Trabectedin for the treatment of relapsed ovarian cancer

D Papaioannou,* R Rafia, MD Stevenson, JW Stevens and P Evans

School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

*Corresponding author

Declared competing interests of authors: none

HTA 08/212/01

Date of ERG submission:

16 April 2010

TAR Centre(s):

School of Health and Related Research (ScHARR)

List of authors:

D Papaioannou, R Rafia, MD Stevenson, JW Stevens and P Evans

Contact details:

D Papaioannou, School of Health and Related Research (ScHARR), University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK

Email: d.papaioannou@sheffield.ac.uk

The research reported in this article of the journal supplement was commissioned and funded by the HTA programme on behalf of NICE as project number 08/212/01. The assessment report began editorial review in June 2010 and was accepted for publication in October 2010. See the HTA programme website for further project information (www.hta.ac.uk). This summary of the ERG report was compiled after the Appraisal Committee's review.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

The paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of trabectedin for the treatment of relapsed platinum-sensitive ovarian cancer, based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submission addressed only part of the decision problem and did not provide evidence to compare trabectedin (Yondelis®, PharmaMar) and pegylated liposomal doxorubicin hydrochloride (PLDH) (Caelyx®, Schering-Plough) with key comparators. The submission's

direct comparison evidence came from one reasonable-quality randomised controlled trial (RCT) of trabectedin and PLDH versus PLDH alone (ET743-OVA-301). The results of the RCT were subdivided into the entire platinum-sensitive population (> 6-month relapse after initial platinum-based chemotherapy) and partially platinum-sensitive (≥ 6- to 12-month relapse) and fully platinum-sensitive (> 12-month relapse) populations. The outcomes included were overall survival, progression-free survival measured by three types of assessor, response rates, adverse effects of treatment, health-related quality of life and cost per quality-adjusted-life-year (QALY) gained. A mixed treatment comparison (MTC) meta-analysis comparing trabectedin and PLDH with single-agent PLDH within the entire platinum-sensitive population, with paclitaxel or with topotecan also formed part of the submission. The RCT data showed that trabectedin plus PLDH compared with PLDH monotherapy had a significant effect on overall survival only within the partially platinum-sensitive subgroup. PFS results reported by the independent radiologists showed significant effects in favour of the trabectedin and PLDH arm for the entire and partially platinum-sensitive populations only. Rates of grade 3 and 4 adverse events were mostly higher in the trabectedin and PLDH arm than in the PLDH alone arm. There were several issues regarding the undertaking of the MTC, and thus the data were not considered robust. Furthermore, the ERG did not believe the MTC to be necessary to answer the decision problem. The manufacturer submitted a de novo cost-effectiveness model. The main analysis compared trabectedin in combination with PLDH versus paclitaxel, topotecan and PLDH (each as monotherapy) in the entire platinum-sensitive population, using results estimated from the MTC. Additional analyses were presented comparing trabectedin in combination with PLDH versus PLDH monotherapy using direct evidence from the OVA-301 trial for the fully, partially and entire platinum-sensitive populations. The cost per QALY gained for trabectedin in combination with PLDH versus PLDH monotherapy was estimated to be £70,076 in the main analysis. In the additional analyses, the cost per QALY gained for trabectedin in combination with PLDH versus PLDH monotherapy was £94,832, £43,996 and £31,092 for the entire, partially and fully platinum-sensitive populations, respectively. Additional work was undertaken by the ERG using patient-level data and amending some assumptions to provide a better statistical fit to the Kaplan–Meier data than the exponential distribution assumed by the manufacturer. The ERG base-case estimate of the cost per QALY of trabectedin in combination with PLDH ranged from £46,503 to £54,607 in the partially platinum-sensitive population. At the time of writing, trabectedin in combination with PLDH for the treatment of women with relapsed platinum-sensitive ovarian cancer is not recommended by NICE in the final appraisal determination.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Trabectedin for the treatment of relapsed ovarian cancer*.[2]

