

# National Horizon Scanning Centre

## Trabectedin (Yondelis) for relapsed ovarian cancer

**December 2007**



This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

## Trabectedin (Yondelis) for relapsed ovarian cancer

### Target group

- Ovarian cancer - relapsed after more than 6 months from completion of first line platinum-based combination therapy (platinum-sensitive and partially platinum-sensitive).

### Technology description

Trabectedin (Yondelis, ecteinascidin-743, ET-743) is a tetrahydroisoquinoline alkaloid that binds to the minor groove of DNA inhibiting transcription activation of key genes, nucleotide excision repair pathways and cell proliferation leading to p53-independent apoptosis of cancer cells. It also inhibits overexpression of the multi-drug resistance-1 gene coding for the P-glycoprotein that is a major factor responsible for cells developing resistance to cancer drugs. Trabectedin is administered as a 3-hour intravenous infusion every 3 weeks.

Trabectedin is approved in the EU and launched in the UK for the treatment of advanced soft tissue sarcoma (STS) where anthracyclines and ifosfamide are contraindicated or have failed. Trabectedin is also in phase II trials in breast, prostate and non-small cell lung cancers and paediatric sarcomas.

### Innovation and/or advantages

Although a significant percentage of patients with ovarian cancer respond to initial chemotherapy, most ovarian cancers recur and respond moderately or poorly to subsequent chemotherapy. Trabectedin might be of potential benefit in these patients as it offers a new mechanism of action.

### Developer

PharmaMar S.A in partnership with Johnson & Johnson Pharmaceutical Research and Development (J&JPRD)

### Place of use

- |   |   |  |
|---|---|--|
| <input type="checkbox"/> Home care e.g. home dialysis                         | <input type="checkbox"/> Community or residential care e.g. district nurses, physio           | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses    |
| <input type="checkbox"/> Secondary care e.g. general, non-specialist hospital | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist services or hospital | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter                 | <input type="checkbox"/> Other:   |  |

### Availability, launch or marketing dates, and licensing plans:

The company anticipate filing in 2008 with an expected marketing authorisation in Q1 2009. Trabectedin has been granted Orphan Drug designation in the EU and US for ovarian cancer and STS.

### NHS or Government priority area:

This topic is relevant to the NHS Cancer Plan.

### Relevant guidance

- NICE clinical guideline in progress. Ovarian cancer: recognition and initial management (17<sup>th</sup> wave).
- NICE technology appraisal:

- Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer. 2005. Review expected February 2008<sup>1</sup>.
- Review of the clinical effectiveness and cost effectiveness of paclitaxel for ovarian cancer. 2003<sup>2</sup>.
- Scottish Intercollegiate Guideline Network (SIGN), Epithelial ovarian cancer. 2003<sup>3</sup> – recommended for review (2007).

### **Clinical need and burden of disease**

Ovarian cancer is the fourth most common cause of cancer mortality in women and resulted in 3,939 deaths in England and Wales in 2005<sup>4</sup>. The total number of new cases registered in 2004 in England and Wales was approximately 5,070<sup>5</sup>. Around 85% of cases occur in women over 50 years. Epithelial ovarian cancer, which involves the formation of malignant cells in the tissue covering the ovary accounts for around 85-90% of all ovarian cancers. The 5-year survival rate in 2000-2001 is estimated at 40%<sup>6</sup>. Ovarian cancer is often asymptomatic in the early stages and over 75% of cases are diagnosed with advanced stage III or stage IV disease, around 3,800 cases per year.

Between 55% and 75% of women whose tumours respond to first-line therapy relapse within 2 years of completing treatment. Patients with recurrent ovarian cancer can be classified by their duration of response to initial platinum therapy<sup>1</sup>:

Platinum-sensitive	Responds to first-line platinum-based therapy but relapses 12 months or more after completion of initial platinum-based chemotherapy
Partially platinum-sensitive	Responds to first-line platinum-based therapy but relapses between 6 and 12 months after completion of initial platinum-based chemotherapy
Platinum-resistant	Relapses within 6 months of completion of initial platinum-based chemotherapy
Platinum-refractory	Does not respond to initial platinum-based chemotherapy.

