NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

PharmaMar response to the Appraisal Consultation Document issued November 2015

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]

December 2015

FOREWORD

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 ON THE ACD

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 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.

Table 1: Baseline characteristics for patients with partially platinum-sensitive and fully platinum-sensitive disease

Baseline characteristics		Partially platinum-sensitive		Fully platinum-sensitive	
		Trabectedin plus PLDH	PLDH	Trabectedin plus PLDH	PLDH
N		120	83	92	117
Race	NON-WHITE	21 (17.5%)	13 (15.7%)	21 (22.8%)	31 (26.5%)
	WHITE	99 (82.5%)	70 (84.3%)	71 (77.2%)	86 (73.5%)
Age (years)	Mean (range)	58 (40-76)	57.5 (37-79)	56 (37-82)	59.6 (33-87)
PFI (months)	Mean (range)	8.4 (6.1-12)	8.6 (6-12)	22.4 (12-107.1)	26.2 (12.1-158.8)
ECOG PS	ECOG = 0	85 (70.8%)	52 (62.7%)	63 (68.5%)	63 (53.8%)
	ECOG > 0	35 (29.2%)	31 (37.3%)	29 (31.5%)	54 (46.2%)
Prior Taxane	NO	29 (24.2%)	17 (20.5%)	22 (23.9%)	29 (24.8%)
	YES	91 (75.8%)	66 (79.5%)	70 (76.1%)	88 (75.2%)
CA125 at BL	CA-125 < 2x ULN	24 (20%)	11 (13.3%)	27 (29.3%)	24 (20.5%)
	CA-125 >= 2x ULN	96 (80%)	72 (86.7%)	65 (70.7%)	93 (79.5%)
Prior lung/liver	NO	71 (59.2%)	53 (63.9%)	53 (57.6%)	66 (56.4%)
	YES	49 (40.8%)	30 (36.1%)	39 (42.4%)	51 (43.6%)

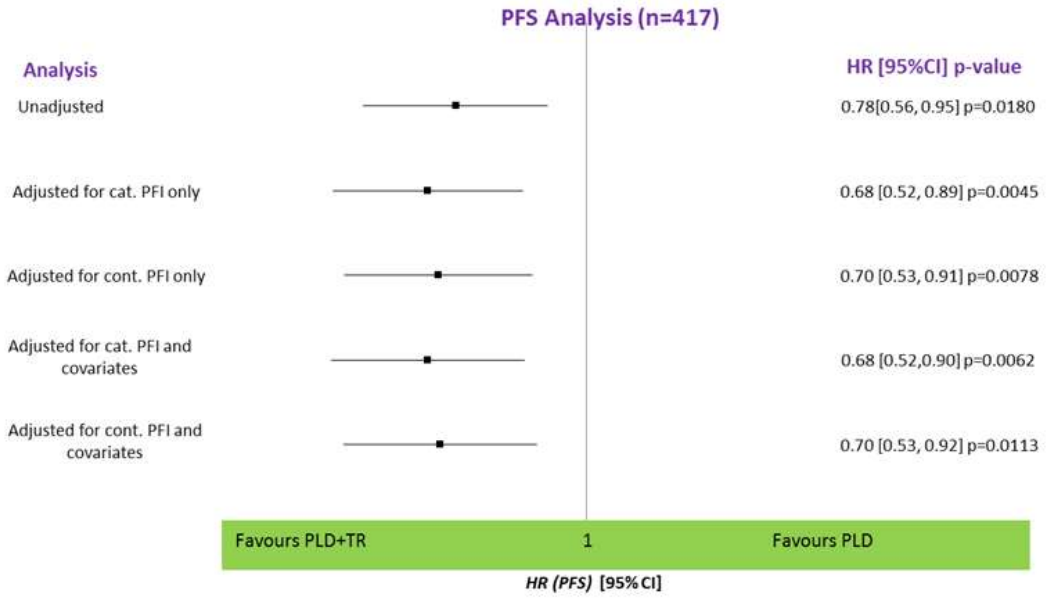
- Figures 1-2 show the results of specifying PFI as a categorical (6-12 months and >12 months) covariate and a continuous covariate in Cox regression analyses when comparing the effect of treatment with trabectedin plus PLDH versus PLDH alone for PFS and OS.

