Trabectedin for the treatment of relapsed ovarian cancer: A Single Technology Appraisal

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Contributions of authors

The review of the clinical evidence was undertaken by Diana Papaioannou. The review of the cost-effectiveness evidence was undertaken by Rachid Rafia and Matt Stevenson. John Stevens undertook the review of the mixed treatment comparison meta-analysis. Philippa Evans re-ran the searches included in the manufacturer's submission. Matt Stevenson advised the project.

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List of Abbreviations

AE	Adverse events
AIC	Akaike's information criterion
BIC	Bayesian information criterion
BSA	Body surface area
BSC	Best supportive care
BNF	British National Formulary
CEAC	Cost effectiveness acceptability curve
CE	Cost effectiveness
CI	Confidence interval
CIC	Commercial in confidence
EQ-5D	EuroQol 5-dimensions
ERG	Evidence Review Group
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
IC	Indirect comparison
ICER	Incremental cost-effectiveness ratio
i.v.	Intra venous
KM	Kaplan-Meier
LCI	Lower confidence interval
MS	Manufacturer’s submission
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OC	Ovarian cancer
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PFS	Progression-free survival
PLDH	Pegylated Liposomal Doxorubicin Hydrochloride
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
q3wk 3-h	every 3 weeks as 3-hour i.v. infusion

q4wk 1.5h	every weeks as 1.5-hour i.v. infusion
q3wk 24-h	every 3 weeks as 24-hour i.v. infusion
RCT	Randomised controlled trial
SmPC	Summary of Product Characteristics
SA	Sensitivity analysis
SE	Standard error
TA	Technology assessment
UCI	Upper confidence interval
ULN	Upper limit of normal

1 SUMMARY

1.1 Scope of the submission

The manufacturer's submission[1] (MS) partly reflects the scope of the appraisal issued by NICE. The MS reports on the use of Yondelis® (trabectedin) in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) in women who have advanced relapsed platinum-sensitive ovarian cancer (OC). The intervention is defined as Yondelis® (trabectedin) in combination with PLDH for the second-line treatment of platinum-sensitive relapsed OC. Within the MS, the following definitions were used to describe the platinum-sensitive population: 1) Platinum-sensitive OC- disease that responds to first-line platinum-based therapy but relapses 6 months or more after completion of initial platinum-based chemotherapy; 2) Partially platinum-sensitive OC - disease that responds to first-line platinum-based therapy but relapses between 6 and 12 months after completion of initial platinum-based chemotherapy; 3) Fully platinum-sensitive OC- disease that responds to first-line platinum-based therapy but relapses 12 months or more after completion of initial platinum-based chemotherapy. The MS considered PLDH monotherapy as an appropriate comparator for the partially platinum-sensitive population, as reflected in the NICE scope. The MS also considered PLDH monotherapy as an appropriate comparator for the fully platinum-sensitive population and the entire platinum-sensitive population, which were not outlined as appropriate comparators for these populations in the scope issued by NICE. No comparison was made with platinum-based chemotherapy (single agent or combination) for the fully or partially platinum-sensitive populations, which was issued in the NICE scope. However it appears that evidence for this comparison does not exist in direct or indirect form. The MS reported the results of mixed treatment comparisons (MTCs) with paclitaxel and topotecan (each as monotherapy) were undertaken for the entire platinum-sensitive population (> 6 month relapse). These comparisons were outside the final NICE scope, which indicated that paclitaxel or topotecan monotherapy are appropriate comparators for the partially platinum-sensitive population only. An indirect comparison with PLDH was also undertaken within the entire platinum-sensitive population (> 6 month relapse). The outcome measures identified in the MS were all relevant and included overall survival (OS), progression-free survival (PFS), overall response rate (ORR), adverse events and health related quality of life. PFS and ORR were measured by three types of assessor: independent radiologists, independent oncologists and an investigator. The assessment of PFS by the independent oncologists is the most relevant to UK clinical practice. The results provided are presented in terms of the cost per quality adjusted life year (QALY) using a lifetime horizon from the perspective of the NHS and Personal Social Services.

1.2 Summary of submitted clinical effectiveness evidence

- The main evidence in the submission is derived from one head-to-head, phase III, multi-centre, randomised, open-label, active controlled, trial comparing a combination of trabectedin and PLDH with PLDH monotherapy. This trial compared the efficacy and safety of 1.1 mg/m^2 of trabectedin (3-hour infusion) and 30mg/ m^2 of PLDH (1.5 hour infusion) every three weeks with 50mg/m^2 PLDH (1.5-hour infusion) every four weeks.

- The results of the randomised controlled trial (RCT) suggest that the combination treatment of trabectedin and PLDH significantly increased OS (hazard ratio, 0.59; 95% CI, 0.42 to 0.82; p=0.0015) and PFS (hazard ratio, 0.54; 95% CI, 0.39 to 0.76; p=0.0002)[a] in the partially platinum-sensitive population compared with PLDH monotherapy. Additional analysis compared trabectedin and PLDH with PLDH monotherapy in the fully platinum-sensitive population and showed non-significant improvements in OS (hazard ratio, 0.89; 95% CI, 0.58 to 1.35; p=0.5746) and significant improvements in PFS (hazard ratio, 0.66; 95% CI, 0.46 to 0.97; p=0.0311)[a]. Within the entire platinum-sensitive population (> 6 months relapse), non-significant improvements were seen in OS (hazard ratio, 0.82; 95% CI, 0.63 to 1.06; p=0.1259) and significant improvements in PFS (hazard ratio, 0.66; 95% CI, 0.52 to 0.85; p=0.0010)[a].

- An MTC of licensed treatments in relapsed ovarian cancer has previously been performed as part of a NICE Multiple Technology Assessment, NICE TA91.[2] Guidance issued as a result of NICE TA91 recommended PLDH as a second-line treatment option for women with partially platinum-sensitive ovarian cancer.[3] When compared with paclitaxel or topotecan monotherapy, PLDH is the most clinically and cost-effective treatment within the platinum-sensitive population.[2] The ERG sought clinical advice to clarify whether in instances whereby PLDH is contraindicated, trabectedin and PLDH combination would also be contraindicated. Clinical experts believed this to be likely. Despite PLDH being administered at a lower dose as it is in combination with trabectedin, the contraindication for use would remain. Clinical advice suggests that the most likely reason for PLDH being contraindicated is the existence of a cardiac history or problem, and clinical experts stated that they would be extremely cautious in administering PLDH even at a lower dose alongside trabectedin in such a scenario. As PLDH is the recommended second-line therapy, and trabectedin and PLDH cannot be used where PLDH is contraindicated, the relative cost-effectiveness of trabectedin and PLDH compared to paclitaxel or topotecan monotherapy is not needed, since there would never be a choice between these

[a] PFS by the independent oncologists' assessment

interventions. As such, a direct comparison of trabectedin and PLDH is sufficient to address the decision problem.

- Several Grade 3 and 4 adverse events were higher in the trabectedin and PLDH combination arm than the PLDH monotherapy arm. This included neutropenia, febrile neutropenia, thrombocytopenia, anaemia, elevated aminotransaminase (ALT) levels, fatigue, fever, diarrhoea, nausea and vomiting. Discontinuation of treatment due to adverse events was also higher within the trabectedin and PLDH arm. However, no statistical analysis comparing the rates of discontinuation or adverse events between the treatment groups were reported in the MS or in the requested supplementary data.

1.3 Summary of submitted cost effectiveness evidence

- The manufacturer submitted a decision-analytic model built in Microsoft Excel software. The model structure was derived from a previously published NICE Multiple Technology Assessment (NICE TA91) comparing topotecan as monotherapy, PLDH as monotherapy and paclitaxel as monotherapy for second-line or subsequent treatment of advanced relapsed ovarian cancer.[2]
- Four interventions were compared: trabectedin in combination with PLDH; topotecan as monotherapy; paclitaxel as monotherapy and PLDH as monotherapy in women whose cancer has relapsed more than 6 months after completion of initial platinum-based chemotherapy; such women are referred to as the platinum-sensitive population. The effectiveness for the main analysis was derived from an MTC meta-analysis due to the absence of direct comparisons of all the relevant comparators outlined in the final NICE scope.
- The manufacturer also compared trabectedin in combination with PLDH versus PLDH as monotherapy only using direct evidence from the OVA-301 trial in three patient populations:
    - in women whose cancer relapsed more than 6 months after completion of initial platinum-based chemotherapy (entire platinum-sensitive population).
    - in women whose cancer relapsed between 6 to 12 months after completion of initial platinum-based chemotherapy (partially platinum-sensitive population).

  - in women whose cancer relapsed more than 12 months after completion of initial platinum-based chemotherapy (fully platinum-sensitive population).

- Treatment effectiveness was described by the mean time to disease progression (i.e. PFS) and mean time to overall survival (OS). This was estimated assuming an exponential distribution which crossed the median Kaplan Meier (KM) survival time.
- Costs relating to treatment, management of stable disease, progressive disease and adverse events (AEs) were included in the economic model. Health utilities for PFS and disease progression were estimated from EQ-5D data collected within the OVA-301 trial.
- Health outcomes were discounted at a rate of 3.5%, however costs were not subjected to discounting. The impact of parameter uncertainty on cost-effectiveness was ascertained in univariate Sensitivity Analyses (SA) or Probabilistic Sensitivity Analyses (PSA).
- An incremental analysis was reported whereby interventions which were dominated or extendedly dominated were excluded. The manufacturer reported that paclitaxel provided the least number of QALYs followed by topotecan, PLDH as monotherapy and trabectedin in combination with PLDH. The manufacturer reported that trabectedin in combination with PLDH provided 0.27 additional QALYs compared to PLDH alone at an extra cost of £19,062. For the entire platinum-sensitive population, the model based on direct evidence produced an ICER for trabectedin in combination with PLDH versus PLDH as monotherapy of £70,076 per QALY gained.
- The manufacturer also presented the ICERs for the three direct comparisons for the entire platinum-sensitive, partially and fully platinum-sensitive populations using the assessment by the independent radiologists, the independent oncologists and the investigators ~~independent investigator~~[b]. The ICER between trabectedin in combination with PLDH versus PLDH as monotherapy in women who relapse between 6 to 12 months after initial platinum-based chemotherapy is estimated to be £39,262 in the MS using the oncologists' assessment. The manufacturer estimates that trabectedin in combination with PLDH provides 0.38 additional QALYs compared to PLDH as monotherapy for an additional cost of £14,910. Results for other scenarios are available in the MS.
- Uncertainties were examined in univariate SA only for the main analysis and PSA was undertaken for each scenario.

[b] Correction/amendment made following comments from the manufacturer

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

- The manufacturer conducted a limited but systematic search for clinical and cost-effectiveness studies of trabectedin and PLDH for the treatment of advanced relapsed platinum-sensitive ovarian cancer. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases.
- The RCT is of reasonable methodological quality (see limitations reported in section 4.1.5), and measured a range of outcomes that were appropriate and clinically relevant.
- The MS model structure replicated the structure developed in the NICE TA91.[2]
- Health state utilities were extracted from the OVA-301 trial.
- Direct evidence from the OVA-301 trial was used for the three additional scenarios comparing trabectedin in combination with PLDH versus PLDH alone.

1.4.2 Weaknesses

- The processes undertaken by the manufacturer for data extraction and for applying quality criteria to included studies are not explicitly clear in the MS. These factors limit the robustness of the systematic review.
- The direct clinical evidence is based on one RCT only. The included RCT is not an absolute reflection of the population with advanced relapsed ovarian cancer in the UK, hence its external validity may be questionable.
- Overall survival results presented in the MS are based on an interim analysis. The manufacturer estimates that final OS data will be available at the end of the second quarter of 2011.
- The ERG has some concerns about the validity of the multivariate analyses presented by the manufacturer to determine the effect of prognostic factors on treatment effect. The manufacturer presented multivariate analyses using the interaction between treatment and each prognostic factor but did not include the main effects in the regression model. This is likely to have biased the results from the regression models

and thus the ERG believes that the analyses presented by the manufacturer do not allow a reasonable interpretation of the effect of prognostic factors in PFS and OS.

- There appeared to be a high degree of censoring within the PFS analysis and reasons for censoring a large number of trial participants (n=178) were not explicitly made clear within the MS.

- The MTC reported in the MS is based on a pre-existing analysis.[2] Key details within the reporting of the MTC in the MS are neither reported nor discussed. These include details of trials included in the MTC and issues relating to heterogeneity of the trials. The manufacturer's replication of the original search undertaken for the pre-existing MTC[2] was poorly undertaken. The resulting MTC should therefore be treated with caution.

- The mean survival time was estimated assuming that data were exponentially distributed and that the distribution crosses the median KM survival time. Indeed, the data does not appear to be well represented by an exponential distribution and the assumptions made by the MS tend to overestimate mean survival.

- PFS assessed by the independent radiologists was used for the base case. However, the ERG believes the independent oncologists' assessment of PFS to be the most appropriate method of assessment to use in the base case, based on clinical advice.

- There were a number of issues in the PSA limiting its interpretation and no univariate SA were presented for the three additional scenarios using direct evidence from the OVA-301 trial.

- Despite the model structure being appropriate, the simplicity of the model structure does not allow discounting to be easily implemented. This was implemented incorrectly in the MS for health outcomes and no discounting was applied for costs.

1.4.3 Areas of uncertainty

- There is uncertainty around the clinical- and cost-effectiveness of trabectedin in combination with PLDH compared with PLDH alone in women with advanced, relapsed, platinum-sensitive ovarian cancer.

- Although it is probable that trabectedin in combination with PLDH increases overall survival and progression-free survival compared with PLDH alone in the partially

platinum-sensitive population, the size of the actual treatment effect of trabectedin and PLDH is uncertain, given trial design limitations such as the open label design, high degree of censoring and imbalance of prognostic factors (see section 4.1.5)

- The validity of results is limited as several assumptions have been made by the manufacturer. The main limitations of the analysis are:
    - the assumption that data are exponentially distributed and that the distribution crosses the median KM survival time
    - the use of the average number of cycles of treatment across all the populations included in the trials for the main analysis only (i.e. platinum-sensitive and platinum-resistant individuals)
    - uncertainty surrounding the method used by the manufacturer to derive estimates of the mean dose per cycle
    - uncertainty concerning the approach used to discount health outcomes and the absence of discounting for costs
    - problems concerning the implementation of the PSA which limit its interpretation
    - the absence of univariate SA for the direct analysis only
- The MS estimated that the ICER of a combination of trabectedin with PLDH versus PLDH as monotherapy was £39,262 using the independent oncologists' assessment in the partially platinum-sensitive population. Additional work was undertaken by the ERG and parameters/assumptions were amended where necessary. This additional work included fitting parametric distributions to individual patient data, estimating the mean dose per cycle from the cumulative dose and the number of cycles, the use of different utility values and correcting the discounting approach. Given difficulties in discriminating between the appropriateness of the Weibull and Gompertz distributions, the ERG believes that the most plausible ICER for trabectedin in combination with PLDH versus PLDH alone in women who relapse between 6 to 12 months after initial platinum-based chemotherapy is in the range £46,503 to £54,607 per QALY gained. However, uncertainties still exist as discounting cannot be easily implemented in such a model structure. Ideally a state transition-type Markov trace element should be constructed to facilitate the

implementation of discounting. Furthermore, there remains uncertainty about the method used to calculate the mean dose per cycle.

1.5 Key issues

- The MS has addressed only one part of the final scope issued by NICE i.e. trabectedin and PLDH vs. PLDH alone for the partially platinum-sensitive population. The remainder of the final scope issued by NICE is not addressed within the MS i.e. trabectedin and PLDH vs. platinum-based chemotherapy (single agent or in combination) in the fully or partially platinum-sensitive populations; trabectedin and PLDH vs. paclitaxel or topotecan monotherapy in the partially platinum-sensitive population.

- The ERG does not believe the MTC meta-analysis was necessary as part of the MS. A previous NICE Multiple Technology Assessment, NICE TA91,[2] found PLDH to be the most clinical and cost-effective treatment for the second-line treatment of women with platinum-sensitive ovarian cancer when compared with paclitaxel or topotecan monotherapy, and thus recommended PLDH as a treatment option for second-line chemotherapy in the partially platinum-sensitive population.[3] Clinical experts thought it likely that when PLDH is contraindicated (usually because of the existence of a cardiac history or problem), a trabectedin and PLDH combination is also contraindicated. Clinical experts stated that they would be extremely cautious in administering PLDH, even at a lower dose as it is alongside trabectedin in that scenario. As PLDH is the recommended second-line therapy, and trabectedin and PLDH cannot be used where PLDH is contraindicated, the relative cost-effectiveness of trabectedin and PLDH compared to paclitaxel or topotecan monotherapy is irrelevant, since a clinical choice between these interventions would not arise. As such, a direct comparison of trabectedin and PLDH is sufficient to address the decision problem.

- The external validity of the evidence is limited. Only a single randomised controlled trial (RCT) using a comparator (PLDH) and the licensed dose of trabectedin applied in England and Wales has been conducted within the platinum-sensitive population. The addition of evidence from any future RCTs may alter the results. Small changes in key parameters could markedly alter the conclusions with respect to cost and clinical effectiveness.

- The key issue in the economic model was the assumption that data were exponentially distributed and that the distribution crosses the median KM survival time. The data does not appear to be well represented by an exponential distribution and the assumptions made by the MS tend to overestimate the mean survival time which is a key driver of the cost effectiveness.

- PFS assessed by the independent radiologists was used within the base case analysis. However, the ERG believes the independent oncologists' assessment of PFS to be the most appropriate method of assessment, based on clinical advice.

- There were also a number of issues in the PSA limiting its interpretation and no univariate SA were presented for the three additional scenarios using direct evidence from the OVA-301 trial.

- Despite the model structure being appropriate, the simplicity of the model structure does not allow discounting to be easily implemented. The MS implemented this poorly for health outcomes and no discounting was applied for costs. Ideally, a state transition-type Markov trace element should be constructed to facilitate discounting.

- There is uncertainty on the approach used to estimate the mean dose per cycle.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The description of advanced ovarian cancer in section 2.1 of the manufacturer submission (MS) is brief and supporting references are not cited within this section. The MS reports within section 2.1 that ovarian cancer (OC) is asymptomatic in the early stages, with diagnosis in 75% or more cases made when OC is at an advanced stage (Stage III/IV disease). The MS states that 80% of women with OC will relapse and require second-line chemotherapy, whilst the long-term prognosis is poor and the 5-year survival rate is reported as less than 30%. There is little or no discussion on the aetiology, pathology, diagnosis and prognostic factors of OC in section 2.1. Despite the omission of supporting references, the figures stated by the MS in Section 2.1 appear to agree with other published figures[2] and appeared reasonable to the ERG's clinical advisors.

Section 2.2 reports an estimation of 5,423 new cases of OC in 2010 based on Cancer Research UK incidence rates[4] and this figure for new OC cases is used for subsequent budgetary calculations. The MS estimate the number of Stage III/IV OC cases as 4,067 and the number who will relapse as 3,253. These assumptions are also used in the Budget Impact analysis (MS, p.183-9). The ERG is satisfied that the figures stated in the MS are a reasonable approximation. The latest figures reported by Cancer Research UK were from 2006 when 5, 528 new cases were reported in the England and 380 in Wales. The crude rate per 100, 000 women was 21.4 in England and 25.0 in Wales.[4]

In Section 2.2, the MS states that expert opinion indicates that of the 80% of patients that relapse, 15% are platinum-refractory (OC that does not respond to initial platinum-based chemotherapy) and 85% respond to platinum-based chemotherapy. Of the platinum responders, the MS states that expert opinion in the UK indicates 19% are platinum-resistant (i.e. relapse < 6 months), 32% are partially platinum-sensitive (relapse within 6-12 months) and 49% are fully platinum-sensitive (relapse >12 months after initial chemotherapy). The ERG sought clinical advice to confirm these figures seemed reasonable. The opinion of the clinical advisors was 20-25% of individuals are platinum-refractory (i.e. do not respond to platinum at all), and 75-80% respond to platinum-based chemotherapy. The clinical advisors suggested that of the 75-80% that are platinum responders, 25% are platinum-resistant (< 6 month relapse), 25% are partially platinum-sensitive (6-12 months) and 50% are fully platinum-sensitive (>12 months).

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision is adequate although some discussion around specific points is required.

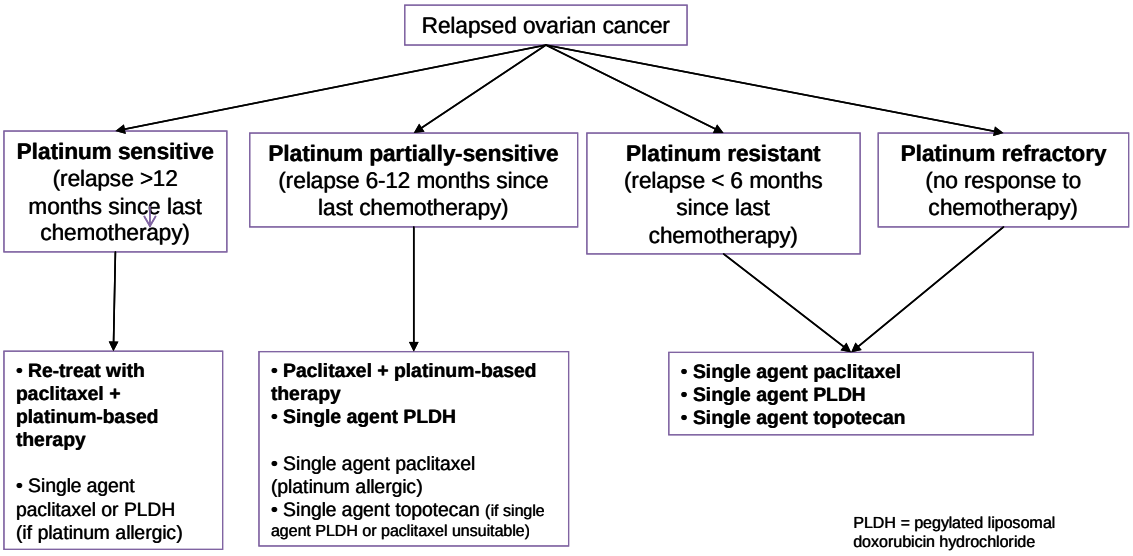
Sections 2.3 and 2.5 of the MS provides details of the relevant NICE guidance published following a Technology Appraisal on the use of paclitaxel, pegylated liposomal doxorubicin hydrochloride (PLDH) and topotecan for second-line or subsequent treatment of advanced ovarian cancer.[2] Section 2.3 provides accurate definitions of platinum-sensitive advanced OC. These definitions are also stated at the beginning of the MS (p.2) and are replicated below:

Definitions of platinum-sensitive disease

- **platinum-sensitive ovarian cancer:** disease that responds to first-line platinum-based therapy but relapses 6 months or more after completion of initial platinum-based chemotherapy
    - **partially platinum-sensitive ovarian cancer:** disease that responds to first-line platinum-based therapy but relapses between 6 and 12 months after completion of initial platinum-based chemotherapy
    - **fully platinum-sensitive ovarian cancer:** disease that responds to first-line platinum-based therapy but relapses 12 months or more after completion of initial platinum-based chemotherapy
- platinum-resistant ovarian cancer: disease that relapses within 6 months of completion of initial platinum-based chemotherapy
- platinum-refractory ovarian cancer: disease that does not respond to initial platinum-based chemotherapy.

Section 2.5 of the MS states that "second-line chemotherapy is palliative and aims to reduce symptoms and prolong survival." Section 2.5 of the MS outlines the clear choices that NICE guidance recommends for the second-line management for advanced OC. At the request of the ERG, the manufacturer provided an extension of the flow diagram on p.20 of the MS, so that the clinical pathway for fully platinum-sensitive disease was also incorporated. The flow diagram provided by the manufacturer and based on NICE TA91 guidance is reproduced below.

Figure 1: Treatment options in relapsed ovarian cancer (provided in supplementary information by manufacturer)



Reference: NICE Guidance TAG91, 2005

Section 2.4 of the MS states that for the fully platinum-sensitive population (> 12 month relapse after initial platinum therapy), common practice in the UK is to re-treat with a platinum-based regimen, unless there are good reasons for this to be contra-indicated. Section 2.4 of the MS states that the second-line treatment options for the partially platinum-sensitive population (6-12 month relapse) are paclitaxel in combination with a platinum-based compound or PLDH. A discussion regarding the relative levels of use of these two comparators has not been provided. Section 2.5 states that gemcitabine is in common use in the UK for second-line management of OC, despite not being formally recommended.

The ERG sought clinical advice to confirm that this is a reasonable description of second-line treatment for the fully and partially platinum-sensitive populations. The opinion of the clinical advisors was that this description of service provision is reasonable; whilst further relevant information was provided on two points within the patient pathway. Firstly, the choice of second-line chemotherapy is influenced by the choice of first-line chemotherapy. First-line treatment is usually a paclitaxel/carboplatin combination. However, carboplatin may be provided as a single agent, often for older patients. Second-line treatment with a paclitaxel/carboplatin combination is only recommended when this regimen has not been the first-line treatment i.e. when carboplatin monotherapy has been received as first-line therapy.

Clinical advice sought by the ERG suggested that the preferred treatment option may differ within a platinum-sensitive subgroup. For example, PLDH is more likely to be used in patients who are at the lower limit of the partially platinum-sensitive subgroup (for e.g. 6-7 months relapse) compared to patients who relapse at the upper limit of this group. Similarly,

patients who are close to being defined as fully platinum-sensitive (for e.g. 10-11 months relapse) are more likely to be treated as fully platinum-sensitive (i.e. by receiving platinum-based chemotherapies in single agent or in combination). Section 2.5 of the MS suggests there is some uncertainty around the most appropriate treatment for women whose disease relapses between 6 and 12 months after initial platinum chemotherapy and that few effective single agents are available for second-line and subsequent therapy after disease progression on platinum and taxanes. However, the clinical advice sought by the ERG does not suggest that uncertainty exists around treatment for the fully and partially platinum-sensitive populations.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

Table 1 shows the decision problem from the final NICE scope, and as addressed in the MS. The ERG requested further rationale from the manufacturer as to why the population and comparators in the decision problem were different to the final scope issued by NICE (MS, p.25-6) and Table 1 incorporates additional information provided by the manufacturer.

Table 1: Decision problem as issued by NICE and addressed by the MS

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Women with ovarian cancer that has relapsed following first-line platinum-based chemotherapy regimen, and whose cancer is platinum-sensitive.	Women with ovarian cancer that have relapsed following first-line platinum-based chemotherapy regimen, and whose cancer is platinum-sensitive.
Intervention	Trabectedin	Yondelis® (trabectedin) in its licensed indication
Comparator(s)	Women whose cancer has relapsed more than 12 months after completion of initial platinum-based chemotherapy: ▪ platinum based chemotherapy (single agent or combination) Women whose cancer has relapsed between 6 and 12 months after completion of initial platinum-based chemotherapy: ▪ platinum based chemotherapy (single agent or combination) ▪ pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy ▪ paclitaxel as monotherapy ▪ topotecan as monotherapy.	Not addressed Women whose cancer has relapsed at least 6 months after initial therapy with platinum-based chemotherapy. ▪ PLDH as monotherapy ▪ topotecan as monotherapy ▪ paclitaxel as monotherapy Women whose cancer has relapsed between 6 and 12 months after completion of initial platinum-based chemotherapy : ▪ PLDH as monotherapy

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • health-related quality of life • adverse effects of treatment.	The outcome measures considered included: • Primary efficacy measure: progression-free survival o Independent radiologists' review o Independent oncologists' review o Investigator review • Overall survival based on interim analyses • Overall objective response rate o Independent radiologists' review o Independent oncologists' review o Investigator review • Health-related quality of life measured by QLQ-C30 Global Health Status Scale • EQ-5D • Safety and tolerability o Grade 3-4 AEs
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	The main analysis compared trabectedin in combination with PLDH versus topotecan as monotherapy, paclitaxel as monotherapy and PLDH as monotherapy in the entire platinum-sensitive population using indirect evidence.

	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	Three additional scenarios were presented comparing trabectedin in combination with PLDH versus PLDH alone in the entire (> 6 months), partially (6 – 12 months) and fully (> 12 months) platinum-sensitive populations. Cost effectiveness is expressed in incremental cost per quality-adjusted life year gained. The time horizon is implicitly assumed to be lifetime as the treatment effectiveness was extrapolated over time. The analysis was conducted from the perspective of the NHS, indirect costs were excluded from the analysis

3.1 Population

The manufacturer's statement of the decision problem appropriately defines the population as women with OC that have relapsed following first-line platinum-based chemotherapy regimen, and whose cancer is platinum-sensitive. However, the MS does not define within the decision problem what is considered as the platinum-sensitive population i.e. >6 months or >12 months relapse following initial platinum-based chemotherapy. The MS also states (p.25) that particular emphasis of the submission is placed upon the use of the technology in patients whose disease is partially platinum-sensitive (6-12 month relapse).

3.2 Intervention

Trabectedin (Yondelis®) is described as an antineoplastic agent that binds to the minor groove of DNA, bending the helix to the major groove.[5] Section 1.3 of the MS states that marketing authorisation for trabectedin in combination with PLDH (Caelyx®) for the treatment of patients with relapsed platinum-sensitive OC was granted by the European

Medicines Agency on October 28, 2009. For the treatment of OC the licensed dose of trabectedin is 1.1 mg/m^2 every 3 weeks as 3-hour i.v. infusion (q3wk 3-h), immediately after PLDH 30mg/m^2.[6] When PLDH is given in combination with trabectedin, the dose is reduced from 50mg/m^2 (as given in PLDH monotherapy) to 30mg/m^2. Trabectedin is administered via a central venous catheter and 20mg of dexamethasone needs to be administered intravenously 30 minutes prior to trabectedin as anti-emetic prophylaxis and also because it appears to provide hepatoprotective effects (MS, p.22).

Treatment in paediatric patients, patients with elevated bilirubin and patients with severe renal impairment (creatinine clearance < 30 ml/min for trabectedin monotherapy and <60ml/min for trabectedin and PLDH) is contraindicated. No studies have been performed in patients with hepatic impairment. However, special caution is advised and dose adjustments may be necessary. For the elderly (>65 years), no specific studies have been performed. In the safety analysis of trabectedin monotherapy clinical trials, 80/333 patients were > 65 years and 20/333 patients were >75 years. No relevant differences were seen in these populations and therefore dose adjustments based uniquely on age criteria are not routinely recommended.[6]

3.3 Comparators

The final NICE scope states the appropriate comparators for the partially platinum-sensitive population and the fully platinum-sensitive population, for which the MS has partly addressed. The relevant comparators for each sub-group are provided below. In addition (and outside the final NICE scope), the MS includes comparators for trabectedin and PLDH for the entire platinum-sensitive population (>6 months relapse).

Fully platinum-sensitive population

The final scope issued by NICE states that platinum-based chemotherapy (single agent or combination) is the appropriate comparator for the fully platinum-sensitive population (> 12 month relapse). The manufacturer stated within the MS, and subsequent clarification requested by the ERG, that the appropriate comparison of platinum-based chemotherapy (single agent or combination) with trabectedin and PLDH was not addressed since neither direct nor indirect evidence is available for this comparison. The MS reports an adequate attempt to locate direct evidence for this comparison. There were limitations with the approach reported in the MS for identifying indirect evidence (see section 4.3.1, ERG report). The ERG was not able to check through the search results for direct or indirect evidence due to time constraints. Clinical advice suggests that it is unlikely that there are any further trials investigating the direct comparison or that could be included to facilitate an indirect comparison of trabectedin/PLDH and platinum-based chemotherapy (single agent or combination).

Partially platinum-sensitive population

The decision problem states that PLDH is the comparator addressed within the MS for the partially platinum-sensitive population (6-12 months relapse). This is the comparator stated within the final NICE scope and the ERG acknowledges that PLDH is an appropriate pharamacological comparator for trabectedin and PLDH within the partially platinum-sensitive population (6-12 month relapse).

Three additional comparators were included in the final NICE scope for the partially platinum-sensitive population: platinum-based chemotherapy (single agent or combination) and paclitaxel or topotecan as monotherapy. After clarification from the ERG, the manufacturer stated that direct comparative data is unavailable within the partially platinum-sensitive population for these three comparators. The manufacturer also stated that the indirect comparison undertaken (Section 5.7, MS p.75) could not be carried out for the partially platinum-sensitive population for trabectedin and PLDH vs. platinum-based chemotherapy (single agent or combination) because were there was no common comparator in the available studies to inform this. There are several limitations regarding the search for evidence reported within the MS to inform the indirect comparison. The ERG was not able to check through the search results due to time constraints, however clinical advice suggests that it is unlikely that there are trials that could be included to facilitate an indirect comparison of trabectedin/PLDH and platinum-based chemotherapy (single agent or combination).

Indirect comparisons were made in a mixed treatment comparison meta-analysis for trabectedin and PLDH vs. topotecan or paclitaxel or PLDH each as monotherapy. However, this analysis used the entire platinum-sensitive population (> 6 month relapse) and not the partially platinum-sensitive population (6-12 month relapse).

Entire platinum-sensitive population (>6 months release)

The decision problem provided in the MS (Section 4) states that the standard comparator to be considered for women whose cancer has relapsed at least 6 months after initial therapy with platinum-based chemotherapy (i.e. entire platinum-sensitive population) is PLDH, topotecan or paclitaxel (each as monotherapy). The final NICE scope did not specify the comparators for the entire platinum-sensitive population.

The ERG has some concerns about the appropriateness of the comparators used within the MS for the entire platinum-sensitive population. The ERG sought clinical advice regarding treatment of fully and partially platinum-sensitive individuals in UK clinical practice. Clinical advice suggests that the choice of second-line chemotherapeutic agent differs between the

fully and partially platinum-sensitive populations, thus this may make combining individuals who are fully or partially platinum-sensitive into one population inappropriate. Single agent PLDH, paclitaxel or topotecan are used very infrequently within the fully platinum-sensitive population and only when there are good reasons for not using platinum-based chemotherapy (single agent or combination) such as platinum-allergy. Clinical advice sought by the ERG suggests that platinum allergy is very rare.

3.4 Outcomes

The MS includes all the outcomes stated in the NICE scope. Clinical outcome measures included PFS, overall survival, overall response rate, adverse effects of treatment and health related quality of life (HRQoL). These are all appropriate and clinically meaningful outcomes, and there are no other valid outcomes which the ERG would have expected to be included.

Progression-free survival (PFS) and overall response rate (ORR) were measured in the OVA-301 trial by three types of assessor: independent radiologists, independent oncologists and an investigator. The independent radiologists' review was based on disease progression by radiological evaluation alone using RECIST[7] criteria and included only those patients who had measurable disease at baseline. The independent oncologists' measurements were based on radiological assessments in conjunction with pre-specified clinical data and included all randomised patients. After a clarification request from the ERG, the manufacturer stated that the investigator measured PFS and ORR according to the RECIST[7] criteria. However, the ERG is unclear how the method of PFS or ORR assessment differs between the independent radiologists and the investigator. Clinical advice sought by the ERG indicates the independent oncologists' review is the most similar to UK practice.

Safety and tolerability were measured by examining the rates of Grade 3 and 4 adverse events. HRQoL was measured by using the EQ-5D and two cancer-specific quality of life measures (Global Health Status/QoL, the Fatigue symptom scale, and the Pain symptom scale from the EORTC QLQ-C30 and the Abdominal/GI symptom scale from the EORTC QLQ-QV28).

Incremental cost per quality adjusted life year (QALY) was used as a measure of cost-effectiveness, which is in accordance with the NICE reference case.

3.5 Time frame

Time is not explicitly modelled but the time horizon is assumed implicitly to be lifetime as treatment effectiveness was extrapolated over time to calculate the mean time in PFS and mean time to death.

3.6 Other relevant factors

There are no other relevant factors to discuss.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The searches undertaken by the manufacturer to identify all relevant randomised controlled trials (RCTs) were conducted in November 2009. The search strategy utilised terms to identify the patient group (ovarian cancer) and the intervention (trabectedin). No search filter was applied to limit the search to a particular type of evidence (study, trial) and this was a reasonable strategy. No language restrictions appear to have been applied. In Appendix 2 of the MS, it is stated that searches were restricted to citations published from 2006 and no justification was provided for this restriction. The ERG sought clarification as to why the searches appeared to be restricted to 2006 onwards. The manufacturer stated that this was an error and that there had in fact been no date restrictions on the literature search.

Five electronic bibliographic databases were searched (MEDLINE, MEDLINE in Process, EMBASE, The Cochrane Library). Key databases overlooked include the Science Citation Index (Web of Science) and BIOSIS. Whilst the ERG was not able to check the search results, clinical advice suggests that searching further databases would not have yielded any additional key results. The manufacturer's own in-house database was also searched. No methods (e.g. handsearching of journals, reference and citation tracking), other than the searching of the above electronic databases, were used to identify studies. The use of such supplementary methods is required by the PRISMA (formerly QUORUM) checklist.[8] No searches for unpublished data (no research registers, such as the National Research Register or Current Controlled Trials, or conference proceedings e.g. American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO)) were searched other than the manufacturer's own in-house database. The MS failed to report the use of such methods, or to explain why these methods were not used. Nevertheless, the search strategies were of adequate quality to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

In order to be robust, the methods for identifying and screening references for inclusion in a systematic review require that two independent reviewers apply pre-specified inclusion and exclusion criteria to citations identified by the searches, and discuss any unclear references until consensus is reached. The methods of identifying and screening references for inclusion in the systematic review were not reported in the MS or in the requested supplementary data.

Therefore, it is not clear if the method of identifying and screening references for inclusion in the systematic review was robust.

Confusingly, the inclusion/exclusion criteria presented in Table B1 in the MS (p.28 and in Appendix 2 of the MS) are titled as "eligibility criteria used in the search strategy". The ERG sought clarification with the manufacturer to determine if these were the inclusion and exclusion criteria applied in the screening process, however this item was not clarified by the manufacturer.

Details of the inclusion and exclusion criteria, as specified in the MS, (p.28) and in Appendix 2, for the systematic review of the literature is summarised in Table 2.

Table 2: Inclusion/exclusion criteria in the MS study selection (reproduction of Table B1, p.28, in MS).

Criteria	Clinical effectiveness
Inclusion	• Population Patients with relapsed ovarian cancer • Intervention Trabectedin • Comparator Not stated in MS • Outcome Stated as not applicable in MS (p.25) and not stated in Appendix 2 • Study design: RCTs and non-RCTs • Language: English
Exclusion	• Population Patients with disease other than ovarian cancer • Intervention Trabectedin for any other indication • Comparator Not stated in MS • Outcome Stated as not applicable in MS (p.25) and not stated in Appendix 2 • Study design: Background, commentary, research paper, reviews, animal or laboratory research, studies where efficacy was no the outcome measure (i.e. phase I pharmacokinetic studies) • Language: Non English language

Despite the confusion regarding the title of Table B1 and the lack of inclusion criteria relating to comparators or outcomes (MS, p.28), the ERG assumes that the outcomes applied in the screening process were those reported in Section 3.4 in the ERG report, which are appropriate.

The MS (p.28) states RCTs and non-RCTs were inclusion criteria for study design. The reporting of clinical harms is often inadequate in controlled clinical trial publications because they exclude patients at high risk from harms,[9] may be too short to identify long-term or delayed harms, or may have sample sizes too small to detect uncommon events.[10,11,12,13] Accordingly, the manufacturer (p.31) included non-randomised controlled trials using trabectedin monotherapy, to inform on safety considerations. The dose ranging study[14] reported is also useful in this instance.

However, the MS does not explicitly report on inclusion criteria relating to the study design for the clinical effectiveness review only. A phase II dose ranging study of trabectedin monotherapy[14] is included within the clinical effectiveness section. The ERG assumes that the review of clinical effectiveness was limited to phase III RCTs only and that the phase II dose-ranging study was included as background information only.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

The MS identified one head to head randomised open label phase III controlled trial (OVA-301) assessing the use of trabectedin and PLDH against PLDH alone in women with relapsed ovarian cancer.[15,16] The OVA-301 trial is described as the pivotal study in the MS (p.8, p.29).

At the request of the ERG, the manufacturer confirmed that the manuscript by Monk *et al.*,[15] that was provided in-full as a reference to the MS, has been accepted by the Journal of Clinical Oncology for publication. However, the manufacturer did not state if the reference provided to the ERG was the final accepted copy. It is therefore unclear if the manuscript provided is the copy pre- or post- the peer review process. Nevertheless, the manuscript provides the relevant data included in the MS. The date of publication has not yet been confirmed. Details of the study design and patient characteristics are summarised in Table 3.

Table 3: Characteristics of included studies

Study	Design	Participants	Interventions (n=treated)	Outcomes	Follow-up
OVA-301[15]	Phase III, multi-centre (n=124), randomised, open-label, active-controlled trial (n=672) in 21 countries, including 8 sites within the UK.	• Women (≥18 years of age) with histologically proven epithelial ovarian, epithelial fallopian tube, or primary peritoneal cancer. • Previous treatment with only one platinum-based chemotherapy regimen and included platinum-resistant (<6 months platinum – free interval (PFI)) and platinum -sensitive disease (PFI≥6 months). • Patient who progressed during first-line platinum therapy (platinum-refractory) were excluded • Other inclusion criteria included life expectancy of at least 3 months, measurable disease according to RECIST[7] guidelines, ECOG performance status ≤2, adequate organ function demonstrated but defined values for a series of peripheral blood counts or serum chemistry values	T1: 90-minute infusion of PLDH 30mg/ m^2 immediately followed by trabectedin 1.1 mg/m^2 administered as a 3-hour IV infusion through a central venous catheter every 21 days (q3wk 3-h regimen, licensed dose) (n=337) N.b. 20mg IV dexamethasone preceded PLDH and trabectedin T2: PLDH 50mg/m^2 q4wk 1.5h regimen (n=335)	Primary efficacy endpoint: • Progression-free survival Secondary endpoints: o Overall survival (interim analysis) o Overall response rate o Adverse events- Grade 3 and 4 only o Health-related quality of life	Participants were randomly assigned to receive trabectedin and PLDH or PLDH alone between 20th April 2005 and 29th May 2007. Follow-up was every eight weeks for the first two years and every three months after that until death or the clinical cut-off date, which was pre-determined as May 15th 2008. Clinical cut-off date for OS extended to 31st May 2009. Duration of the trial at present ranges from 1-3 years for PFS and 2-4 years for OS

The MS (p.30-31) also identified one randomised phase II dose-ranging trial of trabectedin (ET-B-026-03)[14] and two phase II non-randomised controlled trials (ET-743 INT11 and ET-B-009).[17,18] The ET-B-026-03 trial appears to be included as a supporting trial only and its dosing regimens are 1.3mg/m^2 q3wk 24-h and 1.5mg/m^2 q3wk 3-h, which are higher doses than the licensed dose of 1.1mg/m^2. Similarly, the doses used in the non-randomised ET-743 INT11 and ET-B-009 trials differ from the licensed dose of trabectedin for relapsed ovarian cancer: 0.58/m^2 q3 wk 3-h and 1.3-1.65mg/m^2 q3 3-h respectively. The ET-B-026-03, ET-743 INT11 and ET-B-009 trials provide additional data on the safety of trabectedin.