### **Existing comparators and treatments**

- Surgery with either neoadjuvant or adjuvant chemotherapy.
- First-line chemotherapy with a platinum-based therapy alone or in combination with paclitaxel (where the platinum agent is either carboplatin or cisplatin).
- First-line options may be repeated for second (and subsequent) treatments for those patients who have platinum-sensitive or partially platinum-sensitive disease. Other options include single-agent paclitaxel, PLDH (pegylated liposomal doxorubicin hydrochloride), topotecan, gemcitabine or doxorubicin.
- Second-line chemotherapy is palliative and aims to reduce symptoms and prolong survival. Ovarian tumours eventually develop multi-drug resistance.

### **Efficacy and safety**

A pooled analysis of three phase II studies (n=294, 108 platinum resistant, 186 platinum-sensitive) where 3 trabectedin schedules were investigated has been published in abstract form<sup>7</sup>. Overall response rate and median time to progression (TTP) were 8% and 2.1 months in platinum-resistant, and 34% and 5.8 months in platinum-sensitive patients. The three weekly schedule showed a better response rate (33% vs. 16%, p<0.0001) and median TTP (5.8 vs. 2.8, p=0.0001) than the weekly schedule. Response rate and median TTP were similar in patients with 2 prior platinum-based regimens to those with only 1 prior platinum regimen. Most common adverse events were fatigue, vomiting, non-cumulative neutropenia and ALT increase.

Trial name or code	ET-743-OVA-301; Phase III	ET-743-INT-II; Phase II <sup>8</sup> .
Sponsor	PharmaMar and J&JPRD	PharmaMar and J&JPRD
Status	Ongoing, recruitment completed	Published
Location	USA, Europe, Asia and South America.	Multi-centre
Design	Randomised, controlled	Open-label, single-arm
Participants in trial	n=627; advanced ovarian cancer, relapsed after prior treatment with 1 platinum-based chemotherapy regimen. Randomised to liposomal doxorubicin 30 mg/m <sup>2</sup> 90-minute infusion followed by trabectedin 1.1 mg/m <sup>2</sup> 3-hour infusion, every 3 weeks or liposomal doxorubicin 50 mg/m <sup>2</sup> 90-minute infusion every 4 weeks.	n= 147 (141 evaluable); advanced relapsed ovarian cancer previously treated with 1 or 2 platinum-based regimens, either platinum-sensitive or platinum-resistant. Trabectedin 0.58 mg/m <sup>2</sup> weekly as a 3-hr infusion for 3 weeks of a 4-week cycle. All received dexamethasone.
Follow-up	-	Until disease progression or at least 2 cycles beyond a confirmed complete response (CR).
Primary outcome	Progression-free survival (PFS)	ORR
Secondary outcomes	Objective response rate (ORR)	Duration of response, time-to-progression (TTP), PFS, overall survival (OS).
Key results	-	Platinum-sensitive (n=62 evaluable) – ORR 29% (4 CR, 14 partial response (PR)), (95% CI: 18.2-41.9), TTP 5.2 months (95% CI: 3.1-6.5 months), PFS 5.1 months (95% CI: 2.8-6.2 months). 1-year survival rate 55.9% Platinum-resistant (n=79 evaluable) – ORR 6.3% (5 PR) (95% CI: 2.1 –14.2%), TTP 2 months (95% CI: 1.77-3.5 months), PFS 2.0 months (95% CI: 1.7-3.5 months), OS 10.7 months, 1-year survival rate of 24.5%.
Expected reporting date	Q3 2008	-
Adverse effects	-	The most frequent (≥ 2% of patients) grade 3/4 adverse events were reversible liver alanine transferase elevation (10%), neutropaenia (8%), nausea, vomiting and fatigue (5% each).

Trial name or code	SENDO study <sup>9</sup> ;Phase II	Phase II <sup>10</sup>
Sponsor	Pharma Mar	Pharma Mar
Status	Published	Abstract
Location	Southern Europe	Multi-centre
Design	Single-arm, dose-ranging	Open-label, randomised
Participants in trial	n= 59; epithelial ovarian cancer (RECIST <sup>a</sup> criteria) and treatment failure after first-line platinum chemotherapy with taxane. Stratified as platinum-resistant (including platinum-refractory) n= 30 or platinum-sensitive	n=107; recurrent platinum-sensitive ovarian cancer. Randomised to trabectedin 1.5mg/m <sup>2</sup> over 24 hour infusion (schedule A) or 1.3mg/m <sup>2</sup> over 3 hour infusion (schedule B) both every 3 weeks. All received dexamethasone.

