

Response to Appraisal Consultation Document on topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix

GlaxoSmithKline

8 July 2009

Thank you for the opportunity to respond to the Appraisal Consultation Document for topotecan. The key issues that GlaxoSmithKline wish to raise are listed below, and discussed in more detail in Sections 1 to 4.

Key issues

- This draft guidance effectively denies access to a clinically effective treatment which is licensed, and arguably cost-effective, for patients with recurrent carcinoma of the cervix, a particularly aggressive and incurable condition for which few treatment options are available
- Although increasingly few patients have not received prior cisplatin, the draft guidance makes no provision for cisplatin-naïve patients, an identified subgroup in which clinical and cost effectiveness is particularly favourable to the use of topotecan
- We acknowledge that paclitaxel in combination with cisplatin, although not licensed in this indication, is a valid comparator (as captured in the original NICE scope). However, we are concerned that the draft guidance is a de facto endorsement of the use of paclitaxel, when it has not been shown to be more effective or cost-effective than topotecan
- The draft guidance appears to be largely informed by trial GOG-0204 as the primary evidence source rather than two relevant trials, GOG-0169 and GOG-0179. This is inconsistent with the concept of developing a network of evidence as advocated by the ERG.
- GOG-0179 is the only completed trial showing a significant survival benefit for an alternative regimen to cisplatin alone in patients with recurrent carcinoma of the cervix and this benefit is even greater for the cisplatin-naïve population. Moreover, the available data from GOG-0204 do not provide evidence specific to the use of topotecan in cisplatin-naïve patients.
- The Appraisal Committee has given undue weight to 'worst case' assumptions, which does not reflect the range of uncertainty in the available evidence
- The recommendations of the Committee do not appear to have taken account of several equity issues advanced by GSK in response to the manufacturer submission template.
- Whilst NICE may not consider topotecan in combination with cisplatin to provide a cost effective treatment in all women with recurrent or stage IVB cervical carcinoma, analyses of clinically-defined subgroups suggest that topotecan in combination with cisplatin may be considered cost effective in patients who are cisplatin-naïve.
- As stated in our original submission, the use of topotecan in combination with cisplatin thus appears to meet the Institute's key criteria for special appraisal of end-of-life treatments, particularly for such smaller patient groups
- GSK requests that the Appraisal Committee consider the updated evidence presented here to support a recommendation that topotecan in combination with cisplatin be made available for the treatment of recurrent cancer of the cervix in cisplatin-naïve patients who, otherwise, have very limited treatment options in the final stages of their disease.

1 Do you consider that all of the relevant evidence has been taken into account?

The Appraisal Committee appears to have examined the Evaluation Report thoroughly and has taken counsel from clinical specialists. However, we note the ERG's criticism that the technology appraisal should be based on a network of evidence. Although all the individual clinical trials were considered by the Appraisal Committee, a formal evidence synthesis was lacking from the data presented to it. Therefore, we present here a pooling of the clinical data, which has been used to update the estimates of cost-effectiveness of topotecan, to include probabilistic analysis. We ask that the Committee reconsider its recommendations in light of this updated evidence, as proposed below.

1.1 Target population

The ERG expressed some uncertainty around the population that will benefit most from treatment with topotecan plus cisplatin:

“The number of patients who have received chemoradiation is likely to increase in the future, thus the number of cisplatin-naïve patients will diminish. This raises the question of the applicability of the results to current and future clinical practice. It is unclear whether patients receiving cisplatin as a radiosensitiser should still be considered as cisplatin naïve unlike those treated with cisplatin chemotherapy. Limitations in the submitted evidence impacts strongly on the generalisability of the manufacturer's conclusions to clinical practice, particularly in patients with greater exposure to prior chemoradiotherapy with cisplatin. The duration of the cisplatin free interval was not made explicit in the main submission, and the ERG requested further clarification for the assumption that this should be at least 180 days”

We responded by presenting an unplanned sub-group analysis of median survival in patients with prior cisplatin chemoradiotherapy, and in patients with recurrence less than 180 days after chemoradiotherapy with cisplatin, which showed no significant difference between treatment arms. Patients with recurrence after 180 days achieved greater benefit from topotecan plus cisplatin.

Our original submission stated that there is no consensus on the concept of cisplatin-naïvety and this is a key issue in view of the increasing number of women receiving cisplatin as a radiosensitiser (i.e. whether patients receiving cisplatin as a radiosensitiser should still be considered as cisplatin-naïve unlike those treated with cisplatin chemotherapy). Although the length of the treatment-free interval is not explicit in the SmPC, we assumed a period of 180 days in our submission, in line with the GOG-0179 analyses, and as described in Section 5.1 of the SmPC. We acknowledge that the Appraisal Committee heard from clinical specialists that previous cisplatin use has a significant effect on response rates to subsequent cisplatin containing chemotherapy regimens: response rates in cisplatin-naïve patients could exceed 45% but could be as low as 10% in women who had previously received cisplatin, even as a radiosensitiser. We concur that the cisplatin-naïve subpopulation is the one that is likely to benefit most from topotecan plus cisplatin.

1.2 Choice of comparator

Consistent with the scope of the Appraisal, our submission included IMS data from Q3 2004 to Q3 2008, which confirmed that a number of unlicensed products are being used in the treatment of recurrent or stage IVB cervical cancer in the UK, even though there is limited clinical evidence to justify their use. These data suggested that there is a lack of consensus among oncologists regarding the chemotherapy regimens that should be used in this therapy area and that established chemotherapies may be favoured instead of following an evidence-based approach. This highlights the need for NICE to issue recommendations in this therapy area.

The ERG agreed that the IMS data demonstrated that cisplatin monotherapy constitutes the key alternative intervention in the population in which combination therapy with topotecan and cisplatin is licensed. However, feedback from UK clinicians suggested that the use of paclitaxel in combination with cisplatin may be higher than suggested by the IMS database. For this reason, and to provide an approximate indication of the performance of topotecan versus an alternative platinum-based combination regimen, the combination of paclitaxel and cisplatin was addressed in the submission. Due to the limited and inconsistent use of other treatments, and lack of data identified in the literature search, they were not considered as key comparators in this appraisal of topotecan.

2 Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

We believe that the ACD summary of clinical effectiveness is a reasonable interpretation of the evidence, with the following important exceptions.

2.1 Sources of clinical evidence

The ERG did not consider that the submission included all of the evidence available that might have informed indirect comparisons. Moreover, the ERG considered that the omission of trials from the network of evidence (particularly GOG-0204) limited the evidence base and the number of available comparators. Importantly, the ERG did not consider that the rationale for the exclusion of trials based on the treatments not being licensed in the patient population was justified.

Our searches did also identify trials of vinorelbine and gemcitabine in combination with cisplatin (the other comparators in GOG-0204), and while they did not satisfy the inclusion criteria for our analysis, a retrospective review of these papers shows that the studies were not comparable or of sufficient quality to contribute to the network of evidence.

It is understandable that NICE wishes to base its recommendations on all clinical evidence, including the summary pre-publication data from GOG-0204, and we accept that the exclusion of GOG-0204 from the economic model was a limitation of our original submission, even though we justified our approach. Having accepted that GOG-0204, GOG-0169 and GOG-0179 all provide relevant evidence, we feel the Committee appeared to favour GOG-0204 as the primary evidence source, despite GOG-0179 being the only completed trial showing a significant overall survival benefit in patients with recurrent carcinoma of the cervix. This is inconsistent with the concept of developing a network of evidence as advocated by the ERG.

Therefore, we have conducted additional meta-analyses of data from all three studies, which we present in Appendix 1. Recognising that it might have reservations about the heterogeneity of the patient populations, we nevertheless urge the Committee to consider these analyses both as a summary of the clinical evidence and as a basis for the modelled cost effectiveness analyses (see Section 3.2).

2.1.1 Cisplatin-naïve patients

The agreed scope for the STA identified “subgroups of people depending on their prior exposure to platinum-based chemotherapies and duration of response to prior therapy”. While we accept that relatively few patients fall into the cisplatin-naïve subgroup, women that do are particularly important to consider, as they are the most likely to benefit from topotecan plus cisplatin, as GOG-0179 demonstrated. To recap, median survival for patients treated with topotecan was 14.5 months in cisplatin-naïve patients, as compared to 11.9 months in the licence population.

Although the meta-analysis mentioned above includes study GOG-0204, data for cisplatin-naïve patients are not available from the summary reports currently in the public domain. This makes it particularly inappropriate to use the results of GOG-0204 in isolation as the primary driver of any conclusions for this subgroup. Although we ran one version of the

meta-analysis using the cisplatin-naïve patients from GOG-0179, the other two pooled studies do not distinguish cisplatin exposure, so a “pure cisplatin-naïve” meta-analysis was not possible. For this reason, GOG-0179 may still provide the most relevant data for this subgroup.

2.1.2 Interpretation of economic evidence

We note the ERG’s thorough assessment of submitted economic evidence, which in general we find to be balanced and fair. Some of the criticisms of the model-based analysis relate to the limitations in data availability that led us originally to conclude that the trial-based analysis of GOG-0179 would provide the most precise and relevant evidence. Nevertheless, we appreciate that NICE prefers to use the exploratory model we originally developed as a secondary cost-effectiveness analysis, and we have therefore attempted to address some of the limitations of the model, first in response to the ERG’s requests, and now to address issues arising from the ACD.

