

# Horizon Scanning in Oncology

Trabectedin (Yondelis<sup>®</sup>) for  
second-line recurrent platinum-  
sensitive ovarian cancer



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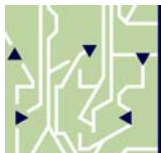
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# 1 Drug description

## Generic/Brand name:

Trabectedin, ET 743 (Yondelis ®)

Trabectedin  
(Yondelis ®)

## Developer/Company:

Pharma Mar, S.A. (Madrid, Spain)

## Description:

Trabectedin belongs to the pharmacotherapeutic group of antineoplastic agents (ATC code: L01CX01). It was originally derived from the marine tunicate *Ecteinascidia turbinata* and is now produced synthetically [1]. Trabectedin binds to the minor groove of DNA to prevent cancer cells from dividing too quickly and therefore slowing down the growth of various types of cancer, including sarcoma and ovarian cancer [2].

antineoplastic agent

The recommended treatment regimen for patients with ovarian cancer (OC) consists of an intravenous infusion of 1.1 mg/m<sup>2</sup> body surface area trabectedin over 3 hours immediately after administration of 30 mg/m<sup>2</sup> body surface area pegylated liposomal doxorubicin (PLD) [3].

recommended dose of  
trabectedin in OC 1.1  
mg/m<sup>2</sup>

# 2 Indication

Trabectedin is indicated for the treatment of patients (pts) with advanced, recurrent/relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin (PLD).

2<sup>nd</sup>-line therapy for  
recurrent/relapsed OC  
patients

# 3 Current regulatory status

Trabectedin was granted orphan drug designation from the European Commission (EC) and the US Food & Drug Administration (FDA) for the treatment of soft tissue sarcoma (2001 by EC and 2004 by FDA) and ovarian cancer (2003 by EC and 2005 by FDA) [1, 4].

orphan drug designation  
in Europe and USA

Currently, trabectedin is approved by the EMEA for the treatment of patients with advanced soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide or for patients who are unsuitable to receive these agents [5].

approved for the  
treatment of patients  
with STS and OC

**CHMP recommended approval of trabectedin for OC**

**FDA voted 14:1 against approval of trabectedin for OC**

**approved in UK**

In September 2009 the Committee for Human Medicinal Products (CHMP) of the EMEA advocated the extension of marketing authorisation of trabectedin for the treatment of patients with relapsed/recurrent platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin (PLD) [6], which was then granted marketing authorisation by the European Commission in October 2009 [7]. However, the US FDA voted 14:1 against the approval of trabectedin for the treatment of patients with recurrent/relapsed advanced ovarian cancer in July 2009 [8]. Since October 2009, trabectedin is approved for the treatment of patients with relapsed platinum-sensitive ovarian cancer in combination with PLD in the United Kingdom [3].

## 4 Burden of disease

**incidence: 8.8 per 100,000**

**yearly death rate: 5.5 per 100,000**

**diagnosis at late stage of disease (75%)**

**1<sup>st</sup>-line therapy: cytoreductive surgery + platinum-based chemotherapy**

**continuous decline of incidence rate**

**risk factors: age, stage of disease, nulliparous, family history regarding cancer, time of menopause and menarche**

**OC classification systems: FIGO and TNM**

Ovarian cancer is the leading gynaecological type of cancer causing death. Every year 13.1 per 100,000 women are diagnosed with ovarian cancer in the US [9] and in 2007 8.8 per 100,000 women were diagnosed with ovarian cancer in Austria [10]. The median age at diagnosis of ovarian cancer is 63 years (out of these women 12% are <45 years, 41.2% are between 45 and 64 years and 44.5% are ≥ 65 years at time of diagnosis) [11].

Overall, the annual age-adjusted death rate per year of patients suffering from ovarian cancer was 8.8 per 100,000 women in the US and 5.5 per 100,000 women in Austria in 2007, respectively [9].

Signs and symptoms of ovarian cancer occur very late, therefore over 75% of ovarian cancer patients suffer from advanced stage III or stage IV disease at time of diagnosis [12-13].

After cytoreductive surgery and platinum-based adjuvant chemotherapy in combination with paclitaxel several factors (disease stage, age, etc.) play an essential role in disease relapse.

Patients with stage I/II disease show a relapse rate of 10-20%, whereas patients at advanced stage III-IV ovarian cancer relapses in 60-85% of cases [14].

According to Statistik Austria the incidence of ovarian cancer and disease related death rate continuously declined over the past decades (e.g., reduction of disease related death rate of 11% over the last 10 years) [10, 15].

