NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple technology appraisal (MTA)

Ovarian cancer - topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer (including review of TA 91 & TA 222) [ID468]

Evidence submission for trabectedin (Yondelis®) for the treatment of patients with relapsed platinum-sensitive ovarian cancer

1. Executive Summary

Ovarian cancer is the fifth most common cancer in women in the UK[i] with almost 7000 new diagnoses in the UK annually[ii] and 4600 deaths from the disease each year.[iii] The outcome of ovarian cancer is generally poor, with an overall 5-year survival rate of approximately 43%.iii For the majority of patients, based on 2005 NICE guidance, first-line chemotherapy consists of platinum-based therapy alone or in combination with paclitaxel.[iv] Unfortunately, despite the high response rate to initial chemotherapy, it is estimated that 55-80% of women with advanced disease will relapse and experience recurrence of the malignant process within two years of completing treatmentiii[,iv,v] and are therefore candidates for a range of possible second-line therapeutic options.

Second line treatment often consists of a platinum-based strategy, dependent on the platinum free interval (PFI) of the patient. However, the decision on the second-line clinical strategy is complex and needs to balance efficacy and safety considerations. There are a significant number of patients with platinum-sensitive disease for whom retreatment with platinum-based agents may not be appropriate or is not recommended. These include patients with a shorter PFI (<12 months) who are less likely to benefit from platinum retreatment[vi,vii] as well as patients who develop allergies or toxicities, such as severe hypersensitivity reactions to platinum containing regimens.[viii] For these patients with relapsed platinum-sensitive disease who are not suitable for platinum retreatment, NICE currently recommends either single agent paclitaxel, pegylated liposomal doxorubicin hydrochloride (PLDH), or topotecan.iv

NICE is currently appraising the clinical and cost-effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine within their licensed indications for the treatment of recurrent ovarian cancer within a multiple technology appraisal (MTA) as part of a review of TA91 and TA222.iii This submission details the evidence available to support the approval of trabectedin as part of this MTA. This evidence submission considers the use of trabectedin in combination with PLDH for patients with relapsed platinum-sensitive ovarian cancer.

Importantly, a clear body of evidence and clinical rationale is presented for restricting the use of trabectedin in combination with PLDH to a subgroup of relapsed platinum-sensitive ovarian cancer patients who are not suitable for, or not best managed with, platinum-based chemotherapy because of:

- allergy or;
- intolerance due to residual toxicities or;
- because they have partially platinum-sensitive disease.

Trabectedin (Yondelis®) is a synthetic, marine-derived antineoplastic agent originally isolated from marine Caribbean tunicate, *Ecteinascidia turbinata*. Trabectedin binds to the minor groove of DNA, bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins and DNA repair pathways, resulting in perturbation of the cell cycle.[ix] Through binding, trabectedin inhibits the transcription of genes involved in cell proliferation, and interferes with the cell cycle.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the 24th September 2009, recommending the granting of a license extension for trabectedin to include use in combination with PLDH for the treatment of patients with relapsed platinum-sensitive ovarian cancer.[x] On 28th October 2009, the extension of the marketing authorisation of Yondelis for its use in this indication was authorised.[xi]

The provision of the marketing authorisation was based upon the results of the pivotal phase III trial, the OVA-301 trial. OVA-301 is a well powered and rigorously conducted randomised trial in advanced, relapsed ovarian cancer after failure of platinum-based chemotherapy. Patients were included in the trial if they had received only 1 prior platinum-based chemotherapy regimen, and had experienced persistence, recurrence or progression, including platinum-resistant (PFI < 6 months) and platinum-sensitive (PFI ≥ 6 months) disease. Importantly, patients were recruited who were not expected to benefit from or who were ineligible for or not willing to receive retreatment with platinum-based chemotherapy.[xii] Therefore, the patient population for the OVA-301 trial closely matches the patient

subgroup that this evidence submission addresses. For the purposes of this submission, the platinum-resistant population is not being considered because it is neither within the marketing authorisation, nor is it within the NICE MTA scope for trabectedin.

The OVA-301 trial compared the combination of trabectedin plus PLDH vs. PLDH monotherapy. The analysis of the primary endpoint (progression free survival [PFS]) by independent radiologist review, demonstrated the following results in the trabectedin plus PLDH arm vs. the PLDH monotherapy arm: [xiii]

- In the overall population (that is, all patients either with platinum-resistant or platinum-sensitive disease), treatment with trabectedin plus PLDH resulted in a statistically significant 21% risk reduction of disease progression or death compared with PLDH monotherapy (median PFS was 7.3 vs. 5.8 months; hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.65-0.96; p=0.0190).
  - In the platinum-sensitive population (PFI ≥ 6 months), a statistically significant 27% risk reduction was observed (median PFS was 9.2 vs. 7.5 months; HR 0.73; 95% CI 0.56-0.95; p=0.017).
  - In the partially platinum-sensitive population (PFI 6-12 months), a statistically significant 35% risk reduction was observed (median PFS was 7.4 vs. 5.5 months; HR 0.65; 95% CI 0.45: 0.92; p=0.015).

