



Trabectedin in ovarian cancer



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For personal use only. Not to be reproduced without permission of the publisher (copyright@ppme.eu). There is new hope for partially platinum-sensitive patients who have relapsed after first-line treatment of ovarian cancer. Trabectedin is a recently approved first-in-class agent for soft tissue sarcoma and ovarian cancer.

Trabectedin is the first of a new class of antitumour agents with special activity in the treatment of patients with soft tissue sarcoma and ovarian cancer. It has received marketing authorisation by the EMA for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines or ifosfamide, or for those who are unsuited to receive these agents. Recently trabectedin has also been licensed for use in ovarian cancer after failure of standard chemotherapy.

Epithelial carcinoma of the ovary is one of the most common gynaecological malignancies and the fifth most frequent cause of cancer death in women, with 50% of all cases occurring in women older than 65 years. The management of ovarian carcinoma depends on the extent of the disease and any prior therapy which the patient has received. The International Federation of Gynecology and Obstetrics (FIGO) staging system is used to both classify and provide the basis for treatment considerations of the disease. The standard of care for advanced disease consists of chemotherapy following surgery and a drug regimen of paclitaxel/carboplatin. Those with high-risk disease receive platinum-based therapy. Patients with advanced disease receive surgical cytoreduction and paclitaxel/carboplatin. Either recurrent or persistent disease will occur in a

high percentage of patients (62%). These patients must then be classified as having either chemosensitive disease (i.e. response to first-line therapy leading to a treatment-free interval of at least six months) or chemoresistant disease (i.e. progression during first-line therapy or best response to first-line therapy: stable disease or recurrence within six months of completing first-line therapy). Those with chemosensitive disease are retreated with a platinum-based regime with an expected response rate (RR) of > 60% and median survival \geq 30 months. Those with chemoresistant disease are treated with alternative drug therapy; expected RR is 12–32% and median survival is \geq 8 months. Clinical recurrences within six months of completion of a platinum-containing regimen are considered platinum-refractory or platinum-resistant recurrences [1].

Trabectedin (Yondelis) has been licensed, in combination with doxorubicin, for the treatment of patients with relapsed platinum-sensitive ovarian cancer. Trabectedin, previously referred to as ecteinascidin (ET-743), is a pure chemical substance of natural origin, isolated from the marine organism, *Ecteinascidia turbinata*. The chemical structure is characterised by three fused tetrahydroisoquinoline rings; two of these rings (subunits A and B) interact with the minor groove of the DNA double helix, whereas the third ring (subunit C) interacts with adjacent nuclear proteins [2]. These

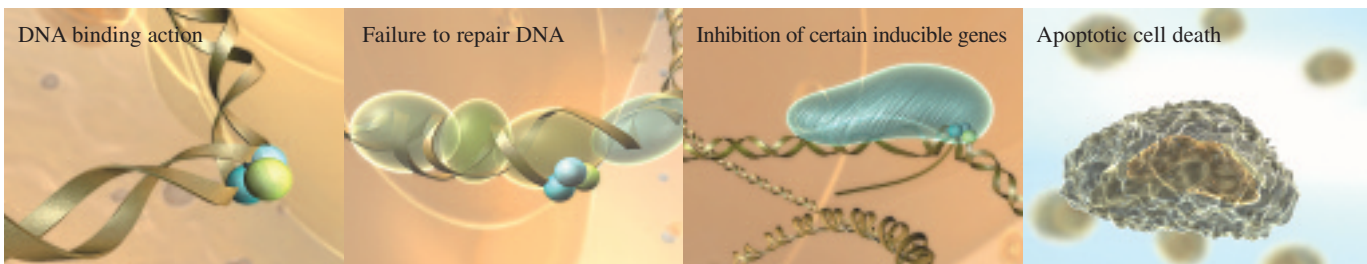
interactions trigger a cascade of events which involves the transcription-dependent nucleotide excision repair system, disrupting the cell cycle [3]. This results in potent antitumour activity against a number of cell lines *in vitro* and important antiproliferative effects *in vivo* against a variety of experimental tumours.

