NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer

Response to consultee, commentator and public comments on the post-appeal Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
PharmaMar	Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) issued in November 2015 for the appraisal of topotecan, pegylated liposomal doxorubicin hydrochloride (PLDH), paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer. We, like NICE, believe it is important for patients to have a range of clinically and cost-effective treatment options for platinum-sensitive recurrent ovarian cancer. From the Appraisal Committee Meeting and resulting ACD we understand that two key concerns led to NICE rejecting results for trabectedin that adjusted for baseline imbalances: 1. The retrospective adjustment for platinum-free interval (PFI) as a continuous variable (rather than a categorical variable) was considered to be an unvalidated approach in ovarian cancer and unacceptable 2. Without similar data being available from other trials from platinum-sensitive network 2, it was not possible to accept the comparative cost-effectiveness analyses based on adjusted results Since the outcome of the appeal, new patient-level data has been identified for platinum-sensitive network 2 and additional analyses have been performed which seek to address these two concerns. Firstly, analysis has been undertaken to adjust progression-free survival (PFS) and overall survival (OS) based on categorical PFI as opposed to continuous PFI, which we feel is a validated approach in ovarian cancer, supported by the stratification of PFI in recent clinical trials and previous NICE guidance. Secondly, patient-level data has been obtained for two clinical trials in the platinum-sensitive network 2, which means that similar data is now available to perform comparative cost-effectiveness analyses based on adjusted results. Using similar data will result in PLDH remaining the most appropriate comparator for trabectedin plus PLDH. In addition, a new Patient Access Scheme (PAS) has been agreed by the Department of Health for trabectedin, which would improve the cost-effectiveness of treatment with trabectedin plus PLDH. The impact of implementing the PAS has not yet been evaluated by NICE. We believe that the evidence presented within this response is important and together with the implementation of the new PAS, would enable NICE to re-review the evidence base and find trabectedin plus PLDH to be a clinically and cost-effective treatment option for women with platinum-sensitive recurrent ovarian cancer.	Comments noted.

Consultee	Comment	Response
	Issue 1: Retrospective adjustment for platinum free interval as a continuous variable We agree that separation of results by platinum-sensitivity is clinically important because PFI is a key prognostic factor (ACD 4.24, page 21). This has been confirmed by experts during the NICE MTA (ACD 4.24, page 21; ACD 4.56, page 44) and clinical practice guidelines (Ledermann et al, 2013) for both platinum and non-platinum therapies. In particular, PFI has been shown to be a significant prognostic factor in predicting PFS and OS, with longer PFIs associated with a better prognosis (Gore et al, 1990; Pujade-Lauraine et al, 2002) Published evidence from the OVA-301 trial has further demonstrated the importance of PFI as a key prognostic factor; Monk et al, 2012 concluded that an unexpected but significant imbalance resulting in longer PFI in the PLDH arm affected the overall survival results (Monk et al, 2012). Therefore, we believe the statement "no trials have yet provided evidence to support this hypothesis for PLDH" (ACD 4.56, page 44) is factually inaccurate and suggest this is removed (see Factual Inaccuracies). We acknowledge the Committee's concerns with regards to the retrospective adjustment of survival outcomes treating PFI as a continuous variable rather than a categorical variable (ACD 4.57, page 45). Indeed, the most recent clinical trials in platinum-sensitive recurrent ovarian cancer recognise the clinical and prognostic importance of PFI, and consequently stratify by two strata: partially platinum-sensitive disease (PFI 6-12) and fully platinum-sensitive disease (PFI >12) (Aghajanian et al, 2012; Pujade-Lauraine, 2010). Furthermore, NICE has acknowledged the importance of platinum-sensitivity strata and has recommended treatments in platinum resistant disease, partially platinum-sensitive disease and platinum-sensitive disease in previous technology appraisals (NICE TA91, 2005). Therefore, in line with recent clinical trials and NICE's feedback, we conducted an analysis which retrospectively adjusted survival outcomes treating PFI as a categorical variable rather than a continuous variable. Since trabectedin plus PLDH is only licensed in platinum-sensitive disease, the analysis followed the stratification procedure adopted by recent clinical trials and categorised platinum-sensitive patients into 1) partially platinum-sensitive disease: PFI 6-12 and 2) fully platinum-sensitive disease: PFI >12. Table 1 in the company's response shows the baseline characteristics of patients in the two platinum-sensitive strata treated with trabectedin plus PLDH and PLDH alone. Mean PFI was balanced in the partially platinum-sensitive group but there was a 3.8 month (17%) difference favouring PLDH in the fully platinum-sensitive group. In addition, fully platinum-sensitive patients were older in the PLDH group (59.6 years) compared to the trabectedin plus PLDH group (56 years). Differences were also observed for CA-125 and ECOG status across the two strata. These notable imbalances indicate that adjusting PFS and OS by categorical PFI strata (6-12 months and >12 months) is warranted.	The Committee carefully considered the additional analyses for trabectedin plus PLDH compared with PLDH alone, and the comments received from the company for trabectedin during consultation on the post-appeal appraisal consultation document, see FAD sections 4.20-4.22. The Committee concluded that the retrospectively adjusted results did not provide a more robust estimate of the clinical effectiveness of trabectedin plus PLDH than the unadjusted results from the properly conducted and randomized OVA-301 trial which had been incorporated into the Assessment Group's network meta-analysis – see FAD section 4.20.

