PharmaMar comments

Issue 1: Retrospective adjustment for platinum free interval as a continuous variable

Description of problem	BMJ-TAG response
1) PharmaMar outlines that PFI has been shown to be a significant prognostic factor in predicting PFS and OS, with longer PFIs associated with a better prognosis. The ACD states that "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" (point 4.56, page 44). PharmaMar proposes that "evidence from the OVA-301 trial has further demonstrated the importance of PFI as a key prognostic factor" and requests that the statement "no trials have yet provided evidence to support this hypothesis for PLDH" be removed from the ACD.	1) The AG notes that PharmaMar's premise that length of PFI may influence response to PLDH, a non-platinum-based therapy, is based on *post hoc* analyses derived from data from a single RCT (OVA-301), which are, as *post hoc* analyses, hypothesis generating. The AG suggests that results from a second, independent study are needed before it can be stated that there is evidence of an association between duration of PFI and response to non-platinum based treatments, including, but not limited to, PLDH.
2) 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. Given this decision, PharmaMar conducted an analysis which retrospectively adjusted survival outcomes treating PFI as a categorical variable rather than a continuous variable for platinum-sensitive ovarian cancer. PharmaMar 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.	2) The AG maintains that unadjusted HRs should be used for PFS and OS. As noted in the original report, the AG acknowledges that adjusting for baseline characteristics might be important because certain characteristics are thought to influence prognosis. However, a consistent dataset of adjusted HRs was not available to inform the analysis. Although patient level data are now available for two additional studies included in the analysis, similar data are not available for the remaining studies identified by the review. Additionally, the new analysis provided by PharmaMar is, as the company acknowledges, another *post hoc* analysis and is therefore subject to the same concerns as the analysis of PFI as a continuous variable for the platinum sensitive subgroup of OVA-301. Adjusting the AG´s model to reflect the newly calculated PFS and OS hazard ratios (HRs), using the PFS adjusted for categorical PFI and covariates and the OS adjusted for categorical PFI and covariates (as presented in Figures 1 and 2 in the response from PharmaMar), led to a reduction in the AG's incremental cost effectiveness ratio (ICER) from £85,212 to £64,503 (based on a previous Patient Access Scheme [PAS]).

	Implementing the most recently provided PAS, together with the revised HRs, generated a change in the AG´s ICER from £64,503 to £59,772. The AG considers it important to note that clinical expert advice throughout the project was to evaluate separately the subgroups of women with partial and full platinum sensitive ovarian cancer. At the time of the original analysis, we were unable to include data for the fully platinum sensitive subgroup from OVA-301. Data for overall survival were not available in the full publication for patients with fully platinum sensitive disease but were presented in Technology Appraisal 222. However, data were based on 81% of the planned 520 deaths for the full trial population and are therefore immature. The AG considers that this should be borne in mind when interpreting the results of the new analysis provided by PharmaMar for overall survival, which encompasses both levels of platinum sensitivity.
3) PharmaMar highlights that "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"	3) The AG considers that the imbalance between the groups in PFI observed in OVA-301 does not warrant analysing the data by categorical variable. The AG suggests, in line with advice from clinical experts, the imbalance indicates that it could be appropriate to analyse data separately by subgroup based on degree of platinum sensitivity (partial versus full), particularly given that PFI was similar between treatment groups in the partially platinum sensitive subgroup. However, this would be a *post hoc* analysis. Given that women with fully platinum sensitive disease and receiving PLDH had a markedly longer PFI than those receiving trabectedin plus PLDH, if duration of PFI influences response to treatment, it is likely that the relative treatment effect of adding trabectedin will be underestimated. However, as noted earlier, the proposal that PFI influences response to non-platinum-based treatment has yet to be substantiated.

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

Description of problem	BMJ-TAG response
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). 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. The company acknowledges states that communications with NICE suggest that there is an option to evaluate trabectedin plus PLDH outside this MTA, as the conclusions for other treatment options will not change in light of these new data.	The AG model was constructed using data available at the time of the analysis. Further analyses, outside the scope of the MTA, are to be agreed by NICE.

Issue 3: Use of doses used in clinical practice as opposed to average doses from the clinical trials in the cost-effectiveness analysis

Description of problem	BMJ-TAG response
When calculating drug costs the AG uses the licensed dose for trabectedin plus PLDH (1.1 mg/m^2 and 30 mg/m^2 respectively) and an unlicensed dose; based on expert opinion for PLDH monotherapy (40 mg/m^2). In comparison, the company's model calculates drug costs based on the mean total dose per patient, recorded for OVA-301 platinum-sensitive patients. These doses are as follows; trabectedin plus PLDH (1 mg/m^2 and 27.43 mg/m^2 respectively) and PLDH monotherapy (44.95 mg/m^2). The company states that the AG decision was based on reassurance from clinicians that the effectiveness of treatments remain unchanged between higher or lower doses of PLDH and that the reasons for using lower doses in clinical practice are primarily to avoid adverse events and toxicities associated with higher doses. The company agrees 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, it points that the average dose observed across clinical 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. The company points that other than expert opinion, there is no study evidence to suggest that the effectiveness of the dose of PLDH monotherapy 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.	The AG thanks the company for their comments. In summary, the company asserts that the AG may have overestimated the incremental benefit of PLDH versus trabectedin plus PLDH as a result of: 1. Overestimating the cost of trabectedin plus PLDH; 2. Underestimating the cost of PLDH monotherapy. **Overestimating the cost of trabectedin plus PLDH** The company considers that the AG has overestimated the cost of trabectedin plus PLDH by using a higher dose of trabectedin plus PLDH in the AG economic model when compared with the average doses of trabectedin plus PLDH in OVA-301. The AG considers that both the company's model and the AG's model estimate trabectedin plus PLDH cost based on the average dose. However, due to the differences in model structure, the average dose is not explicitly stated in the AG model. The AG believes this may have given rise to confusion. In the model developed by the AG, mean times to progression and death were not explicitly modelled. This is because the AG used an area under the curve approach. To estimate the cost of trabectedin plus PLDH, intended drug dose (and therefore drug cost) was applied for each cycle, for the patients remaining in the progression-free health state. Over the six cycles, this gives rise to an average dose below the intended dose, because fewer patients remain in the progression-free health state in subsequent months. The average dose of trabectedin plus PLDH, when estimated across the six cycles of therapy in the AG base case model, is similar to the average dose applied in the company's model (Table 1).

