NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

PharmaMar response to the

Appraisal Consultation Document

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer (including review of technology appraisal no. 91 and technology appraisal no. 222) [ID468]

October 2013

FOREWORD

In providing the following response, the manufacturer (PharmaMar) has sought to address concerns expressed by the Committee and Technology Assessment Group (TAG) in relation to the evidence presented for trabectedin. PharmaMar has undertaken a review of the clinical and cost-effectiveness evidence previously presented to NICE and sought advice from the clinical community in ovarian cancer. Additional information and analysis has been identified to improve the evidence-base and assist with areas of uncertainty highlighted in the Appraisal Committee Document (ACD). One particular area of uncertainty was the adjustment of baseline imbalances observed in the platinum free interval (PFI) and other characteristics, which we address in full within this response. Our proposal acknowledges the comments received from the Committee and has been developed to accurately reflect the needs of ovarian cancer experts and patients. We believe that the additional evidence presented within this response would enable NICE to recommend access to trabectedin plus PLDH; which both experts and trial evidence suggests is the most effective non-platinum agent for platinum-sensitive ovarian cancer.

Comments are provided to the Appraisal Committee in relation to the following areas:

Has all relevant evidence been taken into account?
To assist the Committee in its decision-making we have sought to provide further evidence to support the rationale for the adjustment of baseline imbalances including PFI to determine effectiveness results, including previous technology assessments that have encountered this challenge.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
PharmaMar believes there are some aspects of the data, which require further review in order to appreciate the evidence base for trabectedin and how it relates to ovarian cancer management.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
PharmaMar is concerned with the provisional recommendations. The approach adopted to form these recommendations suggests it is appropriate not to adjust for key prognostic factors where imbalances exist even when it is clear that the imbalance could not be prevented by randomisation techniques. PharmaMar feel this is unfair and results in draft guidance, which cannot reasonably be justified in light of the evidence submitted.

Could the provisional recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology? Equally could the provisional recommendations have any adverse impact on people with a particular disability or disabilities?

Recurrent ovarian cancer is not curable and the goals of therapy should focus on palliation of cancer-related symptoms, extension of life, and maintenance of quality of life [Chia 2013; Foley 2013]. As such women may require several lines of treatment to support these goals. Some patients with relapsed platinum-sensitive ovarian cancer are not the best candidates for retreatment with platinum-based therapy due to hypersensitivity reactions or neurotoxicity with platinum and/or paclitaxel [Sehouli 2012] and therefore a range of effective treatment options is required which should include trabectedin. The current guidance as it stands limits these options. In addition to this, value based pricing is likely to place weight on diseases with high burden of illness and treatments which provide wider societal benefits. In this context, PharmaMar feel that trabectedin for treatment of ovarian cancer would be given additional weighting in future decisions and we ask that this be in front of mind for this appraisal.

EXECUTIVE SUMMARY

CONCERNS WITH THE PROVISIONAL RECOMMENDATIONS

PharmaMar believe the recommendations as they stand will unfairly limit patient treatment options in a disease where recurrence is likely and there is a need to be able to tailor treatment to the individual. In addition, PharmaMar would like to take this opportunity to highlight a number of concerns with the process and evidence for which trabectedin has been provisionally not recommended.

1. **NICE did not follow their usual process**. The TAG's response to the manufacturer's comments on the TAG report was not made available to the manufacturer but was made available to the Committee prior to the AC meeting, which disadvantaged PharmaMar during the AC meeting.
2. **NICE has failed to act fairly and formulated guidance which cannot reasonably be justified in the light of the evidence submitted**. In particular, NICE has shown inconsistency in accepting methodologies evaluating trabectedin during this multiple technology appraisal (MTA) and the previous single technology appraisal (STA) of trabectedin [NICE TA222 2010].

KEY ISSUES TO BE ADDRESSED

- Three factual inaccuracies were identified in the ACD, which have been highlighted to NICE.

- ***The network meta-analysis should have adjusted for imbalances in baseline characteristics where patient level data were available to allow for this adjustment.***
  - The TAG interpretation that the magnitude of differences observed in the baseline characteristics was unlikely to affect estimates of the relative treatment effect is misguided.
  - Significant differences were observed in baseline PFI in OVA-301 comparing trabectedin plus PLDH vs. PLDH alone within platinum-sensitive disease (14.3 months vs. 19.0 months; p=0.002).
  - PFI has been shown to be a significant prognostic factor in predicting progression free survival (PFS) and overall survival (OS), with longer PFIs associated with a better prognosis [Gore 1990; Pujade-Lauraine 2002], thus the PFI imbalance in OVA-301 significantly biased OS and PFS results in favour of PLDH.
  - A multivariate analysis defined within the OVA-301 statistical analysis plan had the advantage of adjusting for imbalances and any associated bias or confounding caused by pre-specified protocol defined covariates (including PFI). The analysis demonstrated significant improvements in both PFS and OS in favour of trabectedin plus PLDH within its licensed indication. A significant improvement in OS with trabectedin plus PLDH was not preserved without multivariate analysis.
  - Therefore, to say that the magnitude of differences observed in key prognostic factors such as PFI is unlikely to affect estimates of the relative treatment effect is a gross inaccuracy.
  - We disagree with the TAG's recommendation to use a 'consistent approach' considering a dataset without adjustments in favour of a more 'accurate approach' comparing trabectedin plus PLDH vs. PLDH alone.

- It is the TAG's own admission that *"Adjustment of clinical-effectiveness data for key prognostic factors was likely to result in more accurate estimates of progression-free survival and overall survival" [ACD 2013]* with regards to the comparison of trabectedin plus PLDH vs. PLDH alone.
- This is of crucial importance when considering the QALY league table produced by the TAG, which suggests the most relevant comparison (based on ranking by QALYs) for trabectedin plus PLDH, is against PLDH alone. Consequently, the need to compare trabectedin plus PLDH vs. paclitaxel and topotecan, and preserving a consistent dataset is of significantly less importance compared to an accurate comparison vs. PLDH alone.
- Furthermore, clinical specialists stated a preference for adjusted results to account for heterogeneity and imbalances between and within trials included in the network meta-analysis. Not accounting for biases and confounding caused by PFI contradicts the fact that NICE make recommendations based on PFI [NICE TA91 2005].
- In summary, PharmaMar suggest that all is done to ensure the most accurate analyses are used in the base case analysis. Where baseline imbalances in prognostic factors such as PFI are unknown or patient level data is unavailable to adjust for imbalances, the TAG can only reasonably assume that unadjusted results are the most reliable for the purposes of their evaluation. However, to purposely ignore results that by their own admission are more accurate estimates of PFS and OS, compared to the most relevant comparator in PLDH, represents a perverse conclusion which will adversely impact patient access to trabectedin plus PLDH.