  - 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.

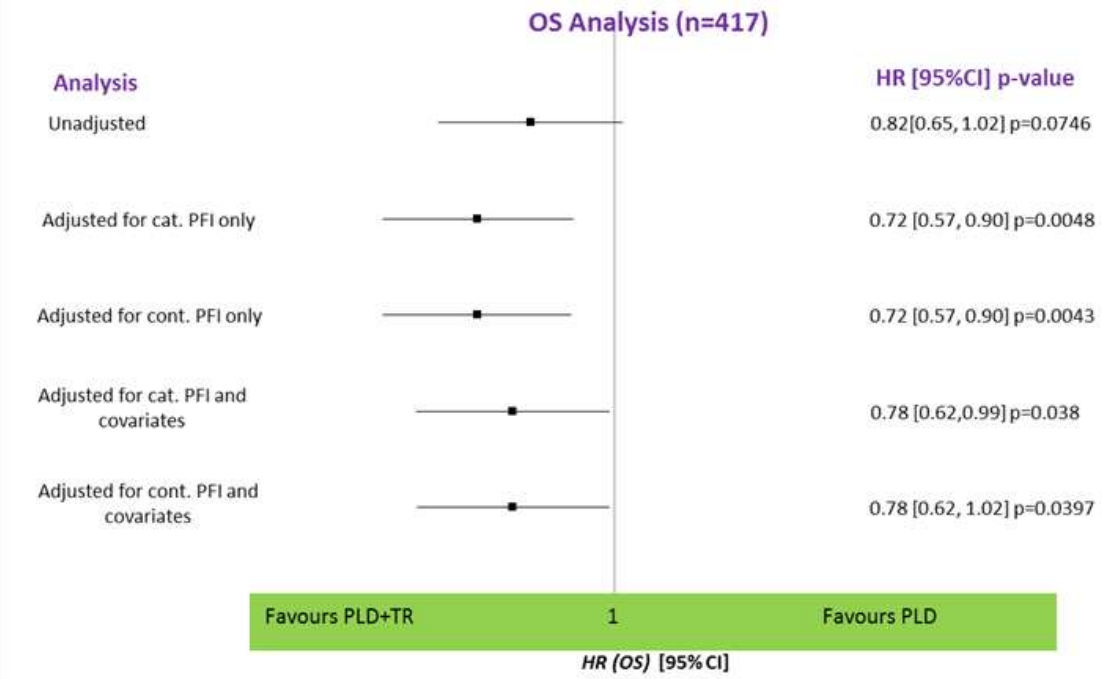
- The analysis shows the significant impact of PFI on the PFS and OS results for trabectedin plus PLDH versus PLDH alone; marginal differences were seen whether PFI was specified as a continuous or categorical covariate.

Figure 1: Cox regression analysis comparing trabectedin plus PLDH versus PLDH alone for progression-free survival (PFS)



*Covariates considered alongside PFI were: age; race; ECOG performance score; CA-125; prior taxane use; and liver or lung involvement

Figure 2: Cox regression analysis comparing trabectedin plus PLDH versus PLDH alone for overall survival (OS)



*Covariates considered alongside PFI were: age; race; ECOG performance score; CA-125; prior taxane use; and liver or lung involvement

- 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).

- 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.

