Pharma Marm

Grupo Zeltia

20 January 2015

[redacted]
Vice chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear [redacted],

Re: Final Appraisal Determination – Ovarian cancer - topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent disease only (Review of TA 91 & TA 222) [10468)

PharmaMar wishes to appeal against the Final Appraisal Determination (FAD) for trabectedin in combination with PLDH in the above mentioned technology appraisal under the basis of the NICE Guide to the technology appraisal and highly specialised technologies appeal process (February 2014). The FAD concluded that trabectedin in combination with PLDH would not be recommended within its marketing authorisation for treating of platinum-sensitive ovarian cancer. A concise history of the MTA to date is provided in Appendix 1.

The appeal is based on the following grounds:

- Ground 1: In making the assessment that preceded the recommendations NICE has a) failed to act fairly or b) exceeded its powers.

- Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

This appeal is made in accordance with Guide to the technology appraisal and highly specialised technologies appeal process, NICE article [PMG18] of February 2014.

We are disappointed with the decision of the Appraisal Committee, which reflects both process failures by NICE and issues arising from the Appraisal Committee's interpretation of key data. Had the appraisal been conducted fairly and data been construed reasonably in a consistent way, PharmaMar believe the Appraisal Committee would have reached alternative conclusions on the evidence for trabectedin in combination with PLDH and NICE could have approved trabectedin in combination with PLDH for use in England and Wales.

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Grupo Zeltia

Executive Summary

Ground 1: **In making the assessment that preceded the recommendations NICE has failed to a) act fairly or b) exceeded its powers.**

Arguments:

1.1 Exclusion by the Appraisal Committee of relevant covariates in the adjusted analysis of trabectedin is unjustified.

1.2. Different interpretation of the evidence by the same Appraisal Committee for the MTA and TA222 regarding the use of direct head-to head data for trabectedin to address the decision problem for the non-platinum network (Network 2) is irrational and unfair.

Ground 2: **The recommendations are unreasonable in the light of the evidence submitted to NICE.**

Arguments:

2.1. The Appraisal Committee's rationale for not using adjusted clinical effectiveness results for the cost-effectiveness evaluation of trabectedin in the MTA is flawed and inconsistent with the previous TA222 appraisal and NICE Decision Support Unit guidance.

2.2 The Appraisal Committee failed to take into account key differences in baseline characteristics and trial design of relevant studies that have informed the clinical and cost-effectiveness results and subsequent recommendations for the FAD including that of trabectedin.

2.3 The different interpretation of the evidence by the same Appraisal Committee for the MTA and TA222 regarding the use of direct head-to head data for trabectedin to address the decision problem for the non-platinum network (Network 2) is irrational and unfair.

2.4 An incorrect adjustment by the Assessment Group of drug costs for trabectedin and PLDH has been applied resulting in an inaccurate ICER being calculated.

2.5 Recommendations within the FAD for the use of paclitaxel within its marketing authorisation are based on extrapolated off-label data and costs in the monotherapy platinum resistant/ refractory patients.

2.6 Recommendations for use of off-label PLDH in combination with platinum are unlawful.

Ground 1: In making the assessment that preceded the recommendation, NICE has a) failed to act fairly or b) exceeded its powers.

1.1 Exclusion by the Appraisal Committee of relevant covariates in the adjusted analysis of trabectedin is unjustified.

The Appraisal Committee's comment that they would have accepted a retrospective adjustment of one covariate (CA-125) for consistency with TA222 but this did not oblige them to accept additional retrospective adjustments (FAD Point 4.3.17}, is unfair since the imbalance in continuous platinum free interval was not discovered during TA222 hence continuous platinum free interval data was not made available to the evidence review group of TA222.

This imbalance was found following the final analysis of OVA-301 (post TA222). Therefore, for this MTA, PharmaMar followed the evidence review group's methods in conducting statistical analysis by performing a rapid analysis on the data to understand where differences in patient characteristics existed between the two arms.

Accordingly: a) CA-125 (already adjusted for by previous ERG}, b) ECOG (recognised by the Assessment Group as important to prognosis: 4.1.4) and; c) platinum-free interval (recognised as important to prognosis in this MTA: 4.3.19 and also previous TAs; TA91 made recommendations based on platinum-free intervals); were adjusted for.

The scope for 10468 states that "the duration of response to first-line platinum-based chemotherapy is a continuous variable and the categories 'platinum resistant' and 'platinum sensitive' should not necessarily be defined rigidly," which means PharmaMar's approach is reasonable and appropriate.