2.1.3 Consistency of assumptions

The main concerns expressed by the ERG were as follows:

- lack of HRQoL considerations
- appropriateness of the metastatic breast cancer utility values adopted in the absence of more suitable cervical carcinoma values
- reasonableness of the costing assumptions, mainly surrounding the cost of administering topotecan
- number of vials of topotecan required
- exclusion of dose reduction
- appropriate source of the hazard ratio used to estimate survival for paclitaxel plus cisplatin (deriving this hazard ratio from GOG-0169 favoured topotecan, but deriving it from GOG-0204 favoured paclitaxel).

All these issues were addressed in response to a request from NICE, and we support the additional analyses conducted by the ERG to address the uncertainty around the economic analyses. For example, the ERG proposes alternative values for the utility of the starting health state and for administration costs for topotecan on days 2 and 3, which we accept. For other parameters, specifically the cost impact of dose reduction and the utility impact of multiple adverse events, the correct values remain a matter of conjecture in the absence of evidence. Indeed, the ERG recognised that their results (Table 1) are subject to a number of remaining uncertainties.

Table 1. Estimate of incremental cost effectiveness ratios (versus cisplatin alone) using ERG revised assumptions (£ per QALY gained)

Scenario	Cisplatin-naïve population	Licensed population
Utility weights 1	25,309	55,926
Utility weights 2	26,156	59,406
Utility weights 3	24,513	54,352
GSK assumed administration costs	24,513	54,352
ERG preferred administration costs	31,831	68,885
Minimum vial wastage	26,778	58,872
Maximum vial wastage	34,327	73,833
Minimum vial wastage (incorporating dose reduction)	19,815	53,868
Maximum vial wastage (incorporating dose reduction)	27,362	68,826

2.1.4 Topotecan wastage

We believe that it is unreasonable to focus solely on maximum wastage, as this is not necessarily the likeliest scenario. When we developed the wastage scenarios, we carried out informal interviews with three hospital pharmacists. While this was not a quantitative sample, the pharmacists did interpret the label for Hycamtin differently. One pharmacist commented that once a vial is punctured and the product dispensed, any remaining product in the vial is discarded, as per the label. However another commented that a 4 mg vial of topotecan would be utilised as completely as possible by making up all three days' worth of infusion solution at once, which would contravene sterility precautions as well as the SmPC recommendations. Moreover, one of the clinicians present at the Appraisal Committee meeting commented that sharing of vials between patients certainly does occur; as usual practice is to schedule patients to receive topotecan on the same day.

2.1.5 Fully incremental analysis of all relevant comparators

We accept that in the modelled CEA, a fully incremental analysis of all relevant comparators is appropriate, but only if it is based on the full network of evidence for the comparators. Notwithstanding the concerns about heterogeneity of the three relevant trials, we believe such an analysis should include a pooling of all clinical trial evidence, using the meta-analysis described in section 3.2 below.

3 Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

In view of the uncertainties described above, we believe that the provisional recommendations are not appropriate, at least for the cisplatin-naïve subgroup. In particular, we are concerned that the Appraisal Committee has apparently placed greater weight on study GOG-0204 even in respect to the cisplatin-naïve subgroup. Our reasoning is as follows:

3.1 Summary of clinical evidence supporting economic analysis

As the Appraisal Committee may recall, the economic analyses in our original submission were based primarily on a trial-based analysis of topotecan plus cisplatin versus cisplatin alone, drawing upon the availability to GSK of patient-level data from study GOG-0179, the only clinical trial that had shown significant survival benefit for alternative regimens to cisplatin alone. The ERG considered that it was “*entirely appropriate to use patient-level data from GOG-0179 to estimate the cost-utility of topotecan plus cisplatin compared to cisplatin alone, and the advantages of this approach outweigh any disadvantages*”.

We also presented an exploratory, modelled CEA of an indirect comparison between topotecan plus cisplatin vs. paclitaxel plus cisplatin based on summary data from trial GOG-0169. We acknowledged the late-breaking data from GOG-0204 but did not include this in the original analysis for reasons discussed above (section 2.1). However, the ERG felt it was important to use the GOG-0204 data to explore the relative effectiveness of cisplatin-based combinations. Moreover, the ERG asserted that the trial population was likely to be more representative of the changing profile of presenting patients, most of whom would have received prior cisplatin as a radiosensitiser, than was the population of either studies GOG-0169 or GOG-0179.

Accordingly, in response to a request from the ERG, we repeated the indirect CEA using the HRs reported for paclitaxel plus cisplatin (Monk 2008, ASCO poster pending publication in JCO). The ERG conducted its own fully incremental analyses using our exploratory model, and also incorporated various cost and utility assumptions. The ERG reported results based on both sets of HRs from GOG-0169 and those from GOG-0204. Using the former, there is a non-significant trend in overall survival in favour of topotecan, while the latter result in a non-significant trend in favour of paclitaxel. Along with the impact of various cost and utility assumptions changed by ERG, these analyses led to opposing economic results: when the GOG-0169 HRs are used topotecan plus cisplatin extendedly dominates paclitaxel plus

cisplatin, but when the GOG-0204 HRs are applied paclitaxel plus cisplatin dominates topotecan plus cisplatin.

3.2 Network meta-analysis

Our main concern stems from the fact that the Appraisal Committee appears to prefer one trial, GOG-0204, as the basis for reaching its provisional recommendation. It apparently places less importance on GOG-0179, even though this is the only clinical trial showing significant overall survival benefit for a combination regimen over cisplatin alone, and the only trial that provides subgroup data for cisplatin-naive patients. This preference seems to rely on the presumption that the study population of GOG-0204 is more representative of current patients. Even if this is true, it is not clear what the differential impact of prior cisplatin use is on the respective efficacy of paclitaxel and topotecan. Moreover, since GOG-0179 was completed and GOG-0204 was terminated early, we believe that there are too many uncertainties to justify a definite selection of one study over another.

While the study populations are in some respects heterogeneous, we believe that pooling the available evidence is preferable to ignoring one recent, well-conducted, published study that was the efficacy basis for market authorisation.

In response to the ERG's expressed concerns around the inclusion of pooled data from GOG-0169 and GOG-0204, given the direct evidence available in GOG-0204, we have conducted a further meta-analysis of all relevant data, which we report in Appendix 1. In this analysis, we have estimated mean HRs and their 95% CIs for paclitaxel plus cisplatin vs. cisplatin alone by pooling the HR from the *direct* placebo comparison (GOG-0169) with the HR from an *indirect* comparison using topotecan plus cisplatin as the common comparator (GOG-0179 and GOG-0204). We have followed a parallel approach for topotecan plus cisplatin, where the indirect common comparator is paclitaxel plus cisplatin. In both meta-analyses, the estimated mean HRs are less than one, but they are significant only for topotecan. Both sets of HRs are slightly less favourable for the combination treatments than those based purely on direct comparisons with cisplatin, though the direct comparisons carry greater weight than the indirect ones.

As already identified, the three contributing trials are quite heterogeneous in terms of patient characteristics, notably performance status and prior exposure to cisplatin, and in terms of results. We applied the same method of pooling to both combinations, in an attempt to balance any bias in the estimated HRs.

In response to the ERG's request for the inclusion of data from GOG-0204, we conducted a network meta-analysis to directly compare data from the topotecan plus cisplatin arm with the paclitaxel plus cisplatin arm from GOG-0204, and indirectly compare the same data with that reported by GOG-0179. This is reported in Appendix 1. The direct comparison favoured the paclitaxel plus cisplatin arm (HR 1.255, $\text{Var}(\ln(\text{HR}))$ 0.025, 95% CI 0.92, 1.71) while the indirect comparison slightly favoured the topotecan plus cisplatin arm (HR 0.98, 95% CI: 0.73, 1.23), although neither of these differences was statistically significant. The ERG also expressed concerns about the differing conclusions on the relative effectiveness of the two doublets from the indirect comparison of GOG-0169 and GOG-0179 and the direct comparison in GOG-0204.

3.3 Probabilistic sensitivity analysis using pooled hazard ratios

The ERG had criticised the lack of probabilistic analysis in the submitted model. The modelled analysis, as opposed to the trial-based analysis, was originally intended to be exploratory only, but NICE has found the model useful to help generalize the economic analyses. In an attempt to respond to this criticism and quantify the uncertainty in the results, we have applied the pooled HRs to the incremental modelled CEA in a probabilistic manner, (using the means and 95% CIs as parameters of beta distributions). Ideally, we would have incorporated these data into the ERG modified version of our HE model to ensure a consistent approach; however, NICE was unable to provide us with a copy of the ERG analysis within the timelines of the response to the Appraisal Consultation Document. The

input data and results of a fully-incremental analysis between cisplatin alone and the two cisplatin-based combinations are shown in Appendix 2. In summary, the results indicate that the analysis is highly sensitive to clinical input parameters.