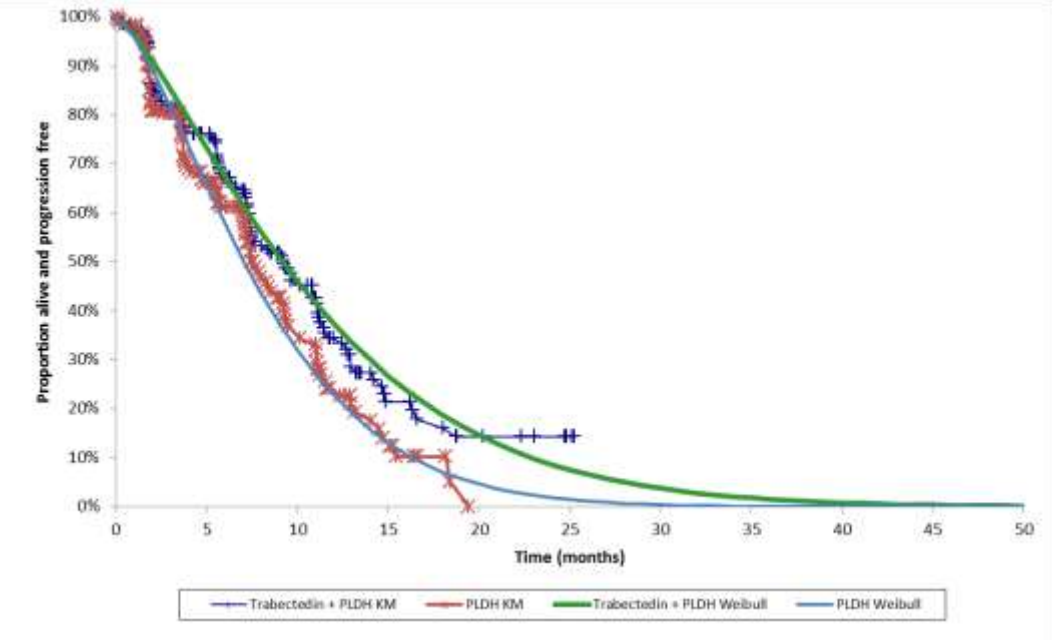
- When considering the goodness of fit criteria, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), results were significantly worse fitting when PFI was not adjusted for as a categorical or continuous variable (Figures 3-5). Visual inspection of the curves was also less plausible 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). 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.

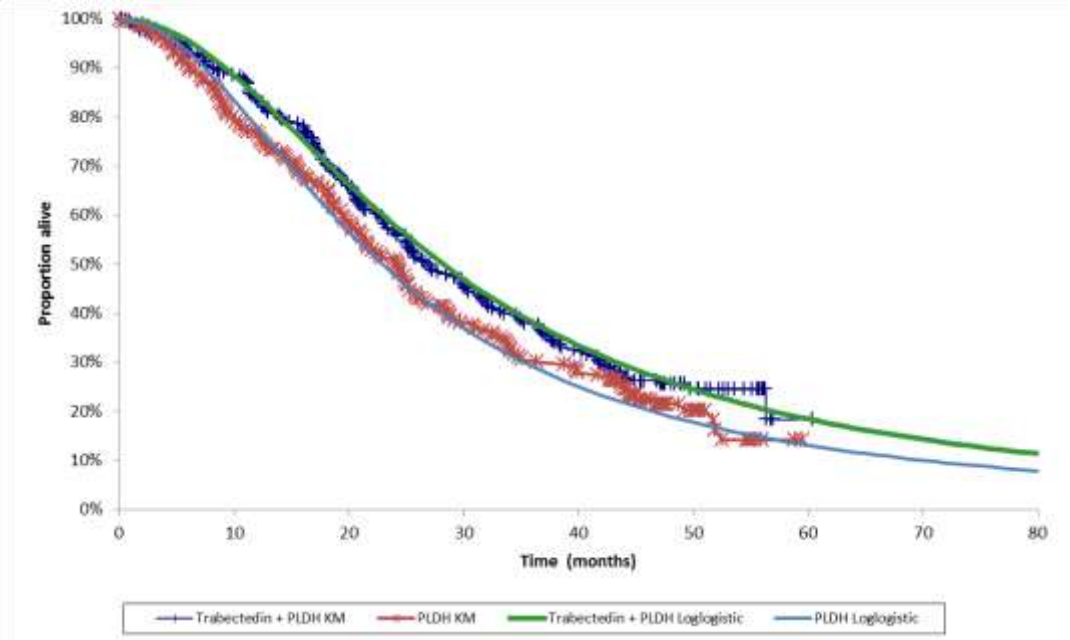
Figure 3: PFS and OS adjusted for categorical PFI