- ***Base case cost-effectiveness results should use a network meta-analysis which adjusts for imbalances in baseline characteristics where such imbalances exist and influence outcomes.***
  - The NICE Decision Support Unit guidance for survival analyses recommend "*adjusting for the characteristics of the patients included in the clinical trial of interest – thus correcting for any patient population differences which may be present between different clinical trials." [DSU 2011]*
  - PharmaMar is consequently confused why NICE do not follow their own guidance, and unadjusted results are considered more relevant. Although randomisation should ideally result in balanced baseline characteristics, as NICE acknowledge, this is difficult with the problematic nature of stratifying by PFI. Thus adjusted results would appear appropriate for OVA-301.
  - NICE has set a precedent in previous technology assessments by accepting approaches within cost-effectiveness analyses which adjust for baseline characteristics where imbalances exist. Importantly, the same NICE Committee appraising technologies in this MTA accepted the approach of retrospectively adjusting survival curves for potential covariates where imbalances existed in OVA-301. This was proposed by the ERG during TA222, which appraised trabectedin for the treatment of platinum-sensitive ovarian cancer: "*The ERG considered that the analysis adjusting the distribution for CA-125 was the most appropriate." [ERG Papaioannou 2010]*
  - Thus, the notion that adjustment of treatment effect for imbalances in factors such as PFI is "a new concept" and an "unvalidated retrospective approach in ovarian cancer trials" is untrue and it is worrying that adjusting for characteristics is acceptable in a STA of trabectedin but not a MTA including trabectedin, particularly when the same NICE Committee is chosen for both appraisals.

- During TA222, *"the Committee accepted that in those cases where single-agent PLDH might be selected as the most appropriate treatment in the setting of partially platinum-sensitive disease or platinum allergy, the manufacturer's comparison could be considered relevant" [NICE TA222 2010].* Thus, cost-effectiveness of trabectedin plus PLDH vs. PLDH alone was considered *"sufficient to address the decision problem" [ERG Papaioannou 2010].*
- In the base case analysis, ranking comparators by QALYs using unadjusted results, PLDH is the most relevant comparator for trabectedin plus PLDH; the base case ICER of £85,200 compares trabectedin plus PLDH vs. PLDH alone. Consequently, the comparison of trabectedin plus PLDH vs. PLDH alone can be considered as the most important and appropriate comparison to determine the cost-effectiveness of trabectedin plus PLDH within its licensed indication.
- In summary, PharmaMar propose the most accurate representation of cost-effectiveness should be used for trabectedin plus PLDH vs. PLDH alone, which by the TAG's own admission is the survival analysis conducted by PharmaMar which adjusts for covariates where imbalances exist (£27,600 per QALY with PharmaMar's model and £35,000 per QALY with the TAG's model).

- ***PharmaMar's method for estimating overall survival and progression free survival overcomes the three main concerns identified by the TAG and the NICE Committee.***
  - Patient level data were available and differences in baseline characteristics were explored and appropriately adjusted for when necessary.
  - Adjusted results were used which reduced the potential bias caused by baseline imbalances.
  - The flawed assumption of proportional hazards was not used, and survival curves fitted by treatment arm, adjusting for covariates where imbalances existed, were selected in a systematic approach aligned with NICE DSU guidelines [DSU 2011].
  - No crossover was observed in OVA-301, making the survival analysis a clean ITT analysis.
  - Interestingly the TAG report states that *"Future trials in recurrent ovarian cancer should endeavour to carry out analysis on patient level data that has been adjusted for a consistent array of variables; of particular importance is the adjustment of clinical effectiveness data for platinum free interval (measured as a continuous rather than categorical variable)." [Edwards 2013]*
  - The research proposed is exactly what PharmaMar have done as part of this appraisal, which contradicts the rationale for NICE to reject methods that the ERG proposes as future research.

- ***PharmaMar propose a more accurate method for calculating treatment costs in the TAG model, which avoids the use of unlicensed doses and uses new patient level data for more accurate results.***
  - The TAG model overestimates the proportion of patients that would receive treatment with trabectedin plus PLDH, when compared to actual data available from OVA-301. The cost of a course of treatment using the TAG model results in average doses of treatment with trabectedin (1.88 mg) and PLDH (51.4 mg) that are above those observed in OVA-301 for trabectedin (1.72 mg) and PLDH (47.23 mg), which overestimates the cost of a treatment course.
  - The TAG model overestimates the proportion of patients that would receive treatment with PLDH alone, when compared to actual data available from OVA-301. The cost of a course of treatment

using the TAG model results in average doses of treatment with PLDH (69.00 mg) that are below those observed in OVA-301 for PLDH (77.40 mg), which underestimates the cost of a course of treatment. This was primarily an unlicensed dose to calculate the cost for PLDH was used.

- Trabectedin plus PLDH would be a cost-effective treatment option compared to PLDH alone, with an ICER of **£28,599 per QALY** (incremental cost = £10,836; incremental QALYs = 0.38) over a 15 year time horizon were the TAG model to be appropriately amended to: a) Adjust for baseline imbalances within the OS and PFS survival curves; b) Change the probability for allergic reaction to 2% with trabectedin plus PLDH and 4% for PLDH based on hypersensitivity reactions observed in OVA-301; c) Change the dosing assumptions such that average doses are used instead of a combination of licensed and unlicensed doses and d) Change the drug cost calculations such that the proportion of patients receiving a dose are based on known patient level data and not OS survival curves.

