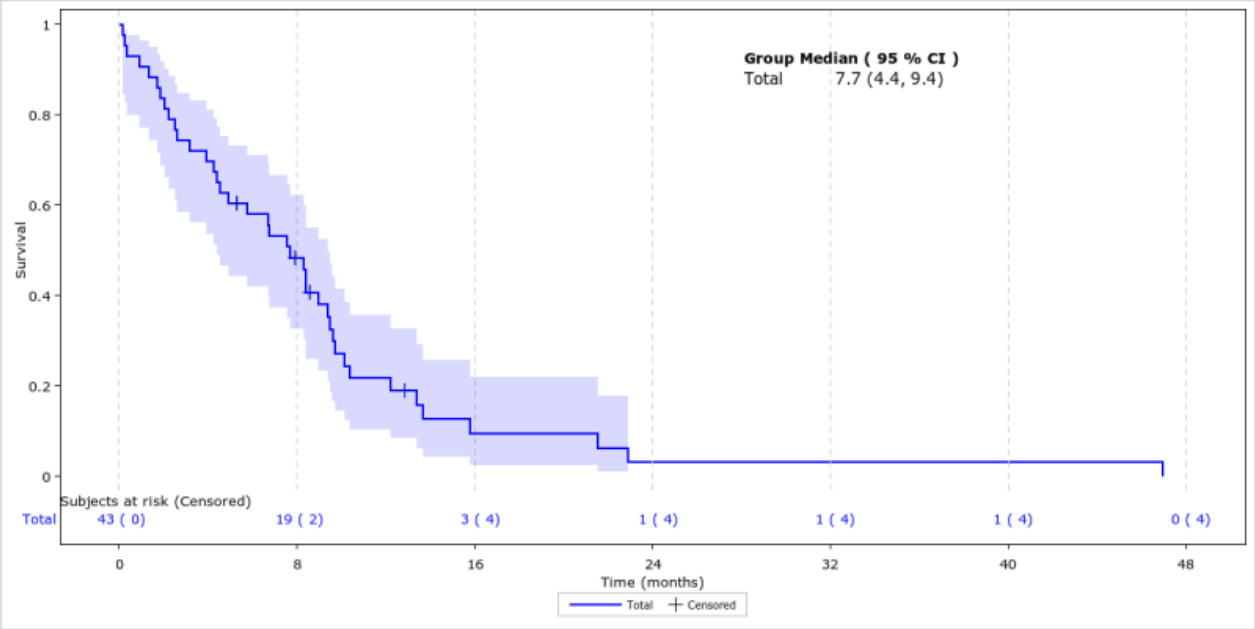
Table 12. Ovarian Cancer. Subsequent Treatments.

	Total (n=43)
Drug/Combination name	
Bevacizumab	1 (1.3%)
Bevacizumab-Cyclophosphamide	5 (6.5%)
Bevacizumab-Paclitaxel	1 (1.3%)
Bevacizumab-Topotecan	1 (1.3%)
Carboplatin	4 (5.2%)
Carboplatin-Bevacizumab-Gembcitabine	2 (2.6%)
Carboplatin-DLP	4 (5.2%)
Carboplatin-Gemcitabine	9 (11.7%)
Carboplatin-Paclitaxel	12 (15.6%)
Carboplatin-Taxol	1 (1.3%)
Cisplatin	2 (2.6%)
Cisplatin-Gemcitabine	4 (5.2%)
Cyclophosfamide	1 (1.3%)
DLP	3 (3.9%)
Etoposide	1 (1.3%)
Folfox	1 (1.3%)
Gemcitabine	4 (5.2%)
Genoxal	1 (1.3%)
Niraparib	3 (3.9%)
Olaparib	7 (9.1%)
Oxaliplatin	1 (1.3%)
Oxaliplatin-Gemcitabine	1 (1.3%)
Paclitaxel	5 (6.5%)
Topotecan	2 (2.6%)
Vb111-Paclitaxel (CT)	1 (1.3%)
Reason end of treatment	
Progression	33 (44.6%)
Toxicity	15 (20.3%)
Doctor's decision	17 (23.0%)
Patient's decision	1 (1.4%)
Death	1 (1.4%)
Completed	2 (2.7%)
Other	4 (5.4%)
Unknown	1 (1.4%)
Ongoing?	
No	74 (96.1%)
Yes	3 (3.9%)

10.3 Outcome data

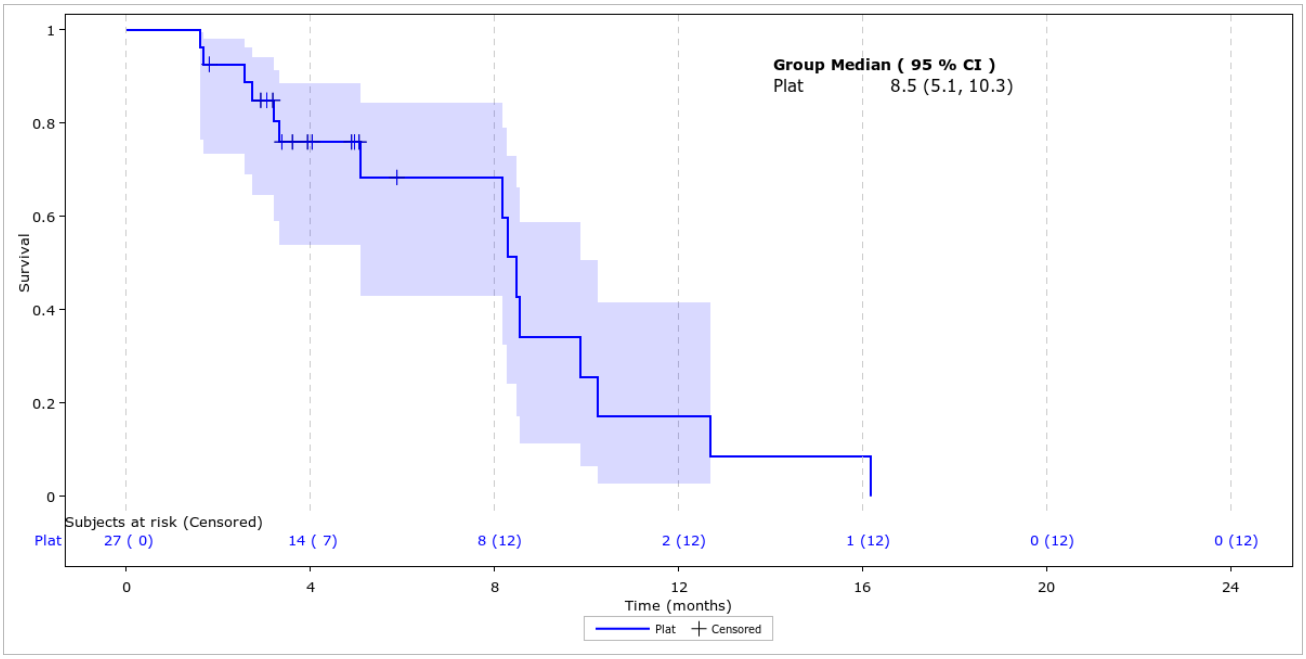
PFS for trabectedin+PLD treatment (43 patients):