3.4 Results of exploratory economic analysis

The calculated ICERs for topotecan plus cisplatin vs. cisplatin alone are consistently more favourable among women who have not previously received cisplatin. Using the ERG's exploratory analyses, based on GOG-0179 HRs alone, the ICERs were £26,778 or £34,327 per QALY gained, assuming minimum or maximum topotecan vial wastage, respectively. However, the Committee was minded to base its draft recommendation on the data from GOG-0204, despite the lack of analysis of uncertainty. We believe the analysis of pooled data provides a more basis for the Committee to make its recommendations. Using the deterministic version of this analysis, the respective figures are £46,054 and £58,911 per QALY gained when the meta-analytic HR is used for topotecan, as compared to our estimate of £23,586 and £30,171 per QALY gained using the HRs from the GOG-0179 observed values. These figures appear to be sufficiently favourable to justify recommendation for cisplatin-naïve patients, particularly if NICE is willing to invoke equity or end-of-life considerations. Although clinical experts assert that few patients who present with recurrent or stage IVB disease will not have received prior cisplatin, it is particularly important that women who for whatever reason do fall into this category should not be denied proven effective treatment with topotecan plus cisplatin.

3.5 End-of-life provision

The target population for topotecan plus cisplatin has a life expectancy of less than 24 months. As described above, the median life expectancy of patients treated with topotecan in combination with cisplatin (licensed population) is 2.86 months greater than those treated with cisplatin alone (9.40 [95% CI 7.85; 11.93 vs. 6.54 [95% CI 5.78; 8.80] months; p=0.03). In a cisplatin-naïve population, the treatment with topotecan plus cisplatin showed an overall survival benefit of 6.97 months compared to patients receiving cisplatin alone (15.74 [95% CI 11.93; 17.74] vs. 8.77 [95% CI 6.41; 11.47] months; p=0.01). There is no alternative licensed treatment that shows a statistically significant improvement in survival compared to cisplatin alone.

As stated in our original submission, the use of topotecan in combination with cisplatin therefore appears broadly to meet the Institute's key criteria for special appraisal of end-of-life treatments. Whilst NICE may conclude that topotecan does not fall below its conventional ICER threshold, we would hope that the Committee will take into account that this medicine is also likely to meet the requirements of the Institute's provisions for end-of-life medicines.

4 Are there any equality related issues that need special consideration that are not covered in the ACD?

We understand equality-related issues are defined as those which concern inequalities in access to therapy across society arising through scientific reasons, such as contraindications due to differing drug metabolism between ethnic groups. We have identified no such issues for topotecan. However, we did identify a number of equity-related issues, i.e. where the relevant patient group is already disadvantaged but the use of the technology could help to redress this inequity.

4.1 Issues raised in our original submission

In our original submission, several equity issues were identified and described, which we believe are relevant to the treatment of women presenting with advanced cervical cancer. These included issues of deprivation, intergenerational equity, end-of-life provision and international considerations. Since the template specifically requests comment on equity and equality, consistent with NICE Social Value Judgements (in particular, Principles 3, 6 and 7), we are concerned that none of the equity-related issues we raised appears to have been considered or acknowledged in the ACD, which has focused only on the technical aspects of

assessing clinical and cost effectiveness, except for a brief mention of deprivation in paragraph 4.17. We would urge NICE to review the issues in section 5 of our original submission which included:

1. patients in the lowest socioeconomic classes, who benefit the least from screening programmes due to lower take-up rates.
2. cohorts of women currently aged 18 years and over who, by virtue of age, do not qualify for the national human papilloma virus (HPV) programme to vaccinate girls now aged 12-13 years and offer catch-up vaccination to 13-18 year old girls.
3. NICE's recent criteria for appraisal of end-of-life treatments
4. the relatively poor prognosis for diagnosed cervical cancer in England and Wales, as compared to other European nations.

In addition, we have become aware of recent statements from Health Minister Ann Keen, following a review performed by the independent Advisory Committee on Cervical Screening (ACCS). According to Ms. Keen,

"They have concluded that the screening age should not be lowered but have recommended that we do more work around the treatment of symptomatic patients. I fully support this conclusion and look forward to beginning this important new work to ensure women with cervical cancer are diagnosed at the earliest possible opportunity.

'There has been a big public debate about this issue and a great deal of publicity about the causes and symptoms of cervical cancer. Together we can build on this work to help even more women across the country to take steps to prevent the disease and to identify symptoms early and save lives.'

If topotecan in combination with cisplatin is recommended for the treatment of patients with recurrent carcinoma of the cervix, this may in part compensate for a potential inequity in screening.

We also note comments attributed to the National Director for Cancer, Professor Mike Richards:

'Importantly, the ACCS has identified the need for urgent action on young women who present to their GPs with gynaecological symptoms. We know that early diagnosis is key to improving survival chances.

'We will develop guidance to support GPs and practice nurses so that young women with cervical cancer are diagnosed at the earliest opportunity.'

Accordingly, a further group of women who arguably merit special care is those who have tested negative in cervical screening but who are subsequently diagnosed with carcinoma of the cervix. For those patients who reach advanced disease with little prior warning and who have not received prior treatment with cisplatin, it would seem harsh to deprive them of an opportunity of improved health status for the duration of their reduced life expectancy.

5 Conclusions

Overall, the Committee considered that topotecan plus cisplatin was more effective than cisplatin alone, as demonstrated by GOG-0179. It noted that results from the subgroup analyses suggested that the combination was even more clinically effective in women who had not previously received cisplatin (true cisplatin-naïve), and that this response was evident even when the cisplatin-free interval exceeded 180 days (consistent with the licensed indication). Topotecan is the only product licensed for this indication, and one that has been shown to be significantly superior to cisplatin alone in peer-reviewed publications.

We therefore believe the network of available evidence supports the following conclusions:

1. Among cisplatin-naïve women with recurrent or stage IVB carcinoma of the cervix, topotecan plus cisplatin is significantly more effective in terms of overall survival than

cisplatin alone and is likely to be deemed cost effective compared to cisplatin alone, under normal NICE criteria. There is insufficient evidence to draw conclusions about its cost-effectiveness compared to other platinum-containing combinations in unlicensed use. We urge the Appraisal Committee to recommend topotecan plus cisplatin for use among cisplatin-naïve patients as the only combination that is formally licensed for use in recurrent or stage IVB carcinoma of the cervix.

2. Among women with recurrent or stage IVB carcinoma of the cervix without regard to prior cisplatin exposure, topotecan plus cisplatin is significantly more effective in terms of overall survival than cisplatin alone, while meta-analysis reveals no significant difference in overall survival as compared to paclitaxel plus cisplatin. No clear conclusions can be reached about the relative cost effectiveness of these two combinations. However, topotecan plus cisplatin may be cost-effective when compared to cisplatin if NICE end-of-life criteria are invoked. We believe the Appraisal Committee should consider how these end-of-life criteria should be applied to topotecan.
3. We would ask the Appraisal Committee to acknowledge that its provisional conclusions not to recommend topotecan plus cisplatin leave open the question of whether or not the commonly-used combination of paclitaxel plus cisplatin, which is outside the scope of this STA and outside the remit of NICE as an unlicensed treatment, represents appropriate use of NHS resources. As the relative clinical and cost-effectiveness of these two doublets are difficult to determine, the Committee's conclusions should not give the appearance of favouring one over the other.

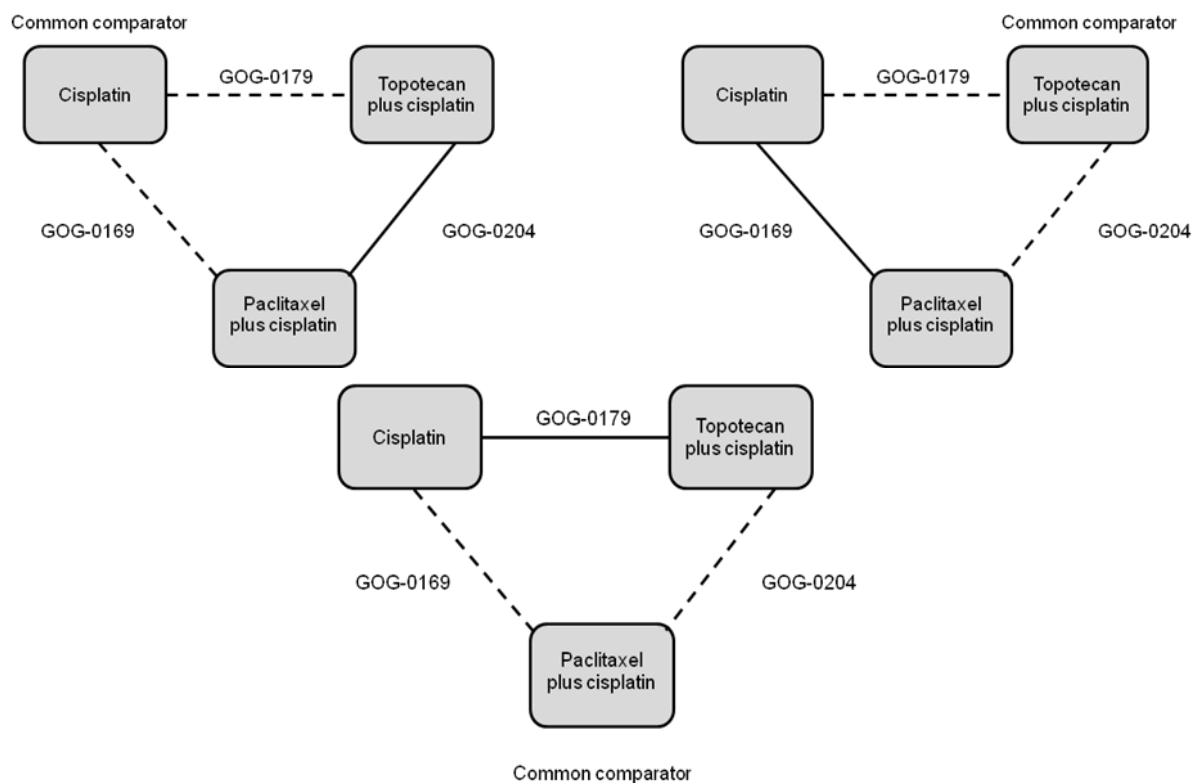
References

1. National Institute for Health and Clinical Excellence. Social Value Judgements. Principles for the development of NICE guidance. Second edition [online]. Available from <http://www.nice.org.uk/>
2. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res.* 2008 Jun;17(3):279-301.