Age is also considered as a risk factor for relapse and survival. While women under 40 years have a 5-year survival rate of 65%, only 20% of ovarian cancer patients older than 40 years are alive five years after diagnosis [14].

Besides age and nulliparity, risk factors for developing the disease are early age of menarche, late age of menopause and family history of ovarian, breast or endometrial (uterine) cancer [16]. An identifiable genetic predisposition (e.g. BRCA1/BRCA2) is present in only 10% - to 15% of patients [17].

Different systems are available to classify cancer stages. The most commonly used for staging ovarian cancer are the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) and the TNM (tumour, node, metastasis) staging system. The five general stages of the FIGO system are:

- ✿ **Stage 0:** “Pre-cancer” or carcinoma in situ.
- ✿ **Stage I:** Tumour limited to ovaries
- ✿ **Stage II:** Tumour involves one or both ovaries with pelvic extension and/or implants
- ✿ **Stage III:** Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
- ✿ **Stage IV:** Patient shows distant metastasis [18]

## 5 Current treatment

The generally recommended first-line therapeutic approach is cytoreductive surgery followed by systemic chemotherapy with a platinum agent plus a taxane (mostly paclitaxel) for patients with poor prognostic factors like advanced stage of disease [12, 14]. Only patients with early stage ovarian cancer and good prognostic factors are not offered adjuvant chemotherapy [12, 14].

Unlike first-line therapy of ovarian cancer no standard of care has been established yet for recurrent ovarian cancer [1]. Choice of second-line therapy does not primarily depend on risk factors such as age or stage of disease, but the duration of response of each patient to first-line therapy helps in selecting a suitable second-line therapy [12, 14]. Generally, recurrent ovarian cancer patients are classified as:

- ✿ **Platinum-sensitive:** progression-free survival (PFS) >6 months after initial platinum-based chemotherapy.
- ✿ **Platinum-resistant:** patients who relapse within 6 months following initial platinum-based chemotherapy.
- ✿ **Platinum-refractory:** patients whose disease progresses while on platinum-containing therapy [12, 19].

Besides platinum agents (cisplatin and carboplatin) the following drugs are active in ovarian cancer patients: paclitaxel, docetaxel, oral etoposide, pegylated liposomal doxorubicin, topotecan, gemcitabine, vinorelbine, ifosfamide, leucovorin-modulated 5-fluorouracil, bevacizumab and tamoxifen [1, 14, 18].

Recommended second-line treatment for

- ✿ **Platinum-sensitive ovarian cancer patients:** data of phase II/III trials strongly support the retreatment with platinum-based chemotherapy regimens (cisplatin or carboplatin) in combination with paclitaxel or docetaxel (60% response rate; 25% complete response). As patients have already responded once to systemic chemotherapy with platinum-agents and taxanes they are likely to do so again [14].

**1<sup>st</sup>-line OC therapy**

**no standard 2<sup>nd</sup>-line OC therapy is established yet**

**choice of 2<sup>nd</sup>-line therapy according to response to 1<sup>st</sup>-line platinum-containing therapy**

**several active agents in OC**

**2<sup>nd</sup>-line therapy for platinum-sensitive and platinum-resistant refractory/relapsed OC**

- ❖ **Platinum-recurrent/resistant ovarian cancer patients:** although combination regimens with non-cross resistant agents are associated with higher objective response rates and a two to three months improvement in PFS, they were also more toxic in clinical trials. Therefore single agent therapy is standard of care for platinum-resistant/refractory ovarian cancer patients [14].

The most suitable single agents for second-line recurrent ovarian cancer are pegylated liposomal doxorubicin, topotecan or gemcitabine which have shown 16-40% response rates [12].

## 6 Evidence

1 phase III trial,  
3 phase II trials  
adverse events:  
neutropenia, elevations  
of transaminases,  
nausea, vomiting,  
fatigue

Based on a limited literature search in several databases (PubMed, CRD and Embase) and on an additional hand search, one phase III trial and three phase II trials evaluating the efficacy of trabectedin in relapsed ovarian cancer were identified. Within these 4 trials 985 patients suffering from recurrent advanced ovarian cancer after initial platinum-based chemotherapy were treated with trabectedin or trabectedin in combination with PLD.

Toxicity profiles were generally regarded as clinically manageable. The most common grade 3/4 adverse events were neutropenia and elevations of transaminases [8]. The most frequently AEs were nausea, vomiting and fatigue of grade 1 or 2.