The manufacturer's PRISMA (formerly QUORUM) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/statement.htm); however, the flow diagram (MS p. 29) is an adequate record of the literature searching and screening process.

The MS states that six studies were excluded but did not provide the references for these excluded studies. At request from the ERG, the manufacturer provided a list of the six excluded studies; four were excluded because they were phase I studies where efficacy was not a primary study objective[19,20,21,22] and two were excluded as they were abstracts of trials already identified by the literature search.[23,24] The original reasons for the six excluded studies reported in the MS (p.29, p. 31) differed slightly in that five studies were excluded as efficacy was not a primary study objective and one study was excluded due to it being an abstract of the OVA-301 trial.[23]

The participant flowcharts provided in the MS (p.52-53, p.91) were mostly in accordance with the requirements of the CONSORT flowchart or point 13 on the CONSORT checklist (http://www.consort-statement.org/consort-statement/flow-diagram/. The overall number of patients randomised was not provided in Figure B2. (MS, p.52).

The MS provides baseline demographic and clinical characteristics for the OVA-301 trial in Table B7 (MS p. 43). Whilst stating that some differences in prognostic factors exist such as age and ECOG performance status (MS, p.42), the MS provides no detailed discussion about the differences in clinical or demographic characteristics or if these differences are significant. The ERG notes that the median age of participants is higher in PLDH monotherapy arm than the trabectedin and PLDH arm. There are also greater numbers of partially platinum-sensitive patients (6-12 month relapse) in the trabectedin and PLDH arm (n=123) when compared with the PLDH monotherapy arm (n=91)[c].

[c] The manufacturer noted in the response to the ERG request for clarification that the actual number of partially platinum -sensitive patients was 91 (not n=90) in the PLDH monotherapy arm as reported in the original MS.

Conversely there are greater numbers of fully platinum-sensitive patients in the PLDH monotherapy arm (n=121) than the trabectedin and PLDH arm (n=95). This could impact upon the entire platinum-sensitive population (> 6 month relapse) analyses.

4.1.4 Details of any relevant studies that were not included in the submission

The ERG believes that all relevant studies were included in the MS. Repeat searches using the manufacturer's search terms were undertaken although the ERG was not able to sift through the search results due to time constraints. However, the ERG sought advice from their clinical advisors who do not believe there to be any additional relevant studies that should be included in the MS. The manufacturer states (p. 14) it does not anticipate that any further evidence will be available to support this indication in the next 12 months. The ERG sought clarification with the manufacturer on the reporting of further relevant data from the OVA-301 trial since OS analysis is reported from the 31st May 2009 cut-off date. The manufacturer stated that the current estimate for 520 deaths to have occurred in the OVA-301 trial, and thus final OS analysis, is by the end of the second quarter of 2011.

4.1.5 Description and critique of manufacturers approach to validity assessment

The MS provides a formal appraisal of the validity (p.54-55) of the pivotal RCT[15] and the dose-ranging study included as background[14] in the MS by using the minimum criteria for assessment of risk of bias in RCTs described by the CRD.[25] However, this validity assessment failed to include some of the criteria that are suggested by NICE in the specification for manufacturer/sponsor submission of evidence.[26] Confusingly, some of these omitted criteria were found within other parts of the MS. A completed validity assessment tool is reproduced in Table 4, for which the ERG has consolidated the responses relating to quality assessment dispersed throughout the MS.

Data for the validity assessment of the OVA-301 trial in the MS was mostly derived from the unpublished trial[15] and supplemented by trial data on file[27,28] made available to the ERG. The ERG checked the validity of the manufacturer's quality assessment which was adequate. The MS does not make it clear whether critical appraisal was done by a single reviewer or consensus of multiple reviewers.

Table 4: Validity assessment of completed trials included by the manufacturer: data provided within MS and consolidated by the ERG.

Validity assessment	OVA-301 trial[15]	ET-B-026-0 trial[14]
How was allocation concealed?	N/A as open-label study (MS, p.54)	N/A as open-label study (MS, p.54)
What randomisation technique was used?	Eligible subjects were randomly assigned in a 1:1 fashion using the permuted-block randomisation method. Randomisation was stratified according to platinum-sensitivity (sensitive versus resistant) and baseline ECOG performance status score (0 and 1 versus 2). (MS, p.54) Central randomisation was used. The randomisation number and treatment code were assigned to the subject after site personnel phoned the Interactive voice response system (IVRS). Based on the information provided, the IVRS assigned a treatment code that dictated the treatment assignment for the subject. (MS, p.33)	The random permuted blocks method was used for randomisation of patients, and the size of the blocks in the randomisation list was fixed and not accessible to the investigator. To select the blocks, a uniform (0, 1) variable with a random seed was applied. (MS, p.54)
Was a justification of sample size provided?	Yes The sample size was calculated to allow demonstration of a statistically significant difference in PFS at a one-sided 2.5% significance with at least 90% power, assuming that the PFS is 16 weeks for PLDH monotherapy	Sample size for each treatment arm was determined using a Simon two-stage design. 20 patients were to be enrolled per arm in the first stage; if 2 or more responses, 30 additional patients were to be

Validity assessment	OVA-301 trial[15]	ET-B-026-0 trial[14]
	and 22 weeks for trabectedin and PLDH combination therapy. (MS, p.49) The sample size was calculated to allow demonstration of a statistically significant difference in OS at a one-sided 2.5% significance with at least 90% power, assuming that the median OS of 62.7 weeks for PLDH monotherapy and 83.4 weeks for trabectedin and PLDH combination therapy. (MS, p.49)	enrolled per arm (total of 50 patients per arm). (MS, p.50). The null hypothesis was that the probability of ORR was p≤10% versus the alternative that p≥25% (probability of early termination= 0.677; alpha ≤0.05; beta≤ 0.1). If less than eight or eight responses in a treatment arm, the schedule was not to be considered for further evaluation in relapsed platinum-sensitive advanced ovarian cancer[14]
Was follow up adequate?	Yes for PFS based on the independent oncologists review. At 15th May 2008 cut-off date, 432 events based on independent oncologists' review (415 events were planned for 90% power). 389 PFS events based on independent radiologists' review (88% power) and 520 events based on the investigator[15] No for OS. At extended 31st May 2009 cut-off date, 419 death events (81% of the 520 deaths required by the protocol for the final OS analysis). (MS, p.104)	Yes Patients who did not progress prior to discontinuation of treatment were planned to have a complete disease assessment performed every 3 months until progression was documented. This was to allow duration of response to be documented in all responding patients. Long-term treatment/follow up was up to 5 years In regard to the safety assessments, a follow-up of all patients was to be carried out until recovery from all toxic

Validity assessment	OVA-301 trial[15]	ET-B-026-0 trial[14]
		effects (MS p.38)
Were the individuals undertaking the outcomes assessment aware of allocation?	Although this was an open-label study, the outcome assessors were blind to treatment allocation (MS, p.54)	N/A as non-comparative study (MS, p.54)
Was the design parallel-group or crossover?	Parallel-group	Parallel-group: dose-ranging study
Was the RCT conducted in the UK; if not, is clinical practice likely to differ from UK practice?	The study was conducted across 124 different centres including 21 different countries. Eight sites were UK-based. (MS, p.32)	The study was conducted across 22 European sites, including one site in the UK (MS, p.32)
How do the included RCT participants compare with patients who are likely to receive the intervention in the UK?	Median age within the trial was 57 (range 26-87) (MS, p.42) The MS states that although patients are diagnosed with OC below 60 years of age, the diagnosis is more commonly made in those over the age of 60. (MS, p.107)	Median age in the trabectedin 1.5/mg/m^2 24-h was 53.5years and in the 1.3mg/m^2 58 years. (MS, p.44) The MS states that although patients are diagnosed with OC below 60 years of age, the diagnosis is more commonly made in those over the age of 60. (MS, p.107)
What dosage regimens were used in the RCT?	Combination therapy: 90-minute infusion of PLDH 30mg/ m^2 immediately followed by trabectedin 1.1 mg/m^2 administered as a 3-hour IV infusion through a central venous catheter every 21 days (q3wk 3-h regimen, licensed dose) (n=337)	The patients were randomised to receive either of the two every-3-week trabectedin dose schedules: 1.5 mg/m^2 24-h (arm A) and 1.3 mg/m^2 3- h (arm B). (MS, p.36)

Validity assessment	OVA-301 trial[15]	ET-B-026-0 trial[14]
	Monotherapy arm: PLDH 50mg/m^2 q4wk 1.5h regimen (n=335), administered as a 90-minute infusion i.v. (MS, p.36)	
Are these dosage regimens used within the SmPC?	The planned doses are the dosage regimens used within the SmPC.	No, the planned doses are higher than the dosage regimens used within the SmPC.
Were the study groups comparable?	Although there were some imbalances in prognostic factors such as ECOG performance status and age, a pre-planned analysis showed that the trabectedin and PLDH combination arm had a significant effect independent from the effect of the covariates and, in consequence, the results have not been influenced by the imbalances observed in some baseline patient characteristics (MS, p.54)	N/A as non comparative study (MS, p.55) Age and tumour size appears to differ (MS, p.44) between groups.
Were the statistical analyses used appropriate	Yes. Standard statistical methodologies were used in all efficacy analyses. The product-limit estimator of Kaplan and Meier was used to estimate the survival curves and PFS rates. An unstratified one-sided log-rank statistic was used to test for treatment differences with respect to PFS and overall survival. (MS, p.49).	Time to-event variables were analysed using the Kaplan-Meier method. The design of the study was non-comparative, although exploratory tests were carried out (MS, p.50)

Validity assessment	OVA-301 trial[15]	ET-B-026-0 trial[14]
Was an intention-to-treat analysis undertaken	Yes- All randomised patients with measurable disease at baseline (645 out of 672 patients) were included in the analysis for the primary endpoint (PFS), assessed in the dataset generated by Independent Radiology review. 27 subjects had non-measurable disease (9 in the trabectedin + PLDH arm and 18 in the PLDH monotherapy arm) and were excluded from this analysis. In addition, an ITT analysis in all randomised patients was conducted on the primary endpoint of PFS as assessed by an Independent Oncology review taking into account clinical data on progression blinded to treatment arm, and adding these to the independent radiology review data. An algorithm was used to deal with missing imaging data (described in Table B9, p.49-50). A sensitivity analysis of the results obtained of the primary endpoint (PFS) as assessed by independent radiology review, independent oncology review and investigator's assessment was conducted. ITT analyses were conducted on	Yes, the primary analysis or ORR was based on the ITT patient population (I.e. all randomised). Patients were deemed non-evaluable if there was an early death, not assessable, insufficient data, early withdrawal, failure to receive the assigned treatment or unknown (MS, p. 50)

Validity assessment	OVA-301 trial[15]	ET-B-026-0 trial[14]
	the secondary outcomes of OS (protocol-specified interim analysis) and ORR. (MS, p.54-5)	
Were there any confounding factors that may attenuate the interpretation of the results	None stated in MS	None stated in MS
Additional information in MS (not part of NICE checklist)		

Validity assessment	OVA-301 trial[15]	ET-B-026-0 trial[14]
Were there any unexpected imbalances in drop-outs between groups?	There were differences in the reasons for discontinuation of therapy i.e. 69 patients in the trabectedin and PLDH combination therapy discontinued therapy due to adverse events compared to 39 treated with PLDH monotherapy. 178 patients treated with PLDH monotherapy discontinued due to disease progression compared to 139 patients treated with trabectedin and PLDH combination therapy. The reasons for censoring were examined in both treatment arms and no substantial differences were found in the two groups. (MS, p.55)	N/A as non-comparative study.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
RCT, randomised controlled trial; SmPC, Summary of Product Characteristics		

Some further discussion around specific points relating to the validity assessment of the pivotal OVA-301 trial[15] is required. The MS states (p.54) that there were some imbalances in prognostic factors such as ECOG performance status (PS) and age. The MS states that a pre-planned analysis (MS, p. 51) was designed to assess whether certain prognostic factors affected response to the two different treatment arms. The manufacturer conducted univariate analyses for treatment effect, multivariate analyses for main effects and multivariate analyses for the interaction of treatment effect and other prognostic factors (MS, p.69). This analysis looked at the following factors as co-variates: baseline

ECOG PS “0 or 1” vs. “2”, platinum-sensitivity (platinum-sensitive vs. platinum resistant), race (white vs. non-white), baseline tumour marker CA-125 (<2x upper limit of normal [ULN] vs. ≥2xULN), baseline age (<65 years vs. ≥65 years), baseline liver/lung involvement (yes vs. no), and prior-taxane use (MS, p.54).

The MS state that analysis showed that the combination of trabectedin and PLDH arm had a significant effect independent from the effect of the covariates and, in consequence, the MS states the results have not been influenced by the imbalances observed in some baseline patient characteristics (MS, p.69).

These analyses were not provided in the original MS but were made available to the ERG after request and are available in Appendix 1.

In the univariate analyses for each variable considered as a prognostic factor, the presence of ascites, bulky disease, higher ECOG PS and shorter platinum-free interval (PFI) resulted in higher risk for disease progression or death ($p<0.05$). CA-125 (tumour marker) and liver/lung metastases were found to influence OS only. Furthermore, treatment was found to be a significant effect only for the risk of disease progression ($p=0.0201$) and not for death ($p=0.0918$) (See Appendix 1).The univariate analyses for each variable considered as a prognostic factor and treatment arm is provided in Appendix 1.

The manufacturer also presented multivariate analyses for PFS and OS for prognostic factors, using main effects only. Treatment, PFI, the presence of ascites and bulky disease were found to be significant predictors ($p<0.05$) of the risk of disease progression or death; whilst prior taxane use, ECOG performance status and liver/lung metastases were significant predictors for risk of death only ($p<0.05$).

The manufacturer also presented a multivariate analysis of the interaction of treatment with each prognostic factor. These analyses showed that only the interaction between CA-125 and treatment was a significant predictor for risk of death only ($p<0.05$). These analyses provided by the manufacturer in the supplementary information requested by the ERG are available in Appendix 1.

Following this analysis, the manufacturer conducted a stepwise multivariate analysis including the main effects for all prognostic factors and the interaction between treatment and CA-125. Results from this analysis are presented in Appendix 1 and showed that treatment group, prior taxane use, ECOG performance status, PFI, liver/lung metastases, ascites and bulky disease were significant predictors of the risk of death ($p<0.05$).

The ERG had some concerns with the multivariate analyses presented by the manufacturer. It is unclear why the main effects were not included in addition to the interaction between treatment and main prognostic factors. The exclusion of the main effects limits the validity of the analyses presented by the manufacturer. Results from the multivariate analyses may be different if the main effects are included in addition to the interaction effects. Therefore, the ERG believes that the analyses presented by the manufacturer do not allow a reasonable interpretation of the effect of prognostic factors in PFS and OS.

In addition, the reporting on how the prognostic factor 'platinum-free interval' was used in the supplementary analyses was unclear. In the MS, (p.51), it states that platinum sensitivity was analysed as a categorical variable (platinum-sensitive vs. platinum resistant). However, in the supplementary analyses provided by the manufacturer to the ERG, platinum-free interval is reported to be treated as a continuous variable.

The ERG also noted that the proportions of individuals that were fully platinum-sensitive (> 12 months relapse) and partially platinum-sensitive (6-12 months relapse) differed between the two study arms. The trabectedin and PLDH combination arm included 123 partially platinum-sensitive patients (56%) and 95 (44%) fully platinum-sensitive patients. The PLDH monotherapy arm included fewer partially platinum-sensitive patients (n=91[d], 43%) and more fully platinum sensitive patients (n=121, 57%). Since clinical efficacy was greatest within the partially platinum-sensitive group of patients, increased numbers of these patients within the combination trabectedin and PLDH arm could influence the efficacy of the trabectedin and PLDH within the > 6 month relapse population. Also, the ERG noted that the numbers of ECOG performance status (PS) 2 were very low within the study participants.

The MS discusses the baseline demographic and clinical characteristics on p.107 in relation to how the OVA-301 participants compare with patients who are likely to receive the intervention in the UK. The MS states that age within the OVA-301 trial participants is lower than seen in clinical practice. The OVA-301 trial included individuals 65 years or older. Twenty-four percent of participants in the trabectedin and PLDH arm and 31% of participants in the PLDH alone arm were aged≥65 years. The MS states that the pre-planned analysis did not reveal age to be a relevant factor for efficacy (p.107). The MS states that there were no marked differences by age in safety profile of trabectedin and PLDH, except for more fatigue in the older age group (≥65 years) compared with younger patients (< 65 years).[29] The ERG sought clinical advice with regard to differences between the participants within

[d] The manufacturer noted in the response to the ERG request for clarification that the actual number of partially platinum -sensitive patients was 91 (not n=90) in the PLDH monotherapy arm as reported in the original MS

the OVA-301 trial and the patients seen in UK clinical practice. The ERG's clinical advisors expressed concern that the age of most patients in the OVA-301 trial was lower than the average age seen in clinical practice and that the very lower numbers of patients with an ECOG PS 2 (ECOG PS was 97% 0/1 in both study arms) did not reflect the larger proportion seen in UK clinical practice. The ERG's clinical advisors suggested that older patients may have been disinclined, at the recruitment stage, to take part in the trabectedin and PLDH arm due to the administration of trabectedin via a central venous line. Clinical advice suggests that it is more difficult to administer a central venous line in ECOG PS 2 patients, and so these patients may also have been disinclined to take part at the recruitment stage. Good performance status (i.e. 0 or 1) has been reported to improve prognosis for ovarian cancer.[5]

The MS reports on the justification of sample sizes for the primary outcome, PFS and secondary outcome OS for the entire trial population. The ERG notes that sample size was powered for the entire study population, i.e. platinum-resistant and platinum-sensitive participants. No separate power calculations were undertaken to determine a statistically significant difference in outcomes for the platinum-sensitive sub-groups.

The MS states that although this was an open-label trial, the outcome assessors were blind to treatment allocation (MS, p.54). It was unclear in the MS if all three groups of assessors: independent radiologists, independent oncologists and the investigator were blinded. On p.106 in the MS, it is stated that the independent oncologists and radiologists were blinded, but this is not stated for the investigator. The ERG sought clarification from the manufacturer who confirmed that the investigator was not blinded to treatment allocation.

For OS and ORR, all randomised patients were included in an intention-to-treat (ITT) analysis. The assessment of PFS by the independent radiologists was based on 'All Measurable Subjects" which was defined as all randomised subjects who have measurable disease at baseline, and thus wasn't based on an ITT analysis. A larger number of participants from the PLDH monotherapy arm (n=18) were excluded from the PFS analysis as they did not have measurable disease in comparison to the number excluded from the trabectedin and PLDH arm (n=9). The assessment of PFS by the independent oncologists and the investigator was based on an ITT analysis.

The MS reports the planned dose of trabectedin administered in the OVA-301 trial as 1.1 mg/m^2 administered as a 3-hour IV infusion. The MS does not make reference to the actual dose received within the OVA-301 trial and how this differs to that stated within the SmPC.[6] After a request from

the ERG, the manufacturer provided additional supplementary information that detailed median and mean dose for the whole study population and for each platinum-sensitive group, which has been consolidated by the ERG in Table 5. Within the partially platinum-sensitive population, the mean dose per cycle of trabectedin was 0.90 mg/m^2 (SE=0.01) and of PLDH was 24.74 mg/m^2 (SE=0.32) in the combination arm. In the PLDH monotherapy arm, the mean dose per cycle was 44.22 mg/m^2 (SE=0.80).[15] Cycle delay was more common within the trabectedin and PLDH arm (83% patients) compared with the PLDH monotherapy arm (55%).[15]

Table 5: Dose intensity per cycle in the OVA-301 trial: supplementary data provided by manufacturer

		Trabectedin + PLDH	
Dose intensity (mg/m^2 per cycle)	PLDH	Trabectedin	PLDH
Whole study population			
N	330	333	333
Mean (SD)	44.39 (6.96)	0.91 (0.14)	24.84 (3.96)
Median	46.78	0.91	24.77
Range	(2.76, 51.60)	(0.54, 1.14)	(14.40, 31.27)
Platinum-sensitive (> 6 months)			
N	208	217	217
Mean (SE)	439.5 (0.49)	0.89 (0.01)	24.39 (0.26)
Median	45.99	0.88	24.23
Range	(2.76, 51.12)	(0.56, 1.11)	(15.06, 30.30)
Partially platinum-sensitive (6-12 months)			
N	89	123	123
Mean (SE)	44.22 (0.80)	0.90 (0.01)	24.74 (0.32)
Median	46.09	0.88	24.56
Range	(2.76, 51.04)	(0.57, 1.11))	(15.64, 30.30)
Fully platinum-sensitive (> 12 months)			
N	120	94	94
Mean (SE)	43.80 (0.62)	0.88 (0.01)	23.82 (0.41)
Median	44.92	0.88	23.64
Range	(5.36, 51.12)	(0.56, 1.10)	(15.06, 30.22)

Critical appraisal of the non-randomised studies[18,17] was undertaken; however the validity assessment tool used in the MS for these trials is not referenced in the MS or provided by the manufacturer after request from the ERG. The validity assessment as completed in the MS is in Table 6.

Table 6: Critical appraisal of non-RCTs (reproduction of Table B24, MS p.92)

	Study ID	
	ET-743 INT11 Phase II trial[17]	**ET-B-009 Phase II trial[18]**
How is the question addressed in the study?	Not completed in MS	Not completed in MS
Appropriateness of study design to the research objective? (Yes, No)	Yes: This was an open-label, non-randomised, single-arm trial designed to assess the ORR of trabectedin in patients with platinum-sensitive and platinum-resistant disease. As this was a non-comparative trial, the study design was appropriate.	Yes: This was an open-label, non-randomised, single-arm trial designed to assess the efficacy and toxicity of trabectedin. As this was a non-comparative trial, the study design was appropriate.
Risk of bias (Yes, No)	Yes: The lack of concealed randomised allocation in any trial increases the risk of bias as does an open-label study design. However, as this was a non-comparative trial any bias would be unlikely to alter the study conclusion.	Yes: The lack of concealed randomised allocation in any trial increases the risk of bias as does an open-label study design. However, as this was a non-comparative trial any bias would be unlikely to alter the study conclusion.
Choice of outcome measure appropriate?	Yes: The primary objective was to determine the overall response rate (ORR) in patients with platinum-sensitive and -resistant disease. ORR is appropriate as a primary endpoint as it is a direct measure of the tumour burden process. ORR may have limitations as	Yes: The primary objective was to determine the overall response rate (ORR) in patients with platinum-sensitive and -resistant disease. ORR is appropriate as a primary endpoint as it is a direct measure of the tumour burden process. ORR may have limitations as an endpoint if it is taken in

	an endpoint if it is taken in isolation, as it could underestimate treatment effects on clinical end points, such as survival, or could overestimate impact on survival[30]	isolation, as it could underestimate treatment effects on clinical end points, such as survival, or could overestimate impact on survival[30]
Statistical issues?	Yes: The efficacy results were not based on an intention-to-treat analysis as only patients who had evaluable disease according to the RECIST (Response Evaluation Criteria in Solid Tumours) criteria[7]	Yes: The efficacy results were not based on an intention-to-treat analysis as only patients who had evaluable disease according to the RECIST (Response Evaluation Criteria in Solid Tumours) criteria[7]
Issues with the quality of reporting?	Yes: Hypothesis objective not clearly stated in the original paper but is clearly stated in the clinical study report[31] • Other aspects of the study e.g. study participation were clearly reported.	Yes: The following information is not reported within the original paper but is clearly stated in the clinical study report: • Hypothesis • Primary and secondary endpoints • Details of follow up[32]
Issues with the quality of the intervention?	No: The intervention (trabectedin) was appropriately defined and was administered as planned i.e. trabectedin was used appropriately within the trial.	No: The intervention (trabectedin) was appropriately defined. It was clearly stated that the dose was reduced during the study period: initially trabectedin was given at the dose of 1,650 µg/m^2 and was subsequently decreased to 1,500 µg/m^2 and then to 1,300 µg/m^2 because of toxicity.
Generalisability?	The results of this study demonstrated that trabectedin	The results of this study have been important in highlighting

	was an active treatment in patients with platinum-sensitive advanced ovarian cancer and these results have been important in highlighting areas for further research in phase III studies.	areas for further research in phase III studies.

4.1.6 Description and critique of manufacturer's outcome selection

As discussed in Section 3.4, the ERG considers the manufacturer's outcome selection to be relevant and appropriate. The outcome measures described in the decision problem generally reflect those in the OVA-301 trial and include progression-free survival, overall survival, overall response rate, HRQoL and adverse events.

There are some differences between the PFS and ORR estimations reported by the three types of outcome assessor i.e. by the independent radiologists, independent oncologists and the investigator. For example, median PFS in the partially platinum-sensitive population was 7.6 months in the trabectedin and PLDH arm by the investigator's review and 8.4 months in the independent oncologists' review (see Section 4.2.1.1 for further discussion).

4.1.7 Description and critique of the statistical approaches used

The statistical analysis of the OVA-301 trial was adequately reported in the MS (p.49-50). The primary aim of the study was to improve progression-free survival; and the study was sized for this outcome. To test a statistical difference at a one-sided 2.5% significance level with at least 90% power and assuming 16 weeks of median PFS for the PLDH monotherapy group and 22 weeks median PFS for the trabectedin and PLDH arm, 415 PFS were required. OS was a secondary outcome and 520 deaths were required to be observed to test a statistical difference at a one-sided 2.5% significance level with at least 90% power assuming 63 weeks median OS for the PLDH monotherapy arm and 83 weeks median OS for trabectedin and PLDH. Using these assumptions, the study planned to randomise 650 patients and a total of 672 patients were randomised.

Overall and progression-free survival curves were calculated according to the Kaplan-Meier product-limit estimator method, from randomisation to the date of the event of interest or the date of last

follow up. PFS and OS were compared between treatment arms using an unstratified one-sided log-rank test. ORR was compared between treatment arms using an unstratified Fisher's Exact Test at a 5% significance level. In several instances in the MS and supplementary information, the Kaplan-Meier plots did not include information on the x axis detailing the number of subjects at risk in each arm over survival time.

For OS and ORR, all randomised patients were included in an intention-to-treat (ITT) analysis. The assessment of PFS by the independent radiologists was based on 'All Measurable Subjects" which was defined as all randomised subjects who have measurable disease at baseline, and thus wasn't based on an ITT analysis. A larger number of participants from the PLDH monotherapy arm (n=18) were excluded from the PFS analysis as they did not have measurable disease in comparison to the number excluded from the trabectedin and PLDH arm (n=9). The assessment of PFS by the independent oncologists and the investigator was based on an ITT analysis.

A Cox proportional hazards regression model was used to compare the effect of demographic and clinical characteristics of the two treatment arms as a secondary analysis. This analysis assessed whether certain prognostic factors affected the response to the two different treatment arms. The ERG has some concerns about the validity of the analysis presented by the manufacturer. The manufacturer presented a multivariate analysis using the interaction between treatment and each prognostic factor but did not include the main effects in the regression model. This is likely to have biased the results from the regression models (see section 4.1.5 for further discussion).

Differences in the incidence of adverse events between treatment groups were not assessed using statistical tests nor were relative risks calculated in the MS or provided in the requested supplementary information.

4.1.8 Summary statement

The manufacturer's search strategy was adequate and the submission appears to contain all relevant head-to-head RCTs. The submission includes one phase III RCT[15] that compares trabectedin and PLDH against PLDH alone, and this trial constitutes the clinical effectiveness evidence. One dose-ranging RCT[14] and two non-RCTs[18,17] are included to provide additional background data and safety data. The validity assessment tool used was not the one recommended by NICE.[26] However, the quality assessment criteria recommended by NICE were addressed throughout the MS and consolidated by the ERG. Some discussion around a few points within the quality assessment process was lacking and details of the process, in terms of whether it was performed by two independent

reviewers, are missing. The outcomes selected were relevant and statistical methods of the OVA-301 trial were well described.

The submission partially reflects the decision problem defined in the scope issued by NICE. The clinical effectiveness data submitted compares trabectedin and PLDH against PLDH alone within the entire platinum-sensitive population (>6 months relapse following initial platinum-based chemotherapy). Sub-group analysis is undertaken within the partially platinum-sensitive population (6-12 month relapse) and fully platinum-sensitive population (>12 months relapse). The NICE scope outlines that PLDH is an appropriate comparator for trabectedin and PLDH within the 6-12 month relapse population. Therefore, the MS addresses this part of the decision problem only (and goes slightly outside scope by including the >6 month relapse and >12 month relapse populations). The decision problem is not addressed for the fully platinum- sensitive population (>12 months relapse). The NICE scope outlines that platinum-based chemotherapy is the appropriate comparator for the fully platinum- sensitive population (>12 months relapse). However, the MS states (Section 5) that there are no clinical trials that capture comparisons of trabectedin and PLDH versus a platinum-based chemotherapy, and the ERG is satisfied that this is the case.

In addition to PLDH, the NICE scope outlines that additional comparators for the 6-12 month relapse population are topotecan and paclitaxel, each as single agents. The MS compared topotecan and paclitaxel each as a single agent in a mixed treatment comparison (MTC) in section 5.7 for the > 6 months relapse population and a critique is provided in section 4.2.2 of the ERG report.

4.2 Summary of submitted evidence

This section presents the main clinical efficacy evidence from a head to head, phase III RCT (OVA-301) comparing the use of trabectedin and PLDH against PLDH alone.

4.2.1 Summary of results

In the MS, the efficacy results were inadequately or incompletely reported (MS, p.56-73). The ERG requested the manufacturer to re-tabulate data in a consistent and more transparent form and include additional missing data. Tabulated summaries of OS (May 2009 data), PFS and ORR (May 2008 data) within the platinum-sensitive populations are presented incorporating data reported in the MS and additional data requested by the ERG. Table 7 provides a summary OS data; tables 8, 9, 10 and 11 provide a summary of PFS and Table 12, 13, 14 and 15 contain a summary of ORR. Statistically significant results are those where $p < 0.05$.

Overall survival

The EMEA requested further OS analysis beyond the initial 15th May 2008 cut-off date, and so a revised cut-off date of 31st May 2009 was used for these analyses.[5] This extends the duration of the trial at present for OS to between 2-4 years. At the revised cut-off date of 31st May 2009, 81% of the planned 520 deaths had occurred for the OS analysis.

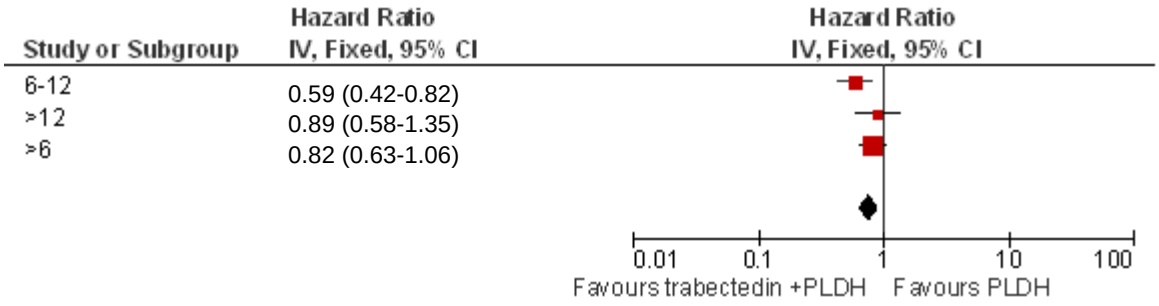
Within the overall trial population (platinum-resistant and platinum-sensitive disease) there was a favourable but not statistically significant trend for the trabectedin and PLDH combination. Within the overall trial population, the hazard ratio for death was 0.85 (95% CI: 0.70 to 1.03; p=0.0920) corresponding to a 15% relative reduction in overall mortality.

Sub-group analyses showed a consistent but not always significant benefit in overall survival for the trabectedin and PLDH arm. The largest and the only significant effect on OS was seen within the partially platinum-sensitive sub-group (6-12 month relapse). The hazard ratio for death within the partially platinum-sensitive group was 0.59 (95% CI: 0.42-0.82; p=0.0015) corresponding to a significant 41% reduction in overall mortality. Within the entire platinum-sensitive population (> 6 month relapse), the hazard ratio was 0.82 (95% CI: 0.63-1.06; p=0.1259) corresponding to a non-significant 18% reduction in overall mortality. Within the fully platinum-sensitive population (> 12 month relapse), the hazard ratio was 0.82 (95% CI: 0.58-1.35; p=0.5746) corresponding to a non-significant 18% reduction in overall mortality. However, the median OS was not reached for the trabectedin and PLDH arm in the fully platinum-sensitive population. Table 7 presents a summary of OS data.

Table 7: Summary of OS from the OVA-301 trial using May 2009 (as requested by EMEA) data set

	Numbers included in analysis	OS: Median (months)	Hazard Ratio (95% CI; p-value)
Entire study population			
Trabectedin + PLDH	337	22.4	0.85 (0.70-1.03) p=0.0920
PLDH	335	19.5	
Population: > 6 months			
Trabectedin + PLDH	218	27	0.82 (0.63-1.06) p=0.1259
PLDH	212	24.3	
Population: > 12 months			
Trabectedin + PLDH	95	Not reached	0.89 (0.58-1.35) p=0.5746
PLDH	122	31.7	
Population: 6-12 months			
Trabectedin + PLDH	91	23.0	0.59 (0.42-0.82) p=0.0015
PLDH	123	17.1	
Population: < 6 months			
Trabectedin + PLDH	119	14.2	0.90 (0.68-1.20) p=0.4806
PLDH	123	12.4	

Figure 2: Forest plot of OS by platinum-sensitive subgroup



The forest plot in figure 2 shows that OS differs between the platinum-sensitive subgroups. The hazard ratios and associated confidence intervals differ between the partially platinum-sensitive (6-12

month relapse) and the fully platinum-sensitive (>12 month relapse) populations. Therefore, it is plausible that there is a difference in treatment effect in terms of OS between these two different platinum-sensitive populations.

Progression-free survival

The primary outcome analyses of the OVA-301 trial focused on progression-free survival, which was defined as time from randomisation to disease progression or death. PFS was measured by three different types of assessor: independent radiologists, independent oncologists and an investigator. PFS analysis was undertaken for the time period between randomisation and pre-determined clinical cut-off date and so the duration of the trial at present ranges between 1-3 years. At the pre-determined May 15th 2008 clinical cut-off date, 389 events were recorded by the independent radiologists, 432 events were recorded by the independent oncologists and 520 events were recorded by the investigator.[33] This meant that when the analysis of PFS was undertaken, the planned 415 events had been judged to have taken place by two out of the three types of PFS outcome assessor (i.e. by the independent oncologists and the investigator).

Trabectedin and PLDH increased progression-free survival compared with PLDH alone, although this was not always statistically significant. For the overall trial population, the hazard ratio for remaining progression-free was 0.79 (95% CI: 0.65-0.96, p=0.0190) measured by the independent radiologists, 0.72 (95% CI: 0.60-0.88, p=0.0008) measured by the independent oncologists and 0.72 (95% CI: 0.61-0.86, p=0.0002) measured by the investigator. This corresponded to a significant relative reduction in disease progression in the trabectedin and PLDH study arm of 21% (using the independent radiologists' measurement) and 28% (using the independent oncologists' or investigator's measurement), compared with the PLDH alone arm.

Within the partially platinum-sensitive population (6-12 month relapse), the hazard ratio for remaining progression-free was 0.65 (95% CI: 0.45-0.92, p=0.0152) measured by the independent radiologists, 0.54 (95% CI: 0.39-0.76, p=0.0002) measured by the independent oncologists and 0.57 (95% CI: 0.42-0.78, p=0.0003) measured by the investigator. This corresponded to a significant relative reduction in disease progression, recurrence or death in the trabectedin and PLDH study arm of 35% (using the independent radiologists' measurement), 46% (using the independent oncologists' measurement) and 43% (using the investigator's measurement) compared with the PLDH alone arm.

Within the fully platinum-sensitive population, the hazard ratio for remaining progression-free was 0.70 (95% CI: 0.47-1.03, p=0.0707) measured by the independent radiologists, 0.66 (95% CI: 0.46-0.97, p=0.0311) measured by the independent oncologists and 0.59 (95% CI: 0.43-0.81, p=0.001)

measured by the investigator. This corresponds to a significant relative reduction of 41% or 34% of disease progression, recurrence or death in the trabectedin and PLDH study arm compared with the PLDH arm, when using the investigator's or independent oncologists' measurements, respectively. This relative risk reduction decreases to a non-significant 30% when using the independent radiologists' measurement.

Within the entire platinum-sensitive population (> 6 months), the hazard ratio for remaining progression-free was 0.73 (95% CI: 0.56-0.95, p=0.0170) as measured by the independent radiologists, 0.66 (95% CI: 0.52-0.85, p=0.001) as measured by the independent oncologists and 0.62 (95% CI: 0.50-0.78, p<0.0001) as measured by the investigator. Table 8 presents a summary of PFS for the entire study population. Tables, 9, 10 and 11 present summaries of PFS data per platinum-sensitive population.

Table 8: Summary of PFS for entire study population using May 2008 dataset

	Numbers included in analysis	PFS: Median, months	Hazard Ratio (95% CI; p-value)
Independent radiologists' review			
Trabectedin + PLDH	328	7.3	0.79 (0.65-0.96) p=0.0190
PLDH	317	5.8	
Independent oncologists' review			
Trabectedin + PLDH	336	7.4	0.72 (0.60-0.88) p=0.0008
PLDH	335	5.6	
Investigator's review			
Trabectedin + PLDH	337	7.4	0.72 (0.61-0.86) p=0.0002
PLDH	335	5.6	

Table 9: Summary of PFS for partially platinum-sensitive population (6-12 month relapse following initial platinum-based chemotherapy) using May 2008 dataset

	Numbers included in analysis	PFS: Median, months	Hazard Ratio (95% CI; p-value)
Population: 6-12 months			
Investigator's review			
Trabectedin + PLDH	123	7.6	0.57 (0.42-0.78) p=0.0003
PLDH	91	5.4	
Independent radiologists' review			
Trabectedin + PLDH	122	7.4	0.65 (0.45- 0.92) p=0.0152
PLDH	86	5.5	
Independent oncologists' review			
Trabectedin + PLDH	123	8.4	0.54 (0.39- 0.76) p=0.0002
PLDH	91	3.8	

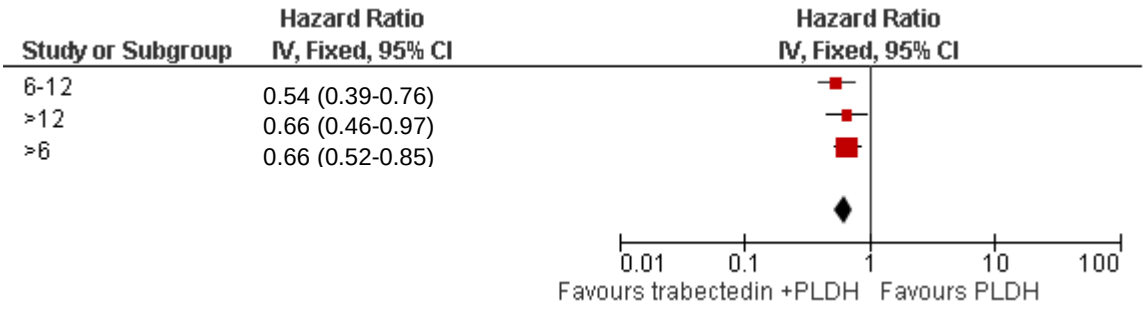
Table 10: Summary of PFS for fully platinum-sensitive population (>12 month relapse following initial platinum-based chemotherapy) using May 2008 dataset

	Numbers included in analysis	PFS: Median, months	Hazard Ratio (95% CI; p-value)
Population: > 12 months			
Investigator's review			
Trabectedin + PLDH	95	10.9	0.59 (0.43-0.81) p=0.0010
PLDH	122	7.0	
Independent radiologists' review			
Trabectedin + PLDH	93	11.1	0.70 (0.47-1.03) p=0.0707
PLDH	117	8.9	
Independent oncologists' review			
Trabectedin + PLDH	94	11.1	0.66 (0.46-0.97) p=0.0311
PLDH	122	9	

Table 11: Summary of PFS for entire platinum-sensitive population (>6 month relapse following initial platinum-based chemotherapy) using May 2008 dataset

	Numbers included in analysis	PFS: Median, months	Hazard Ratio (95% CI; p-value)
Population: > 6 months			
Investigator's review			
Trabectedin + PLDH	218	9.4	0.62 (0.50-0.78) p<0.0001
PLDH	212	5.8	
Independent radiologists' review			
Trabectedin + PLDH	215	9.2	0.73 (0.56-0.95) p=0.0170
PLDH	202	7.5	
Independent oncologists' review			
Trabectedin + PLDH	217	9.7	0.66 (0.52-0.85) p=0.0010
PLDH	212	7.2	

Figure 3: Forest plot of PFS by platinum-sensitive subgroup



The forest plot in figure 3 shows that the PFS for each platinum-sensitive subgroup are relatively similar, and therefore it cannot be ruled out that the results are from the same distribution. The ERG undertook an exploratory sensitivity analysis looking at the effects of using the hazard ratio from the entire platinum-sensitive population (> 6 months relapse) rather than the hazard ratio from the partially platinum-sensitive subgroup (6-12 month relapse) - see section 6.2.2 of the ERG report.

Overall response rate

Overall response rate (ORR) was measured by three types of assessor: independent radiologists, independent oncologists and an investigator. In order to compare treatment effect between the two study arms, the manufacturer calculated odds ratios stating that these were the most appropriate analyses to undertake for ORR. Comparative analyses for PFS and OS were both undertaken by calculating hazard ratios. An advantage of a hazard ratio is that time is explicitly taken into account within analyses whereas the odds ratio would be expressed as a comparison at a fixed, defined time point. The ERG requested that the manufacturer provide hazard ratios to compare ORR between the two study arms, however these were not provided.

Among the entire study population (n=672), a statistically significant increase in ORR was demonstrated with the trabectedin and PLDH combination therapy versus monotherapy (28% vs. 19% respectively, p=0.008) based on the independent radiologists' review.