Appendix 1: Meta-analysis of clinical data

The available trial data formed a triangular network of evidence. Each trial represented one side of the triangle and contributed the direct evidence. The other two trials formed the other sides of the triangle and used their shared point as the common comparator, which provides the indirect evidence. Hence our network allowed us to consider three comparisons which, in all cases, consisted of both direct and indirect analyses. These relationships are shown below:

Figure 1. Network of evidence



Direct comparison —————
 Indirect comparison - - - - -

The indirect comparisons are made between two treatment arms for which we have data that are not in direct comparison. The basis of this relates to results against a third arm which they both share. With both the indirect and direct evidence available to us we can combine the data through meta-analysis. Due to the paucity of information available (having only one source of both direct and indirect evidence in each comparison) we decided to remain parsimonious and conduct fixed effects meta-analyses. This would not account for any between study variation which may exist, although we report the I^2 statistic for heterogeneity.

This method of network analyses has become prominent over the last few years and its benefits and validity has recently been reported.²

Our final output is the following three hazard ratios for survival which compare all two-way possibilities between the three treatments. In the final pooled results detailed below, a score <1 indicates benefit to the first named arm while a confidence interval not containing 1 indicates significance at the 95% level.

These results consider the cisplatin-naïve population from study GOG-0179

Cisplatin + topotecan vs. cisplatin + paclitaxel HR = 0.98 (95% CI 0.73; 1.23)

Cisplatin + topotecan vs. cisplatin HR = 0.75 (95% CI 0.53; 0.97)

Cisplatin + paclitaxel vs. cisplatin HR = 0.83 (95% CI 0.63; 1.08)

The complete results with details of every comparison (direct, indirect or pooled) are summarised below:

Summary results of hazard ratios and meta-analyses				
Source		Comparison	Population contributed by GOG-0179, where applicable	
			Naive HR (95% CI)	Licensed HR (95% CI)
Direct				
0169		cis+pac vs. cis	NA	0.87 (0.68, 1.11)
0179		cis+top vs. cis	0.63 (0.43, 0.94)	0.76 (0.6, 0.97)
0204		cis+top vs. cis+pac	NA	1.255 (0.92, 1.71)
Indirect	Common comparator			
0204, 0179	cis+top	cis+pac vs. cis	0.5 (0.3, 0.83)	0.61 (0.41, 0.89)
0204, 0169	cis+pac	cis+top vs. cis	NA	1.09 (0.74, 1.62)
0169, 0179	cis	cis+top vs. cis+pac	0.72 (0.46, 1.15)	
Pooled results				
	Fixed effects	cis+pac vs. cis	0.83 (0.68, 1.08) $I^2 = 56\%$	0.81 (0.67, 1.03) $I^2 = 46\%$
	Fixed effects	cis+top vs. cis	0.75 (0.53, 0.97) $I^2 = 62\%$	0.81 (0.62, 0.98) $I^2 = 46\%$
	Fixed effects	cis+top vs. cis+pac	0.98 (0.73, 1.23) $I^2 = 77\%$	

Forest plots are presented below for the three comparisons:

Figure 2. Cisplatin + paclitaxel vs. cisplatin + topotecan, using cisplatin-naïve population from GOG-0179

Mixed treatment comparison of cisplatin + topotecan with cisplatin + paclitaxel

	← Favours cisplatin + topotecan	Hazard Ratio (95% CI)	Weight
Indirect		0.72 (0.46, 1.15)	52.50
Direct		1.26 (0.95, 1.67)	47.50
Overall (I-squared = 77.6%, p = 0.034)		0.98 (0.73, 1.23)	100.00

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Figure 3. Cisplatin vs. cisplatin + paclitaxel, all patients

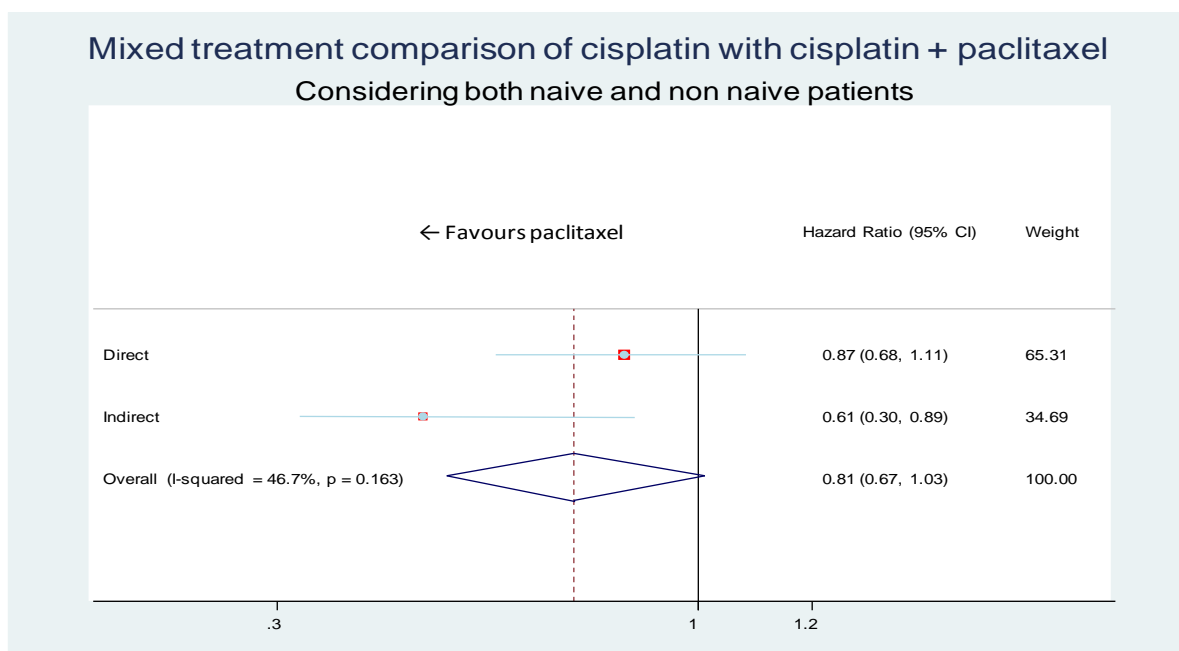


Figure 4. Cisplatin vs. cisplatin + paclitaxel, using cisplatin-naïve population from GOG-0179

Mixed treatment comparison of cisplatin with cisplatin + paclitaxel
Considering only naive patients