The Appraisal Committee's concerns regarding the use of a continuous variable as opposed to a dichotomous variable are unjustified considering that previous TAs (e.g. NICE TA309) have used continuous variables in the adjustment of survival curves.

Were continuous platinum free intervals made available to the evidence review group of TA222 PharmaMar believe this would have been adjusted for, since goodness of fit statistics (AIC and BIC) as well as visual inspection of the plots showed that the adjusted curves were a significantly better statistical and visual fit with the addition of continuous platinum free interval (Fisher 2013; Table 6). This once more follows guidance outlined by the NICE DSU for survival analysis (Latimer 2012).

Therefore the Appraisal Committee acted unfairly and unreasonably in not allowing the use of important co-variates that influence prognosis including the PFI interval to be adjusted from

the trabectedin study, despite the FAD consistently acknowledging importance of this baseline factor (4.1.5, 4.2.9, 4.3.19).

1.2. Different interpretation of the evidence by the same Appraisal Committee for the MTA and TA222 regarding the use of direct head-to head data for trabectedin to address the decision problem for the non-platinum network (Network 2) is irrational and unfair.

It is inconsistent and unfair that the same Appraisal Committee (Committee A) attended the MTA and TA222 but came to different conclusions regarding the use of head-to-head comparisons in which individual patient level data (IPD) are available versus the use of evidence synthesis for the evaluation of trabectedin plus PLDH.

The three platinum networks created to synthesise all the interventions and comparators are discrete, separate networks and are not comparable in terms of the ICERs estimated (4.1.2). Therefore network 2, (PLDH, trabectedin plus PLDH, paclitaxel and topotecan) may be considered to provide information on the treatments suitable for platinum sensitive patients who are unable at the time of relapse to receive platinum based therapies due to residual toxicities or allergies, or unwilling to tolerate further platinum based therapy. In TA222 for trabectedin, the only clinically relevant comparator in this network for trabectedin plus PLDH is PLDH alone, and therefore the IPD for trabectedin can be used taking into account important prognostic baseline factors without: a) compromising the results for the other products in network 2 nor; b) affecting the decision making on the clinical and cost-effectiveness in networks 1 (platinum based therapy for platinum sensitive patients) and 3 (platinum resistant/ refractory).

Based on TA222 it was reasonable and within PharmaMar's legitimate expectations that evidence for trabectedin would be evaluated and compared in the same way, especially as there were discrete networks, which could not be compared directly as stated by the Assessment Group (4.1.2, 4.1.3).

Ground 2: The recommendations are unreasonable in the light of the evidence submitted to NICE

2.1 The Appraisal Committee's rationale for not using adjusted clinical effectiveness results for the cost-effectiveness evaluation of trabectedin in the MTA is flawed and inconsistent with the previous TA222 appraisal and NICE Decision Support Unit guidance.

The Appraisal Committee failed to accept the adjusted trabectedin IPD using the most evidence-based and robust method available despite the fact that:

- The evidence review group of TA222 (single technology assessment of trabectedin plus PLDH in 2011) adopted this approach (ERG Report TA222, page 125);
- NICE Decision Support Unit guidance recommends this approach (NICE DSU, page 41);
- The Assessment Group of the MTA "acknowledged that adjustment of clinical-effectiveness data for key prognostic factors was likely to result in more accurate estimates of progression-free survival and overall survival" (4.2.19).

The way evidence has been synthesised in this appraisal is a consequence of the fact that the Assessment Group has focused on estimating clinical and cost-effectiveness for the purposes of a MTA where many interventions and comparisons were needed to be assessed across the three platinum sensitivity networks. IPD was available for trabectedin plus PLDH versus PLDH alone but not in relation to the other technologies. As a consequence, the Assessment Group incorporated unadjusted hazard ratios where the results are flawed creating perverse outcomes and conclusions (4.1.6, 4.2.9).

One of the main concerns of the Assessment Group with the use of data from the network meta-analyses in the heath economic model was the lack of IPD (4.2.9). It stated that IPD network meta-analysis would have afforded the Assessment Group the opportunity to account for differences in baseline characteristics **within** and **between** trials through the incorporation of covariates (4.2.9). However, because the Assessment Group saw fit not to seek to obtain access to such IPD by treatments or by subgroup (other than trabectedin plus PLDH versus PLDH alone), this was not done.