All authors concluded that trabectedin as a single agent or in combination with PLD is more effective in platinum-sensitive patients than in platinum-refractory patients.

### 6.1 Efficacy and safety - Phase III studies

*Table 1: Efficacy and safety of Phase III trials*

<b>Reference</b>	OVA-301 trial, ongoing (NCT00113607 until May 2011), abstract LBA4 (ESMO 2008) [20] Further information: Platinum-Sensitive Recurrent Ovarian Cancer (non-platinum Doublets) [21] FDA – Background information for Oncologic Drugs Advisory Committee Meeting July 15, 2009 [8]
<b>Sponsor</b>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
<b>Country</b>	124 centres in 21 countries in USA, Europe, Asia and South America [13]
<b>Design</b>	Open-label, multi-centre, randomized trial, radiologists were blinded to treatment and clinical data
<b>Participants characteristics</b>	672 pts (I: 337, C: 335) Median age: I: 56 years, C: 58 years Platinum-sensitive: I: 65%, C: 63% Platinum-resistant: I: 35%, C: 37% ECOG PS <sup>1</sup> 0/1/2 (%): I: 68/29/3, C: 57/39/3
<b>Treatments</b>	I( <b>ntervention</b> ): pegylated liposomal doxorubicin (PLD) 30 mg/m <sup>2</sup> 90-min infusion followed by trabectedin 1.1 mg/m <sup>2</sup> 3-hr infusion every 3 weeks C( <b>ontrol</b> ): PLD 50 mg/m <sup>2</sup> 90-min infusion once in 4 weeks



<b>In-/exclusion criteria</b>	<p><b>Inclusion criteria:</b>  histologically proven epithelial ovarian cancer, epithelial fallopian tube cancer, or primary peritoneal cancer.  Prior treatment with only 1 platinum based chemotherapy regimen.  ECOG PS status ≤ 2.  Progression &gt; 6 months after start of initial chemotherapy</p> <p><b>Exclusion criteria:</b>  More than 1 prior chemotherapy regimen.  Progression within 6 months after starting initial chemotherapy.  Prior exposure to anthracyclines.</p>
<b>Follow-up</b>	Follow-up, not recruiting
<b>Outcomes</b>	<p><b>Primary:</b> progression free survival (PFS) based on independent radiology review (IR) by RECIST</p> <p><b>Secondary:</b> response rate (RR) by IR, interim survival at 300 deaths revealed (OS), quality of life (QoL)</p>
<b>Key results by predetermined clinical cut-off date (15 May 2008; study start: April 2005)</b>	<p><b>Primary:</b>  Median PFS (no. censored: 256) for I: 7.3 months (95% CI 5.9-7.9) vs C 5.8 months (95% CI 5.5-7.1). HR= 0.79 (95% CI 0.65 to 0.96), p=0.019,  for patients with a platinum-free interval &gt; 6 months (PFI &gt;6 m): I 9.2 months (95% CI 7.4 to 11.1 months) C 7.5 months (95% CI 7.0 to 9.2 months), HR= 0.73, p=0.017</p> <p><b>Secondary:</b>  RR: I 28% vs. C 19% (p=0.008)  for patients with PFI &gt;6 m RR was I 35% vs. C 23% (p=0.0042)  OS (interim analysis, no. censored: 372): I 20.5 (18.7-24.2) months vs. C 19.4 (17.3-21.7) months, HR= 0.85 (95% CI 0.67-1.16) p=0.15  Deaths: 300 at time of the PFS cut-off date (55% censored data; I 145 and C 155 deaths)  QoL: no significant differences (EORTC-QLQ C30, OV 28, EQ-5D)</p>
<b>Adverse effects</b>	<p>Treatment discontinuation due to treatment related adverse events. I 16% vs. C 10%.</p> <p>Grade 3/4 adverse events:</p> <ul style="list-style-type: none"> <li>- Haematological laboratory abnormalities: neutrophils I 72% vs. C 30%, WBC I 63% vs. C 20%, platelets I 23% vs. C 4%</li> <li>- Biochemistry (laboratory abnormalities): ALT<sup>2</sup> increase I 51% vs. C 2%</li> <li>- Selected AEs: neutropenia I: 63% vs. C: 22%, febrile neutropenia I 8% vs. C 3%, hand-foot syndrome I 4% vs. C 19%, mucositis/stomatitis I 3% vs. C 12%, fatigue I 9% vs. C 6%, vomiting I 13% vs. C 4 %, nausea I 10% vs. C 4%</li> </ul>
<b>Commentary</b>	<p>The data presented in this table are an interim analysis of the OVA-301 phase III trial. Final data collection is estimated for May 2011 (see: <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> → NCT00113607).</p> <p>This interim analysis shows that the combination of pegylated liposomal doxorubicin and trabectedin is superior regarding the surrogates PFS and RR in women with advanced ovarian cancer compared to pegylated liposomal doxorubicin alone.</p>