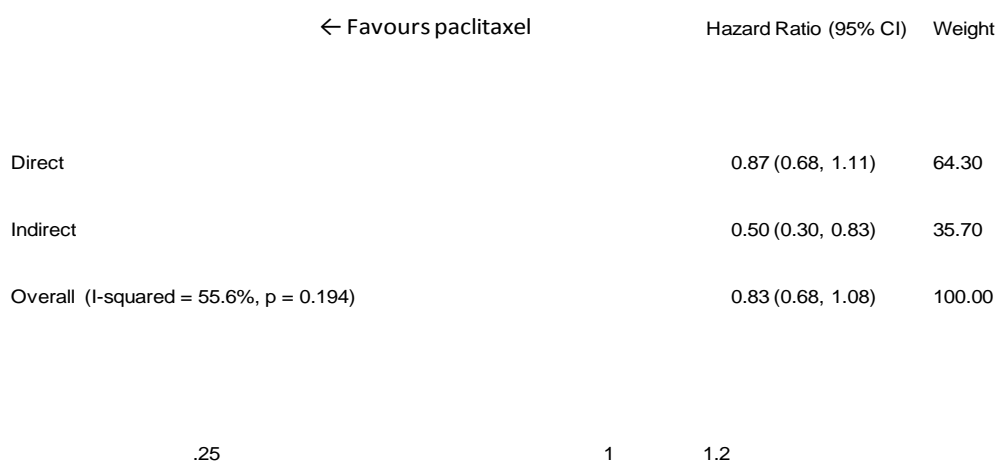


Figure 5. Cisplatin vs. cisplatin + topotecan, all patients

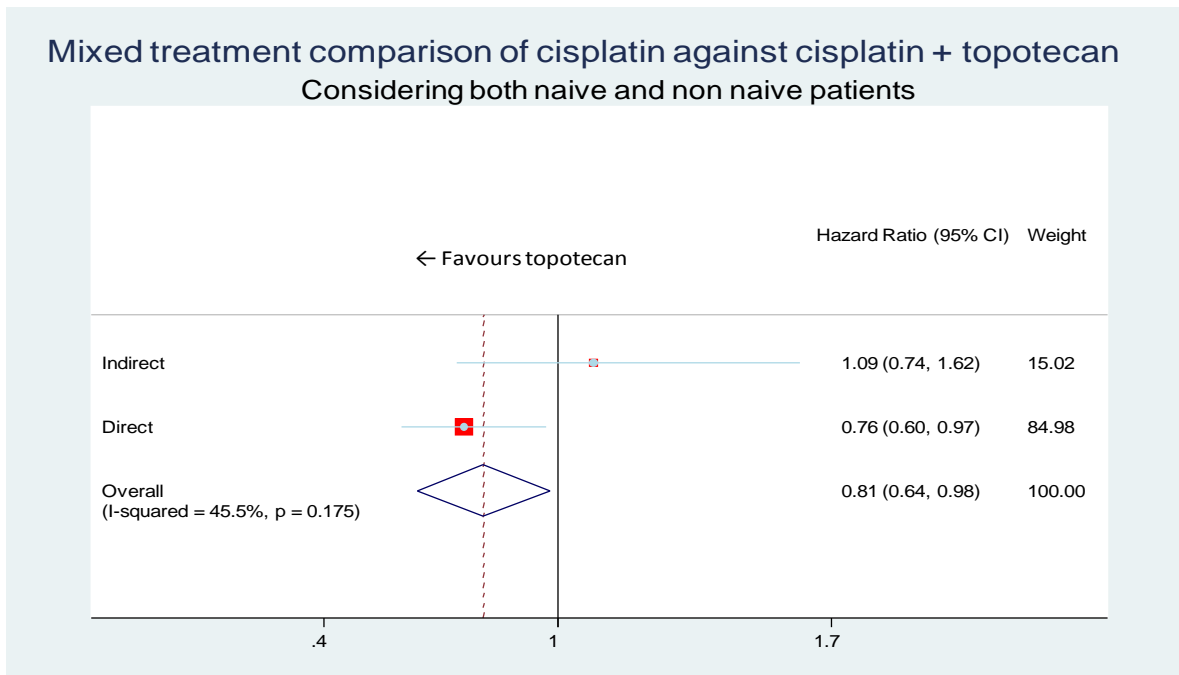
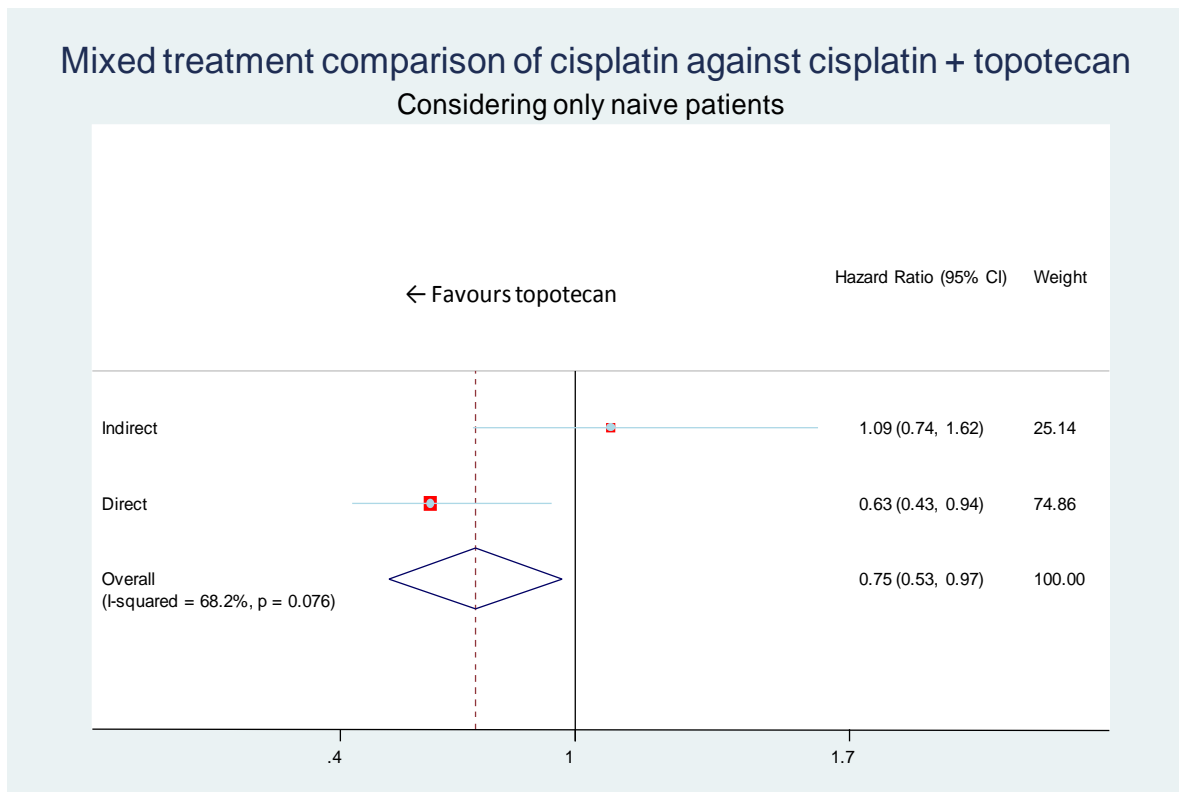


Figure 6. Cisplatin vs. cisplatin + topotecan, using cisplatin-naïve population from GOG-0179



Appendix 2: Probabilistic incremental cost effectiveness analysis

The indirect analysis model submitted to NICE for the appraisal of topotecan for the treatment of recurrent and stage IVB carcinoma of the cervix has been updated to reflect the ERG comments in the ACD, to investigate the deterministic effect of applying the hazard ratios (HRs) described in Appendix 1 and to examine probabilistically the effect of the uncertainty surrounding the HRs.

The previous version of the model indirectly compared cisplatin plus topotecan (from study GOG-0179) with cisplatin plus paclitaxel (from GOG-0169). In each of these trials, cisplatin was the comparator and was used as the indirect link in the meta-analysis. The model then used the observed topotecan data from GOG-0169 and estimated paclitaxel survival curves using the paclitaxel versus cisplatin hazard ratio from the meta-analysis and was based on the cisplatin survival curve from GOG-0179.

The meta-analysis described in Appendix 1 provides hazard ratios for topotecan versus cisplatin in the full licensed population (0.81 [95% CI 0.62; 0.98]) and the naïve population (0.75, [0.53; 0.97]) and paclitaxel versus cisplatin in the full licensed population (0.81 [95% CI 0.67; 1.03]) and the naïve population (0.83 [95% CI 0.68; 1.08]), synthesizing across all the available trial data. These are then used to construct survival and progression free survival curves for topotecan and paclitaxel based on the cisplatin curves from GOG-0179.

The model then examines probabilistically the effect of the uncertainty by creating survival curves based on sampled HRs from the distribution surrounding each HR estimate, the results of which are used to generate a multi-intervention cost effectiveness acceptability curve (CEAC) to determine the probability that each intervention is the most cost effective choice based on a range of acceptability thresholds.

In each scenario, we assume that the utility values are those used by the ERG (a progression free utility of 0.72 and a post progression value of 0.39) and examine the effect of assuming maximum wastage of topotecan (resulting in a cycle drug cost of £585.90) and minimum wastage (resulting in a cycle drug cost of £290.62). The updated administration cost of £699 per drug delivery cycle is assumed for topotecan in all scenarios. All the scenarios are for a 36 month time frame.

Results are presented for the full population and the cisplatin-naïve subgroup.

Scenario 1: Full licensed population

Analysis using hazard ratios from meta-analysis to construct both topotecan and paclitaxel curves.

Maximum wastage

The deterministic analysis, assuming maximum wastage of topotecan and constructing the survival curves from the hazard ratios for topotecan and paclitaxel, results in a cost per QALY gained for topotecan in the licensed population of £81,756 versus cisplatin and is dominated by branded and generic paclitaxel.

The multi-intervention CEAC analysis shows that paclitaxel plus cisplatin become more likely than cisplatin to be cost effective at a £40,000 willingness to pay (WTP) threshold, while topotecan is least likely to be cost effective over a wide range of WTP.

