Evidence Review Group Report commissioned by the NHS R&D HTA Programme on behalf of NICE

Vinflunine for the second line treatment of transitional cell carcinoma of the urothelial tract

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Rider on responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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K Cooper (Senior Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; GK Frampton (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; D Mendes (Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; J Bryant (Principal Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report and project managed the review.

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LIST OF ABBREVIATIONS

BNF	British National Formulary
BSC	Best Supportive Care
CEA	Cost Effectiveness Analysis
CI	Confidence Interval
CR	Complete Response
CRD	Centre for Reviews and Dissemination
DCR	Disease Control Rate
DSA	Deterministic Sensitivity Analysis
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
GC	Gemcitabine and Cisplatin
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HSUV	Health State Utility Value
ICER	Incremental Cost Effectiveness Ratio
IRC	Independent Review Committee
IRP	Independent Review Panel
IRRC	Independent Response Review Committee
ITT	Intention to Treat
KM	Kaplan-Meier
mg/m^2	Milligrams per square metre (of body surface)
MS	Manufacturer's Submission
MVAC	Methotrexate + Vinblastine + Doxorubicin + Cisplatin
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
ORR	Overall and objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PPS	Post Progression Survival
PR	Partial Response
PS	Performance Status
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiotherapy
SD	Stable Disease
SE	Standard Error
SPC	Summary of Product Characteristics
TCCU	Transitional Cell Carcinoma of the Urothelial tract
VBA	Visual Basic for Applications
VFL	Vinflunine
WHO	World Health Organisation

SUMMARY

Scope of the submission

The manufacturer's submission (MS) reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE). This was to consider vinflunine (VFL) plus best supportive care (BSC) compared to BSC for the second line treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of prior platinum-containing chemotherapy.

Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence in the MS comes from:

- One phase III randomised controlled trial (RCT) comparing VFL plus BSC against BSC (study 302); this is the primary source of evidence.
- Two open-label, single arm, phase II studies which were used to support the RCT evidence and assess the safety of VFL.

The primary outcome is overall survival (OS). In the intention to treat (ITT) population median OS was 6.9 months for the VFL plus BSC group and 4.6 months for the BSC group, a difference which was not statistically significant. In the eligible ITT population (excluding 13 inappropriately randomised patients) median OS was 6.9 months for the VFL plus BSC group and 4.3 months for the BSC care group, a difference which was statistically significant (p=0.04).

Secondary outcomes included response rates, disease control and progression free survival (PFS). The overall and objective response rate [(ORR) the total rate of complete and partial responses and disease control rate [(DCR) complete responses + partial responses + stable disease] as assessed in evaluable patients were both statistically significantly higher in the VFL plus BSC group than the BSC group. Median duration of disease control and PFS, presented for the ITT population, were also significantly longer in the VFL plus BSC group compared with the BSC group. Quality of life experienced by patients treated with VFL was reported not to be compromised over those who had BSC, and there was no difference between groups in a composite measure of clinical benefit. The main adverse events associated with VFL were neutropenia, fatigue, anaemia and constipation and were reported in the MS as acceptable and manageable.

Summary of submitted cost effectiveness evidence

The manufacturer conducted a systematic review of published economic evaluations of VFL in the treatment of adult patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen. Searches yielded no pertinent studies and the MS concluded that there were no published relevant cost effectiveness studies.

The economic evaluation developed for the MS consists of a cost utility analysis using a survival model to estimate the effect of treatment with VFL plus BSC compared to BSC, as per the NICE scope. The model includes three mutually exclusive health states (Alive, pre-progression; Alive, post-progression; and Dead) and calculates the proportion of patients in each treatment cohort that is expected to be in each health state, based on estimates of OS and PFS from the relevant RCT (Study 302).

Results are presented as incremental cost per quality adjusted life year (QALY) gained, with incremental costs, QALYs and life years gained also presented separately. The MS reported an ICER of £100,144 per QALY gained for VFL plus BSC versus BSC. The manufacturer states that VFL meets the criteria for NICE's end of life advice in health technology appraisals, and presents a more favourable ICER (£61,890/QALY) as the impact of giving greater value to the quality of life in the later stages of terminal diseases. The ratio of the new cost effectiveness estimate to the willingness-to-pay threshold of £30,000/QALY is 2.06.

Deterministic sensitivity analyses results presented in the MS ranged from £27,478 to £133,094 per QALY. The lower ICER was obtained assuming an acquisition cost for VFL of zero. Results of scenario analyses with alternative methods of estimation of the effectiveness of VFL were also reported. Mean probabilistic sensitivity analysis (PSA) results were not presented although a PSA was undertaken, with the probability of VFL plus BSC being cost effective compared to BSC at a £30,000/QALY threshold reported as 6%.

Commentary on the robustness of submitted evidence

Strengths

- The MS contains systematic searches for clinical and cost effectiveness studies of VFL. It appears unlikely that these have missed any studies that would have met the inclusion criteria.
- Overall the systematic review meets the Centre for Reviews and Dissemination (CRD) criteria for methodological adequacy.
- The economic model presented in the MS used an appropriate approach for the disease area, given the available data.

Weaknesses

- The MS does not report details of the processes used to conduct the systematic review although meeting criteria for methodological quality.
- The evidence base is limited and for clinical effectiveness consists primarily of a single RCT of uncertain methodological quality.
- There are inconsistencies in the reporting of data throughout the MS. The different trial populations used for different outcomes are not always reported clearly and consistently.
- The RCT analyses have limitations. The primary ITT analysis included participants who should not have been randomised (2% in the VFL plus BSC group and 8% in the BSC group) and the 'eligible' ITT analysis excluded these patients but may not be valid due to the breaking of randomisation.
- Summaries of OS in the MS focus on the eligible participants ITT analysis which may not be appropriate.
- There is too little information about the measurement of quality of life and clinical benefit to be sure that the stated interpretation of the evidence is unbiased.
- The MS economic model uses BSC as a comparator for VFL which meets the scope of the review but a more appropriate comparator would be an alternative second-line therapy (although no RCT evidence exists in this patient group).
- The MS economic model uses data from the eligible participants ITT analysis, rather than from the ITT analysis.
- The utilities in the model have not been derived according to the NICE reference case.

Areas of uncertainty

- Due to uncertainty about the validity of the methods of analysis of trial data it is not possible to say that the MS contains an unbiased estimate of treatment effect. The conservative ITT approach did not meet statistical significance whereas the eligible participants ITT analysis just reached statistical significance.
- There are also uncertainties about whether the included trial is generalisable or relevant to the UK in terms of the included population. Due to the trial exclusion criteria (poor performance status, prior adjuvant therapy) the population may not be representative of patients who proceed to second line chemotherapy in the UK.
- There is uncertainty about the impact of adverse events associated with VFL. In the MS the adverse event profile is considered to be reasonable but this does not concur with clinical information received by the ERG.

- There is considerable uncertainty around the health state utility values used in the economic model.

Key issues

- It is unclear from the evidence presented in the MS whether there is convincing data to show the superiority of VFL plus BSC over BSC alone.
- The results from the economic analysis have not demonstrated that VFL is a cost effective treatment compared to BSC.
- The MS has used BSC as a comparator for VFL to reflect the scope issued by NICE. However, a more appropriate comparator would be an alternative second-line therapy.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Pierre Fabre on the clinical effectiveness and cost effectiveness of Vinflunine (VFL) for the treatment of transitional cell carcinoma of the urothelial tract. It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 12 August 2010. A response from the manufacturer via NICE was received by the ERG on 3 September 2010 with outstanding information received on 13 September 2010; this has been included as an Addendum in the ERG report (Appendix 1).

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS generally provides a clear and accurate overview of transition cell carcinoma of the urothelial tract (TCCU).

2.2 Critique of manufacturer's overview of current service provision

The MS generally provides a fair overview of current service. It states that 'if patients receive further chemotherapy, the choice of drug is subject to considerable inter- and intra-hospital variation.' However, clinical advice to the ERG, whilst confirming that there is no standard second line therapy for patients with advanced TCCU after failure of prior platinum-containing chemotherapy and that some variation in practice exists, suggests that most patients are offered further chemotherapy which is dependent on response to first line therapy. If the patient had a good response to initial chemotherapy, usually cisplatin or carboplatin with or without gemcitabine, or gemcitabine with paclitaxel, this will be repeated; if not, an alternative platinum-based regimen will be used, or taxanes used either in combination or as single agents.

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The population described in the decision problem is appropriate for the UK National Health Service (NHS).

2.3.2 Intervention

The description of the intervention in the decision problem is appropriate for the NHS. The product was granted EU marketing authorisation in September 2009 and will be launched in the UK in September 2010. Standard dose of VFL is 280-320 mg/m^2 every three weeks.

2.3.3 Comparators

The main comparator in the MS decision problem is BSC (palliative radiotherapy, antibiotics, analgesics, corticosteroids, transfusions). The MS reports that there is no standard therapy for patients with advanced TCCU after failure of prior platinum-containing chemotherapy. However, as stated above, alternative chemotherapies are available in practice as TCCU is a chemo-sensitive cancer, although there are no RCTs of them as second line treatment.

2.3.4 Outcomes

The outcomes included in the MS are appropriate and clinically meaningful to patients.

2.3.5 Economic analysis

The economic evaluation in the MS decision problem appears to be appropriate, being a cost utility analysis from the NHS and Personal Social Services (PSS) perspective. The exclusion of comparators used in practice is appropriate as this meets the NICE scope; however, a more appropriate comparator would be an alternative second-line therapy, although as stated above no trial data are available for alternative treatments in this population of patients.

2.3.6 Subgroups

The MS states that subgroups are not applicable. The ERG clinical advice suggests that subgroups for performance status and visceral status could be considered.

2.3.7 Special considerations

The MS states that special considerations, including issues relating to equity and equality are not applicable (MS, page 21). However, 'end of life' issues are discussed throughout the decision problem and the manufacturer proposes that VFL should be used to pilot the Innovation Pass/New Cancer Drug Fund.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The search strategies are documented and reproducible and fit for purpose despite a few minor omissions and inconsistencies. The ERG re-ran the searches and no additional data relevant to the submission were identified.

3.1.1.1 Clinical effectiveness searches

The clinical effectiveness search strategies are documented and reproducible and a flow chart of search results is tabulated. The minimum NICE database search criteria have not been precisely met as Embase and Medline ® In Process (MEIP) were not mentioned although Pubmed was searched, which should have also identified the Medline non-indexed records, obviating the need to search MEIP. Only the Central database in the Cochrane Library is recorded as searched. The ERG ran a search on all Cochrane databases and did not identify any other relevant records. Searches were restricted to the English language. The host stated for the clinical searches in MS Appendix 2, section 9.2 was DIMDI, which the ERG does not have access to. All years are recorded as being searched, however the exact range is not clarified.

It seemed sensible to start with a wide "one search fits all" approach and to subsequently narrow it down to retrieve the relevant data. An RCT search filter was not used and thus the search would have retrieved non-RCT evidence as stated in MS section 9.6.1 and adverse events as in MS section 9.8.1. It is noted that Vinflunine was the search term used in DIMDI, with no mention of the trade name Javlor, nor a search on CAS registry drug number. The ERG ran a search on Vinflunine or Javlor on Medline, Embase and Pubmed and no additional relevant results were retrieved. The MS Appendix 9.2.5 states N/A for search of company databases.

There is no record of documentation for ongoing trials databases having been searched. Major oncology meetings are documented as hand searched along with Biosis and CAB Abstracts listed as checked for conference proceeding abstracts. There is no reference in the text to hand-searching bibliographic lists to identify further studies.