<sup>1</sup> ECOG PS – Eastern Cooperative Oncology Group performance status

<sup>2</sup> ALT - Alaninaminotransferase

The data presented in Table 1 are an interim analysis of an ongoing phase III trial evaluating the efficacy and safety of trabectedin in combination with PLD in patients with recurrent, advanced ovarian cancer.

**Results from interim analysis**

<b>trabectedin more effective in platinum-sensitive OC patients regarding the surrogates PFS, RR, OS</b>	Patients included in this trial progressed after initial response to first-line therapy and were randomized to two treatment arms: pegylated liposomal doxorubicin in combination with trabectedin (PLD+T) or PLD alone. The demographic characteristics between the study arms were well balanced. A subgroup analysis showed that PLD+T was more effective regarding PFS than PLD alone in platinum-sensitive (platinum free interval (PFI) > 6 months) patients I: 9.2 months (95% CI 7.4 to 11.1 months) vs. C: 7.5 months (95% CI 7.0 to 9.2 months). The response rate for platinum-sensitive patients was 35% vs. 23% (p=0.0042) for PLD+T vs. PLD only by IR and 47% vs. 33% (p=0.0022) by investigator for PLD+T vs. PLD alone.
<b>assessment of QoL &amp; PRO</b>	Additional to the data presented in the table above, two abstracts from the ASCO annual meeting 2009 were found evaluating the health related quality of life (QoL) and patient reported outcomes (PRO) [22] in the OVA-301 trial and the correlation of CA-125 and RECIST evaluation to determine response rates [23] in recurrent ovarian cancer.
<b>no difference in QoL</b>	The instruments used to assess QoL/PRO were EORTC-QLQ C30, OV28 and EQ-5D, which were completed by patients at screening on day 1 and at the end-of-treatment visit of every other treatment cycle (starting with cycle 1). Mixed effects models showed no significant differences between the treatment arms for the pre-specified scales (global health status/QoL, fatigue, pain, subscales from QLQ C30, abdominal pain/GI symptoms scale from OV28) [22]. Though, treatment related adverse events like neutropenia and elevated ALT level were more frequent in the intervention arm than in the control arm.
<b>AEs (grade 3, 4): more frequent &amp; severe in combination arm</b>	Dose reduction of PLD of 20mg/m <sup>2</sup> in the intervention arm compared to the control arm led to a decrease in PLD-related AEs (e.g. hand-foot syndrome I 24% vs. C 54%, stomatitis I 20%, C 33%). However, general toxicity assessment showed that AEs were more frequent and more severe in the trabectedin+PLD arm (e.g. hospitalization due to AEs I 36%, C 27%, discontinuation due to AEs I 69 (of 325) patients, C 39 (of 322) patients.)

## 6.2 Efficacy and safety - further studies

<b>dose-finding and determination of response rates</b>	Three phase II trials were identified [12, 24-25]. Two of these phase II trials evaluated the overall response rate of platinum-sensitive vs. platinum-resistant/refractory patients [12, 24] and one phase II trial evaluated the optimal dose of trabectedin in platinum-sensitive patients [25].
<b>59 relapsed/refractory OC patients included</b>	The studies included demonstrated the effectiveness of trabectedin as a single agent in the platinum-sensitive patient population with respect to objective response rate (ORR). The table below shows that trabectedin is more effective in treating women with platinum-sensitive recurrent ovarian cancer than in platinum-refractory ovarian cancer patients.  <i>Sessa et al.</i> [24] conducted a phase II study to determine the efficacy and toxicity of trabectedin in treating patients with histologic or cytologic confirmed epithelial ovarian cancer who relapsed after first-line treatment with platinum-containing regimens with taxanes and/or other drugs. 59 patients from 4 institutions were stratified according to their response to prior chemotherapy as either platinum-sensitive (n=29; progression free interval ≥ 6months between the last chemotherapy cycle and documentation of re-

lapse) or platinum-resistant (n=30; progression-free interval of less than 6 months or progressive disease while receiving platinum-based chemotherapy).