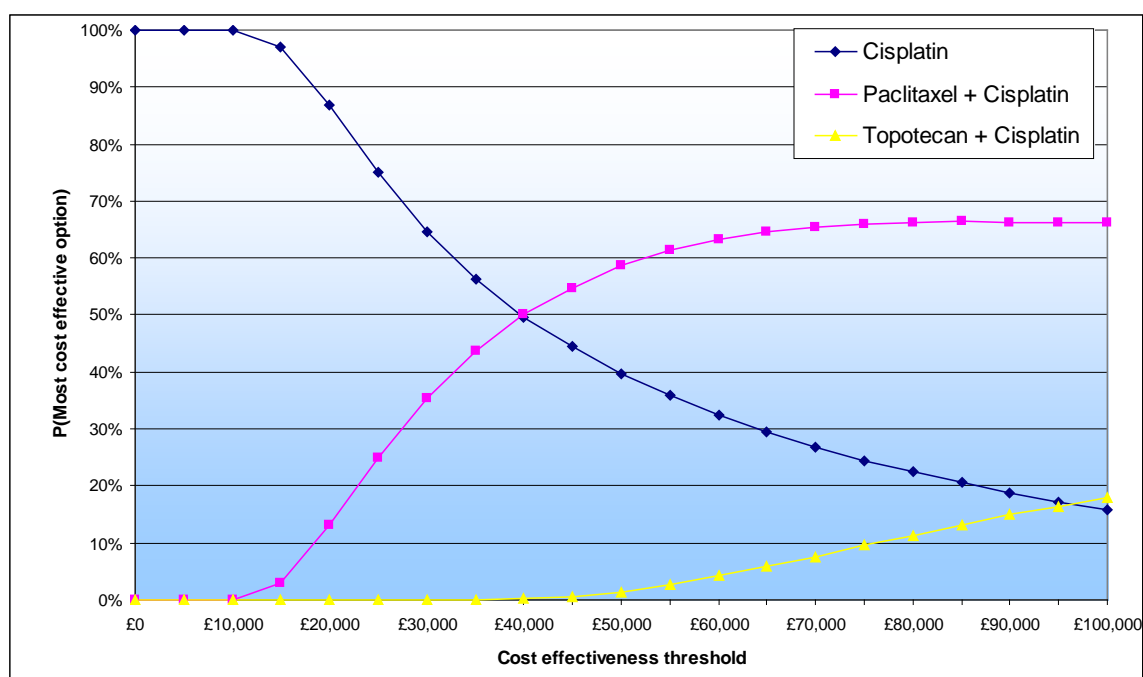
Deterministic evaluation of the cost effectiveness of topotecan in the full licensed population assuming maximum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£9,286	0.92	0.52	-	-	-	-	-
Cisplatin	£2,352	0.79	0.43	£6,934	0.12	0.08	£56,129	£81,756
Paclitaxel + cisplatin	£7,587	0.92	0.52	£1,699	0.00	0.00	Dominated	Dominated

Sensitivity analysis: paclitaxel price 50% of branded Taxol®

Topotecan + cisplatin	£9,286	0.92	0.52					
Paclitaxel + cisplatin	£5,860	0.92	0.52	£3,426	0.00	0.00	Dominated	Dominated

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the full licensed population, assuming maximum topotecan wastage.



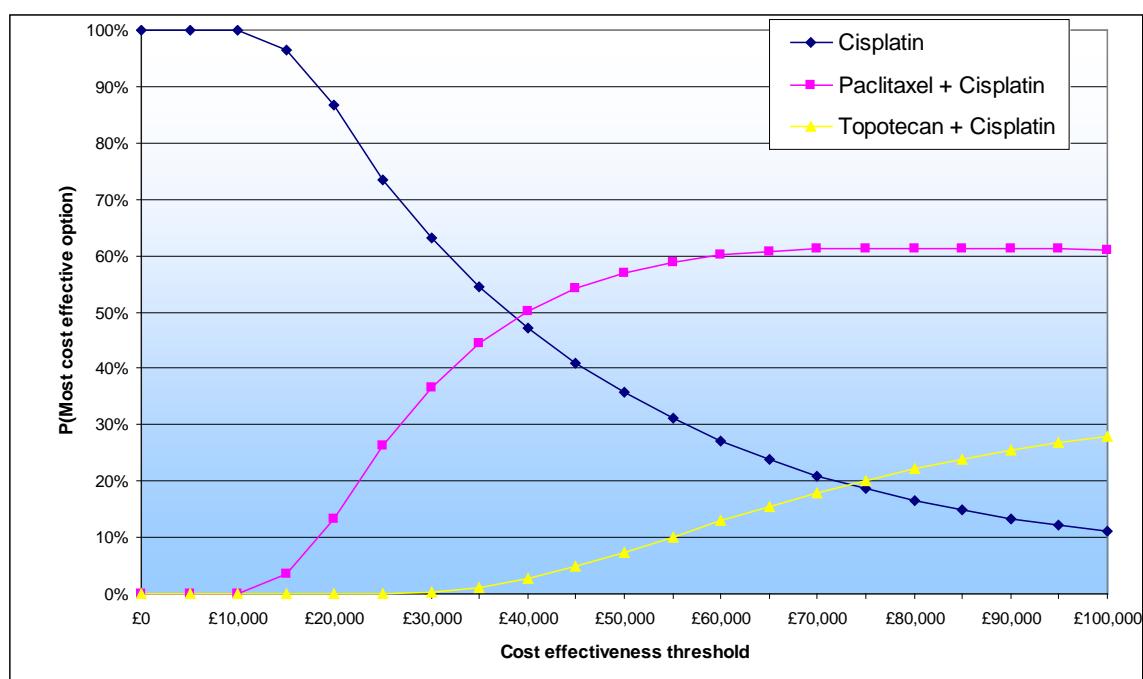
Minimum wastage

The deterministic analysis, assuming that there is minimum wastage of topotecan and constructing the survival curves from the hazard ratios for both topotecan and paclitaxel, results in a cost per QALY for topotecan in the licensed population of £63,913 versus cisplatin and is dominated by both branded and generic paclitaxel. The multi-intervention CEAC analysis shows a similar pattern to that based on the maximum wastage scenario, except that topotecan becomes cost effective in a larger minority of simulations, though never exceeding 18%.

Deterministic evaluation of the cost effectiveness of topotecan in the full licensed population assuming minimum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£7,773	0.92	0.52	-	-	-	-	-
Cisplatin	£2,352	0.79	0.43	£5,421	0.12	0.08	£43,879	£63,913
Paclitaxel + cisplatin	£7,587	0.92	0.52	£186	0.00	0.00	Dominated	Dominated
<i>Sensitivity analysis: paclitaxel price 50% of branded Taxol®</i>								
Topotecan + cisplatin	£7,773	0.92	0.52					
Paclitaxel + cisplatin	£5,860	0.92	0.52	£1,912	0.00	0.00	Dominated	Dominated

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the full licensed population, assuming minimum topotecan wastage.



Analysis using GOG-0179 observed values for topotecan survival and hazard ratio from meta-analysis for cisplatin survival curves.

Maximum wastage

The deterministic analysis, assuming that there is maximum wastage of topotecan and constructing the survival curves using observed data for topotecan and the hazard ratios for paclitaxel, results in a cost per QALY for topotecan in the licensed population of £60,903 versus cisplatin, £65,364 versus branded paclitaxel, and £131,792 versus generic paclitaxel.

When GOG-0179 observed survival curves are used, the number of simulations, in which topotecan is cost effective, increases in the multi-intervention CEAC analysis, reaching 30% at a WTP threshold of £60,000.

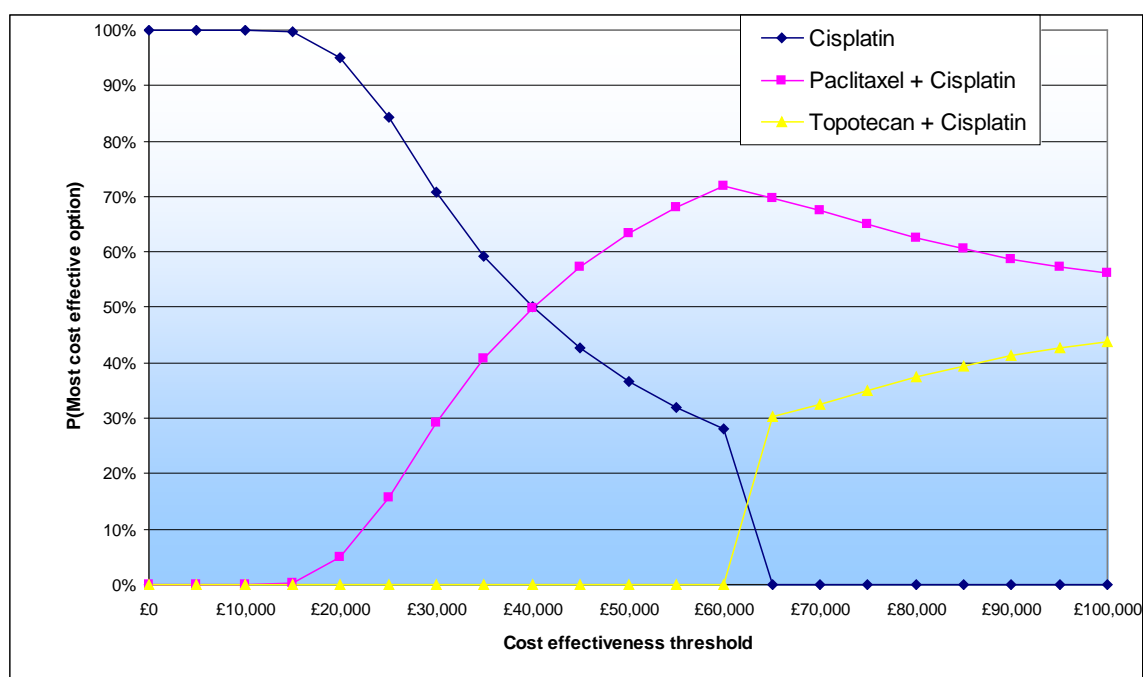
Deterministic evaluation of the cost effectiveness of topotecan in the full licensed population assuming maximum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£9,286	0.95	0.55	-	-	-	-	-
Cisplatin	£2,352	0.79	0.43	£6,934	0.16	0.11	£43,893	£60,903
Paclitaxel + cisplatin	£7,587	0.92	0.52	£1,699	0.03	0.03	£49,337	£65,364

Sensitivity analysis: paclitaxel price 50% of branded Taxol®

Topotecan + cisplatin	£9,286	0.95	0.55					
Paclitaxel + cisplatin	£5,860	0.92	0.52	£3,426	0.03	0.03	£99,478	£131,792

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the full licensed population, assuming maximum topotecan wastage.