Similarly, the company disagrees with how the costs and effects have been applied for trabectedin plus PLDH in the cost-effectiveness analysis of platinum-sensitive network 2. The company report that the dose used in the AG model is the licensed dose for trabectedin plus PLDH (1.1 mg/m^2 and 30 mg/m^2 respectively. However in ten the OVA-301 study, patients received an average dose of 1.0mg/day due to patients discontinuing treatment and dose interruptions due to adverse events. Additionally, the average dose of PLDH (in combination with trabectedin) used in OVA-301 was 27.43mg/day. Therefore, the company is concerned that assuming the dose used in the AG model (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) is underestimating the benefits of treatment with trabectedin.

The company model accounted 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.

The company also reports that when the AG 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.

Table 1. Average drug dose per patient m^2

	PharmaMar model		AG model	
	Trabectedin	**PLDH**	**Trabectedin**	**PLDH**
Average dose per patient (mg/m^2)	1.0	27.43	1.0	28.38

Underestimating the cost of PLDH monotherapy

The AG acknowledges that the costs associated with PLDH monotherapy used in the AG sensitivity analysis of head-to-head data are based on the dose expected to be used in clinical practice. The rationale for assessing the cost of regimens likely to be used in clinical practice was based on expert clinical opinion that the efficacy of PLDH monotherapy is likely to be equivalent at 40 mg/m^2 and 50 mg/m^2. The AG carried out a scenario analysis (of the base case analysis) in which the intended dose of 50 mg/m^2 was used to calculate PLDH monotherapy costs (note – the average dose of PLDH given an intended dose of 50 mg/m^2 was 44.10 mg/m^2, which is similar to the company's estimate of 44.95 mg/m^2). In this scenario, the deterministic ICER for trabectedin plus PLDH versus PLDH fell from [redacted] (with the new PAS) to [redacted] (with the new PAS).

Issue 4: Use of PFS as opposed to proportion of patients on treatment to determine treatment and administration costs for trabectedin and PLDH

Description of problem	BMJ-TAG response
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 AG 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. The company is concerned that 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.	As discussed in Issue 3, the AG notes that the drug dose per patient m^2 is similar across the company's and the AG's models (Table 1 above). Therefore, the issue raised by the company is unlikely to carry any substantial impact on the estimation of costs and QALYs in the AG's economic analysis.

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

Description of problem	BMJ-TAG response
The company reports that 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 company adds that 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). The company reported a Table summarising the ICERs incorporating the comments from Issues stated in 1-5, which the AG reproduces in Table 2, with some modifications.	The AG acknowledges the new PAS submitted by the company to the Department of Health, the full details of the company´s updated analyses have not been provided to the AG. Therefore it was not possible to validate the company´s updated ICERs. Furthermore, the AG reached substantially different ICERs from the ones reported by the company when using the AG model. The difference in the values reported in Table 2 cannot be explained given that the AG does not have access to the company´s new analysis. **Table 2. Summary table of ICERs incorporating the comments from Issues 1-5**

	PharmaMar model ICER (£)	TA model ICER as reported by PharmaMar (£)	AG model ICER (£)
Base case as per ACD	27,572	77,290*	85,212
Base case including new PAS	Not reported	Not reported	[redacted]
Issue 1 and 5: Adjusting for categorical PFI and new PAS	28,573	32,348	59,772†
Issue 1, 3 and 5: Adjusting for categorical PFI, average doses from OVA-301 and new PAS	28,573	£29,323	54.059‡
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	The AG notes that the drug dose per patient m^2 is similar across the company's and the AG's models. Therefore, this issue is unlikely to carry any substantial impact on the estimation of costs and QALYs in the AG's economic analysis.
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	Due to time constraints the AG could not conduct this analysis.

	*This is the AG's ICER for the sensitivity analysis conducted when the PLDH monotherapy dose was changed from 40 mg/m^2 to 50 mg/m^2. The AG has been unable to validate any of the other ICERs reported in this column by PharmaMar. †The AG has used the PFS adjusted for categorical PFI and covariates and the OS adjusted for categorical PFI and covariates, as presented in Figures 1 and 2 in the response from PharmaMar. ‡To note is that when the AG model was adjusted to reflect Issue 3, only the PLDH monotherapy dose was changed from 40 mg/m^2 to 50 mg/m^2 for the reasons previously provided within the discussion of Issue 3.