The Appraisal Committee justified basing the cost-effectiveness of trabectedin plus PLDH on unadjusted results as it "understood from the Assessment Group that the focus of the Decision Support Unit guidance is on head-to-head comparisons in which IPD are available and where evidence synthesis between trials is not required" (4.3.16) but neglected to acknowledge that the evidence review group of TA222 concluded that a direct comparison of trabectedin plus PLDH with PLDH alone was sufficient to address the decision problem (i.e. evidence synthesis was not required) (ERG Report TA222).

Evidence synthesis was not required to evaluate the cost-effectiveness of trabectedin plus PLDH during TA222 since "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." (ERG Report TA222).

In this MTA for patients with platinum-sensitive disease, it was not possible to construct a complete network based on the trials identified, and therefore it was necessary to generate 2 discrete networks. Platinum-sensitive network 1 evaluated platinum-based treatments and platinum-sensitive network 2 evaluated non-platinum-based treatments. The Assessment Group emphasised that these networks cannot be compared directly (4.1.3).

Since TA222, no new trial evidence has contributed to the network of evidence in platinum-sensitive network 2, other than OVA-301 publishing final results (as opposed to interim results used during TA222). Consequently, PLDH was shown to be the most effective and cost-effective comparator to which trabectedin plus PLDH should be compared (FAD MTA 4.3.12). Hence, comparisons of trabectedin plus PLDH vs paclitaxel and topotecan are irrelevant for the decision problem in this MTA, as they were in TA222. As a result the use of the IPD data from the OVA-301 study to compare trabectedin plus PLDH vs PLDH is the most appropriate, evidence-based method to use.

In summary, previous acceptance (in TA222) by Committee A (including the same chair) of the IPD data from the OVA-301 study to compare trabectedin plus PLDH directly has been rejected by the same Committee and is arbitrary and unreasonable and not does not meet PharmaMar's legitimate expectations in the light of the assessments and the NICE DSU guidance.

2.2 The Appraisal Committee failed to take into account key differences in baseline characteristics and trial design of relevant studies that have informed the clinical and cost-effectiveness results and subsequent recommendations for the FAD including that of trabectedin.

Differences in key baseline prognostic factors (CA-125 levels, PFI, ECOG score) and entry criteria for individual patients are clearly seen in some of the trials that were included in the network meta analysis (NMA) for the platinum-sensitive population. The Assessment Group specified that unadjusted hazard ratios were used for progression-free survival and overall survival in the NMA. It acknowledged that adjusting for baseline characteristics may be important because certain characteristics are considered to influence prognosis (4.1.5) and that adjustment of clinical-effectiveness data for key prognostic factors was likely to result in

more accurate estimates of progression-free survival and overall survival (4.2.19). However, in the absence of a consistent dataset for all comparisons, the Assessment Group did not consider it appropriate to analyse a blend of unadjusted and adjusted hazard ratios (4.1.5) and the Assessment Group and the Appraisal Committee wrongly appear to have assumed that these baseline differences were unlikely to affect estimates of the relative effect of treatment and further concluded that the trials were sufficiently clinically homogeneous to compare the clinical effectiveness of treatments (4.1.4).

PharmaMar strongly disagrees with these determinations and PharmaMar notes that expert responses received by NICE from the Royal College of Physicians and NCRI-RCR-ACP-JCCO, and Health Improvement Scotland regarding the level of importance attached to baseline differences and trial inclusion criteria appears to have been ignored (NICE ACD responses). The Royal College of Physicians highlighted that the overall survival benefit seen with the ICON4/AGO-OVAR2.2 trial needed to be taken in the context of the timing of the trial when little post progression therapy was available compared to later studies included in the Assessment Group's analysis. Health Improvement Scotland noted for example that if progression were defined by CA125 criteria, this would result in a different population from that defined by RECIST and as a result the PFS and OS between trials may be very different.

Indeed, the Assessment Group itself stated that these differences in baseline characteristics was one of its main concerns with its analysis (4.2.9} The Assessment Group analysis in the FAD clearly states that the results of all three platinum networks are most sensitive to the relative effect of treatment on overall survival (4.2.15, 4.2.18, 4.2.21} and in so failing to take into account important study baseline differences and study design these have resulted in unsound conclusions being drawn from the results of the NMA.

Specific examples of key studies used in this appraisal where there was significant variation in baseline factors and study inclusion criteria are provided in Appendix 2. Such variation should have meant either the studies were excluded from the network meta-analyses or more appropriately taken into account in interpreting the results and subsequent recommendations.