Consultee	Comment	Response
	Figures 1-2 in the company's response show the results of specifying PFI as a categorical (6-12 months and >12 months) covariate and a continuous covariate in Cox regression analyses when comparing the effect of treatment with trabectedin plus PLDH versus PLDH alone for PFS and OS. Whilst the significant effect of trabectedin plus PLDH versus PLDH alone on PFS was maintained across all Cox models with or without adjustment for PFI, the hazard ratio improved markedly when either categorical or continuous PFI were treated as a covariate. When categorical or continuous PFI were considered as covariates in the Cox models, trabectedin plus PLDH was shown to have a significant effect on OS versus PLDH alone, and the hazard ratios improved substantially. This significant effect was maintained when additional covariates were included in the Cox models. The analysis shows the significant impact of PFI on the PFS and OS results for trabectedin plus PLDH versus PLDH alone; marginal differences were seen whether PFI was specified as a continuous or categorical covariate. Due to the observed imbalances by platinum-sensitivity strata (Table 1) and the impact on survival by specifying categorical PFI as a covariate in Cox models (Figures 1-2), the cost-effectiveness analyses were updated to include the adjustment for PFI specified as a categorical variable (rather than a continuous variable). Both the PharmaMar and TAG models were updated. The PharmaMar model was updated such that mean PFS and OS for platinum-sensitive patients were calculated based on parametric survival distributions adjusted for categorical PFI (6-12 months and >12 months), ECOG performance score (0-1 or 2) and CA-125 (< 2 x upper limit of normal (ULN) or ≥ 2 x ULN). Whilst ECOG performance score was a pre-specified stratification factor in the OVA-301 trial, CA-125 and categorical PFI (6-12 months and > 12 months) were not pre-specified at randomisation. We noted that the Evidence Review Group (ERG) of TA222 found it appropriate to adjust for CA-125 retrospectively once the imbalance was observed (ScHARR 2010); this is in line with NICE Decision Support Unit (DSU) guidance (Latimer 2013). However, since the imbalances observed in mean PFI were not known during TA222, these were not adjusted for during TA222. Given that we and NICE are now aware of the PFI imbalance, we believe the same principle of adjusting for CA-125 can be justified for categorical PFI (6-12 months and > 12 months) since both variables are clinically important prognostic factors, measured by experts and used in clinical trials for platinum-sensitive ovarian cancer. Indeed, NICE have also recognised the importance of separating PFI by categorical strata within platinum-sensitive disease (NICE TA91, 2005).	