3.1.1.2 Cost effectiveness searches

The cost-effectiveness search strategies are documented and reproducible but there are some minor discrepancies. The minimum NICE database search criteria have not been

precisely met. MS section 9.10.1 records Medline and Embase which were searched using Ovid (no explanation of the rationale for changing host for the cost-effectiveness searches is given). There are no details given of in-house company databases, nor ongoing trials databases, being searched. There is no record of Econlit nor NHSEED being searched. The ERG searched both of these databases and no results were returned for Vinflunine/Javlor. The search was widened out to bladder cancer on NHSEED, with no additional references not already in the manufacturers' bibliography being retrieved. MS section 6.1.1 (p. 68) states that "no restrictions were applied to publication date within searches", however line 4 of the Medline strategy, in MS Appendix 9.10.4 (p. 129) clearly limits the search from 2000 to current. The search strategies are limited by English language in the Embase search. A full economic filter has not been used in either database – however relevant cost indexing terms have been exploded.

Health related quality of life searches were undertaken on Medline and Embase. MS section 6.4.5 (page 85) states that "no restrictions were applied to publication date within searches", however line 4 of the Medline strategy (page 134) and line 13 of the Embase strategy (page 135) in MS section 9.12, clearly limits the search from 2000 to current. The Embase search is restricted to English language. A full quality of life filter has not been applied, although some key index terms have been used. Resource utilisation searches have also been undertaken on Medline and Embase.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The MS clearly states the inclusion and exclusion criteria (MS p. 24) and these are consistent with the final scope issued by NICE, with one exception. The final scope specifies response rates as an outcome but the MS justifies not including this outcome as there would be "no comparative data for response rate in this end of life population with a heavy tumour burden". Note that an additional exclusion criterion not listed on MS p. 24 is introduced in the flow chart (MS, p. 25; see below).

The systematic review reported in the MS was not limited to RCTs. Study quality was not stated as an inclusion or exclusion criterion. The only limits specified for study design were that RCTs, phase II studies, systematic reviews and meta-analyses were included whereas non-inferiority studies were excluded.

Setting was not explicitly stated either in the final scope or the inclusion and exclusion criteria. Patients would be under the care of a multi-disciplinary oncology team receiving chemotherapy and other best supportive end of life care.

The MS presents a flow chart (MS, p. 25), indicating the number of publications identified and excluded at each stage. Reasons for excluding the papers after detailed review are summarised briefly in the flow chart but the number and identity of papers excluded for each reason are not given in the MS. The flow chart introduces an exclusion criterion that was not listed among the exclusion criteria defined a priori: trials that did not reach primary endpoints were excluded. It is unclear whether this would have resulted in any relevant secondary outcomes being excluded.

The MS does not consider bias or study quality at the stages of study searching, screening and selection. Critical appraisal of the RCT is reported in the MS (p. 36) and Appendix 3 (p. 124).

3.1.2.1 Identified studies

The MS identified one RCT and two non-RCTs, all of which were sponsored by the manufacturer (Pierre Fabre or Bristol-Myers Squibb).

The RCT was a phase III trial reported on in two publications (Bellmunt et al. 2009[1]; Culine et al. 2010[2]). Summary details of the RCT[1] are tabulated (MS, p. 27), including design, method of randomisation, number of randomised patients, primary and secondary outcomes and follow up. Outcomes are also reported in the text (MS, p. 31). Inclusion criteria of the RCT[1] and baseline characteristics of the RCT[1] participants are tabulated (MS, p. 29-30). The primary statistical hypothesis, sample size calculation and statistical power are reported (MS, p. 32). Statistical test methods and six defined analysis populations, including ITT, are specified (MS, p. 33-34). A copy (electronic) was provided of only one of the two RCT reports.[1] The second report[2] is a conference abstract that the ERG was able to locate on the internet.

The two non-randomised studies were open label, single arm, phase II studies (Culine et al. 2006[3]; Vaughn et al. 2009[4]). The populations and interventions in the non-randomised studies are relevant to the decision problem. However, the primary outcomes in these non-randomised trials were response rates; the MS states (p. 21) that response rates are not included in the decision problem due to lack of comparative data in this population (as noted above; ERG report section 3.1.2).

In the RCT,[1] the VFL plus BSC group and BSC group were comparable in age (predominantly elderly), gender (predominantly male), creatinine clearance, organ and visceral involvement, and proportion with relapse within six months of prior chemotherapy (MS, p. 30). Both the MS and primary publication highlight that the VFL plus group had a higher proportion of poorer performance status (PS) patients than the BSC-only group (71.5% and 61.5% respectively had an ECOG (Eastern Cooperative Oncology Group) PS score of 1 [restricted but ambulatory]) but this difference was not statistically significant (see Appendix 1, A4). There were also slight differences between groups in the prior platinum therapy received: 64.8% of the VFL plus BSC group and 72.6% of the BSC-only group had received cisplatin alone (difference was not statistically significant), whilst 29.6% and 19.7% respectively had received carbopolatin alone which was a statistically significant difference, p=0.044 (tabulated but not discussed by the authors). Other baseline demographic variables (e.g. ethnicity) were not reported in the MS or primary publication.

It should be noted that the participants of the RCT may not be properly representative of patients who proceed to second line chemotherapy in the UK. Clinical advice suggests that the inclusion criteria of PS 0 or 1 and the exclusion of patients with previous neoadjuvant or adjuvant chemotherapy is more restrictive than in clinical practice.

Different baseline variables were reported in the RCT[1] and the two non-RCTs,[3,4] which limits comparison of the included populations. All three studies appear comparable in age and gender. Ethnicity was only reported in one of the non-RCTs[4] (MS p. 58). The proportion of patients who had visceral disease, which is associated with poor prognosis, was higher in the RCT[1] (74%, MS, p. 30) than in either of the non-RCTs[3,4] (49% but not reported for either study in the MS). There were also some differences in the prior platinum therapy received by patients: in the RCT[1] this was mainly cisplatin or carboplatin alone (MS, p. 30); in study 202[3] patients received mainly MVAC (methotrexate + vinblastine + doxorubicin + cisplatin) or CMV (cisplatin + methotrexate + vinblastine), or platinum + gemcitabine (MS, p. 55); and in study CA001[4] patients received mainly platinum + gemcitabine (not reported in the MS).

The MS appears to have identified all relevant RCTs meeting the inclusion criteria of the systematic review, and the two non-RCTs also meet the inclusion criteria.

The MS mentions (p. 10) that several phase I studies are ongoing or have been recently completed in specific populations with chronic liver disease (completed), renal impairment (ongoing), and cancer in elderly patients (ongoing). No references or any other details of these trials are provided. The ERG has identified one relevant ongoing trial (scheduled for

completion in June 2012). This is an observational study sponsored by the manufacturer which is focusing on tolerability of VFL (NCT01103544; JONAS-1).

3.1.3 Description and critique of the approach to validity assessment

The MS provides a quality assessment of the RCT[1] that follows the NICE criteria, based on CRD methods,[5] and appears appropriate (in the text p. 36 and Appendix 3, p. 124). Quality assessment of the two non-RCTs[3,4] (in Appendix 7, p. 126) is based on an ad hoc list of five criteria (how patient responses were addressed; occurrence of any unexpected drop outs; appropriateness of the patients studied; selective outcome reporting and intent-to-treat analysis) without reference to any validated assessment instruments for non-randomised studies.

Table 1 shows the assessment of study quality for the RCT[1] by the manufacturer and ERG and indicates limited agreement between the two.

Table 1: Manufacturer and ERG assessments of trial quality

NICE QA Criteria for RCT	MS response	ERG response
1. Was the method used to generate random allocations adequate?	Yes	Unclear. Randomisation was carried out by the manufacturer's biostatistics department, but the method of randomisation is not specified.
2. Was the allocation adequately concealed?	Not applicable (open-label study)	Unclear. The method of allocation concealment is not reported. Allocation concealment is relevant to the preservation of the randomisation sequence to determine whether intervention allocation could have been foreseen in advance of enrolment and should be reported irrespective of whether a study is open label or blinded. Patients may change their willingness to participate in a trial if they know or suspect which treatment they will receive.
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes, with the exception of PS which was biased in favour of the BSC group.	Unclear. As stated in the MS, the groups clearly differed in PS but this was not statistically significantly different and the impact of this is unclear.
4. Were the care providers, participants	Yes	Unclear. The outcome

and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		assessors were blinded but no information is provided on whether care providers were blinded (according to the description of the study as open label, participants would not have been blinded).
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes (but this may be an error, as the accompanying description actually supports a 'No' answer) Confirmed in clarifications to be an error and should read 'No' (See 7.1 Clarification from manufacturer A22).	Unclear. Reasons for discontinuation differed between the study groups. For example, discontinuation due to progressive disease occurred in 55% of the randomised population treated with VFL + BSC but only in 26% of the randomised population that received BSC only. Deaths from progression in these groups were 2.0% and 16.0% of the randomised populations respectively (MS, p. 35).
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
7. Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Unclear. A primary ITT analysis was included. However, the ITT population included some patients randomised in error, so an eligible ITT analysis was also conducted. Methods for missing data not clear.

3.1.4 Description and critique of manufacturer's outcome selection

The primary outcome (OS) matches the decision problem and is defined as the time elapsed between randomisation and death or last follow-up. Some secondary outcomes concerning response rates match the decision problem but are inconsistent with an earlier statement in the MS (p. 21) that there would be no comparative data for response rates in this end of life population with a heavy tumour burden. (See Appendix 1, Clarification from manufacturer A1).

Secondary outcomes are:

- Best confirmed complete responses (CR) and partial responses (PR) from randomisation to end of treatment, used to calculate: overall and objective response rate (total of CR + PR); time to first CR or PR; and duration of CR or PR.
- Duration of stable disease (SD) (time from randomisation to progression or death).
- Rate of disease control (total rate of CR + PR + SD).

- Duration of disease control (for SD, CR and PR patients as the time from randomisation to progression or death).
- Progression-free survival (PFS, time from randomisation to progression or death).

'Other' outcomes (synonymous with secondary outcomes, See Appendix 1) are quality of life (QoL) and response in terms of clinical benefit (an improvement in PS, weight, and/or pain intensity without deterioration of another parameter). Health-related QoL (HRQoL) was assessed using the EORTC (European Organisation for Research and Treatment of Cancer) QoL Questionnaire (QLQ-C30). This is a popular instrument for measuring general cancer HRQoL and has been validated in a wide range of cancers and populations. The ERG notes that a paper published by Gerharz EW et al[6] concluded that there is no single HRQoL tool preferably used in bladder cancer.

There do not appear to be any outcomes reported in the trial publications for the RCT[1] or the two non-randomised studies[3,4] that are not reported in the MS. Adverse events are reported (not listed as outcomes, but reported in the adverse events section MS, p. 63-65).

3.1.5 Description and critique of the manufacturer's approach to trial statistics

Results of all relevant outcome measures are reported. However, the primary and secondary outcomes appear to be given equal priority in the overall synthesis of clinical effectiveness, with the primary outcome (OS) listed after secondary outcomes (response rates, response duration, disease control rate, disease control duration) (MS, p. 62). Continuous variables (OS, PFS, disease duration, and response duration) are presented as median and 95% CI and reflect duration of follow-up with no interim data presented. Response rates are presented as N, % and 95% CI. Quality of life and clinical benefit are reported only briefly, without any estimates of variance.