Description of the underlying health problem

Trabectedin (Yondelis®, PharmaMar) in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) (Caelyx®, Schering-Plough) is licensed for patients with platinum-sensitive ovarian cancer (OC).[3] OC is asymptomatic in the early stages, with diagnosis in ≥ 75% cases made when OC is at an advanced stage (stage III/IV disease). Of women with OC, 80% will relapse and require second-line chemotherapy; the long-term prognosis is poor, with the UK 5-year survival rate reported as around 30%.[4] The number of new cases of OC in 2010 was estimated as 5423, based on Cancer Research UK incidence rates.[5] The estimated number of stage III/IV OC cases will be 4067; the number who will relapse will be 3253. Expert opinion[2,6] suggests that, of those patients who relapse, 15–25% are platinum refractory (OC that does not respond to initial platinum-based chemotherapy). Of the remaining patients, expert opinion in the UK indicates that 20–25% are platinum resistant (i.e. relapse within < 6 months), 25–30% (813–976 in 2010) are partially platinum sensitive (relapse within 6–12 months) and 50% (1626 in 2010) are fully platinum sensitive (relapse > 12 months after initial chemotherapy). In total, therefore, 75–80% of relapsing patients are potentially eligible for treatment: 2440–2602 patients in 2010.[2,6]

Scope of the evidence review group report

The principal research question was to appraise the clinical effectiveness and cost-effectiveness of trabectedin in combination with PLDH within its licensed indication for the treatment of relapsed cases of platinum-sensitive OC. The comparator defined in the NICE scope was platinum-based chemotherapy (single agent or in combination) for the fully and partially platinum-sensitive populations. Additional comparators for the partially platinum-sensitive population were single-agent PLDH, paclitaxel or topotecan. Relevant clinical outcomes were overall survival (OS), progression-free survival (PFS) and overall response rate, with the last two outcomes being measured by three types of assessor – independent radiologists, independent oncologists and an investigator – and adverse effects of treatment. Health-related quality-of-life outcomes were measured by subscales from two cancer-specific quality-of-life instruments [European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC QLQ-QV28], and the EQ-5D (European Quality of Life-5 Dimensions). Cost per quality-adjusted life-year (QALY) gained was the relevant outcome for the cost-effective analysis.

The manufacturer submitted a cost-effectiveness model developed in Microsoft© EXCEL (Microsoft Corporation, Redmond, WA, USA). The main analysis compared trabectedin in combination with PLDH versus paclitaxel, topotecan and PLDH (each as monotherapy) in the entire platinum-sensitive population only (> 6-month relapse) using results estimated from a mixed treatment comparison (MTC). Additional analyses were presented by the manufacturer comparing trabectedin in combination with PLDH versus PLDH as monotherapy using direct evidence from the ET743-OVA-301 trial[7] for the fully, partially and entire platinum-sensitive populations. The model used a lifetime horizon and the main outcome was the cost per QALY gained.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The review of the clinical evidence included repeating the searches undertaken by the manufacturer. The ERG does not believe that any relevant clinical effectiveness or

cost-effectiveness studies have been missed. The ERG critiqued the economic model supplied. In addition, the ERG made changes to the model structure and data used to form an ERG base-case cost per QALY.

Results

Summary of submitted clinical evidence

The main evidence in the manufacturer's submission (MS)[6] is derived from one phase III randomised controlled trial (RCT) comparing the efficacy and safety of a combination of 1.1 mg/m^2 trabectedin and 30 mg/m^2 PLDH with 50 mg/m^2 PLDH.[7] *Table 1* presents the OS and PFS data for the trial. The largest and only significant effect on OS was seen within the partially platinum-sensitive subgroup, for which the median OS for the trabectedin plus PLDH arm was 23.0 months compared with 17.1 months for patients treated with PLDH alone.

The MS presented PFS results from the independent radiologists' assessment. Within the partially platinum-sensitive subgroup, there was a significant effect on PFS where the median PFS for the trabectedin and PLDH arm was 7.4 months compared with 5.5 months for PLDH alone [hazard ratio 0.65 (95% confidence interval 0.45 to 0.92); $p = 0.0152$]. Significant effects were also seen in the entire platinum-sensitive population but not in the fully platinum-sensitive population.