For the partially platinum-sensitive sub-group (6 to 12 months relapse), the ORR was 33.3% in the trabectedin and PLDH group and 15.4% in the PLDH monotherapy arm based on the independent radiologists' review. The odds ratio calculated showed that participants receiving trabectedin and PLDH arm were 2.75 times more likely to respond to treatment than participants receiving PLDH alone (95% CI: 1.39; 5.44: p=0.0041) and this was statistically significant.

For the fully platinum-sensitive sub-group (> 12 months relapse), the ORR was 36.8% in the trabectedin and PLDH group and 27.9% in the PLDH monotherapy arm based on the independent radiologists' review. The odds ratio calculated showed that participants receiving trabectedin and PLDH arm were 1.51 times more likely to respond to treatment than participants receiving PLDH alone (95% CI: 0.85; 2.68: p=0.1866), although this was not statistically significant.

For the entire platinum-sensitive sub-group (> 6 months relapse), the ORR was 35.3% in the trabectedin and PLDH group and 22.6% in the PLDH monotherapy arm based on the independent radiologists' review. The odds ratio calculated showed that participants receiving trabectedin and PLDH arm were 1.87 times more likely to respond to treatment than participants receiving PLDH alone (95% CI: 1.22; 2.85: p=0.0042), which was statistically significant.

ORR recorded by the independent oncologists and the investigator provided further estimates of ORR for the entire study population and each different platinum-sensitive sub-group. ORR recorded by the three methods of measuring ORR is presented in Tables 12, 13, 14 and 15.

Table 12: Summary of ORR for entire study population using May 2008 dataset

	Numbers included in analysis	ORR: n, %	Odds Ratio (95% CI; p-value)
Entire study population			
Investigator's review			
Trabectedin + PLDH	Not provided	n=130 38.6%	Not provided
PLDH	Not provided	n=89, 26.6%	
Independent radiologists' review			
Trabectedin + PLDH	337	n=93, 28.0%	1.65 (1.14- 2.37) p= 0.0080
PLDH	335	n=63, 19.0%	
Independent oncologists' review			
Trabectedin + PLDH	Not provided	Not provided	Not provided
PLDH	Not provided	Not provided	

Table 13: Summary of ORR for partially platinum-sensitive population (6-12 month relapse following initial platinum-based chemotherapy) using May 2008 dataset

	Numbers included in analysis	ORR: n, %	Odds Ratio (95% CI; p-value)
Population: 6-12 months			
Investigator's review			
Trabectedin + PLDH	123	n=54 43.9%	2.18 (1.22 - 3.93) p= 0.0098
PLDH	91	n=24 26.4%	
Independent radiologists' review			
Trabectedin + PLDH	123	n=41, 33.3%	2.75 (1.39- 5.44) p=0.0041
PLDH	91	n=14, 15.4%	
Independent oncologists' review			
Trabectedin + PLDH	123	n=46, 37.4%	3.03 (1.56 - 5.88) p=0.0008
PLDH	91	n=15, 16.5%	

Table 14: Summary of ORR for fully platinum-sensitive population (>12 month relapse following initial platinum-based chemotherapy) using May 2008 dataset

	Numbers included in analysis	ORR: n, %	Odds Ratio (95% CI; p-value)
Population: >12 months			
Investigator's review			
Trabectedin + PLDH	95	n=50 52.6%	1.90 (1.10- 3.28) p= 0.0271
PLDH	122	n=45 36.9%	
Independent radiologists' review			
Trabectedin + PLDH	95	n=35; 36.8%	1.51 (0.85 - 2.68) p=0.1866
PLDH	122	n=34; 27.9%	
Independent oncologists' review			
Trabectedin + PLDH	94	n=38; 40.4%	1.69 (0.96 - 2.98) p=0.0823
PLDH	122	n=35;28.7%	

Table 15: Summary of ORR for entire platinum-sensitive population (>6 month relapse following initial platinum-based chemotherapy) using May 2008 dataset

	Numbers included in analysis	ORR: n, %	Odds Ratio (95% CI; p-value)
Population: > 6 months			
Investigator's review			
Trabectedin + PLDH	218	n=103 47.2%	1.86 (1.25- 2.75) p= 0.0022
PLDH	212	n=69, 32.5%	
Independent radiologists' review			
Trabectedin + PLDH	218	n=77, 35.3%	1.87 (1.22- 2.85) p= 0.0042
PLDH	212	n=48, 22.6%	
Independent oncologists review			
Trabectedin + PLDH	217	n=85, 39.2%	2.09 (1.37- 3.17) p= 0.0006
PLDH	212	n=50, 23.6%	

Health-related quality of life

Health-related quality of life (HRQoL) was measured using two cancer-specific QoL checklists during the OVA-301 trial. Data from the Global Health Status/QoL, the Fatigue symptom scale, and the Pain symptom scale for the EORTC QLQ-C30 and the Abdominal/GI symptom scale from the EORTC QLQ-QV28 were collected at every other cycle (approximately every 1.5 months) and the results are reported in the MS (p.71). No statistically significant differences were found between treatment arms in global measures of QoL. Only minor, sporadic differences in the fatigue symptom scale were found in cycles 3 and 9, with some worsening of fatigue for subjects in the combination arm.

The MS states (p.48) that EQ-5D data (index and visual analogue scale) was collected during the OVA-301 trial, however complete results were not presented in the MS. At the request of the ERG, the manufacturer provided EQ-5D data, which is presented in Tables 16, 17, 18 and 19. However the

EQ-5D data reported by the manufacturer in the supplementary analyses is presented in a 0 to 100 scale, so the ERG is unclear whether this is EQ-5D index data (which is measured on a -0.59 to 1 scale on the UK tariff). The data shows that the baseline mean EQ-5D scores were lower in the trabectedin and PLDH arm than the PLDH alone arm in the >6 months and >12 months relapse populations. Mean EQ-5D scores were higher within the trabectedin and PLDH arm than the PLDH alone arm in the 6-12 month population. At the end of treatment, mean EQ-5D scores were higher in the trabectedin and PLDH arm when compared with the PLDH monotherapy arm for the entire study population and for all platinum-sensitive sub-groups. However, it is not clear how the mean EQ-5D at the end of treatment was calculated.

In general, at Cycles 17, 19 and 21, mean EQ-5D scores were substantially higher in the trabectedin and PLDH arm when compared with the PLDH monotherapy arm (for the entire study population and the platinum-sensitive sub-groups). However, for earlier cycles, this was not always the case with EQ-5D scores frequently being higher in the PLDH monotherapy arm, most notably in the >6 months and >12 months relapse populations. Generally, EQ-5D scores were higher within the trabectedin and PLDH arm throughout treatment in the partially platinum-sensitive population (6-12 month relapse).

Table 16: EQ5D for the whole study population in the OVA-301 trial

	PLDH		**Trabectedin/PLDH**	
Cycle	**n**	**Mean (Lower CI, Upper CI)**	**n**	**Mean (Lower CI, Upper CI)**
Baseline	294	66.3 (64.0, 68.6)	296	66.3 (64.0, 68.6)
Cycle 3	184	66.5 (63.8,69.1)	214	63.1 (60.7, 65.6)
Cycle 5	141	65.6 (62.8, 68.4)	160	64.7 (62.1, 67.2)
Cycle 7	63	66.2 (61.4, 71.0)	92	67.3 (64.4, 70.2)
Cycle 9	39	66.1 (61.0, 71.2)	58	67.3 (63.7, 71.0)
Cycle 11	21	67.2 (58.7, 75.7)	34	65.9 (60.8, 71.0)
Cycle 13	12	67.9 (57.0, 78.8)	22	68.0 (62.6, 73.5)
Cycle 15	3	78.3 (74.5, 82.1)	9	63.7 (55.2, 72.1)
Cycle 17	4	64.3 (32.7, 95.8)	6	69.8 (57.6, 82.1)
Cycle 19	4	71.0 (32.2, 100.0)	2	77.5 (0.0, 100.0)
Cycle 21	1	35.0 (0.0, .)	1	87.0 (0.0,.)
End of treatment	182	59.0 (55.6, 62.3)	197	61.6 (58.7, 64.5)

Table 17: EQ5D for the entire platinum sensitive population (> 6 month relapse) in the OVA-301 trial

	PLDH		Trabectedin/PLDH	
Cycle	**n**	**Mean (Lower CI, Upper CI)**	**n**	**Mean (Lower CI, Upper CI)**
Baseline	191	68.4 (65.6, 71.2)	188	67.5 (64.8,70.2)
Cycle 3	126	66.5 (63.3, 69.8)	142	64.0 (61.2, 66.7)
Cycle 5	100	64.2 (60.7, 67.7)	116	66.3 (63.5, 69.2)
Cycle 7	48	67.4 (61.6, 73.2)	71	67.4 (64.1, 70.7)
Cycle 9	29	68.4 (62.4, 74.4)	46	67.7 (63.6, 71.7)
Cycle 11	16	71.1 (61.6, 80.5)	27	65.8 (60.4, 71.3)
Cycle 13	10	65.6 (52.7, 78.5)	20	67.5 (61.5, 73.4)
Cycle 15	2	78.5 (59.4, 97.6)	7	62.1 (52.1, 72.1)
Cycle 17	3	62.0 (3.3, 100.0)	5	71.8 (57.0, 86.6)
Cycle 19	4	71.0 (32.2, 100.0)	1	90.0 (0.0,.)
Cycle 21	1	35.0 (0.0,.)	1	87.0 (0.0,.)
End of treatment	125	60.4 (56.3, 64.5)	128	65.0 (61.8, 68.2)

Table 18: EQ5D for the partially platinum-sensitive population (6-12 month relapse) in the OVA-301 trial

	PLDH		Trabectedin/PLDH	
Cycle	**n**	**Mean (Lower CI, Upper CI)**	**n**	**Mean (Lower CI, Upper CI)**
Baseline	82	65.3 (61.1, 69.6)	109	66.7 (63.0, 70.3)
Cycle 3	45	65.4 (60.5, 70.2)	82	62.2 (58.6, 65.7)
Cycle 5	39	61.9 (56.6, 67.2)	68	65.1 (61.1, 69.0)
Cycle 7	17	64.1 (52.0, 76.1)	39	68.0 (64.3, 71.7)
Cycle 9	11	66.2 (59.8, 72.5)	23	71.4 (64.9, 77.9)
Cycle 11	5	71.2 (59.4, 83.0)	13	67.5 (56.6, 78.5)
Cycle 13	3	62.0 (32.2, 91.8)	11	70.5 (62.3, 78.6)
Cycle 15	1	77.0 (0.0, .)	1	80.0 (0.0, .)
Cycle 17	1	72.0 (0.0, .)	0	
Cycle 19	1	80.0 (0.0, .)	0	
End of treatment	54	57.7 (51.8, 63.6)	76	65.3 (61.4, 69.2)

Table 19: EQ5D for the fully platinum-sensitive population (>12 month relapse) in the OVA-301 trial

	PLDH		Trabectedin/PLDH	
Cycle	**n**	**Mean (Lower CI, Upper CI)**	**n**	**Mean (Lower CI, Upper CI)**
Baseline	111	70.7 (67.1, 74.4)	79	67.5 (63.2, 71.9)
Cycle 3	80	67.6 (63.3, 71.8)	61	66.6 (62.3, 70.9)
Cycle 5	61	65.7 (61.0, 70.3)	50	66.1 (61.4, 70.8)
Cycle 7	31	69.2 (62.5, 75.9)	32	66.7 (60.7, 72.6)
Cycle 9	18	69.8 (60.4, 79.2)	23	63.9 (59.0, 68.8)
Cycle 11	11	71.0 (56.9, 85.1)	14	64.2 (59.4, 69.0)
Cycle 13	7	67.1 (47.9, 86.4)	9	63.8 (53.6, 74.0)
Cycle 15	1	80.0 (0.0, .)	6	59.2 (50.7, 67.7)
Cycle 17	2	57.0 (0.0, 100.0)	5	71.8 (57.0, 86.6)
Cycle 19	3	68.0 (0.0, 100.0)	1	90.0 (0.0..)
Cycle 21	1	35.0 (0.0.)	1	87.0 (0.0, .)
End of treatment	71	62.8 (57.1, 68.6)	53	63.2 (57.5, 69.0)

4.2.1.1 Critique of clinical efficacy data reported

The clinical efficacy data reported in the MS addresses only part of the scope issued by NICE. The direct evidence reported in the MS provides a comparison of trabectedin and PLDH in a partially platinum-sensitive population (6-12 month relapse). No direct evidence is reported for a comparison of trabectedin and PLDH vs. platinum-based chemotherapy (single agent or combination) for the fully platinum-sensitive population (>12 month relapse). No direct evidence is reported for a comparison of trabectedin and PLDH vs. single agent paclitaxel or topotecan for the partially platinum-sensitive population (6-12 month relapse). The ERG is satisfied that no direct evidence exists for the comparisons that were not addressed in the MS.

There are a number of issues that may limit the robustness of the efficacy data reported in the MS. The OS data is based on interim analysis (31st May 2009) and thus is underpowered to detect a difference in OS between the two interventions at present (81% powered).

Whilst adequate sample size calculations are described to inform the entire study population recruited, the study does not appear to have been powered to detect a difference in PFS or OS between the study arms for each of the platinum-sensitive sub-groups (relapse following initial platinum-based chemotherapy: >6 month, 6-12 month and >12 month).

A large number of participants have been censored in the OVA-301 trial. For OS, 197 study participants were censored in the entire platinum-sensitive population (> 6 month relapse) and 70 were censored in the partially platinum-sensitive population (6-12 months relapse). Numbers censored within the fully-sensitive population were not provided but the ERG assumes that 127 were censored. Reasons for censoring OS were not provided in the MS. However, as the recruitment stage of the OVA-301 trial ran between 20th April 2005 and 29th May 2007, it is assumed that those recruited at the latter end of this period were still alive at the 31st May 2009 cut-off and thus were censored.

For PFS, the number of study participants censored are provided in Table 20. A full account of the reasons for censoring patients for PFS is not provided in the MS. However, further information is provided in a reference of data on file.[28] Reasons given for censoring include:

- Twenty-eight patients (n=15 for PLDH and n=13 for trabectedin and PLDH) had their PFS censored at randomisation +1 because they did not undergo tumour evaluations while on treatment.

- Two patients (one in each treatment arm) had their PFS censored because a gap of > 18 weeks was observed between the last evaluation without progression and the date of progression

- One hundred and seventy-eight patients (n=88 PLDH and n=90 trabectedin and PLDH) had their PFS censored at the last evaluation before subsequent therapy

- Forty-eight patients (n=19 PLDH and n=29 for trabectedin and PLDH) had not received subsequent therapy at the time of the data cut-off (May 2008) and had PFS by the independent radiologists censored at the time of the last evaluation. This includes 15 patients (n=7 for PLDH and n=18 for trabectedin and PLDH) who had disease progression documented by the investigator and had no further tumour evaluations, and 18 patients who were still receiving treatment or had the following tumour assessment scheduled beyond the cut-off (n=5 for PLDH and n=13 for trabectedin and PLDH).

The ERG is concerned about the lack of clarity within the OVA-301 trial in the reasons given for censoring PFS. Firstly, there is uncertainty around the reasons for censoring 178 patients at the first

evaluation before subsequent therapy as stated in the data on file.[28] As stated in the unpublished report of the trial by Monk *et al.*, treatment was continued until disease progression or confirmation of a complete response and could be continued for ≥2 cycles beyond confirmed complete response.[15] It can only be assumed that these 178 patients did not experience disease progression which would be recorded as an event and thus not be censored. Therefore, it appears that there is another reason (or reasons) other than disease progression which meant 178 patients received subsequent therapy; meaning that they were censored at the time of their last tumour assessment. However, since these reasons are not discussed and we are not aware of an amendment to the protocol detailing why patients would receive subsequent therapy without disease progression, the large number of patients censored in this way means that considerable bias may exist in the PFS results.

Secondly, there is no discussion in the MS regarding either the discrepancy in disease progression assessment between the three different methods of PFS measurement (independent radiologists, independent oncologists and investigator) or the discrepancies which existed between the two independent radiologists' PFS assessment. The FDA background information for the FDA Oncologic Drugs Advisory Committee Meeting on July 15, 2009[33] (p.38) states that the majority of subjects (58/65 in PLDH and 55/62 in trabectedin and PLDH) were censored by the independent radiologists as a result of receiving subsequent therapy i.e. they were judged to have not progressed by the independent radiologists but were started on subsequent therapy based on the Investigator's assessment of progression. Whilst this indicates the Investigator gave treatment during the trial, in practice this role would normally be carried out by the oncologist (s). The FDA briefing document[34] also discusses the high level of disagreement between the two independent radiologists on the progression status of 39% (252/645) of the patients with measurable disease requiring adjudication by a third radiologist. Table 20 demonstrates the discrepancies in the numbers censored between the three methods of measurement. A full and explicit account of and the reason for the discrepancies was not provided in the MS.

Table 20: Numbers censored within platinum-sensitive populations

	Numbers censored		
Platinum sensitivity	Radiologists	Oncologists	Investigator
Partially platinum- sensitive (6-12 month relapse)	84	73	51
Fully platinum- sensitive (>12 month relapse)	105	104	59
Entire platinum-sensitive population (>6month relapse)	Not provided	Not provided	Not provided

In most instances, the three methods of measuring PFS or ORR assessment (independent radiologists, independent oncologists and investigator) provided similar estimates of PFS and ORR. However, there are some occasions where these differed considerably. For example for median PFS in the partially platinum-sensitive population was 7.6 months in the trabectedin and PLDH arm by the investigator's review and 8.4 months in the independent oncologists' review.

As discussed in section 4.1.5, there are trial design limitations such as the comparability of trial participants with patients seen in UK clinical practice (for e.g. age, ECOG PS) that could limit the external validity of the trial findings. The ERG has some concerns about the validity of the multivariate analyses presented by the manufacturer to determine the effect of prognostic factors on treatment effect (see 4.1.5 for further discussion).

The imbalance in the numbers of partially platinum-sensitive and fully platinum-sensitive patients between the two study arms may over-estimate the efficacy of trabectedin and PLDH in the entire platinum-sensitive population (> 6 month relapse), since the 6-12 month relapse population may respond better to trabectedin and PLDH than the >12 month relapse population. However, after examining the treatment effect for PFS (see figure 3 and Table 9, 10, 11); it appears that there is little difference between the hazard ratios and associated confidence intervals for each platinum-sensitive subgroup. This means that it can not be ruled out that the PFS results for each platinum-sensitive subgroup are from the same distribution. The ERG undertook an exploratory sensitivity analysis looking at the effects on the ICER of using the hazard ratio from the entire platinum-sensitive

population (> 6 months relapse) rather than the hazard ratio from the partially platinum-sensitive subgroup (6-12 month relapse), see section 6.2.2 of the ERG report. For OS, it is plausible that a difference in treatment effect exists between the platinum-sensitive subgroups.

4.2.2 Safety and tolerability

The MS reports safety and tolerability data from the OVA-301 trial. Additional safety data were reported from one dose-ranging phase II RCT and two phase II non-RCTs.

A summary of the rates of discontinuation for all participants within the OVA-301 trial of treatment are presented in the patient flow diagram in the MS (p.52) and the ERG has tabulated this data within Table 21. The rates of discontinuation due to adverse events and as a result of a complete response are higher within the trabectedin and PLDH arm whilst rates of discontinuation due to progressive disease are higher within the PLDH alone arm. However, statistical analyses comparing the rates of discontinuation between the treatment groups were not reported in the MS or in the requested supplementary data.

The safety profile for all-treated subjects was presented in the MS (p.95) and replicated in Table 22. It is unclear why the number of all-treated subjects differs in this table presented in the MS on p.95 and the numbers presented in the patient flow diagram on p. 52. Within the safety profile data table (p.95), all-treated subjects are 330 in the PLDH arm and 333 in the trabectedin PLDH arm. Within the patient flow diagram, the numbers are 329 and 334 respectively. Drug-related Grade 3-4 TEAEs and serious drug-related TEAEs appear higher within the trabectedin and PLDH arm than the PLDH alone arm. Drug-related TEAEs leading to treatment termination are also higher within the trabectedin and PLDH arm. However, no statistical analysis was provided within the MS or in the requested supplementary data comparing these rates. The numbers of patients who discontinued treatment and the reasons for treatment discontinuation were not provided for the platinum-sensitive sub-groups in the MS.

Table 21: Number (%) of patients discontinuing treatment in the OVA-301 trial (Data derived from patient flow diagram in MS, p.52)

	Interventions (n)	
	Trabectedin and PLDH (337)	PLDH (335)
Subjects randomised	337	335
Subjects who received intervention	334 (99.1 %)	329 (98.2%)
Subjects who did not receive intervention*	3 (0.9 %)	6 (1.8%)
Subjects analysed for OS, ORR	337 (100%)	335 (100%)
Subjects analysed for PFS**	328 (97%)	317 (95%)
Discontinued intervention	325 (96%)	322 (96%)
Primary reason for discontinued intervention:		
Progressive Disease	139 (42.8%)	178 (55.3%)
Withdrew consent	57 (17.5%)	50 (15.5%)
Adverse events	69 (21.2%)	39 (12.1%)
Complete response	24 (7.4%)	14 (4.3%)
Investigator's decision	19 (5.8%)	17 (5.3%)
Death	8 (2.5%)	8 (2.5%)
Lack of further response/benefit	4 (1.2%)	7 (2.2%)
Partial response	3 (0.9%)	4 (1.2%)
Non-compliance to protocol	1 (0.3%)	0 (0%)
Completion of 6 cycles	1 (0.3%)	0 (0%)
Due to an error	0 (0%)	2 (0.6%)
Decreased LVEF ***	0 (0%)	2 (0.6%)
Ascites-adenocarcinoma	0 (0%)	1 (0.3%)
Lost to follow-up	2 (0.6%)	0 (0%)

Note: Percentages may not add up to 100% due to rounding

*Reasons for not receiving allocated intervention: Trabectedin and PLDH- 3 screening failures; PLDH alone-4 screening failures and 2 by subject choice.

** Reasons for exclusion from PFS analysis: Non-measurable disease (n=9 for trabectedin and PLDH and n=18 for PLDH alone)

*** LVEF- Left ventricular ejection fraction

Table 22: Safety profile of OVA-301 trial: All-treated subjects analysis set (Table replicated from MS, p.95)

	Trabectedin + PLDH (N=333)	PLDH (N=330)
	n (%)	n (%)
Treatment-emergent adverse events (TEAEs)	333 (100)	326 (99)
Drug-related	332 (>99)	312 (95)
Grade 3-4 TEAEs	304 (91)	237 (72)
Drug-related	295 (89)	193 (58)
Serious TEAEs	130 (39)	101 (31)
Drug-related	90 (27)	44 (13)
Grade 3-4	112 (34)	77 (23)
TEAE leading to treatment termination*	78 (23)	50 (15)
Drug-related	57 (17)	31 (9)
All deaths within 30 days of last dose	11 (3)	8 (2)
Deaths due to TEAE	5 (2)	1 (<1)
Progressive disease	6 (2)	6 (2)
Other	0	1 (<1)

Note: Percentages may not add up to 100% due to rounding

*The information regarding TEAE leading to treatment termination in this table is based on data collected on the Adverse Event page of the case report form

In the OVA-301 trial, serious (Grade 3) and life-threatening (Grade 4) severity events were recorded as well as a combined figure reporting all grades of adverse events (Grade I and II adverse events were not reported as separate figures). A summary of the adverse events reported at ≥5% for the all study participants and the platinum-sensitive sub-group populations (>6 month, 6-12 month and >12 month relapse periods) is presented in Table 23. This table includes data presented in the MS and additional data requested by the ERG.

However, some aspects of adverse events data remain missing. Firstly, the MS states (p.99) that for the purposes of the economic analysis, the frequency of adverse events considered to have a significant clinical and cost impact were presented for the platinum-sensitive sub-groups; thus the adverse events reported for all study participants differ to those reported for the platinum-sensitive sub-groups. The ERG asked the manufacturer to clarify exactly why these particular events were chosen, particularly if adverse events considered having a clinical and/or costing impact rather than both a clinical and cost impact (as stated in the MS, p.99) were considered, however no response was received. Secondly, not all numbers or percentages of adverse events were provided in the supplementary information. Lastly, the MS and requested supplementary information did not provide any statistical analyses to compare the rates of serious and life-threatening adverse events between the two study arms in the form of p-values and relative risks.

[redacted]

[redacted]	[redacted]	[redacted]			[redacted]		
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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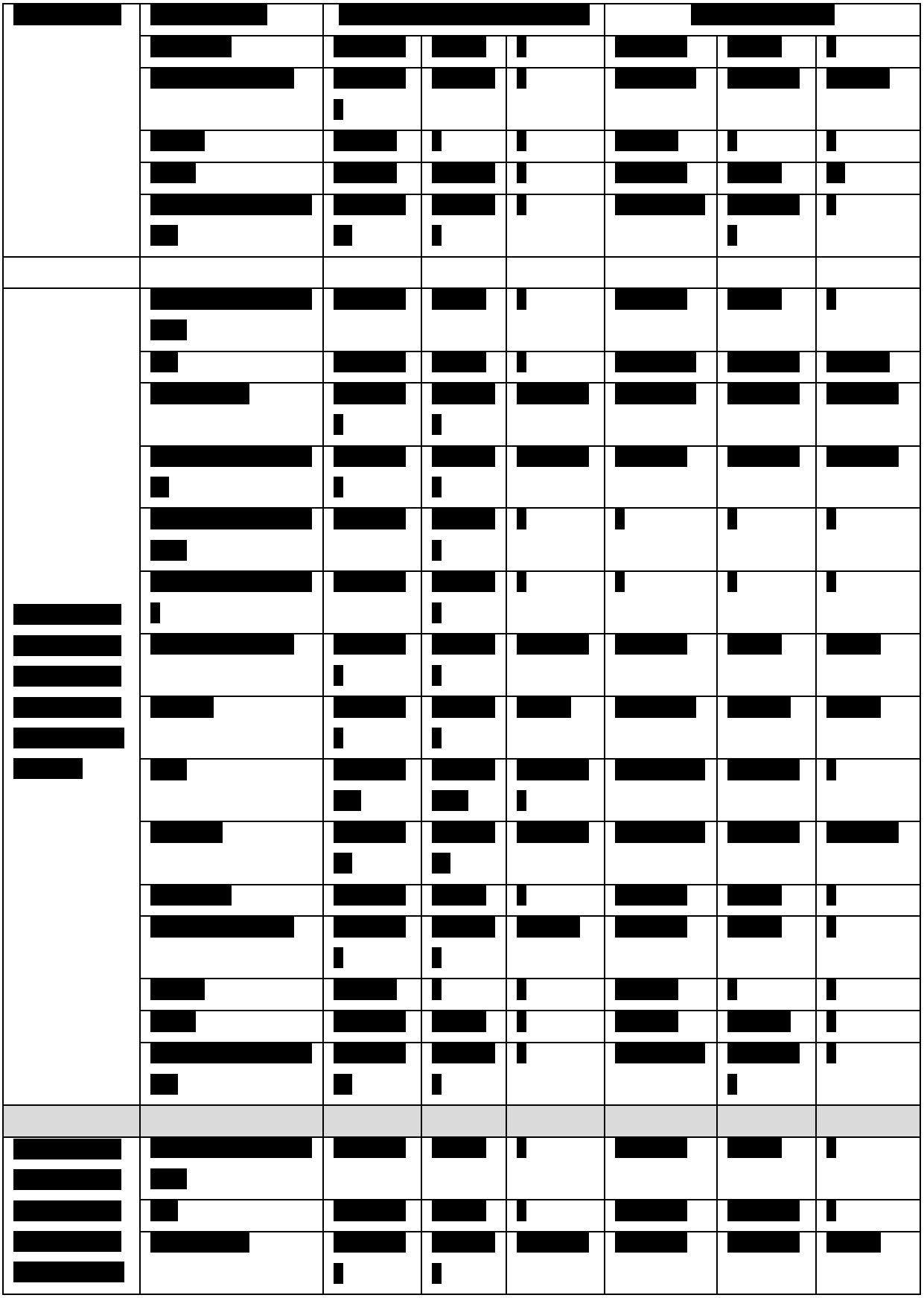


[redacted]

In general, most of the reported adverse events, were higher within the trabectedin and PLDH arm than the PLDH monotherapy arm, including neutropenia, febrile neutropenia, thrombocytopenia, anaemia, elevate alanine aminotransaminase (ALT) levels, fatigue, fever, nausea and vomiting, and diarrhoea. The three exceptions were mucosal inflammation, Palmer-plantar erythyrodysaesthesia (PPE) and stomatitis which were seen in higher rates in the PLDH monotherapy arm. This pattern was seen in the entire study population as well the different platinum-sensitive sub-groups. Despite the absence of p-values and relative risks from the MS and supplementary information to compare adverse event rates between the two study arms, the absolute differences in some of the rates were substantial. For example, for neutropenia, the rate for all grades of AEs combined was 20-25% higher in the trabectedin arm for all platinum-sensitive sub-groups; grade 4 neutropenia was approximately 30% higher in the combination arm compared with the PLDH monotherapy arm. Similarly, considerable differences in rates were seen for thromobocytopenia, febrile neutropenia and fatigue, with the largest difference seen in the rates of elevated ALT levels which were around 60-65% higher in the 'all grades' category and approximately 45% higher in the grade 3 category for the >6 month and 6-12 month relapse populations (>12 month relapse rates not provided).

The MS reported the incidence of adverse events for the trabectedin and PLDH arm occurring with a frequency <5% in patients which include neutropenic infection (< 1%), neutropenic sepsis (< 1%), pancytopenia (1.8%), bone marrow failure (1.5%), granulocytopenia (1.5%), dehydration, insomnia, peripheral sensory neuropathy, syncope, left ventricular dysfunction (< 1%), pulmonary embolism (1.2%), pulmonary oedema (< 1%), cough, hepatotoxicity (< 1%), gamma-glutamyltransferase increased, bilirubin conjugated increased, musculoskeletal pain, myalgia, blood creatinine increased,

oedema/peripheral oedema, catheter site reaction.[6] However, this information was not provided for the PLDH monotherapy arm in the MS or in the requested supplementary information.

The MS reported that the incidences of grade 3 or 4 adverse events (96% versus 87%) and serious adverse reactions (44% versus 23% all grades) were higher in non-white patients (mainly Asian) when compared with white patients. However, no numbers of such events or relative risks were provided to compare the rates between white and non-white patients. Nevertheless, the differences observed between white and non-white patients for specific adverse events reported in the MS were substantial: neutropenia (93% versus 66%), anaemia (37% versus 14%) and thrombocytopenia (41% versus 19%). The MS states (p.98) that the incidence of clinical complications related to haematological toxicity such as severe infections or bleeding, or those leading to death or treatment termination, were similar in both subpopulations.

The MS (p.101) acknowledges that treatment with trabectedin and PLDH added some toxicities primarily associated with transient laboratory abnormalities (neutropenia and transaminase increases), although with minimal clinical sequelae (i.e. low rates of febrile neutropenia, sepsis and hepatobiliary adverse events). The MS states that these adverse events were generally manageable with adequate monitoring and dose reductions and/or delays as per protocol recommendations.

Additional data was reported from a pooled analysis of the three phase II trials of trabectedin as second or third-line monotherapy in patients with relapsed ovarian cancer[35] which includes data from 294 patients. The dose schedules used in each of the respective trials were two every 3 weeks (q3w; Del Campo *et al.*,[14]: 1.3 mg/m^2 3-h or 1.5 mg/m^2 24-h; Sessa *et al.*,[18]) and one weekly (0.58 mg/m^2 3-h x3 q4w; Krasner *et al.*,[17]). These regimens differ from the recommended dose of 1.1 mg/m^2 q3wk 3-h regimen (in combination with PLDH 30mg/ m^2). The MS (p.101) provides a summary table detailing the safety profile of treatment emergent adverse events (TEAEs) for the entire study populations for the three phase II trials which shows that drug-related Grade 3-4 TEAEs were relatively common in the three studies (between 34% and 70% incidence). However, the number of TEAEs leading to discontinuation was lower at 12% to 24%. Data is presented within this pooled analysis in Table 24 below. The pooled analysis provides data for all participants within the three trials and does not provide data for platinum-sensitive sub-groups.

The MS states (p.101) that the most common drug-related AEs of any grade in the three trials were fatigue (ranging from 35-63% patients) and nausea and vomiting (16-27% patients). Grade 3/4 laboratory abnormalities were non-cumulative: neutropenia ranging between 1-28% and ALT increase ranging between 3-26% patients.[14,17,18] Whilst the MS states that there was a low incidence of febrile

neutropenia, neurotoxicity, stomatitis and alopecia regardless of schedule in the three trials, the manufacturer did not clarify what is considered to be a 'low' incidence as requested by the ERG.

Table 24: Safety Profile of trabectedin -integrated phase II Ovarian Studies (All-Treated Subjects Analysis Set) (Table B29, p.73, replicated from MS)

	q 3 wk; 24-h (1.5 mg/m^2) (N=54) n (%)	q wk; 3-h (0.58 mg/m^2) (N=147) n (%)	q 3 wk; 3-h (1.3 mg/m^2) (N=94) n (%)	Total (N=295) n (%)
Treatment-emergent adverse events (TEAEs)	52 (96)	146 (99)	92 (98)	290 (98)
Drug-related	50 (93)	141 (96)	87 (93)	278 (94)
Grade 3-4 TEAEs	39 (72)	91 (62)	43 (46)	173 (59)
Drug-related	38 (70)	58 (39)	32 (34)	128 (43)
Serious TEAEs	13 (24)	48 (33)	24 (26)	85 (29)
Drug-related	8 (15)	22 (15)	14 (15)	44 (15)
Grade 3-4	13 (24)	40 (27)	21 (22)	74 (25)
Drug-related Grade 3-4	8 (15)	14 (10)	14 (15)	36 (12)
TEAE leading to discontinuation	13 (24)	18 (12)	11 (12)	42 (14)
Death due to TEAE	0	3 (2)	3 (3)	6 (2)
Within 30 days of last dose	0	3 (2)	1 (1)	4 (1)
Within 60 days of first dose	0	2 (1)	3 (3)	5 (2)
Drug-related TEAE leading to death	0	1 (1)	1 (1)	2 (1)

4.2.2.1 Critique of safety data reported

The reporting and interpretation of the safety and tolerability data had missing elements. No statistical analysis of the difference in rates of adverse events is provided in the MS or in supplementary information requested by the ERG. It appears by examining the numbers of adverse events that many were seen more frequently in the trabectedin and PLDH arm in the entire study population as well as the platinum-sensitive sub-groups, which is acknowledged in the MS (p.101). The MS also

acknowledges that the incidence rates for Grade 3 or 4 adverse events, serious adverse events and adverse events leading to treatment discontinuation were higher for trabectedin administered in combination with PLDH in the pivotal phase III study compared with trabectedin as a single agent in the pooled phase II studies.[5] The ERG would have wished to see all adverse events reported, as a high proportion of patients suffering mild effects could represent cumulative QALY loss.

The additional information provided by the pooled analysis of the three phase II trials was limited to a brief synopsis of their pooled analysis[35] including a table which did not include incidence of specific adverse events. The most frequent adverse events within each of the three trials are reported but the MS is vague about the occurrence of other adverse events, whose incidence is termed as 'low'.

4.3 Critique of submitted evidence syntheses

No evidence synthesis in the form of a meta-analysis was possible as there was only one RCT, and this was reported by narrative means.

An MTC of licensed treatments in relapsed ovarian cancer has previously been performed as part of a NICE multiple technology assessment, NICE TA91.[2] Guidance issued as a result of NICE TA91 recommended PLDH as a second-line treatment option for women with partially platinum-sensitive ovarian cancer.[3] When compared with paclitaxel or topotecan monotherapy, PLDH is the most clinically and cost-effective treatment within the platinum-sensitive population.[2] The ERG sought clinical advice to clarify whether in instances whereby PLDH is contraindicated, trabectedin and PLDH combination would also be contraindicated. Clinical experts believed this to be likely. Despite PLDH being administered at a lower dose as it is in combination with trabectedin, the contraindication for use would remain. Clinical advice suggests that the most likely reason for PLDH being contraindicated is the existence of a cardiac history or problem, and clinical experts stated that they would be extremely cautious in administering PLDH, even at a lower dose alongside trabectedin in such a scenario.

As PLDH is the recommended second-line therapy, and trabectedin and PLDH cannot be used where PLDH is contraindicated, the relative cost-effectiveness of trabectedin and PLDH compared with paclitaxel or topotecan monotherapy is not needed, since there would never be a choice between these interventions. As such, a direct comparison of trabectedin and PLDH is sufficient to address the decision problem.

However, given the MTC meta-analysis was included in the MS, the ERG provides a critique.

4.3.1 Indirect/ mixed treatment comparisons

The MS presents the results of a mixed treatment comparison (MTC) meta-analysis in an attempt to provide a coherent comparison of a set of treatments. The MTC undertaken in the MS allows the indirect comparison of trabectedin and PLDH with three comparators outlined in the final NICE scope: PLDH, paclitaxel and topotecan (each as monotherapy).

A literature search was undertaken by the manufacturer in order to identify articles published since the NICE TA91 in order to update the MTC. Searches were undertaken to retrieve material from 2004 onwards (the date for which the searches were undertaken for the original review).

The search reported in the MS (Appendix 4a) was confusingly structured and did not replicate the original searches undertaken in 2004 for NICE TA91, with several search terms being omitted. The ERG re-ran the searches, replicating exactly that which had been undertaken in 2004 for NICE TA91. Incorporating the extra terms into the search gave 113 results in Medline and 283 results in Embase. The searches reported in the MS gave 45 results in Medline and 95 in Embase. The searches undertaken in the Cochrane Library were poorly reported and using a database index term that did not exist within the Cochrane Library databases. The manufacturer did not respond to clarifications raised by the ERG in relation to the reported search for evidence to inform the MTC.

The MS did not report (or subsequently provide after a request from the ERG) a PRISMA diagram (formerly QUORUM) and so the process of identifying, screening and including/excluding articles for the MTC is unclear and therefore cannot be appraised. The inclusion criteria (MS, p.76) list carboplatin, cisplatin, paclitaxel, PLDH and topotecan as interventions. However, there is no mention of a carboplatin or cisplatin combination treatment within the inclusion criteria, which are comparators included within the final NICE scope. The outcomes of interest are not specified within the inclusion criteria.

In Section 5.7.2 (MS, p. 76), the MS states that two relevant RCTs were identified from the literature search to update the MTC. One trial was subsequently excluded[36] as this trial contained no data that could further inform the MTC undertaken in 2004. The remaining trial was the OVA-301 trial[15] and this trial was included in the updated MTC in the MS.

The ERG were concerned that studies to update the MTC may have been missed due to the failure of the MS to replicate the searches exactly undertaken in NICE TA91 (and the effect this had on the search results produced) as well as the lack of transparency in the sifting and selection of studies to update the MTC. The ERG sought clinical advice on whether any trials that could inform the MTC

network of trials had been missed by the MS. The clinical advisors did not believe there to be any trials missing that could inform the MTC.

The MS includes a summary of the trials used within the MTC in Table B19 (p.78); however it is not clear within this table which trials were included in the MTC. Following clarification, the manufacturer stated that three trials were included in the MTC analysis: 039[37,38,39] 30-49[40,41] and OVA-301.[15] The ERG believes that trial 30-57 was also included in the MTC[42] for OS in order to provide the paclitaxel and PLDH comparison in the network of evidence. These four trials included in the MTC provide a network of evidence assuming that the trials are linked by common treatment regimens. Unless the treatment regimens are the same this could give raise to inconsistency between studies in the estimated treatment effects. However, information on treatment regimens was not provided in the MS or following the request for clarification raised by the ERG, and it is thus unclear if there are any differences in treatment regimens.

The trials included in the MTC present for the entire platinum-sensitive population (i.e. > 6 month relapse). However, the chemotherapeutic agents included in the MTC are the comparators issued in the final scope as appropriate for the partially platinum-sensitive population (6-12 month relapse). The comparators included within the MTC are not appropriate for the fully platinum-sensitive population (>12 month relapse) and, as discussed previously in Sections 3.3 and 4.15 in the ERG report, it may not be appropriate to pool the partially and fully platinum-sensitive populations in an analysis.

The trials and data included in the MTC have not been summarised in Section 5.7.3 and 5.7.4, as required for such a comparison, nor have any potential sources of heterogeneity between these trials been highlighted or discussed, again as required. In Section 5.7.7 (p.80), the MS states that there is no basis to assess heterogeneity as the MTC comprises a string of linked studies, but no replication (e.g. no two studies asking the same question). However, additional evidence about relative treatment effects exists other than what comes from specific trials. For example, we have a direct estimate of the effect of PLDH vs. topotecan, but we also have an indirect estimate through PLDH vs. paclitaxel and topotecan vs. paclitaxel. In addition, it is not necessary to have replication of trials in order to allow an assessment of heterogeneity and consistency of treatment effect across studies; this is the essence of a mixed treatment meta-analysis. Assuming that the between trial standard deviation is common across treatment effects it should be possible to perform a random effects mixed treatment meta-analysis, thereby allowing for heterogeneity between trials. The current analysis presented in the MS assumes that the studies are all estimating the same fixed effect which may not be correct, and

there has been no attempt to model differences between studies or assess the goodness-of fit of the model.

Although not raised as an issue in the original comments from the ERG, Table B20 (MS, p.79) presents results in such a way as to be confusing to the reader and indicates a possible misunderstanding regarding the results of the analysis. The mixed treatment meta-analysis generates the posterior distributions of the rate parameters, λ, for each treatment group under the assumption that the times-to-event are exponentially distributed. The inverse of the posterior distributions of the rate parameters gives the posterior distributions of the mean time-to-event of interest. The characteristics of the posterior distributions such as their means and 95% credible intervals can be provided. When the posterior distributions are skew the location statistic of choice is often the median rather than the mean of the posterior distributions, although they are still estimates of the population mean time to event. The median of an exponential distribution is $\frac{\ln(2)}{\lambda} \approx 0.6931 \times mean.$ Table B20 (MS, p.79) is incorrectly labelled and, if median times-to-event are of interest, the medians need to be calculated correctly.

There has not been any reporting of the goodness-of-fit of the model such as checking the deviances between the observed and fitted values and the appropriateness of the assumption that the data are exponentially distributed, and that the treatment effects are proportional. Without some comment on the appropriateness of the model is it difficult to judge the adequacy of the inferences.