Several different population analyses are presented. ITT analyses are reported, together with "eligible patients ITT analyses". The eligible ITT analyses excluded 13 patients who were incorrectly randomised and did not meet the inclusion criteria at baseline (a narrative justification for conducting the eligible ITT analyses is provided). The ITT analysis, whilst giving a more conservative estimate of treatment effect, is probably to be preferred because the eligible ITT analysis may not be justified as it breaks the randomisation sequence. Also there are concerns about when and how the eligible population was identified; it is not known if the decision was made by researchers blinded to treatment allocation or if it was on the basis of information related to outcomes after random allocation. These issues may be

relevant as blinding was described in the MS as not applicable to an open label study. However, interpretation of results is difficult as both analyses have limitations.

A per protocol analysis is also reported for overall survival (MS p. 43) but not considered in the overall synthesis of results. The evaluable populations were those analysed for response rates and disease control rates and included patients that were 'eligible, evaluable and treated in the arm assigned by randomisation'.

Both univariate and multivariate analyses were conducted for the survival outcomes; the latter take into account seven prognostic baseline variables that were specified a priori. A potentially clinically important difference between the study arms was that the BSC arm had a higher proportion of patients with a better PS at baseline. This is accounted for as a prognostic factor in the multivariate analyses but not accounted for in univariate analyses that were applied to both primary and secondary outcomes.

3.1.6 Description and critique of the manufacturer's approach to the evidence synthesis

The tabulated data generally reflect those reported in the primary publications of the three included trials. Within the MS however there are numerous inconsistencies and errors in the summary of clinical effectiveness data in Table B26 (MS, p. 62):

- Some data summarised in the table are not reported elsewhere in the MS (e.g. overall response rate data for study CA 001[4] and disease control rate confidence intervals for study 202[3]);
- Some data reported elsewhere in the MS are not included in the summary table B26 (e.g. confidence intervals for progression-free survival for study 202[3]);
- Some data are incorrect (e.g. the p-value for the evaluable patients ITT analysis of overall response rate in the RCT[1] should be 0.0063, not 0.00063 as reported in Table B26).

A meta–analysis is not reported in the MS as only one RCT[1] met the inclusion criteria.
No indirect comparison is reported in the MS as no other relevant trials met the inclusion criteria specified in the NICE scope.

3.2 Summary statement of manufacturer's approach

The quality of the MS based on CRD criteria[5] for a systematic review as assessed by the ERG is shown in Table 2.

Table 2: Quality assessment of MS review

CRD Quality Item[5]: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Inclusion and exclusion criteria are reported
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes. Extensive searches were conducted for clinical and cost-effectiveness and adverse events.
3. Is the validity of included studies adequately assessed?	Yes. The validity of the included RCT was assessed using standard CRD criteria for assessing the quality of RCTs (presented in narrative form in text and tabulated in Appendix). Quality assessment of the non-RCTs was conducted using a tabulated checklist not referenced (MS, p. 126) comprising 5 items (method of assessing outcomes, dropouts reported, appropriate participants, all outcomes reported, ITT analysis). However, no narrative discussion or explanation of the items is given and blinding was not assessed.
4. Is sufficient detail of the individual studies presented?	Yes. Study characteristics are described for the one RCT and the two non-RCTs in numerous tables.
5. Are the primary studies summarised appropriately?	Yes. The primary studies are appropriately summarised. The RCT is summarised through narrative means and tabulation of results, for the different populations analysed (ITT and eligible ITT) and for all outcomes. Summary strengths and weaknesses are briefly mentioned, and the clinical interpretation reports results using the eligible ITT analysis. The executive summary also focuses on the eligible ITT analysis. There are some inconsistencies within the MS due to poor reporting.

The systematic review is of good quality according to CRD criteria and the submitted evidence reflects the decision problem defined in the MS. However, no details are given for any of the processes used in the systematic review; it is not reported whether inclusion/exclusion, data extraction and quality assessment were undertaken by a single reviewer or independently by two reviewers.

In summary, the overall risk of systematic error in the systematic review appears to be low. However, details of the processes used to conduct the review are not given and throughout the MS there are inconsistencies and errors in data and text, and interpretation errors (e.g. stating that a non-statistically significant result suggests a reduced risk of death, MS p.38).

3.3 Summary of submitted evidence

In this section of the report the ERG provides a summary of the evidence presented in the MS from the included RCT.[1] Data have been checked by the ERG and summarised for each of the key outcomes below. There were a few discrepancies between the data provided in the MS and the published paper of the RCT,[1] and inconsistencies within the MS. Discrepancies are noted below. Clarification was requested from the manufacturer.

3.3.1 Summary of results for overall survival

The stated primary outcome measure of the RCT[1] was overall survival (see Table 3). In the ITT population, median overall survival was 6.9 months for the VFL plus BSC group and 4.6 months for the BSC group, with an HR of 0.88 that was not statistically significant (MS Table B8). In the eligible ITT population median overall survival was 6.9 months for the VFL plus BSC group and 4.3 months for the BSC arm, with an HR of 0.78 that was statistically significant (p=0.04) (MS Table B8). Multivariate analysis using pre-specified prognostic factors showed a statistically significant treatment effect of VFL plus BSC over BSC alone for the ITT population (MS Table B9).

The MS has an 'extended' multivariate analysis also incorporating pre-specified prognostic factors (MS Table B10, page 42) that is not reported in the published paper. It is not clear whether this is an additional analysis or the same as the multivariate analysis reported in Table B9 (MS page 40) as no explanation is given and data do not match. It showed a statistically significant treatment effect of VFL plus BSC over BSC alone for both the ITT and eligible ITT populations (MS Table B10). Clarification from the manufacturer confirmed that this was an additional 'extended' multivariate analysis using additional prognostic factors (see Appendix 1, A16).

Table 3: Overall survival for the ITT and eligible ITT populations

	Median Overall survival, mths (95%CI)		HR (95%CI) p value		
	VFL + BSC (median follow-up 21.5 mths)	BSC (median follow-up 22.3 mths)	Stratified log rank	Multivariate Analysis	Extended multivariate analysis
ITT	6.9 (5.7 to 8.0) n=253	4.6 (4.1 to 7.0) n=117	0.88 (0.69 to 1.12) p=0.287 (MS Table B8 & Table B10)	0.77 (0.61 to 0.98) p=0.036 (MS Table B9)	0.74 (0.57 to 0.96) p=0.0221 (MS Table B10)
Eligible ITT	6.9 (5.7 to 8.0) n=249	4.3 (3.8 to 5.4) n=108	0.78 (0.61 to 0.99) p=0.040 (MS Table B8 & Table 10)	Not reported	0.68 (0.52 to 0.88) p=0.0035 (MS Table B10)

The MS states that the ineligible patients had a longer median survival time than eligible patients (13mths vs 4.3mths) and the higher proportion of ineligible patients in the BSC group (9 vs 4 in the VFL plus BSC group) could explain why the treatment effect did not reach statistical significance for the primary ITT analysis population. It should be noted that the result for the VFL plus BSC group is exactly the same for the ITT and eligible ITT populations. (Clarification was sought from the manufacturer and results confirmed. See Appendix 1, A14). Another possible reason given in the MS for lack of statistical significance

in the ITT analysis of overall survival is the imbalance in PS which favoured the BSC group but it was not shown that the imbalance was statistically significant. Clarification was requested from the manufacturer and it was confirmed that there was no statistically significant difference between the groups in PS (see Appendix 1, A4). Therefore it is unlikely that this can be the explanation for lack of statistical significance in the ITT analysis.

Long term follow-up (42mths in the VFL plus BSC arm and 45mths in the BSC arm) published only in abstract form[2] showed similar results. OS was not significantly different between groups in the ITT population (VFL plus BSC 6.9 mths vs 4.6 mths for BSC, HR: 0.88 [95%CI: 0.70 to 1.10], p=0.26). In the eligible ITT population OS was significantly longer in treated patients (VFL plus BSC 6.9 vs 4.3 mths, HR: 0.78 [95%CI: 0.61 – 0.96], p=0.02). The planned multivariate analysis adjusting for prognostic factors in the ITT population showed a statistically significant effect of VFL on OS (p=0.025) with risk of death reduced by 23% versus BSC (HR: 0.77 [95%CI: 0.61 to 0.97]).

3.3.2 Summary of results for secondary outcomes

Secondary outcomes included response rates, disease control and PFS and are shown in Table 4. The overall and objective response rate (ORR, the total rate of CR and PR) as assessed in evaluable patients by the Independent Review Committee (IRC) was 8.6% in the VFL plus BSC group compared with 0% in the BSC group (p=0.0063). Disease control rate (CR + PR + SD) was significantly higher in the VFL plus BSC group, although there are differences between the results reported in different places within the MS and those presented in the published paper, dependent on the population analysed. Median duration of disease control and PFS are presented for the ITT population and were also significantly longer in the VFL plus BSC group compared with the BSC group.

Table 4: Secondary outcomes

Outcome	VFL + BSC	BSC	P value	Source in MS
Evaluable patients*	185	85		
Complete response	0 (0%)	0 (0%)	nr	Table B12, p45
Partial response	16 (8.6%)	0 (0%)	nr	Table B12, p45
Stable disease	86 (46.5%)	23 (27.1%)	nr	Table B12, p45
Progressive disease	83 (44.9%)	62 (72.9%)	nr	Table B12, p45
ORR % (95%CI)	8.6% (5.0 to 13.7)	0%	p=0.0063	Table B26, p62
Disease control rate (ITT analysis)	55.1% 41.1% (35 to 47.4)	27.1% 24.8% (17.3 to 33.6)	p<0.0001 p=0.0024	Text, p45 Table B13, p48 and Table B26 p62 and paper[1]
Duration of response, mths, median (95%CI)	7.4 (4.5 to 17.0)			

No of patients (ITT)	253	117		
Duration of disease control, mths median (95%CI)	5.7 (5.0 to 6.3)	4.2 (3.8 to 4.9)	p=0.0233	Text p45 Table B13, p48 Table B26, p62
Progression free survival, mths median (95%CI)	3.0 (2.1 to 4.0)	1.5 (1.4 to 2.3)	p=0.0012 HR 0.68	p45, FigB6 p46, Table B13, p48 Table B26, p62

* IRC best overall response for evaluable patients

In the abstract reporting long term follow-up[2] ORR, disease control and PFS all significantly favoured VFL plus BSC (p=0.006, p=0.002, p=0.001, respectively).

3.3.3 Sub-group analyses results

No subgroup analyses reported.

3.3.4 Mixed Treatment Comparison results

No mixed treatment comparison because no other RCTs exist in this population.

3.3.5 Summary of adverse events

An overview of the safety of VFL is provided in the MS. This is not based on adverse events reported separately by study arm for the RCT[1] but pooled data from the three included studies[1,3,4] for 450 treated patients.

The MS states that overall the most frequently observed adverse events with VFL were neutropenia, anaemia, constipation, fatigue and asthenia. However, data shown in Table B28 (MS page 64) from the 3 studies included for adverse events does not support this. The statement seems to refer to the RCT evidence alone as reported in the trial paper[1] and is shown below in Table 5.

Table 5: Most frequent adverse events associated with VFL as reported in the RCT

	VFL + BSC		BSC	
Adverse event	Overall n (%)	Grade 3 or 4 n (%)	Overall n (%)	Grade 3 or 4 n (%)
Neutropenia	190 (77.2)	123 (50)	3 (2.7)	1 (0.9)
Fatigue, asthenia	124 (50.0)	48 (19.3)	71 (60.7)	21 (17.9)
Anaemia	229 (93.1)	47 (19.1)	68 (61.3)	9 (8.1)
Constipation	118 (47.6)	40 (16.1)	29 (24.8)	1 (0.9)

The principal toxicity is reported in the MS to be neutropenia, which presumably refers to Grade 3 or 4 as reported in the trial paper.[1] Any grade of febrile neutropenia and infection associated with severe neutropenia are reported in the MS as 6.7% and 4.7% of patients respectively using the combined data from the 3 studies (MS Table B28, page 64).