After start of therapy, the original dose had to be reduced once in 29% and twice in 13% of patients due to toxicity. Trabectedin was administered as a 3-hour infusion using an ambulatory infusion pump through a separate line every 3 weeks. Patients received a median of 4 treatment cycles (range 1-13). 5 patients were excluded early from the trial because of severe toxicity.

Efficacy data are shown in Table 2, suggesting that trabectedin is more effective in platinum-sensitive patients compared to platinum-resistant/refractory patients.

The most common toxicity was a severe but reversible increase of liver function tests. Grade 3/4 toxicities reported in this phase II trial were neutropenia (41%), thrombocytopenia (7.5%), asthenia (7% - only grade 3) and nausea and vomiting (5% - only grade 3). Neurotoxicity and alopecia were not observed. Two patients discontinued treatment, because of lack of hematologic recovery and none because of liver toxicity.

*Krasner et al. (2007)* [12] conducted a multicenter phase II trial to determine the ORR in patients with platinum-sensitive or –resistant/recurrent ovarian cancer when treated with trabectedin. Patients (n=147) were eligible to participate in the study if they demonstrated measurable relapsed advanced OC and if they had not receive more than two prior platinum-containing regimens. Depending on the treatment-free interval (TFI) patients were assigned to the study cohort, being either platinum-sensitive (n=66) or platinum resistant (n=81). Platinum sensitive and platinum-resistant/refractory patients received a median number of 4 and 2 cycles of trabectedin with a median treatment duration of 18.6 and 8.9 weeks, respectively.

Major reasons for cycle delays, dose withholds and dose reductions were liver transaminase elevations and myelosuppression which were more frequent in the platinum-sensitive than in the platinum-resistant/refractory cohort. 31.8% of the platinum-sensitive and 10.1% of the platinum-resistant/refractory cohort remained on therapy longer than 6 months.

Response rates were generally better within the platinum-sensitive compared to the platinum-resistant cohort, supporting the findings of Sessa et al. 2005 (see Table 2).

Toxicity evaluation was presented for all 147 evaluable patients of whom 146 patients reported at least one laboratory abnormality. The most common laboratory grade 3 and grade 4 adverse events were neutropenia (7%/1%), elevated ALT (12%/0%), hyponatraemia (8%/1%) and hypoalbuminemia (7%/0%). Other adverse events (grades 1-4) were nausea (69%), vomiting (47%), fatigue (60%) and constipation (33%). 7% of patients discontinued the therapy due to drug-related AEs and one of the 5 death cases in the trial was caused by drug-related AEs [12].

*DeI Campo et al.* [25] conducted a randomized, open-label phase II trial to explore the benefit-risk ratio and the optimal treatment regimen with trabectedin in patients with platinum-sensitive, relapsed advanced ovarian cancer. Patients with histological proven progressive ovarian adenocarcinoma, with a platinum-sensitive disease (defined as  $\geq 6$  months platinum-free interval) and ECOG PS 0 or 1 were eligible. The two study cohorts re-

**dose reduction due to toxicities**

**grade 3/4 toxicities: neutropenia, thrombocytopenia, asthenia, nausea, vomiting**

**147 resistant/recurrent OC patients included**

**median cycles of therapy: platinum-sensitive: 4**

**reasons for dose withholds or reductions**

**AEs: neutrophils, elevated ALT, hyponatraemia, hypoalbuminemia, neutropenia, nausea, vomiting, fatigue, constipation**

**death caused by drug-related AEs**

**determination of benefit-risk ratio in 107 relapsed OC patients**

ceived either 1.5 mg/m<sup>2</sup> over 24 hours (arm A, n=54) or 1.3 mg/m<sup>2</sup> over 3 hours (arm B, n=53) of trabectedin administered as an intravenous infusion through a central line.

Primary study endpoint was ORR and secondary endpoints included duration of response and time to progression (TTP).

**median number of treatment cycles: 5-6**

A median of 5 (range 1-19) and 6 (1-29) cycles per patient were administered in arm A and B, respectively. Response rates and stable disease are presented in Table 2. Median time to progression was 6.2 months (95% CI 5.3-8.6) in arm A and 6.8 months (95% CI 4.6-7.4) in arm B.