Consultee	Comment	Response
	The Weibull distribution for PFS and Log-logistic distribution for OS remained the most clinically plausible and best-fitting distributions. As shown in Figures 3-5, the adjusted results considering categorical PFI were similar to the adjusted results considering continuous PFI, whilst results not adjusting for PFI were substantially more favourable for PLDH. • With the adjustment for categorical PFI (Figure 3), mean PFS was 11.19 months with trabectedin plus PLDH and 8.28 months with PLDH alone, suggesting an incremental improvement in PFS of 2.92 months with trabectedin plus PLDH. Mean OS was 45.03 months with trabectedin plus PLDH and 36.68 months with PLDH alone, suggesting an incremental improvement in OS of 8.36 months with trabectedin plus PLDH. • With the adjustment for continuous PFI (Figure 4) results were slightly more favourable for trabectedin plus PLDH; improvement in PFS and OS were 3.00 months and 9.72 months. • Without any adjustment for PFI, but maintaining the adjustments for ECOG performance score and CA-125 (Figure 5), improvement in PFS reduced to 2.45 months whilst improvement in OS reduced dramatically to 2.72 months. Of interest, results for mean PFS and OS with trabectedin plus PLDH were similar with and without adjustment for PFI (Figures 3-5); the largest difference was the change in OS for PLDH alone; PLDH patients survived for at least 5 months longer when PFI was not adjusted for. When considering the goodness of fit criteria, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), results were significantly worse fitting when PFI was not adjusted for as a categorical or continuous variable (Figures 3-5). Visual inspection of the curves was also less plausible without adjustment for PFI. Hence, not accounting for the PFI imbalance (either as a continuous or categorical variable) in the fitting of parametric curves is statistically inappropriate and would significantly underestimate the incremental benefit of treatment with trabectedin plus PLDH compared to PLDH alone for PFS and OS. We therefore challenge the statement that the OS benefit with trabectedin plus PLDH lacks credibility when considering adjustments for PFI (ACD, 4.58 Pages 45-46). We have shown that when PFI is not adjusted for, incremental improvement in OS for trabectedin plus PLDH vs. PLDH alone is similar whether considering our approach fitting parametric survival curves to patient level data (2.72 months) or the TAG's approach using unadjusted hazard ratios from a network meta-analysis (2.9 months). However, we have also shown that not accounting for the PFI imbalance is statistically inappropriate because it leads to worse fitting parametric survival curves that are visually and clinically less plausible than when PFI is adjusted for (Figures 3-5).	

Consultee	Comment	Response
	The limitations of unadjusted HRs are well documented (ACD 4.25, Page 22) and given the similar results to our approach the TAG model survival outcomes have the same inaccuracies. The magnitude of benefit observed in OS considering adjustments for PFI relative to the magnitude of benefit observed in PFS is clinically plausible when considering the significant increase in the number of active agents in ovarian cancer over the last two decades that has led to a dilution in the correlation between PFS and OS (Herzog et al, 2014). Marksman et al. found significantly different results for carboplatin plus gemcitabine when considering two independent studies separated in their conduct by approximately 8 years; median PFS remained unchanged whilst median OS almost doubled [PFS 8.6 months vs. 8.4 months; OS 18.0 months vs. 35.2 months] (Marksman, 2013). The reason for this substantial increase in OS was considered to be the influence of subsequent therapies on a patient's survival (Marksman, 2013). Therefore, by preserving PFS by 2.92 months, patients treated with trabectedin plus PLDH are able to benefit more from subsequent treatments which explains why an incremental benefit of 8.36 months is plausible. Indeed, the ratio of OS to PFS times from trials involving ovarian cancer patients who appear sensitive to chemotherapy range from 2.5 to 4:1 (Herzog et al, 2014). In the case of trabectedin plus PLDH and PLDH alone, the OS to PFS ratio for each treatment is 4:1 when considering the adjustment for PFI (Figure 3-4); falling in a clinically plausible range. When PFI is not adjusted for, the ratio for PLDH becomes almost 5:1 (Figure 5). Hence, it appears that the OS benefit placed on PLDH without adjusting for PFI lacks credibility as opposed to the incremental benefit of trabectedin plus PLDH. We suggest NICE account for this when evaluating results of the PharmaMar and TAG models with adjustments for PFI. The cost-effectiveness results were updated with the parametric curves adjusted for categorical PFI (6-12 months and >12 months). Under the new PAS accepted by the Department of Health, the deterministic base case ICER of £28,573 was higher than that originally submitted by PharmaMar (£27,572), since the adjustment for categorical PFI was slightly less favourable than the adjustment for continuous PFI. The TAG model sensitivity analysis considering the adjusted results for trabectedin plus PLDH and PLDH was updated. The parametric curves adjusting for categorical PFI (6-12 months and >12 months), ECOG performance score (0-1 or 2) and CA-125 (< 2 x upper limit of normal (ULN) or ≥ 2 x ULN) were used rather than the parametric curves adjusting for continuous PFI, ECOG performance score and CA-125. Similarly to the PharmaMar model, under the new PAS accepted by the Department of Health, the deterministic base case ICER of £32,348 was higher than that calculated using PFI as a continuous variable (£32,289). However, the ICER reduced to £24,341 with 1) use of average doses from the OVA-301 trial as opposed to doses used in clinical practice 2) drug and administration costs based on actual proportions of patients receiving treatment whilst progression-free from OVA-301.	