Constipation is common, reported in 47.6% overall (16.1% Grade 3 or 4) of patients receiving VFL in the RCT[1] and 54.9% (15.3% Grade 3 or 4) in the combined analysis. Prophylactic use of laxatives is recommended.

The MS states that overall the safety profile of VFL is predictable, acceptable and manageable by prophylactic and therapeutic measures (MS page 65). This does not concur with clinical advice received by the ERG which is that VFL does not have an acceptable safety profile and is not well tolerated by patients, especially in relation to constipation which can be difficult to treat. In addition, the MS does not mention the vesicant (tissue blistering) nature of VFL which can result in patients suffering soft tissue damage at the site of infusion. (Clarification was requested from manufacturer; which states that due to lack of information on this for VFL it is not discussed, see Appendix 1).

3.3.6 Summary of Health related quality of life

Clinical benefit and QoL are briefly reported in the MS using the RCT[1] data. There were no statistically significant differences in overall HRQoL, as measured by the EORTC QLQ-C30, or in clinical benefit parameters between the group receiving VFL plus BSC and the group receiving BSC. The clinical benefit parameter is a composite measure (based on PS, weight, pain, analgesia, palliative radiaotherapy) but no details are given of the relative weighting of each factor which may impact on results, or whether it is a validated measure. More patients in the BSC group received at least one palliative radiotherapy treatment delivered earlier than in the VFL plus BSC group (23% vs 4%). It is not known whether this is due to factors relating to patients' QoL and clinical benefit or to the treating clinicians offering earlier palliative radiotherapy to patients not receiving any chemotherapy.

3.4 Summary

In summary it is not possible to say that the MS contains an unbiased estimate of treatment effect based on the single available RCT. The primary ITT analysis, which included participants who should not have been randomised, showed no statistically significant survival benefit from treatment, whereas the 'eligible' ITT analysis, which may not be valid due to the breaking of randomisation, showed statistically significant findings. There are also issues about the methodology of the RCT[1] in addition to the data analyses, relating to randomisation and blinding, which mean that bias cannot be ruled out. As both ITT and 'eligible' ITT analyses have methodological limitations and give different results it is difficult to reach firm conclusions about treatment effect. However, summaries of OS in the MS (Executive summary and on pages 47 and 61) emphasise the eligible participants ITT analysis and conclude there is a survival benefit.

There are also concerns that the participants in the RCT[1] may not be properly representative of patients in the UK who proceed to second line chemotherapy due to exclusion criteria restrictions relating to PS and neoadjuvant or adjuvant chemotherapy. In addition, there is too little information about QoL and clinical benefit measurements to be sure that the stated interpretation of the evidence is unbiased. In the MS the adverse event profile is considered to be reasonable but this does not concur with clinical information received by the ERG.

Due to these concerns about inadequacies in the analyses of OS, uncertainties about QoL, clinical benefit and adverse events, it is unclear whether the MS interpretation of the evidence is fully justified. The ERG opinion is that the data does not definitely show VFL plus BSC to be superior to BSC alone and that further work would be needed to clarify this.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

i) a review of published economic evaluations of VFL in the treatment of patients with advanced TCCU,

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of VFL plus BSC is compared with BSC in the treatment of patients with advanced TCCU.

4.1.1 Manufacturer's review of published economic evaluations

The MS conducted a systematic review of published economic evaluations of VFL in the treatment of patients with advanced TCCU. Studies were included if a) the study referred to VFL, b) the study population related to adult patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen and c) the study was an economic evaluation. The search yielded no pertinent studies and the MS concluded that there were no relevant cost effectiveness studies.

4.1.2 CEA Methods

The cost utility analysis uses a 'partitioned-survival' model to estimate the effect of treatment with VFL plus BSC compared to BSC in adult patients with TCCU who have failed a prior platinum-containing regimen. The results are presented as incremental cost effectiveness ratios (cost per quality adjusted life year (QALY) gained).

4.1.2.1 Natural history

The model has three mutually exclusive health states (Alive, pre-progression; Alive, post-progression; and Dead). The model calculates the proportion of patients in each treatment cohort that is expected to be in each health state, based on estimates of OS and PFS. For the BSC cohort, OS and PFS are taken from the RCT[1] for the eligible ITT population and a Weibull survival model is used to extrapolate beyond the duration of the follow-up in the trial. For the VFL plus BSC cohort, OS and PFS are derived by adjusting the BSC survival using the hazard ratio from the RCT[1] with the proportional hazards assumption. The model uses daily cycles with a time horizon of 5 years.

4.1.2.2 Treatment effectiveness

The clinical effectiveness data from the RCT[1] eligible ITT analysis, showing a relative benefit in time to disease progression (HR = 0.47) and a relative benefit in OS (HR = 0.7), were applied to the baseline BSC survival. The hazard of experiencing an event for patients receiving VFL plus BSC were assumed to be proportional to the event hazard rates in the BSC group, based on the finding from multivariate Cox regression analysis which adjusted for significant prognostic factors.

Adverse events were included in the model as additional costs of treating these events. The frequency of these events was based on those seen in the RCT.[1] Adverse events were included in the model for the most frequently experienced grade 3 and 4 adverse events of constipation, febrile neutropenia and abdominal pain.

4.1.2.3 Health related quality-of-life

HRQoL was incorporated in the model by applying health state utility values for the time spent in each health state. The utility value for pre-progression was obtained by transforming responses to the EORTC QLQ C-30 questionnaire item #30 ('How would you rate your overall quality of life during the past week' Scale 0-100), from the RCT,[1] using a published regression model (O'Leary, 1995[7]) (u=0.65).

The utility value for post-progression was derived from a HRQoL study for terminally ill lung cancer patients, that reported EQ-5D values (u=0.25).[8]

4.1.2.4 Resources and costs

Dosing data for VFL were derived from the RCT.[1] A mean dose of 287 mg/m^2, a mean cycle cost of £2,337, and a mean number of treatment cycles of 4.2 were used. VFL is available in vials of size 250 mg and 50 mg. The model assumed there was no vial wastage. VFL was administered intravenously in an outpatient setting.

BSC pre- and post-progression was assumed not to vary by treatment arm and included GP, community nurse specialists, health visitor, dietician and oncologist visits. Cost of palliative radiotherapy was included and varied between treatments, based on data from the RCT.[1] Other costs were also included for post progression, such as palliative chemotherapy and hospice care.

4.1.2.5 Discounting

A discount rate of 3.5% is used for future costs and QALYs (MS Table B30, p72).

4.1.2.6 Sensitivity analyses

Deterministic sensitivity analyses (DSA) are presented for most parameters. Additional analyses are presented for alternative analytical scenarios to estimate PFS and OS for VFL plus BSC and BSC. Probabilistic sensitivity analysis (PSA) was undertaken based on 1000 random iterations.

4.1.2.7 Model validation

The model was validated through a series of tests on the model's internal consistency, such as observing whether changes to the model inputs make the expected changes to the model results.

4.1.2.8 Results

Results are presented as cost per QALY gained, with incremental costs, QALYs and life years gained also presented separately. The base case analysis presents an incremental QALY gain of 0.131, with an additional cost of £13,071, and an ICER of £100,144 per QALY gained (see

Table 6).

Table 6: Base-case cost-effectiveness results

	BSC	VFL + BSC
Technology acquisition cost, £	0	9,485
Other costs, £	8,642	12,229
Total costs, £	8,642	21,714
Difference in total costs, £	N/A	13,071
Life Years Gained (LYG)	0.630	0.898
LYG difference	N/A	0.267
QALYs	0.234	0.364
QALY difference	N/A	0.131
ICER	N/A	100,144

The parameters that had the most effect on the model results in the MS DSA were the assumed acquisition cost of VFL, the number of cycles of therapy, the assumptions on wastage, and the health state utilities assigned to patients in pre- and post progression health states. The MS also states that the incremental clinical efficacy of VFL (OS and PFS) is a key driver of the cost effectiveness results although no analyses are shown for this parameter in the MS.

The results of the PSA for VFL plus BSC versus BSC were presented as the percentage of simulations in which VFL plus BSC is preferred to BSC for different cost effectiveness ceiling ratios (£/QALY) (1.1% for £25,000; 11.7% for £50,000; 45.6% for £100,000).

The MS also presents an 'end of life' analysis to be considered in light of NICE's recent publication of 'end of life' advice in health technology appraisals. [9] The MS justifies the inclusion to be appraised as an 'end of life' treatment by the following criteria:

i) The treatment is indicated for patients with a short life expectancy (5 months);
ii) There is evidence that the treatment offers extension to life (increases survival by 2.6 months);
iii) The treatment is licensed for a small population with an incurable illness.

According to NICE advice,[9] the MS should include the following information for an end-of-life analysis; the ERG agrees that this has been provided:

i) *the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age*, and
ii) *the magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold range*.

The MS uses a trial-based utility of 0.79 for a healthy individual of the same age for the post-progression phase, which results in a more favourable ICER of £61,890 per QALY (ICER value reported only in MS Executive Summary). The ratio of the new cost effectiveness estimate to the willingness-to-pay threshold of £30,000/QALY is 2.06.

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

4.2.1 Critical appraisal of economic evaluation methods

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 7 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[10]). In general, the MS is well reported and uses reasonable methodology although there are concerns about the comparator used, the derivation of the utilities and the effectiveness of the intervention.

Table 7: Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	ERG Reviewer Comment
Is there a well defined question?	Yes	MS Section 4, p21
Is there a clear description of alternatives?	Yes	VFL + BSC vs BSC
Has the correct patient group / population of interest been clearly stated?	Yes	The population included in the economic evaluation is adult patients with advanced or metastatic TCCU who have failed a prior platinum-containing regimen and directly reflects the population of the phase III RCT[1]

		and the scope. The population is within the licensed indication for VFL. However, the population may not necessarily be representative of clinical practice.
Is the correct comparator used?	?	VFL is compared to best supportive care. This is the correct comparator in terms of the scope and decision question. However, our clinical expert advised us that BSC is unlikely to be used; instead an alternative chemotherapy agent would routinely be used.
Is the study type reasonable?	Yes	Cost utility analysis
Is the perspective of the analysis clearly stated?	Yes	UK NHS and PSS
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	?	Effectiveness of intervention based on the RCT. The ITT analysis shows non-statistically significant benefit. CUA used estimate of effectiveness from eligible ITT population.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	
Are the costs and consequences consistent with the perspective employed?	?	Uncertainty around the utility estimates used as standard methods have not been used for health state utility values, i.e. rating scale used for one and the wrong patient group has been used for the other. (See section 4.3.2.3)
Is differential timing considered?	Yes	
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	

The MS only fulfils some aspects of the NICE reference case (as shown in Table 8). There are concerns over the derivation of the health state utility values and the comparator used.