In vivo data

In vivo studies using trabectedin have been carried out in several tumour xenografts of rodent and human origin [4]. A comparison between different treatment schedules indicated that higher doses given less frequently may be more effective than repeated administration at lower doses [5]. In combination with some antitumour agents currently used in clinical practice, additive or even synergistic effects were observed, providing the rationale for trabectedin-containing combination chemotherapy in clinical research [6]. Most *In vivo* synergism was reported in ovarian cancer and sarcoma xenografts in combination with doxorubicin and cisplatin [7]. The main toxic effects of trabectedin were myelosuppression, hepatotoxicity, intestinal epithelial atrophy and ulcerations.

Clinical data

More than 5,500 patients with advanced malignancies have been treated with trabectedin, administered either as a single agent or in combination with other chemotherapeutic agents.



Phase I studies

Trabectedin, as a single agent, was tested in ovarian cancer patients in several phase I trials, using different IV schedules of administration. Trabectedin was well tolerated with prolonged administration. Myelosuppression, with neutropenia as its primary component, elevated transaminases and fatigue were the major dose-limiting toxicities (DLTs) in phase I studies. Although neutropenia was commonly reported with trabectedin treatment, drug-related infection, mucositis or stomatitis was infrequent and there was no evidence of cumulative toxicity.

Phase I trials were also conducted with trabectedin in combination with doxorubicin, pegylated liposomal doxorubicin (PLD), gemcitabine, carboplatin, cisplatin, paclitaxel and docetaxel. Epithelial ovarian cancer was the most represented tumour type in the studies with PLD and cisplatin. Trabectedin and PLD demonstrated their synergic antineoplastic activity, showing the different mechanisms of action, targets and toxicities of the two drugs. In this phase I study, six dose levels of trabectedin (0.4–1.3 mg/m² infused over three hours) were investigated, with PLD administered at a fixed dose of 30 mg/m² [8]. The recommended dose of trabectedin was defined as 1.1 mg/m². The pharmacokinetics of trabectedin in combination with PLD was similar to those of the individual drugs.

Phase II studies

Three Phase II studies have been conducted in patients with ovarian cancer: one study using an every 3-weeks schedule [9], the second one using a weekly schedule [4] and the last one comparing 3-hour infusions or 24-hour infusions in a 3-weekly schedule [10]. All studies demonstrated trabectedin is active in relapsed advanced ovarian cancer, particularly in platinum-sensitive disease. Three-weekly trabectedin, either in a 3 or 24-hour infusion, is more active than a weekly schedule, but myelotoxicity and transaminase increase are more common with q3w regimen.

Pharmacokinetic results (3-h q3w schedule)

Maximum concentrations of trabectedin in plasma were typically observed either during or immediately before the end of the 3-hour infusion. The drug concentrations then declined in a multiexponential manner upon cessation of the IV infusion. Initially, a marked and rapid decline in plasma concentrations was observed, which was followed by more prolonged distribution and terminal phases [11]. During cycle 1, trabectedin exhibited a high plasma clearance with mean values ranging from 51–103.9 L/h across the range of dose regimens administered. The mean apparent volume of distribution (V_{ss}) ranged from 1407–2178 L. The terminal half-life (t_{1/2}) ranged from 25.8–46.2 hours. Inter-subject variability (expressed as coefficient of variation [CV]) in the plasma maximum concentration (C_{max}) and area under the concentration-time curve (AUC_∞) values ranged from 24–57%. Statistically significant differences were not observed upon comparison of plasma clearance and distribution volume values of trabectedin in cycle 2 relative to cycle 1 (student's *t*-test) (see Figure 1).