Progression-free survival results from assessments by the independent oncologists and the investigator are available in the ERG report.[2]

Discontinuation of treatment owing to adverse events and most grade 3 and 4 adverse events were higher in the trabectedin and PLDH combination arm than in the PLDH monotherapy. The

TABLE 1 Summary of OS and PFS from the OVA-301 trial

	Numbers included in analysis	Median OS (months)	HR (95% CI, *p*-value)	Numbers included in analysis	Median PFS by independent radiologists' assessment[a] (months)	HR (95% CI, *p*-value)
Population > 6 months						
Trabectedin + PLDH	218	27	0.82 (0.630 to 1.060), $p = 0.1259$	215	9.2	0.73 (0.56 to 0.95), $p = 0.0170$
PLDH	212	24.3		202	7.5	
Population > 12 months						
Trabectedin + PLDH	95	Not reached	0.887 (0.584 to 1.348), $p = 0.5746$	93	11.1	0.70 (0.47 to 1.03), $p = 0.0707$
PLDH	122	31.7		117	8.9	
Population 6–12 months						
Trabectedin + PLDH	123	23.0	0.59 (0.420 to 0.820), $p = 0.0015$	122	7.4	0.65 (0.45 to 0.92), $p = 0.0152$
PLDH	91	17.1		86	5.5	
Population < 6 months						
Trabectedin + PLDH	119	14.2	0.901 (0.675 to 1.203), $p = 0.4806$	113	4.0	0.95 (0.70 to 1.30), $p = 0.7540$
PLDH	123	12.4		115	3.7	

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride.
a PFS by independent oncologists and the investigator are available in the ERG report.[2]

main adverse events were neutropenia, febrile neutropenia, thrombocytopenia, anaemia, elevated aminotransaminase levels, fatigue, fever, diarrhoea, nausea and vomiting.

The MS also presented the results of an MTC to allow a coherent comparison of trabectedin and PLDH with PLDH, paclitaxel and topotecan (each as monotherapy). This was undertaken for the entire platinum-sensitive population only, and based on an MTC that had previously been performed as part of a NICE Multiple Technology Assessment (TA) – NICE TA91.[4]

Summary of submitted cost-effectiveness evidence

The model structure was derived from a previously published NICE Multiple TA (TA91[4]), and the effectiveness was modelled using the mean survival time derived from the median survival time, using an assumption that data were exponentially distributed. Utilities were extracted from the OVA-301 trial,[7] and costs were assessed from an NHS perspective. In the main analysis, the manufacturer reported that paclitaxel provided the least number of QALYs, followed by topotecan, PLDH as monotherapy and trabectedin in combination with PLDH. The incremental cost-effectiveness ratio (ICER) for trabectedin in combination with PLDH versus PLDH as monotherapy was estimated to be £70,076 per QALY gained.

The manufacturer also presented the ICERs for the three direct comparisons for the entire, partially and fully platinum-sensitive populations. The ICERs between trabectedin in combination with PLDH versus PLDH as monotherapy, using the independent radiologists' assessment, were £94,832, £43,996 and £31,092 by population, respectively. Results using the independent oncologists' assessment and the investigator's assessment are available in the clarification letter provided by the manufacturer.[8]

Uncertainties were examined in univariate sensitivity analyses only for the main analysis, whereas probabilistic sensitivity analyses (PSA) were undertaken for each scenario.

Commentary on the robustness of submitted evidence

Limited data were available and the MS addressed only one part of the final scope issued by NICE, i.e. trabectedin and PLDH versus PLDH alone for the partially platinum-sensitive population. The remainder of the final scope issued by NICE was not addressed within the MS, i.e. trabectedin and PLDH versus platinum-based chemotherapy (single agent or in combination) in the fully or partially platinum-sensitive populations, and trabectedin and PLDH versus paclitaxel or topotecan monotherapy in the partially platinum-sensitive population.

The main evidence in the MS is derived from one phase III RCT that is of reasonable methodological quality and measured a range of outcomes that were appropriate and clinically relevant. The included RCT is not an absolute reflection of the population with advanced relapsed OC in the UK, hence its external validity may be questionable. There appeared to be a high degree of censoring within the PFS analysis; reasons for censoring a large number of trial participants ($n = 178$) were not made explicitly clear within the MS. PFS analysis was also based on the independent radiologists' assessment. Clinical advice sought by the ERG suggested that the independent oncologists' assessment of PFS was more appropriate. OS results presented in the MS are based on an interim analysis.

The ERG did not believe that the MTC was necessary to answer the scope set by NICE. This is because PLDH had previously been estimated to be the most clinically effective and cost-effective treatment within the platinum-sensitive population when compared with paclitaxel or topotecan monotherapy,[4] and clinical advice sought by the ERG indicated that in instances whereby PLDH monotherapy is contraindicated, a trabectedin and PLDH combination would also be contraindicated. Therefore, the relative cost-effectiveness of trabectedin and PLDH compared

with paclitaxel or topotecan monotherapy is not needed, as there would never be a choice between these interventions. As such, a direct comparison of trabectedin and PLDH was deemed sufficient to address the decision problem.