Overall survival (OS) was a secondary endpoint of OVA-301 and is considered to be the gold-standard when assessing therapies in oncology as it has the greatest clinical relevance to patients.[xiv] The following final OS results were demonstrated for trabectedin plus PLDH compared to PLDH monotherapy[xv]:

- In the overall population, treatment with trabectedin plus PLDH resulted in a non-statistically significant 14% risk reduction of death compared with PLDH monotherapy (median OS was 22.2 vs. 18.9 months; HR 0.86; 95% CI 0.72-1.02; p=0.0835).
  - In the platinum-sensitive population, a non-statistically significant 17% risk reduction was observed (median OS 27.0 vs. 24.1 months; HR 0.83; 95% CI: 0.67-1.04; p=0.106)
  - In the partially platinum-sensitive population, a statistically significant 36% risk reduction was observed (median OS 22.4 vs. 16.4 months; HR 0.64; 95%CI: 0.47-0.86; p=0.0027)
- However, it was noted that despite study stratification by platinum-sensitivity which resulted in well-balanced arms in terms of platinum-resistant and platinum-sensitive, an unanticipated but statistically significant imbalance in the PFI favouring the PLDH arm was identified (mean PFI: PLDH=13.3 months, trabectedin plus PLDH=10.6 months; p=0.009).[xv]
  - This significant imbalance was even more pronounced in the platinum-sensitive group (mean PFI: PLDH=19.0 months, trabectedin plus PLDH=14.3 months; p=0.002) though no significant imbalance was observed in the partially platinum-sensitive group (p=0.200).[xvi]
- PFI has been shown to be a significant predictor of both OS and PFS, and therefore not accounting for this imbalance could potentially bias results in favour of PLDH monotherapy.[xv]
- Therefore, following the statistical analysis plan of the trial, a multivariate analysis Cox regression was performed to provide a result for treatment effect adjusting for pre-specified key prognostic factors (including PFI). The analysis showed that treatment with trabectedin plus PLDH resulted in a statistically significant 18% risk reduction of death compared to PLDH monotherapy (median OS 22.6 vs. 19.4 months; HR 0.82; 95% CI: 0.69–0.98; p=0.0285).[xv]
  - In the platinum-sensitive population, treatment with trabectedin plus PLDH resulted in a statistically significant 22% risk reduction of death compared to PLDH monotherapy (median OS 28.4 vs. 24.1 months; HR 0.78; 95%CI: 0.62-0.98; p=0.0319).[xvii]
  - In the partially platinum-sensitive population, treatment with trabectedin plus PLDH resulted in a statistically significant 35% risk reduction of death compared to PLDH monotherapy (median OS 21.0 vs. 17.2 months; HR 0.65; 95%CI: 0.48-0.88; p=0.0056).[xviii]

OVA-301 demonstrated that the safety profile of trabectedin plus PLDH was consistent with the known toxicities characteristic of each agent alone and no new or unexpected toxicities were observed. The most common adverse reactions of any severity grade which occurred at a higher frequency in the trabectedin plus PLDH arm compared to the PLDH monotherapy arm were neutropenia, nausea, vomiting, increases in AST/ALT, anaemia, fatigue, thrombocytopenia, anorexia and diarrhoea. The incidence of known toxicities associated with PLDH, such as hand-foot syndrome, stomatitis or mucosal inflammation was found to be lower in the trabectedin plus PLDH than the PLDH monotherapy arm. Unlike established platinum and taxane-based regimens, trabectedin plus PLDH was associated with greatly diminished incidence of neuropathy and alopecia, as well as lack

of end organ, cumulative toxic effects. Finally, quality of life (QoL) assessments showed no detrimental effect when adding trabectedin to PLDH.[xiii] Furthermore, subgroup analysis demonstrated an improved QoL effect in the partially platinum-sensitive population after cycle 5.[xix]

Given that the target population for the OVA-301 trial and this submission only includes patients who are not suitable for platinum-based chemotherapy, it is only appropriate to compare the clinical and cost-effectiveness of trabectedin to other non platinum-containing treatments for relapsed platinum-sensitive ovarian cancer aforementioned in the NICE scope (i.e. PLDH, topotecan, paclitaxel, etoposide and best supportive care). A systematic review is detailed within this submission which identifies no relevant randomised controlled trials (RCTs) to add to the network of evidence that was previously available during the 2010 single technology appraisal (STA) for trabectedin (TA222). During the previous submission for trabectedin, the Evidence Review Group (ERG) recommended that based on the available evidence in 2010, a mixed treatment comparison (MTC) was not necessary, and the only suitable comparator for trabectedin plus PLDH was PLDH monotherapy. Therefore, since no further evidence has become available, to align with the ERG's recommendations, a MTC was deemed inappropriate and comparisons for trabectedin have been made directly with PLDH using the OVA-301 trial.