Phase III studies

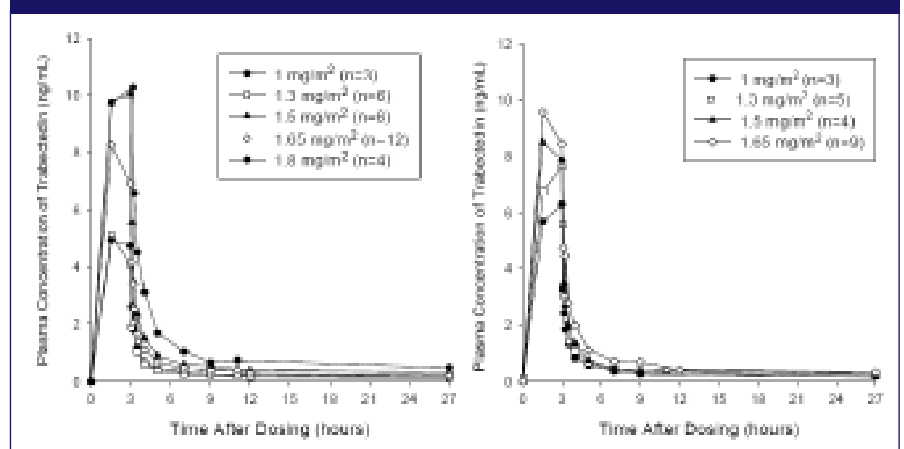
On the basis of phase I and II studies, an open-label, multicenter, randomised, phase III studies (OVA301) were conducted in 672 patients, comparing the

combination of PLD 30 mg/m² 90-minute infusion followed by trabectedin 1.1 mg/m² 3-hour infusion every three weeks with the approved standard PLD alone 50 mg/m² 90-minute infusion every four weeks, in subjects with advanced relapsed ovarian cancer or primary peritoneal cancer [12]. The end-point of the study was to investigate the efficacy and safety of the association of the two drugs, and to demonstrate if the combination improved overall survival (OS) and progression-free survival (PFS) in second-line therapy, after one platinum-based treatment. This is currently the widest/largest study on recurrent ovarian cancer and the first where all radiographic assessments of tumour response and progression have been forwarded for central review.

The results showed that PFS was significantly longer with trabectedin and PLD (hazard ratio (HR) 0.79) with a 21% of risk reduction versus monotherapy, and a higher RR with the combination (26% vs 19%). At the moment only an *ad interim* analysis can be performed for overall survival data, but this has shown a trend towards a clinical benefit in the combination arm (risk reduction of 15%; HR = 0.85).

In the partially platinum-sensitive subpopulation: i.e. patients with platinum-free interval (PFI) 6–12 months, tra-

Figure 1: Mean concentration of trabectedin in plasma following administration as a 3-hour IV infusion during cycle 1 (left) and cycle 2 (right)



bectedin/PLD resulted in a highly significant 41% decrease in the risk of death compared with PLD alone (HR = 0.59; 95% CI, 0.42–0.82; $p = 0.0015$) and a 6-month advantage in median survival related to PLD single agent (23.0 months versus 17.1 months).

The safety results demonstrated that grade 3–4 neutropenia was more frequent with combination versus monotherapy, but with fewer cases of neutropenic fever (8%); grade 3–4 alanine aminotransferase (ALT) increase was more common in the combination group, but with short duration and a decrease in magnitude with subsequent cycles. Similar safety profiles has been demonstrated both in platinum-sensitive and resistant patients. Final results suggest a statistically significant benefit and a clinical advantage for the combination of PLD and trabectedin versus PLD alone [12].

Clinical safety

No new or unexpected serious adverse events were seen with the administration of trabectedin in combination with PLD relative to administration of PLD monotherapy or trabectedin alone. The overall clinical safety assessment of the proposed combination of trabectedin and PLD does not cause any major concern since the toxicity profile is predictable from the known safety profiles of both substances and such toxicity can be routinely managed. The most important additive toxicity is neutropenia and infection-related adverse events due to neutropenia with increasing frequency and severity with the combination as compared to both agents used as monotherapy. Two percent of patients receiving PLD alone developed grade 3 or 4 febrile neutropenia compared with 8% being treated with trabectedin and PLD. Thrombocytopenia, increases in liver transaminases and in CPK (and rhabdomyolysis in rare cases) were seen more often in those patients receiving the combination treatment [1].