- ***The time horizon for the model is too short to capture all relevant costs and outcomes for interventions under evaluation.***
  - In keeping with the 2013 NICE Guide to the methods of technology appraisal – (sections 5.1.15-5.1.17), we believe a lifetime horizon should be used, since at year 15 when comparing trabectedin plus PLDH vs. PLDH alone, 1% of patients are alive in the PLDH arm and 2% are alive in the trabectedin plus PLDH arm.
  - Were a lifetime horizon adopted within the TAG model, the time horizon would extend to 47 years. When accounting for the factors detailed in the issue of treatment costs, the ICER decreases from £28,599 to **£27,139 per QALY** (incremental cost = £11,149; incremental QALYS = 0.41), which is very similar to the PharmaMar ICER with cyclic discounting of £28,334 (incremental cost = £11,644; incremental QALYS = 0.41).

- ***End of life criteria should be reconsidered by NICE based on adjusted results for trabectedin plus PLDH.***
  - Median overall survival based on the PLDH arm of the OVA-301 study is less than 24 months in the population for which trabectedin plus PLDH is sought (platinum-sensitive ovarian cancer, unsuitable for retreatment with platinums).
  - Median overall survival gain with trabectedin plus PLDH is > 3 months based on the adjusted results for PFI and other covariates, as performed in the multivariate analysis of OVA-301.

- ***Recommendations are ambiguous and are inconsistent with the scope of the MTA.***
  - Recommendations are based on 16 trials of which only 5 trials evaluated the drugs within their marketing authorisations; PharmaMar is concerned that recommendations are based on evidence using dosing regimens outside of licensed doses, particularly for PLDH and paclitaxel.
  - Hence the decision making appears not to be in line with that defined in the MTA scope and seems to have been selectively applied. Greater explanation is required in the ACD to enable NHS stakeholders to understand what exactly has been done to arrive at the recommendations and the assumptions made.

FACTUAL INACCURACIES IN THE ACD

Description of problem	Description of proposed amendment	Justification for amendment
Page 9: *"The cost of a course of treatment of trabectedin 1.1 mg/m^2 and PLDH 30 mg/m^2 on day 1 of every 21 day cycle is £3679 (with patient access scheme included)."*	Please remove "*(with patient access scheme included)*"	The patient access scheme for trabectedin provides free cycles after 5 cycles and therefore the cost of trabectedin 1.1 mg/m^2 and PLDH 30 mg/m^2, as calculated by the TAG model, is £3659 for the first five cycles only.
Page 14: *"No statistically significant differences were reported in the OVA-301 trial for progression-free survival."*	Please delete this sentence.	This is potentially misleading as statistical significant differences were observed in favour of trabectedin plus PLDH compared to PLDH for progression free survival in the OVA-301 trial. Indeed the AC report states on Page 14: *"The OVA-301 trial reported a statistically significant improvement in progression-free survival with trabectedin plus PLDH compared with PLDH alone (HR=0.65, 95% CI 0.45 to 0.92; p=0.015)."*

Page 22-23: *"The costs of adverse events in the model were £111 for paclitaxel, £78 for paclitaxel plus platinum, £69 for PLDH alone, £97 for PLDH plus platinum, £172 for gemcitabine plus carboplatin, £198 for trabectedin plus carboplatin, and £200 for topotecan."*	Delete carboplatin and replace with PLDH for trabectedin part of sentence so it should read: *""The costs of adverse events in the model were £111 for paclitaxel, £78 for paclitaxel plus platinum, £69 for PLDH alone, £97 for PLDH plus platinum, £172 for gemcitabine plus carboplatin, £198 for trabectedin plus PLDH, and £200 for topotecan."*	Typographical error.

COMMENTS ON THE ACD

Issue 1: Adjustment for baseline imbalances in the network meta-analysis

Relevant quotes from the ACD

- Page 11: *"In general, the Assessment Group stated that treatment groups within trials were well matched. Some differences in baseline characteristics between trials were identified, in particular with respect to length of the platinum-free interval, number of previous lines of chemotherapy and the method used to diagnose recurrence. However, the Assessment Group considered that the magnitude of these differences was unlikely to affect estimates of the relative effect of treatment and the trials were sufficiently clinically homogeneous to compare the clinical effectiveness of treatments."*

- Page 12: *"The Assessment Group specified that unadjusted hazard ratios were used for progression-free survival and overall survival in the network meta-analysis. It acknowledged that adjusting for baseline characteristics may be important because certain characteristics are considered to influence prognosis. However, in the absence of a consistent dataset for all comparisons, the Assessment Group did not consider it appropriate to analyse a blend of unadjusted and adjusted hazard ratios."*

- Page 32: *"The Committee also heard from the clinical specialists that the results of the network meta-analyses were broadly in line with those expected from the trial data and experience in clinical practice. The Committee acknowledged that the analyses had methodological limitations but, on balance, concluded that the Assessment Group's approach was reasonable given the data available and accepted the clinical-effectiveness results from the network meta-analyses."*

PharmaMar's response

- The interpretation that the magnitude of differences observed in the baseline characteristics, and in particular the PFI, was unlikely to affect estimates of the relative effect of treatment is misguided. A prime example of this is the OVA-301 trial, where significant differences were observed in baseline PFI: patients in the PLDH monotherapy arm had a significantly longer mean PFI (19.0 months) than patients in the trabectedin plus PLDH arm (14.3 months) (p=0.002).

- Ovarian cancer patients who respond to platinum-based chemotherapy and receive no additional treatment for an extended period of time have a reasonable likelihood of responding to a second or third retreatment of a platinum-based regimen [Gore 1990; Markman 1991]. The likelihood that a patient will obtain clinically relevant benefit from retreatment with a platinum regimen is a continuum, with increasing response rates associated with longer PFI periods. For example, with a PFI of 6-12 months, 20% to 30% of patients are likely to achieve an objective response to reintroduction of platinum-based therapy, whereas with an interval of 18-24 months, that rate may increase to 60% to 70% [Markman 1991]. These observations are crucial since it translates into a longer time to disease

progression, a higher survival rate, and longer treatment-free intervals [Markman 2004].