Consultee	Comment	Response
	Therefore, when adjusting for categorical PFI as opposed to continuous PFI, trabectedin plus PLDH was cost-effective when considering the new PAS in both the PharmaMar and TAG models. To summarise, given NICE's concern regarding the unvalidated retrospective adjustment of results using continuous PFI, we conducted an analysis which adjusted results using categorical PFI; this has been accepted by experts and NICE as a key clinical prognostic factor and for this reason, remains a stratification factor in clinical trials for platinum-sensitive recurrent ovarian cancer. Evaluation of baseline characteristics by platinum-sensitivity strata found that there were imbalances in mean PFI for patients with fully platinum-sensitive disease, but not partially platinum-sensitive disease. Based on results adjusted for categorical PFI (6-12 months vs. >12 months), trabectedin plus PLDH was found to significantly improve OS and PFS, and was also found to be cost-effective considering either the PharmaMar or TAG models. ***Issue 2: Patient level data unavailable for other trials in the PS network 2 resulting in rejection of cost-effectiveness analyses based on adjusted results*** New patient-level data has recently been obtained for two clinical trials in the platinum-sensitive network 2, Study 30-49 (Gordon et al, 2001) and Study 30-57 (NICE TA91, 2005), from a free source called Project Data Sphere (www.projectdatasphere.org): Study 30-49 (Gordon et al, 2001) is a randomised controlled study comparing PLDH 50 mg/m2 as a 1-hour infusion every 4 weeks (N=239) with topotecan 1.5 mg/m2/day for 5 consecutive days every 3 weeks (N=235) Study 30-57 (NICE TA91, 2005) is a randomised controlled study comparing PLDH 50 mg/m2 every 28 days (N=109) with paclitaxel 175 mg/m2 as a 3-hour infusion every 21 days (N=108) In light of this new evidence, patient-level data would now be available for trabectedin plus PLDH, PLDH, paclitaxel and topotecan; all interventions under evaluation in platinum-sensitive network 2. Inclusion of this new data into the MTA could allow for a consistent approach using adjusted survival data as opposed to unadjusted hazard ratios when evaluating cost-effectiveness of treatments in platinum-sensitive network 2. This would improve the overall accuracy of cost-effectiveness results, as adjusting for baseline imbalances was recognised as important by the TAG (ACD 4.5, Page 13) and shown to be important through Issue 1. In addition, using the new data for the platinum-sensitive network 2 would address two of three concerns raised by the TAG regarding the use of network meta-analysis in the cost-effectiveness analysis since differences in baseline characteristics could be adjusted for, and proportional hazards would no longer be required:	The Committee was aware of the limitations of the Assessment Group's network meta-analysis, including the differences in baseline characteristics between trials, but it agreed on balance that the Assessment Group's approach was reasonable given the data available, and accepted the clinical-effectiveness results from the network meta-analyses (see FAD section 4.5).

Consultee	Comment	Response
	1. Individual patient data would have allowed for differences in baseline characteristics within and between trials to be incorporated. In addition, as discussed in section 4.5, unadjusted hazard ratios were incorporated, which could include potential bias (ACD 4.25, Page 22). 2. 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 (ACD 4.25, Page 22). We understand that this new data has not been accounted for within the MTA, and in any case will still lead to the situation where PLDH remains the most appropriate comparator trabectedin plus PLDH should be compared to, as concluded by QALY league table with unadjusted results from the TAG report of this MTA (Edwards 2013, Table 142) and the ERG of TA222: *"PLDH is the most clinically and cost-effective treatment within the platinum-sensitive population. As PLDH is the recommended second-line therapy, and trabectedin plus PLDH cannot be used where PLDH is contraindicated, the relative cost-effectiveness of trabectedin plus PLDH compared to paclitaxel or topotecan monotherapy is not needed, since there would never be a choice between these interventions. As such, a direct comparison of trabectedin plus PLDH is sufficient to address the decision problem." (ScHARR 2010)* In all cases, unadjusted/ adjusted / with new data, PLDH is the appropriate comparator for which costs and QALYs should be compared to trabectedin plus PLDH. Hence, the DSU guidelines which recommend adjustments for baseline imbalances on head-to-head comparisons in which patient-level data are available and where evidence synthesis between trials is not required, should be adhered to (ACD 4.53, Page 43). Communicating this situation with NICE, we understand that there is an option to evaluate trabectedin plus PLDH outside of this MTA, as the conclusions for other treatment options will not change in light of this new data. We would welcome this option, as we appreciate that it is difficult to apply a different (but more accurate) methodology to trabectedin plus PLDH vs. PLDH alone, compared to other treatments. We ask NICE to provide information on the process and timelines for this assessment.	