<sup>a</sup> RECIST criteria – Response Evaluation Criteria in Solid Tumours Group criteria

	(including partially platinum-sensitive) n=29. Trabectedin (1650 – 1300 µg/m <sup>2</sup> ) administered as a 3-hour infusion every 3-weeks.	
Follow-up	Until tumour progression or development of unacceptable toxicity.	
Primary outcome	Response rate	Response rate according to RECIST
Secondary outcomes	Progression free survival (PFS)	Response duration, CA-125 response, time-to-progression and safety
Key results	Platinum-sensitive (n=23), overall objective response rate 43% (95% CI, 23%-65%), 1 CR (4%) maintained for 8.7 months, median TTP 7.9 months (95% CI, 7.5-14.1). Platinum-resistant patients (n=28), 2 PR (7%) lasting 2 and 2.5 months, TTP 4 and 4.6 months, respectively. Progression occurred in 64% overall, and after the first cycle in 22%.	Objective responses were 29% (8% CR, 21% PR) in A; and 28% (11% CR, 17% PR) in B. 11 patients not evaluable for response at the time of reporting. CA-125 responses >50% were 23% in A and 26% in B. (Preliminary data – manuscript of final data in progress).
Adverse effects	The predominant toxicities at 1300 µg/m <sup>2</sup> were neutropenia, asthenia, and self-limited increase of aminotransferases.	Adverse effects included: fatigue, nausea, vomiting, constipation, non-cumulative neutropenia, reversible ALT increase. 4 deaths <30 days last infusion date – 3 in A unrelated to study drug, 1 in B due to related multi-organ failure.

### Estimated cost and cost impact

The cost of a 1mg vial of trabectedin (currently licensed for STS) is £1,366. Based on the dosage and regimen used in the ET-743-OVA-301 trial, one cycle of trabectedin (assuming body surface area of 1.6m<sup>2</sup>) will cost £2,732 (assuming wastage).

### Potential or intended impact – speculative

#### Patients

- |   |   |   |
|---|---|---|
| <input checked="" type="checkbox"/> Reduced morbidity   | <input checked="" type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other:   | <input type="checkbox"/> Non identified   |

#### Services

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> Increased use | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use | <input type="checkbox"/> Other:                          | <input checked="" type="checkbox"/> Non identified  |

#### Costs

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input checked="" type="checkbox"/> New costs                        | <input type="checkbox"/> Savings:  | <input type="checkbox"/> Other:                                     |

**References**

- <sup>1</sup> National Institute for Health and Clinical Excellence. Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer. Technology Appraisal 91. London: NICE, May 2005.
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- <sup>3</sup> SIGN, Epithelial ovarian cancer. Guideline no.75, October 2003
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- <sup>5</sup> Cancer Research UK, [Hhttp://info.cancerresearchuk.org/cancerstats/types/ovary/incidence/H](http://info.cancerresearchuk.org/cancerstats/types/ovary/incidence/H) accessed on 3/12/07
- <sup>6</sup> Cancer Research UK, [Hhttp://info.cancerresearchuk.org/cancerstats/types/ovary/survival/H](http://info.cancerresearchuk.org/cancerstats/types/ovary/survival/H) accessed on 3/12/07
- <sup>7</sup> McMeekin S, Del Campo J, Colombo N, Krasner C. *et al.* Trabectedin (T) in relapsed advanced ovarian cancer (ROC): A pooled analysis of three phase II studies, Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I, Vol 25, No. 18S (June 20 Supplement), 2007: 5579.
- <sup>8</sup> Krasner CN, McMeekin DS, Chan S, Braly PS, Renshaw FG, Kaye S *et al* for the ET-743-INT-11 study group, A phase II study of trabectedin single agent in patients with recurrent ovarian cancer previously treated with platinum-based regimens, British Journal of Cancer advance online publication, 13 November 2007; doi:10.1038/sj.bjc.6604088.
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