- This is recognised in the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines which also emphasises the need to evaluate PFI as a continuous variable:

  "The prognosis and probability of response to second-line therapy and subsequent lines depends in great part on the progression-free interval after the last dose of the preceding line of chemotherapy. These categories are based on the response to a rechallenge with platinum-based drugs but probably apply to non-platinum therapies as well. A categorisation, recently updated and confirmed by the GCIG 4th Ovarian Cancer Consensus Meeting, defines 'platinum-refractory' as patients progressing during therapy or within 4 weeks after the last dose; 'platinum-resistant' patients progressing within 6 months of platinum-based therapy; 'partially platinum-sensitive, patients progressing between 6 and 12 months; and 'platinum-sensitive' patients progressing with an interval of more than 12 months. ***It should be noted that these categories are based on observational studies and that the categorisation is probabilistic, with the likelihood of response being a continuous variable.****" [Lederman 2013]*

- Since PFI is an important prognostic factor in predicting progression free survival (PFS) and overall survival (OS), with longer PFIs associated with a better prognosis [Gore 1990; Pujade-Lauraine 2002], **the PFI imbalance resulted in patients with a significantly better prognosis entering the PLDH arm, which significantly biased OS and PFS results in favour of PLDH**.

- Following the statistical analysis plan of the trial, pre-specified key prognostic factors (including PFI) were included in the multivariate analysis. This was particularly important as differences in these prognostic factors existed in the OVA-301 study, and multivariate analysis has the advantage of adjusting for such imbalances and any associated bias or confounding it causes.

- The results of the multivariate analysis demonstrated a statistically and clinically significant improvement in both PFS and OS in favour of trabectedin plus PLDH. Whereas results without adjustment using multivariate analysis demonstrated a statistically and clinically significant improvement in PFS, but no statistically significant improvement in OS.

- It is of particular note that statistically significant improvements in PFS and OS were observed in the partially platinum-sensitive subgroup (PFI 6-12) both with and without adjustment using multivariate analysis. The primary reason for this is that no imbalance in PFI existed in this subgroup: patients in the PLDH monotherapy arm had a similar mean PFI (8.6 months) compared to the combination arm (8.2 months) (p=0.200). Consequently, there was no significant bias or confounding due to PFI imbalances, and the effectiveness of trabectedin plus PLDH was preserved.

- Therefore, to say that the magnitude of differences observed in key prognostic factors such as PFI is unlikely to affect estimates of the relative treatment effect is a gross inaccuracy when considering the

effect of PFI in the OVA-301 study. Furthermore, to say that the trials were sufficiently clinically homogeneous to compare the clinical effectiveness of treatments is also untrue as a consequence.

- We agree with the TAG's interpretation that adjusting for baseline characteristics may be important because certain characteristics are considered to influence prognosis, and as shown by the above it can change results in OS from non-significance to significance. We also acknowledge the difficulty in using adjusted results where non adjusted results exist for other interventions.

- However, we disagree with the approach of not considering more accurate results adjusted for baseline imbalances using multivariate analysis, particularly when one has the knowledge that these results significantly affect final outcomes. It would appear that a 'consistent approach' considering a dataset without adjustments is being used in favour of a more 'accurate approach' comparing trabectedin plus PLDH vs. PLDH alone. Indeed, it is by the TAG's own admission in relation to the comparison of trabectedin plus PLDH vs. PLDH alone, that:

  "Adjustment of clinical-effectiveness data for key prognostic factors was likely to result in more accurate estimates of progression-free survival and overall survival" [ACD 2013]

  This is of crucial importance when considering that the QALY league table produced by the TAG, which suggests the most relevant comparison (based on ranking by QALYs) for trabectedin plus PLDH, is against PLDH alone. Consequently, the need to compare trabectedin plus PLDH vs. paclitaxel and topotecan, and preserving a consistent dataset is of significantly less importance compared to an accurate comparison vs. PLDH alone.

- Finally, PharmaMar recall that clinical specialists disagreed with the approach of using unadjusted results. It was drawn to the attention of NICE during the AC meeting that because results did not consider the number of lines of previous chemotherapy nor the PFI within trials or between treatment arms, unadjusted results were likely to be biased and confounded in many ways. Consequently, clinical specialists stated a preference for adjusted results to account for heterogeneity and imbalances between and within trials included in the network meta-analysis. Thus, not accounting for biases and confounding caused by PFI contradicts the fact that NICE make recommendations based on PFI (platinum-sensitive, partially platinum-sensitive, and platinum-resistant) [NICE TA91 2005].

- To summarise, PharmaMar understand the TAG's position in that it is difficult to justify adjusting for results in some instances but not others. However, we suggest that all is done to ensure the most accurate analyses are used in the base case analysis – could efforts have been made to obtain patient level data from trial authors for example? Where baseline imbalances in prognostic factors such as PFI are unknown or patient level data is unavailable to adjust for imbalances, the TAG can only reasonably assume that unadjusted results are the most reliable for the purposes of their evaluation. However, to purposely ignore results that by their own admission are more accurate estimates of PFS and OS, compared to the most relevant comparator in PLDH, represents a perverse conclusion, which will adversely impact patient access to trabectedin plus PLDH.

Issue 2: Bias and confounding caused by using unadjusted results from the network meta-analysis in the cost-effectiveness analysis

Relevant quotes from the ACD

- Page 35: *"The Committee carefully considered the manufacturer's post hoc adjustment of the treatment effects, which resulted in the non-statistically significant overall survival benefit reported for the platinum-sensitive population in the trial becoming statistically significant. The Committee agreed that adjustment of the treatment effect for imbalances in platinum-free interval (a major prognostic indicator) between treatment arms was a new concept and an interesting approach, and more precise stratification in respect of platinum-free interval might be considered in future trials. However, the Committee noted that this was an unvalidated retrospective approach in ovarian cancer trials. It also noted that the Assessment Group had incorporated unadjusted effect estimates for all the comparisons in the analyses, and without similar data being available from other trials for comparison it was not possible to accept the cost-effectiveness analyses based on these adjusted results. The Committee noted that the OVA-301 trial included only women with a first recurrence of ovarian cancer and no clinical effectiveness evidence for trabectedin was available for subsequent recurrences. The Committee concluded that trabectedin plus PLDH could not be considered a cost-effective uses of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer."*