Consultee	Comment	Response
	Issue 3: Use of doses used in clinical practice as opposed to average doses from the clinical trials in the cost-effectiveness analysis We acknowledge the challenge of choosing whether to base drug costs on licensed doses, doses used in clinical practice, or average doses from the clinical trials for the cost-effectiveness analysis. However, we are concerned with the assumption of calculating drug costs based on lower doses used in clinical practice (ACD 4.50, Pages 39-40) without altering the effectiveness of treatment, which has been demonstrated with much higher doses in clinical trials. We understand the decision to adopt this approach was based on reassurances from clinicians that the effectiveness of treatments remain unchanged between higher or lower doses. However, we note from the NICE Committee Meeting that the reasons for using lower doses in clinical practice are primarily to avoid adverse events and toxicities associated with higher doses. We agree that licensed doses allow for dose reductions in the case of toxicities (ACD 4.50, Pages 39-40) and therefore may over-estimate the drug costs compared to clinical practice. However, for licensed doses used in clinical trials, the average dose across these trials would be a more scientific real-world expectation for actual doses used in clinical practice as opposed to estimation by expert opinion, considering that dose reductions are allowed in clinical trials. Without a randomised controlled trial to confirm the hypothesis that effectiveness remains unchanged with higher or lower doses, the potential to over-estimate the benefit of lower-dose treatment is concerning. Expert opinion is generally not accepted by NICE as robust evidence to inform the relative effectiveness of treatments, and is considered the lowest form of evidence in the hierarchy of study designs to assess the effects of interventions (CRD 2008). We disagree with how the costs and effects have been applied for PLDH in the cost-effectiveness analysis of platinum-sensitive network 2. Other than expert opinion, there is no study evidence to suggest the effectiveness of the dose used in clinical practice (40mg/day) is the same as the licensed dose of (50mg/day) or the average dose observed in the OVA-301 trial (44.95mg/day). Therefore, in assuming the dose used in clinical practice (40mg/day) has the same effectiveness as the average dose used in the OVA-301 trial (44.95 mg/day), the benefits of treatment with PLDH alone have been over-estimated.	Comments noted. The Committee was aware that the company had reiterated its concern that cost estimates were based on doses used in clinical practice instead of average doses from the clinical trials. However, the Committee maintained its view that this was appropriate because average doses were not uniformly available, and doses used in clinical practice are both generally agreed and consistent, and most relevant to the NHS. Furthermore, it acknowledged that accounting for this had a minimal impact on the ICER. See FAD sections 4.22 and 4.8.

Consultee	Comment	Response
	We disagree with how the costs and effects have been applied for trabectedin plus PLDH in the cost-effectiveness analysis of platinum-sensitive network 2. The licensed dose of trabectedin (1.1mg/day) is assumed to be the same as the dose used in clinical practice (1.1mg/day). However, effectiveness is based on one clinical trial (OVA-301), where patients received an average dose of 1.0mg/day due to patients discontinuing treatment and dose interruptions due to adverse events. The dose used in clinical practice is expected to be the same as the average dose taken in the clinical trial; assuming no dose discontinuations, interruptions or modifications of treatment is highly optimistic. Similarly, the combination treatment, PLDH, is licensed for use with trabectedin at 30mg/day and this is assumed to be the same dose as used in clinical practice. The average dose actually used in OVA-301 was 27.43mg/day. Therefore, in assuming the dose used in clinical practice with no discontinuations or dose modifications (1.1mg/day: trabectedin, 30mg/day: PLDH) has the same effectiveness as the average dose used in the OVA-301 trial (1.0 mg/day: trabectedin; 27.43mg/day: PLDH), the benefits of treatment with trabectedin plus have been under-estimated. With the aforementioned reasons discussed in Issues 1-2, there is the opportunity to assess the costs and effects of trabectedin plus PLDH versus PLDH alone considering the effectiveness from the OVA-301 trial, with adjustments made for categorical PFI, CA-125 and ECOG performance score. When considering effectiveness based on the OVA-301 trial, costs should also reflect the average dose received in the trial, to ensure there is no over and under-estimation of costs or benefits. This is in line with the approach adopted by the ERG in TA222 (TAG 222; ScHARR 2010). The PharmaMar model accounts for the average doses received in the OVA-301 trial, and the corresponding ICER when adjusting for categorical PFI, ECOG performance score and CA-125 was £28,573 with the new PAS accepted by the Department of Health. When the TAG model sensitivity analysis considering adjusted results was updated to: 1) include PFI as a categorical (rather than continuous) variable and 2) determine drug costs based on average doses received in the OVA-301 trial, the corresponding ICER was £29,323 with the new PAS accepted by the Department of Health.	