In summary, the Appraisal Committee have failed to recognise the significant differences in the baseline characteristics of the trials included in the NMA and their potential to confound the overall survival results of the different treatments and should have reasonably sought to interpret the evidence on this basis or at least excluded such trials from the NMA.

2.3 The different interpretation of the evidence by the same Appraisal Committee for the MTA and TA222 regarding the use of direct head-to head data for

trabectedin to address the decision problem for the non-platinum network (Network 2) is irrational and unfair.

The 3 platinum networks created to synthesise all the interventions and comparators are discrete, separate networks and are not comparable in terms of the ICERs estimated (4.1.2). Therefore network 2, (PLDH, trabectedin plus PLDH, paclitaxel and topotecan) may be considered to provide information on the treatments suitable for platinum sensitive patients who are suitable for non-platinum based regimens, such as those unable at the time of relapse to receive platinum based therapies due to residual toxicities or allergies, or unwilling to tolerate further platinum based therapy. In TA222 for trabectedin, the only clinically relevant comparator in this network for trabectedin plus PLDH is PLDH alone, and therefore the IPD for trabectedin can be used taking into account important prognostic baseline factors without: a) compromising the results for the other products in network 2 nor; b) affecting the decision making on the clinical and cost-effectiveness in networks 1 (platinum based therapy for platinum sensitive patients) and 3 (platinum resistant/ refractory).

Based on TA222 it was reasonable for PharmaMar to expect that evidence for trabectedin would be evaluated and compared in the same way, especially as there were discrete networks, which could not be compared directly as stated by the Assessment Group (4.1.2, 4.1.3).

Therefore, it is inconsistent and unfair that the same Appraisal Committee (Committee A) attended the MTA and TA222 but came to different conclusions regarding the use of head-to-head comparisons in which IPD are available versus the use of evidence synthesis for the evaluation of trabectedin plus PLDH. We would argue that the conclusions of the Appraisal Committee in relation to TA 222 was contrary to PharmaMar's legitimate expectations.

2.4 An incorrect adjustment by the Assessment Group of drug costs for trabectedin and PLDH has been applied resulting in an inaccurate ICER being calculated.

The Appraisal Committee accepted our comment that the Assessment Group had overestimated the cost of a course of trabectedin plus PLDH and underestimated the cost of a course of PLDH alone. However the consequential ICER reduction concluded by the Appraisal Committee was far less than that suggested in the PharmaMar response to the ACD (FAD MTA 4.3.15 suggested a reduction from £35,000 to £33,000 per QALY, whilst the PharmaMar ACD response suggested a reduction from £35,000 to £28,599 per QALY).

Upon investigation, it appears that the Assessment Group instead opted to change the dosage of PLDH alone only to 50mg/m^2 as opposed to the unlicensed dose of 40mg/m^2; this reduces the ICER to £32,289. However, this is not in keeping with what the Appraisal Committee's comment that they accepted our comment that both trabectedin plus PLDH was overestimated, whilst PLDH alone was also underestimated. We advised the Assessment Group and Appraisal Committee on how to rectify this in our response, but it appears this has not been appropriately incorporated into the final FAD, which is misleading. It should be noted that we followed the same methods applied in TA222 for the derivation of treatment costs, and it is once more unfair that the Assessment Group has not correctly applied the methodology as previously used in TA222 by the evidence review group and accepted by the Appraisal Committee.

This has resulted in an inaccurate ICER being attributed to trabectedin plus PLDH which has consequently contributed to the negative NICE recommendation for trabectedin plus PLDH.

2.5 Recommendations within the FAD for the use of paclitaxel within its marketing authorisation are based on extrapolated off-label data and costs in the monotherapy platinum resistant/ refractory patients.

The wording in the FAD for paclitaxel is as follows:

- *"Paclitaxel in combination with platinum or as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer."*

Paclitaxel is licensed at a dose of 175 mg/m^2 of body surface area administered over a period of 3 hours, with a 3-week interval between treatment cycles (3.5). For the platinum resistant/refractory population (which would be included in the above recommendation), weekly (unlicensed dose) administration was perceived to be more efficacious than administration every three weeks (based on expert medical opinion) and was described as being current clinical practice (3.5). The Assessment Group estimated that the cost of a course of 3-weekly treatment with paclitaxel 175 mg/m^2 (based on an average body surface area of 1.71m^2) for 18 weeks is £638. The cost of weekly treatment with paclitaxel 80 mg/m^2 (unlicensed dose and frequency of treatment) for 18 weeks is £306 (3.6). The cost-effectiveness analysis modelled the cost of a weekly paclitaxel regimen of 80 mg/m^2 whilst the PFS and OS of the licensed dose of 175 mg/m^2 paclitaxel administered every three weeks is used to model the clinical effectiveness (Assessment Group report Table 118, p301). The cost-effectiveness analysis for paclitaxel as monotherapy should have used the costs of the licensed dose of paclitaxel as the recommendation of the FAD is for the use of paclitaxel within its marketing authorisation.