Conclusion

In patients with advanced ovarian carcinoma, long-term survival is still unsatisfactory, even after the introduction of front-line platinum and taxane combina-

tions. Identifying new drugs for patients having undergone treatment with platinum and taxanes is a priority. The need for new therapeutic options justifies testing agents with completely new structures and mechanisms of action in second-line therapy. Trabectedin has activity in the treatment of patients with relapsed advanced ovarian cancer, including some with known low sensitivity to platinum compounds. Trabectedin administered every three weeks in combination with pegylated liposomal doxorubicin has now been licensed as a treatment option for patients with advanced ovarian carcinoma.

Following the recommended dose regimen of PLD 30 mg/m², as a 60-minute IV infusion followed by trabectedin administered at 1.1 mg/m² as a 3-hour IV infusion once every three weeks (q3wk) a median benefit of the combination in overall survival was an increase from 19.5–22.4 months, however, with wide and overlapping 95% confidence intervals (17.4–22.1 vs 19.4–25.1 months). Results to date indicate that trabectedin is a beneficial treatment for recurrent ovarian cancer after failure of first-line, platinum-based chemotherapy when administered in conjunction with PLD, particularly in the partially platinum-sensitive population.

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References

1. EMEA Assessment report for Yondelis® (Trabectedin). Procedure No. EMEA/H/C/000773/II/0008. Available from: www.ema.europa.eu/humandocs/PDFs/EPAR/yondelis/EMEA-H-773-II-08-AR.pdf. [cited 2010 May 04].
2. Aune GJ, Furuta T, Pommier Y. Ecteinascidin 743: a novel anticancer drug

with a unique mechanism of action. *Anticancer Drugs*. 2002;13(6):545-55.

3. D'Incalci M, Colombo T, Giavazzi G, Nicoletti I, Erba E, Ubezio P, et al. In human tumor xenografts the resistance to ET-743 or to cisplatin can be overcome by giving the two drugs in combination. *Eur J Cancer*. 2002;38(suppl 7): S34.
4. Krasner CN, McMeekin DS, Chan S, et al. A phase II study of trabectedin single agent inpatient with recurrent ovarian cancer previously treated with platinum-based regimens. *Br J Cancer*. 2007;97(12):1618-24.
5. Hendricks HR, Fiebig HH, Giavazzi R, Langdon SP, Jimeno JM, Faircloth GT. High antitumour activity of ET 743 against human tumour xenografts from melanoma, non-small-cell lung and ovarian cancer. *Ann Oncol*. 1999;10(10):1233-40.
6. Takahashi N, Li WW, Banerjee D, Scotto KW, Bertino JR. Sequence-dependent enhancement of cytotoxicity produced by Ecteinascidin 743 (ET-743) with doxorubicin or paclitaxel in soft tissue sarcoma cells. *Clin Cancer Res*. 2001;7(10):3251-7.
7. D'Incalci M, Colombo T, Ubezio P, Nicoletti I, Gavazzi R, Erba E, et al. The combination of yondelis and cisplatin is synergistic against human tumor xenografts. *Eur J Cancer*. 2003;39(13):1920-6.
8. Cohen RB, Schilder RJ, Cheng J, et al. Final results of a combination study between trabectedin and pegylated liposomal doxorubicin (PLD) in patients with advanced malignancies. 2005 ASCO Annual Meeting Proceedings. (Abstract # 3074).
9. Sessa C, De Braud F, Perotti A, Bauer J, Curigliano G, Noberasco C, Zanaboni F, Gianni L, Marsoni S, Jimeno J, D'Incalci M, Dall'ó E, Colombo N. Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails. *J Clin Oncol*. 2005;23(9):1867-74.
10. Del Campo JM, Vilar E. New challenges for molecular oncology in ovarian carcinoma. *Med Clin (Barc)*. 2007;128(1):15-7. [Article in Spanish]
11. Investigator's Brochure YONDELIS® Intravenous Formulation1 (Trabectedin), Edition No: 4 (12 October 2007).
12. Monk BJ, Herzog T, Kaye S, et al. A randomized phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) versus PLD in relapsed, recurrent ovarian cancer (OC). *Ann Oncol*. 2008;19 Suppl 8:viii1-viii4.