Figure 1. Progression Free Survival. Kaplan-Meier Estimates. Per Protocol.



Median PFS = 7.7 months. IC 95: (4.4, 9.4)

PFS for platin-containing regimens when given right after trabectedin+PLD (27 patients):



PFS listings for trabectedin+PLD treatment:

Listing 7. Progression Free Survival. Full Analysis Set.

Subjid	Site	Start Date	PFS Date	PFS	Event*
06-001	HCSC	29-OCT-2019	03-NOV-2019	0.16	1
10-002	HVAL	08-MAY-2015	15-MAY-2015	0.23	1
04-007	HLEO	04-JUL-2016	15-JUL-2016	0.36	1
02-001	HRYC	08-SEP-2016	06-OCT-2016	0.92	1
04-006	HLEO	09-OCT-2017	19-NOV-2017	1.35	1
15-002	HUDP	27-MAY-2016	18-JUL-2016	1.71	1
12-004	HUVR	12-DEC-2017	06-FEB-2018	1.84	1
09-003	HUJF	23-MAY-2019	24-JUL-2019	2.04	1
15-001	HUDP	15-FEB-2016	23-APR-2016	2.23	1
07-001	HUBA	28-AUG-2015	13-NOV-2015	2.53	1
06-002	HCSC	25-OCT-2019	13-JAN-2020	2.63	1
06-005	HCSC	13-FEB-2018	21-MAY-2018	3.19	1
05-004	HURS	07-JAN-2015	06-MAY-2015	3.91	1
03-001	ICOG	17-SEP-2019	24-JAN-2020	4.24	1
04-004	HLEO	06-NOV-2017	20-MAR-2018	4.40	1
04-005	HLEO	04-MAY-2017	19-SEP-2017	4.53	1
12-002	HUVR	18-DEC-2018	16-MAY-2019	4.90	1
02-002	HRYC	16-NOV-2018	26-APR-2019	5.29	0
06-006	HCSC	08-MAR-2019	30-AUG-2019	5.75	1
06-003	HCSC	14-SEP-2017	06-APR-2018	6.70	1
06-004	HCSC	07-AUG-2018	28-FEB-2019	6.74	1
10-003	HVAL	21-JAN-2019	08-SEP-2019	7.56	1
10-001	HVAL	28-JUL-2015	18-MAR-2016	7.69	1
06-009	HCSC	12-FEB-2018	11-OCT-2018	7.92	0
05-003	HURS	22-MAR-2017	29-NOV-2017	8.28	1
04-002	HLEO	20-JUN-2018	02-MAR-2019	8.38	1
06-007	HCSC	25-MAY-2017	05-FEB-2018	8.41	1
04-001	HLEO	17-MAY-2016	02-FEB-2017	8.58	0
05-006	HURS	18-MAY-2015	15-FEB-2016	8.97	1
11-001	IVOG	15-APR-2015	26-JAN-2016	9.40	1
14-001	HCVA	29-MAY-2017	13-MAR-2018	9.46	1
04-008	HLEO	29-NOV-2017	17-SEP-2018	9.60	1
12-003	HUVR	29-MAR-2017	18-JAN-2018	9.69	1
09-001	HUJF	11-APR-2016	13-FEB-2017	10.12	1
01-002	HUB	27-MAR-2019	06-FEB-2020	10.38	1
11-002	IVOG	19-JAN-2015	26-JAN-2016	12.22	1
01-001	HUB	20-MAY-2016	15-JUN-2017	12.85	0
04-003	HLEO	08-FEB-2016	22-MAR-2017	13.41	1
09-002	HUJF	21-OCT-2015	10-DEC-2016	13.67	1
03-002	ICOG	15-MAY-2017	07-SEP-2018	15.77	1

*Events: Progression or death by treatment
Patients censored at post treatment or lost to follow up