**AEs: nausea, vomiting, fatigue, asthenia, dyspnoea, neutropenia, leukopenia**

The most common observed drug related AEs were nausea, vomiting and fatigue, most of them being grade 2 or 3. Grade 4 fatigue, asthenia and dyspnoea were reported each in at least one patient. The most common hematologic AEs (grade 3/4) were grade 4 neutropenia 36% and 26%, and grade 3 leukopenia 30% and 26% for arm A and arm B, respectively. However, severe clinical consequences of neutropenia were uncommon and febrile neutropenia occurred in one patient in arm A and in 4 patients in arm B. The most frequent biochemical abnormalities were increased ALT and AST.

**two treatment related deaths**

During the study, 27 patients died. Two of them were treatment related and the others were caused by disease progression.

Finally, the authors concluded that trabectedin administered as 1.5 mg/m<sup>2</sup> over 24 h and 1.3mg/m<sup>2</sup> over 3 h is effective in patients with platinum-sensitive relapsed, advanced ovarian cancer and shows a clinically tolerable toxicity profile.

Table 2: Objective response rate, partial response and stable disease

	Platinum-sensitive				Platinum-resistant/refractory			
	ORR in %	CR in %	PR in %	SD in %	ORR in %	CR in %	PR in %	SD in %
Krasner et al. 2007 [12]	29 (95% CI 18.2-41.9)	6	23	35	6.3 (95% CI 2.1-14.2)	0	6	46
Sessa et al. 2005 [24]	43 (95% CI 23-65)	4	39	39	n.e.	0	7	29
Del Campo et al. 2009 [25]	A: 38.9 (95% CI 25.9-53.1) B: 35.8 (95% CI 23.1-50.2)	A: 11.1 B: 11.3	n.e.	A: 38.9 B: 47.2	n.e.	n.e.	n.e.	n.e.

ORR – overall response rate, CR – complete response, SD – stable disease, n.e. – not evaluable, n.r. – not reported

A: 24-h 1.5 mg/m<sup>2</sup> q3wk

B: 3-h 1.3 mg/m<sup>2</sup> q3wk

**efficacy regarding RR & PFS**

The data presented above suggest that trabectedin is more effective in platinum-sensitive than in platinum-refractory patients regarding the surrogates RR and PFS.

## 7 Estimated costs

Price estimate for one vial containing 0.25 mg of trabectedin is € 530.- and for 1 mg € 1994.- (pharmacy retail price). One vial containing 25 ml PLD (Caelyx<sup>®</sup>) 2 mg/ml costs € 1,148.65 [26].

The dosing regimen used in the included OVA-301 phase III trial was 1.1 mg/m<sup>2</sup> trabectedin and 30 mg/m<sup>2</sup> PLD. Thus, assuming an average body surface area of 1.7 m<sup>2</sup> would result in 1.87 mg trabectedin (i.e. 2 vials) for one cycle, and would cost € 3,988.- (pharmacy retail price). Additionally, on average 50 mg PLD are needed, corresponding to one 25 ml vial. Hence, the overall costs for one treatment cycle with PLD and trabectedin is € 6,285.3.

As no long term data for the use of trabectedin in the treatment of recurrent platinum-sensitive ovarian cancer is available, we based the calculation of treatment costs on the median duration of treatment presented in the interim data analysis of the OVA-301 trial [22].

As the median treatment duration of trabectedin + PLD was 6 cycles (range 1-22) with a median treatment duration of 20.4 weeks we propose here the calculation of therapy costs per patient for 6 cycles of therapy which are € 37,711.8 [8].

**Treatment costs for one cycle: 6,300.-**

**6 cycles: 37,700.-**

**median number of cycles PLD+trabectedin was 6**

## 8 Ongoing research

There are several phase I, II and III trials evaluating the effectiveness of trabectedin in different kinds of cancer (prostate cancer, solid tumours, sarcomas, breast cancer) listed at ClinicalTrial.gov.

Besides the Phase III trial NCT00113607 evaluating the efficacy and safety of trabectedin and pegylated liposomal doxorubicin (PLD) or PLD alone in patients with advanced, relapsed ovarian cancer, one further phase II trial has to be mentioned in this report.

The purpose of NCT00569673 is to study the side effects and docetaxel and trabectedin in combination with either G-CSF or pegfilgrastim for the treatment of patients with recurrent or persistent ovarian epithelial cancer, fallopian tube cancer or primary peritoneal cavity cancer.

**several phase I, II & III trials are evaluating the efficacy of trabectedin**

## 9 Commentary - English

Both, phase II and phase III trials presented in chapter 6 showed that trabectedin is effective regarding the surrogate outcome response rate (RR) in patients with relapsed ovarian cancer. Subgroup analyses demonstrated that platinum-sensitive patients had higher objective RR compared to platinum-resistant/refractory ovarian cancer patients (see Table 2).