Table 8: NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE	Yes
Comparator: Alternative therapies routinely used in the UK NHS	No
Perspective on costs: NHS and PSS	Yes
Perspective on outcomes: All health effects on individuals	?
Type of economic evaluation: Cost effectiveness analysis	Yes
Synthesis of evidence on outcomes: Based on a systematic review	Yes
Measure of health benefits: QALYs	Yes
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	No
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	No
Source of preference data: Representative sample of the public	No

Discount rate: 3.5% pa for costs and health effects	Yes

4.3 Critical appraisal of modelling methods in the manufacturer's economic evaluation

An outline critical review of modelling methods has been undertaken by the ERG. The review has used the framework for good practice in modelling presented by Philips and colleagues[11] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.3.1 Modelling approach / Model Structure

The MS provides commentary on the model structure, including a schematic of the model (MS p69, Figure B7). The MS describes the model structure as a 'partitioned-survival model', which is similar to a state-transition (Markov) model. The model has 3 mutually exclusive health states ('Alive pre-progression', 'Alive post-progression', and 'Dead'). The model calculates the proportion of patients in each treatment cohort that is expected to be in each health state, based on estimates of OS and PFS. The model time horizon was five years which corresponds to patient life time as less than 1% of all patients were still alive after 3.8 years. The model uses a cycle length of one day.

The MS states that the model structure is consistent with the clinical outcomes employed in oncology trials and specifically those in the RCT.[1] Furthermore, the MS justifies the use of PFS as patients are usually treated until disease progression and differences in costs and potentially HRQoL between the time periods before and after progression should be expected. The MS justifies these health states citing studies which have reported them to be key determinants of health state utility. The MS also states that similar methods have been employed in other UK based evaluations of the cost effectiveness of oncology interventions (eg lapatinib, bevacizumab).

Patients start in the state *Alive pre-progression* and are initially treated with VFL in cycles of 21 days, until disease progression, major toxicity or other reason for therapy discontinuation, or death (before progression). Patients who experience disease progression are assumed to discontinue treatment and transition to the *Alive Post-progression* health state and to remain in that state until death.

The model derives survival curves for OS and PFS for VFL plus BSC and BSC. An area-under-the-curve analysis is used to estimate mean time prior to disease progression and

mean survival. The difference between the two curves provides a direct estimate of the mean time alive following disease progression.

The ERG considers the modelling approach and model structure used by the manufacturer to be appropriate and reasonable.

4.3.1.1 Structural Assumptions

The OS and PFS survival curves for BSC were taken from the Kaplan-Meier (KM) data for the RCT.[1] A Weibull survival model was used to extrapolate OS and PFS for patients receiving BSC beyond the duration of follow-up in the RCT (i.e. 2.4 years) to the model time horizon of 5 years.

The VFL survival curves were derived by multiplying the BSC curves by hazard ratios obtained from a multivariate analysis. The MS has not justified or clearly explained the rationale for extrapolating the VFL OS and PFS curves in this way. The MS states that the hazard of experiencing an event (either disease progression or death) for patients receiving VFL plus BSC was assumed to be proportional to the event hazard rates in the BSC group, based on findings from multivariate Cox regression analysis. The regression adjusted for significant prognostic factors at randomisation or baseline, including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin. The MS has a scenario analysis that uses the KM survival data for both the BSC and VFL plus BSC survival curves.

4.3.2 Data Inputs

4.3.2.1 Patient Group

The patient group in this economic analysis is adult patients with advanced or metastatic TCCU who have failed a prior platinum-containing regimen and directly reflects the population of the phase III study. However our clinical expert suggests that the patients in this trial may not be representative of the majority of patients progressing after first line therapy; for example, the trial excluded patients who had received prior neoadjuvant or adjunvant platinum-based chemotherapy. No subgroups were considered by the analysis.

4.3.2.2 Clinical Effectiveness

Only one relevant RCT was identified and data were derived from this source.[1] The evaluation was based on patient-level data from this trial. BSC was used as the comparator in the trial. However, according to our clinical expert BSC is not often used as second line

treatment in the UK; instead an alternative chemotherapy agent would be used. The trial data has been reported in several formats, including ITT and eligible ITT. For the model, data from the eligible ITT analysis were used. However the ERG is concerned that this may be an inappropriate source and it would be more appropriate to use the ITT analysis (as discussed in section 3 above).

All the inputs to the model are listed in the MS, but there is some confusion over the source of some of these inputs (see section 4.3.3.1). The relative hazard ratio for OS in the modified ITT population used in the model differed from that reported in the trial (HR = 0.7 vs 0.78). The hazard ratios used in the model were derived from a separate multivariate Cox regression analysis that adjusted for the five prognostic factors. The MS states that the effect of VFL plus BSC on OS and PFS was statistically significant after adjusting for these prognostic factors. The MS does not present the regression analysis so the ERG is unable to comment upon it. The manufacturer states that they used the Grambsch and Therneau test to show that there was not a violation of the proportional hazards assumption, but the MS does not present these analyses.

4.3.2.3 Patient outcomes

HRQoL estimates were used for the health states for *Alive, pre-progression* and *Alive, post-progression*. The MS states that a systematic search was conducted to identify published reports providing information on HRQoL among patients with TCCU but no studies were found relevant to the decision problem. Furthermore, the RCT did not collect EQ-5D data although it did collect EORTC QLQ-C30 data. The MS states that there were no mapping algorithms available to map from EORTC QLQ-C30 to EQ-5D. The ERG notes, however, that there are two available mapping algorithms for transforming EORTC QLQ-C30 data to EQ-5D which could have been used: McKenzie and van der Pol[12] and Kontodimopoulos and colleagues.[13]

The mean EORTC-QLQ-C30 score (for one question) was converted into a utility index using a published regression model (O'Leary 1995[7]) for the *Alive, pre-progression* health state utility values. It was assumed that the *Alive, pre-progression* health state utility values were the same for VFL and BSC cohorts. The MS did not present data for each of the cohorts.

Alive, pre-progression health state utility values were estimated by transforming response values for the EORTC-QLQ-C30 questionnaire #30 ('How would you rate your overall quality

of life during the past week'? scale 0-100) using the functional relationship between rating scale values and time-trade off utilities (O'Leary 1995[7]):

T = 1.18 x R for R <= 85%

T = 1 x R >= 85%

The MS provides details of when the questionnaire was given (MS, p83) and the numbers of patients who were evaluated. The MS does not include the last assessment evaluated as it was expected it would reflect the impact of disease among some patients. A utility value of 0.65 was used for pre-progression. The MS states this value is consistent with utility values from other studies for advanced cancers.

Post progression values were used from a study for a different population[8] reporting EQ-5D values in a sample of 1270 terminally ill lung cancer patients. The mean EQ-5D value of 0.25 was for the last 6 months of life. The MS states that the values for post progression are consistent with those from other studies for terminal cancer patients.

The ERG considers that the utility values used in the economic evaluation do not fit with the NICE reference case. For the pre-progression health state utility value (HSUV) they have not used EQ-5D or other approved generic questionnaire or used Standard Gamble or Time Trade Off. For the post progression HSUV, they have used a HSUV from a different patient group. The ERG suggests that there is considerable uncertainty around the utility estimates used in the model due to a lack of utility studies for the appropriate populations or appropriate methodology.

4.3.2.4 Resource use

The MS conducted a targeted literature search on medical resource use and cost but this yielded no data and so clinical advisors provided information to the manufacturer on the frequency of resource use. Resource use for BSC pre and post-progression was assumed not to vary by treatment arm and included GP visits, community nurse specialist, health visitor, dietician and oncologist. Also included was resource use for palliative radiotherapy and chemotherapy. The estimation of use of palliative radiotherapy (pre- and post-progression) was supplemented with analyses of data from the included RCT.[1]

The proportion of patients receiving palliative radiotherapy (3.3% vs. 22.2%) and mean radiation dose (16.2 Gys vs. 26.9 Gys) was lower for VFL patients than for BSC patients, based on findings from the RCT[1] for pre-progression. For post-progression, more patients

with VFL than BSC had radiotherapy (22.1% vs. 15.7%) and the dosage was the same for both groups.

Post-progression also included the resources for hospice care based on data from a published survey of 17 breast cancer specialists. In that survey, 70% of patients were estimated to have received hospice care (30% day visits, and 40% averaged five overnight stays). Roughly a third of patients (VFL plus BSC 29% vs. BSC 34.2%) of patients received palliative chemotherapy, based on findings from the RCT.[1] Patients received two cycles of either gemcitabine; methotrexate, carboplatin and vinblastine ('Mvcarbo'); or docetaxel.

Resources associated with adverse events were included for the most frequently experienced grade 3 and 4 events: constipation (VFL plus BSC 20.2% vs. BSC 0.9%), abdominal pain (VFL plus BSC 1.2% vs. BSC 0.7%) and febrile neutropenia (VFL plus BSC 5.2% vs. BSC 0%). Clinical management of constipation was assumed to include one GP consultation and use of laxatives. Febrile neutropenia and abdominal pain were assumed to include an elective and non elective hospitalization. The ERG notes that there were minor differences (~1%) between actual values reported in the trial and those used in the model.

4.3.2.5 Costs

The price year for costs was 2009; where 2009 costs were not available, cost data from the nearest possible year were reported and inflated where necessary. Costs were based on the latest National Reference Group for 2007/08[14] for hospital procedures and consultations and were taken from Curtis 2007[15] for health professional staff costs.

The ERG checked the unit costs presented and these appeared to be correct and reasonable. There were minor differences, such as the one in the cost of bisacodyl 5mg in the MS which differs from that reported in the British National Formulary (BNF),[16] and the cost for abdominal pain presented in MS Table B32 and used in the model as £577, which is shown in MS Table B40 as £551. The ERG checked the calculations used for the resources and these all appeared correct except for the palliative therapy costs for which the ERG obtained a similar but different cost from the data in the MS.

Treatment cost is calculated from therapy given (doses administered) in the RCT,[1] using a price supplied in the MS. According to the Summary of Product Characteristics (SPC),[17] the recommended posology is 320 mg/m² VFL as a 20 minute intravenous infusion every 3 weeks. VFL is supplied as individual vials containing 250 mg or 50 mg VFL at a concentration of 25 mg/mL. In the case of WHO/ECOG PS 1 or 0 and prior pelvic irradiation,

the treatment should be started at the dose of 280 mg/m². In the absence of any haematological toxicity during the first cycle causing treatment delay or dose reduction, the dose should be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

The cost of VFL is £1,062.50 per 250 mg vial or £212.50 for 50mg.[18] The dosage used in the model was assumed to be equal to the mean reported dose in the RCT[1] (287 mg/m^2). A patient's average body surface area was assumed to be equal to the mean reported body surface area (1.85 m^2) in the RCT. There was assumed to be zero vial wastage in the base case. The ERG notes a discrepancy in dose used: the MS reported that the cost was £2,337.50 per cycle (MS Table B37), equivalent to two large vials and one small vial (550 mg), whereas in the model, patient dosage was 530 mg (£2,257), equivalent to two 250 mg vials and a shared 50 mg vial). The ERG's clinical advisor stated that a patient's dose would be rounded up to the nearest whole vial. The ERG considers the estimate for the cost of VFL to be a reasonable estimate.

Treatment continued until disease progression, patient refusal, other reasons for discontinuation (e.g. unacceptable toxicity) or death, according to information in the RCT.[1] The mean number of cycles was 4.2.[1] VFL was assumed to be administered in the outpatient setting, as seen in the RCT. The cost of IV administration was assumed to be based on NHS HRG costs (2007/8). The ERG notes that the costs of IV administration roughly doubled in the next year (2008/9). There were also monitoring costs for complete blood counts prior to administration of each cycle of chemotherapy and constipation prophylaxis (one week).

The ERG considers that the estimation of costs and resource use to be reasonable.