Progression-free survival



	Trabectedin plus PLDH	PLDH
Mean	11.19	8.28
AIC	448.30	378.16
BIC	465.04	394.44

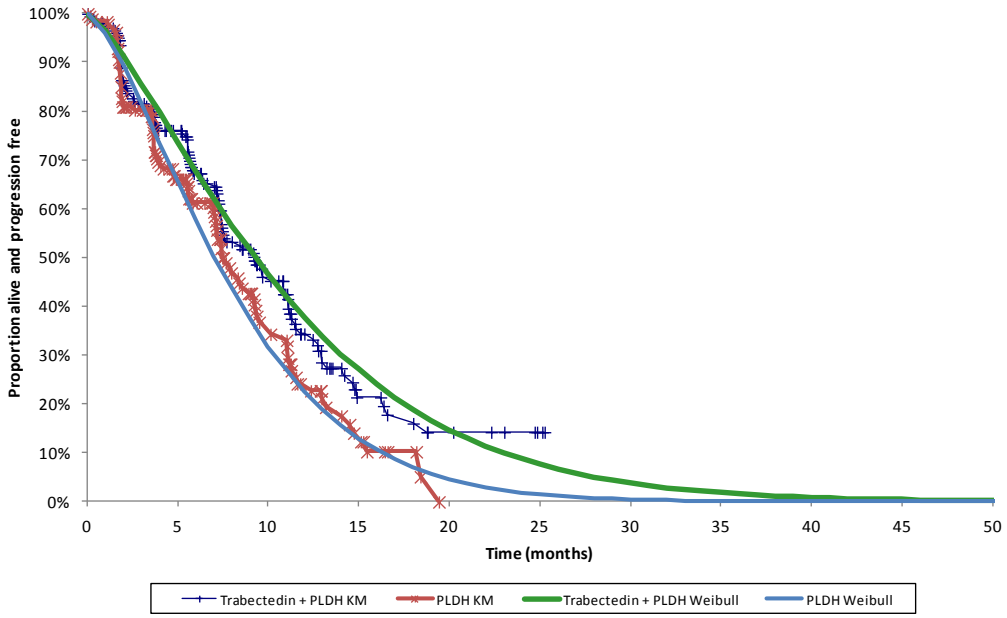
Overall survival



	Trabectedin plus PLDH	PLDH
Mean	45.03	36.68
AIC	502.98	481.81
BIC	519.79	498.33

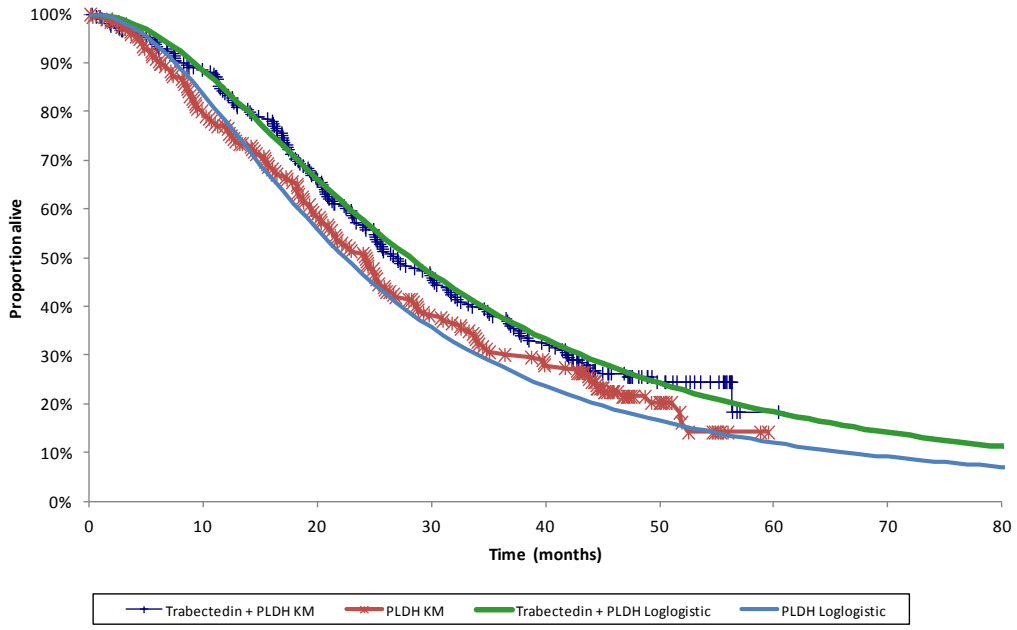
Figure 4: PFS and OS adjusted for continuous PFI