Minimum wastage

The deterministic analysis, assuming that there is minimum wastage of topotecan and constructing the survival curves using observed data for topotecan and the hazard ratios for paclitaxel, results in a cost per QALY for topotecan in the licensed population of £47,616 versus cisplatin, £7,142 versus branded paclitaxel, and £73,571 versus generic paclitaxel.

When GOG-0179 observed survival curves are used together with the minimum wastage assumption, the number of simulations in which topotecan is cost effective reaches 40% at a WTP threshold of £50,000 and becomes the treatment most likely to be cost effective at a WTP threshold above £75,000.

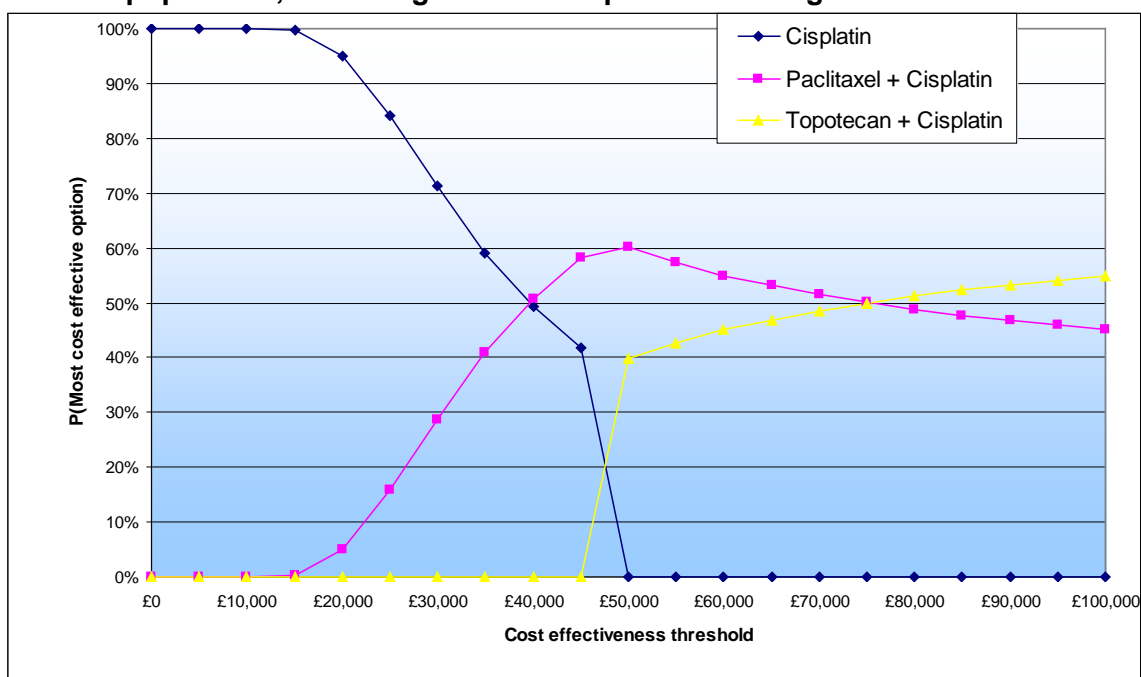
Deterministic evaluation of the cost effectiveness of topotecan in the full licensed population assuming minimum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£7,773	0.95	0.55	-	-	-	-	-
Cisplatin	£2,352	0.79	0.43	£5,421	0.16	0.11	£34,314	£47,611
Paclitaxel + cisplatin	£7,587	0.92	0.52	£186	0.03	0.03	£5,391	£7,142

Sensitivity analysis: paclitaxel price 50% of branded Taxol®

Topotecan + cisplatin	£7,773	0.95	0.55					
Paclitaxel + cisplatin	£5,860	0.92	0.52	£1,912	0.03	0.03	£55,532	£73,571

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the full licensed population, assuming minimum topotecan wastage.



Scenario 2: Cisplatin-naïve population

Analysis using hazard ratios from meta-analysis to construct both topotecan and paclitaxel curves.

Maximum wastage

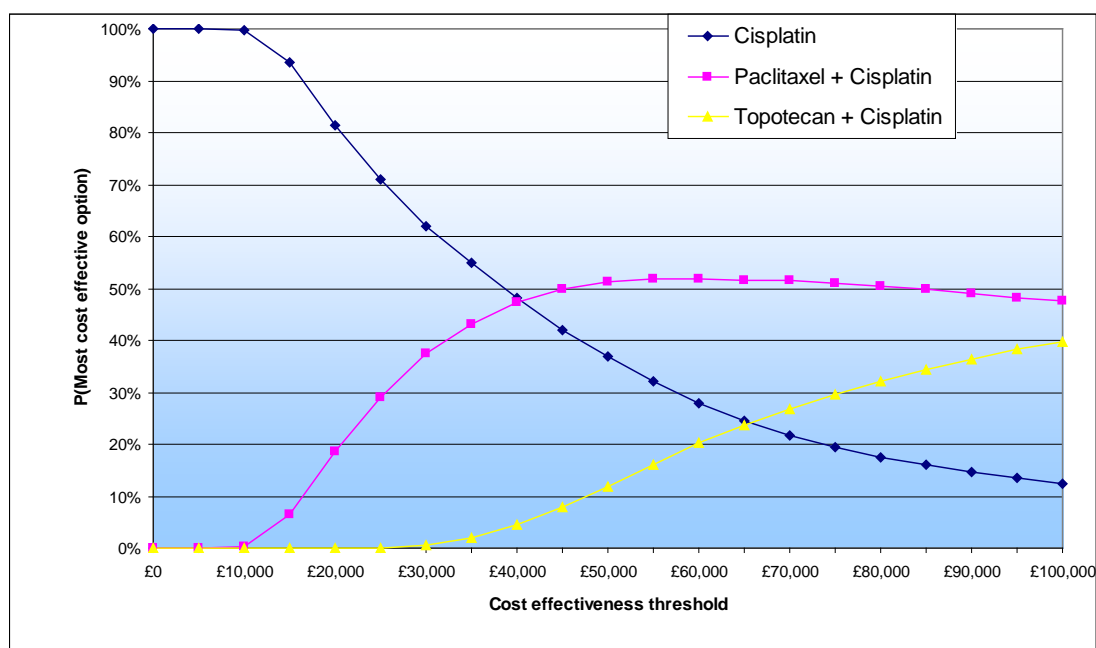
The deterministic analysis, assuming that there is maximum wastage of topotecan and constructing the survival curves from the hazard ratios for both topotecan and paclitaxel, results in a cost per QALY for topotecan in the cisplatin-naïve population of £58,911 versus cisplatin, £49,964 versus branded paclitaxel, and £100,743 versus generic paclitaxel.

The multi-intervention CEAC analysis shows that paclitaxel plus cisplatin becomes more likely than cisplatin alone to be cost effective when the WTP threshold exceeds £40,000, while the minority of simulations in which topotecan plus cisplatin is cost effective increases with WTP, reaching 40% at a WTP threshold of £100,000.

Deterministic evaluation of the cost effectiveness of topotecan in the cisplatin-naïve population assuming maximum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£9,286	1.08	0.60	-	-	-	-	-
Cisplatin	£2,352	0.90	0.48	£6,934	0.18	0.12	£39,143	£58,911
Paclitaxel + cisplatin	£7,587	1.01	0.56	£1,699	0.06	0.03	£26,424	£49,964
<i>Sensitivity analysis: paclitaxel price 50% of branded Taxol®</i>								
Topotecan + cisplatin	£9,286	1.08	0.60					
Paclitaxel + cisplatin	£5,860	1.01	0.56	£3,426	0.06	0.03	£53,278	£100,743

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the cisplatin-naïve population, assuming maximum topotecan wastage.