4.3.3 Consistency

4.3.3.1 Internal consistency

The model is fully executable and user-friendly with the analysis options contained in the spreadsheet "Analyse". However, the fact that the model is mostly run by Visual Basic for Applications (VBA) programming, makes it non-transparent. The ERG obtained logical results when varying inputs, for instance while conducting sensitivity analyses. However, some differences between the ERG and the MS results were found as detailed later in this section.

The MS reports a summary of the tests performed to assess the model's internal consistency in Table B48 of the MS (p.107). These involved setting main parameters to extreme values, for instance utilities to 1 or 0, and checking whether the observed effect matched the expected one. The MS states that no actions were required since the model produced the expected results. The ERG confirmed some of the validation tests' results reported by the manufacturer.

The ERG did not check comprehensively all cells in the model. Random checking was done by the ERG for some of the key equations of the manufacturer's model, for instance in some of the spreadsheets that involve trial data transformation; the selection of data sets for analysis; calculation of disaggregated mean survival results, QALYs and costs for each strategy; VBA code for ICER calculation and results summary; and the random sampling of the variables' mean values for probabilistic sensitivity analysis.

In the spreadsheet "Analyse" the user can choose which input set to use as this sheet provides the mean and SE estimates for each parameter in the model. Parameter inputs used for the base case analysis are reported in Table B32 of the MS (p.78). The ERG identified some differences between this table and those values used in the model and these can be found in detail in 7.1.

In MS Table B32, under the column labelled "Source", the manufacturer cross-refers to other MS sections. However, the cross-references do not match the sections in the MS (for instance, section 6.5.1 does not relate to the variable it is associated with in the table, and sections 5.9, 6.5.5, 6.5.6, 6.5.7 do not exist in the MS). The sections referred to in table B32 match the ones of the current template [Specification for Manufacturer/Sponsor Submission online version published on 15 July 2010];[19] however, an older version of the template was actually used in the MS.

The model deterministic results for the base case analysis match those reported in the MS for the ITT modified analysis, which corresponds to using data from the eligible ITT population from the RCT[1] (MS Table B44, p.102). Similarly, the results for the sensitivity analyses presented in the MS Table B45 (p.103) match the ones obtained by the ERG. Differences between the MS and results obtained by the ERG are detailed in Table 10 (section 4.3.4.1).

The ERG ran the PSA and found similar results as the ones reported in the MS p.104-105 (MS Tables B46a and B46b, and Figures B11a (scatterplot) and B11b (CEAC)). This

analysis was conducted for 1,000 iterations. The manufacturer does not provide any justification for selecting this number of iterations for the PSA.

4.3.3.2 External consistency

In general, the results of the model make intuitive sense. The MS does not refer to any model calibration against independent data. The survival model used for the base case analysis was compared to alternative approaches to modelling survival in two scenario analyses conducted by the manufacturer (further details provided in section 4.3.4.3). According to the MS (p 108), comparisons of findings are not possible, given that no previous models have been identified.

However, running the ITT analysis with a VFL acquisition cost of £1,062.50 per 250 mg vial provided an ICER of £99,792 per QALY gained, i.e. similar to the one obtained for the ITT Modified base case analysis (£100,144 per QALY gained). The ERG notes that the only variables in which these analyses differ are the HR values (Table 9). Given that the HR of the ITT analysis is a less favourable effectiveness estimate, the ICER would be expected to increase instead of decrease. The ERG confirmed that this result is in fact correct, being driven by differences in the survival data from each analysis (ITT and ITT modified).

A more intuitive result was obtained by the ERG when the analysis was re-run with KM estimates only (from the trial data), and in this case the ICER became £126,422 per QALY.

Table 9: Hazard ratios obtained from ITT and ITT modified analyses

	ITT mean (SE)	**ITT Modified** mean (SE)
Hazard ratio OS	0.770 (0.0978)	0.690 (0.0877)
Hazard ratio PFS	0.530 (0.0570)	0.470 (0.0582)

The ERG has compared the survival curves in the model for consistency with the trial data. These curves are shown for OS in Figure 1. This figure shows that the base case analysis overestimates the benefits of VFL compared with the KM trial data (in the post progression period). The analysis using a gamma distribution as an approximation to the survival curve shows a reasonable fit to the trial data. The MS presents scenario analyses for the alternative methods for fitting the survival curves. The ERG suggests that the most realistic results are those using the KM data or the gamma modelled data for VFL. However the choice of alternative survival curves does not have a significant impact on the model results

and the results vary between £100,000 and £105,000 per QALY gained for all analyses. Therefore the ERG suggests that the base case analysis used by the model is a reasonable approach.

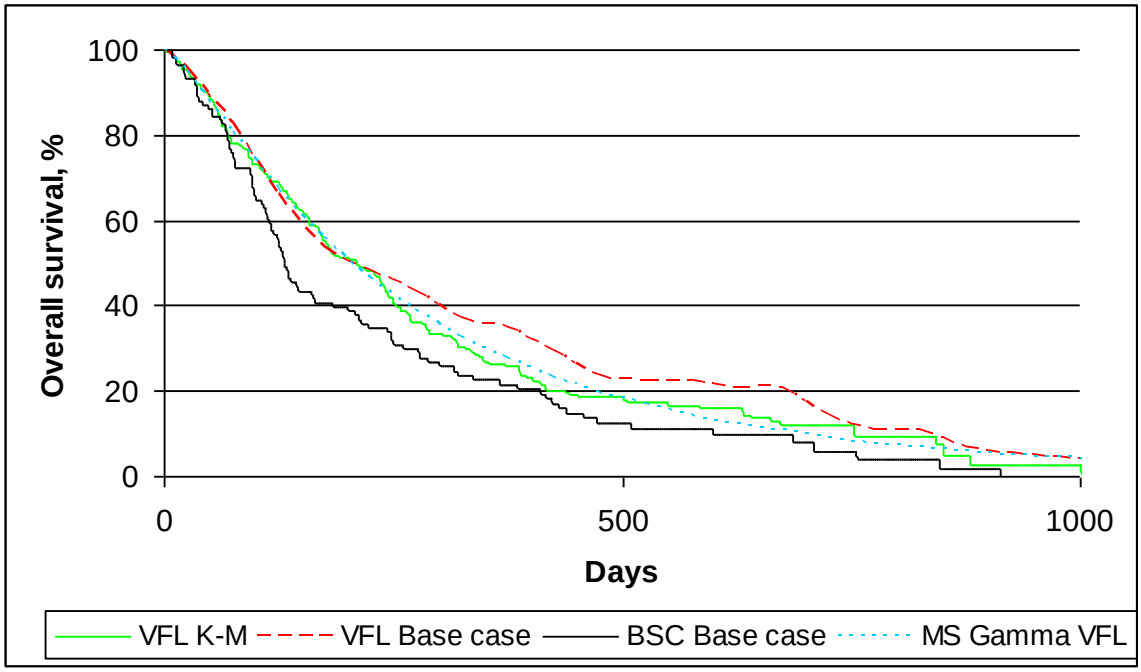


Figure 1: Overall survival in the eligible ITT population for trial analysis (KM), base case and gamma estimate

4.3.4 Assessment of Uncertainty

The MS reports results for the assessment of parameter uncertainty (p.103-105) performed via both one-way sensitivity analysis and probabilistic sensitivity analysis (PSA). Assessment of structural uncertainty is presented as well under the scenario analysis section (MS p.98, 105 and 106), where alternative types of survival analyses (different methods for estimation of clinical effect) were considered.

4.3.4.1 One-way sensitivity analyses (DSA)

According to the MS (p.99), DSA were conducted either using variables' 95% CI estimates or, when alternative mean estimates were not available, the manufacturer multiplied the base case value by factors of 0.5 and 1.5 (MS p.98). The following variables were subject to DSA (MS p.103): acquisition cost of 250 mg vial of VFL; VFL vial wastage; body surface area; number of cycles of therapy; VFL cost of outpatient administration; model time horizon; risk of adverse events; cost of adverse events; cost of BSC per month of PFS; cost of BSC per month of post progression survival (PPS); cost of palliative RT per month of PFS and PPS; cost of palliative CT per month of PPS; health state utility of PFS; health state utility of PPS reduction; and discount rate. In addition to the omitted variables reported by the

manufacturer (vial size and risk of side effects, MS p.98), the hazard ratio estimates were also not subject to sensitivity analysis.

The values/ranges chosen for DSA are clearly stated in Table B45 (MS p.103); however, the rationale for their use is not explained. In some cases the selected ranges consider only values below the mean value, instead of a lower and a higher value as the CI lower and upper limits. Furthermore the ERG considered that some of the values chosen were unrealistic, such as zero cost for VFL.

The manufacturer found that the ICER for VFL plus BSC vs BSC ranged from £27,478 - £133,094 per QALY in the DSA conducted (MS Table B45, p.103). The greatest variations of the ICER were caused by changes in health state utilities (particularly for post progression), the acquisition cost of VFL, the number of cycles with VFL, and VFL vial wastage, shown in Table 10 below. Additionally, the manufacturer states that another key driver of the cost-effectiveness results is the incremental efficacy of VFL. However, effectiveness estimates were not tested for in sensitivity analysis. In general, the ERG obtained the same DSA results as the ones reported in MS table B45. The differences between the MS and results obtained by the ERG are detailed in Table 10. As the MS does not describe clearly how the DSA was conducted the reason for the discrepancies found is not clear. The main implication is that the ICER is found to vary up to £133,094 per QALY in the MS DSA, compared to £162,734 per QALY in the DSA conducted by the ERG, for the health state utility for PFS.

Table 10: Results of DSA on parameters that caused most variation on ICER

Parameter	Base case value	DSA value	ICER (£/QALY) *(ERG value)*	Difference from base case (£/QALY)
VFL acquisition cost (250 mg vial)	£1,062.5	£0	27,478	-72,666
		£200	41,156	-58,988
		£400	54,835	-45,309
VFL vial wastage	287 mg/m^2	297 mg/m^2	102,676	2,532
		Based on assumed distribution of BSA	121,095 *(121,085)*	20,591
Number of cycles of treatment	4.2	3	70,233 *(70,223)*	-29,911
Model time horizon	5 years	Trial based (2.4 years)	88,236 *(102,726)*	-11,908
Health state utility PFS	0.65	0.7	76,054 *(92,991)*	-24,090
		0.5	106,474 *(130,187)*	6,330
		0.4	133,094 *(162,734)*	32,950
Health state utility PPS reduction	61%	20%	81,904	-18,240
		30%	85,712	-14,432
		40%	89,891	-10,253
		50%	94,498	-5,646

4.3.4.2 ERG sensitivity analysis

The ERG has undertaken additional sensitivity analyses to those presented in the MS. Sensitivity analyses were run for changes in the HR for OS and PFS using the confidence intervals around these data used in the model (see Table 11). The model results are fairly robust to changes in HR. For these analyses, the cost effectiveness ratios ranged from £87,871 to £117,938 per QALY.

Table 11: ERG one-way sensitivity analyses

		Input		ICER (£/QALY)		
Variable	**Base case**	**Low**	**High**	**Low**	**High**	**Range**
Hazard ratio OS	0.69	0.52	0.86	£87,871	£117,938	£30,067
Hazard ratio PFS	0.47	0.36	0.58	£88,845	£111,923	£23,078

4.3.4.3 Scenario Analysis

According to the MS (p.98, 105-106), structural uncertainty was explored by conducting scenario analyses on two alternative methods of estimation of VFL effectiveness. While the base case analysis relied on KM estimates for BSC and a multivariate-adjusted HR for VFL, the first scenario analysis was performed using KM estimates for both BSC and VFL. The second scenario analysis used gamma modelled parameters from both BSC and VFL trial data. The gamma parameter estimates for BSC are presented in MS Appendix 9.14 (p.139) as well as the plots of the KM and gamma survival curves for OS and PFS.