Progression-free survival



	Trabectedin plus PLDH	PLDH
Mean	11.26	8.25
AIC	451.24	380.94
BIC	468.05	397.25

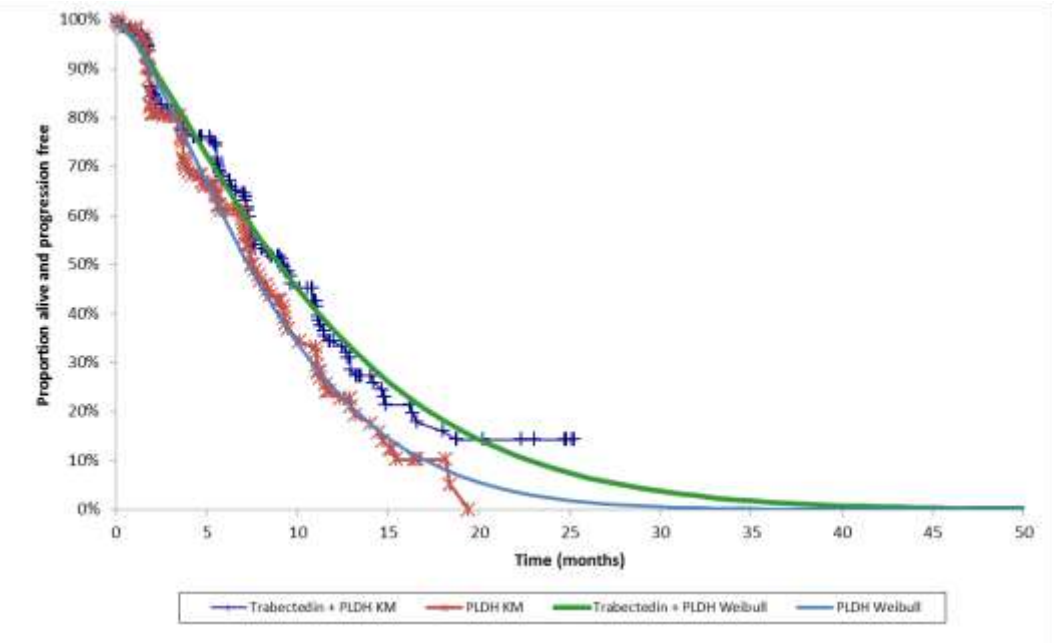
Overall survival



	Trabectedin plus PLDH	PLDH
Mean	44.69	34.97
AIC	508.00	472.68
BIC	524.87	489.22

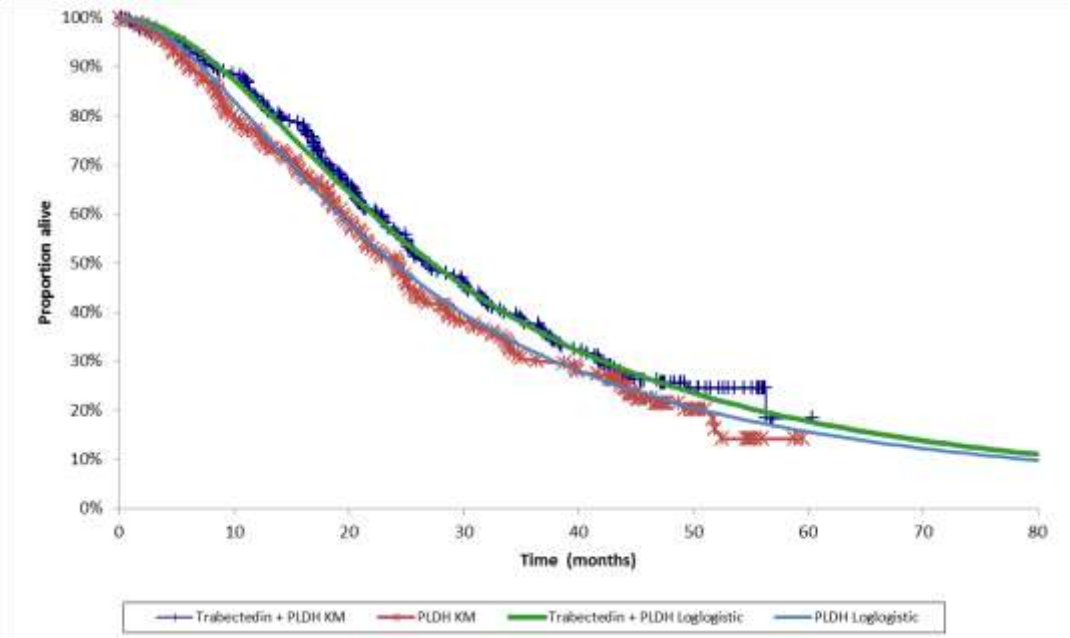
Figure 5: PFS and OS not adjusted for PFI

Progression-free survival



	Trabectedin plus PLDH	PLDH
Mean	11.06	8.61
AIC	456.26	385.82
BIC	469.71	398.87

Overall survival



	Trabectedin plus PLDH	PLDH
Mean	44.16	41.44
AIC	514.26	504.74
BIC	527.76	517.97

- 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) the use of average doses from the OVA-301 trial as opposed to doses used in clinical practice 2) drug and administration costs based on the actual proportions of patients receiving treatment whilst progression-free from the OVA-301. See Issues 3-5 for further details.

- 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:

  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.

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.

- 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.

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.

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%