A cost-effectiveness analysis was conducted to compare trabectedin plus PLDH with PLDH monotherapy based on head to head data from the OVA-301 trial for the treatment of patients with relapsed platinum-sensitive ovarian cancer who are not suitable for platinum-based chemotherapy because of allergy or intolerance due to residual toxicities or because they have partially platinum-sensitive disease.

PLDH is currently recommended by NICE (TA91) in two important subgroups of this population: patients with partially platinum-sensitive disease; and patients with platinum-sensitive disease who are allergic to platinum-based compounds.iv Additionally, during the technology appraisal of trabectedin (TA222), NICE acknowledged PLDH as a relevant comparator in patients with platinum-sensitive disease where platinum-based regimens would be unsuitable.v Therefore, results from this analysis should only be interpreted for platinum-sensitive patients where PLDH would be considered an appropriate treatment option.

A decision analytic model estimated the cost per quality adjusted life year (QALY) gained for trabectedin plus PLDH compared to PLDH monotherapy from the UK NHS and Personal Social Services perspective over a lifetime horizon. The model was constructed in Microsoft® Excel and the structure was based on the NICE MTA (TA91), which was designed to facilitate the comparison of interventions for second-line treatment of ovarian cancer. After the commencement of second-line treatment, patients in the model are classified by three health states; either stable disease, progressive disease or dead.[xx] Mean PFS and OS were calculated using parametric survival distributions adjusted for imbalances discovered in the final survival data from OVA-301. Between-arm imbalances included the PFI, cancer antigen 125 (CA-125), and Eastern Cooperative Oncology Group (ECOG) performance score. Cost categories included drug, administration, medical management, and treatment of adverse events. Quality of life was measured by using the EQ-5D. Uncertainty was addressed by deterministic and probabilistic sensitivity analysis.

In the base-case analysis it was found that over a lifetime horizon, a patient receiving trabectedin plus PLDH accrued 3.72 life years and 2.33 QALYs at a cost of £43,907. Patients receiving PLDH accrued 2.91 life years and 1.85 QALYs at a cost of £24,809. The corresponding incremental cost per QALY was calculated as £39,306. One-way sensitivity analysis and scenario analyses showed that results were sensitive to the calculation of mean OS and the adjustment of PFI. The probabilistic sensitivity analysis (PSA) showed that at a willingness to pay (WTP) of £20,000 per QALY and £30,000 per QALY, the probability of trabectedin plus PLDH being cost-effective was 1% and 20%, respectively. However, trabectedin plus PLDH could be a candidate for end of life criteria since the treatment is indicated for a small population of patients with a short life expectancy (less than 24 months), and both mean and median survival estimates suggest that trabectedin offers an extension of life well in excess of 3 months. Therefore, NICE may choose to consider higher thresholds for achieving cost-effectiveness.

It is anticipated that there will be approximately 491 patients in England and Wales with relapsed platinum-sensitive ovarian cancer who are not suitable for treatment with platinum-based

chemotherapy because of allergy or intolerance due to residual toxicities and patients who have partially platinum-sensitive disease. The total budget impact of introducing trabectedin plus PLDH in 2014 is £3,284,036 and this is anticipated to increase up to £4,359,077 in 2018. However, the actual budget impact may be lower since it assumes all patients receiving non platinum agents will be initiated on PLDH in a world without trabectedin plus PLDH.

In conclusion, based on the final efficacy outcomes and the manageable safety profile of trabectedin plus PLDH, the benefit-risk ratio favours trabectedin plus PLDH.[xi] Hence, treatment with trabectedin plus PLDH offers a new non platinum, non-taxane therapeutic alternative to patients with relapsed platinum-sensitive ovarian cancer, who are unsuitable to receive retreatment with platinum-based chemotherapy and would otherwise be treated with PLDH monotherapy. Trabectedin plus PLDH is associated with clinically and statistically significant increases compared to PLDH monotherapy in the platinum-sensitive population for both PFS (p=0.017) and OS (p= 0.0319) following adjustment for imbalances in prognostic factors including PFI. Considering these benefits within the context of cost-effectiveness, there is a significant case to be made that trabectedin plus PLDH fulfils end of life criteria; the patient population is small, the life expectancy of the disease is less than 2-years and the increase in OS is estimated to be in excess of 4 months. NICE applies higher incremental cost-effectiveness ratio (ICER) thresholds to end of life treatments, and therefore the base case ICER of £39,306 per QALY could be considered cost-effective in the UK NHS. Finally, the small population budget impact appears manageable.

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