These analyses seem reasonable but there is a lack of explanation of the selection of these functions, or the results obtained. The justification for the use of the multivariate adjusted HR for VFL in the base case analysis instead of using KM estimates for both treatment arms is lacking. Additionally, the goodness-of-fit of gamma and Weibull models and subsequent choice of the Gamma function for scenario analysis were not discussed by the manufacturer.

Regarding the main findings from the scenario analyses, the manufacturer only presents the ICERs and their difference from the base case ICER in MS Table B47 (p.106), as presented in Table 12 below.

Table 12: Scenario analyses results

Scenario	**ICER (£/QALY)** ***(ERG value)***	**Difference from base case (£/QALY)** ***(ERG value)***
Base case	100,144	
KM (trial duration)	104,751 *(104,158)*	4,607 *(4,014)*
Gamma (5 years)	103,370	3,226

There is no discussion in the MS of the scenario analyses results, and no discussion on the most appropriate method for estimation of the clinical effectiveness of VFL.

4.3.4.4 ERG scenario analysis

The model provides two analyses ‘ITT modified’ and ‘ITT’ which correspond to using data from the eligible ITT and ITT populations from the RCT.[1] Parameter inputs are contained in the “Defaults_ITT” and “Defaults_ITTMOD” spreadsheets. The differences between these two data sets are shown in Table 13.

Table 13: Differences in parameter inputs between ITT and ITT Modified analyses

Parameter name	Worksheet "Defaults_ITT" mean (SE)	Worksheet "Defaults_ITTMOD" mean (SE)
VFL acquisition cost (250mg vial)	£854[a]	£1,062.50
Hazard ratio OS	0.770 (0.0978)	0.690 (0.0877)
Hazard ratio PFS	0.530 (0.0570)	0.470 (0.0582)
[a] corresponds to 80% of £1,062.50 (the acquisition cost stated by the manufacturer for 250mg VFL vial, MS p.12)		

The ERG undertook a scenario analysis using the ITT population, rather than the modified ITT population, as these results were not presented in the MS. Using the corrected VFL cost, these analyses produced ICERs of £99,792 per QALY gained using the multivariate analysis method (base case) and £126,422 per QALY gained using the KM trial data.

4.3.4.5 Probabilistic Sensitivity Analysis

The MS probabilistic sensitivity analysis (PSA) is run by pressing the option "probabilistic sensitivity analysis" on the "Analyse" spreadsheet of the model, which activates a VBA macro that takes approximately an hour to run 1,000 simulations and present the summary results on spreadsheet "ProbSensSummary". Total and incremental discounted costs and QALYs, and the ICER per iteration are presented on spreadsheet "ProbSensRes". The manufacturer did not present the rationale for choosing 1,000 iterations for the PSA, nor discuss the PSA results.

PSA results are reported in the MS (p.104) in Table B46a in terms of the number of simulations per cost effectiveness scatterplot quadrant and 95% CI for discounted costs and QALYs and for the ICER (as shown in Table 14 below). The expected mean PSA results (mean discounted incremental cost and QALY and the mean ICER) are not reported in the MS; Table B46a reports only their 95% CI.

Table 14: PSA summary results

	Value
Number of simulations	
NE	92%
SE	0.1%
SW	0.0%
NW	7.9%
CI discounted QALYs	(-0.029, 0.291)
CI discounted Cost	(5,977;20,791)
CI ICER	(32,288, dominated)

The MS also presents PSA results graphically on a cost effectiveness scatterplot (MS Figure B11a, p104) and on a CEAC (MS Figure B11b, p105). The probability that VFL is cost effective [P(CE)] is reported (MS Table B46b , p.105) for 6 different cost effective ceiling ratios, as presented in the following Table 15. The range of ceiling ratios chosen is not very informative considering NICE's cost effectiveness threshold of £20,000 – 30,000 / QALY. The MS does not provide any explanation of the selection of the considered ceiling ratios. Additionally, on page 106, the manufacturer states that the probability of VFL being cost effective at a £30,000 per QALY threshold is 6%.

Table 15: Probability of VFL being cost effective

CE Ceiling Ratio (£/QALY)	P(CE) (%)
25,000	1.1
50,000	11.7
75,000	29.9
100,000	45.6
125,000	55.4
150,000	62.6

MS Table B32 (MS p.78) shows the variables included in the PSA, including their mean values, distributions assigned and variability estimates. According to the MS (p.99), standard errors for the risks of side effects, medical resource use and NHS reference unit costs were not available, and so these were estimated by assuming a standard error of 25% of the mean base case value.

Overall, parameter inputs reported in Table B32 of the MS (p.78) for the PSA correspond to the ones input in spreadsheet "Defaults_ITTMOD", which have been used for the base case analysis. However, some differences between model base case inputs and table B32 were

found and are shown in 7.2. The following variables have not been included in the PSA: VFL vial size, cost per vial, cycles per year and average body surface.

In general, the distributions assigned to each parameter type were reasonable. Costs and HR were assigned the lognormal distribution, whereas the beta distribution was applied to risks of adverse events and utilities (MS p.78 and 99). The normal distribution was only used for VFL dose delay.

Despite stating in Table B32 (MS p.78) that the beta distribution was assigned to both treatments' pre-progression utility, in the model for VFL this parameter was assigned the gamma distribution and random sampling of its value is given as "not applicable" (spreadsheet "Variables"). In the base case analysis, the pre-progression utility for the VFL arm was assigned the gamma distribution, while the beta distribution was used for the other utilities. In practice, the pre-progression utility value is not randomly sampled in the PSA and kept fixed.

Summary of assumptions for manufacturer's PSA:

- The health state utilities and the risks of adverse events are assumed to be beta distributed, except for the pre-progression health state utility for VFL which is fixed (in the MS model).
- VFL acquisition cost is assumed to be fixed.
- Average body mass and the number of cycles of VFL treatment per year are assumed to be fixed.
- The standard errors of variables for which no variation estimates were available were assumed to be 25% of the corresponding mean value.

4.3.4.6 ERG Probabilistic Sensitivity Analysis

The ERG conducted two PSAs with HR from the ITT and the ITT modified analyses. In contrast to the MS base case analysis, both ERG PSAs also incorporated the uncertainty associated with the following parameters: VFL acquisition cost (standard errors assumed to be 25% of the mean value, as per MS), pre-progression utility (assigned beta distribution), and average body mass (SE= 0.19 and assumed to be normal distributed according to trial data). Table 16 presents the mean and SE values and distributions used for these variables.

Table 16: Variables updated for ERG PSA

Variable	Mean value	SE	Distribution
VFL acquisition cost, £	1,062.5	265.63 [a]	Lognormal
Pre-progression utility	0.65	0.01	Beta
Average body mass area (m^2)	1.85	0.19	Normal
[a] 25% of mean value			

Table 17 shows the results from the ERG PSA. Generally the results for the ITT and ITT modified analyses were similar to each other and to the MS deterministic base case.

Table 17: ERG PSA results

	ITT analysis	ITT modified analysis
Credible interval[a] for discounted incremental QALY	(-0.041, 0.291)	(-0.033, 0.297)
Credible interval for discounted incremental Cost	(4,546; 23,848)	(5,283; 23,112)
Credible interval for ICER	(24,688; Dominated)	(27,994; Dominated)
Median ICER (£/QALY)	105,541	101,941
P(CE) at £20,000/QALY (%)	1.4	0.5
P(CE) at £30,000/QALY (%)	3.3	3.1
[a] Credible intervals calculated using 2.5% and 97.5% percentiles		

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

In general the approach taken to model disease progression and cost effectiveness in this patient group seems reasonable. A number of concerns have been raised above by the ERG, some general and some specific.

4.3.6 Summary of uncertainties and issues

- The MS uses BSC as a comparator for VFL. The ERG believes this is an inappropriate comparator as it is not normally used in UK treatment practice although there are no RCTs of relevant comparators for the population of interest.
- The MS uses data from the eligible ITT analysis, rather than from the ITT analysis. However the ERG is concerned that this may be an inappropriate source and it would be more appropriate to use the ITT analysis.
- There is large uncertainty around the utility estimates used in the MS as standard methods have not been used for health state utility values, i.e. a rating scale was used for the pre-progression health state and the wrong patient group was used for the post-

progression one. The ERG suggests that a better approach would be to derive EQ-5D utility values by transforming available EORTC-QLQ C30 data for this patient group using an existing mapping algorithm.

5 DISCUSSION

5.1 Summary of clinical effectiveness issues

The MS includes evidence on the effectiveness of VFL plus BSC compared with BSC from one RCT supported by two uncontrolled Phase II studies. Results presented in the MS suggest that VFL plus BSC is superior to BSC in OS and PFS although whether these are unbiased estimates of effectiveness is uncertain.

5.2 Summary of cost effectiveness issues

The MS includes a cost utility analysis for VFL plus BSC compared with BSC. The results from the economic analysis have not demonstrated that VFL is a cost effective treatment compared to BSC.

6 REFERENCES

1. Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G *et al*. Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract. *J Clin Oncol* 2009;27:4454-61.

2. Culine, S., Lucas, C., Salhi, Y., and Bellmunt, J. Updated survival results of the phase III trial comparing vinflunine (V) to Best Supportive Care (BSC) in advanced Transitional Cell Carcinoma of the Urothelium (TCCU) after failure of a prior platinum-containing regimen. 25th Annual EAU Congress http://www.uroweb.org/publications/abstracts-online/?id=108&no_cache=1&AID=26994. 2010.

3. Culine S, Theodore C, De Santis M, Bui B, Demkov T, Lorenz J *et al*. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Brit J Cancer* 2006;94:1394-401.

4. Vaughn DJ, Srinivas S, Stadler WM, Pili R, Petrylak D, Sternberg CN *et al*. Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma. *Cancer* 2009;115:4110-7.

5. Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness. CRD Report 4 (2nd Edition). 2001. York, University of York.

6. Gerharz EW, Mansson A, Mansson W. Quality of life in patients with bladder cancer. *Urol Oncol* 2005;23:201-7.

7. O'Leary J, Fairclough D, Jankowski M, Weeks J. Comparison of time trade-off utilities and rating scale values of cancer patients and their relatives: Evidence of a possibly plateau relationship. *Med Decis Making* 1995;15:132-7.

8. van den Hout, W. B. EuroQol data in terminally-ill cancer patients (Poster). 10th Biennial European meeting of the Society for Medical Decision Making. 2006.

9. National Institute for Health and Clinical Excellence. Appraising life-extending, end of life treatments. 2009.

10. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313:275-83.

11. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8:iii-xi, 1.

12. McKenzie L, van der PM. Mapping the EORTC QLQ C-30 onto the EQ-5D Instrument: The Potential to Estimate QALYs without Generic Preference Data. *Value Health* 2008.

13. Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the Cancer-Specific EORTC QLQ-C30 to the Preference-Based EQ-5D, SF-6D, and 15D Instruments. *Value Health* 2009.

14. Department of Health. NHS Reference Costs. UK: 2008.

15. Curtis L. Unit costs of health and social care. University of Kent, Canterbury: Personal Social Services Research Unit; 2008.