PharmaMar's response

- We would like to draw attention to the NICE Decision Support Unit (DSU) guidance for conducting survival analysis:

  "Ideally, patient-level data from relevant external data sources should be obtained so that regression analysis can be completed to allow survival to be estimated ***adjusting for the characteristics of the patients included in the clinical trial of interest – thus correcting for any patient population differences which may be present between different clinical trials.****" [DSU 2011]*

  Although this relates to the provision of external data, the premise of adjusting for characteristics where important differences exist in clinical trials is an important one, as this is precisely what was conducted by PharmaMar with regards to the adjustment of covariates (PFI, CA-125 and ECOG performance score) in OVA-301 survival analyses. It would therefore appear that using unadjusted results in survival analysis as part of the cost-effectiveness analysis is at odds with the guidance NICE's DSU has issued for survival analysis. Indeed, it would appear that PharmaMar's approach to adjusting for covariates is more aligned to what NICE would recommend in this regard. Whilst PharmaMar acknowledge that adjustment for covariates may not be necessary in all trials since randomisation should result in balanced baseline characteristics, due to the problematic nature of stratification based on PFI (which is acknowledged by NICE in the ACD) an important imbalance was observed which could not be prevented by randomisation in OVA-301.

- The method of adjustment allows for coefficients to be derived for specified covariates within each survival curve, and consequently the covariates relative impact on predicting survival. The adjustment occurs in the calculation of survival; coefficients are multiplied by the covariate mean across both arms within the trial as opposed to arm-specific means within the trial. This method (like multivariate analysis) removes the effect of bias or confounding caused by imbalances in the covariates.

- Furthermore, NICE has set a precedent in accepting approaches within cost-effectiveness analyses which adjust for baseline characteristics. During TA185, which appraised trabectedin for the treatment of soft tissue sarcoma, at the request of the ERG, PharmaMar submitted a revised model which adjusted for baseline characteristics within the survival curves:

  "In response to requests for clarification, the manufacturer submitted a revised model in which the survival curves were adjusted for the differences in patient characteristics between the trabectedin and BSC arms." [NICE TA185 2010]

  Subsequently, the NICE Committee and ERG considered that the methods for estimating overall survival *"appeared robust and appropriate"*, and it was utility calculations that were scrutinised during the appraisal [NICE TA185 2010].

- Importantly, the same NICE Committee appraising technologies in this MTA accepted the approach, proposed by the ERG during TA222, of retrospectively adjusting survival curves for potential covariates where imbalances existed in OVA-301:

  "Distributions were fitted to each treatment separately and adjusting for potential covariates. A rapid analysis on the data showed that there were differences in the proportion of patients with CA-125 < 2 ULN or CA-125 >= 2 ULN between the two treatment arms. Consequently, to account for the potential effect of CA-125, two types of models were constructed:

  - Either adjusting for covariates using CA-125 (categorical) as covariate
  - Without adjustment for covariates

  <u>The ERG considered that the analysis adjusting the distribution for CA-125 was the most appropriate.</u>*" [ERG Papaioannou 2010]*

- Thus, the notion that adjustment of treatment effect for imbalances in factors such as PFI is "a new concept" and an "unvalidated retrospective approach in ovarian cancer trials" is untrue. In particular, it is worrying that adjusting for covariates is acceptable in a STA of trabectedin but not a MTA including trabectedin, particularly when the same NICE Committee is chosen for both appraisals.

- One could propose that NICE have actually validated the same approach which is said to be

unvalidated in ovarian cancer trials during TA222. However, for this MTA, additional differences were found in prognostic factors in light of the final OS analysis (unavailable during TA222), importantly one of these has been the imbalance in continuous PFI.

- Table 1 shows the results of a rapid analysis (as previously considered by the ERG during TA222) on protocol-defined covariates following the final OS results of OVA-301. The analysis found differences between the treatment conditions in three explanatory variables: a 4.7 month (25%) difference in continuous PFI; a 10% difference in the proportion of patients with ECOG performance score of 2; and a 9% difference in the proportion of patients with CA-125 ≥ 2 x ULN. It is acknowledged that PFI, CA-125 and ECOG performance score are all statistically significant predictors of survival [ERG Papaioannou 2010].

Table 1: Baseline covariates by treatment arm

Treatment arm	Mean PFI	% with ECOG 2	% with CA125 >= 2x ULN	Mean Age	% White	% Asian	% Black	% Other	% with lung/liver involvement	% who have had prior taxane
Trabectedin plus PLD	14.3	31%	76%	57.0	80%	18%	1%	1%	41%	76%
PLD	19.0	41%	85%	59.0	78%	21%	1%	0%	39%	77%

- Finally, PharmaMar understand the difficulty in that similar adjusted data were unavailable from other trials for comparison, which makes it difficult to compare trabectedin plus PLDH vs. paclitaxel or topotecan using adjusted vs. unadjusted results. However, during TA222:

  "The Committee accepted that in those cases where single-agent PLDH might be selected as the most appropriate treatment in the setting of partially platinum-sensitive disease or platinum allergy, the manufacturer's comparison could be considered relevant." [NICE TA222 2010]

  "PLDH is the most clinically and cost-effective treatment within the platinum-sensitive population. As such, a direct comparison of trabectedin plus PLDH is sufficient to address the decision problem." [ERG Papaioannou 2010]

  This is further emphasised by the fact that in the base case analysis, ranking comparators by QALYs using unadjusted results, PLDH is the most relevant comparator for trabectedin plus PLDH. Indeed, the base case ICER of £85,200 is comparing trabectedin plus PLDH vs. PLDH alone. Consequently, the comparison of trabectedin plus PLDH vs. PLDH alone can be considered as the most important and appropriate comparison to determine the cost-effectiveness of trabectedin plus PLDH.

- In summary, as discussed at length, the most accurate representation of cost-effectiveness should be used for trabectedin plus PLDH vs. PLDH alone, which by the TAG's own admission is the survival analysis conducted by PharmaMar which adjusts for covariates where imbalances exist (£27,600 per QALY with PharmaMar's model and £35,000 per QALY with the TAG's model).