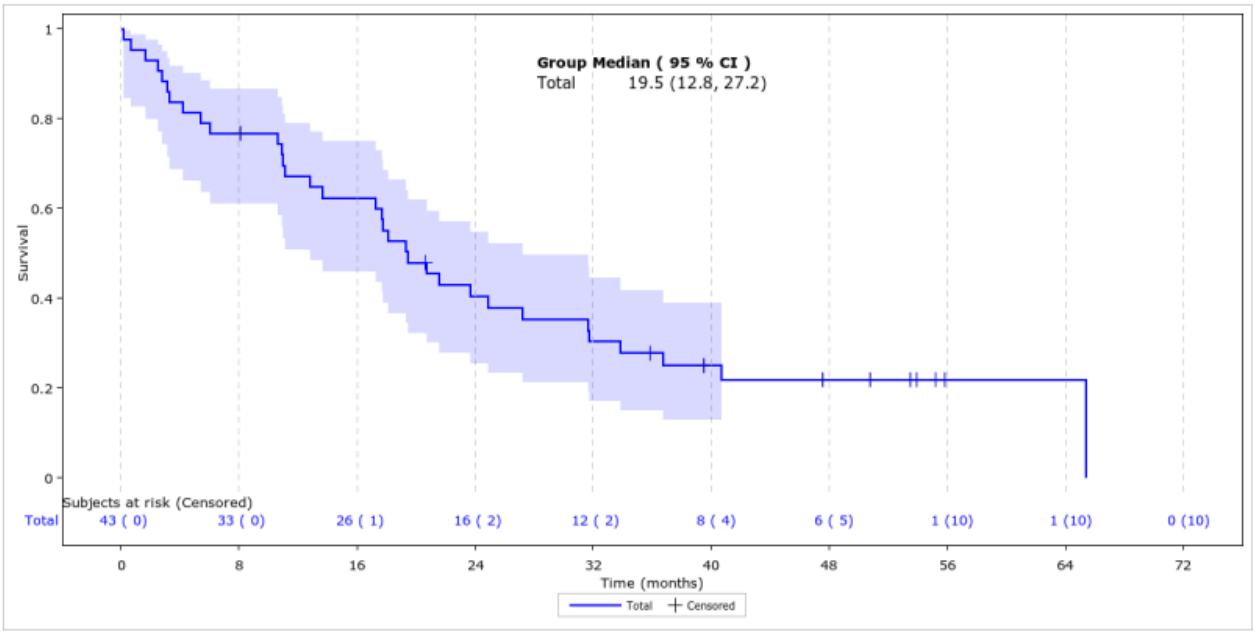
Listing 7. Progression Free Survival. Full Analysis Set.

Subjid	Site	Start Date	PFS Date	PFS	Event*
13-001	HVVA	07-MAY-2015	20-FEB-2017	21.52	1
05-002	HURS	09-NOV-2017	07-OCT-2019	22.91	1
12-001	HUVR	25-JUL-2017	22-JUN-2021	46.93	1

*Events: Progression or death by treatment
Patients censored at post treatment or lost to follow up

Overall survival for trabectedin+PLD treatment:

Figure 2. Overall Survival. Kaplan-Meier Estimates. Full Analysis Set.



Median OS = 19.5 months. IC 95: (12.8, 27.2)

Listing 8. Overall Survival. Full Analysis Set.

Subjid	Site	Start Date	OS Date	Overal Survival	Event*
06-001	HCSC	29-OCT-2019	03-NOV-2019	0.16	1
10-002	HVAL	08-MAY-2015	29-MAY-2015	0.69	1
02-001	HRYC	08-SEP-2016	28-OCT-2016	1.64	1
12-004	HUVR	12-DEC-2017	27-FEB-2018	2.53	1
15-001	HUDP	15-FEB-2016	09-MAY-2016	2.76	1
04-006	HLEO	09-OCT-2017	12-JAN-2018	3.12	1
15-002	HUDP	27-MAY-2016	03-SEP-2016	3.25	1
09-003	HUJF	23-MAY-2019	27-SEP-2019	4.17	1
06-002	HCSC	25-OCT-2019	07-APR-2020	5.42	1
05-004	HURS	07-JAN-2015	09-JUL-2015	6.01	1
04-002	HLEO	20-JUN-2018	21-FEB-2019	8.08	0
12-003	HUVR	29-MAR-2017	16-FEB-2018	10.65	1
06-005	HCSC	13-FEB-2018	11-JAN-2019	10.91	1
07-001	HUBA	28-AUG-2015	27-JUL-2016	10.98	1
10-003	HVAL	21-JAN-2019	26-DEC-2019	11.14	1
03-001	ICOG	17-SEP-2019	11-OCT-2020	12.82	1
12-002	HUVR	18-DEC-2018	06-FEB-2020	13.64	1
04-004	HLEO	06-NOV-2017	15-APR-2019	17.25	1
04-003	HLEO	08-FEB-2016	30-JUL-2017	17.68	1
04-007	HLEO	04-JUL-2016	27-DEC-2017	17.78	1
06-003	HCSC	14-SEP-2017	19-MAR-2019	18.11	1
01-002	HUB	27-MAR-2019	03-NOV-2020	19.29	1
10-001	HVAL	28-JUL-2015	11-MAR-2017	19.45	1
13-001	HVVA	07-MAY-2015	23-JAN-2017	20.60	0
06-004	HCSC	07-AUG-2018	29-APR-2020	20.74	1
04-001	HLEO	17-MAY-2016	05-MAR-2018	21.59	1
01-001	HUB	20-MAY-2016	10-MAY-2018	23.66	1
06-007	HCSC	25-MAY-2017	21-JUN-2019	24.88	1
09-001	HUJF	11-APR-2016	18-JUL-2018	27.21	1
06-009	HCSC	12-FEB-2018	03-OCT-2020	31.68	1
11-002	IVOG	19-JAN-2015	10-SEP-2017	31.71	1
09-002	HUJF	21-OCT-2015	16-AUG-2018	33.85	1
11-001	IVOG	15-APR-2015	10-APR-2018	35.85	0
04-005	HLEO	04-MAY-2017	26-MAY-2020	36.74	1
06-006	HCSC	08-MAR-2019	22-JUN-2022	39.50	0
02-002	HRYC	16-NOV-2018	08-APR-2022	40.72	1
05-002	HURS	09-NOV-2017	26-OCT-2021	47.55	0
04-008	HLEO	29-NOV-2017	21-FEB-2022	50.77	0
14-001	HCVA	29-MAY-2017	12-NOV-2021	53.50	0
12-001	HUVR	25-JUL-2017	21-JAN-2022	53.93	0

*Events: Death
Patients censored at lost to follow up

Listing 8. Overall Survival. Full Analysis Set.

Subjid	Site	Start Date	OS Date	Overal Survival	Event*
03-002	ICOG	15-MAY-2017	20-DEC-2021	55.21	0
05-003	HURS	22-MAR-2017	15-NOV-2021	55.83	0
05-006	HURS	18-MAY-2015	29-OCT-2020	65.43	1

*Events: Death
Patients censored at lost to follow up

Table 13. Objective Response Rate. Descriptive and Inferential Statistics.
Full Analysis Set.