The additional trial in this submission relative to the original submission (NICE TAR 91) provides no additional information on the effect of PLDH relative to topotecan. Given that relative effects should be the same and, assuming that the same baseline treatment is being used in both submissions (MS and NICE TA91), the absolute effects of topotecan and PLDH should be the same subject to Monte Carlo error. However, the table presented on page 180 in the MS indicates significant differences in Life Years Gained (LYG) values for paclitaxel and PLDH when the NICE TA91 and Yondelis submission are compared side by side. Without an explanation of why this discrepancy exists it casts some doubt as to whether the results are presented correctly.

The purpose of the mixed treatment meta-analysis is to characterise the joint posterior distribution of the treatment effects. The joint posterior distribution will not necessarily follow a particular parametric form and treatment effects will be correlated. The inputs to the decision analytic model must reflect the efficacy evidence generated from the mixed treatment meta-analysis. At the moment,

Table B32 (MS, p.121) implies that treatment effects are given independent normal distributions in the decision analytic model. If this is the case then this is incorrect. The input to the decision analytic model must be Convergence Diagnostic and Output Analysis software CODA samples of WinBUGS monitored values from the mixed treatment meta-analysis.

Table B32 (MS, p.121) suggests that the effect on PFS is independent of the effect on OS. However, the effect of treatment on PFS is correlated with the effect of treatment on OS. The mixed treatment meta-analysis should have been modelled to ensure that the mean time to progression could not exceed the mean time to overall survival.

It is not a requirement to assume an exponential distribution to enable the calculation of the mean time to event. Without some evidence on model checking it is not possible to conclude that the exponential distribution provides an appropriate representation of the sample data.

4.3.2 Summary

The MS contains an estimate of the treatment effect of trabectedin (in combination with PLDH) for part of the stated scope of the decision problem. An estimate of the efficacy (using PFS, OS and ORR) of trabectedin and PLDH vs. PLDH monotherapy is provided for the partially platinum-sensitive population (6-12 month relapse), which is one of the comparisons outlined within the final NICE scope. There are no estimates of treatment effect for trabectedin and PLDH vs. platinum-based chemotherapy (single agent or combination) in the fully (>12 month relapse) or partially (6-12 month relapse) platinum-sensitive populations or estimates of trabectedin and PLDH vs. paclitaxel or topotecan monotherapy in the partially platinum-sensitive population (6-12 month relapse). However, as is pointed out within the MS, evidence to inform these comparisons, either directly or indirectly, is not believed to exist.

Treatment effects are provided for the entire platinum-sensitive population (> 6 month relapse) for trabectedin and PLDH vs. PLDH or paclitaxel or topotecan each as monotherapy. In the case of paclitaxel or topotecan monotherapy, treatment effect is estimated only by indirect comparison in an MTC. It may not be clinically appropriate to combine fully and partially platinum-sensitive individuals into one group when analysing OS. The treatment effect with trabectedin and PLDH differs substantially between these two groups, being much more favourable in the partially platinum-sensitive sub-group (see figure 2).

It is also worth noting that clinical advice sought by the ERG suggests that in practice individuals with fully platinum-sensitive disease, and patients who are close to being defined as fully platinum-sensitive (for e.g. 10-11 months relapse), would very rarely be given a second-line chemotherapeutic agent that was not platinum-based.

The treatment effect is based on the results of a single RCT, which is of reasonable methodological criteria when judged using the NICE quality assessment criteria outlined in the manufacturer's specification.[26] However, the reporting of the trial results including clinical and safety data is not totally transparent and nor are the results fully tabulated for each outcome.

There are factors that make it difficult to interpret the data with full confidence. Firstly, there is a lack of transparency around censoring patients within the OVA-301 trial. A large number of patients are censored for PFS (n=178) at their last assessment prior to receiving subsequent therapy. It is unclear why these patients received subsequent therapy, other than if they had experienced disease progression, in which instance an event should have been recorded as opposed to censoring for these patients.

Secondly, some demographic and clinical characteristics of the trial population are not representative of patients seen in UK clinical practice, namely age and ECOG performance status (PS). The median age of study participants (57 years) was lower than that seen in practice (>60 years), and fewer ECOG PS 2 patients were included in the trial than that seen in UK clinical practice. Statistical analyses that demonstrated an independent treatment effect of trabectedin and PLDH in spite of imbalances of prognostic factors were undertaken. Adverse events rates did not differ significantly between the >65 years and ≤65 years age groups, except for fatigue.[29] However, the ERG's clinical advisors believed that older and sicker patients may be dissuaded from receiving trabectedin since it is administered via a central venous catheter. It is possible this aspect of treatment administration may have affected recruitment of these patients to the OVA-301 trial.

Thirdly, OS analysis is interim (31st May 2009) and presently underpowered (81%). The manufacturer believes that final analysis will be available at the end of the second quarter of 2011.

Finally, although an MTC meta-analysis was presented for the entire platinum-sensitive population (>6 month relapse), this was not deemed necessary by the ERG (see section 4.3). Furthermore, the ERG had several concerns about the way in which the MTC meta-analysis was undertaken.

The results from the OVA-301 trial suggest that a combination of trabectedin and PLDH is beneficial in the partially platinum-sensitive population (6-12 month relapse) when compared with PLDH. The

exact treatment effect as measured by PFS varies according to the method of assessment (independent radiologists, independent oncologists or investigator). Based on clinical advice, the independent oncologists' measurement is the most comparable method of measurement to UK clinical practice. Additionally, it is worth noting that the investigator was not blinded to treatment arm. Estimates for treatment effects that answer the remaining elements of the decision problem outlined in the final NICE scope are not possible based on the information included within the MS.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

The manufacturer submitted a decision-analytic model built in Microsoft Excel software. The model structure was derived from a previously published NICE Multiple Technology Assessment (NICE TA91) comparing topotecan as monotherapy, PLDH as monotherapy and paclitaxel as monotherapy for second-line or subsequent treatment of advanced relapsed ovarian cancer.[2]

Four interventions were compared: trabectedin in combination with PLDH; topotecan as monotherapy; paclitaxel as monotherapy and PLDH as monotherapy in women whose cancer has relapsed more than 6 months after completion of initial platinum-based chemotherapy; such women are referred to as the platinum-sensitive population. The effectiveness for the main analysis was derived from a Mixed Treatment Comparison (MTC) meta-analysis in the absence of direct comparisons of all the relevant comparators outlined in the final NICE scope.

The manufacturer also compared trabectedin in combination with PLDH versus PLDH as monotherapy only using direct evidence from the OVA-301 trial in three patient populations:

- in women whose cancer relapsed more than 6 months after completion of initial platinum-based chemotherapy (entire platinum-sensitive population).
- in women whose cancer relapsed between 6 to 12 months after completion of initial platinum-based chemotherapy (partially platinum-sensitive population).
- in women whose cancer relapsed more than 12 months after completion of initial platinum-based chemotherapy (fully platinum-sensitive population).

Treatment effectiveness was described by the mean time to disease progression and mean time to overall survival (OS). This was calculated from the median survival time, assuming that data were exponentially distributed and that the distribution crossed the median Kaplan Meier (KM) survival time.

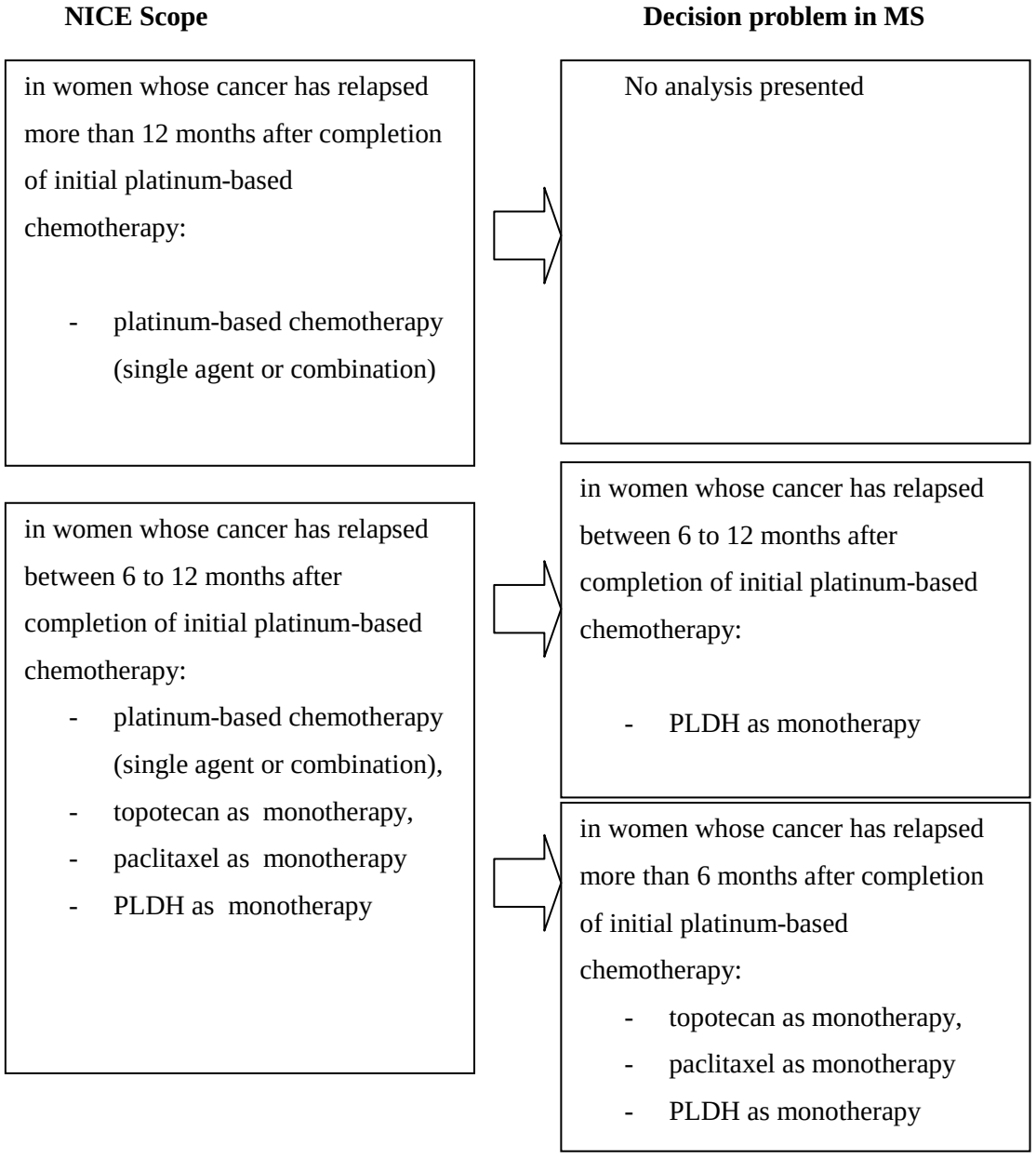
Costs relating to treatment, management of stable disease, progressive disease and adverse events (AEs) were included in the economic model. Health utilities were extracted from the OVA-301 trial and had been calculated from EQ-5D questionnaires.

Only health outcomes were discounted at a rate of 3.5% and the uncertainty was ascertained in univariate Sensitivity Analysis (SA) or Probabilistic Sensitivity Analysis (PSA).

5.1.1 Decision problem

Figure 4 compares the decision problem addressed by the manufacturer to the final scope issued by NICE.

Figure 4: Final scope issued by NICE and decision problem addressed in the MS



Only part of the scope was addressed in the MS. The MS main analysis compared trabectedin in combination with PLDH versus topotecan as monotherapy, paclitaxel as monotherapy and PLDH as monotherapy in women whose cancer has relapsed more than 6 months after completion of initial platinum-based chemotherapy (entire platinum-sensitive population). The MS included most of the comparators defined in the final NICE scope, whilst no comparison was provided for platinum-based therapy in the absence of a link in the evidence synthesis. The population modelled in the main analysis in the MS was also different from the population defined in the final NICE scope. This was due to the absence of data to link the effectiveness of relevant comparators for the appropriate population defined in the final NICE scope.

In addition, the MS presented three additional scenarios using direct evidence from the OVA-301 trial comparing trabectedin in combination with PLDH versus PLDH alone in the following populations; entire platinum-sensitive (> 6 months relapse), partially platinum-sensitive (6 – 12 months relapse) and fully platinum-sensitive (> 12 months relapse). Only the comparison for the partially platinum-sensitive population (6 – 12 months) was originally presented in the MS. Other scenarios were included following request by the ERG. Although the population considered was in accordance with the NICE final scope (partially platinum-sensitive, fully platinum-sensitive), the MS did not include all the relevant comparators defined in the final scope.

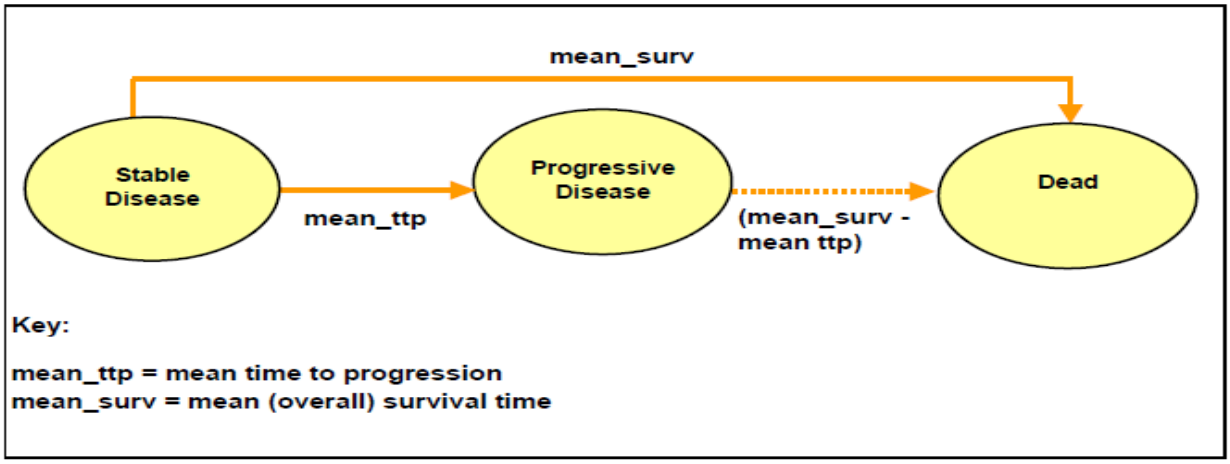
Whilst the ERG acknowledges the differences in the decision problem addressed in the MS and the scope developed by NICE for this appraisal, the ERG does not consider that this was a major issue, as the ERG believes that the most relevant decision problem is a comparison of trabectedin in combination with PLDH versus PLDH as monotherapy in women whose cancer has relapsed between 6 to 12 months after completion of initial platinum-based chemotherapy (partially platinum sensitive). This analysis was presented by the manufacturer as a secondary analysis and was based on direct data from the OVA-301 trial.

This was justified after seeking clinical advice. A detailed description of the discussion with clinical experts is presented earlier in the report (see section 4.3). The discussion confirmed that trabectedin in combination with PLDH is unlikely to be recommended when patients are contraindicated for PLDH as monotherapy. In addition, PLDH was shown to dominate paclitaxel and topotecan as monotherapy in the entire platinum-sensitive population. It is likely that this may also be the case for the partially platinum-sensitive population.

5.1.2 Model structure

The MS model structure replicated the structure developed in the NICE TA91.[2] The model evaluates two distinct periods: the progression-free period, and the time from progression to death (calculated as the difference between overall survival and PFS). As a Markov model was not developed, no transition probabilities were provided. Time is also not explicitly modelled but the time horizon is assumed implicitly to be lifetime as treatment effectiveness was extrapolated over time to calculate the mean time in PFS and mean time to death.

Figure 5: Model structure as reported in the MS (reproduction of Figure B23, p.115 in the MS)



The ERG believes that the model structure is reasonably appropriate to describe the decision problem. This type of model structure is especially common for economic evaluation alongside clinical trials. However, the ERG believes that there are potential limitations to this simplicity, which can impose constraints regarding the assignment of costs, utilities and discounting.

5.1.3 Effectiveness data and extrapolation

In the main analysis, the efficacy of each intervention was estimated via an MTC meta-analysis conducted by the manufacturer. This replicated the method employed in the NICE TA91[2] but was extended to include data from the OVA-301 trial, which compared trabectedin in combination with PLDH versus PLDH as monotherapy. The MTC meta-analysis was described earlier in this report in section 4.3.1.

Direct evidence from the OVA-301 trial was used to inform the effectiveness of trabectedin in combination with PLDH and PLDH as monotherapy in the three additional scenarios presented in the MS.

As the model evaluates two distinct periods: the progression-free period, and the time from progression to death, the efficacy/natural history associated with each intervention was modelled using the mean PFS and mean time to death as selected in the NICE TA91.[2] Identical methodology was also employed in the MS to calculate the mean survival time. This was derived from the median survival time, assuming that data are exponentially distributed. Consequently, the MS implicitly assumed that the estimated exponential distribution crosses the median Kaplan Meier (KM) survival time.

The MS calculated the mean survival time from the median survival time as follow:

Equation 1: Calculation of the mean survival time

$$\beta = t / \ln(2)$$

where β = mean survival time and t = median survival time

The estimated mean survival time in the MS for the main analysis and the three additional scenarios is presented in Table 25 and Table 26 respectively.

Table 25: Mean survival time calculated from the MTC (in weeks) – Extracted from the economic model

Treatment	PFS	OS
Topotecan	33.02	101.98
Paclitaxel	27.09	94.25
PLDH	37.07	124.56
Trabectedin + PLDH	47.10	147.28

Table 26: Treatment effectiveness used in the economic model for the three scenario analysis (in months) – Extracted from the economic model

	PFS (months)		OS (months)	
	PLDH only	Trabectedin + PLDH	PLDH only	Trabectedin + PLDH
Platinum-sensitive	10.66	13.22	34.79	38.96
Partially platinum-sensitive	7.93	10.68	24.69	33.18
Fully platinum-sensitive	13.32	16.02	45.79	60.24

The ERG had several concerns about the mean PFS and OS presented in the MS. Firstly, the ERG noted some inconsistencies for the median PFS and OS included in the economic evaluation and those included in the clinical section. For instance, the manufacturer used a median OS of 41.76 months for the fully platinum-sensitive population; however it was stated elsewhere that the median was not reached for this population (Table 3 in Appendix 1 in the clarification letter from the manufacturer). While it is possible to estimate the median OS by extrapolating data using a parametric distribution, the ERG believes that the MS used the last data point from the KM as this was close to the median. Furthermore, the analysis performed in the fully platinum-sensitive population assumed a median PFS of 9.23 months for PLDH assessed by independent radiologists, 5.75 months for PLDH assessed by the investigators ~~independent investigator~~[e] and 9.36 for trabectedin in combination with PLDH assessed by the investigators ~~independent investigator~~[e]. The figures presented in the clinical section differed and were 8.9, 7.0 and 10.9 months respectively. Inconsistencies were also found for the direct comparison for the entire platinum-sensitive population. The ERG noted some inconsistencies in the number of decimal points reported for the median PFS or OS, with the numbers of decimal points ranging between one and four.

The ERG had concerns with the assumptions made by in the MS to estimate the mean survival time, i.e. that data are exponentially distributed and that the parametric distribution crosses the median KM survival time. Indeed, the ERG was concerned these assumptions would not reasonably represent the observed KM data. Patient data was made available to the ERG after request, and a plot of the exponential distribution assumed by the MS (estimated by the ERG) and the observed KM data is shown from figure 6 to figure 9 in women whose cancer has relapsed between 6 to 12 months after completion of initial platinum-based chemotherapy (partially platinum-sensitive). We selected this

[e] Correction/amendment made following comments from the manufacturer

subpopulation as the ERG believes that this is most relevant population for the decision problem and presented these figures to illustrate potential biases of the assumption made by the MS.

Figure 6: Comparison of the observed KM data and distribution assumed by the MS for PFS for trabectedin in combination with PLDH in women with partially platinum-sensitive ovarian cancer (analysis conducted by the ERG using individual patient data from the OVA-301 trial).

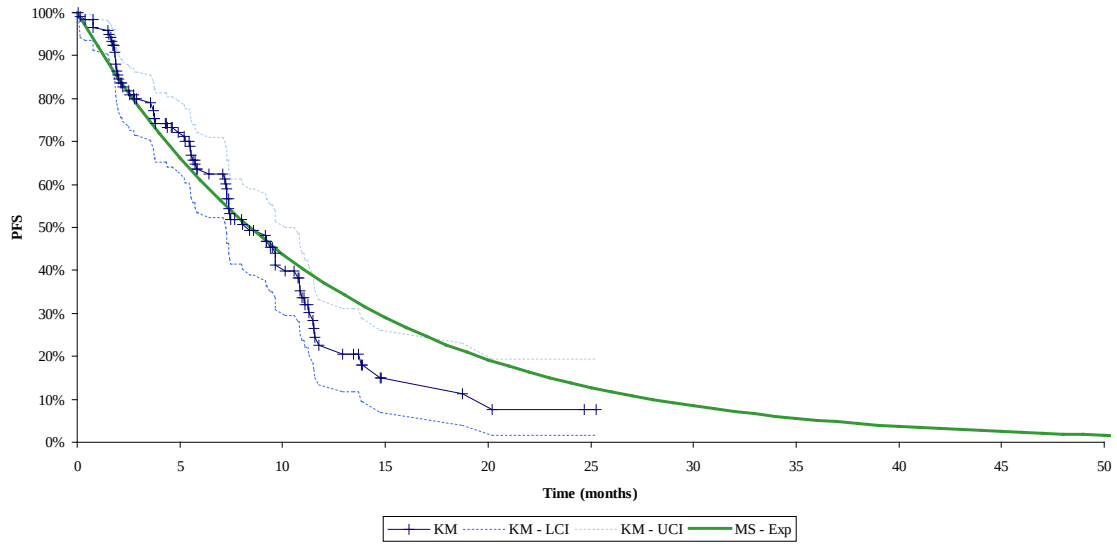


Figure 7: Comparison of the observed KM data and distribution assumed by the MS for PFS for PLDH monotherapy in women with partially platinum-sensitive ovarian cancer (analysis conducted by the ERG using individual patient data from the OVA-301 trial).

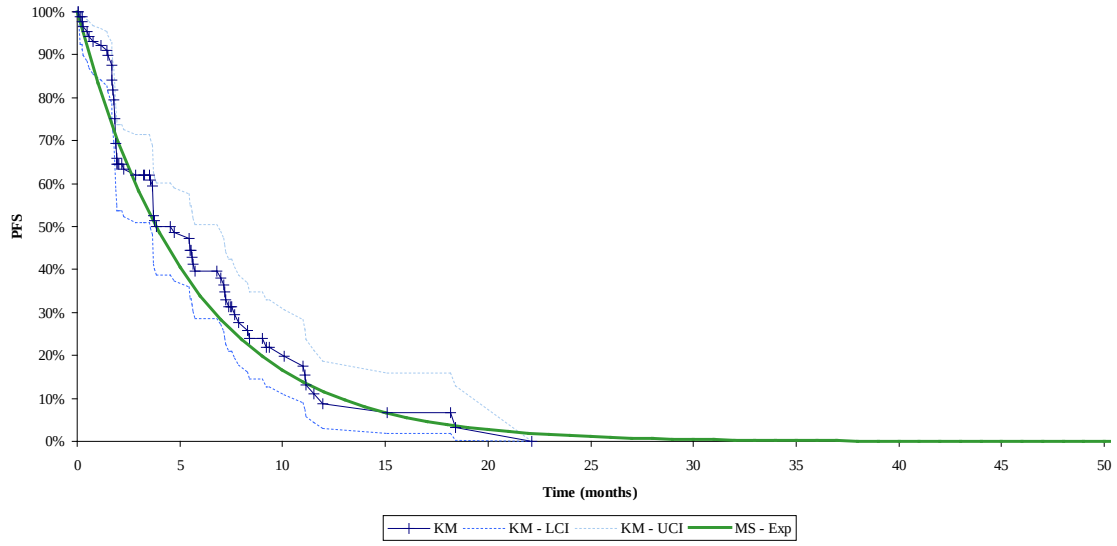


Figure 8: Comparison of the observed KM data and distribution assumed by the MS for OS for trabectedin in combination with PLDH in women with partially platinum-sensitive ovarian cancer (analysis conducted by the ERG using individual patient data from the OVA-301 trial).

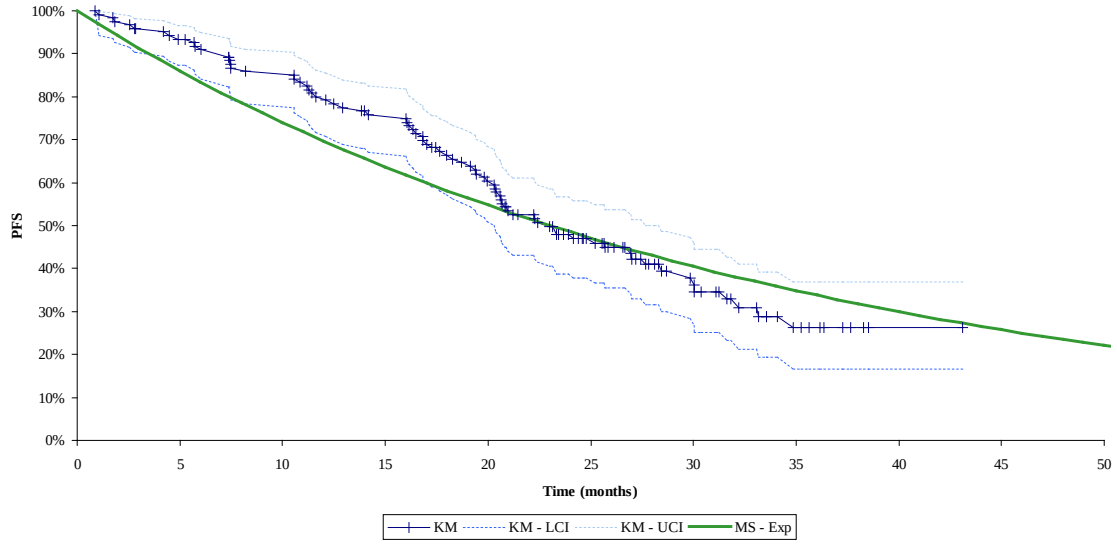
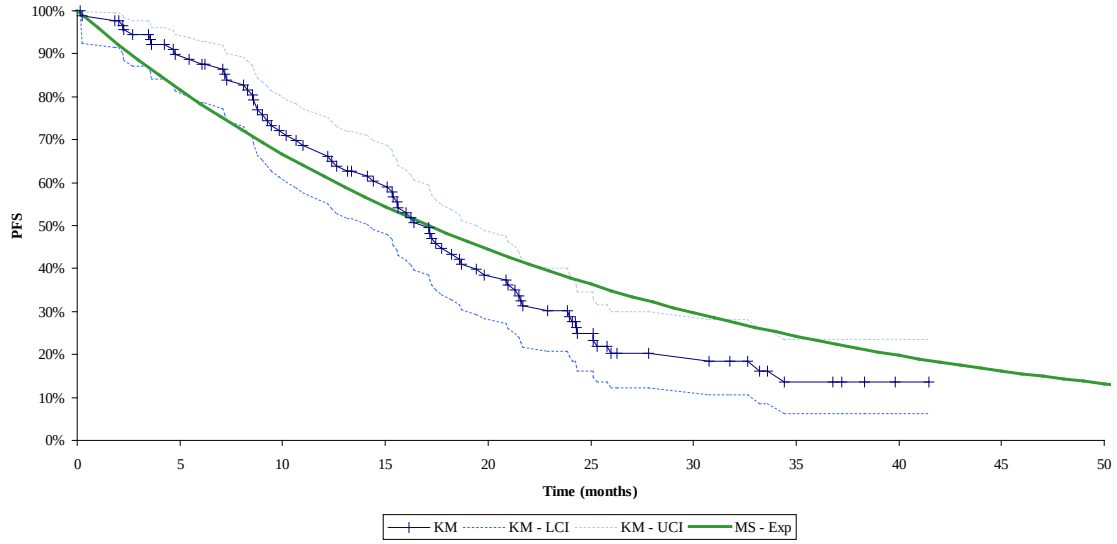


Figure 9: Comparison of the observed KM data and distribution assumed by the MS for OS for PLDH monotherapy in women with partially platinum-sensitive ovarian cancer (analysis conducted by the ERG using individual patient data from the OVA-301 trial).



Overall, the exponential assumption for PFS for trabectedin in combination with PLDH appears reasonable up to 10 months (Figure 6), after which there appears to be a change in the hazard of event. The consequence is an overestimate of the mean time to event relative to the sample estimate. The exponential assumption appears however reasonable for PFS for PLDH as monotherapy (Figure 7).

The exponential assumption does not appear to be consistent for OS across the entire follow up period for either trabectedin in combination with PLDH or PLDH as monotherapy (Figure 8 and Figure 9 respectively). Consequently, the data does not appear to be well represented by an exponential distribution and the assumptions made by the MS tend to overestimate the mean survival time.

The ERG was concerned that no other distributions or approaches were presented in the MS. The ERG requested that the manufacturer explore different-fitting distributions, especially for the scenarios using direct evidence from the OVA-301 trial. Unfortunately, the manufacturer did not provide these analyses due to time constraints. Individual patient data were however made available to the ERG.

The median PFS estimated from the independent radiologists' review was used for the base case in the MS and no justification was provided. The ERG had concerns as the reported median PFS estimated by the independent radiologists was different compared with the median PFS reported by the independent oncologists or the investigators ~~independent investigator~~[f] (Table 27). The ERG sought clinical advice and experts suggested that the assessment by the oncologists is a better representation of UK clinical practice. The ERG requested that the manufacturer provide additional analysis using PFS estimated by the independent oncologists and the investigators ~~independent investigator~~[f]. These additional analyses are now included in the revised economic model for the direct comparison analysis only and showed to influence the ICER. As suggested by clinical experts, the ERG believes the appropriate base case to be the analysis using PFS assessed by the independent oncologists.

The manufacturer also reported that some differences were observed for patient characteristics included in the two arms of the OVA-301 trial and presented results from a pre-planned analysis. The ERG was concerned that these differences may have influenced the outcomes from the trial and requested that the manufacturer test for significant differences between the two arms by platinum-sensitivity and to adjust the estimated curves if appropriate. This was not provided by the manufacturer due to time constraints.

Table 27: Median PFS in the partially platinum-sensitive population (by assessors)

	PLDH	Trabectedin in combination with PLDH
Independent radiologists	5.5	7.4
Independent oncologists	3.8	8.4
Investigators ~~Independent investigator~~[f]	5.4	7.6

Finally, OS and PFS results from the MTC do not appear to have been used correctly as the mean across the 10,000 iterations from the MTC was used for the deterministic scenario, while the model should have been run probabilistically for each iteration of the MTC using the CODA output. A correct PSA would reflect the joint distributions of the mean OS and mean PFS across treatment by using as inputs the results from each iteration of the Markov chain Monte Carlo simulation which are available as CODA samples within WinBUGS.

[f] Correction/amendment made following comments from the manufacturer

5.1.4 Health related quality of life

The latest search undertaken by the manufacturer to identify all relevant health related quality of life data was conducted in January 2010 (Appendix 12 in MS). It is not clear if searches in all five databases were undertaken in January 2010. The search strategy utilises terms to identify the patient group (ovarian cancer) and non-specific terms to identify the intervention (drug therapy). An unknown search filter was applied to limit the search to evidence on health related quality of life, which was reasonable to do so and of reasonable quality to use. Overall, this was an adequate search strategy, although the ERG would have liked to have seen further synonyms to describe the intervention. Searches were limited to English language only, studies on humans only and restricted to citations published from 2004-2010. No justification was provided for these restrictions.

Five electronic bibliographic databases were searched (MEDLINE, EMBASE, NHS Economic Evaluation Database, Health Technology Assessment databases and Database of Abstracts of Reviews of Effects). There are no further sources that the ERG would expect to see.

The search strategies were of adequate quality to retrieve important citations relating to health related quality of life data that the ERG is aware.

The MS base case used health state utilities from the OVA-301 trial and was estimated using the EQ-5D. As patients had repeated measurements, the manufacturer selected the earliest utility value for patients either in stable disease or in the progressive disease to calculate health state utilities. The manufacturer justified this assumption stating that no variations were observed in utilities over time after analysis of the data using a random mixed-effect model using time, treatment and the interaction between time and treatment as covariates. It was not possible for the ERG to comment on the validity of this analysis conducted as results from these analyses were not presented in the MS. The ERG however believes the assumption made by the manufacturer to be appropriate.

The original MS used health state utilities estimated from the combined treatment groups within the OVA-301 trial and are presented in Table 28. This was justified by the manufacturer in the absence of separate health state utilities for other comparators included in the main analysis (topotecan and paclitaxel). The estimated health state utilities were also deemed to have incorporated the effects of treatment-related adverse events from the treatment arms. Consequently, there is an implicit assumption that the profile of adverse events is similar between treatments.

Table 28: Health state utilities used in the original MS (reproduction of table 36, p 141 in the MS)

	Mean	Std Error	Lower 95% CI for Mean	Upper 95% CI for Mean
Stable	0.718	0.01	0.699	0.737
Progressive	0.649	0.019	0.611	0.686

A sensitivity analysis was also conducted by the manufacturer using health state utilities selected in the NICE TA91, i.e. 0.63 for stable disease and 0.34 for progressive disease. However, the utility for the progressive state was assumed by the assessment group using data from other cancers.

Whilst the ERG was satisfied with health state utilities presented in the MS, the ERG was interested in exploring other scenarios using health state utilities by treatment and platinum-sensitivity to provide more accurate estimates and capture the potential differential effect of adverse events and administration mode (central venous line). Consequently, the ERG requested that the manufacturer provide health state utilities by treatment and platinum-sensitivity and test the impact in the economic model.

Health state utilities by treatment and platinum sensitivity are presented in Table 29 and Table 30. The manufacturer did not describe the method used to derive these utility values. However, the ERG believes that a similar approach was employed, i.e. the use of the earliest utility by state and the assumption that utilities do not vary over time.

Table 29: Health state utilities for the stable disease state by platinum sensitivity (Reproduction of Table 15 and Table 17 in the clarification letter)

	Platinum sensitivity	N	Mean	Std Error
PLDH	> 6 months	**198**	0.732	0.016
	6 – 12 months	**82**	0.689	0.029
	> 12 months	**113**	0.762	0.019
Trabectedin + PLDH	> 6 months	**209**	0.719	0.017
	6 – 12 months	**117**	0.719	0.024
	> 12 months	**90**	0.722	0.024

Table 30: Health state utilities for the progressive disease state by platinum sensitivity (Reproduction of Table 16 and Table 17 in the clarification letter)

	Platinum sensitivity	N	Mean	Std Error
PLDH	> 6 months	**98**	0.709	0.022
	6 – 12 months	**38**	0.654	0.044
	> 12 months	**32**	0.717	0.038
Trabectedin + PLDH	> 6 months	**108**	0.698	0.024
	6 – 12 months	**38**	0.672	0.045
	> 12 months	**18**	0.734	0.053

The ERG expressed several concerns on the use of the provided health state utilities by treatment and platinum sensitivity:

- First, inconsistencies were found in the sample size used to estimate these utility values. In theory, the sample size for the entire platinum-sensitive population should be equal to the sum of the sample size for the partially and fully platinum-sensitive populations. This does not appear to be the case (Table 29 and Table 30).
- Second, inconsistencies in the direction of health state utilities were also noted by the ERG, i.e. that health state utilities were higher for PLDH compared to trabectedin in combination with PLDH in the entire platinum and fully platinum-sensitive women, but not in the partially platinum-sensitive population.
- Additionally, whilst health state utilities for stable disease were derived from a reasonable sample size, the ERG is concerned by the small number of patients used to derive health state utilities for the progressive state.
- Whilst the assumption of using the earliest utility by state was appropriate when pooling all treatments, this may not be the case when health state utilities are estimated for each treatment separately.
- Finally, baseline utility values (the ERG is unclear if the EQ-5D data provided by the manufacturer is EQ-5D Index or Visual Analogue Scale (VAS) data-see section 4.2.1) appear to be different between treatment arms. Whilst the manufacturer did not test for the differences in utility values at baseline, the ERG believes that this may have influenced the outcomes. Interestingly, the direction of health state utility values by treatment seemed to have been influenced by the direction of the baseline utility value, i.e. that when the utility at baseline was higher for PLDH compared to trabectedin with PLDH, the estimated utility by

health state was also higher for PLDH. However, the ERG acknowledges that this could be due to the play of chance.

Consequently, after reviewing the health state utilities by treatment and platinum sensitivity, and despite the comments made to the manufacturer, the ERG believes that the most sensible health state utility values are those originally presented in the MS, i.e. health state utilities estimated for the combined treatment group across all platinum-sensitive women (Table 28). The health state utilities by treatment and platinum-sensitivity should be considered with caution and the impact should be examined in sensitivity analysis.

5.1.5 Resources and costs

5.1.5.1 Drug and administration costs

The cost of the drug for each relevant intervention was calculated from a range of sources. The manufacturer calculated the dose per cycle from the Body Surface Area (BSA) reported in the OVA-301 trial (1.72 m^2) and the recommended/licensed dose from the SmPC.[6] The ERG requested that the manufacturer provide the mean dose/cycle from the OVA-301 trial. This analysis was presented by the manufacturer, but no justification was provided for the approach used to estimate the mean dose per cycle. Individual patient data from the OVA-301 trial was made available to the ERG and analysis for the partially platinum-sensitive population showed a cumulative dose of 6.53 mg/ m^2 for women receiving trabectedin. This was compared to the cumulative dose estimated in the economic model from the mean dose per cycle and number of cycles received. In the MS, the mean dose per cycle was 0.90 mg/ m^2 and patients received on average 6.3 cycles, translating into a mean cumulative dose of 5.67 mg/ m^2. The ERG was unclear why such differences were present and was not able to reproduce the figure provided by the manufacturer. Sensitivity analyses were conducted by the ERG to test the impact of the mean dose per cycle.

The manufacturer also approximated the number of vials required per cycle to match the estimated dose per cycle assuming a combination of vials (Table 31), which implicitly incorporated potential wastage. This was considered appropriate by the ERG given the method selected to estimate drug costs. Unit costs for drugs were extracted from the BNF and are presented in Table 32.[43]

Table 31: Drug regimen cost per cycle of chemotherapy (Reproduction of Table B39, p 147 in the MS)

	Dose administered based on BSA of 1.72m^2	**Cost per cycle of chemotherapy at full dose**	**Total cost per cycle**
Intervention			
Trabectedin (Yondelis®)	1.89 mg	£2,732 (2* x 1mg vials used)	
PLDH	51.6mg	£1,125.72 (3 x 20 mg vials used)	**£3,857.72**
Comparators			
PLDH	86.0mg	£1,492.66 (2 x50 mg vials used)	**£1,492.66**
Paclitaxel	301.0mg	£601.30 (1 x 50 ml vial)	**£601.30**
Topotecan	12.9 mg (2.625 mg daily for 5 days)	£1,453.10 (5 x 4 mg vials used)	**£1,453.10**

* corrected typographical error in the MS

Table 32: Unit costs per vial (Reproduction of Table B37, p 146 in the MS)

	Formulation	Strength/ Vial size	Cost (ex. VAT)	Source
Intervention				
Trabectedin (Yondelis®)	Injection	250 micrograms 1 mg	£363 £1,366	BNF, No 58, 2009 [43]
Comparators				
PLDH	Injection	20 mg in 10 ml vial 50 mg in 50 ml vial	£375.24 £742.18	BNF, No 58, 2009 [43]
Paclitaxel	Injection	6 mg in 1ml 5 ml vial (30 mg) 16.7 ml vial (100.2 mg) 25 ml vial (150 mg) 50 ml vial (300 mg)	 £66.85 £200.35 £300.52 £601.03	
Topotecan	Injection	1 mg vial 4 mg vial	£97.65 £290.62	

The cost of administration of chemotherapy per cycle was estimated from the NHS reference costs 2007/2008 and is presented in Table 33.[44] The ERG did not have concerns about the choice of HRGs for the administration of the relevant interventions included in the MS. For simplicity, the manufacturer assumed no costs associated with the administration of pre-medications and supportive care medicines as these were considered similar between treatments and that the cost of these drugs should be covered under the HRG codes. The ERG believed that this was a reasonable assumption and anticipates the impact on the ICER to be minimal if these costs were included.

Furthermore, the SmPC for trabectedin[6] strongly recommends that it be administered using a central line catheter. In the original MS, this cost was not included in the economic model despite the manufacturer stating that this cost was considered. The manufacturer was contacted regarding this issue, and included a subsequent cost associated with the use of central venous line from the NHS reference costs (Table 34).[44] No costs were included for the removal of the central line as it was assumed to be straightforward. Central line removal would be done either on completion of

chemotherapy or at the next follow-up outpatient clinic appointment after completion of therapy and that this would not be coded as a specific procedure, therefore, not incurring additional costs. The ERG believed that this was a reasonable assumption.

Table 33: Drug administration costs (Reproduction of the Table B40, p.148 in the MS)

Chemotherapy regimen	**HRG code (applied to each cycle of chemotherapy)**	**National Average Unit Cost**	**Lower Quartile Unit Cost**	**Upper Quartile Unit Cost**
Trabectedin and PLDH	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (SB14Z)	**£307**	£211	£406
PLDH only	Deliver simple Parenteral Chemotherapy at first attendance (SB12Z)	**£212**	£116	£280
Paclitaxel	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (SB14Z)	**£307**	£211	£406
Topotecan	Day 1: Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (SB14Z)	**£307**	£211	£406
	Day 2-5: Deliver subsequent elements of a chemotherapy cycle (SB15Z)	**£220**	£138	£277

Table 34: Cost associated with the central venous line (Reproduction of p.20 in the clarification letter)

Central venous line access	**HRG code**	**Day Case Cost (NHS Reference Costs 2007/08)**
	Vascular Access except for Renal Replacement Therapy without CC (QZ14B) as a Day Case.	**£432** **Lower quartile - £263** **Upper quartile £475**

Finally, the total cost of drug per treatment was calculated from the above (cost of drug per cycle and cost of administration per cycle) and the number of cycles. In the main analysis, clarification was sought as to whether the number of cycles for each comparator was specific to the platinum-sensitive population. This was not the case as the manufacturer stated that the number of cycles for topotecan and paclitaxel has been extracted from the NICE TA91 and that it is likely that they relate to the overall population included within the trial as no data by subgroups was available in the original studies. Similar assumptions have therefore had to be made for trabectedin in combination with PLDH and PLDH as monotherapy. The ERG had concerns that this may not be appropriate as the profile of platinum sensitivity is likely to be different between the different trials included in the MTC and therefore results might be biased toward the trials that included more platinum-resistant participants. Furthermore, the number of cycles for PLDH was originally extracted from the OVA-301 trial, despite other trials including a figure for the number of cycles for PLDH being included in the MTC. This was corrected by the MS after clarification of the ERG.