Consultee	Comment	Response
	Issue 4: Use of PFS as opposed to proportion of patients on treatment to determine treatment and administration costs for trabectedin and PLDH The PharmaMar model accounts for the average number of treatment cycles received for trabectedin plus PLDH and PLDH alone in the OVA-301 trial. The corresponding ICER when adjusting for categorical PFI, ECOG performance score and CA-125 was £28,573 with the new PAS accepted by the Department of Health. For the TAG model sensitivity analysis considering adjusted results for trabectedin plus PLDH and PLDH alone, the proportions of patients receiving treatment are based on the exact proportions of patients residing in the stable state, determined by the adjusted PFS curves. However, evidence from the OVA-301 trial suggests that the proportions of patients receiving treatment are less than the proportions of patients without progression or death (Table 2). This makes clinical sense as some patients will discontinue treatment, whilst others may have dose interruptions/modifications due to adverse events. The TAG model sensitivity analysis considering adjusted results was updated to: 1) include PFI as a categorical (rather than continuous) variable 2) determine treatment costs based on average doses received in the OVA-301 trial, and 3) calculate drug and administration costs based on the actual proportions of patients receiving treatment whilst progression-free from the OVA-301 trial. The corresponding ICER was £28,691 with the new PAS accepted by the Department of Health. Furthermore, in the event that clinical practice is in line with the results from Table 2, patients receive trabectedin plus PLDH and PLDH for more than 6 treatment cycles. If drug and administration costs are updated based on the actual proportion receiving treatment from the OVA-301 trial, effectively removing the cap on 6 treatment cycles (Edwards 2013), the corresponding ICER was £24,341 with the new PAS accepted by the Department of Health. The ICER of £24,341 is the most representative base case ICER comparing trabectedin plus PLDH with PLDH alone using the TAG model because effectiveness (adjusting for categorical PFI) and treatment costs are based on the effects, dosing and persistence observed in the OVA-301 trial.	The Committee acknowledged that the company had reiterated this concern, but that accounting for this had a minimal impact on the ICER. See FAD section 4.22.

Consultee	Comment	Response
	As shown in Issues 1-4, implementation of the new PAS agreed with the Department of Health would improve the cost-effectiveness of treatment with trabectedin plus PLDH to an extent that would make trabectedin plus PLDH a cost-effective use of NHS resources. The new PAS has not been accounted for in the current ACD (ACD 3.14, Page 10) and should be evaluated in the near-future for trabectedin plus PLDH either within this MTA or separately from the MTA (see Issue 2). Table 3 summarises the ICERs incorporating the comments from Issues stated in 1-5.	The cost-effectiveness results based on the updated patient access scheme were taken into account by the Committee, see FAD sections 4.21-4.22. Trabectedin plus PLDH was not considered to be cost-effective because the Committee did not accept the company's retrospective adjustment of the platinum-free interval.
Department of Health	A 'no comment' response was submitted	Noted.
Royal College of Nurses	A 'no comment' response was submitted	Noted.

Comments received from commentators

Commentator	Comment	Response
Healthcare Improvement Scotland, Consultant Clinical Oncologist 1	They have not included the SAPPROC study. Although it does not compare between the agents in the appraisal it is a randomised study of weekly paclitaxel +/- saracatanib in platinum resistant recurrent ovarian cancer and therefore gives data on response, PFS and OS for weekly paclitaxel 80mg/m2. (A randomised placebo-controlled trial of weekly paclitaxel and saracatinib (AZD0530) in platinum-resistant ovarian, fallopian tube or primary peritoneal cancer I.A. McNeish et al Annals of Oncology 2014.) I do not think this would change the conclusions significantly but would support the inclusion of the unlicensed dose and schedule that is in routine clinical use. They have not considered the use of dose dense platinum regimens in the platinum resistant setting. They have not included any data from trials including bevacizumab. I understand that bevacizumab was not included in this analysis but nevertheless I think it needs to be noted in the discussion that the combination of bevacizumab/carboplatin/gemcitabine has improved PFS over carboplatin/gemcitabine and at present this is the only licensed combination that includes bevacizumab**.** In the platinum resistant setting they have not considered the Aurelia trial which showed improved PFS with the addition of bevacizumab to PLDH, Weekly paclitaxel or weekly topotecan. This is more relevant since it has been approved by the SMC for use in the first line treatment of platinum resistant disease. In Scotland women with platinum sensitive relapse will receive combination platinum based therapy where their performance status allows and after discussion, they accept the increased toxicity. The choice of combination depends on prior toxicities and co-morbidities. Not all centres have access to carboplatin/PLD on their formularies, although individual requests can be made, so in these centres carboplatin/paclitaxel is standard therapy but where carboplatin/PLD is available this may be standard based on the CALYPSO trial. Women with hypersensitivity to paclitaxel or persistant neuropathy may be treated with carboplatin and gemcitabine. As a result I am not clear that it is appropriate to use single agent carboplatin as the comparator in the cost-effectiveness analysis but overall would be happy with the conclusion that now includes carbo/PLDH as well as carboplatin/paclitaxel.	Comments noted. All studies that met the inclusion criteria at the time of the review were included.