7	12	45%	12	45%
8	28	39%	28	39%
9	8	26%	8	26%
10	9	23%	9	23%
11	10	18%	10	18%
12	5	14%	5	14%
13	10	12%	10	12%
14	4	7%	4	7%
15	3	5%	3	5%
16	1	4%	1	4%
17	3	3%	3	3%
18	2	2%	2	2%
20	1	1%	1	1%
21	1	0%	1	0%
22	0	0%	0	0%

- 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.

Issue 5: Cost-effectiveness results unrepresentative of implementation of the new PAS for trabectedin

- 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.

Table 3: Summary table of ICERs incorporating the comments from Issues 1-5

	PharmaMar model ICER (£)	TAG model ICER (£)
Base case as per ACD	27,572	77,290
Issue 1 and 5: Adjusting for categorical PFI and new PAS	28,573	32,348
Issue 1, 3 and 5: Adjusting for categorical PFI, average doses from OVA-301 and new PAS	28,573*	£29,323
Issue 1, 3, 4 and 5: Adjusting for categorical PFI, average doses from OVA-301, actual proportion on treatment from OVA-301 (capped at 6 cycles) and new PAS	N/A (not capped at 6 cycles)	£28,691
Proposed base case for evaluation (Issue 1, 3, 4 and 5): Adjusting for categorical PFI, average doses from OVA-301, actual proportion on treatment from OVA-301 (no cap at 6 cycles) and new PAS	**28,573***	**24,341**