Issue 3: Not overcoming limitations to the cost-effectiveness analysis by exploring other plausible methods as a base case

Relevant quotes from the ACD

- Page 21-22: *"The Assessment Group noted 3 main concerns with the use of data from the network meta-analyses in the model. First, due to lack of individual patient data, the network meta-analyses synthesised data from the whole trial population. Individual patient data would have allowed for differences in baseline characteristics within and between trials to be incorporated. In addition, as discussed in section 4.1.6, unadjusted hazard ratios were incorporated, which could include potential bias. Second, using hazard ratios based on the literature assumes proportional hazards, that is, the relative treatment effects captured by the hazard ratios hold true across all time points. However, log-cumulative hazard plots indicated that this assumption may not be appropriate. The Assessment Group highlighted that where the relative hazard decreases over time for both progression-free survival and overall survival, the model is likely to overestimate the relative benefit of treatment and vice versa. Third, it was noted that several of the included trials allowed for crossover, which could have confounded overall survival data."*

PharmaMar's response

- PharmaMar would like to highlight that their methods for calculating the clinical effectiveness of trabectedin plus PLDH vs. PLDH alone, in terms of PFS and OS, overcomes the three main concerns of the Committee:
  a) Patient level data were available and differences in baseline characteristics were explored and appropriately adjusted for when necessary
  b) Adjusted results were used which reduced the potential bias caused by baseline imbalances
  c) The flawed assumption of proportional hazards was not used, and as discussed in PharmaMar's response to the TAG report, survival curves fit by treatment arm, adjusting for covariates where imbalances existed, were selected in a systematic approach aligned with NICE DSU guidelines [DSU 2011]
  d) No crossover was observed in OVA-301, making the survival analysis a clean ITT analysis

- A quote from the TAG report is quite telling, since the research proposed is exactly what PharmaMar have done as part of this appraisal. Hence, it seems contradictory for NICE to reject methods that the ERG propose as future research (e.g. multivariate analysis and adjusted survival curves).

  "Future trials in recurrent ovarian cancer should endeavour to carry out analysis on patient level data that has been adjusted for a consistent array of variables; of particular importance is the adjustment of clinical effectiveness data for platinum free interval (measured as a continuous rather than categorical variable)." [Edwards 2013]

Issue 4: Calculations for treatment cost and use of unlicensed doses

Relevant quotes from the ACD

- Page 9: *"The cost of a course of treatment of trabectedin 1.1 mg/m^2 and PLDH 30 mg/m^2 on day 1 of every 21 day cycle is £3,679."*

PharmaMar's response

- PharmaMar would like to highlight a difference between undiscounted treatment costs calculated in the TAG model (which considers adjusted OS and PFS results) compared to those calculated in the PharmaMar model (adapted to include cyclic discounting as per TAG recommendations). The cost of treatment with trabectedin plus PLDH is higher in the TAG model compared to the PharmaMar model and cost of treatment with PLDH is lower in the TAG model compared to the PharmaMar model. We investigate the reasons for these differences below.

- For trabectedin plus PLDH, the TAG model calculates the cost of a course of treatment as £3,679 without PAS and the total cost of treatment as £17,624. On the other hand, the PharmaMar model calculates the cost of a course of treatment as £3,167 without PAS and the total cost of treatment as £16,935. The reason for the difference in total cost is two-fold:
  a) The proportion of patients receiving trabectedin plus PLDH for the first 5 cycles of treatment using the TAG model is based on the number of patients alive, as calculated by OS curves. On the other hand, the proportion of patients receiving trabectedin plus PLDH for the first 5 cycles of treatment using the PharmaMar model is based on the <u>known</u> proportion of patients receiving treatment within that cycle (see Table 2). For example, only 71% of patients received 5 cycles or more with trabectedin plus PLDH whereas the TAG model estimated this to be 91% based on the OS curve (adjusting for PFI and other covariates).
  b) The cost of a course of treatment using the TAG model (£2,759 with trabectedin and £920 with PLDH) is based on licensed doses (trabectedin 1.1 mg/m^2 and PLDH 30 mg/m^2) combined with a UK samples of body surface area (BSA) to calculate cost. Average doses per cycle were 1.88 mg and 51.4 mg, average BSA was 1.71 m^2. On the other hand, the cost of a course of treatment using the PharmaMar model (£2,455 with trabectedin and £713 with PLDH) are based on <u>average doses</u> used during the OVA-301 study (trabectedin 1.00 mg/m^2 and PLDH 27.43 mg/m^2) combined with the average BSA from the trial to calculate cost. Average doses per cycle were 1.72 mg and 47.23 mg, average BSA was 1.72 m^2.

- Thus it would appear that the TAG model overestimates the proportion of patients that would receive treatment with trabectedin plus PLDH, when compared to actual data available from OVA-301. In addition, the cost of a course of treatment using the TAG model results in average doses of treatment with trabectedin (1.88 mg) and PLDH (51.4 mg) that are above those observed in the clinical trial for trabectedin (1.72 mg) and PLDH (47.23 mg), which consequently overestimates the cost of a course of treatment.

- Consequently, the total cost of treatment for trabectedin plus PLDH with the TAG model of £17,624 overestimates the true treatment cost based on observed results from OVA-301. On the other hand, the PharmaMar model estimates a more accurate total cost of £16,935.

- For PLDH alone, the TAG model calculates the cost of a course of treatment as £1,211 and the total cost of treatment as £6,545. On the other hand, the PharmaMar model calculates the cost of a course of treatment as £1,425 and the total cost of treatment as £8,077. The reason for the difference in total cost is two-fold once again:
  a) The proportion of patients receiving PLDH alone using the TAG model is based on the number of patients alive, as calculated by OS curves. On the other hand, the proportion of patients receiving PLDH alone using the PharmaMar model is based on the known proportion of patients receiving treatment within that cycle (see Table 2). For example, only 58% of patients received 5 cycles or more with PLDH alone whereas the TAG model estimated this to be 86% (when using OS adjusting for PFI and other covariates).
  b) The cost of a course of treatment using the TAG model (£1,211) is based on an **unlicensed dose (PLDH 40mg/m^2)** combined with UK samples of BSA to calculate cost. Average doses per cycle were 69.00 mg, average BSA was 1.71 m^2. On the other hand, the cost of a course of treatment using the PharmaMar model (£1,425) is based on average doses used during the OVA-301 study (PLDH 44.95 mg/m^2) combined with average BSA from the trial to calculate cost. Average doses per cycle were 77.40 mg, average BSA was 1.72 m^2.