Minimum wastage

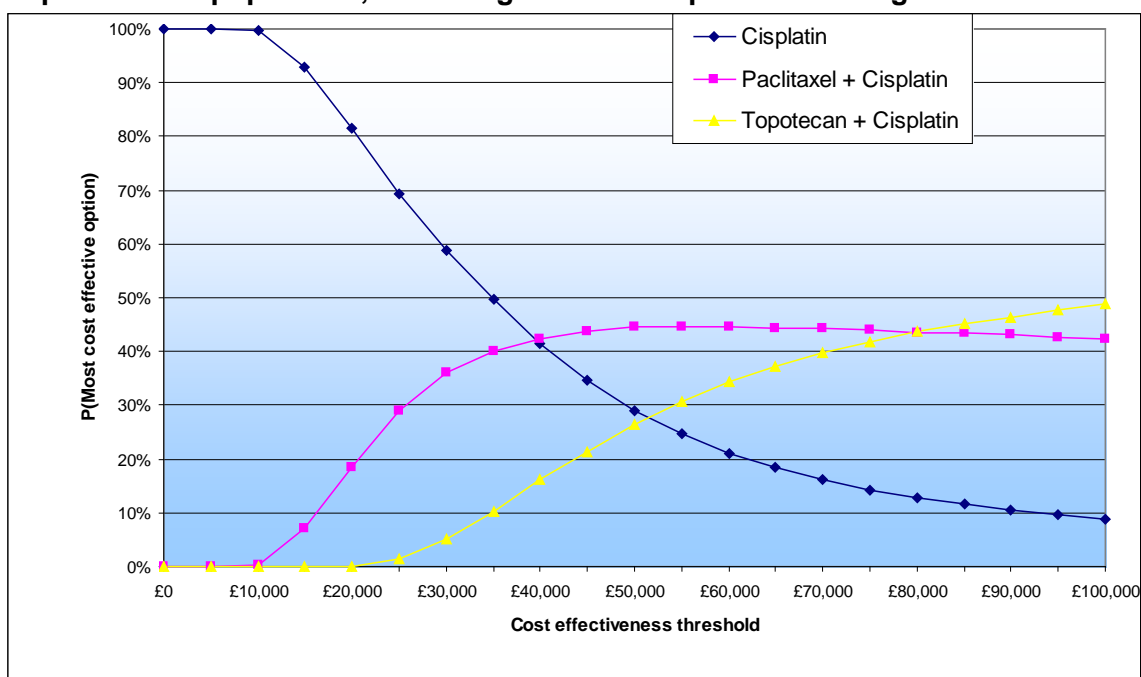
The deterministic analysis, assuming that there is minimum wastage of topotecan and constructing the survival curves from the hazard ratios for both topotecan and paclitaxel, results in a cost per QALY for topotecan in the cisplatin-naïve population of £46,054 versus cisplatin, £5,459 versus branded paclitaxel, and £56,238 versus generic paclitaxel.

Compared to the maximum wastage scenario, the proportion of simulations in the minimum wastage scenario in which topotecan is cost effective, increases such that topotecan becomes more likely than paclitaxel to be cost effective when the WTP threshold for marginal QALYs exceeds £80,000.

Deterministic evaluation of the cost effectiveness of topotecan in the cisplatin-naïve population assuming minimum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£7,773	1.08	0.60	-	-	-	-	-
Cisplatin	£2,352	0.90	0.48	£5,421	0.18	0.12	£30,600	£46,054
Paclitaxel + cisplatin	£7,587	1.01	0.56	£186	0.06	0.03	£2,887	£5,459
<i>Sensitivity analysis: paclitaxel price 50% of branded Taxol®</i>								
Topotecan + cisplatin	£7,773	1.08	0.60					
Paclitaxel + cisplatin	£5,860	1.01	0.56	£1,912	0.06	0.03	£29,742	£56,238

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the cisplatin naïve population, assuming minimum topotecan wastage.



Analysis using GOG-0179 observed values for topotecan survival and hazard ratio from meta-analysis for cisplatin survival curves.

Maximum wastage

The deterministic analysis, assuming that there is maximum wastage of topotecan and constructing the survival curves using observed data for topotecan and the hazard ratios for paclitaxel, results in a cost per QALY for topotecan in the cisplatin-naïve population of

£30,171 versus cisplatin, £11,627 versus branded paclitaxel, and £23,443 versus generic paclitaxel. The multi-intervention CEAC analysis shows that topotecan is the treatment most likely to be cost effective when the WTP threshold exceeds £32,500 per QALY gained, and is cost effective in 80% of simulations at a £35,000 WTP threshold.

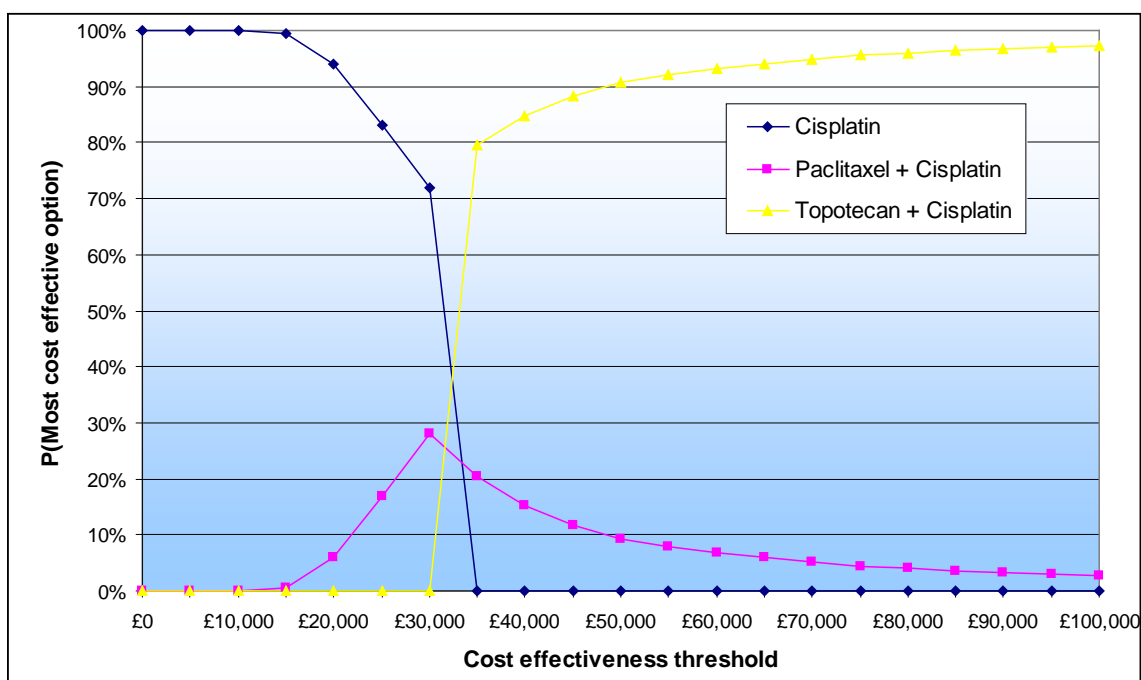
Deterministic evaluation of the cost effectiveness of topotecan in the cisplatin-naïve population assuming maximum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£9,286	1.18	0.71	-	-	-	-	-
Cisplatin	£2,352	0.90	0.48	£6,934	0.28	0.23	£24,790	£30,171
Paclitaxel + cisplatin	£7,587	1.01	0.56	£1,699	0.17	0.15	£10,182	£11,627

Sensitivity analysis: paclitaxel price 50% of branded Taxol®

Topotecan + cisplatin	£9,286	1.18	0.71					
Paclitaxel + cisplatin	£5,860	1.01	0.56	£3,426	0.17	0.15	£20,530	£23,443

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the cisplatin-naïve population, assuming maximum topotecan wastage.



Minimum wastage

The deterministic analysis, assuming that there is minimum wastage of topotecan and constructing the survival curves from the hazard ratios for both topotecan and paclitaxel, results in a cost per QALY for topotecan in the cisplatin-naïve population of £23,586 versus cisplatin, £1,270 versus branded paclitaxel, and £13,086 versus generic paclitaxel. The multi-intervention CEAC analysis shows that topotecan is the treatment most likely to be cost effective when the WTP threshold exceeds £22,500 per QALY gained, and is cost effective in 92% of simulations at a £30,000 WTP threshold.

Deterministic evaluation of the cost effectiveness of topotecan in the cisplatin-naïve population assuming minimum topotecan wastage.

Treatment	Mean cost per patient	Mean discounted life years	Mean discounted QALYs	Marginal values compared to Topotecan				
				Incremental cost	Incremental discounted life years	Incremental discounted QALYs	Cost per life years gained	Cost per QALY gained
Topotecan + cisplatin	£7,773	1.18	0.71	-	-	-	-	-
Cisplatin	£2,352	0.90	0.48	£5,421	0.28	0.23	£19,380	£23,586
Paclitaxel + cisplatin	£7,587	1.01	0.56	£186	0.17	0.15	£1,112	£1,270

Sensitivity analysis: paclitaxel price 50% of branded Taxol®

Topotecan + cisplatin	£7,773	1.18	0.71					
Paclitaxel + cisplatin	£5,860	1.01	0.56	£1,912	0.17	0.15	£11,460	£13,086

Multi-intervention CEAC evaluating the effect of hazard ratio uncertainty in the cisplatin-naïve population, assuming minimum topotecan wastage.