**trabectedin more effective in platinum-sensitive pts than in platinum-resistant pts**

**trabectedin shows efficacy regarding the increased response rate**

**OS: 1.1 months**

The findings of phase II trials are supported by the results the OVA-301 phase III trial. This trial compared trabectedin + PLD with PLD alone which is a well established therapy and hence an appropriate control. It was shown that the RR by independent radiology review is 28% vs. 19% in favour of the trabectedin + PLD arm compared to the PLD alone arm. RR for the platinum-sensitive subgroup analysis was 35% vs. 23% [20]. In an analysis three years after the study's start, interim OS was slightly improved by 1.1 months when trabectedin was added to PLD [8].

**slight, yet statistical significant improvement regarding PFS (6 weeks) when trabectedin added to PLD**

Further, the OVA-301 trial showed that the combination of trabectedin with PLD leads to a gain of, overall, 1.5 months of median PFS. Within the platinum-sensitive subgroup a gain of PFS of 1.7 months compared to PLD alone was reached. Grade 3/4 adverse events were more frequent in the intervention group, resulting in treatment discontinuation due to treatment related AEs in 16% of the intervention group and in 10% of the control group [8].

**comparable quality of life between study groups**

According to a presentation at the 2009 ASCO annual meeting, the addition of trabectedin neither led to a decline nor to an improvement in quality of life for patients treated with the PLD + trabectedin combination [22].

**different opinions regarding benefit-risk assessment**

Considering the results of the pivotal OVA-301 trial and several phase II trials, EMEA and FDA issued different opinions regarding benefit-and-risk assessment which has consequently led to deviating decisions for marketing authorisation of trabectedin for the treatment of relapsed platinum-sensitive ovarian cancer.

**prolongation of PFS not impressive**

**EMEA: benefit-risk ratio considered as being positive for OC patients**

The EMEA acknowledged that, despite favourable results for PFS, the magnitude of the observed effect of 1.5 months is not impressive but within an expected range for this type of cancer. Supported by an ad-hoc interim analysis, the benefit-risk ratio was finally considered as being positive for patients with platinum-sensitive ovarian cancer, by reasons that the combination of trabectedin with PLD showed increased efficacy without worsening clinical safety substantially and without compromising quality of life. However, due to other available treatment options for patients with platinum-sensitive tumours (foremost platinum based regimens) the lack of direct head-to-head comparisons between these treatment regimens and hence the demonstration of their relative efficacy was criticised [5].

**FDA: rejection of application for marketing authorisation call for mature OS data**

On the other hand, a vote conducted by the FDA led to the rejection of the application of Yondelis® by the Oncologic Drug Advisory Group, although, study results show a reduction in the risk of progression similarly to that of other drug combinations already approved [8]. Concerns included whether toxicities were outweighed by the established clinical benefit without demonstration of an increased overall survival. Hence, the FDA, like the EMEA, calls for mature OS data to support the prolonged surrogate PFS [27].

**benefit for pts has to be carefully balanced**

Thus, considering the prolongation of PFS of 1.7 months in platinum-sensitive OC patients, neither decline nor amelioration of quality of life, the additional treatment costs and the frequency and severity of adverse events, the net benefit for affected patients has to be carefully balanced.

## 10 Commentary – German

Sowohl die Phase II als auch die Phase III Studie, die in Kapitel 6 dieses Assessments dargestellt wurden, zeigen die Wirksamkeit von Trabectedin bei rezidiviertem Ovarialkarzinom anhand verbesserter Ansprechraten. In Subgruppen-Analysen wird ersichtlich, dass die Wirksamkeit in Patientinnen, welche als platin sensitiv eingestuft wurden, höher ist als bei nicht-platin sensitiven Patientinnen (vgl. Tabelle 2).

Die Resultate der Phase II Studien konnten durch die Ergebnisse der OVA-301 Phase III Studie bekräftigt werden. Diese Studie verglich die Kombination von Trabectedin und PLD versus PLD als Monotherapie. PLD gilt als gut etablierte Monotherapie und stellt daher eine adäquate Kontrolle dar. Bei der unabhängigen radiologischen Untersuchung konnte zu Gunsten des Kombinationsarms eine Ansprechrate (RR) von 28% vs. 19% beim PLD-Arm gezeigt werden. RR für die platin sensitive Subgruppenanalyse war 35% im Interventionsarm vs. 23% im Kontrollarm [20]. Drei Jahre nach Studienbeginn zeigte eine Analyse ein leicht verbessertes Gesamtüberleben von 1,1 Monate beim Kombinationsarm [8].