Commentator	Comment	Response
	One concern remains that there is a variation in the baseline characteristics of the trials included. The RR, PFS and OS is likely to be lower in trials that include patients beyond 1st relapse compared to 1st relapse only. The time to progression following last platinum is a very important prognostic factor but it is a continuous variable and the way that progression is defined eg clinical symptoms, CA125 criteria or RECIST will affect the prognosis of the group included in the trial as progression by CA125 may occur many months before clinical or radiological progression. Prior therapy is also important hence one reason why an overall survival advantage might not have been seen in the carboplatin/gemcitabine v carboplatin where it was seen in the ICON 4 study of carboplatin/paclitaxel v carboplatin is that in ICON 4, the majority of patients had not received prior taxane where as in the gemcitabine study they had received prior taxane and might therefore have had more resistant disease. I am not familiar with the methodology of network analyses but as I understand it they have not compared platinum based and non platinum based therapies in the platinum sensitive group. This would be very interesting as an important question is whether PLDH/trabectadin is as effective as PLDH/carboplatin. This is the subject of an ongoing randomised trial but in the absence of this data this would be a useful comparison. This is particularly important for patients with platinum sensitive disease who are platinum allergic. At present the recommendation is for the use of PLDH or paclitaxel alone in this group as trabectadin/PLDH was not cost effective compared to single agent PLDH but really for this group the comparator should be a platinum/combination ie if using a platinum combination as the comparator, which of PLDH, paclitaxel or trabectadin+PLDH is better for women who cannot receive platinum?	Comments noted. The Committee discussed the limitations of the Assessment Group's network meta-analysis including the differences in baseline characteristics between trials, see the FAD section 4.5.
	Overall I think the conclusions are sound but would like to see the option for carbo/gemcitabine for those where PLDH/carbo or paclitaxel/carbo is not appropriate: eg taxane sensitivity or neuropathy where PLDH cannot be given eg due to cardiac history or prior exposure to anthracyclnes in any guidelines based on this appraisal.	The Committee's discussion of the cost effectiveness of gemcitabine is outlined in sections 4.8-4.10 of the FAD.

Commentator	Comment	Response
	Q Are the patient pathways and treatment options described in the assessment applicable to NHSScotland. If not, how do they differ in Scotland? There are some differences in Scotland compared to England. Carboplatin/PLD is not routinely available in all centres for platinum sensitive treatment. Carboplatin/gemcitabine/bevacizumab is not available in Scotland. It was previously available in England via the Cancer Drug Fund but this has now been removed from the CDF, however bevacizumab is available in combination with weekly paclitaxel (approved by the SMC) for the treatment of first relapse in platinum resistant disease and this needs to be taken in account in any guidelines. **Q Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.** I do not think there would be a significant change to current practice in Scotland for the first line treatment of platinum sensitive relapse as this broadly follows clinical practice. It may increase the use of carboplatin/PLDH compared to carboplatin/paclitaxel, where this has not been routinely available**.** In platinum resistant disease women may now receive weekly paclitaxel plus bevacizumab (see above). It is important to emphasise that this is only guidance for first relapse. Clinical judgement must be allowed in subsequent lines of therapy as there is very limited evidence to support practice but nevertheless a clinical need for subsequent lines of therapy and these should not be restricted on the basis of this guidance. **Q Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.** No apart from that in platinum resistant disease women may now receive weekly paclitaxel plus bevacizumab (see above).	Comments noted.