- Thus it would appear that the TAG model overestimates the proportion of patients that would receive treatment with PLDH alone, when compared to actual data available from OVA-301. However, the cost of a course of treatment using the TAG model results in average doses of treatment with PLDH (69.00 mg) that are below those observed in the clinical trial for PLDH (77.40 mg), which consequently underestimates the cost of a course of treatment. This was primarily because an unlicensed dose to calculate the cost for PLDH was used. PharmaMar would remind NICE that using unlicensed doses should be justified if these will form part of the evidence generation for which recommendations regarding the cost-effectiveness with the licensed dose of PLDH are made.

- Consequently, the total cost of treatment for PLDH alone with the TAG model of £6,545 underestimates the true treatment cost and uses unlicensed doses within the calculation, which is outside of NICE's remit to inform decisions. On the other hand, the PharmaMar model estimates a more accurate total cost of £8,077.

- To understand the impact of assuming the drug costs as derived by PharmaMar, the TAG model was amended using the following methods:

a) Firstly, drug costs in the "Drug cost calculations" sheet were based on average doses from OVA-301 (1.00 mg/m^2 , 27.43 mg/m^2 and 44.95 mg/m^2) as opposed to licensed and unlicensed doses (1.1 mg/m^2 , 30 mg/m^2 and 40 mg/m^2).
b) Average cost per cycle with trabectedin plus PLDH and PLDH alone were £3,358 and £1,361, respectively. This was similar to the costs calculated by PharmaMar of £3,167 and £1,211 but differed due to the fact that a UK sample was used to calculate average cost per cycle as opposed to the OVA-301 trial data.
c) Secondly, drug costs in PFS in the "Engine (PLDH vs. Trab)" sheet were amended such that the proportion of patients receiving a cycle with either trabectedin plus PLDH (column T) or PLDH alone (column Q) were based on the known patient level data from the OVA-301 trial, as shown in Table 2. This replaced the method of linking receiving cycles with OS which as shown previously, inaccurately represents the data. In keeping with the TAG assumptions, up to 5 cycles were assumed with trabectedin plus PLDH and up to 6 cycles were assumed with PLDH alone.
d) The ICER comparing trabectedin plus PLDH vs. PLDH decreased from £35,646 (incremental cost = £13,506; incremental QALYs = 0.38) to **£28,599 per QALY** (incremental cost = £10,836; incremental QALYs = 0.38) over the 15 year time horizon.

- Therefore, were the TAG and NICE Committee to appropriately:
  a) Adjust for baseline imbalances within the OS and PFS survival curves
  b) Amend the probability for allergic reaction to 2% with trabectedin plus PLDH and 4% for PLDH based on hypersensitivity reactions observed in OVA-301
  c) Amend the dosing assumptions such that average doses are used instead of a combination of licensed and unlicensed doses
  d) Amend the drug cost calculations such that the proportion of patients receiving a dose are based on known patient level data and not OS survival curves

Trabectedin plus PLDH would be a cost-effective treatment option compared to PLDH alone, which as discussed is the most appropriate comparator (as it has been shown to be the most clinically and cost-effective of all other non-platinums)

Table 2: Patients receiving treatment cycles with trabectedin plus PLDH and PLDH alone

Treatment cycles	Trabectedin plus PLDH		PLDH alone	
	Frequency	% receiving at each cycle	Frequency	% receiving at each cycle
1	13	100%	16	100%
2	17	94%	36	92%
3	20	86%	13	75%
4	14	77%	22	69%
5	24	71%	19	58%
6	32	59%	42	49%

Issue 5: Time horizon for model evaluation

Relevant quotes from the ACD

- Page 19: *"The model had a lifetime time horizon, which was set as 15 years because at this point over 99.9% of patients in the model would have died."*

PharmaMar's response

- PharmaMar is concerned that an arbitrary cut off has been used to define the time horizon for which ovarian cancer patients are expected to survive. The NICE guide for technology appraisal states:

  "Many technologies have impacts on costs and outcomes over a patient's lifetime. In such instances, a lifetime time horizon for clinical and cost effectiveness is usually appropriate. A lifetime time horizon is required when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life. For a lifetime time horizon, it is often necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty. When the impact of treatment beyond the results of the clinical trials is estimated, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects using different statistical models are desirable. These should include assuming that the treatment does not provide further benefit beyond the treatment period as well as more optimistic assumptions. Analyses that limit the time horizon to periods shorter than the expected impact of treatment do not usually provide the best estimates of benefits and costs." [NICE 2013]

  Consequently, in keeping with NICE guidelines, we believe a lifetime horizon should be used.

- Although it may be the case that when results are not adjusted for covariates 99.9% of patients in the model would have died, this is certainly not the case when adjusting for covariates – which as discussed is the most accurate representation of cost-effectiveness. Indeed, at year 15 when comparing trabectedin plus PLDH vs. PLDH alone in the "Engine (PLDH vs. Trab)" sheet, 1% of patients are alive in the PLDH arm and 2% are alive in the trabectedin plus PLDH arm.

- Were a lifetime horizon adopted within the TAG model, the time horizon would be extend to the 563 months or ~47 years (since this the longest time horizon available in the TAG model). When accounting for the factors as discussed is Issue 4, the ICER decreases from £28,599 to **£27,139 per QALY** (incremental cost = £11,149; incremental QALYS = 0.41), which is very similar to the PharmaMar ICER with cyclic discounting o £28,334 (incremental cost = £11,644; incremental QALYS = 0.41).