	Total (n=43)
Radiological best overall responce	
Progression Disease (PD)	5 (11.6%)
Stable Disease (SD)	13 (30.2%)
Partial Response (PR)	14 (32.6%)
Complete Response (CR)	4 (9.3%)
Not assessable	7 (16.3%)
Biological best overall responce	
Progression	3 (7.0%)
Stabilization	3 (7.0%)
Response	14 (32.6%)
Response and normalization	11 (25.6%)
Not assessable	12 (27.9%)
Objective Response Rate	
PD or SD	18 (41.9%)
PR or CR	18 (41.9%)
NE	7 (16.3%)

ORR Binomial's confidence interval 95 with 36 patients
prob = 0.5 with CI (0.345 - 0.655)

Listing 9. Objective Response Rate. Full Analysis Set.

Subjid	Site	Best Response	OS Date
01-001	HUB	Stable Disease (SD)	21-SEP-2016
01-002	HUB	Partial Response (PR)	16-JUN-2019
02-001	HRYC	Stable Disease (SD)	11-OCT-2016
02-002	HRYC	Partial Response (PR)	19-FEB-2019
03-001	ICOG	Partial Response (PR)	18-NOV-2019
03-002	ICOG	Partial Response (PR)	12-JUL-2017
04-001	HLEO	Partial Response (PR)	12-JUL-2016
04-002	HLEO	Partial Response (PR)	05-DEC-2019
04-003	HLEO	Not assessable	.
04-004	HLEO	Stable Disease (SD)	14-DEC-2017
04-005	HLEO	Stable Disease (SD)	19-MAY-2017
04-006	HLEO	Not assessable	.
04-007	HLEO	Progression Disease (PD)	15-JUL-2016
04-008	HLEO	Partial Response (PR)	03-APR-2018
05-002	HURS	Complete Response (CR)	28-MAY-2018
05-003	HURS	Partial Response (PR)	06-SEP-2017
05-004	HURS	Stable Disease (SD)	10-MAR-2015
05-006	HURS	Complete Response (CR)	21-OCT-2015
06-001	HCSC	Not assessable	.
06-002	HCSC	Not assessable	.
06-003	HCSC	Partial Response (PR)	28-DEC-2017
06-004	HCSC	Stable Disease (SD)	16-NOV-2018
06-005	HCSC	Progression Disease (PD)	21-MAY-2018
06-006	HCSC	Partial Response (PR)	14-JUN-2019
06-007	HCSC	Stable Disease (SD)	07-NOV-2017
06-009	HCSC	Stable Disease (SD)	23-APR-2018
07-001	HUBA	Progression Disease (PD)	13-NOV-2015
09-001	HUJF	Stable Disease (SD)	26-JUL-2017
09-002	HUJF	Complete Response (CR)	07-JUL-2016
09-003	HUJF	Not assessable	.
10-001	HVAL	Partial Response (PR)	26-OCT-2015
10-002	HVAL	Not assessable	.
10-003	HVAL	Stable Disease (SD)	25-APR-2019
11-001	IVOG	Partial Response (PR)	02-SEP-2015
11-002	IVOG	Complete Response (CR)	03-JUN-2015
12-001	HUVR	Stable Disease (SD)	22-SEP-2017
12-002	HUVR	Partial Response (PR)	05-MAR-2019
12-003	HUVR	Partial Response (PR)	31-JUL-2017
12-004	HUVR	Not assessable	.
13-001	HVVA	Stable Disease (SD)	17-SEP-2015

Listing 9. Objective Response Rate. Full Analysis Set.

Subjid	Site	Best Response	OS Date
14-001	HCVA	Stable Disease (SD)	28-AUG-2017
15-001	HUDP	Progression Disease (PD)	23-APR-2016
15-002	HUDP	Progression Disease (PD)	18-JUL-2016

Table 14. Disease Control Rate. Descriptive and Inferential Statistics. Full Analysis Set.

	Total (n=43)
Radiological best overall responce	
Progression Disease (PD)	5 (11.6%)
Stable Disease (SD)	13 (30.2%)
Partial Response (PR)	14 (32.6%)
Complete Response (CR)	4 (9.3%)
Not assessable	7 (16.3%)
Biological best overall responce	
Progression	3 (7.0%)
Stabilization	3 (7.0%)
Response	14 (32.6%)
Response and normalization	11 (25.6%)
Not assessable	12 (27.9%)
Objective Response Rate	
PD	5 (11.6%)
CR or PR or SD	31 (72.1%)
NE	7 (16.3%)

DCR Binomial's confidence interval 95 with 36 patients
prob = 0.8611111111 with CI (0.713 - 0.939)

Listing 11. Duration of Response Treatment. Full Analysis Set.