The ERG also noted that the number of cycles from the overall population from the OVA-301 trial was originally used for the direct comparison analysis, and requested that the manufacturer use the mean number of cycles by platinum sensitivity from the OVA-301 trial. The estimated number of cycles by platinum sensitivity is presented in Table 35.

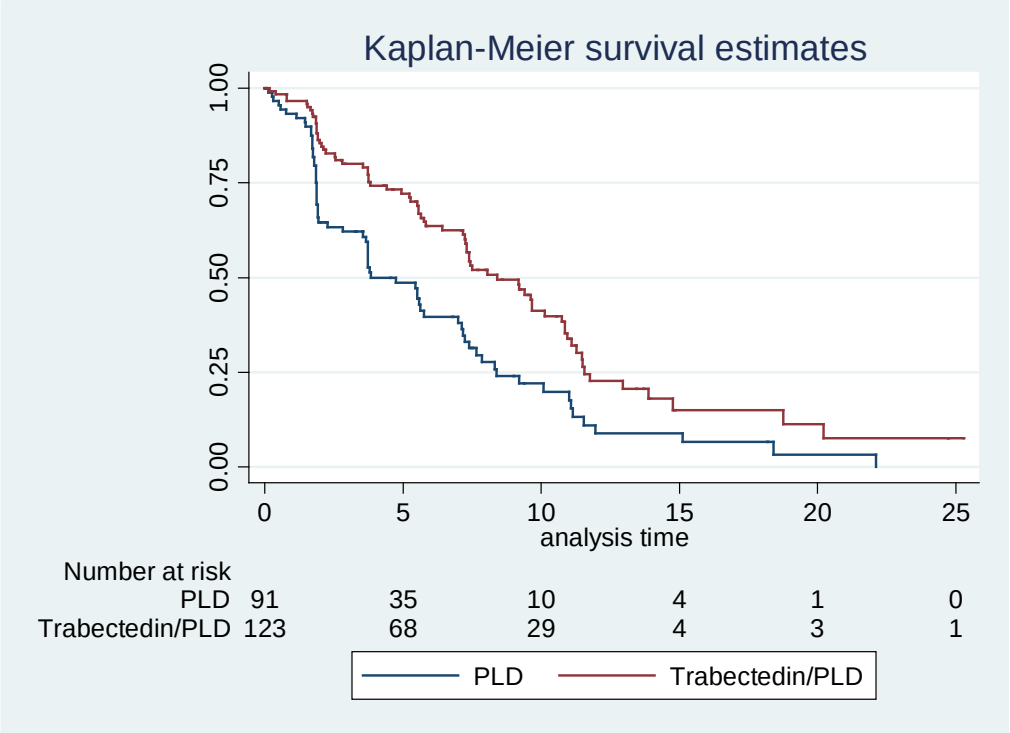
Table 35: Mean number of cycles by platinum sensitivity (Reproduction of Table 23 in the clarification letter)

	Platinum sensitivity	N	Mean	Standard Error	Lower limit	Upper limit
PLDH	> 6 months	208	5.7	0.3	5.1	6.2
	6 – 12 months	89	5.1	0.4	4.3	5.9
	> 12 months	120	6.0	0.4	5.3	6.8
Trabectedin + PLDH	> 6 months	217	6.9	0.3	6.3	7.4
	6 – 12 months	123	6.3	0.3	5.7	7.0
	> 12 months	94	7.7	0.5	6.7	8.6

Whilst the use of the mean number of cycles appears appropriate, the ERG believes that the mean number of cycles from the OVA-301 trial is still likely to be an underestimation of the true number of cycles, especially for trabectedin in combination with PLDH as some patients did not progress and

were still at risk at the end of the trial duration (Figure 10). Sensitivity analysis was conducted by the ERG around this assumption assuming an increase in the mean number of cycles for trabectedin in combination with PLDH only.

Figure 10: Kaplan Meier plot and number at risk for using the oncologists' assessment for the 6-12 month relapse population (Estimated by the ERG from patient level data)



5.1.5.2 Management costs

The MS stated that the management of patients in stable disease, i.e. whilst on chemotherapy consisted of one outpatient review by a consultant oncologist and one CT scan every 2 months. The ERG requested clarification from the manufacturer as this was not incorporated correctly in the economic model; only the cost associated with one outpatient visit and 0.5 CT scan was included at baseline. The manufacturer rectified the economic model, but inconsistencies remained as the model assumed that women in stable disease received one outpatient visit every cycle and one CT scan every 2 cycles. Clinical advice sought by the ERG suggests that women in stable disease would receive one outpatient visit every month and one CT scan every 3 cycles. This was tested in sensitivity analysis by the ERG. The cost associated with the outpatient visit and CT scan were extracted from the NHS

reference cost 2007/2008.[44] Inconsistencies were also noted as rounding was used for the number of CT scans. This was not necessary as the model work around the mean.

Originally, no management costs were included for women in the progressive disease state as in the NICE TA91. This was justified by the lack of data on the differential impact of alternative treatment on the long term treatment of patients. However, the ERG requested further clarification from the manufacturer as this would bias the estimate toward trabectedin in combination with PLDH as these patients were found to remain longer in the progressive disease state, therefore incurring additional costs compared to other alternative therapeutics. Women who are partially platinum-sensitive and treated with second-line trabectedin in combination with PLDH spend on average 22.51 months in the progressive state, compared to 16.74 months for women treated with PLDH as monotherapy. After clarification, the manufacturer included a cost derived from the annual cost of palliative care in patients with cancers estimated in a previous economic report issued by NICE.[45] This study reported the annual cost of palliative care to be £3,236 and was inflated to current prices by the manufacturer (£4,096). The manufacturer highlighted that it could be argued that the greatest cost of care is in the last few months of life but this was omitted from the economic model for simplicity.

Despite the effort made by the manufacturer to include a cost associated with the management in progressive disease, the ERG believes that the cost used by the manufacturer may be an underestimate of the true cost associated with the management of the progressive state as the source used was not cancer-specific. A UK study published in 2005 was identified by the ERG and reported the cost associated with the management of palliative care in women with ovarian cancer from the start of treatment with opioids.[46] The cost was estimated to be £4,789 (2000/2001 price) for a mean length of palliative care of 399 days. Whilst the ERG believes that this figure may be more appropriate, it is unclear what the true cost of managing BSC and palliative care in women with ovarian cancer is. Therefore, some sensitivity analyses were conducted by the ERG.

5.1.5.3 Costs associated with adverse events

The manufacturer stated that adverse events were included if they met the following criteria:

- grade 3 or 4 AEs
- and incidence greater or equal to 5%

However, additionally, the MS also included adverse events considered to be associated with significant costs despite the incidence being less than 5%, such as neutropenic infection and neutropenic sepsis. The manufacturer also stated that some adverse events (despite grade 3 or 4 incidence being greater than 5%) were excluded as they were deemed not clinically significant and would not routinely warrant intervention such as fatigue and leukopenia. The ERG asked the manufacturer to clarify exactly why these particular events were chosen, particularly if adverse events considered having a clinical and/or costing impact rather than both a clinical and cost impact (as stated in the MS, p.99) were considered, however no response was received.

The manufacturer also stated that the adverse events included were representative of the adverse events modelled in the NICE TA91. In the main analysis, adverse events for trabectedin in combination with PLDH and PLDH as monotherapy were extracted directly from the OVA-301 trial whilst adverse events for topotecan and paclitaxel were extracted from the MTC conducted in the NICE TA91. This was not considered appropriate by the ERG and requested clarification from the manufacturer. However, this was considered a minor issue by the ERG and was not rectified by the manufacturer probably due to time constraints. The manufacturer stated that no data were available for neutropenia and febrile neutropenia in the NICE TA91. Two scenarios were therefore presented by the manufacturer:

- assuming that these AEs occur only for trabectedin in combination with PLDH and PLDH as monotherapy
- assuming no cost for neutropenia.

Furthermore, the profile of AEs for the direct comparison analysis was directly extracted from the OVA-301 trial by platinum sensitivity as requested by the ERG (section 4.2.2). The ERG expressed some concerns as inconsistencies were noted. A detailed description is presented earlier in the report (section 4.2.2)

NHS reference costs from 2007/2008 were used to estimate the cost associated with each AE.[44] The ERG noted that the HRG cost was the same whether or not the severity of adverse event was grade 3 or 4. HRGs used in the MS are presented in Table 36. Despite a clarification request from the ERG, the manufacturer did not justify the rationale of using the same cost for grade 3 and 4 AEs. The manufacturer was also asked to test the impact using costs used in the previous NICE TA91. This was explored by the manufacturer and showed to have a limited impact on the results.

It was also unclear why tariffs from the NHS reference costs 2007/2008 [44] was used as the 2008/2009 version is available. The ERG also noted slight differences between the costs used in the MS and the costs reported in the NHS reference costs.

Table 36: HRGs and unit cost

AE	Severity	Cost	HRG – description
Anaemia	3	£464	SA13Z: Single Plasma Exchange, Leucophoresis or Red Cell Exchange
Anaemia	4	£464	SA13Z: Single Plasma Exchange, Leucophoresis or Red Cell Exchange
Diarrhoea	3	£141	Gynaecological Oncology outpatient - Consultant Led: Follow Up Attendance Non-Admitted Face to Face (Treatment function 503) + drugs
Diarrhoea	4	£934	FZ35C General Abdominal Disorders without CC. (Non-elective admission)
Nausea/vomiting	3	£215	Gynaecological Oncology outpatient - Consultant Led: Follow Up Attendance Non-Admitted Face to Face (Treatment function 503) + drugs
Nausea/vomiting	4	£934	FZ32C: Stomach or Duodenum Disorders without CC
Neutropenia Febrile	3	£2,149	SA01F: Aplastic Anaemia without CC
Neutropenia Febrile	4	£2,149	SA01F: Aplastic Anaemia without CC
Neutropenic infection	3	£2,149	SA01F: Aplastic Anaemia without CC
Neutropenic infection	4	£2,149	SA01F: Aplastic Anaemia without CC
Neutropenic sepsis	3	£2,149	SA01F: Aplastic Anaemia without CC
Neutropenic sepsis	4	£2,149	SA01F: Aplastic Anaemia without CC
Neutropenia	3	£137*	Gynaecological Oncology outpatient - Consultant Led: Follow Up Attendance Non-Admitted Face to Face (Treatment function 503) + drugs
Neutropenia	4	£2,149*	SA01F: Aplastic Anaemia without CC
PPE	3	£140	Gynaecological Oncology outpatient - Consultant Led: Follow Up Attendance Non-Admitted Face to Face (Treatment function 503) + drugs
PPE	4	£973	JD05C: Minor Skin disorders Category 2 without CC

Thrombocytopenia	3	£464	SA13Z: Single Plasma Exchange, Leucophoresis or Red Cell Exchange
Thrombocytopenia	4	£464	SA13Z: Single Plasma Exchange, Leucophoresis or Red Cell Exchange
Stomatitis	3	£155	Gynaecological Oncology outpatient - Consultant Led: Follow Up Attendance Non-Admitted Face to Face (Treatment function 503) + drugs
Stomatitis	4	£1,026	CZ23Y Major Head, Neck and Ear Disorders 19 years and over without CC

* note that the MS performed a sensitivity analysis around the cost of neutropenia.

The manufacturer also assumed that the mean length of stay of hospitalisation due to AEs was similar to that reported in the NHS reference costs [44] and did not include the costs associated with additional hospitalisation days.

Finally, the costs associated with AEs is likely to be underestimated as the model implicitly assumed that patients can only report each AE by severity once.

5.1.5.4 Discounting

The MS discounted health outcomes at 3.5% which was considered appropriate by the ERG.

Costs were not discounted as these were considered to be confined to the initial treatment period (under 1 year). The manufacturer stated that this assumption comes from the NICE TA91[2] and was also used for sake of simplicity. However, in the model amended by the manufacturer following request by the ERG, subsequent costs were included for the management in stable disease and for the management in the progressive state. The lack of discounting for cost would be unfavourable to trabectedin in combination with PLDH as the intervention is expected to keep patients alive longer.

The ERG was unclear regarding the appropriateness of the method used in the model to discount health outcomes. The ERG used what they believed to be the correct approach to discount health outcomes. The ERG was concerned by the method used in the MS to discount health outcomes. Indeed, the MS discounted utilities instead of QALYs, which was considered inappropriate. As the implementation of discounting is not easy within the current model structure, an alternative approach

was employed by the ERG and compared to the approach presented by the MS (see section 6.2). This approach was also used to discount costs as this was not done in the MS.

5.1.5.5 Half-cycle correction

No half cycle correction was applied; this was considered appropriate by the ERG.

5.1.5.6 Model validation

The MS stated that the model had been reviewed by a person independent of the model construction process. The MS also stated that the model was subjected to an extreme value analysis where parameter values were varied beyond what would be considered "reasonable" and the effects on the simulated costs and utilities observed to ascertain if the model was consistent with a priori expected differences in costs and benefits between the treatments modelled.

However, despite model validation being undertaken, a number of errors were found in the final model submitted to the ERG. This included:

- Inconsistencies in the median survival time reported in the clinical section and the economic model (section 5.1.3)
- Inconsistencies in the number of decimals reported for the median survival time
- Slight errors in the NHS reference costs for some HRGs
- Inconsistencies between the report and rules applied in the economic model to cost the management whilst on chemotherapy
- Errors in the utility values used for the partially platinum-sensitive population for the undiscounted analysis
- Errors in the cost for AEs for topotecan and paclitaxel for neutropenic infection and neutropenic sepsis

The MS also stated that the model was subjected to an extreme value analysis where parameters values were varied beyond what would be considered "reasonable". However, it appears that OS and PFS were varied using a range of ± 25%, despite the CI being beyond that range.

5.1.5.7 Univariate sensitivity analysis

The following variables were subject to deterministic sensitivity analysis:

1. Average number of treatment cycles
    a. This was varied between 1 to 8 cycles based on experts' opinion.
2. Discount rate
    a. This was varied using a rate of 1.5% and 6% as per NICE TA91.[2]
3. Overall survival
    a. This was varied assuming an arbitrary increase and decrease of 25% of the mean value.
4. Progression free survival
    a. This was varied assuming an arbitrary increase and decrease of 25% of the mean value.
5. Health state utility
    a. This was varied assuming an arbitrary increase and decrease of 25% of the mean value
6. Resource cost parameters:
    a. This was varied assuming an arbitrary increase and decrease of 30% of the mean value

Univariate sensitivity analysis (SA) was conducted only for the main analysis, and no deterministic sensitivity analysis was presented for the direct analysis by platinum sensitivity. The ERG believes that the ranges tested by the manufacturer were not appropriate and relevant, usually based on assumptions. Ideally, parameters should have been varied using a reasonable range, and correlation between parameters should have been included when possible. It is also unclear from the univariate SA when trabectedin in combination with PLDH was dominant or was dominated by PLDH as monotherapy. Furthermore, it appears that OS and PFS were varied using a range of ± 25%, despite the CI being beyond that range.

Sensitivity scenarios were also conducted assuming different assumptions for the costs of adverse events or the use of electrocardiogram and echocardiogram for the management of PFS.

5.1.5.8 Probabilistic Sensitivity Analysis

A Probabilistic Sensitivity Analysis was performed by the manufacturer, but several issues were identified by the ERG. The method used by the manufacturer, as well as corrections made by the ERG are presented in Table 37.

Table 37: Parameters varied in PSA in the MS and corrections made by the ERG

Parameter	Approach used in the MS	Approach used by the ERG
Mean OS	Main analysis: the CODA sample from the MTC was used incorrectly (different iteration by treatment) Direct comparison: The manufacturer sampled the mean OS from a gamma distribution assuming a 25% standard error around the mean. An additional rule was added to constrain the generated random number to be greater than 0.025 and lower than 0.975. Correlation between OS and PFS was included using the same random number. Note that only one random number was generated and was applied to all treatments, assuming they are highly correlated.	Main analysis: The ERG did not amend the main analysis, but suggested that the CODA sample was used (same iteration for all treatments to preserve the correlation estimated from the MTC) Direct comparison: The ERG used a different method to estimate the mean time in OS. Survival curves were fitted and the uncertainty was derived from the coefficients of the estimated parametric distribution, the variance-covariance matrix and the cholesky decomposition. PFS and OS were correlated using the same random number.
Mean PFS	Same as above	Same as above
Number of cycles	None – kept fixed in MS	The ERG sampled from the mean and standard error assuming a normal distribution
BSA	None – kept fixed in MS	The ERG sampled from the mean and standard error assuming a normal distribution
Dose/cycle	None – kept fixed in MS	The dose per cycle was implicitly sampled from the mean number of cycles and cumulative dose. First, we estimated the relationship between the cumulative dose and the number of cycles from individual patient data using a linear regression model. The uncertainty in the

		regression model was then derived from the coefficient, the variance-covariance matrix and cholesky decomposition. The dose per cycle was then calculated as a function of the number of cycles and cumulative dose
Proportion of AEs	The MS sampled from the mean proportion using a beta distribution and assuming a 25% standard error around the mean	The ERG sampled from a beta distribution from the number of patients with and without AEs
HRGs costs	The MS sampled from the mean costs and standard deviation using a gamma distribution. The standard deviation was estimated from the interquartiles. Note that only one random number was used to sampled all costs	The ERG sampled from the mean costs and standard error using a normal distribution as the SE was calculated assuming that the data are normally distributed. The standard deviation was first estimated from the interquartiles assuming that the data were normally distributed. The standard error was then calculated from the standard deviation and number of data submission
Cost associated with palliative care	None – kept fixed in MS	The ERG sampled from the mean and standard error (arbitrarily 10% of the mean) assuming a normal distribution
Utilities	The MS sampled from the mean and standard error assuming a beta distribution. An additional rule was added to constrain the generated random number to be greater than 0.025 and lower than 0.975. Correlation between utilities was included using the same random number. Note that only one random	The ERG sampled from the mean and standard error. Correlation between utility for PFS and PD was taken into account by using the same random number.

	number was generated and was applied to all treatments, assuming they are highly correlated.	
CA-125	Not used in the MS	The ERG sampled from a beta distribution from the number of patients with and without CA-125 > 2 ULN

5.2 Results included in manufacturer's submission

This section presents the main results from the MS included in the economic evaluation.

The deterministic result for the main analysis is presented in Table 38. An incremental analysis was reported whereby interventions which were dominated or extendedly dominated were excluded. The manufacturer reported that paclitaxel provided the least number of QALYs (1.17) followed by topotecan (1.27 QALYs). The corresponding ICER between paclitaxel and topotecan was estimated to be £81,320 per QALY gained. Topotecan was then compared to the next least effective treatment, i.e. PLDH which provided 0.27 additional QALYs for a cost saving of £2,585. Consequently, topotecan was found to be dominated by PLDH. Finally, the manufacturer reported that trabectedin in combination with PLDH provided 0.27 additional QALYs at an extra cost of £19,062. The ICER between trabectedin in combination with PLDH versus PLDH as monotherapy was £70,076 per QALY gained.

Table 38: Deterministic results included in the economic model for the main analysis (Reproduction of part of the Table 21 in the clarification letter)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Incremental analysis ranking technologies in terms of dominance and extended dominance								
Paclitaxel	£11,704	1.81	1.17	-	-	-	-	-
PLDH	£16,621	2.39	1.54	£5,547	0.58	0.36	£15,234	£15,234
Topotecan	£19,206	1.95	1.27	£8,132	0.14	0.10	£82,410	Dominated
Trabectedin + PLDH	£35,683	2.82	1.81	£24,609	1.01	0.64	£38,685	£70,076

The manufacturer also presented the ICERs for the three direct comparisons for the entire platinum-sensitive, partially and fully platinum-sensitive populations using the assessment by the independent radiologists, the independent oncologists and the investigators ~~independent investigator~~[g]. Only the ICER for partially platinum-sensitive women assessed by the independent oncologists is presented in this report (Table 39) as it was deemed to be the most appropriate scenario by the ERG. The manufacturer estimates that trabectedin in combination with PLDH provides 0.38 additional QALYs compared to PLDH as monotherapy for an additional cost of £14,910. The ICER between trabectedin in combination with PLDH versus PLDH as monotherapy in women who relapse between 6 to 12 months after initial platinum-based chemotherapy is estimated to be £39,262 in the MS. Detailed results for other scenarios are available in the MS.

[g] Correction/amendment made following comments from the manufacturer

Table 39: Deterministic results for partially platinum-sensitive women using oncologist assessment (Reproduction of the table submitted by the MS after clarification requested by the ERG)

(6-12)	Independent oncologists						
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
PLDH	£16,346	2.06	1.32	-	-	-	-
Trabectedin + PLDH	£31,256	2.76	1.70	£14,910	0.7	0.38	£39,262

As previously mentioned, univariate SA was conducted only for the main analysis and results for the comparison of trabectedin in combination with PLDH versus PLDH as monotherapy is presented in Figure 11. As expected, the ICER is influenced by OS, PFS and the number of cycles. Results for other comparison pairs in the main analysis are presented in the MS.

The MS also presented results from the PSA in terms of CE plane and CEAC for the main analysis and direct comparison. Only results of the PSA for the direct comparison in women with partially platinum-sensitive disease, using the oncologists' assessment are presented in this report. As results from the PSA for this scenario were not presented in the original submission, the ERG ran the economic model to provide the CE plane and CEAC using the oncologists' assessment but not amending other parameters (Figure 12 and Figure 13).

Figure 11: Univariate sensitivity analysis for the main analysis only (Extracted from the economic model)

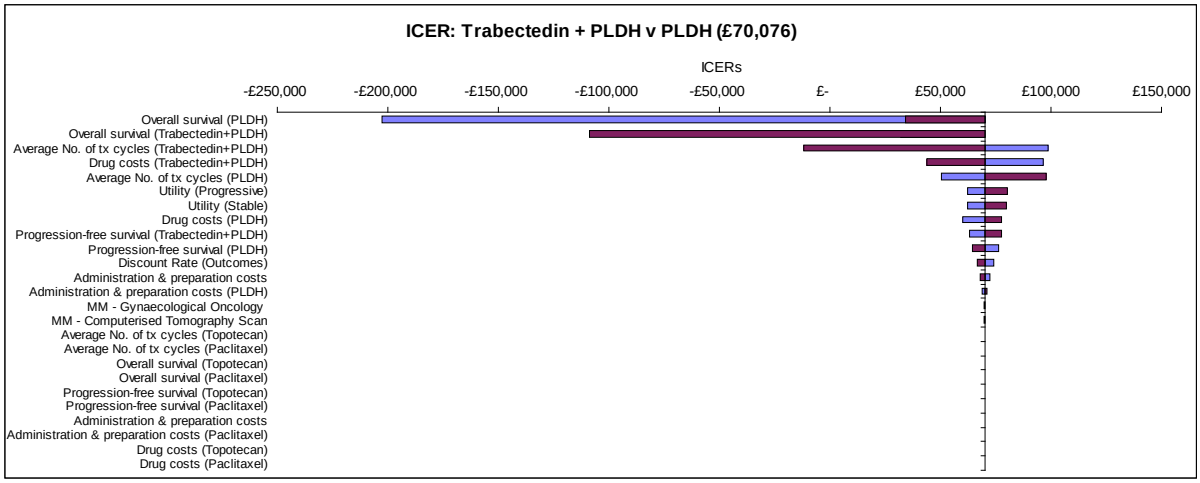


Figure 12: CE plane for the direct comparison for partially platinum-sensitive women (estimated by the ERG from the economic model using the oncologists' assessment)

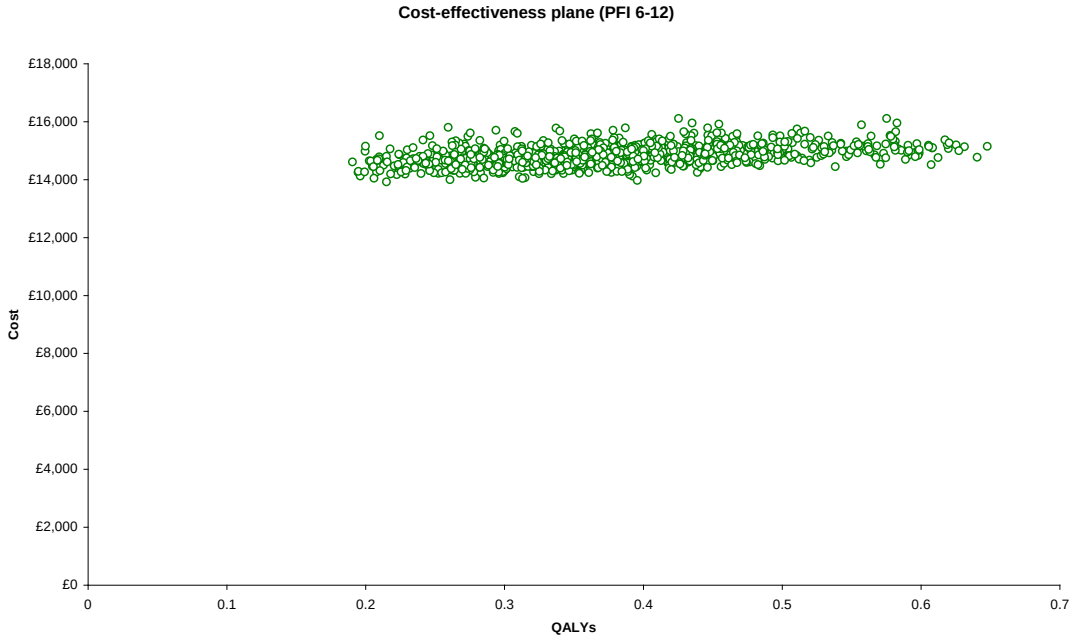
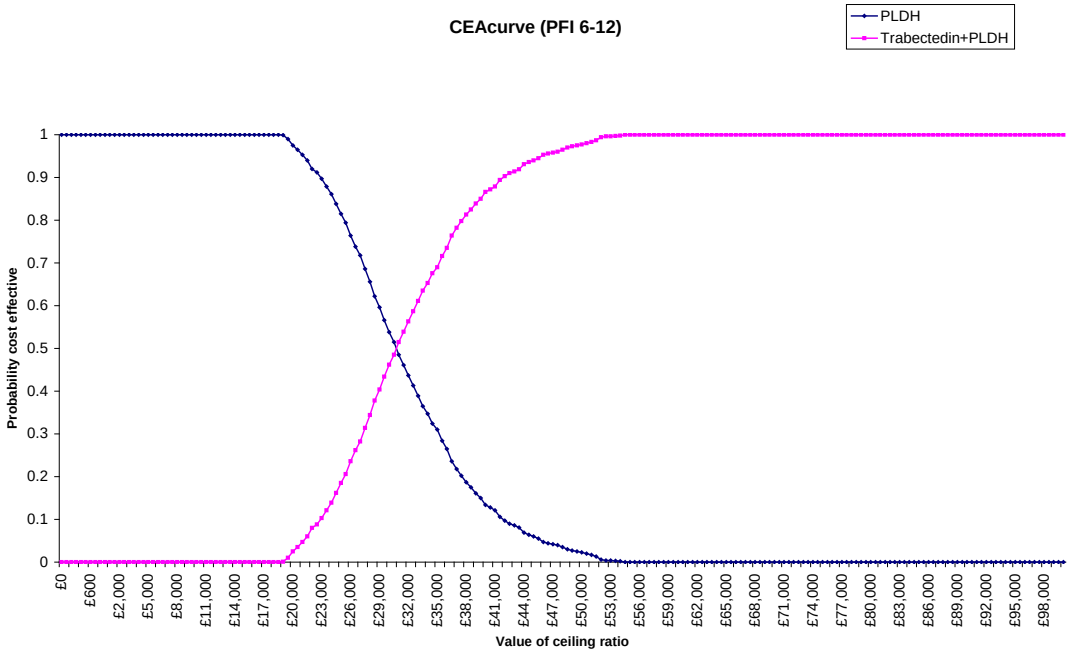


Figure 13: CEAC for the direct comparison for partially platinum-sensitive women (estimated by the ERG from the economic model using the oncologists' assessment)



5.3 Comment on validity of results presented with reference to methodology used

The manufacturer replicated an existing model developed for the NICE TA91. The main analysis in the MS is a comparison of trabectedin in combination with PLDH versus topotecan as monotherapy, paclitaxel as monotherapy and PLDH as monotherapy in women whose cancer has relapsed more than 6 months after completion of initial platinum-based chemotherapy.

The validity of results is limited as several assumptions have been made by the manufacturer in the absence of data and the simplicity of the model structure. The main limitations to this analysis are:

- the assumption that data are exponentially distributed and that the distribution was assumed to cross the median KM survival time
- the use of the average number of cycles of treatment across all the populations included in the trials (i.e. platinum-sensitive and resistant individuals) for the main analysis only

- the absence of discounting for costs and the inappropriate method used to discount health outcomes
- a number of issues in the implementation of the PS
- the absence of univariate sensitivity analyses for the three additional scenarios using direct evidence from the OVA-301 trial
- the uncertainty about the approach used to estimate the mean dose per cycle

The ERG also believes that the appropriate base case should be a comparison of trabectedin in combination with PLDH versus PLDH as a monotherapy using the oncologists' assessment in women whose cancer relapses between 6 to 12 months after initial platinum-based chemotherapy.

5.4 Summary of uncertainties and issues

The main uncertainty/issue is the assumptions made by the manufacturer to estimate the mean survival time, i.e. that data are exponentially distributed and that the distribution cross the median KM survival time. Indeed, the ERG demonstrated the data do not appear to be well represented by an exponential distribution and this tends to over- or underestimate the mean survival time.

The ERG also believes that the appropriate base case should be a comparison of trabectedin in combination with PLDH versus PLDH as monotherapy using the oncologists' assessment in women whose cancer relapses between 6 to 12 months after initial platinum-based chemotherapy.

There is also a potential limitation associated with the absence of discounting for costs and the approach used to discount health outcomes. This is likely to be unfavourable to trabectedin in combination with PLDH as patients live longer.

Finally, there were a number of issues in the implementation of the PSA, which limit its interpretation (Table 37).

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

As the most pertinent decision problem is a comparison of trabectedin in combination with PLDH versus PLDH as monotherapy assessed by the oncologists in women whose cancer has relapsed between 6 to 12 months after completion of initial platinum-based chemotherapy, additional work was undertaken only for this scenario, given time constraints.

Additional work included:

- Amending mistakes and/or assumptions used in the economic model (section 5.1.5.6)
- Deriving treatment effectiveness using individual patient data supplied by the manufacturer
- Amending issues identified in the PSA (section 5.1.5.8)
- Conducting univariate sensitivity analysis

6.1 Brief summary of changes made by the ERG

6.1.1 Changes to model parameters made by the ERG

The following parameters were amended by the ERG:

- Oncologist assessment for the base case.
    - The parametric distribution is fitted to the KM data estimated by independent oncologists only
- Parametric distribution to calculate the mean survival time (PFS and OS)
    - Individual patient data from the OVA-301 trial were analysed to fit different parametric distributions. The distributions were also adjusted for differences in clinical characteristics between the two treatment arms (more details are available in section 6.1.2). The uncertainty was also included.

- Mean number of cycles
    - More decimals were used (estimated from individual patient data) and the uncertainty was included
- Health state utility
    - Use of health state utilities for the combined treatment group for the overall platinum-sensitive population as used in the original MS. The uncertainty was also considered.
- Management cost of palliative care in the progressive state
    - Use of cost specific to ovarian cancer and the uncertainty was included
- Management in PFS
    - Use of one outpatient visit every month and one CT scan every 3 cycles (assumption based on clinical advice)
- HRGs costs
    - Corrected the slight error in HRGs costs and included the uncertainty in costs
- The proportion of AEs
    - Use of more decimals and inclusion of uncertainty.
    - The proportion was calculated using the total number of patients randomised in each treatment arm as it was unclear in the MS how this was calculated.
- The method used to estimate the mean dose per cycle
    - The mean dose per cycle was calculated as a function of the cumulative dose and the mean number of cycles for the deterministic scenario. In the PSA, the relationship between the cumulative dose and number of cycles was estimated via linear regression models. The number of cycles was therefore sampled, allowing prediction of the cumulative dose.

- The BSA
    - Use of more decimals and inclusion of uncertainty
- Discounting
    - Alternative method to discount health outcomes
    - Discount costs

For transparency, the impact associated with each of these change is presented in the section 6.2 (Table 41).

6.1.2 Assumptions used to calculate the mean survival time

As individual patient level data from the OVA-301 trial was made available to the ERG, it was possible to analyse these data and fit different parametric distributions to the data.

The ERG explored the fitting of five common parametric distributions (Exponential model, Weibull, Gompertz, log-logistic, Lognormal). These curves were fitted to PFS data estimated by the independent oncologists only. These parametric distributions were also fitted to OS.

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

- either adjusting for covariates using CA-125 (categorical) as covariate
- without adjustment for covariates

The ERG considered that the analysis adjusting the distribution for CA-125 was the most appropriate. The significance level of the coefficients in the estimated regression model was not considered a valid criteria as the aim was to adjust for differences between the 2 arms. However, the ERG noted that the proportion of patients with CA-125 < 2 ULN or CA-125 >= 2 ULN was a significant predictor for OS only but not for PFS.

6.1.3 Amendment of the PSA

The PSA was amended, and changes made to the PSA are described in section 5.1.5.8 in Table 37.

6.1.4 Univariate sensitivity analysis conducted

As the manufacturer did not present univariate SA for the direct comparison of trabectedin in combination with PLDH versus PLDH as monotherapy, the ERG explored the impact of the main parameters in univariate SA.

The following univariate SA were explored:

Table 40: Univariate SA

Number of cycles	Lower CI	Upper CI
Number of cycles	+ 5 %	+ 10%
Dose per cycle	Mean dose per cycle provided by the MS	
Health state utility	Lower CI	Upper CI
Health state utility	Health state utilities by treatment for partially platinum-sensitive women	
Health state utility	Health state utilities by treatment for platinum-sensitive women	
Health state utility	Health state utilities by treatment for fully platinum-sensitive women	
HRGs	Lower quartile	Upper quartile
Cost of palliative care	- 10%	+ 10%
Cost of palliative care	As presented in MS	
Management of PFS	As presented in MS	
Cost of neutropenia	None	

6.2 Results of analyses conducted by the ERG

As mentioned previously, the MS reported that the ICER for trabectedin in combination with PLDH versus PLDH as monotherapy is £39,262 for partially platinum-sensitive women using the oncologists' assessment.

For transparency, the ERG presented the impact of each single change made to the economic model. Note that most of the changes were minor, and were implemented to allow more flexibility when conducting the PSA (Table 41).

Table 41: Impact on the ICER associated with each single change made to the economic model

	ICER	% diff
Base	**£ 39,262**	
Weibull distribution - Adjusted for CA125	£ 49,084	25.0%
Weibull distribution - No adjustment	£ 47,295	20.5%
Gompertz distribution - Adjusted for CA125	£ 60,779	54.8%
Gompertz distribution - No adjustment	£ 57,175	45.6%
Number of cycle - more decimals	£ 39,500	0.6%
Health state utility - combined treatment	£ 39,201	-0.2%
Inconsistencies in HRGs costs	£ 39,260	0.0%
Proportion of AE	£ 39,271	0.0%
Mean number of dose per cycle	£ 43,969	12.0%
BSA - more decimals	£ 39,262	0.0%
Management of PFS	£ 41,018	4.5%
Discounting utilities	£ 29,591	-24.6%
Discounting costs	£ 37,917	-3.4%
Cost of palliative care	£ 40,133	2.2%

The main parameters that influenced the change in ICER compared to the ICER presented in the MS are the assumption used to estimate the mean time to OS and PFS (distribution used to represent the KM data), the approach used to discount health outcomes and the method used to calculate the mean dose per cycle.

6.2.1 ICER estimated by the ERG

Based on the updated model, the ERG believes that the most plausible ICER for trabectedin in combination with PLDH versus PLDH alone in women who relapse between 6 to 12 months after initial platinum-based chemotherapy ranges between £46,503 and £54,607, using the most plausible parametric distribution (as it was not straightforward to discriminate the Weibull over the Gompertz distribution). The ICER assuming alternative distributions is presented below in Table 42. The ERG however acknowledges that the use of parametric distribution is associated with several limitations

and may not fully represent the data. The ERG also believes that the most plausible ICER accounts for differences at baseline for CA-125 in the OVA-125 trial (see Table 42). The ICER for each distribution, without adjustment for CA-125 is presented in Table 43.

The ERG examined five different parametric distributions and overall, the fits produced by the Weibull and Gompertz distribution were similar as were the fits produced by the loglogistic and lognormal distribution. The estimation using the exponential model fell between the two pairs of fit.

The choice of the most plausible distribution of the observed data is not straightforward as available tests for goodness of fit (AIC or BIC) assess the fit of the distribution of the observed data and does not provide information on the fit of the unobserved data. For transparency, the ERG present both the AIC and BIC (Table 42 and Table 43). Consequently, the most plausible distribution was selected using an iterative process, looking at the AIC, BIC, and a visual inspection of each distribution of the observed data and the extrapolation at the end of the evidence. Overall, the Weibull distribution produced the best fit in terms of AIC and BIC, but the goodness of fit for other distributions was very close. Consequently, the ERG visually inspected each distribution to determine the most plausible distribution to the observed data. It appears that the Weibull and Gompertz distribution were very similar and were the most plausible distributions. The exponential, loglogistic and lognormal distributions had long tails, implying that the mean survival time was overestimated by these distributions. Plots of the observed Kaplan Meier data and the Weibull and Gompertz distribution are presented from Figure 14 to Figure 21. The plot of the observed KM and other distributions is presented in Appendix 2.