Commentator	Comment	Response
Healthcare Improvement Scotland, Consultant Clinical Oncologist 2	The management of relapsed ovarian cancer has changed considerably over the past 20 years evolving from single agent carboplatin to platinum-based combinations for platinum sensitive disease whereas the use of platinum alone is reserved for those less fit all with poor performance status. In platinum resistant disease non-platinum agents such as liposomal doxorubicin and weekly paclitaxel are more commonly used. The recent recognition that bevacizumab improves the year progression free survival is probably come to late for this consideration. For platinum sensitive disease for many years carboplatin and paclitaxel was the standard of care but the Calypso study showed a noninferiority for carboplatin and liposomal doxorubicin hence it has generally replaced the former regime is the standard of care particularly if there is persisting neuropathy or other toxicity. Carboplatin and gemcitabine is also an important invaluable alternative schedule particularly in those with hypersensitivity and form the backbone of a number of studies including Oceans. We would therefore challenge the view that gemcitabine should not be used for ovarian cancer relapse. It is worth pointing out that grossly all clinicians use Caelyx at a dose of 40 mg/m² rather than the licensed 50 mg/m² . These alternative schedule should be approved for use and certainly on the formulary for the West of Scotland. Clinician should be given licensed to use which ever of the 3 regimes they feel most appropriate in platinum sensitive disease taking into account the previous schedules and current toxicities. Withdrawal of the approval of topotecan is relatively little consequence since it is rarely used, trabectedin is still being investigated although some important new data suggest that it may be more useful in patients known to have a BRCA mutation. New data will emerge over the course of the next few years but there is a reasonable case to consider its use in platinum' partially sensitive disease in the 6-12 month window. However there are ongoing trials such as INNOVATYON which are addressing this and will provide further information in due course.	Comments noted. The Committee reconsidered the clinical and cost effectiveness results for gemcitabine, but it concluded that on the basis of the evidence it could not be considered a cost-effective option for the first recurrence of relapsed ovarian cancer, see FAD section 4.8-4.10.

Commentator	Comment	Response
	Over the course of the past 10 years most of these drugs have become generic in the cost of dramatically reduced therefore affecting the value for money and cost effectiveness her calculations furthermore Caelyx is used at a dose 20% less in the manufacturers licensed schedule. Many patients receiving gemcitabine will also finish up with dose reductions which will lead to a lower cost. The summaries do not take into account changes in clinical usage in practice, the availability of generic combinations and relative reductions in the price of the drugs For the reasons given above, I believe that there is flawed interpretation of the data and that the recommendations are too restrictive. These drugs are prescribed by a limited number of clinicians experienced in the treatment of gynaecological cancers and who behaves very responsibly and are aware of many of the issues regarding cost effectiveness. Evidence from clinical practice in Scotland would support responsible prescribing by the oncology community **Q Are the patient pathways and treatment options described in the assessment applicable to NHSScotland. If not, how do they differ in Scotland?** There are clear pathways for prescribing of these drugs by the 3 cancer network's in Scotland and there is remarkable concord between them. Clinicians will often determine which schedule is used dependent on prior toxicity and patient's performance status and it is essential that some flexibility is retained to allow clinicians to adapt treatment according to these predictive factors. The CMGs reflect this and it is hoped that this flexibility will be continued. **Q Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.** Some of the restrictions would have potential negative effects particularly if it was insisted that we used the higher dose of Caelyx which is associated with higher toxicity as well as unnecessarily higher cost. Restriction on the use of gemcitabine would affect some clinical trials were carboplatin and gemcitabine is the standard of choice but would also affect patients with pre-existing neuropathy or hypersensitivity who were unsuitable treatment with paclitaxel. Withdrawal of topotecan will another very minor effect since there its use has been very limited in the past few years. Weekly paclitaxel has relatively little evidence base to support it from large randomised trials but again it is become the backbone of treatment particularly in platinum resistant cases and refractory disease at a later stage although this is outwith the considerations of the document.	Comments noted. The Committee's considerations regarding the cost-effectiveness of gemcitabine are in outlined in sections 4.8-4.10 of the FAD.

Commentator	Comment	Response
	Q Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. I think most of these are being covered by the points raised above **Q Please add any other information which you think would be useful to the Appraisal Committee, or helpful to us in guiding the Scottish response to this assessment.** It is important that the responsibility of the oncology community who treat ovarian cancer is recognised. We will all work within carefully scripted CMGs which have been approved by the 3 Scottish networks which represent multidisciplinary working groups. These are carefully controlled and not abused. Virtually all of the drugs discussing this document are now generic and cost saving have substantially increased over the course of the past decade.	Comments noted
Roche	A 'no comment' response was submitted	Noted.