A scenario analysis was done for PLDH monotherapy in the platinum resistant/refractory population using the 50 mg/m^2 dose for clinical effectiveness and both the off-label dose of 40 mg/m^2 and licensed 50 mg/m^2 dose as the cost of treatment (4.2.22). However, no results were presented based used the costs for the licensed dose of paclitaxel175 mg/m^2 on which the FAD recommendation is based. This demonstrates an inconsistent process has been applied which could mean the cost-effectiveness results are different and could thus alter the recommendations of the FAD.

In summary, the selective use of off-label data for analysis of costs and within label clinical effectiveness results is confusing and may not reflect the real costs and clinical effectiveness of paclitaxel as monotherapy in platinum resistant/ refractory patients when used within its marketing authorisation.

2.6 Recommendations for use of off-label PLDH in combination with platinum are unlawful.

The wording in the FAD for this is:

- *"PLDH in combination with platinum* is *recommended* as *an option for treating recurrent ovarian cancer."*

NICE states in the FAD that the use of PLDH (Caelyx) in combination with platinum is outside the terms of the marketing authorisation for Caelyx. 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.

However we consider that NICE has misdirected itself in accepting this remit as the Department of Health was unable to require such appraisal on economic grounds rather than patient needs. In this regard we refer to the judgement the European Court in Case C-185/10 *European Commission v. Republic of Poland.*

This case concerned Poland allowing the placing on the Polish market. without national authorisation, of medicinal products imported from outside Poland which are almost identical to those already authorised on that market, provided that the price of those foreign medicinal products is 'competitive' in relation to the price of the medicinal products which have obtained national authorisation. Article 6(1) of Directive 2001/83/EC requires that no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued.

Article 5 of Directive 2001/83/EC provides that "A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility".

The European Court of Justice concluded that the derogation can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market. Financial considerations cannot, in themselves, lead to recognition of the existence of such special needs capable of justifying the application of the derogation provided for in Article 5(1) of the Directive.

The same principles similarly apply to off-label use of authorised products. We would therefore argue that as the three least expensive technologies were recommended and the three most, not, then it was an economic rather than patient-related rationale which was behind the Minister's support of off-label dose of PLDH in combination with platinum. Accordingly we would further argue the Appraisal Committee misdirected itself in seeking and acting upon this remit.

Conclusions

For the reasons set out above, PharmaMar believes that the Appraisal Committee's assessment of trabectedin plus PLDH was procedurally unfair and unreasonable. PharmaMar requests an oral hearing for the determination of this appeal

We believe if a fairer and more consistent approach was applied in reviewing the evidence for trabectedin it would enable the Appraisal Committee to recommend access to trabectedin plus PLDH (supported by a new approved Patient Access Scheme), which both experts and trial evidence suggests is the most effective non platinum agent for platinum-sensitive ovarian cancer.

I look forward to hearing from you.

Yours incerely,

[redacted]

Managing Director

References

Fisher M, Gore M. Cost-effectiveness of trabectedin plus pegylated liposomal doxorubicin for the treatment of women with relapsed platinum-sensitive ovarian cancer in the UK: analysis based on the final survival data of the OVA-301 trial. Value Health. 2013 Jun;16(4):507-516.

Latimer L. NICE Decision Support Unit (DSU) Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials: extrapolation with patient-level data. June 2011 (last updated March 2013).

Appendix 1 – Background to the MTA

Introduction to the Technology

Trabectedin (Yondelis, PharmaMar) is an anticancer agent that binds to the minor groove of the DNA and as a result bends the helix to the major groove, which disrupts the cell cycle. It has a UK marketing authorisation, in combination with PLDH, for the treatment of women 'with relapsed platinum-sensitive ovarian cancer'. The recommended dosage is 1.1 mg/m^2 of body surface area, immediately after PLDH 30 mg/m^2, administered every 3 weeks as a 3-hour infusion

History of the Appraisal

PharmaMar was invited to participate in the following Multiple Technology Appraisal: Ovarian cancer- topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent disease only (Review of TA 91 & TA 222) [ID468]. A brief history of the appraisal is as follows:

August2012	Draft scope issued
28 November 2012	NICE's response to consultee and commentator comments on the draft scope
12 February 2013	Final scope issued
12 February 2013	Notice on NICE website that trabectedin in combination with pegylated liposomal doxorubicin hydrochloride was omitted from the list of relevant interventions for people who are allergic to platinum-based compounds. This omission has been corrected in final scope.
13 March 2013	PharmaMar evidence submission (closing date for invited submissions / evidence submission)
04 September 2013	1s Appraisal Committee meeting
17 October 2013	PharmaMar Comments on Appraisal Consultation Document ACD
06 November 2013	2"" Appraisal Committee meeting
09 December 2013	Release of the Final Appraisal Determination (FAD) delayed.
23 April2014	Email from PharmaMar to ask when FAD will be released
30 April 2014	Email response received from NICE with no explanation for the delay
28 August 2014	Email from PharmaMar to ask when FAD will be released
2 September	Email response received from NICE with no explanation for the delay
23 December 2014	Publication of FAD
7 January 2015	Appeal period for this appraisal will close at 5pm 20 January 2015 (correction of original error on website which stated 27 January 2015)

Appendix 2 – Examples of key studies with important baseline differences that affect prognosis in ovarian cancer (all described in Assessment Group report)

- Clinical heterogeneity in the duration of PFI between trials was seen. Considering patients with platinum-sensitive disease, a potential source of heterogeneity within the trials is the proportion of patients with FPS (relapse >12 months after last platinum-based treatment) versus PPS (relapse 6-12 months after last platinum-based treatment) at baseline. The greater the duration of PFI, the more favourable the prognosis. In trials involving patients with only platinum-sensitive disease, **the proportion of patients with PPS ovarian cancer ranges from 28.6% to 43.0%.** In particular, **patients enrolled in the ICON4/AGO-OVAR2.2 trial (used in the platinum network 1 analysis) had a comparably longer PFI than patients enrolled in the other trials included in NMA of OS and PFS data. I**n this trial the proportion of patients PPS vs FPS disease was 25.3% and 74.7% respectively. ICON4/AGO-OVAR2.2 has been reported to have longer median PFS and OS for both groups compared with other trials involving platinum-sensitive patients, which is thought to be attributable to the comparatively larger proportion of patients with FPS who have an improved prognosis compared with those who are PPS. The OVA-301 study (trabectedin plus PLDH vs PLDH) found that **despite stratification by platinum-sensitive and platinum-resistant disease before randomisation, there was an imbalance between groups in patients with platinum-sensitive disease in mean baseline PFI that favoured PLDH alone** (13.3 months with PLDH alone vs 10.6 months with trabectedin plus PLDH; $p = 0.009$).

- Similarly, a comparatively high proportion of patients enrolled in the trial carried out by Gonzalez-Martin et al. were diagnosed as recurrent based on assessment of CA125 levels; therefore these patients are likely to be more susceptible to platinum therapy and gain a greater benefit than patients enrolled in the other included trials.

- Diagnosis of recurrent disease based on raised CA125 levels alone has been found to predate evidence of disease progression from clinical examinations or radiological scans by a median of 4 months in 70% of patients with ovarian cancer. Thus. there is uncertainty as to whether patients diagnosed as having recurrent disease by only CA125 level would have the same diagnosis on radiological scan. It is also possible that the degree of sensitivity to platinum could differ. For example, based on CA125 alone, a patient could be categorised as partially platinum-sensitive at baseline but as fully platinum-sensitive 4 months later with radiological confirmation. Of the 16 trials identified, 7 RCTs reported that patients with only CA125 as an indicator of recurrent disease were enrolled. In trials in patients with platinum-sensitive disease, there was

considerable variation across the trials in the proportion of patients with non-measurable disease at baseline, ranging from 8.5% to 38.2%. (Assessment Group report)

- The baseline characteristics of trials included in NMAs of platinum-based therapies also revealed an imbalance in baseline performance score (ECOG) within one of the included trials. In particular, the trial carried out by Gonzalez-Martin et al., in which paclitaxel plus carboplatin is compared with platinum monotherapy; the proportion of patients with a baseline ECOG score of 2 that were randomised to treatment with platinum monotherapy was 17.9% vs 5.6% of patients randomised to treatment with paclitaxel plus carboplatin. The Assessment Group noted that this imbalance was likely to result in an overestimation of the relative treatment effect of paclitaxel plus carboplatin vs platinum monotherapy.