Subjid	Progression Site	Best Response	Progression Date	type*	Date	Duration
01-001	HUB	Stable Disease (SD)	21-SEP-2016		.	0.00
01-002	HUB	Partial Response (PR)	16-JUN-2019	R	06-FEB-2020	7.72
02-001	HRYC	Stable Disease (SD)	11-OCT-2016	C	06-OCT-2016	0.00
02-002	HRYC	Partial Response (PR)	19-FEB-2019		.	0.00
03-001	ICOG	Partial Response (PR)	18-NOV-2019	R	24-JAN-2020	2.20
03-002	ICOG	Partial Response (PR)	12-JUL-2017	R, B (ca 125)	07-SEP-2018	13.87
04-001	HLEO	Partial Response (PR)	12-JUL-2016	B (ca 125)	04-FEB-2017	6.80
04-002	HLEO	Partial Response (PR)	05-DEC-2019	R	02-MAR-2019	0.00
04-003	HLEO	Not assessable	.	R	22-MAR-2017	0.00
04-004	HLEO	Stable Disease (SD)	14-DEC-2017	R	20-MAR-2018	3.15
04-005	HLEO	Stable Disease (SD)	19-MAY-2017	R	19-SEP-2017	4.04
04-006	HLEO	Not assessable	.	R, C, B (ca125)	19-NOV-2017	0.00
04-007	HLEO	Progression Disease (PD)	15-JUL-2016	R	15-JUL-2016	0.00
04-008	HLEO	Partial Response (PR)	03-APR-2018	R, B (ca 125)	17-SEP-2018	5.49
05-002	HURS	Complete Response (CR)	28-MAY-2018	R	07-OCT-2019	16.33
05-003	HURS	Partial Response (PR)	06-SEP-2017	R	29-NOV-2017	2.76
05-004	HURS	Stable Disease (SD)	10-MAR-2015	R	06-MAY-2015	1.87
05-006	HURS	Complete Response (CR)	21-OCT-2015	R	15-FEB-2016	3.84
06-001	HCSC	Not assessable	.	C	03-NOV-2019	0.00
06-002	HCSC	Not assessable	.	R, C	13-JAN-2020	0.00
06-003	HCSC	Partial Response (PR)	28-DEC-2017	R	06-APR-2018	3.25
06-004	HCSC	Stable Disease (SD)	16-NOV-2018	R	28-FEB-2019	3.42
06-005	HCSC	Progression Disease (PD)	21-MAY-2018	R, C, B (ca125)	21-MAY-2018	0.00
06-006	HCSC	Partial Response (PR)	14-JUN-2019	R, B (ca 125)	30-AUG-2019	2.53

Duration in months.
*R-Radiological, C-Clinical, B-Biological.

Listing 11. Duration of Response Treatment. Full Analysis Set.

Subjid	Progression Site	Best Response	Progression Date	type*	Date	Duration
06-007	HCSC	Stable Disease (SD)	07-NOV-2017	R, B (ca 125)	05-FEB-2018	2.96
06-009	HCSC	Stable Disease (SD)	23-APR-2018	C	03-NOV-2018	6.38
07-001	HUBA	Progression Disease (PD)	13-NOV-2015	R	13-NOV-2015	0.00
09-001	HUJF	Stable Disease (SD)	26-JUL-2017	R	13-FEB-2017	0.00
09-002	HUJF	Complete Response (CR)	07-JUL-2016	R	10-DEC-2016	5.13
09-003	HUJF	Not assessable	.	C	24-JUL-2019	0.00
10-001	HVAL	Partial Response (PR)	26-OCT-2015	R, B (ca 125)	18-MAR-2016	4.73
10-002	HVAL	Not assessable	.	C	15-MAY-2015	0.00
10-003	HVAL	Stable Disease (SD)	25-APR-2019	C	08-SEP-2019	4.47
11-001	IVOG	Partial Response (PR)	02-SEP-2015	R, C, B (ca125)	26-JAN-2016	4.80
11-002	IVOG	Complete Response (CR)	03-JUN-2015	R, C, B (ca125)	26-JAN-2016	7.79
12-001	HUVR	Stable Disease (SD)	22-SEP-2017	R, B (ca 125)	22-JUN-2021	44.99
12-002	HUVR	Partial Response (PR)	05-MAR-2019	R, B (ca 125)	16-MAY-2019	2.37
12-003	HUVR	Partial Response (PR)	31-JUL-2017	R, C	18-JAN-2018	5.62
12-004	HUVR	Not assessable	.	C	06-FEB-2018	0.00
13-001	HVVA	Stable Disease (SD)	17-SEP-2015	R	20-FEB-2017	17.15
14-001	HCVA	Stable Disease (SD)	28-AUG-2017	R	13-MAR-2018	6.47
15-001	HUDP	Progression Disease (PD)	23-APR-2016	R, C	23-APR-2016	0.00
15-002	HUDP	Progression Disease (PD)	18-JUL-2016	R, C, B (ca125)	18-JUL-2016	0.00

Duration in months.
*R-Radiological, C-Clinical, B-Biological.

10.4 Main results

Between November 2021 and June 2022, 43 patients were recruited with median age 74 years (70-86). At initial diagnosis, most common FIGO stages were IIIC (51.2%), IVB (11.6%), and IIIB (7.0%). Before trabectedin+PLD (baseline), patients had ECOG performance status 0, 1, or 2 (34.1%, 41.5%, and 9.8%) and 81.4% had measurable disease. The median number of previous lines was 2 (1-6). The initial dose of trabectedin was 1.1 mg/m^2 in 76.7% of patients (16.3% with <1.1 and 4.7% with >1.1 mg/m^2) while 76.7% of patients had PLD at 30 mg (18.6% with <30 mg and 2.3% with >30 mg). The median of trabectedin+PLD cycles was 5 (1-21) and 53.5% of patients had at least one cycle delayed. All patients ended treatment for the following reasons: patient's decision (7.0%), doctor's decision (23.3%), disease progression (39.5%), toxicity (23.83%) and 7.0% due to other factors. Median PFS for the trabectedin+PLD combination was 7.7 months (95% CI 4.4-9.4) with best overall response rates of 4 CR (9.3%), 14 PR (32.6%), 13 SD (30.2%), and 5 PD (11.6%). Median overall survival (OS) was 19.5 months (95% CI 12.8-27.2). Overall, the most common G3-4 hematological events were neutropenia (23.3%), thrombocytopenia (7.0%), and anemia (2.3%), being asthenia (11.6%), mucositis (4.7%), and transaminitis (4.7%) the most frequent G3 non-hematological toxicities.

10.5 Other analyses

No other analyses were performed.

10.6 Adverse events/adverse reactions

Table 15.1. Adverse Events by Haematology or Non - Haematology.
Descriptive Statistics. Safety Analysis Set.