Table 42: ICERs estimated by the ERG using different types of distribution (adjustment for CA – 125)

	PFS – PLDH			PFS - Trabectedin			OS - PLDH			OS - Trabectedin			ICER		
	Mean	AIC	BIC	Mean	AIC	BIC	Mean	AIC	BIC	Mean	AIC	BIC	Inc Cost	Inc QALYs	ICER
Exponential	6.50	227.68	232.61	10.88	275.84	281.44	21.58	222.04	226.97	34.03	279.95	285.56	£19,976	0.65	£30,905
Weibull	6.23	227.40	234.80	9.46	268.62	277.03	19.51	212.72	220.12	26.81	262.64	271.05	£18,020	0.39	£46,503
Gompertz	6.28	228.85	236.24	9.34	272.03	280.44	19.04	217.15	224.55	24.99	263.54	271.95	£17,439	0.32	£54,607
LogLogistic	8.93	228.68	236.08	14.27	272.58	280.99	25.65	214.10	221.50	37.77	267.93	276.34	£19,321	0.63	£30,758
Lognormal	7.63	229.34	236.73	12.78	276.27	284.68	24.77	222.24	229.64	36.68	273.44	281.85	£19,335	0.62	£31,260

Table 43: ICERs estimated by the ERG using different types of distribution (without adjustment for CA – 125)

	PFS – PLDH			PFS - Trabectedin			OS - PLDH			OS - Trabectedin			ICER		
	Mean	AIC	BIC	Mean	AIC	BIC	Mean	AIC	BIC	Mean	AIC	BIC	Inc Cost	Inc QALYs	ICER
Exponential	6.33	235.04	237.55	11.04	274.98	277.79	21.80	226.92	229.43	33.92	287.53	290.34	£19,677	0.63	£31,164
Weibull	6.09	234.70	239.72	9.66	268.11	273.73	19.62	215.61	220.63	27.14	272.35	277.98	£17,988	0.40	£44,944
Gompertz	6.14	236.21	241.23	9.54	271.59	277.21	19.14	220.56	225.58	25.38	275.01	280.63	£17,438	0.34	£51,979
LogLogistic	8.72	236.18	241.21	14.51	271.74	277.36	25.22	216.73	221.75	38.45	274.94	280.56	£19,671	0.69	£28,692
Lognormal	7.39	236.97	241.99	13.03	275.54	281.16	24.53	225.86	230.88	37.41	280.64	286.26	£19,597	0.67	£29,293

Figure 14: Plot of the Kaplan-Meier data and Weibull distribution for PFS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

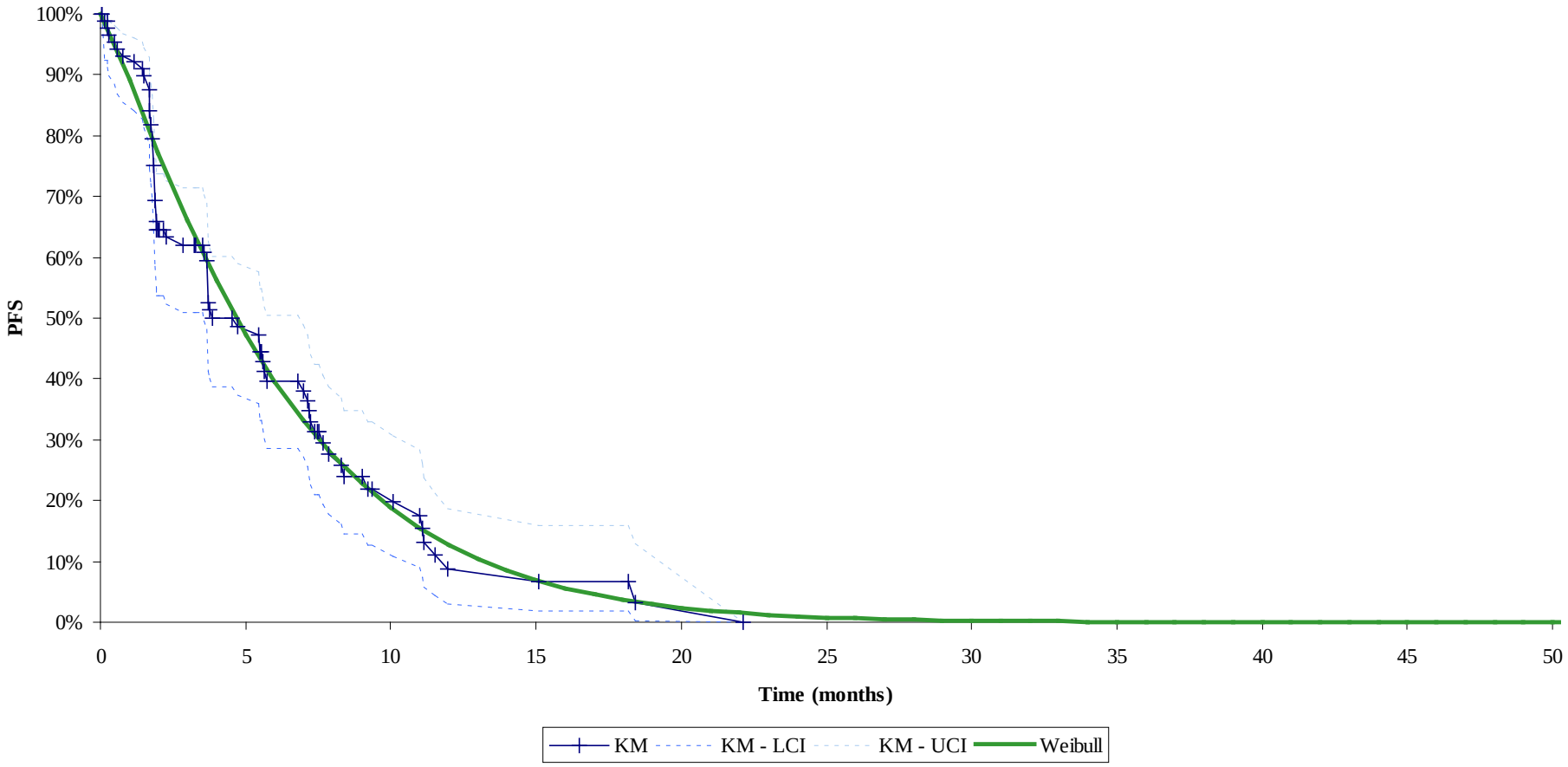


Figure 15: Plot of the Kaplan-Meier data and Weibull distribution for PFS for PLDH as monotherapy (estimated by the ERG using individual patient data from the OVA-301 Trial)

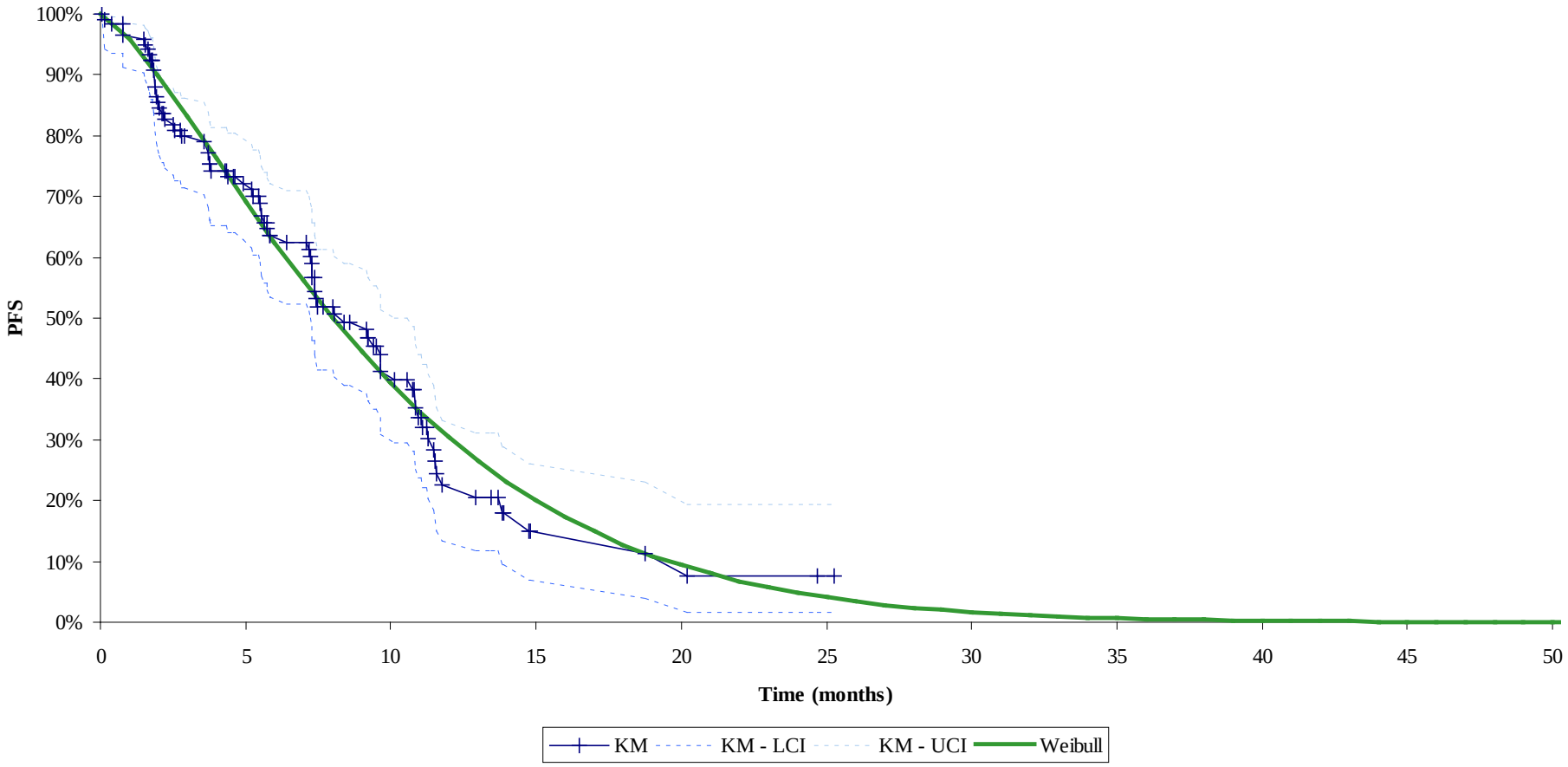


Figure 16: Plot of the Kaplan-Meier data and Weibull distribution for OS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

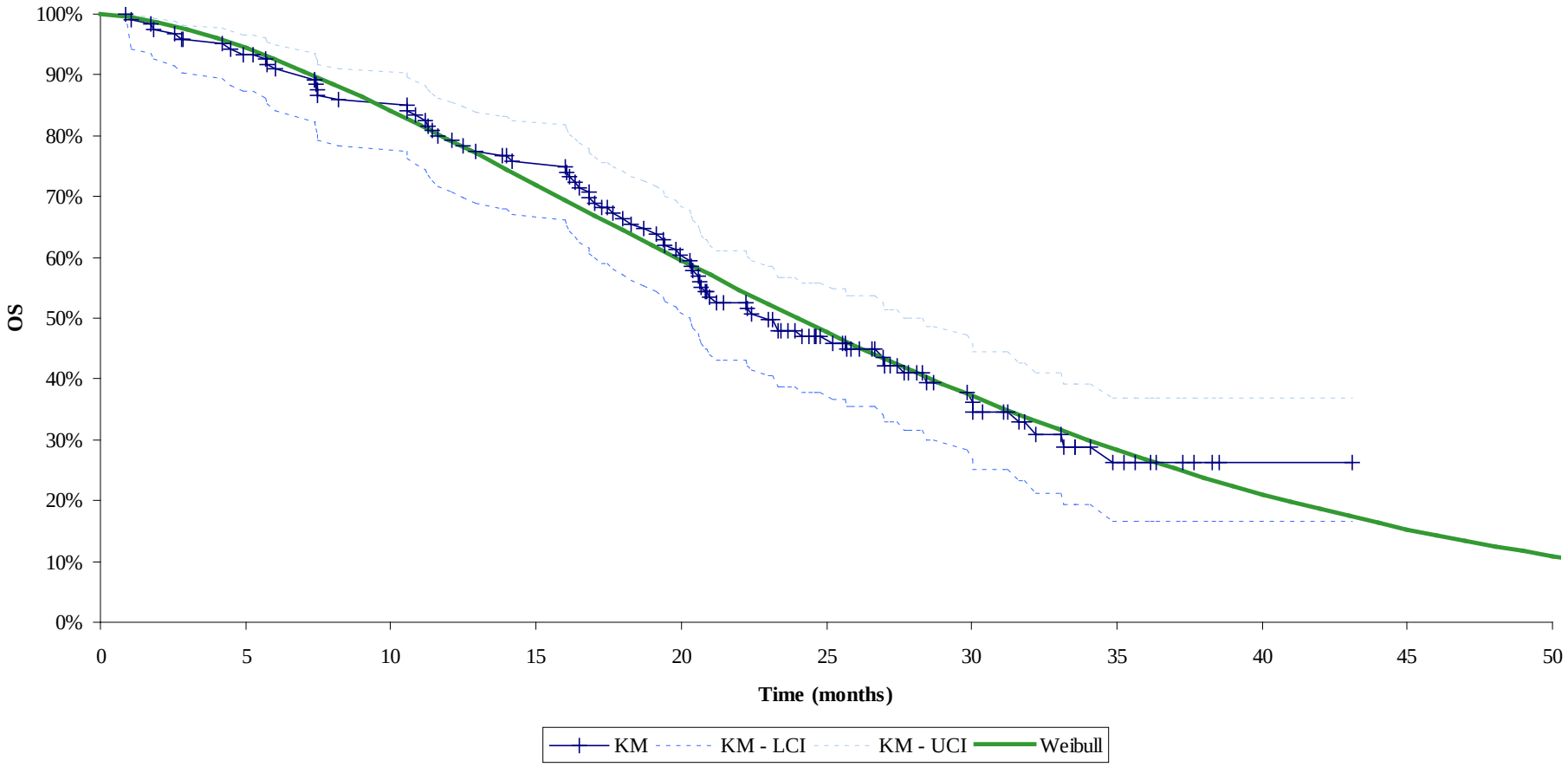


Figure 17: Plot of the Kaplan-Meier data and Weibull distribution for OS for PLDH as monotherapy (estimated by the ERG using individual patient data from the OVA-301 Trial)

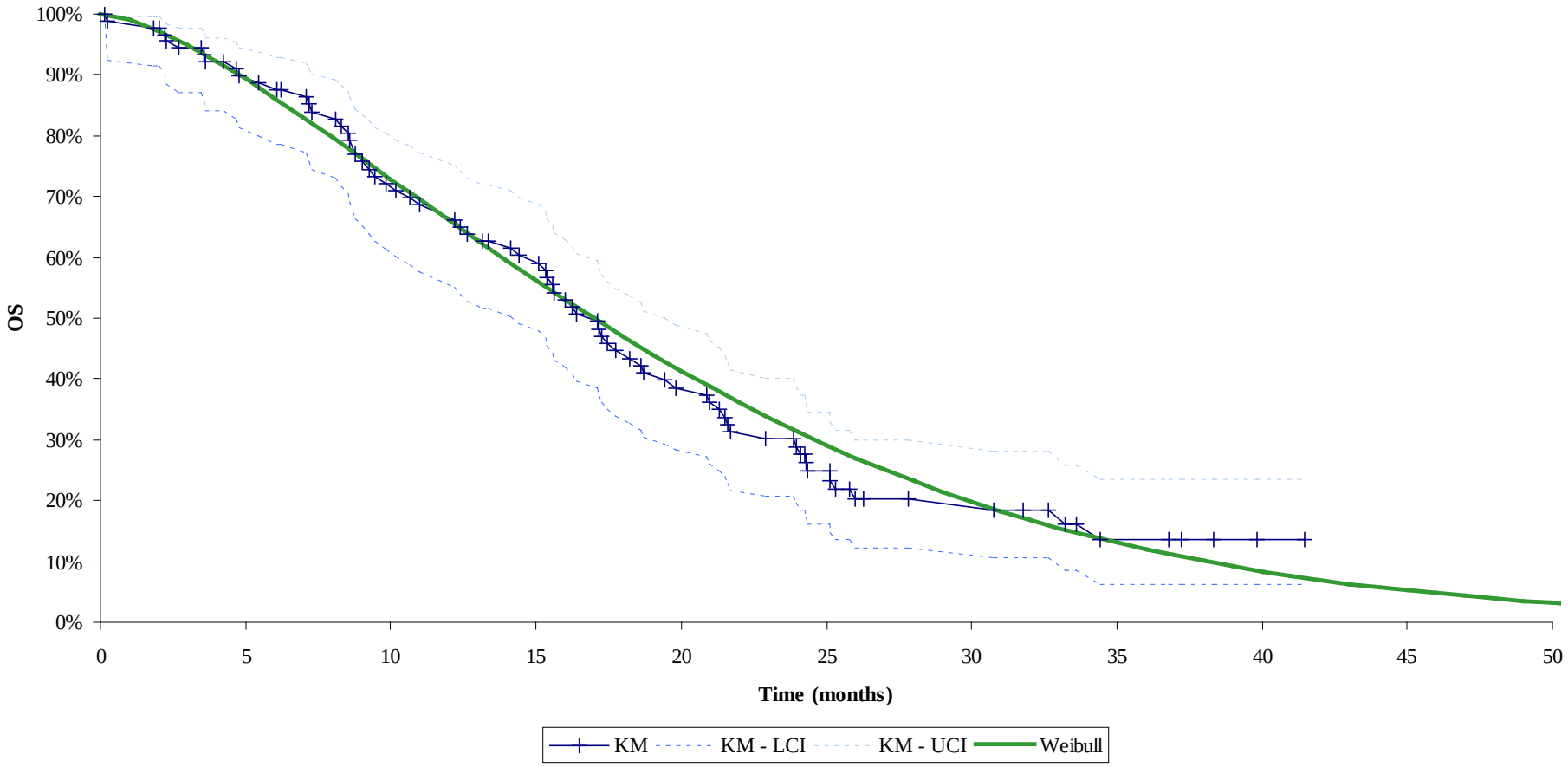


Figure 18: Plot of the Kaplan-Meier data and Gompertz distribution for PFS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

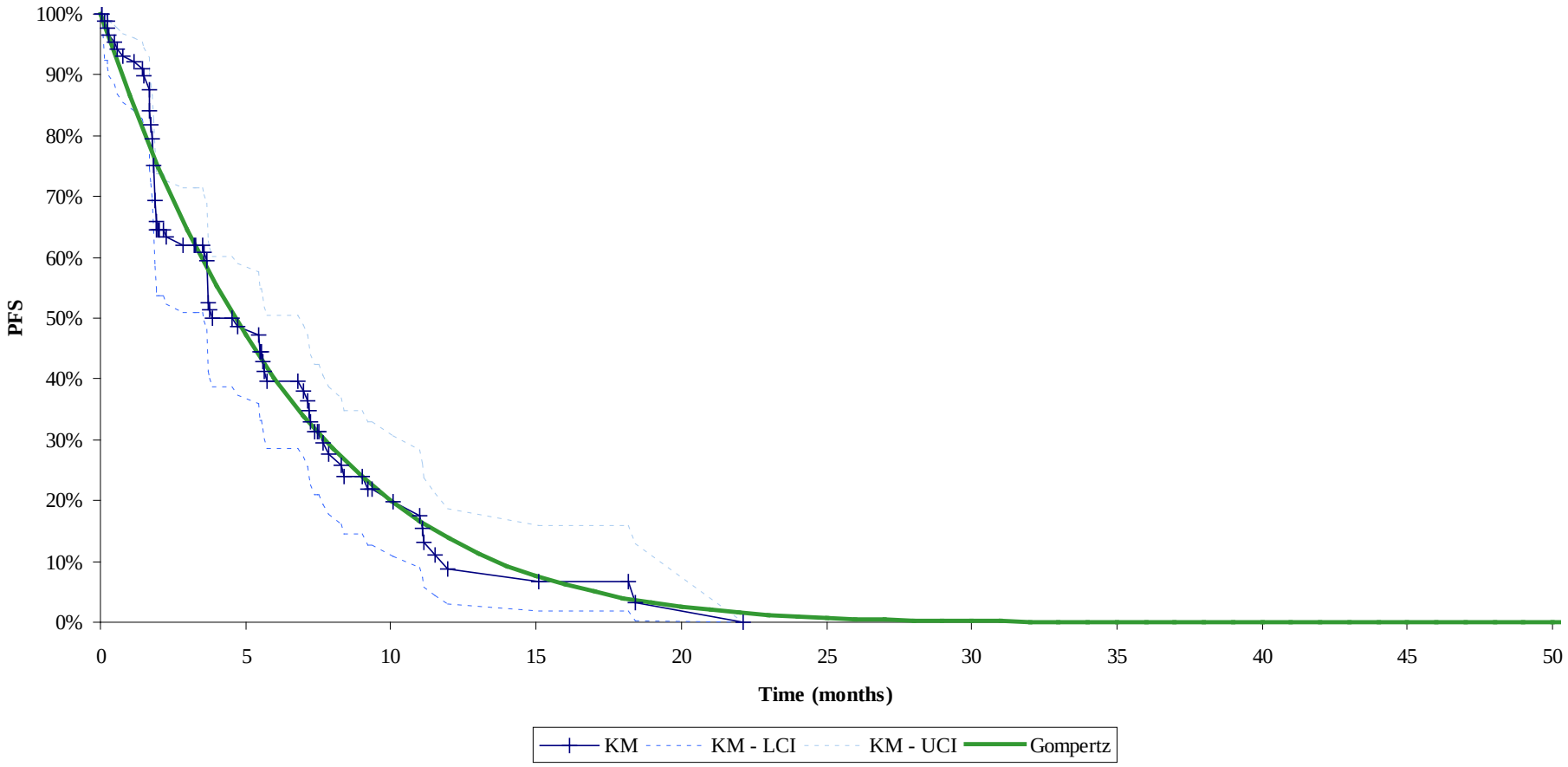


Figure 19: Plot of the Kaplan-Meier data and Gompertz distribution for PFS for PLDH as monotherapy (estimated by the ERG using individual patient data from the OVA-301 Trial)

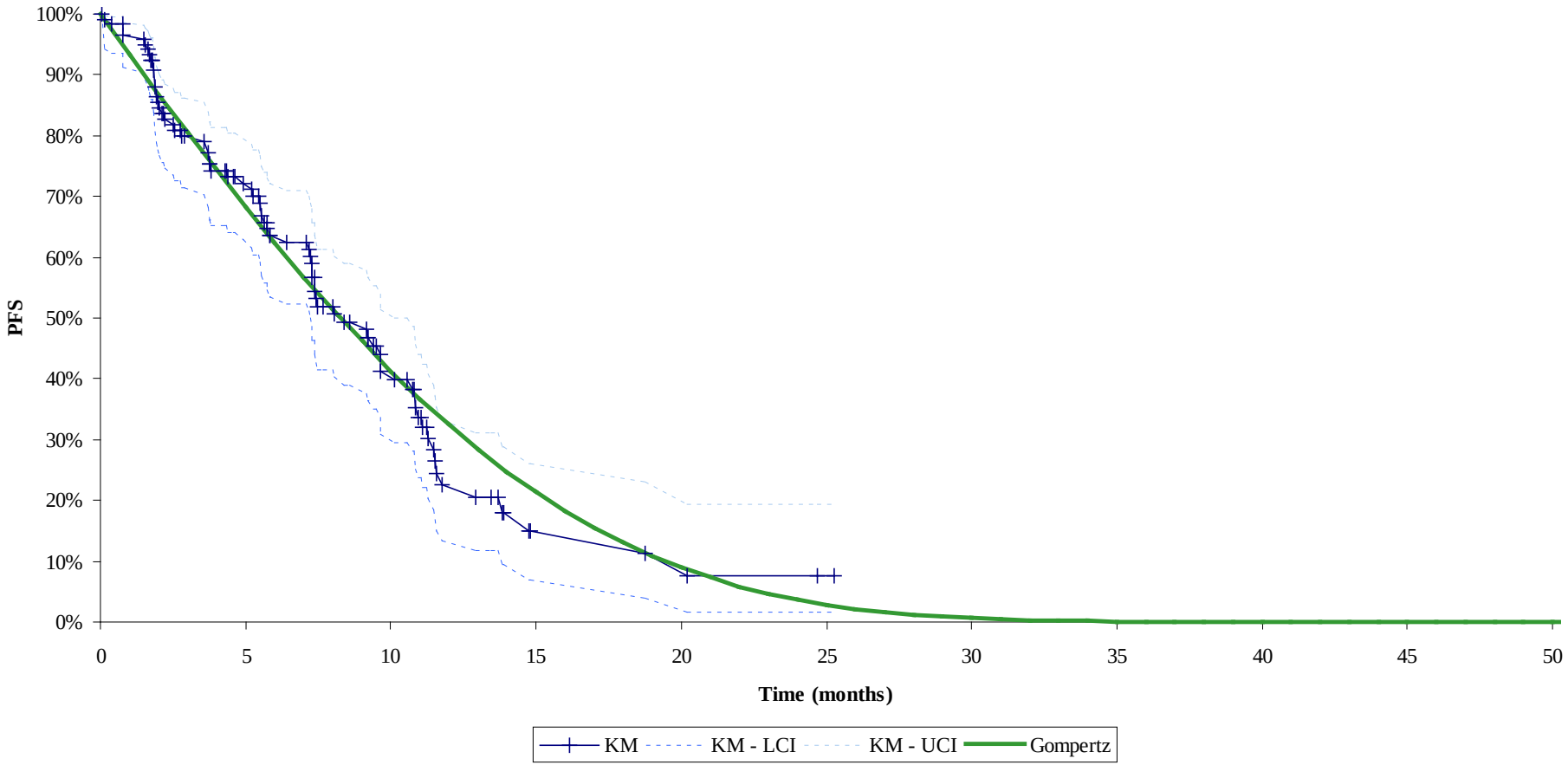


Figure 20: Plot of the Kaplan-Meier data and Gompertz distribution for OS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

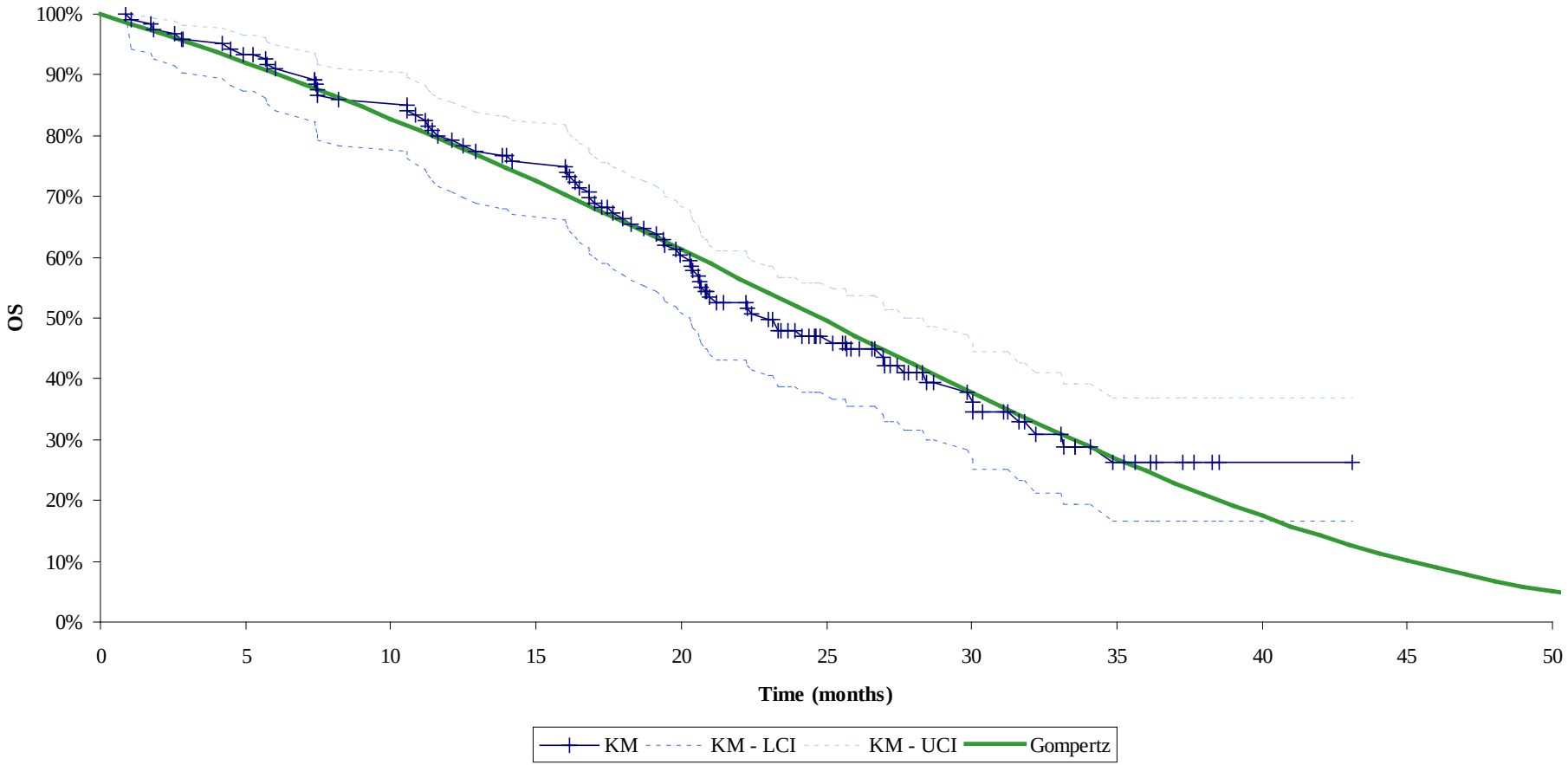
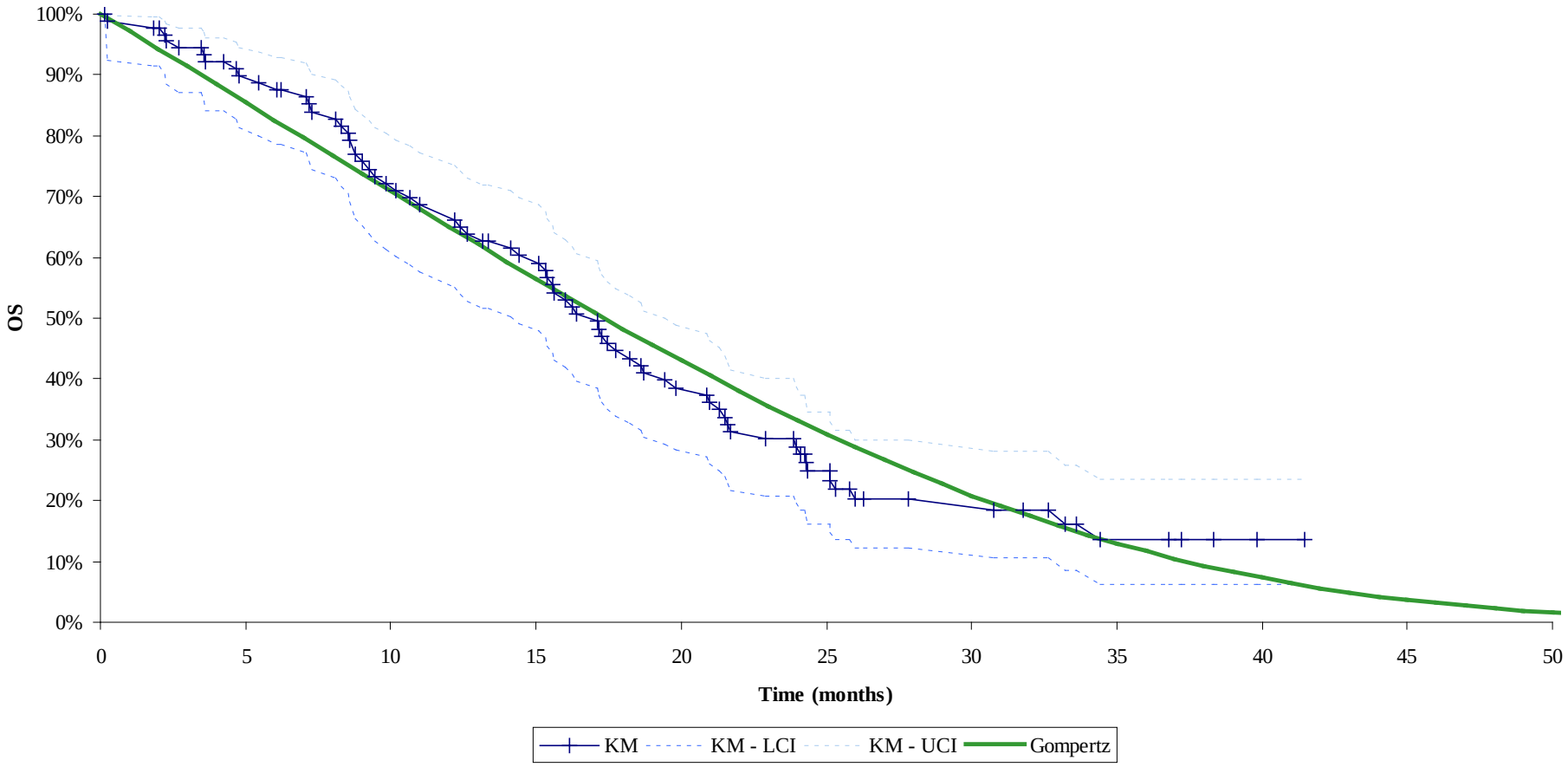


Figure 21: Plot of the Kaplan-Meier data and Gompertz distribution for OS for PLDH as monotherapy (estimated by the ERG using individual patient data from the OVA-301 Trial)



6.2.2 Univariate sensitivity analysis

A range of parameters were varied in univariate SA. Results from the univariate SA are presented in Table 44 and Figure 22-23

Table 44: Univariate SA

	ICER	% diff	ICER	% diff
Base	**£ 46,503**		**£ 54,607**	
Number of cycles - LCI	£ 49,345	6.1%	£ 58,054	6.3%
Number of cycles - UCI	£ 49,766	7.0%	£ 58,566	7.3%
Number of cycles - +5% trab	£ 44,644	-4.0%	£ 52,351	-4.1%
Number of cycles - +10% trab	£ 47,263	1.6%	£ 55,530	1.7%
Dose per cycle_MS	£ 42,025	-9.6%	£ 49,172	-10.0%
Utility - LCI	£ 48,579	4.5%	£ 56,912	4.2%
Utility - HCI	£ 44,597	-4.1%	£ 52,481	-3.9%
Utility - Platinum sensitive	£ 41,960	-9.8%	£ 48,632	-10.9%
Utility - Sensitive	£ 46,884	0.8%	£ 55,863	2.3%
Utility - Fully sensitive	£ 43,723	-6.0%	£ 51,991	-4.8%
HRGs – LQ	£ 46,292	-0.5%	£ 54,350	-0.5%
HRGs – UQ	£ 46,649	0.3%	£ 54,784	0.3%
Palliative Care -10%	£ 46,009	-1.1%	£ 54,184	-0.8%
Palliative Care +10%	£ 46,997	1.1%	£ 55,029	0.8%
Palliative Care - MS	£ 44,805	-3.7%	£ 53,154	-2.7%
Management - PFS	£ 46,344	-0.3%	£ 54,416	-0.3%
Cost neutropenia	£ 48,196	3.6%	£ 56,661	3.8%

The main parameters that influence the ICER are health state utilities, the method used to estimate the mean dose per cycle and the mean number of cycles. The costs associated with palliative care and the costs of managing neutropenia also have an impact on the ICER to a lesser extent.

Figure 22: Tornado diagram (Weibull) – Estimated by the ERG

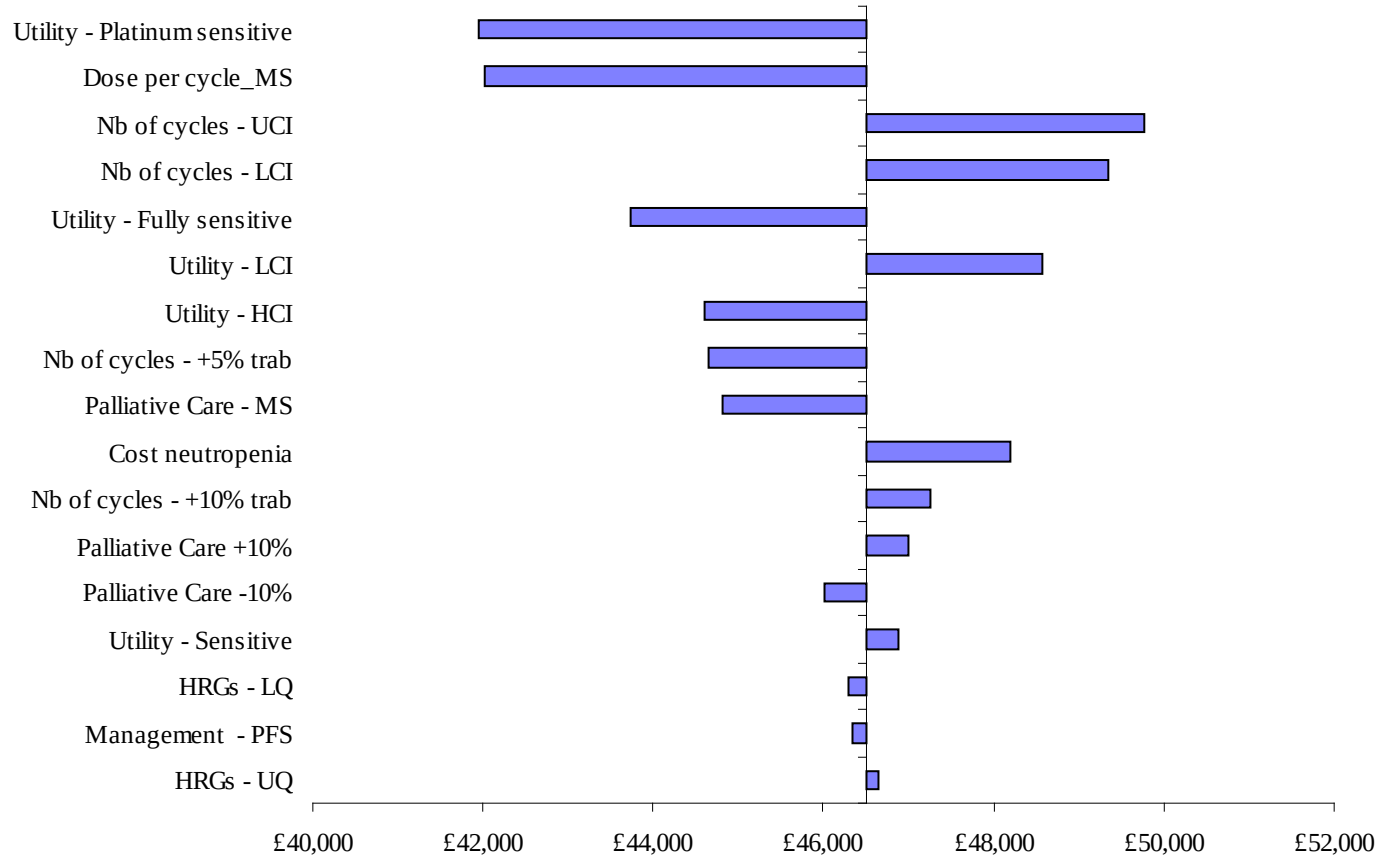
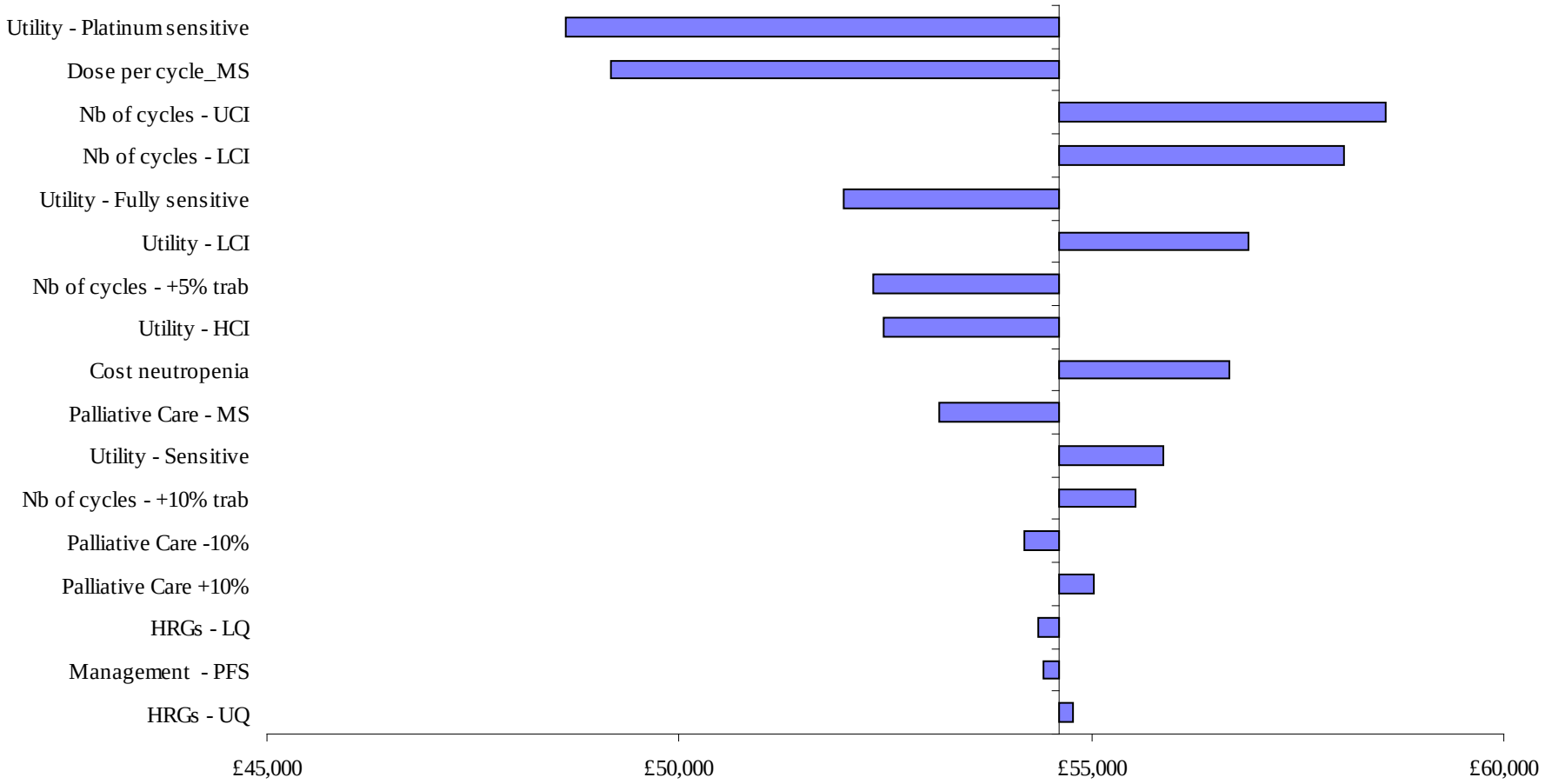


Figure 23: Tornado diagram (Gompertz) – Estimated by the ERG



An additional analysis was also conducted by the ERG to estimate the likely impact of a different hazard ratio between trabectedin in combination with PLDH versus PLDH as monotherapy, assuming a proportional hazard between treatments.

The distribution (without adjustment for covariates) for PLDH was estimated from individual patient data and the hazard ratios from the clinical section (see Table7 for OS and Tables 8, 9 and 10 for PFS) were applied to estimate the survival time for trabectedin in combination with PLDH. Such analysis assumes that there is proportional hazard between the two treatments, but this may not be the case in real life.

By doing so, the ERG estimated that the mean survival time for PFS and OS was 8.72 months and 27.99 months respectively using the Weibull distribution. Using a Gompertz distribution PFS and OS were 8.75 months and 26.34 months respectively. In comparison, the PFS and OS by fitting a separate distribution to trabectedin in combination with PLDH were 9.66 months and 27.14 months using the Weibull distribution and 9.54 and 25.38 months using a Gompertz distribution.

The estimated ICER was £42,932 assuming a Weibull distribution and £48,029 assuming a Gompertz distribution respectively (compared to £44, 944 to £51, 979 not assuming a proportional hazard between treatments).

The ERG tested a range of different hazard ratios for PFS and OS, and the ICER ranged from £40,539 to £45,289 using hazard ratios for the entire platinum-sensitive population and £102,096 and £110,772 using the hazard ratios for the fully platinum-sensitive population. ICERs using a wider range of hazard ratios are presented in Appendix 3.

Table 45: Analysis using the hazard ratios from the clinical section using the Weibull distribution for PLDH as monotherapy

			PFS		OS				
	HR pfs	HR os	PLDH	Trab	PLDH	Trab	Inc Cost	Inc Qalys	ICER
> 6 months	0.54	0.59	6.09	10.37	19.62	27.99	£18,106	0.45	£40,539
6 to 12 months	0.66	0.59	6.09	8.72	19.62	27.99	£18,779	0.44	£42,932
>12 months	0.66	0.82	6.09	8.72	19.62	22.43	£16,087	0.16	£102,096

Table 46: Analysis using the hazard ratios from the clinical section using the Gompertz distribution for PLDH as monotherapy

			PFS		OS				
	HR pfs	HR os	PLDH	Trab	PLDH	Trab	Inc Cost	Inc Qalys	ICER
> 6 months	0.54	0.59	6.14	10.32	19.14	26.34	£17,587	0.39	£45,289
6 to 12 months	0.66	0.59	6.14	8.75	19.14	26.34	£18,228	0.38	£48,029
>12 months	0.66	0.82	6.14	8.75	19.14	21.68	£15,964	0.14	£110,772

6.2.3 PSA

The results from the PSA are presented for the Weibull distribution in Figure 24 and Figure 25 for the CE plane and the CEAC respectively. Figure 26 and Figure 27 show the PSA results for the Gompertz distribution for the CE plane and CEAC respectively.