Weiters zeigt die OVA-301 Studie, dass die Kombination von Trabectedin mit PLD zu einem Gewinn von 1,5 Monaten an durchschnittlichem progressionsfreiem Überleben (PFS) führt. Innerhalb der platin sensitiven Untergruppe konnte ein Zugewinn an durchschnittlichem PFS von 1,7 Monaten erreicht werden. Grad 3/4 Nebenwirkungen traten häufiger in der Interventionsgruppe auf. Bei 16% der Interventionsgruppe und bei 10% der Patientinnen in der Kontrollgruppe führten behandlungsbezogene Nebenwirkungen zum Therapieabbruch [8].

Die 2009 beim jährlichen ASCO-Meeting präsentierten Daten zur Lebensqualitätsauswertung der OVA-301 zeigten keinen Unterschied in der Lebensqualität (QoL) zwischen den beiden Vergleichsgruppen [22].

Hinsichtlich des Nutzen-Risiko Verhältnisses der Trabectedin-Kombinationstherapie im Vergleich zu anderen Therapieoptionen urteilten EMEA und FDA unterschiedlich, was schlussendlich auch zu konträren Entscheidungen bei der Marktzulassung von Trabectedin beim rezidiviertem platin sensitiven Ovarialkarzinom führte.

Die EMEA führte zwar an, dass trotz der positiven PFS Resultate, das Ausmaß des beobachteten Effekts nicht beeindruckend ist, allerdings in einem für diese Krebsart erwarteten Bereich liegt. Die Nutzen-Risiken Abwägung wurde nach einer Ad-hoc-Zwischenanalyse schlussendlich als positiv für Patientinnen mit rezidiviertem platin sensitivem Ovarialkarzinom eingestuft. Grund dafür war, dass die Kombination von Trabectedin mit PLD zu erhöhter klinischer Wirksamkeit, ohne substantieller Verschlechterung der klinischen Sicherheit und ohne Beeinträchtigung der Lebensqualität führte. Trotzdem wurde aufgrund von anderen bereits verfügbaren Therapieoptionen für Patientinnen mit Ovarialkarzinom (hauptsächlich platin-basierte Therapien) das Fehlen von direkten Head-to-head Studien von diesen Behandlungsoptionen und dadurch auch der fehlende Nachweis für deren relative Wirksamkeit kritisiert [5].

**erhöhte Wirksamkeit von Trabectedin in platin sensitivem OC**

**RR im Kombinationsarm höher als im Vergleichsarm**

**OS: +1,1 Monate**

**Trabectedin + PLD: leichter Zugewinn an PFS (6 Wochen)**

**Therapieabbruch aufgrund Nebenwirkungen**

**vergleichbare QoL zwischen Studiengruppen**

**Unterschiedliche Ansichten zum Nutzen-Risiko Verhältnis**

**Zugewinn an PFS nicht beeindruckend**

**EMEA: Nutzen-Risiko-Verhältnis wird als positiv für OC Patientinnen erachtet**

<b>FDA: Ablehnung des Antrags auf Marktzulassung</b>	Auf der anderen Seite führte eine Abstimmung der FDA zu einer Ablehnung der Marktzulassung von Yondelis ®, obwohl bei der OVA-301 Studie eine ähnliche Risikoreduktion des progressionsfreien Überlebens wie bei anderen, bereits zugelassenen Therapieoptionen nachgewiesen werden konnte [8]. Es wurde in Frage gestellt, ob die Toxizität der Therapie durch den erreichten klinischen Nutzen, ohne Nachweis eines verlängerten Gesamtüberlebens, ausgeglichen werden kann. Infolgedessen fordern sowohl die FDA, als auch die EMEA die Untermauerung des Surrogats PFS durch ausgereifte OS-Daten [27].
<b>forderung von ausgereiften OS-Daten</b>	
<b>Netto-Nutzen muss sorgfältig abgewogen werden</b>	Berücksichtigt man demnach den Gewinn von 1,7 Monaten an PFS, die gleichbleibende Lebensqualität, zusätzliche Behandlungskosten und die zusätzlichen Nebenwirkungen, ist der Netto-Nutzen von Trabectedin mit PLD für Patientinnen mit rezidiviertem Ovarialkarzinom sorgfältig abzuwägen.



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