Haematology Term		Total
Haematological		
Anemia	SUBJECTS	10 (23.3%)
	EPISODES	13
Neutrophil count decreased	SUBJECTS	16 (37.2%)
	EPISODES	26
Platelet count decreased	SUBJECTS	6 (14.0%)
	EPISODES	6
White Blood Cells Decreased	SUBJECTS	1 (2.3%)
	EPISODES	4
Non-Haematological		
Abdominal pain	SUBJECTS	1 (2.3%)
	EPISODES	1
Alopecia	SUBJECTS	1 (2.3%)
	EPISODES	1
Asthenia	SUBJECTS	21 (48.8%)
	EPISODES	25
Constipation	SUBJECTS	2 (4.7%)
	EPISODES	2
Dissociated Cholestasis	SUBJECTS	1 (2.3%)
	EPISODES	1
Dysuria	SUBJECTS	1 (2.3%)
	EPISODES	1
General Muscular Pain	SUBJECTS	1 (2.3%)
	EPISODES	1
Headache	SUBJECTS	1 (2.3%)
	EPISODES	1
Hiporexia	SUBJECTS	1 (2.3%)
	EPISODES	1
Hypersensitization To Trabectidin	SUBJECTS	1 (2.3%)
	EPISODES	1
Hypertension	SUBJECTS	2 (4.7%)
	EPISODES	2
Hypokalemia	SUBJECTS	1 (2.3%)
	EPISODES	1
Mucositis	SUBJECTS	6 (14.0%)
	EPISODES	6
Nausea	SUBJECTS	10 (23.3%)
	EPISODES	10
Palmar-Plantar Erythrodysesthesia	SUBJECTS	1 (2.3%)
	EPISODES	1

Adverse events related or possibly related to treatment.

Table 15.1. Adverse Events by Haematology or Non - Haematology.
Descriptive Statistics. Safety Analysis Set.

Haematology Term		Total
Respiratory Infection	SUBJECTS	1 (2.3%)
	EPISODES	1
Serum Urea Increased	SUBJECTS	1 (2.3%)
	EPISODES	1
Skin Disorders	SUBJECTS	2 (4.7%)
	EPISODES	2
Transaminitis	SUBJECTS	4 (9.3%)
	EPISODES	4
Urinary Tract Infection	SUBJECTS	3 (7.0%)
	EPISODES	4
Vomiting	SUBJECTS	6 (14.0%)
	EPISODES	6

Adverse events related or possibly related to treatment.

Table 15.2. Adverse Events by Grade. Descriptive Statistics.
Safety Analysis Set.

Grade / Term		Total
Any grade		
Abdominal pain	SUBJECTS	1 (2.3%)
	EPISODES	1
Alopecia	SUBJECTS	1 (2.3%)
	EPISODES	1
Anemia	SUBJECTS	10 (23.3%)
	EPISODES	13
Asthenia	SUBJECTS	21 (48.8%)
	EPISODES	25
Constipation	SUBJECTS	2 (4.7%)
	EPISODES	2
Dissociated Cholestasis	SUBJECTS	1 (2.3%)
	EPISODES	1
Dysuria	SUBJECTS	1 (2.3%)
	EPISODES	1
General Muscular Pain	SUBJECTS	1 (2.3%)
	EPISODES	1
Headache	SUBJECTS	1 (2.3%)
	EPISODES	1
Hiporexia	SUBJECTS	1 (2.3%)
	EPISODES	1
Hypersensitization To Trabectidin	SUBJECTS	1 (2.3%)
	EPISODES	1
Hypertension	SUBJECTS	2 (4.7%)
	EPISODES	2
Hypokalemia	SUBJECTS	1 (2.3%)
	EPISODES	1
Mucositis	SUBJECTS	6 (14.0%)
	EPISODES	6
Nausea	SUBJECTS	10 (23.3%)
	EPISODES	10
Neutrophil count decreased	SUBJECTS	16 (37.2%)
	EPISODES	26
Palmar-Plantar Erythrodysesthesia	SUBJECTS	1 (2.3%)
	EPISODES	1
Platelet count decreased	SUBJECTS	6 (14.0%)
	EPISODES	6
Respiratory Infection	SUBJECTS	1 (2.3%)
	EPISODES	1
Serum Urea Increased	SUBJECTS	1 (2.3%)
	EPISODES	1

Adverse Events related or possibly related to treatment.

Table 15.2. Adverse Events by Grade. Descriptive Statistics.
Safety Analysis Set.

Grade / Term		Total
Skin Disorders	SUBJECTS	2 (4.7%)
	EPISODES	2
Transaminitis	SUBJECTS	4 (9.3%)
	EPISODES	4
Urinary Tract Infection	SUBJECTS	3 (7.0%)
	EPISODES	4
Vomiting	SUBJECTS	6 (14.0%)
	EPISODES	6
White Blood Cells Decreased	SUBJECTS	1 (2.3%)
	EPISODES	4
Grade 1		
Abdominal pain	SUBJECTS	1 (2.3%)
	EPISODES	1
Alopecia	SUBJECTS	1 (2.3%)
	EPISODES	1
Anemia	SUBJECTS	4 (9.3%)
	EPISODES	7
Asthenia	SUBJECTS	5 (11.6%)
	EPISODES	5
Constipation	SUBJECTS	2 (4.7%)
	EPISODES	2
Dissociated Cholestasis	SUBJECTS	1 (2.3%)
	EPISODES	1
Dysuria	SUBJECTS	1 (2.3%)
	EPISODES	1
General Muscular Pain	SUBJECTS	1 (2.3%)
	EPISODES	1
Headache	SUBJECTS	1 (2.3%)
	EPISODES	1
Hiporexia	SUBJECTS	1 (2.3%)
	EPISODES	1
Hypertension	SUBJECTS	2 (4.7%)
	EPISODES	2
Hypokalemia	SUBJECTS	1 (2.3%)
	EPISODES	1
Mucositis	SUBJECTS	2 (4.7%)
	EPISODES	2
Nausea	SUBJECTS	5 (11.6%)
	EPISODES	5
Neutrophil count decreased	SUBJECTS	3 (7.0%)
	EPISODES	4

Adverse Events related or possibly related to treatment.

Table 15.2. Adverse Events by Grade. Descriptive Statistics.
Safety Analysis Set.