Figure 24: CE plane (Weibull) – Estimated by the ERG

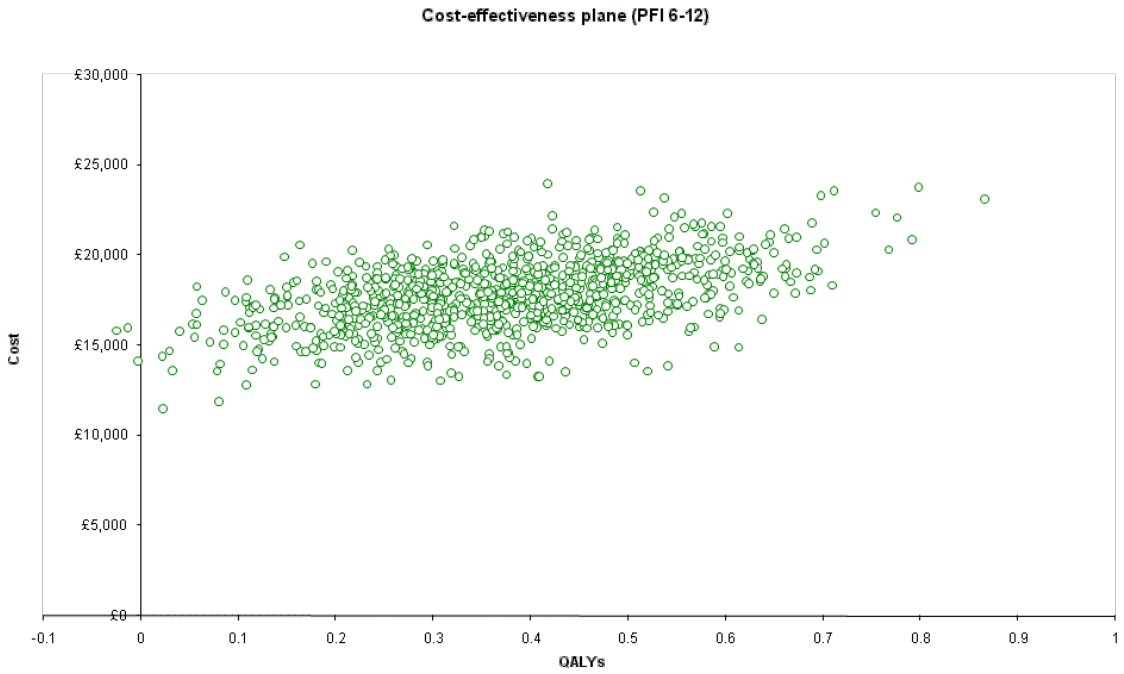
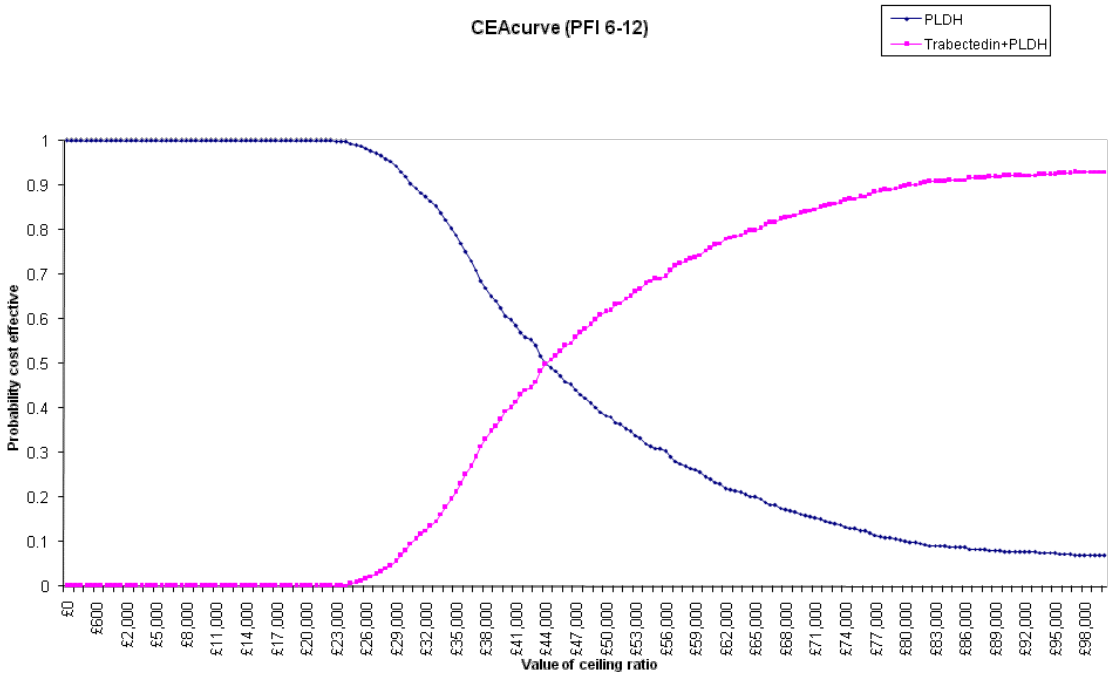


Figure 25: CEAC (Weibull) – Estimated by the ERG



Overall, assuming a Weibull distribution, trabectedin in combination with PLDH had a probability of being cost-effective at 0.0%, 4.3%, 31.5% and 55.5% assuming a cost-effectiveness threshold of £20,000, £30,000, £40,000 and £50,000 respectively.

Figure 26: CE plane (Gompertz) – Estimated by the ERG

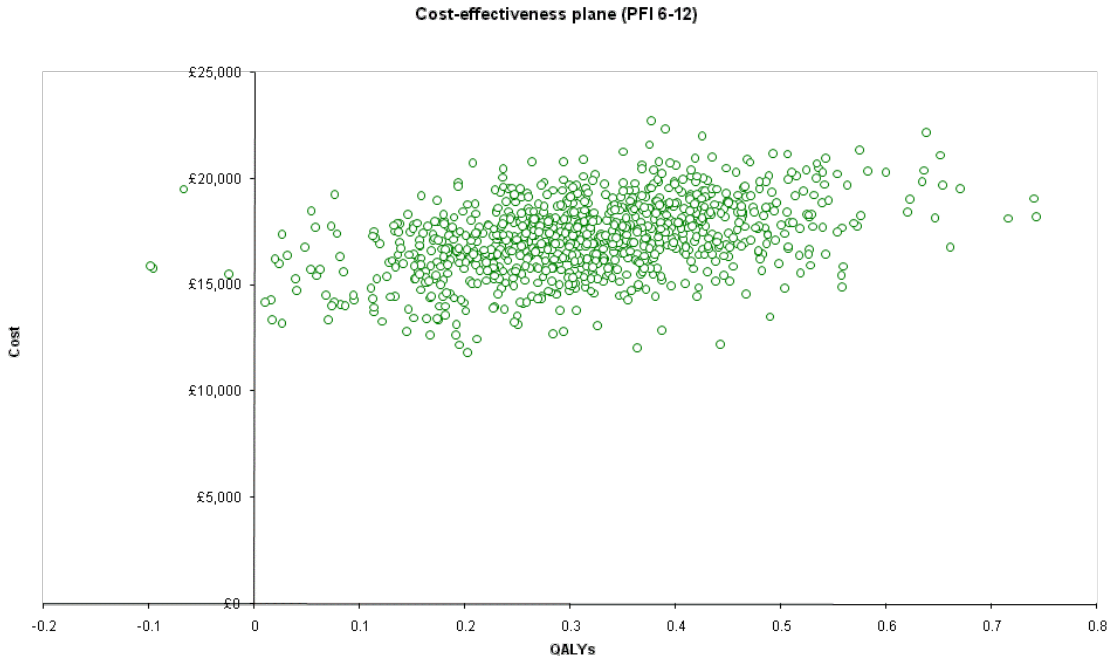
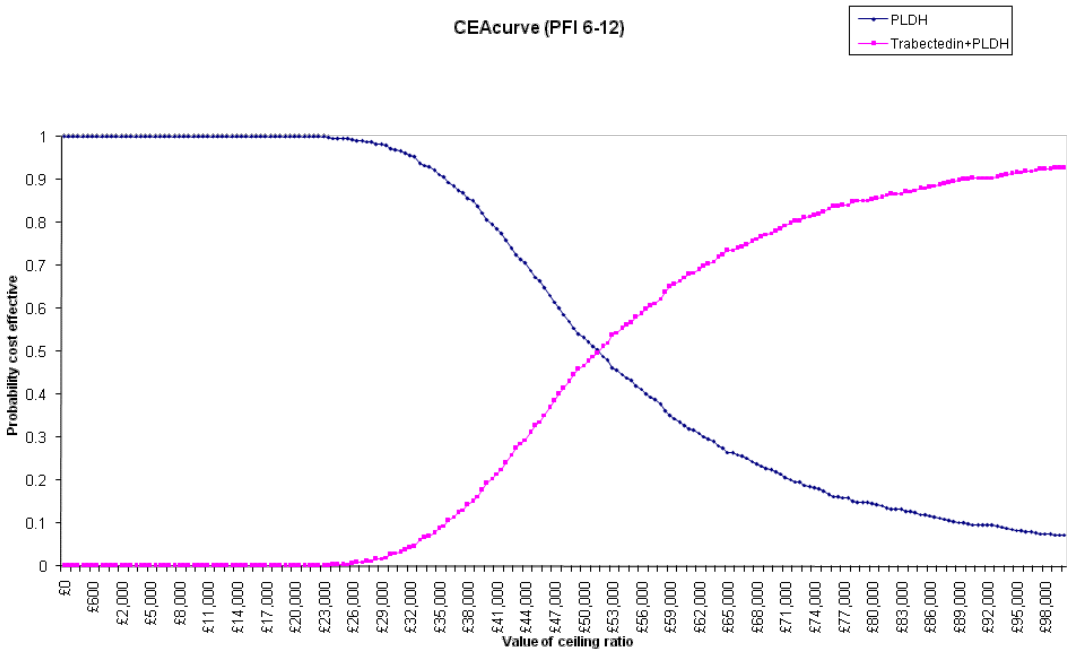


Figure 27: CEAC (Gompertz) – Estimated by the ERG



Overall, assuming a Gompertz distribution, trabectedin in combination with PLDH had a probability of being cost-effective at 0.0%, 1.3%, 13.7% and 38.7% assuming a cost-effectiveness threshold of £20,000, £30,000, £40,000 and £50,000 respectively.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The manufacturer's submission to NICE includes a systematic review of the clinical-effectiveness literature and narrative reporting of a single RCT that met the inclusion criteria of the review (OVA-301 trial). The reporting of the efficacy results and the quality assessment of the OVA-301 trial within the MS was often inadequate, incompletely reported or confusingly dispersed throughout the MS. The manufacturer's search strategy was adequately reported and the submission appears to contain all of the relevant head-to-head RCTs. Processes and validation of study screening and data extraction were not reported in full. The outcomes selected were relevant and appropriate.

The ERG has two main areas of concern relating to clinical effectiveness issues in the manufacturer's submission; first, the failure of the MS to address all populations and comparators outlined in the final NICE scope and second, the limited evidence base and its relevance to the NHS for the part of the scope that was addressed.

The MS contains an estimate of the treatment effect of trabectedin (in combination with PLDH) for part of the stated scope of the decision problem. An estimate of the efficacy (using PFS, OS and ORR) of trabectedin and PLDH vs. PLDH monotherapy is provided for the partially platinum-sensitive population (6-12 month relapse), which is one of the comparisons outlined within the final NICE scope. There are no estimates of treatment effect for trabectedin and PLDH vs. platinum-based chemotherapy (single agent or combination) in the fully (>12 month relapse) or partially (6-12 month relapse) platinum-sensitive population or estimates of trabectedin and PLDH vs. paclitaxel or topotecan monotherapy in the partially platinum-sensitive population (6-12 month relapse). However, as is pointed out within the MS, evidence to inform these comparisons, either directly or indirectly, is not believed to exist.

Whilst the submitted evidence generally reflects the part of the final NICE scope that was addressed in the MS, it is not totally representative of women with relapsed, advanced platinum-sensitive ovarian cancer in the UK. For example, age and ECOG performance status of the OVA-301 trial participants are not representative of women with relapsed, advanced ovarian cancer seen in UK clinical practice. The ERG has some concerns about the validity of the multivariate analyses presented by the manufacturer to determine the effect of prognostic factors on treatment effect (see 4.1.5 for further discussion), and believes that the analyses

presented by the manufacturer do not allow a reasonable interpretation of the effect of prognostic factors in PFS and OS.

The submitted evidence consists of the only RCT concerning the combination treatment of trabectedin and PLDH and as such may be helpful for answering some questions concerning treatment of relapsed, advanced platinum-sensitive ovarian cancer that will impact on the NHS. The MS states that the combination treatment of trabectedin and PLDH significantly increased overall survival (hazard ratio, 0.59; 95% CI, 0.42 to 0.82; p=0.0015) and PFS (hazard ratio, 0.54; 95% CI, 0.39 to 0.76; p=0.0002) in the partially platinum-sensitive population compared with PLDH monotherapy; where PFS is by the independent oncologists' assessment. The rate of most adverse events and the rate of discontinuing treatment as a result of adverse events was higher in the trabectedin and PLDH combination arm when compared with PLDH alone arm.

The results of a mixed treatment comparison meta-analysis were presented in the MS. The ERG had concerns about how the MTC was undertaken; however the results of the MTC did not provide further useful information for the final scope issued by NICE (see section 4.3 for further discussion).

7.2 Summary of cost effectiveness issues

The ERG had several concerns about the validity of results presented in the MS. Notably, the mean survival time was estimated assuming that data were exponentially distributed and that the distribution crosses the median KM survival time. As the data does not appear to be well represented by an exponential distribution, the assumptions made by the MS tend to overestimate the mean survival time, which is a driver of the cost-effectiveness. The MS also used PFS assessed by the independent radiologists for the base case. The ERG believes the independent oncologists' assessment of PFS to be the most appropriate method of assessment to use in the base case, based on clinical advice. There were a number of issues in the PSA limiting its interpretation and no univariate SA were presented for the three additional scenarios using direct evidence from the OVA-301 trial. The ERG was also concerned about the approach used to estimate the mean dose per cycle as the ERG was unable to replicate the figures presented by the MS. Finally, despite the model structure being appropriate, the simplicity of the model structure does not allow discounting to be easily implemented. This was implemented incorrectly in the MS for health outcomes and no discounting was applied for costs. Ideally, a state transition model should be constructed to facilitate discounting.

The MS estimated that the ICER for a combination of trabectedin with PLDH versus PLDH as monotherapy was £39,262 per QALY gained using the independent oncologists' assessment in the partially platinum-sensitive population. Additional work was undertaken by the ERG and parameters/assumptions were amended where necessary. This notably included fitting parametric distributions to individual patient data, estimating the mean dose per cycle from the cumulative dose and the number of cycles, the use of different utility values and correcting the discounting approach. The ERG believes that the most plausible ICER for trabectedin in combination with PLDH versus PLDH alone in women who relapse between 6 to 12 months after initial platinum-based chemotherapy ranges between £46,503 and £54,607 per QALY gained. However, uncertainties still exist as discounting cannot be easily implemented in such a model structure. Ideally a state transition model should be constructed to facilitate the implementation of discounting.

7.3 Implications for research

Further trials of trabectedin and PLDH compared to PLDH in the partially platinum-sensitive population would serve to lessen the uncertainty surrounding the effectiveness and cost-effectiveness of these treatments. Head to head trials of trabectedin and PLDH versus platinum-based chemotherapy (single agent or in combination) in the fully and partially platinum-sensitive populations would provide the much-needed evidence base for this comparison. Further research is need in other patient groups, namely older patients and patients with ECOG performance status 2.

8 APPENDICES

Appendix 1: Supplementary analyses provided by the manufacturer on the effect of prognostic factors on PFS and OS

Table 47: PFS Cox regression for each variable considered as prognostic factor

	Hazard ratio	95% CI	p-value
PFS - Age (years)	1.002	(0.992-1.011)	0.7115
PFS – Ascites at baseline (no *vs.* yes)	2.142	(1.752-2.618)	<.0001
PFS - Bulky disease (no *vs.* yes)	1.399	(1.146-1.708)	0.0010
PFS - CA-125 (<2xULN *vs.* ≥2xULN)	1.249	(0.965-1.616)	0.0910
PFS – Liver/lung metastases (no *vs.* yes)	1.175	(0.960-1.439)	0.1179
PFS - ECOG PS (0 *vs.* 1-2)	1.261	(1.030-1.546)	0.0251
PFS - Platinum sensitivity (PFI)	0.972	(0.961-0.983)	<.0001
PFS - Prior taxane (no *vs.* yes)	1.053	(0.824-1.345)	0.6814
PFS - Race (white *vs.* others)	1.174	(0.928-1.487)	0.1811
PFS - Treatment arm (PLD *vs.* T+PLD)	0.789	(0.646-0.963)	0.0201

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PS, performance status; T, trabectedin; ULN, upper limit of normal.

Table 48: PFS Cox regression for each variable considered as prognostic factor and treatment arm

		Hazard ratio	95% CI	p-value
PFS - Treatment and age	Treatment group	0.790	(0.646-0.966)	0.0216
	Age (years)	1.000	(0.991-1.010)	0.9214
PFS - Treatment and ascites at baseline	Treatment group	0.810	(0.663-0.989)	0.0389
	Ascites at baseline	2.126	(1.739-2.599)	<.0001
PFS - Treatment and bulky disease	Treatment group	0.788	(0.645-0.962)	0.0194
	Bulky disease	1.400	(1.147-1.709)	0.0009
PFS - Treatment and CA-125	Treatment group	0.805	(0.658-0.985)	0.0350
	CA-125	1.204	(0.928-1.561)	0.1616
PFS - Treatment and liver/lung metastases	Treatment group	0.782	(0.640-0.955)	0.0159
	Liver/lung metastases	1.191	(0.973-1.459)	0.0907
PFS - Treatment and ECOG PS	Treatment group	0.808	(0.661-0.989)	0.0384
	ECOG PS	1.228	(1.001-1.507)	0.0491
PFS - Treatment and platinum sensitivity	Treatment group	0.757	(0.620-0.925)	0.0064
	PFI	0.971	(0.960-0.983)	<.0001
PFS - Treatment and prior taxane	Treatment group	0.790	(0.647-0.965)	0.0210
	Prior taxane	1.038	(0.812-1.327)	0.7636
PFS - Treatment and race	Treatment group	0.790	(0.647-0.965)	0.0210
	Race	1.170	(0.924-1.481)	0.1916

Groups: treatment arm (PLD *vs.* trabectedin + PLD); age and platinum sensitivity (continuous variables); ascites (no *vs.* yes); bulky disease (no *vs.* yes); CA-125 (< 2x ULN *vs.* ≥ 2x ULN); liver/lung metastases (no *vs.* yes); ECOG PS (0 *vs.*>0); prior taxane (no *vs.* yes); race (white *vs.* others).
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PS, performance status.

Table 49: Overall survival: Cox regression of each variable considered as prognostic factor

	Hazard Ratio	95% CI	p-value
OS - Age (years)	1.005	(0.996-1.014)	0.2703
OS - Ascites at baseline (no *vs.* yes)	2.591	(2.135-3.146)	<.0001
OS - Bulky disease (no *vs.* yes)	1.625	(1.341-1.970)	<.0001
OS - CA-125 (<2xULN *vs.* ≥2 xULN)	1.452	(1.120-1.883)	0.0049
OS - Liver/lung metastases (no *vs.* yes)	1.388	(1.145-1.684)	0.0009
OS - ECOG PS (0 *vs.* 1-2)	1.621	(1.335-1.968)	<.0001
OS - Platinum sensitivity (PFI)	0.948	(0.935-0.962)	<.0001
OS - Prior taxane (no *vs.* yes)	1.236	(0.963-1.587)	0.0967
OS – Race (white *vs.* others)	1.054	(0.839-1.323)	0.6536
OS - Treatment arm (PLD *vs.* T+PLD)	0.848	(0.700-1.027)	0.0918

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFI, platinum-free interval; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PS, performance status; T, trabectedin; ULN, upper limit of normal.

Table 50: Overall survival: Cox regression for each variable considered as prognostic factor and treatment arm

		Hazard ratio	95% CI	p-value
OS - Treatment and age	Treatment group	0.857	(0.707-1. 039)	0.1162
	Age (years)	1.004	(0.995-1.014)	0.3560
OS - Treatment and ascites at baseline	Treatment group	0.920	(0.759-1.115)	0.3963
	Ascites at baseline	2.571	(2.116-3.124)	<.0001
OS - Treatment and bulky disease	Treatment group	0.848	(0.700-1.027)	0.0909
	Bulky disease	1.626	(1.341-1.970)	<.0001
OS - Treatment and CA-125	Treatment group	0.873	(0.720-1.058)	0.1663
	CA-125	1.427	(1.099-1.852)	0.0077
OS - Treatment and liver/lung metastases	Treatment group	0.841	(0.694-1.019)	0.0768
	Liver/lung metastases	1.395	(1.150-1.691)	0.0007
OS - Treatment and ECOG PS	Treatment group	0.881	(0.727-1.068)	0.1959
	ECOG PS	1.604	(1.320-1.948)	<.0001
OS - Treatment and platinum sensitivity	Treatment group	0.757	(0.625-0.918)	0.0046
	PFI	0.947	(0.934-0.960)	<.0001
OS - Treatment and prior taxane	Treatment group	0.850	(0.701-1.029)	0.0955
	Prior taxane	1.234	(0.961-1.584)	0.0996
OS - Treatment and race	Treatment group	0.849	(0.701-1.028)	0.0937
	Race	1.051	(0.837-1.320)	0.6705

Groups: treatment arm (PLD *vs.* trabectedin + PLD); age and platinum sensitivity (continuous variables); ascites (no *vs.* yes); bulky disease (no *vs.* yes); CA-125 (< 2x ULN *vs.* ≥ 2x ULN); liver/lung metastases (no *vs.* yes); ECOG PS (0 *vs.*>0); prior taxane (no *vs.* yes); race (white *vs.* others).
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PS, performance status.

Table 51: Multivariate analysis of progression-free survival (PFS) for prognostic factors. Full model with main effects

Analysis of maximum likelihood estimates								
Variable	**DF**	**Parameter estimate**	**Standard error**	**Chi-square**	**Pr > ChiSq**	**Hazard ratio**	**95% Hazard ratio confidence limits**	
Treatment group	1	-0.25260	0.10454	5.8390	0.0157	0.777	0.633	0.953
Prior taxane	1	0.06006	0.13232	0.2060	0.6499	1.062	0.819	1.376
ECOG PS	1	0.14249	0.10951	1.6931	0.1932	1.153	0.930	1.429
Race	1	0.19746	0.12157	2.6382	0.1043	1.218	0.960	1.546
PFI	1	-0.02867	0.00591	23.5480	<.0001	0.972	0.961	0.983
CA-125	1	0.02458	0.13447	0.0334	0.8550	1.025	0.787	1.334
Age (years)	1	0.00144	0.00489	0.0862	0.7690	1.001	0.992	1.011
Liver/lung metastases	1	0.10517	0.10784	0.9511	0.3295	1.111	0.899	1.372
Ascites at baseline	1	0.62412	0.10659	34.2816	<.0001	1.867	1.515	2.300
Bulky disease	1	0.34511	0.10717	10.3706	0.0013	1.412	1.145	1.742

Groups: treatment arm (PLD *vs.* trabectedin + PLD); age and platinum sensitivity (continuous variables); ascites (no *vs.* yes); bulky disease (no *vs.* yes); CA-125 (< 2x ULN *vs.* ≥ 2x ULN); liver/lung metastases (no *vs.* yes); ECOG PS (0 *vs.*>0); prior taxane (no *vs.* yes); race (white *vs.* others).
DF, degrees of freedom; ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PS, performance status.

Table 52: Multivariate analysis of overall survival (OS) for prognostic factors. Full model with main effects

Analysis of maximum likelihood estimates								
Variable	**DF**	**Parameter estimate**	**Standard error**	**Chi-square**	**Pr > ChiSq**	**Hazard ratio**	**95% Hazard ratio confidence limits**	
Treatment group	1	-0.20317	0.09926	4.1892	0.0407	0.816	0.672	0.991
Prior taxane	1	0.30410	0.13249	5.2683	0.0217	1.355	1.045	1.757
ECOG PS	1	0.44599	0.10362	18.5266	<.0001	1.562	1.275	1.914
Race	1	0.14759	0.11804	1.5631	0.2112	1.159	0.920	1.461
PFI	1	-0.05602	0.00725	59.6664	<.0001	0.946	0.932	0.959
CA-125	1	0.17498	0.13453	1.6916	0.1934	1.191	0.915	1.551
Age (years)	1	0.00586	0.00491	1.4231	0.2329	1.006	0.996	1.016
Liver/lung metastases	1	0.34530	0.10024	11.8665	0.0006	1.412	1.160	1.719
Ascites at baseline	1	0.75307	0.10256	53.9168	<.0001	2.124	1.737	2.596
Bulky disease	1	0.47060	0.10232	21.1543	<.0001	1.601	1.310	1.956

Groups: treatment arm (PLD *vs.* trabectedin + PLD); age and platinum sensitivity (continuous variables); ascites (no *vs.* yes); bulky disease (no *vs.* yes); CA-125 (< 2x ULN *vs.* ≥ 2x ULN); liver/lung metastases (no *vs.* yes); ECOG PS (0 *vs.*>0); prior taxane (no *vs.* yes); race (white *vs.* others).
DF, degrees of freedom; ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PS, performance status.

Table 53: Multivariate analysis of progression-free survival (PFS). Summary of treatment by covariates interaction.

Analysis of maximum likelihood estimates								
Variable	**DF**	**Parameter estimate**	**Standard error**	**Chi-square**	**Pr > ChiSq**	**Hazard ratio**	**95% Hazard ratio confidence limits**	
Treatment by prior taxane	1	0.21931	0.26527	0.6835	0.4084	1.245	0.740	2.094
Treatment by ECOG PS	1	-0.11184	0.22352	0.2503	0.6168	0.894	0.577	1.386
Treatment by race	1	-0.23578	0.24600	0.9186	0.3378	0.790	0.488	1.279
Treatment by CA-125	1	0.25872	0.27188	0.9055	0.3413	1.295	0.760	2.207
Treatment by liver/lung metastases	1	-0.08284	0.21708	0.1456	0.7028	0.921	0.602	1.409
Treatment by ascites at baseline	1	-0.35559	0.21618	2.7058	0.1000	0.701	0.459	1.070
Treatment by bulky disease	1	0.13084	0.21675	0.3644	0.5461	1.140	0.745	1.743
Treatment by PFI	1	-0.02248	0.01271	3.1279	0.0770	0.978	0.954	1.002
Treatment by age	1	-0.00190	0.00994	0.0366	0.8483	0.998	0.979	1.018

DF, degrees of freedom; ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; PS, performance status.

Table 54: Multivariate analysis of overall survival (OS). Summary of treatment by covariates interaction

Analysis of maximum likelihood estimates								
Variable	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	
Treatment by prior taxane	1	-0.28595	0.26728	1.1445	0.2847	0.751	0.445	1.269
Treatment by ECOG PS	1	-0.40014	0.21120	3.5894	0.0581	0.670	0.443	1.014
Treatment by race	1	0.08885	0.23783	0.1396	0.7087	1.093	0.686	1.742
Treatment by CA-125	1	0.56722	0.27128	4.3718	0.0365	1.763	1.036	3.001
Treatment by liver/lung metastases	1	0.29459	0.20184	2.1302	0.1444	1.343	0.904	1.994
Treatment by ascites at baseline	1	-0.18046	0.20614	0.7664	0.3813	0.835	0.557	1.251
Treatment by bulky disease	1	-0.10455	0.20673	0.2558	0.6130	0.901	0.601	1.351
Treatment by PFI	1	0.01433	0.01463	0.9587	0.3275	1.014	0.986	1.044
Treatment by age	1	0.01756	0.00980	3.2104	0.0732	1.018	0.998	1.037

DF, degrees of freedom; ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; PS, performance status.

Table 55: Multivariate analysis of overall survival (OS). Stepwise regression model testing main effects and treatment by CA-125 interaction.

Analysis of maximum likelihood estimates								
Variable	**DF**	**Parameter estimate**	**Standard error**	**Chi-square**	**Pr > ChiSq**	**Hazard ratio**	**95% Hazard ratio confidence limits**	
Treatment group	1	-0.21707	0.09893	4.8141	0.0282	0.805	0.663	0.977
Prior taxane	1	0.33721	0.13149	6.5767	0.0103	1.401	1.083	1.813
ECOG PS	1	0.44254	0.10339	18.3216	<.0001	1.557	1.271	1.906
PFI	1	-0.05591	0.00722	60.0214	<.0001	0.946	0.932	0.959
Liver/lung metastases	1	0.33970	0.10020	11.4939	0.0007	1.405	1.154	1.709
Ascites at baseline	1	0.77615	0.10153	58.4444	<.0001	2.173	1.781	2.652
Bulky disease	1	0.46838	0.10217	21.0147	<.0001	1.597	1.308	1.952

Groups: treatment arm (PLD *vs.* trabectedin + PLD); platinum sensitivity (continuous variables); ascites (no *vs.* yes); bulky disease (no *vs.* yes); liver/lung metastases (no *vs.* yes); ECOG PS (0 *vs.*>0); prior taxane (no *vs.* yes).
DF, degrees of freedom; ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PS, performance status.

Appendix 2: Distributions fitted to the KM data (exponential, loglogistic, lognormal) – Figure 28 to 39

Figure 28: Plot of the Kaplan-Meier data and Exponential distribution for PFS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

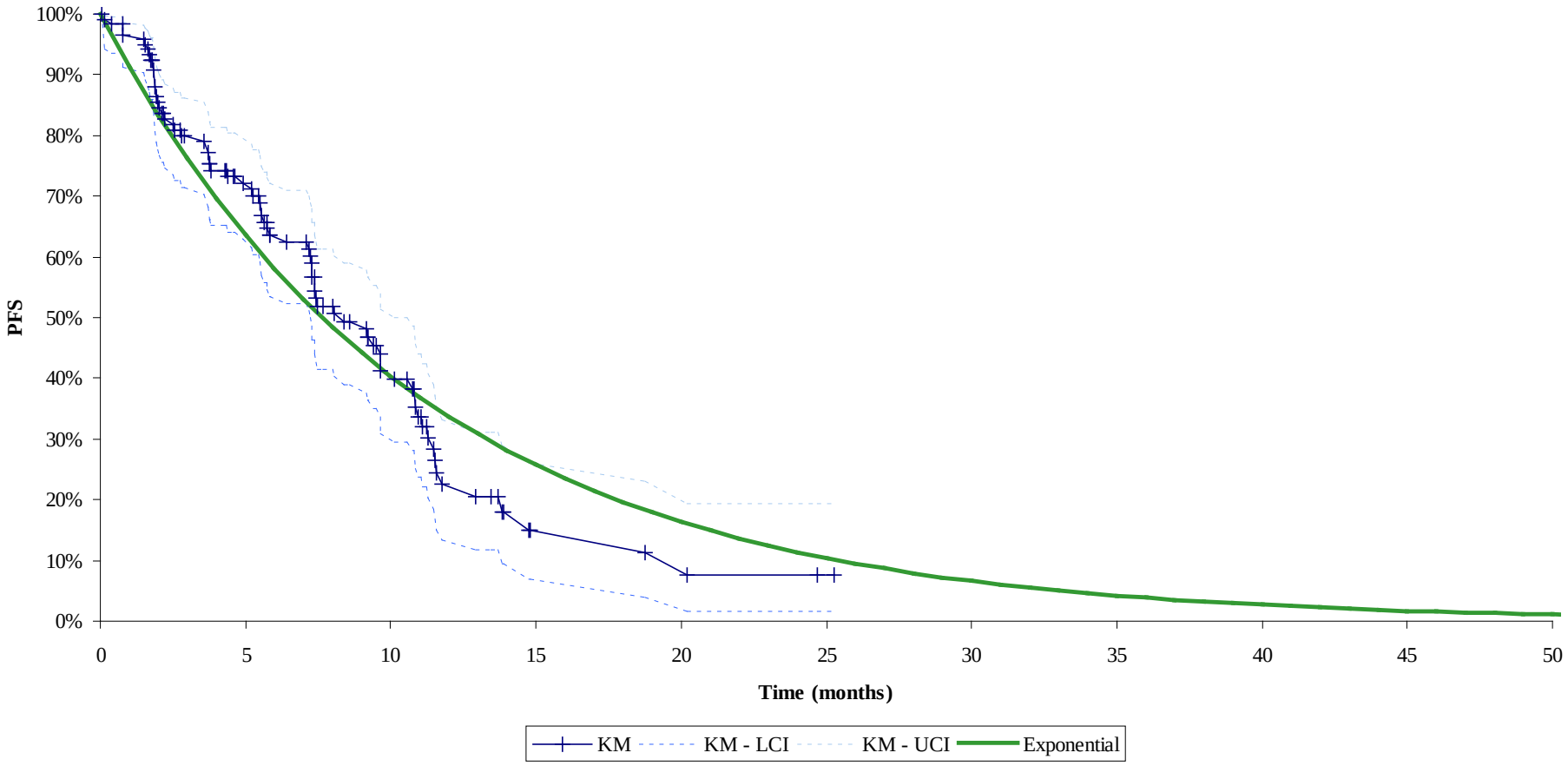


Figure 29: Plot of the Kaplan-Meier data and Exponential distribution for PFS for PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

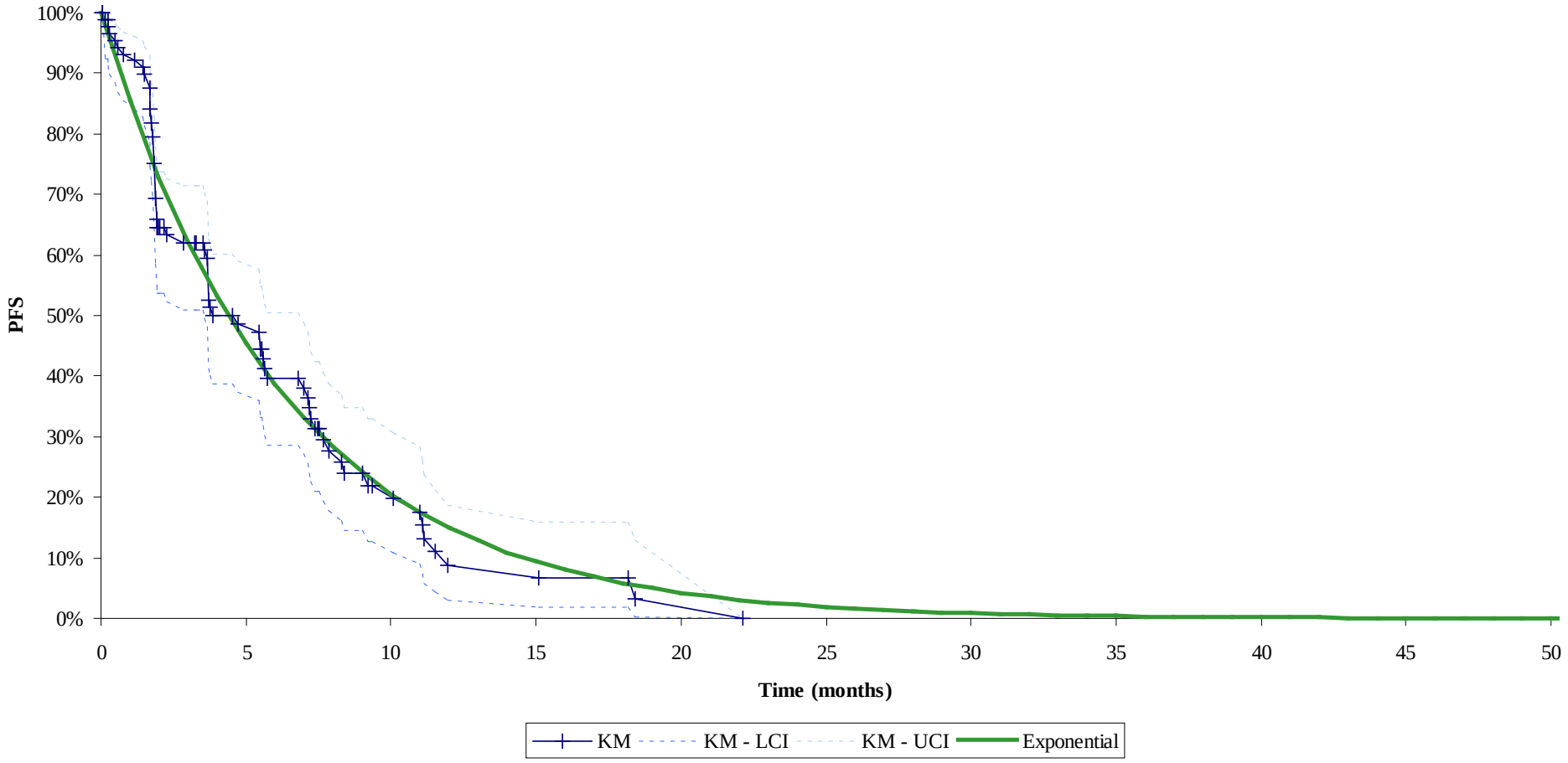


Figure 30: Plot of the Kaplan-Meier data and Exponential distribution for OS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

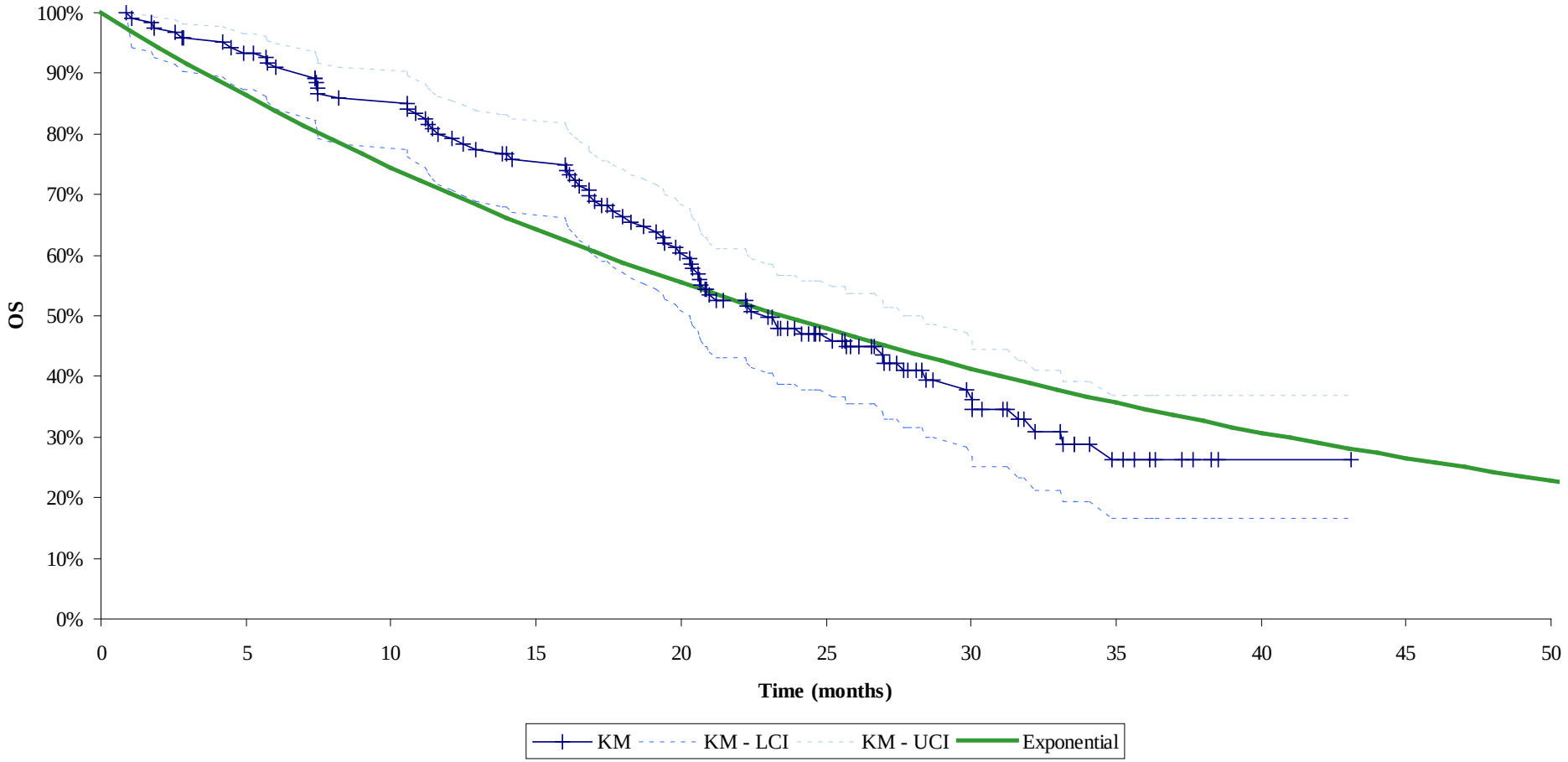


Figure 31: Plot of the Kaplan-Meier data and Exponential distribution for OS for PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

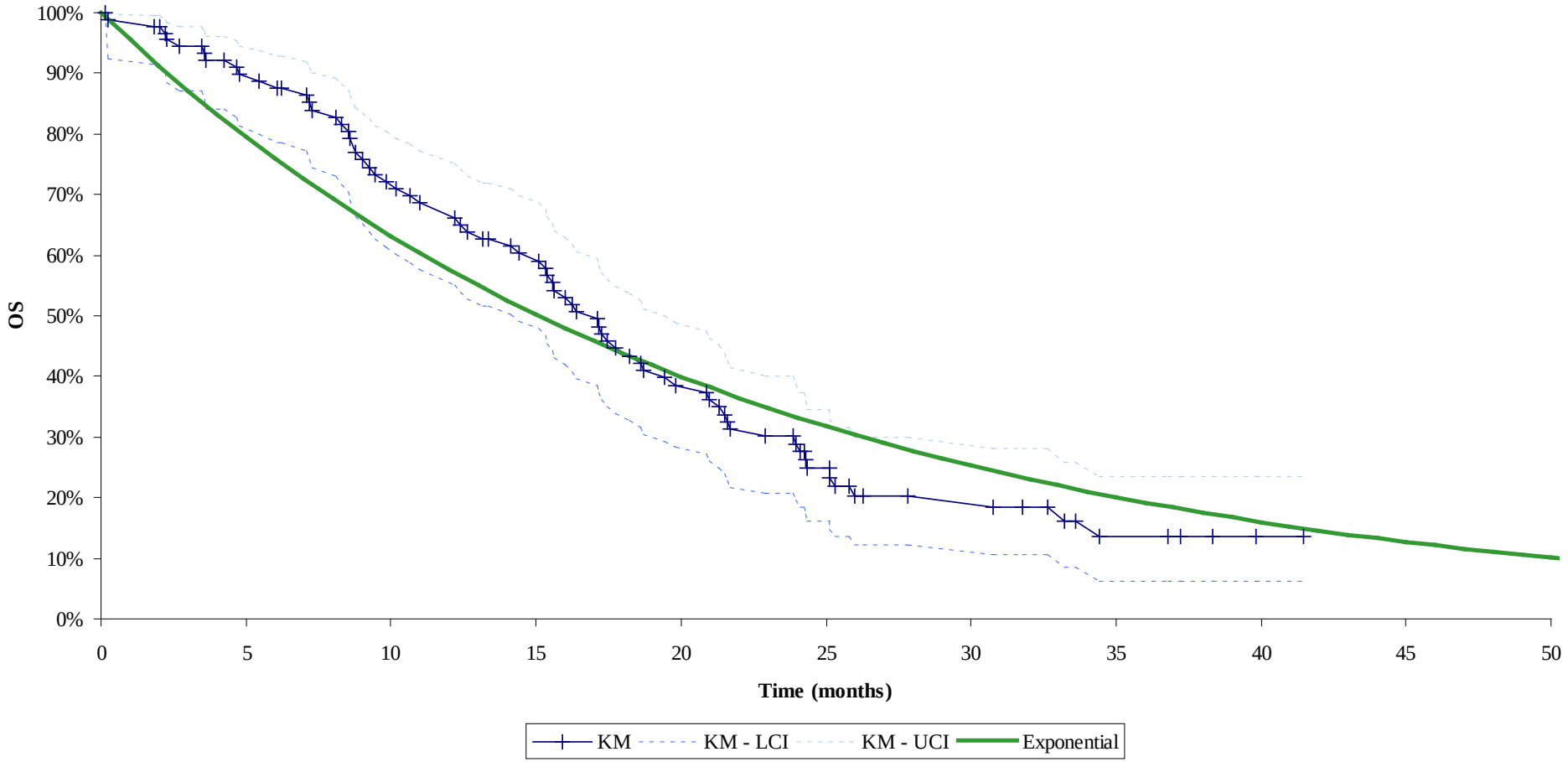


Figure 32: Plot of the Kaplan-Meier data and Loglogistic distribution for PFS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