Issue 6: End of life criteria

Relevant quotes from the ACD

- Page 37: *"The Committee was aware that the manufacturer of trabectedin had stated that using the adjusted trial results, the median life expectancy in the platinum-sensitive population was 19.4 months, and a gain in median life expectancy of 4 months was estimated with trabectedin for the platinum-sensitive and partially platinum-sensitive population. However, the Committee noted that it could not accept estimates based on adjusted results for just one of the technologies being appraised (see section 4.3.6) and that estimates from the OVA-301 trial discussed in NICE technology appraisal guidance 222 would continue to be relevant. The Committee noted that the median overall survival for people treated with PLDH in the entire platinum-sensitive population was 24.3 months and the overall survival gain was less than 3 months. The Committee concluded that trabectedin in combination with PLDH did not fulfil the criteria for being a life-extending, end-of-life treatment."*

PharmaMar's response

- PharmaMar would ask that NICE reconsider their conclusion not to accept estimates based on adjusted results for trabectedin plus PLDH (please see Issues 1-3)

- Median overall survival based on the PLDH arm of the OVA-301 study is less than 24 months in the population for which trabectedin plus PLDH is sought (platinum-sensitive ovarian cancer, unsuitable for retreatment with platinums)

- Median overall survival gain with trabectedin plus PLDH is >3 months based on the adjusted results for PFI and other covariates, as performed in the multivariate analysis of the OVA-301 study.

Issue 7: Recommendations are ambiguous and are inconsistent with the scope of the MTA

Relevant quotes from the ACD

- Page 9-10 (Section 4.1.1): *"The Assessment Group carried out a systematic review and identified 16 randomised controlled trials, evaluating 14 different pairwise comparisons that met the inclusion criteria…..…..The interventions in the trials were paclitaxel (6 trials) pegylated liposomal doxorubicin hydrochloride (PLDH), (5 trials), topotecan (3 trials) gemcitabine (1 trial) and trabectedin (1 trial). The Assessment Group stated that 5 of these trials evaluated the interventions and comparators within their licensed indications, dosage and routes of administration. The remaining 11 trials included dosages or routes of administration different from the relevant marketing authorisations. The population in 9 of the 16 trials was restricted to women experiencing a first recurrence. This included the main trials available for gemcitabine plus carboplatin and trabectedin plus PLDH, and 3 of the 4 trials for topotecan. One trial comparing weekly topotecan with 3-weekly topotecan included women with platinum-resistance experiencing subsequent recurrences."*

- Page 30-31 (Section 4.3.4): *"The clinical specialists stated that weekly paclitaxel, rather than the licensed 3-weekly paclitaxel, was established clinical practice for treating platinum-refractory or platinum-resistant disease. However, the licensed 3-weekly regimen was more often used for those with platinum-sensitive disease. The Committee was aware that the trials used 3-weekly paclitaxel. The Committee also heard that PLDH dose in practice was usually lower than in the licence, especially for combination therapy, to reduce the toxicity. However, the Committee noted that any recommendations needed to be in line with the respective marketing authorisations."*

- Appendix B - MTA scope (page 5): *"Guidance will only be issued in accordance with the marketing authorisation"*

PharmaMar's response

- The table below highlights the issues in the recommendations that require clarification with respect to the marketing authorisations particularly for paclitaxel and PLDH.

The NICE Appraisal Committee's preliminary recommendations	**Licensed indications**	**Issue for clarification**
1.1 Paclitaxel is recommended, within its marketing authorisation, as an option for treating recurrent ovarian cancer.	In second-line chemotherapy of ovarian cancer, paclitaxel is indicated in the treatment of metastatic carcinoma of the ovary after failure of standard platinum based therapy. Second-line treatment of ovarian cancer: The recommended dose of paclitaxel is 175 mg/m^2 administered over 3 hours, with a 3-week interval between courses.	Does this mean NICE is restricting use of paclitaxel to 2nd line therapy only? What dose regimen is NICE recommending? Is it 175 mg/m^2 every 3 weeks?
1.2 Pegylated liposomal doxorubicin hydrochloride (PLDH) is recommended, within its marketing authorisation, as an option for treating recurrent ovarian cancer.	For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen. Caelyx is administered intravenously at a dose of 50 mg/m^2 once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.	Does this mean NICE is restricting PLDH for 2nd line therapy only? What dose regimen is NICE recommending – is it 50 mg/m^2 every 4 weeks?
1.3 Gemcitabine in combination with carboplatin is **not** recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive ovarian cancer.	Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.	Does this mean NICE imply gemcitabine could be used for a 2nd or later recurrence?
1.4 Trabectedin in combination with PLDH is **not** recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive recurrent ovarian cancer.	Yondelis in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.	Does this mean NICE imply trabectedin could be used for a 2nd or later recurrence?

1.5 Topotecan is **not** recommended, within its marketing authorisation, for treating the first recurrence of platinum-sensitive ovarian cancer.	Topotecan monotherapy is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.	Does this mean NICE imply topotecan could be used for a 2nd or later recurrence?
1.6 Topotecan is **not** recommended, within its marketing authorisation, for treating platinum-resistant or refractory recurrent ovarian cancer.	Topotecan monotherapy is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.	
1.7 Women currently receiving gemcitabine in combination with carboplatin, topotecan, or trabectedin in combination with PLDH that is not recommended according to 1.3, 1.4, 1.5 and 1.6 should be able to continue treatment until they and their clinician consider it appropriate to stop.		

- Firstly, the recommendations appear to be based on 16 trials of which only 5 trials evaluated the drugs within their marketing authorisations. Of note, the OVA-301 study compared trabectedin plus PLDH and PLDH alone within their marketing authorisations and should be considered a more robust representation of clinical effectiveness within marketing authorisations.

- Secondly, only 7 trials included patient populations who had experienced more than 1 recurrence. Of these only 4 were in a platinum sensitive population and the proportion of patients experiencing second or higher relapse ranged from 4% to 18.4% and were overall low in number. How is this accounted for?

- It is unclear how these two factors above have been taken into consideration for the recommendations. PharmaMar is concerned that recommendations are based on evidence using dosing regimens outside of the marketing authorisation particularly for PLDH and paclitaxel. Hence the decision-making is not in line with that defined in the MTA scope and appears to have been selectively applied.

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