Grade / Term		Total
Platelet count decreased	SUBJECTS	2 (4.7%)
	EPISODES	2
Serum Urea Increased	SUBJECTS	1 (2.3%)
	EPISODES	1
Transaminitis	SUBJECTS	2 (4.7%)
	EPISODES	2
Vomiting	SUBJECTS	4 (9.3%)
	EPISODES	4
White Blood Cells Decreased	SUBJECTS	1 (2.3%)
	EPISODES	2
Grade 2		
Anemia	SUBJECTS	5 (11.6%)
	EPISODES	5
Asthenia	SUBJECTS	15 (34.9%)
	EPISODES	15
Mucositis	SUBJECTS	2 (4.7%)
	EPISODES	2
Nausea	SUBJECTS	3 (7.0%)
	EPISODES	3
Neutrophil count decreased	SUBJECTS	7 (16.3%)
	EPISODES	9
Palmar-Plantar Erythrodysesthesia	SUBJECTS	1 (2.3%)
	EPISODES	1
Skin Disorders	SUBJECTS	2 (4.7%)
	EPISODES	2
Urinary Tract Infection	SUBJECTS	3 (7.0%)
	EPISODES	4
Vomiting	SUBJECTS	1 (2.3%)
	EPISODES	1
White Blood Cells Decreased	SUBJECTS	1 (2.3%)
	EPISODES	2
Grade 3		
Anemia	SUBJECTS	1 (2.3%)
	EPISODES	1
Asthenia	SUBJECTS	5 (11.6%)
	EPISODES	5
Mucositis	SUBJECTS	2 (4.7%)
	EPISODES	2
Nausea	SUBJECTS	1 (2.3%)
	EPISODES	1

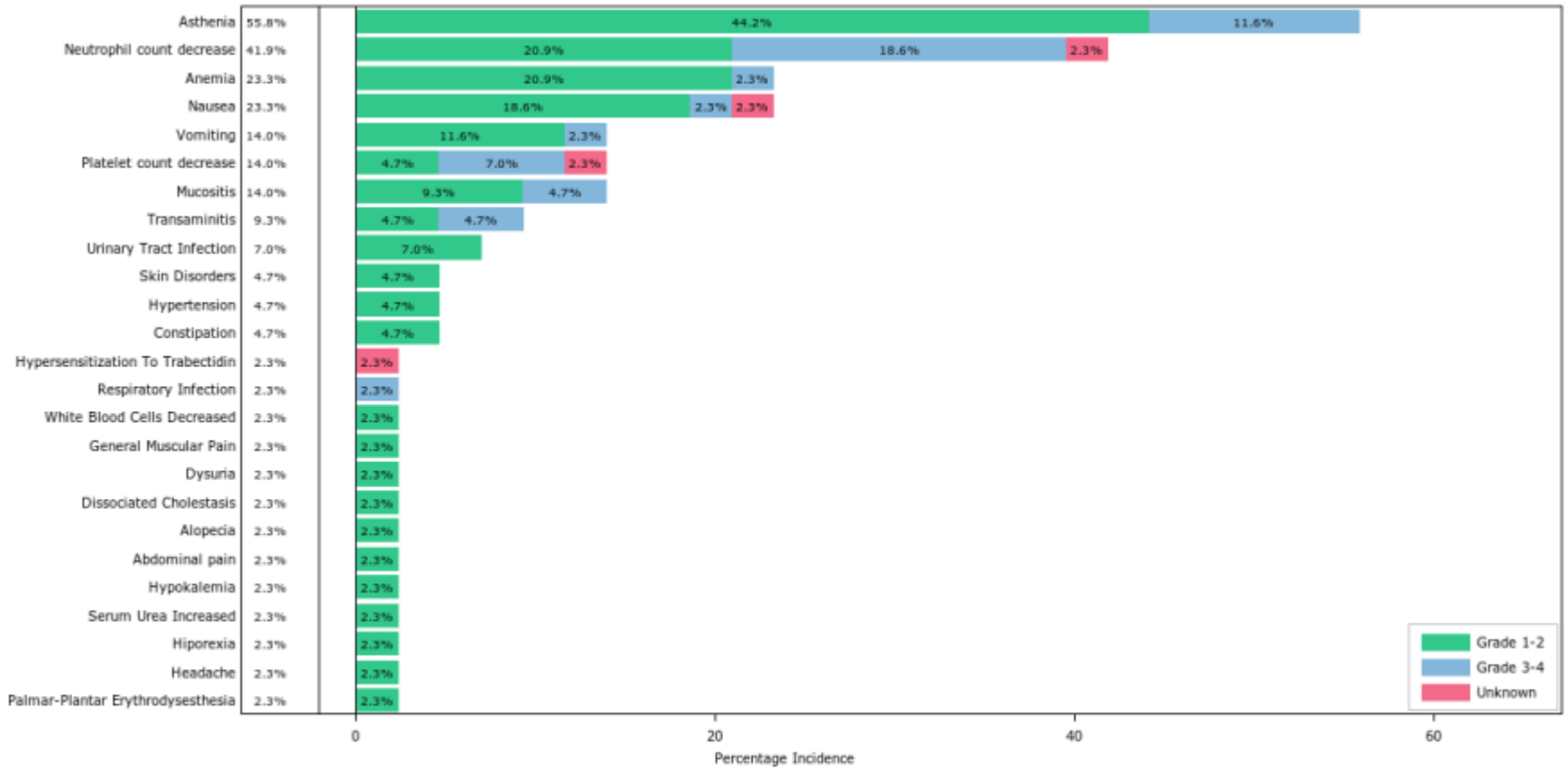
Adverse Events related or possibly related to treatment.

Table 15.2. Adverse Events by Grade. Descriptive Statistics.
Safety Analysis Set.