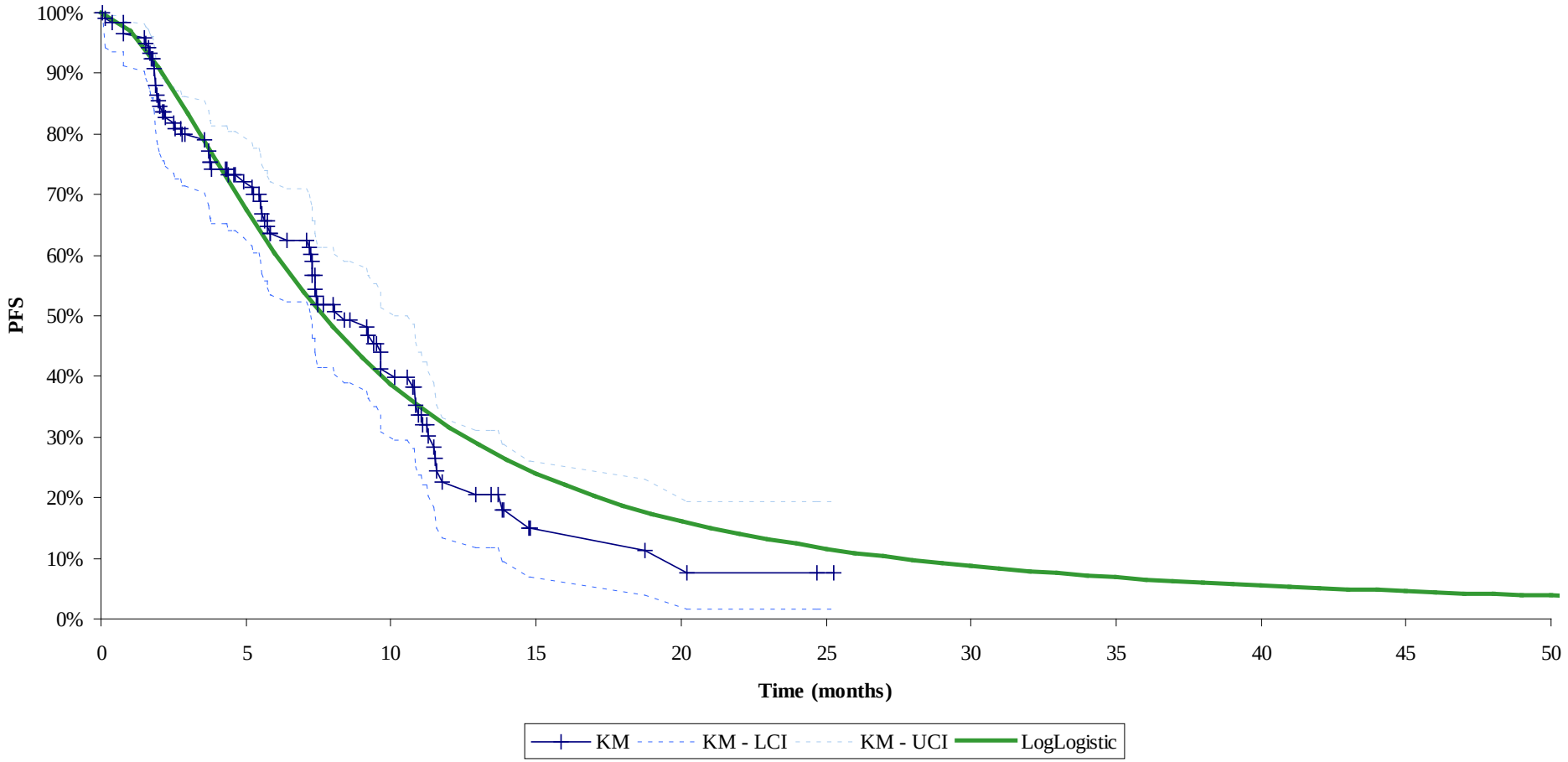


Figure 33: Plot of the Kaplan-Meier data and Loglogistic distribution for PFS for PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

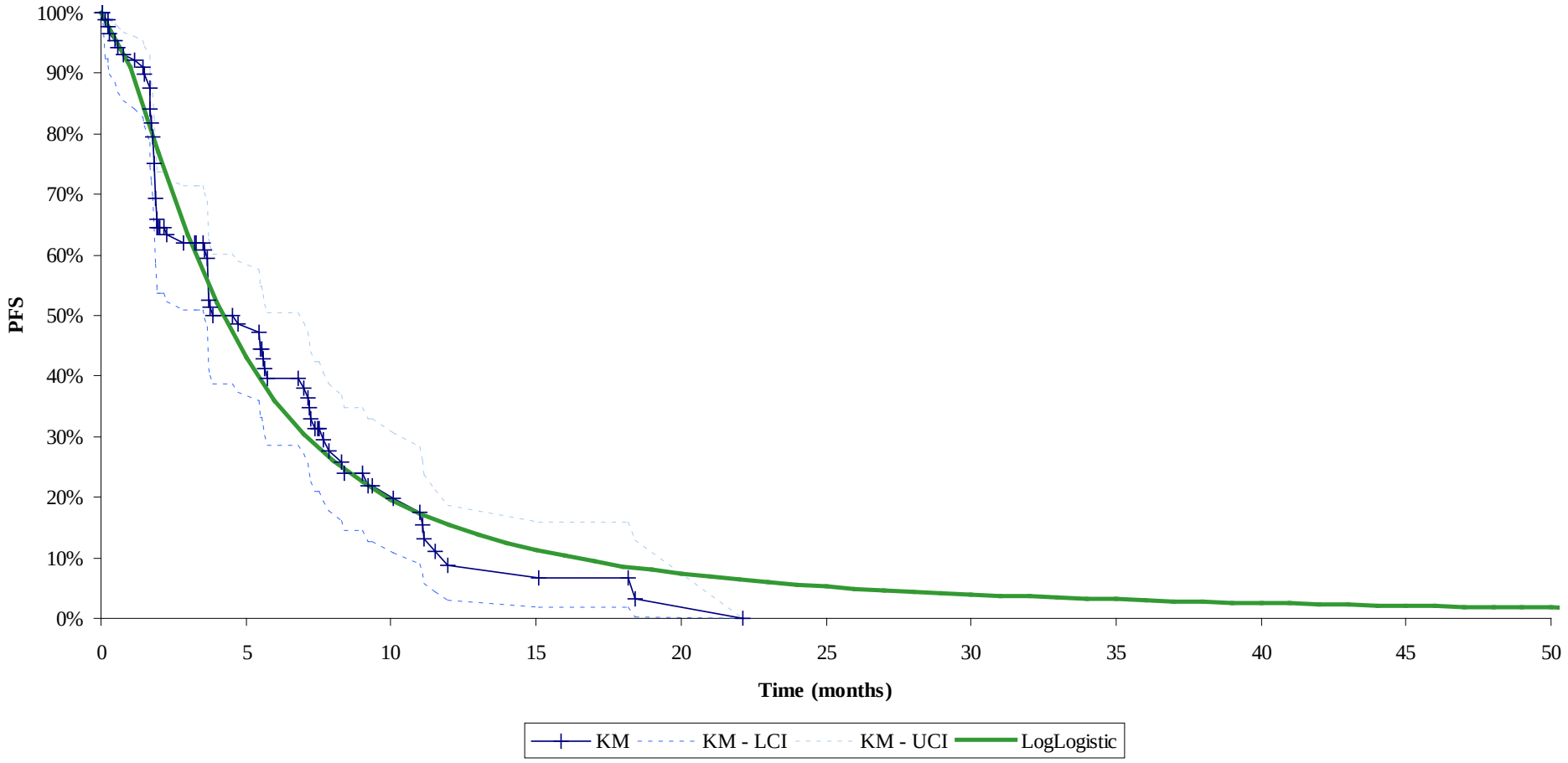


Figure 34: Plot of the Kaplan-Meier data and Loglogistic distribution for OS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

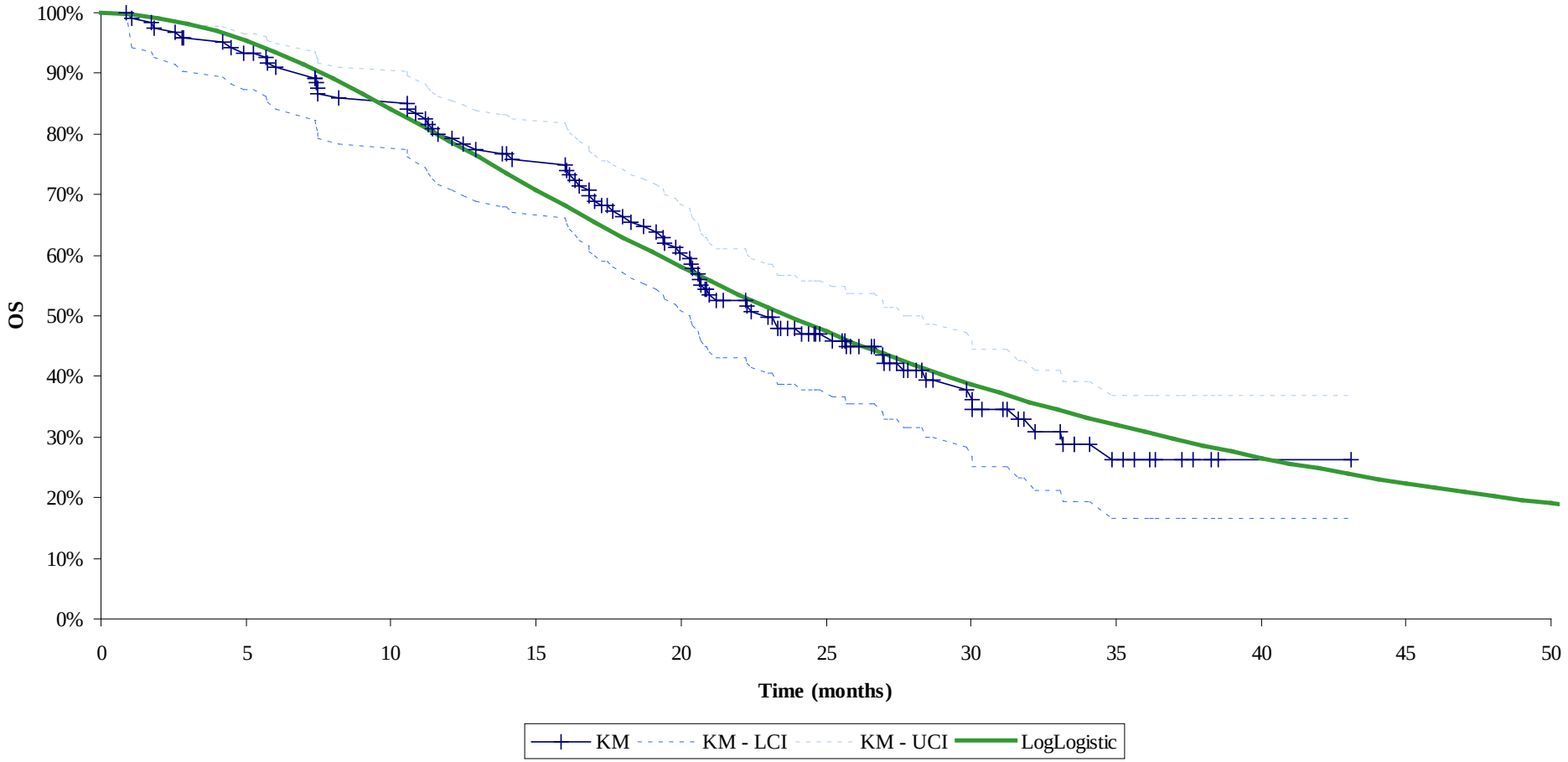


Figure 35: Plot of the Kaplan-Meier data and Loglogistic distribution for OS for PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

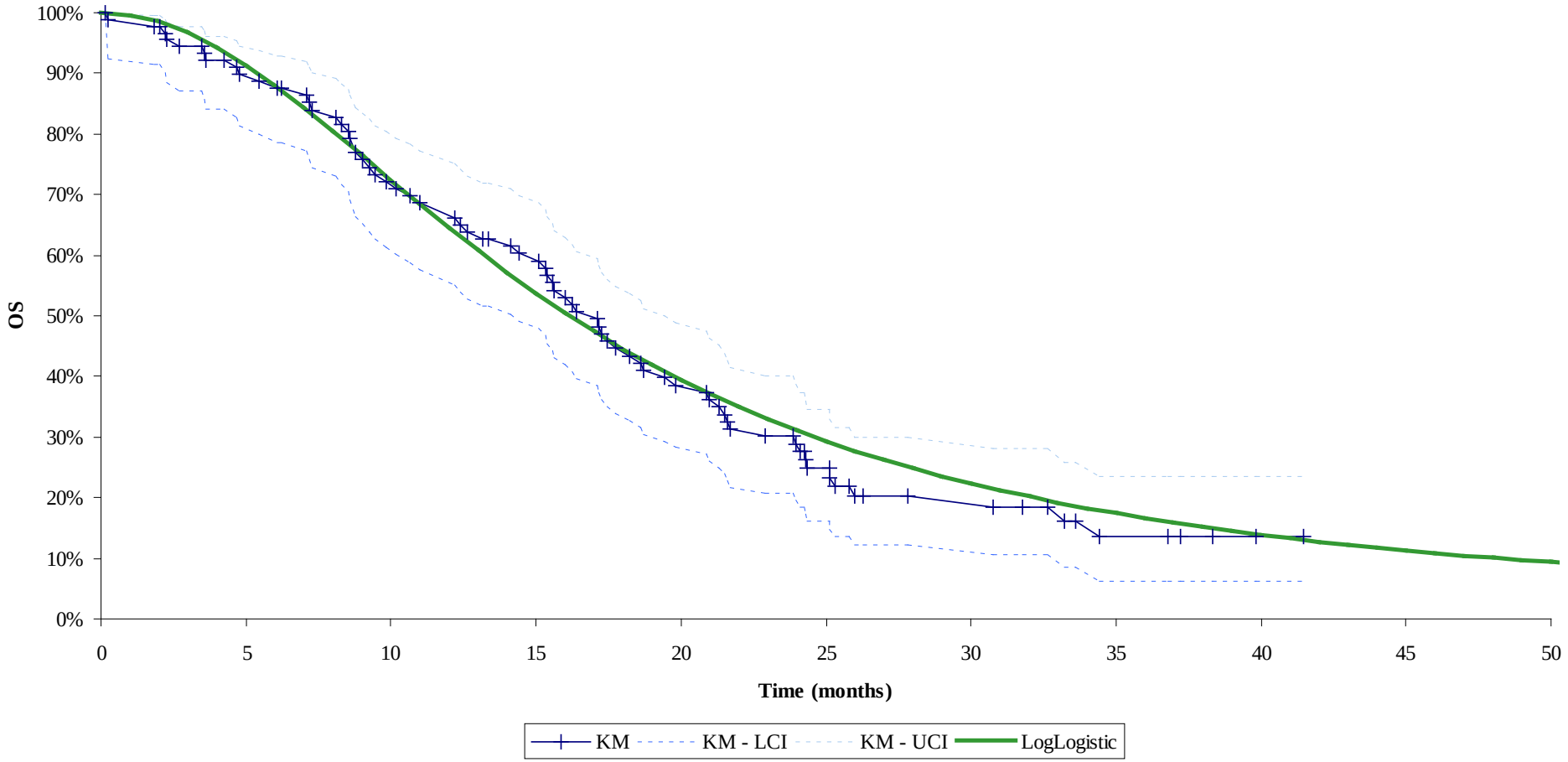


Figure 36: Plot of the Kaplan-Meier data and Lognormal distribution for PFS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

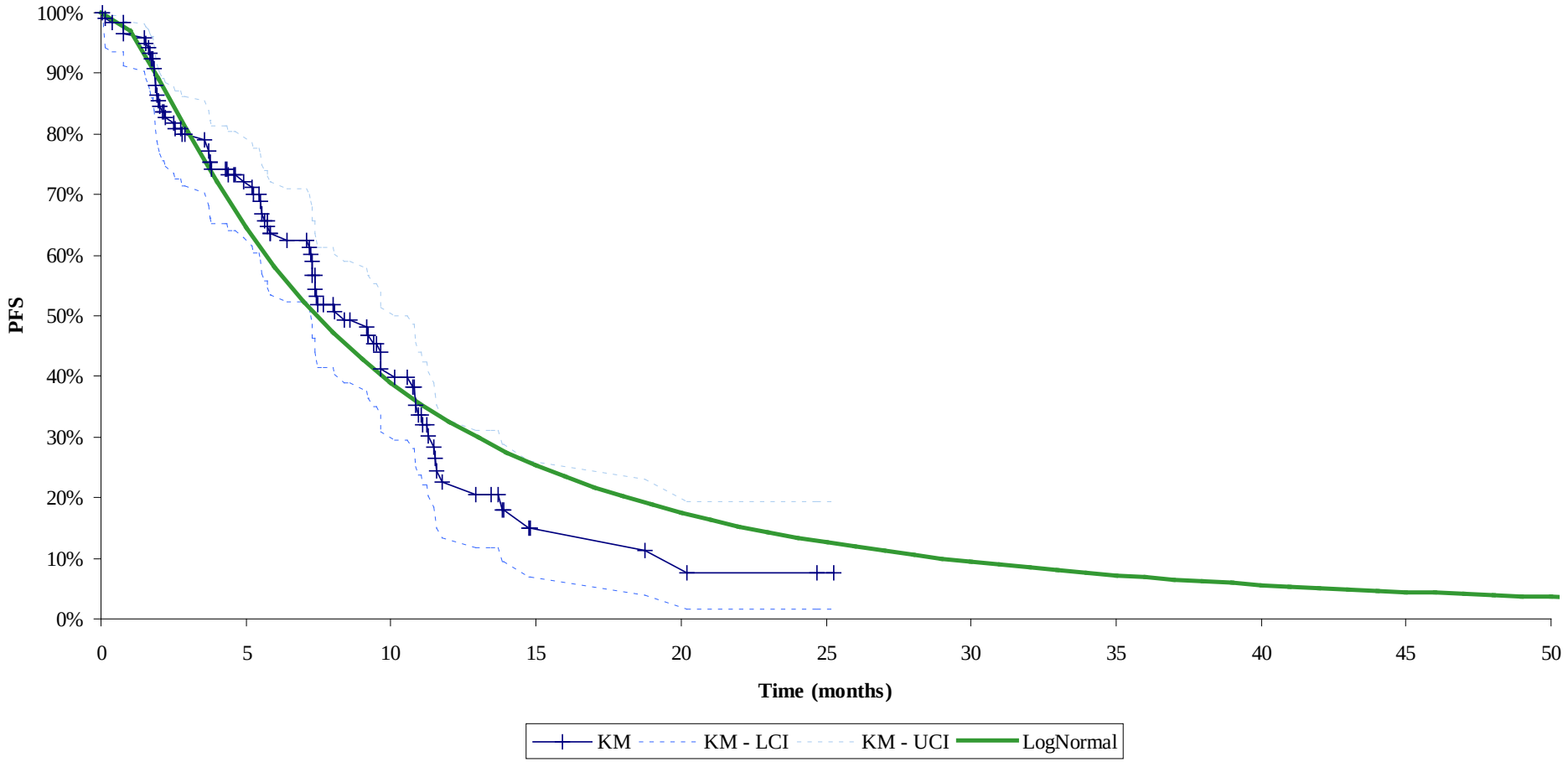


Figure 37: Plot of the Kaplan-Meier data and Lognormal distribution for PFS for PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

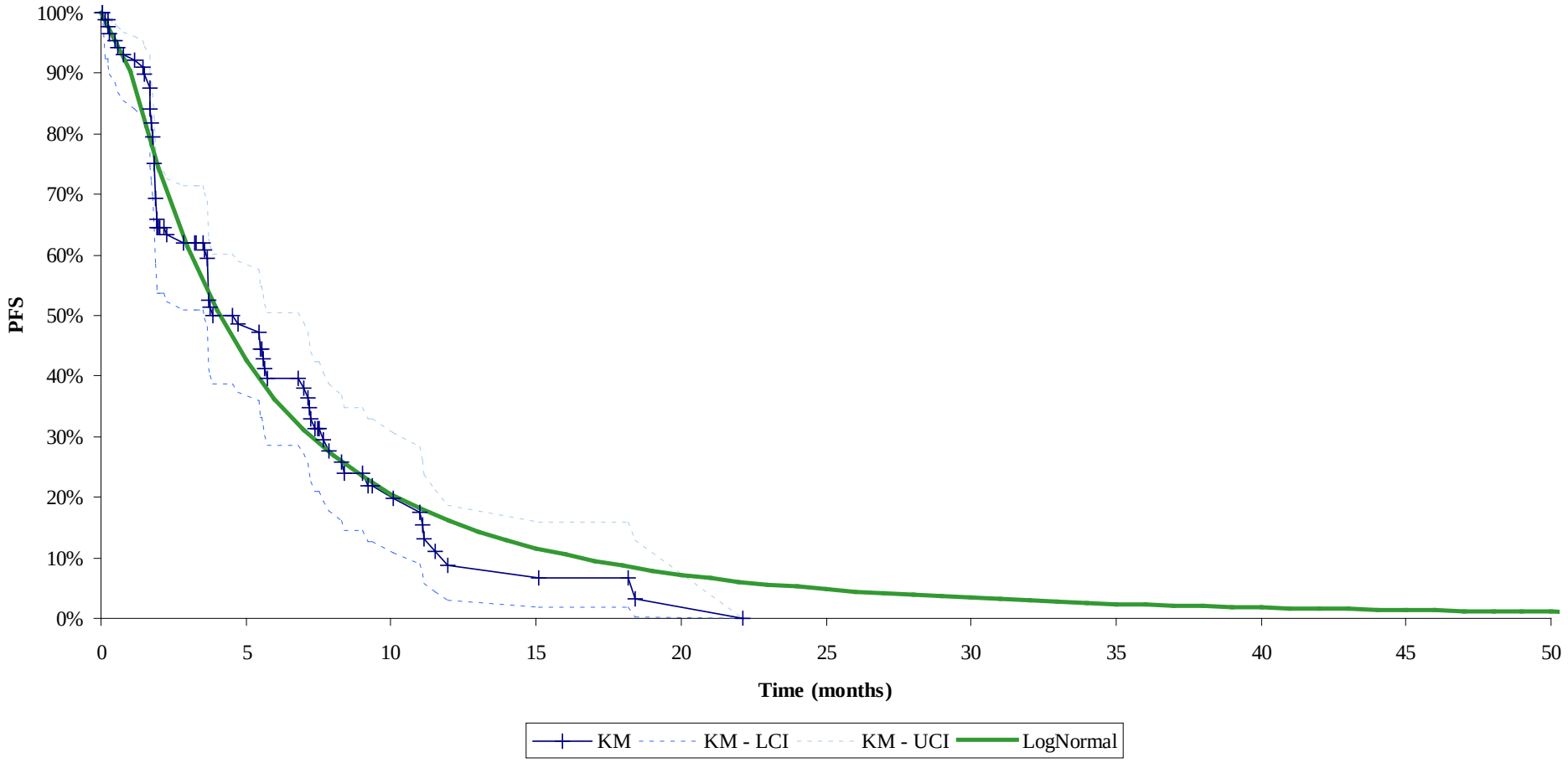


Figure 38: Plot of the Kaplan-Meier data and Lognormal distribution for OS for trabectedin in combination with PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)

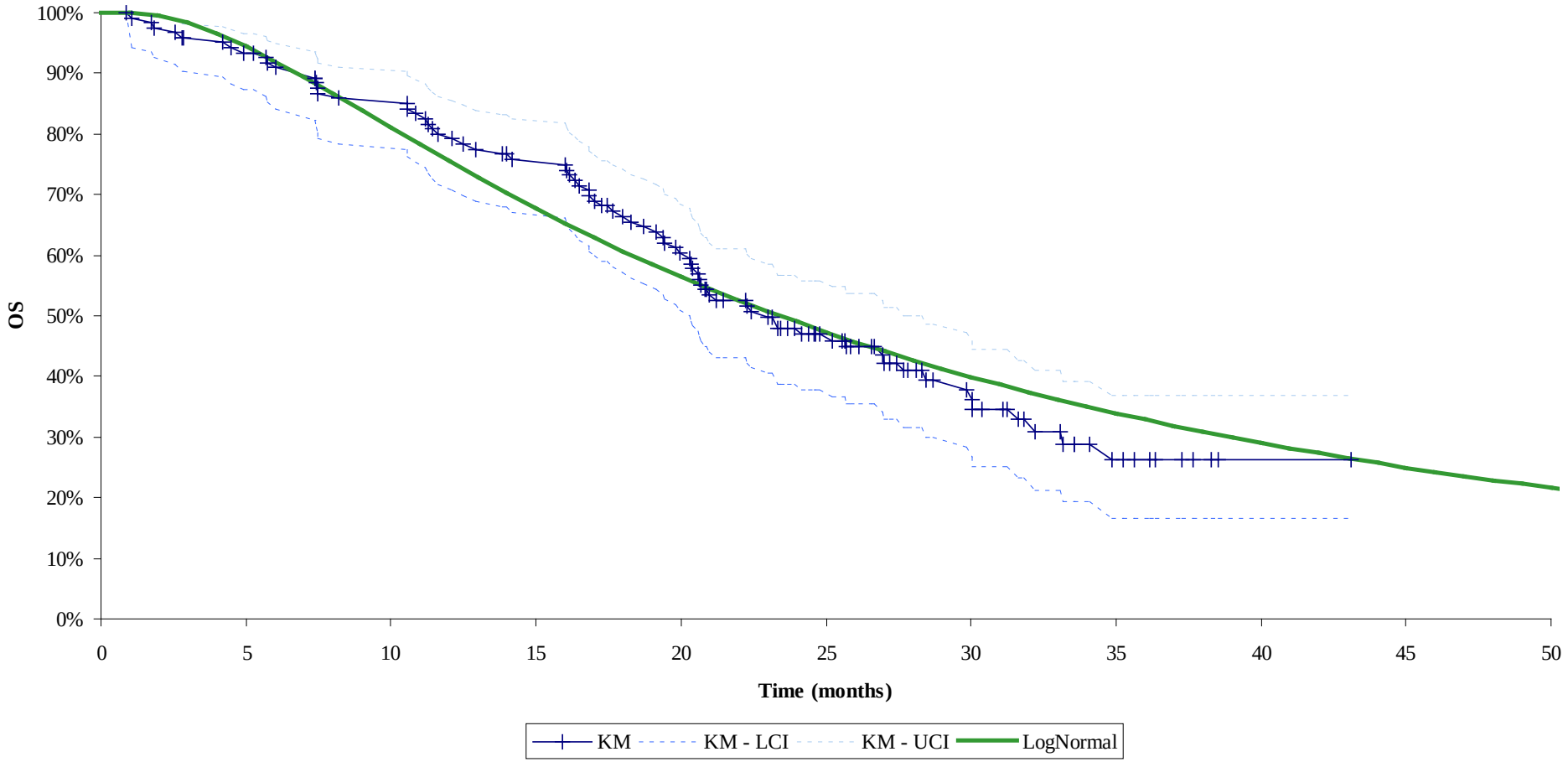
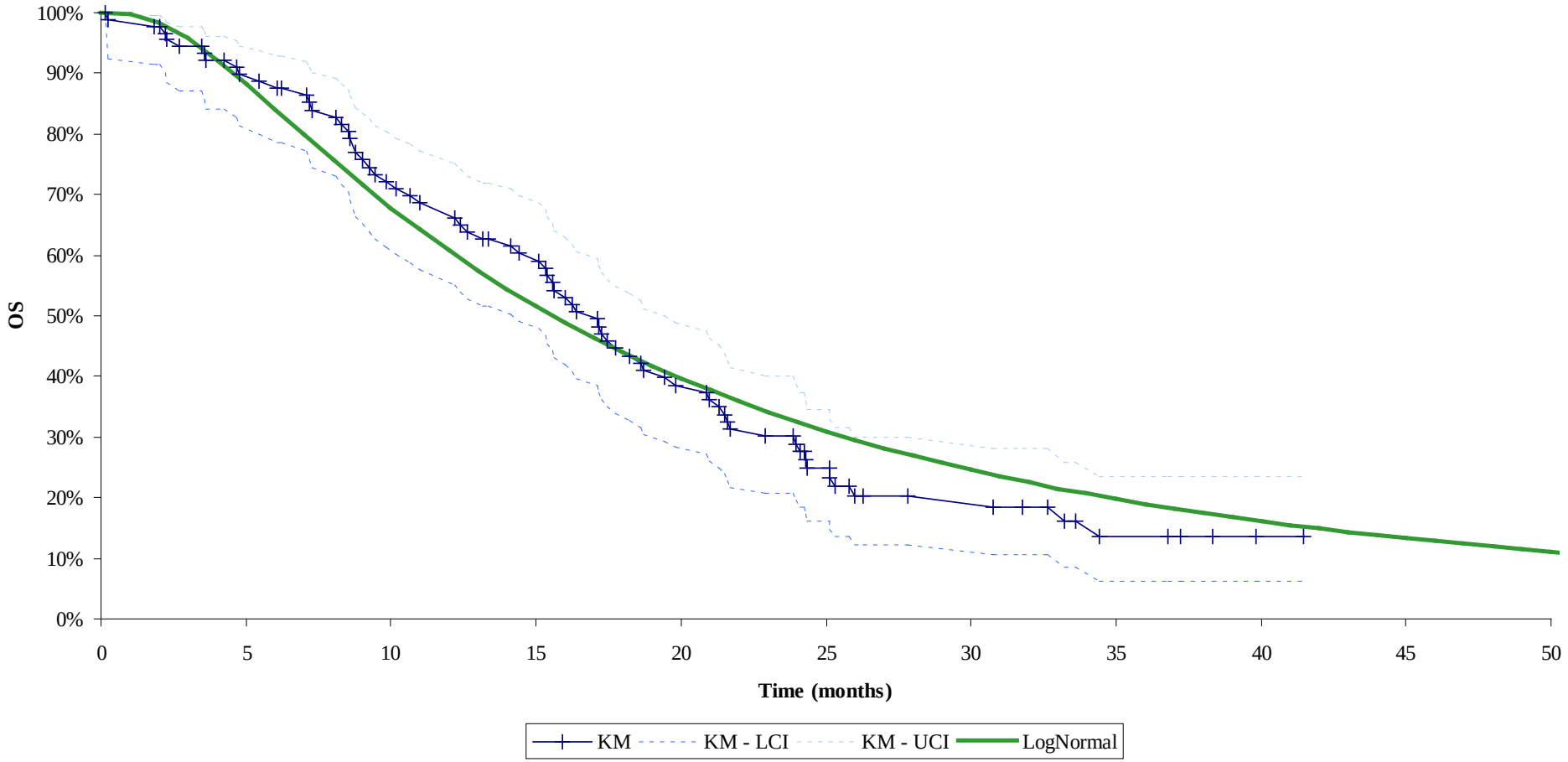


Figure 39: Plot of the Kaplan-Meier data and Lognormal distribution for OS for PLDH (estimated by the ERG using individual patient data from the OVA-301 Trial)



Appendix 3: ICERs using different HR – Table 56 to 57

Table 56: ICERs assuming different hazard ratios between Trabectedin in combination with PLDH and PLDH only (Weibull)

		PFS																				
		0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
	0.05	£6,945	£9,416	£10,411	£10,958	£11,308	£11,551	£11,731	£11,871	£11,981	£12,072	£12,148	£12,212	£12,266	£12,314	£12,356	£12,393	£12,426	£12,456	£12,483	£12,507
	0.1	£5,437	£9,295	£10,889	£11,775	£12,344	£12,742	£13,038	£13,267	£13,450	£13,599	£13,724	£13,830	£13,921	£14,000	£14,070	£14,131	£14,186	£14,235	£14,280	£14,320
	0.15	£4,021	£9,178	£11,359	£12,585	£13,377	£13,935	£14,350	£14,672	£14,930	£15,141	£15,317	£15,467	£15,595	£15,707	£15,806	£15,893	£15,971	£16,041	£16,104	£16,162
	0.2	£2,626	£9,059	£11,845	£13,429	£14,460	£15,189	£15,733	£16,156	£16,495	£16,773	£17,006	£17,204	£17,375	£17,523	£17,653	£17,769	£17,872	£17,965	£18,049	£18,125
	0.25	£1,219	£8,934	£12,360	£14,331	£15,623	£16,540	£17,228	£17,764	£18,194	£18,548	£18,845	£19,097	£19,315	£19,504	£19,671	£19,819	£19,951	£20,070	£20,178	£20,275
	0.3	dominant	£8,802	£12,914	£15,310	£16,892	£18,022	£18,872	£19,537	£20,072	£20,513	£20,883	£21,198	£21,470	£21,707	£21,916	£22,101	£22,267	£22,416	£22,551	£22,674
	0.35	dominant	£8,661	£13,518	£16,387	£18,298	£19,671	£20,708	£21,521	£22,178	£22,720	£23,176	£23,565	£23,900	£24,194	£24,452	£24,682	£24,888	£25,073	£25,241	£25,393
	0.4	dominant	£8,508	£14,182	£17,585	£19,874	£21,528	£22,784	£23,773	£24,574	£25,236	£25,794	£26,271	£26,683	£27,044	£27,362	£27,646	£27,899	£28,128	£28,335	£28,524
	0.45	dominant	£8,342	£14,921	£18,934	£21,661	£23,647	£25,164	£26,363	£27,337	£28,145	£28,827	£29,411	£29,918	£30,361	£30,753	£31,102	£31,415	£31,697	£31,953	£32,186
	0.5	dominant	£8,159	£15,751	£20,469	£23,715	£26,099	£27,931	£29,386	£30,573	£31,561	£32,397	£33,115	£33,739	£34,286	£34,770	£35,201	£35,589	£35,939	£36,256	£36,546
	0.55	dominant	£7,956	£16,693	£22,238	£26,108	£28,977	£31,198	£32,974	£34,428	£35,643	£36,676	£37,564	£38,337	£39,017	£39,620	£40,159	£40,643	£41,081	£41,478	£41,842
	0.6	dominant	£7,730	£17,773	£24,305	£28,937	£32,412	£35,126	£37,311	£39,110	£40,621	£41,910	£43,022	£43,994	£44,850	£45,611	£46,292	£46,905	£47,461	£47,967	£48,429
	0.65	dominant	£7,476	£19,030	£26,758	£32,343	£36,593	£39,948	£42,672	£44,932	£46,840	£48,475	£49,894	£51,136	£52,235	£53,215	£54,094	£54,887	£55,607	£56,264	£56,866
	0.7	dominant	£7,186	£20,510	£29,720	£36,531	£41,803	£46,022	£49,483	£52,381	£54,846	£56,972	£58,826	£60,459	£61,909	£63,206	£64,373	£65,431	£66,393	£67,273	£68,082
	0.75	dominant	£6,854	£22,284	£33,374	£41,812	£48,487	£53,919	£58,440	£62,269	£65,559	£68,420	£70,933	£73,161	£75,151	£76,941	£78,559	£80,031	£81,376	£82,610	£83,747
	0.8	dominant	£6,468	£24,451	£38,005	£48,691	£57,385	£64,625	£70,764	£76,048	£80,651	£84,702	£88,300	£91,518	£94,416	£97,042	£99,434	£101,622	£103,633	£105,488	£107,204
	0.85	dominant	£6,014	£27,162	£44,068	£58,033	£69,834	£79,979	£88,819	£96,608	£103,533	£109,741	£115,342	£120,427	£125,066	£129,320	£133,237	£136,857	£140,214	£143,337	£146,250
	0.9	dominant	£5,470	£30,656	£52,364	£71,467	£88,515	£103,884	£117,853	£130,632	£142,388	£153,253	£163,337	£172,729	£181,506	£189,732	£197,461	£204,741	£211,614	£218,114	£224,274
	0.95	dominant	£4,807	£35,331	£64,413	£92,459	£119,702	£146,288	£172,321	£197,876	£223,012	£247,772	£272,194	£296,309	£320,141	£343,712	£367,041	£390,143	£413,032	£435,722	£458,222
OS	1	dominant	£3,981	£41,917	£83,529	£129,926	£182,352	£242,343	£311,898	£393,705	£491,508	£610,695	£759,336	£950,101	£1,204,096	£1,559,303	£2,091,678	£2,978,442	£4,751,245	£10,068,326	#DIV/0!

Table 57: ICERs assuming different Hazard Ratios between Trabectedin in combination with PLDH and PLDH only (Gompertz)

		PFS																				
		0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
	0.05	£8,465	£10,775	£11,971	£12,730	£13,263	£13,662	£13,972	£14,222	£14,427	£14,599	£14,746	£14,872	£14,982	£15,079	£15,166	£15,243	£15,312	£15,374	£15,431	£15,483
	0.1	£8,091	£11,163	£12,777	£13,809	£14,538	£15,084	£15,511	£15,855	£16,139	£16,377	£16,580	£16,756	£16,909	£17,043	£17,163	£17,270	£17,367	£17,454	£17,533	£17,605
	0.15	£7,747	£11,527	£13,537	£14,833	£15,753	£16,445	£16,987	£17,425	£17,786	£18,090	£18,350	£18,574	£18,771	£18,943	£19,097	£19,234	£19,358	£19,470	£19,572	£19,665
	0.2	£7,407	£11,893	£14,311	£15,882	£17,002	£17,848	£18,513	£19,051	£19,496	£19,871	£20,191	£20,469	£20,711	£20,926	£21,116	£21,286	£21,440	£21,579	£21,705	£21,821
	0.25	£7,057	£12,276	£15,127	£16,993	£18,332	£19,347	£20,147	£20,795	£21,333	£21,787	£22,176	£22,513	£22,807	£23,068	£23,299	£23,507	£23,694	£23,864	£24,018	£24,159
	0.3	£6,692	£12,683	£16,003	£18,197	£19,778	£20,982	£21,935	£22,709	£23,353	£23,897	£24,363	£24,768	£25,122	£25,436	£25,715	£25,966	£26,192	£26,397	£26,583	£26,754
	0.35	£6,305	£13,123	£16,961	£19,519	£21,376	£22,797	£23,924	£24,844	£25,610	£26,259	£26,816	£27,300	£27,725	£28,102	£28,437	£28,738	£29,010	£29,256	£29,481	£29,687
	0.4	£5,891	£13,603	£18,019	£20,993	£23,166	£24,838	£26,171	£27,261	£28,172	£28,945	£29,611	£30,190	£30,699	£31,150	£31,553	£31,915	£32,242	£32,538	£32,809	£33,058
	0.45	£5,443	£14,134	£19,202	£22,655	£25,199	£27,168	£28,744	£30,039	£31,124	£32,047	£32,844	£33,539	£34,150	£34,693	£35,178	£35,615	£36,010	£36,369	£36,696	£36,997
	0.5	£4,957	£14,725	£20,541	£24,554	£27,537	£29,862	£31,734	£33,278	£34,577	£35,686	£36,645	£37,484	£38,223	£38,881	£39,470	£40,000	£40,481	£40,918	£41,317	£41,684
	0.55	£4,425	£15,390	£22,072	£26,750	£30,266	£33,027	£35,265	£37,120	£38,688	£40,031	£41,197	£42,218	£43,122	£43,927	£44,649	£45,300	£45,891	£46,430	£46,923	£47,377
	0.6	£3,838	£16,147	£23,846	£29,329	£33,501	£36,809	£39,510	£41,764	£43,677	£45,325	£46,760	£48,022	£49,142	£50,142	£51,041	£51,854	£52,594	£53,269	£53,887	£54,457
	0.65	£3,185	£17,018	£25,931	£32,407	£37,407	£41,417	£44,722	£47,502	£49,877	£51,933	£53,733	£55,323	£56,738	£58,006	£59,150	£60,188	£61,133	£61,998	£62,793	£63,525
	0.7	£2,454	£18,032	£28,421	£36,151	£42,226	£47,168	£51,289	£54,788	£57,803	£60,432	£62,747	£64,803	£66,642	£68,298	£69,797	£71,161	£72,408	£73,553	£74,607	£75,582
	0.75	£1,628	£19,229	£31,452	£40,811	£48,332	£54,561	£59,832	£64,364	£68,312	£71,787	£74,872	£77,632	£80,118	£82,369	£84,418	£86,292	£88,013	£89,598	£91,064	£92,424
	0.8	£687	£20,668	£35,227	£46,780	£56,330	£64,428	£71,417	£77,530	£82,934	£87,753	£92,082	£95,996	£99,554	£102,803	£105,784	£108,530	£111,067	£113,420	£115,607	£117,647
	0.85	dominant	£22,429	£40,065	£54,708	£67,277	£78,280	£88,043	£96,794	£104,700	£111,888	£118,460	£124,497	£130,066	£135,221	£140,009	£144,468	£148,634	£152,534	£156,195	£159,637
	0.9	dominant	£24,639	£46,493	£65,763	£83,188	£99,166	£113,948	£127,709	£140,580	£152,666	£164,048	£174,796	£184,968	£194,614	£203,778	£212,497	£220,805	£228,733	£236,307	£243,552
	0.95	dominant	£27,497	£55,459	£82,263	£108,457	£134,304	£159,951	£185,489	£210,979	£236,463	£261,971	£287,526	£313,145	£338,843	£364,631	£390,517	£416,509	£442,613	£468,835	£495,179
OS	1	dominant	£31,339	£68,848	£109,573	£154,823	£205,912	£264,393	£332,250	£412,139	£507,745	£624,366	£769,933	£956,894	£1,205,985	£1,554,522	£2,077,125	£2,947,903	£4,689,167	£9,912,457	#DIV/0!

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