The ERG requested individual patient data from the manufacturer. From these it was shown that the PFS and OS data were not exponentially distributed, and the ERG conducted analyses using alternative distributions. Secondly, the use of the average number of cycles of treatment across all the populations included in the trials for the main analysis only (i.e. platinum-sensitive and platinum-resistant individuals) is likely to have biased the cost-effectiveness estimate. Thirdly, there was uncertainty regarding the estimates of the mean dose per cycle. Fourthly, the ERG was concerned about the absence of discounting for costs and an incorrect approach used to discount health outcomes. Finally, there were problems concerning the implementation of the PSA, which limit its interpretation. This notably included the lack of variation for some main parameters, the choice of distribution and assumptions used.

Additional work was undertaken by the ERG only for the partially platinum-sensitive population. This included fitting more appropriate distributions for PFS and OS using individual patient-level data and estimating the mean dose per cycle from the mean number of cycles and mean cumulative dose from the trial, discounting costs and health outcomes using a conventional methodology, and amending the PSA. Assuming a Weibull or Gompertz distribution for both OS and PFS, and using the independent oncologists' assessment, the ERG estimated that the ICER of trabectedin in combination with PLDH when compared with PLDH as monotherapy would range from £46,503 to £54,607, respectively, in the partially platinum-sensitive population. The ICER reported by the manufacturer was £39,262 using the independent oncologists' assessment.

Conclusions

The MS contained only one phase III RCT, which may not be an absolute reflection of the population with advanced relapsed OC in the UK, and had some trial design limitations, such as the open-label design and a high degree of censoring. This RCT showed a significant increase in OS for the trabectedin and PLDH arm in the partially platinum-sensitive population compared with PLDH monotherapy. Non-significant improvements in OS were seen in the fully and entire platinum-sensitive populations. However, clinical evidence is based on only one RCT. In addition, the MS answered only part of the final scope issued by NICE, and so the clinical effectiveness of trabectedin and PLDH versus the key comparator, platinum-based chemotherapy (single agent or combination), is unknown.

The cost-effectiveness estimates presented in the MS are limited owing to the assumptions used and limitations of the submitted cost-effectiveness model. Additional work was undertaken by the ERG to provide an alternative estimate of the cost-effectiveness of trabectedin in combination with PLDH versus PLDH as monotherapy in the partially platinum-sensitive population. Despite the additional work, uncertainties still exist, as no comparison between platinum-based chemotherapy (single agent or in combination) and trabectedin was provided.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance issued by NICE in the final appraisal determination in March 2011 states that:[9]

- Trabectedin in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) is not recommended for the treatment of women with relapsed platinum-sensitive ovarian cancer.
- Women with relapsed platinum-sensitive ovarian cancer currently receiving trabectedin plus PLDH should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Key references

1. National Institute for Health and Clinical Excellence (NICE). *Guide to the single technology appraisal process*. London: NICE; 2009.
2. Papaioannou D, Rafia R, Stevens JW, Stevenson M, Evans P. *Trabectedin for the treatment of relapsed ovarian cancer: a single technology appraisal*. Sheffield: ScHARR, University of Sheffield; 2010.
3. European Medicines Agency (EMEA). *Assessment report for Yondelis® (trabectedin)*. London: EMEA; 2009.
4. Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al.* Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation. *Health Technol Assess* 2006;**10**(9).
5. Cancer Research UK. *Ovarian cancer – UK incidence statistics*. London: Cancer Research UK; 2009.
6. PharmaMar. *Trabectedin (Yondelis®) for the treatment of patients with ovarian cancer (relapsed): single technology appraisal (STA)*. Madrid: PharmaMar; 2010.
7. Monk BJ, Herzog T, Kaye S, Krasner CN, Vermorken JB, Muggia FM, *et al.* Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. *J Clin Oncol* 2010;**28**(19):3107–14.
8. PharmaMar. *Re: single technology appraisal – trabectedin for relapsed ovarian cancer*. Madrid: PharmaMar; 2010.
9. National Institute for Health and Clinical Excellence. *Final appraisal determination: Trabectedin for the treatment of relapsed ovarian cancer.* 2011. URL: www.nice.org.uk/nicemedia/live/12094/53470/53470.pdf (accessed 1 April 2011).