Grade / Term		Total
Neutrophil count decreased	SUBJECTS	4 (9.3%)
	EPISODES	6
Platelet count decreased	SUBJECTS	3 (7.0%)
	EPISODES	3
Respiratory Infection	SUBJECTS	1 (2.3%)
	EPISODES	1
Transaminitis	SUBJECTS	2 (4.7%)
	EPISODES	2
Vomiting	SUBJECTS	1 (2.3%)
	EPISODES	1
Grade 4		
Neutrophil count decreased	SUBJECTS	6 (14.0%)
	EPISODES	6
Unknown		
Hypersensitization To Trabectidin	SUBJECTS	1 (2.3%)
	EPISODES	1
Nausea	SUBJECTS	1 (2.3%)
	EPISODES	1
Neutrophil count decreased	SUBJECTS	1 (2.3%)
	EPISODES	1
Platelet count decreased	SUBJECTS	1 (2.3%)
	EPISODES	1

Adverse Events related or possibly related to treatment.

Figure 3. Adverse Events by Grade. Descriptive Statistics. Safety Analysis Set.



Adverse Events related or possibly related to treatment.

Table 15.6 Adverse Events by Highest grade per patient by Grade group.
Descriptive Statistics. Safety Analysis Set.

Haematology Term	Total	I-II	III	IV
Haematological				
Neutrophil count decreased	15 (34.9%)	9 (20.9%)	4 (9.3%)	6 (14.0%)
Anemia	10 (23.3%)	9 (20.9%)	1 (2.3%)	0
Platelet count decreased	5 (11.6%)	2 (4.7%)	3 (7.0%)	0
White Blood Cells Decreased	1 (2.3%)	1 (2.3%)	0	0
Non-Haematological				
Asthenia	21 (48.8%)	19 (44.2%)	5 (11.6%)	0
Nausea	9 (20.9%)	8 (18.6%)	1 (2.3%)	0
Mucositis	6 (14.0%)	4 (9.3%)	2 (4.7%)	0
Vomiting	6 (14.0%)	5 (11.6%)	1 (2.3%)	0
Transaminitis	4 (9.3%)	2 (4.7%)	2 (4.7%)	0
Urinary Tract Infection	3 (7.0%)	3 (7.0%)	0	0
Constipation	2 (4.7%)	2 (4.7%)	0	0
Hypertension	2 (4.7%)	2 (4.7%)	0	0
Skin Disorders	2 (4.7%)	2 (4.7%)	0	0
Abdominal pain	1 (2.3%)	1 (2.3%)	0	0
Alopecia	1 (2.3%)	1 (2.3%)	0	0
Dissociated Cholestasis	1 (2.3%)	1 (2.3%)	0	0
Dysuria	1 (2.3%)	1 (2.3%)	0	0
General Muscular Pain	1 (2.3%)	1 (2.3%)	0	0
Headache	1 (2.3%)	1 (2.3%)	0	0
Hiporexia	1 (2.3%)	1 (2.3%)	0	0
Hypokalemia	1 (2.3%)	1 (2.3%)	0	0
Palmar-Plantar Erythrodysesthesia	1 (2.3%)	1 (2.3%)	0	0
Respiratory Infection	1 (2.3%)	0	1 (2.3%)	0

Adverse Events related or possibly related to treatment.

11. Discussion

11.1 Key results

- Between November 2021 and June 2022, 43 patients were recruited with median age 74 years (70-86).
- At initial diagnosis, most common FIGO stages were IIIC (51.2%), IVB (11.6%), and IIIB (7.0%).
- Before trabectedin+PLD (baseline):
- Patients had ECOG performance status 0, 1, or 2 (34.1%, 41.5%, and 9.8%) and 81.4% had measurable disease.
- The median number of previous lines was 2 (1-6).
- The initial dose of trabectedin was 1.1 mg/m^2 in 76.7% of patients (16.3% with <1.1 and 4.7% with >1.1 mg/m^2) while 76.7% of patients had PLD at 30 mg (18.6% with <30 mg and 2.3% with >30 mg).
- The median of trabectedin+PLD cycles was 5 (1-21) and 53.5% of patients had at least one cycle delayed.
- All patients ended treatment for the following reasons: patient's decision (7.0%), doctor's decision (23.3%), disease progression (39.5%), toxicity (23.83%) and 7.0% due to other factors.
- Median PFS for the trabectedin+PLD combination was 7.7 months (95% CI 4.4-9.4) with best overall response rates of 4 CR (9.3%), 14 PR (32.6%), 13 SD (30.2%), and 5 PD (11.6%).
- Median overall survival (OS) was 19.5 months (95% CI 12.8-27.2).
- Overall, the most common G3-4 hematological events were neutropenia (23.3%), thrombocytopenia (7.0%), and anemia (2.3%), being asthenia (11.6%), mucositis (4.7%), and transaminitis (4.7%) the most frequent G3 non-hematological toxicities.

11.2 Limitations

Potential study limitations included:

- Heterogeneous population in terms of baseline characteristics (retrospective study)
- Limited follow-up and missing data

11.3 Interpretation

This study demonstrated that the safety profile of the trabectedin+PLD combination for elderly patients in real-life setting is manageable and efficacy results are comparable to those of previous clinical trials.

11.4 Generalisability

The safety and efficacy results of this study are comparable to those of previous clinical trials with trabectedin and PLD.

12. Other information

All patients participating in the study (accessible, alive patients who could be interviewed in the hospital) received a Patient Information Sheet (PIS) describing, in simple language, the goals, scope, procedures and relevant implications of the study.

The PIS integrated an Informed Consent Form (ICF) to be signed by the patient, which was indispensable for study participation (for accessible patients).

Written informed consent had to be given by each accessible/reachable patient before study initiation (prior to registration of the patient in the e-CRF). The PIS/ICF included the consent of patients for the collection and analysis of their clinical data.

Data of inaccessible/unreachable patients (dead, lost, etc.) could still be used according to the permissions of ethics committees and Spanish law, regarding the use of data in retrospective studies.

13. Conclusion

The safety profile of the trabectedin+PLD combination for elderly women in real-life setting is manageable and efficacy results are comparable to those of previous clinical trials. The results of this study are aligned with those reported in the literature for the general population.

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