*No change as already incorporated in the model

FACTUAL INACCURACIES

Appeal Hearing Document

Description of problem	Description of proposed amendment	Justification for amendment
Some of the titles of representatives of the Appellant are incorrect. Page 1: "The Appellant was represented by: Mark Harries, Chief Executive Officer, MAP Biopharma Beatriz Garcia, Senior Manager, Market Access José Miguel, Health Economics Research Manager, Pharma Mar Christian Hill, Director Market Access, MAP Biopharma Paul Ranson, Legal Representative, Pinsent Masons LLP"	Include the correct titles: "The Appellant was represented by: Mark Harries, Chief Operating Officer, MAP Biopharma Beatriz Garcia, Senior Manager, Market Access, PharmaMar José Miguel, Health Economics Research Manager, Pharma Mar Christian Hill, Director Market Access, MAP Biopharma Paul Ranson, Legal Representative, Pinsent Masons LLP"	To ensure the Appeal Hearing Document is accurate

Appraisal Consultation Document

Description of problem	Description of proposed amendment	Justification for amendment
Misleading sentence, as patient level data were available for OVA-301. Page 12: "In the absence of individual patient data, the network meta-analysis synthesised data on relative treatment effect from the whole study populations."	Reword to: "In the absence of individual patient data for all trials, the network meta-analysis synthesised data on relative treatment effect from the whole study populations."	Improve the transparency and accuracy of the ACD
Clarification that patient level data was available for OVA-301.	Reword to: "First, due to lack of individual	Improve the transparency and accuracy of the ACD

Page 22: “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 4.5, unadjusted hazard ratios were incorporated, which could include potential bias.”	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. However, individual patient data were only available for the OVA-301 trial comparing trabectedin plus PLDH with PLDH. As a consequence, as discussed in section 4.5, unadjusted hazard ratios were incorporated, which could include potential bias.”	
The results from the sensitivity analyses appear to be incorrect. The base case ICER for trabectedin plus PLDH found by the TAG was £85,212. Therefore, using upper and lower bounds for survival, it is expected that the ICER is lower in one and higher in the other. The results below suggest trabectedin plus PLDH has a better ICER (and dominates in one instance) when the upper or lower bound is considered. Page 27: “When the lower bound of the hazard ratio for survival for trabectedin plus PLDH compared with PLDH alone was used, the ICER for trabectedin plus PLDH compared with PLDH alone was £44,266 per QALY gained. When the upper bound was used, trabectedin plus PLDH dominated PLDH alone.”	Provide the correct results.	Improve the accuracy of the ACD
The ICER is rounded up, and not to the nearest 000. The correct ICER incorporating adjusted results is £32,289 per QALY. Page 42: The Committee noted that the Assessment Group also performed an analysis incorporating these adjusted results into its model, which gave an ICER of £35,600 per QALY gained, and that this fell to £33,000 per QALY gained after corrections to the costs had been made (see section 4.35).	Reword to: The Committee noted that the Assessment Group also performed an analysis incorporating these adjusted results into its model, which gave an ICER of £35,600 per QALY gained, and that this fell to £32,300 per QALY gained after corrections to the costs had been made (see section 4.35).	Improve the accuracy of the ACD

Clarification that the imbalance in platinum-free interval was not known during TA222. Page 42: The Committee heard from the company that the substantial reduction in the ICER since NICE technology appraisal guidance 222 was predominantly because of the post-hoc adjustment for imbalances in the platinum-free interval, and that pre-specified adjustments to ECOG status and CA125 had less of an effect.	Reword to: The Committee heard from the company that the substantial reduction in the ICER since NICE technology appraisal guidance 222 was predominantly because of the post-hoc adjustment for imbalances in the platinum-free interval; this imbalance was discovered after the completion of technology appraisal 222. Pre-specified adjustments to ECOG status and CA125 had less of an effect.	Improve the transparency and accuracy of the ACD
OVA-301 has shown that a longer platinum-free interval is associated with a better response. This has been published by Monk et al. 2012 Page 44: One of the clinical experts indicated that the platinum-free interval was important, subject to ongoing research, and that a longer platinum-free interval may be associated with a better response to non-platinum therapies as well. However, no trials have yet provided evidence to support this hypothesis for PLDH.	Reword to: Page 44: One of the clinical experts indicated that the platinum-free interval was important, subject to ongoing research, and that a longer platinum-free interval may be associated with a better response to non-platinum therapies as well. OVA-301 has published data to support this hypothesis for PLDH.	Monk et al. 2012 shows that PLDH had a longer mean platinum free interval compared to trabectedin plus PLDH “An unexpected but significant imbalance in the PFI favouring the PLD arm (mean PFI: PLD=13.3 months, trabectedin+PLD=10.6 months) was identified.” (Monk 2012) The publication concludes that “despite stratification on platinum sensitivity, there was an imbalance in mean platinum free interval that had an effect on OS.”
Clarification that the imbalance in platinum-free interval was not known during technology appraisal 222. Page 45: “The company responded that the platinum-free interval was not considered as important a prognostic indicator at the time of the trial. It acknowledged that it	Reword to: “The company responded that the platinum-free interval was not considered as important a prognostic indicator at the time of the trial. It acknowledged that it had not included adjustments for platinum-free interval in its submission for the whole platinum-sensitive population for NICE technology appraisal guidance 222. It was explained	Improve the transparency and accuracy of the ACD

had not included it in its submission for the whole platinum-sensitive population for NICE technology appraisal guidance 222, but was of the opinion that it should now be retrospectively adjusted for."	that this was because the imbalance in platinum-free interval was not known until the final analysis on overall survival was available, which was published after the final guidance from technology appraisal guidance 222. The manufacturer was of the opinion that it should now be retrospectively adjusted for."	
We suggest repeating the footnotes in the summary of conclusions. Page 49: PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.	Reword to: PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.[1,2] [1] At the time of publication (November 2015), PLDH (Caelyx) in combination with platinum did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. [2] The use of PLDH (Caelyx) in combination with platinum is outside the terms of the marketing authorisation for Caelyx. Consequently the statutory funding requirement does not apply to this recommendation. NICE received a remit to appraise this combination under Regulation 5 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013.	Ensure conclusions are clear

REFERENCES

Aghajanian C, Blank SV, Goff BA et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-2045.

Centre for Reviews and Dissemination (CRD). Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. University of York. 2008.

Edwards SJ, Barton S, Thurgar E, Trevor N. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer: A Multiple Technology Appraisal. BMJ-TAG, London, 2013.

Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. Clinical Oncology 2001;19:3312-22.

Gore ME, Fryatt I, Wiltshaw E, and Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecologic Oncology 1990; 36(2): 207-211.

Herzog TJ, Armstrong DK, Brady MF et al. Ovarian cancer clinical trial endpoints: Society of Gynecologic Oncology white paper. Gynecol Oncol. 2014;132(1):8-17.

Latimer N. NICE Decision Support Unit: Technical Support Document 14. Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data. 2013. Available at http://www.nicedsu.org.uk/Survival-analysis-TSD(2892878).htm

Lederman JA, Raja FA, Fotopoulou C et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2013; 24 (Supplement 6): vi24–vi32.

Marksman M. The Waning Relationship Between Progression-Free Survival and Overall Survival in Randomized Cancer Therapy Trials. The American Journal of Hematology/Oncology. 2014; Vol 10 No. 6: Pages 30-32.

Monk BJ, Herzog TJ, Kaye SB et al. Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: overall survival analysis. Eur J Cancer. 2012 Oct;48(15):2361-2368.

NICE Technology Appraisal (TA) guidance 91. Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. May 2005. Available at https://www.nice.org.uk/guidance/ta91

Pujade-Lauraine E, Paraiso D, Cure H, et al. Predicting the effectiveness of chemotherapy (Cx) in patients with recurrent ovarian cancer (ROC): a GINECO study. Proc Am Soc Clin Oncol 2002;21. 208a (Abstract 829).

Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 2010 Jul 10;28(20):3323-3329.

School of Health and Related Research (ScHARR). Trabectedin for the treatment of relapsed ovarian cancer: A Single Technology Appraisal. April 2010. Available from: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0004/82552/ERGReport-08-212-01.pdf