16. Joint Formulary Committee. *British National Formulary 59*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2010.

17. Summary of Product Characteristics for Vinflunine. 2010. European Public Assessment Report No. Published 09/02/10

18. MIMS. MIMS March 2010. Monthly Index of Medical Specialities; 2010.

19. NICE. Single Technology Appraisal - Specification for manufacturer/sponsor submission of evidence. http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp?domedia=1&mid=4D9D8C83-19B9-E0B5-D4B0E148B3FE727F (accessed 1 September 2010)

7 APPENDICES

7.1 Appendix 1: Clarifications from the manufacturer and excluded references list

Pierre Fabre Response to Clarification Requests

Section A: Clarification on effectiveness data

A1. Page 21: Table A3, decision problem). Please explain asterisk in outcomes box.

Response: Study 302 is the only randomised study at this stage of treatment and there is no comparable response rate data. The implications for patients entering studies that randomised against BSC tend to recruit patients that are closer to the end of life, with relatively high tumour burden and relatively short expected survival, as discussed in 2.6 (page 17). In these circumstances, when we have been commissioned to respond to a scope that includes "Response rates", we sometimes draw on results from published phases II studies, even if it is only to set an expectation. This would be unfair as patients entered into cancer phase II studies tend to be much fitter than those willing to be randomised to BSC, with a smaller tumour burden and an objective response (and longer survival) is more likely. An apparent response rate of 29% (gemcitabine) in a phase II would normally be expected to prompt urgent development of the indication but clearly did not (see page 111 point (3)). This asterisk was to remind us to explain why we had not compared response rates. Clearly we forgot, so thank you for this opportunity for a supplementary response.

A2. (Page 24). Please explain why non-inferiority trials were explicitly stated as an exclusion criterion whereas equivalence trials were not.

Response: The term non-inferiority was used to generically describe trials that were designed to reject the possibility that differences in treatment effects equal or exceed preset limits and therefore included both non-inferiority and equivalence trials. In retrospect it would have been better to use both terms in the Table on page 24.

A3. (Page 25). Please supply a list of the 77 excluded references grouped by reason for exclusion, plus any other excluded references that relate to second line therapy.

Response: These references are in the appendix accompanying this response, grouped under reasons for exclusion headings. Appendix of excluded papers). They are summarised by; numbers of papers in each excluded group, the titles and citations of the papers in each group and citations with abstracts of the papers in each group.

A4. (Page 30: Table B6) Was the difference in performance status between the VFL+BSC arm and the control arm statistically significant?

Response: The difference in performance status between the Vinflunine+BSC arm and the control arm was not statistically significant (p=0.071)

A5. (Page 30: Table B6). Were the differences in prior cisplatin therapy and prior carboplatin therapy between the vinflunine plus BSC arm and the control arm statistically significant?

Response: The difference in prior cisplatin/carboplatin therapies between the vinflunine plus BSC arm and the control arm was globally not statistically significant (p=0.114).

- The difference in prior cisplatin therapy between the vinflunine plus BSC arm and the control arm was not statistically significant (p=0.153) while the difference in prior carboplatin therapy between the vinflunine plus BSC arm and the control arm was statistically significant (p=0.044).

A6. (Page 30: Table B6). Please clarify sample size for prior CTx.

Response: The number of patients with data does not match the total for each group because the dates of relapse or progression after first line were missing for patients who did not receive a first line chemotherapy for advanced disease, or non applicable for three patients in the control arm who have never progressed after the first line chemotherapy.

A7. (Page 31). Response rates are listed as secondary outcomes. This appears inconsistent with an earlier statement in the manufacturer submission (MS; p. 21) that there would be no comparative data for response rates in this end of life population with a heavy tumour burden. Please clarify.

Response: See response to A1 above.

A8. (Page 31). Quality of life and clinical benefit are included as outcomes but are not classified either as primary or secondary outcomes – instead they are referred to as "other criteria". What does this mean and how does it influence their analysis and interpretation?

Response: According to the protocol (section 2.2), Quality of life and clinical benefit are considered as secondary outcomes.

A9. (Page 31-32). Please clarify the relationship between the independent review committee (IRC), independent review panel (IRP), independent response review panel (IRRC) and Synarc. It is stated later in the MS that the IRC was blinded to the intervention received. Does this blinding apply to IRP, and IRRC and Synarc?

Response: The independent review panel (IRP) was consulted to review tumour assessments of data for investigator-identified responders and patients with long duration of stable disease in the vinflunine plus BSC arm only; as per the original charter this review was not blinded.

A second independent, blinded review (IRC) of all tumour assessments for all patients in both arms was scheduled at the end of study in order to better substantiate the response rate and progression free survival and ensure the comparability of both arms in respect of these items. For this purpose Synarc Inc. a contract Research Organisation (CRO), was committed to perform this blinded independent review.

The Independent Response Review Committee (IRRC) only pertains to one of the phase II studies (Vaughn et al Cancer 2009;115:4110-7) and was the body that reviewed all tumour assessments and the duration of response or stable disease.

A10. (Page 32). Please explain the rationale for the superiority hypothesis. Only two publications referred to on page 32 (von der Maase 2000; Sternberg 1988) and two different publications are referred to on page 38 (Culine et al. 2006; von der Maase et al. 2006 – the latter not in the reference list).

Response: When the protocol was written, there was still no standard salvage therapy for patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) whose disease has progressed after or during a prior platinum-containing regimen. These patients have a poor prognosis and a median survival rarely exceeded 3 to 6 months (von der Maase 2000; Sternberg 1988).

The analysis of data from the first Phase II study (L 00070 IN202 P1) of VFL as second-line therapy conducted in Europe, showed that overall survival (OS) was 6.6 [4.8-7.6] months respectively (Culine et al, 2006). This observation suggested that vinflunine might improve survival for patients with TCCU who had been previously treated with platinum-containing regimens.

Based on these publications, the target population in the protocol and the discussion with some medical key leaders, a phase III study was performed to demonstrate the superiority of vinflunine plus BSC over BSC in terms of overall survival on the basis of statistical hypothesis that the median survival in the vinflunine plus BSC group would be 6 months (Culine et al, 2006) versus a median survival of 4 months in BSC group (von der Maase 2000; Sternberg 1988).

Please replace the reference "von der Masse 2006" by "von der Masse 2000"

A.11 (Page 32). Please clarify the meaning of the bullet point stating “A follow up time of 6 months after randomisation of the last topic”.

Response: The correct sentence is: A follow up time of 6 months after randomisation of the last patient.

A12. (Pages 32-33). The MS reports that data were censored at the start date of further chemotherapy or the date of last news but it is unclear what this means. Please provide further explanation of the method of censoring used and the implications of these censored data when interpreting the statistical analyses.

Response: Overall survival is defined as the duration between the date of randomisation and the date of death due to any cause. For those patients lost to follow up or who have not died when the target OS event goal is reached, survival duration was censored at the date of last news (i.e. : date of last administration, tumour assessment, clinical examination, ECG, neurological examination, audiogram examination, haematological or biochemistry assessment or date of last contact).

In order to determine the role of the study treatments arms in survival, an additional supportive analysis was done with the overall survival time censored at the time of the first further chemotherapy. For patients who received secondary chemotherapy, survival duration was censored at the start date of the further chemotherapy. For patients who did not receive any further chemotherapy but were lost to follow-up or did not have a record of death, the survival duration was censored at the date of last news.

A13. (Page 33). The MS refers to prognostic factors including “the presence of lymph nodes”. Please clarify whether this means the involvement of lymph nodes/presence of metastases rather than just presence of lymph nodes.

Response: This means the involvement of lymph node metastases. Lymph node metastases were identified as potential prognostic factors in first-line therapy (Bajorin et al 1999 J Clin Oncol 17:3173-81).

A14. (Page 38: Table B8). Results for vinflunine plus BSC are exactly the same for all 3 analyses (ITT, eligible ITT and per protocol) even though the groups have different numbers of patients. Please confirm if these are the correct data.

Response: We confirm that the results for vinflunine plus BSC are exactly the same for all 3 analyses (ITT, eligible ITT and per protocol) even though the groups have different numbers of patients. The correct P value and HR in the per protocol are given in the following table.

Table B8: Summary of OS results for the ITT and eligible ITT populations

Efficacy primary endpoint: overall survival				
Population	Median months (95% CI)		Stratified log rank *P* value	Hazard ratio (95% CI)
	Vinflunine+BSC	BSC		
ITT	6.9 (5.7 to 8.0)	4.6 (4.1 to 7.0)	0.2868	0.88 (0.69 to 1.12)
Eligible ITT	6.9 (5.7 to 8.0)	4.3 (3.8 to 5.4)	0.0403	0.78 (0.61 to 0.99)
Per-Protocol	6.9 (5.7 to 8.0)	4.3 (3.8 to 5.4)	0.0197	0.75 (0.59-0.96)

The above HR and P value (0.75, p=0.0197) correspond to the date of initial cut-off (November 2006) while the HR and P value in the MS (0.74, p=0.013) correspond to the update of OS on May 2007.

For more details, you can have a look at Overall Survival (OS) - Per protocol population (Page 43, EMEA report)

"*Median OS for per protocol analysis was 6.9 months in the vinflunine arm and 4.3 months in the BSC arm. The risk of death is reduced by 25% in the vinflunine + BSC arm compared to the BSC arm: HR of 0.75 (95% CI: 0.59; 0.96 p=0.0197). In a subsequent update, OS in the per protocol patient population showed a 2 months advantage favouring vinflunine + BSC (6.9 month versus 4.3 months), with a reduction of risk of death by 26% HR 0.74 (95% CI: 0.59, 0.94). This difference was statistically significant (p = 0.0130).*"

A15. (Page 39). Please provide rationale (and give reference if applicable) for the choice of prognostic factors in the planned multivariate analysis. Please also explain why the involvement of lymph nodes/presence of metastases is not included in this analysis.

Response: The choice of prognostic factors in the planned multivariate analysis was based on the publication of Bajorin et al. "Long term survival in metastatic transitional cell carcinoma and prognostic factors predicting outcome of therapy".

The presence of lymph nodes metastases was not kept as a prognostic factor in the model because it was not statistically significant (p=0.481) (Bajorin et al 1999 J Clin Oncol 17:3173-81)..

A16. (Pages 41 & 42: Table B10). Please clarify what is meant by an extended multivariate analysis and why the results for this analysis in the ITT population differ from the results for the pre-specified multivariate analysis in the same population presented table B9 (page 40).

Response: Excluding patients from the ITT analysis leads to a non-respect of the randomisation scheme from which potential biases may arise when the analysis of OS was conducted in the eligible population. Possible imbalances in the patient characteristics between the treatment groups may result from this exclusion.
So, to address these potential biases, a set of covariates for OS in TCCU patients including the pre-specified prognostic factors and additional baseline characteristics was identified: sex, age, disease stage at diagnosis, time from diagnosis to randomisation, bone, liver, visceral involvement, lymph nodes, number of organs involved, disease status at randomisation, creatinine clearance, ASAT, AKP, Hb, PS, Pelvic irradiation, refractory status.
Then, an extended multivariate Cox analysis was performed including this set of covariates to adjust the effect of the treatment arm on potential confounding factors. The aim of this analysis was to verify whether or not the VFL has still a significant impact on OS in the targeted population.
The results of this analysis could be different from those presented in table B9 because the extended multivariate analysis was adjusted on more covariates than the pre-specified multivariate analysis.

A17. (Page 43). It is not clear why results of a per protocol (PP) analysis are reported, as this is not the analysis population used to test superiority. Although PP may be used to support results from an ITT analysis no discussion of this is given. Please clarify.

Response: The per protocol (PP) population was defined in the protocol as secondary efficacy analysis but as stated by the CHMP review in the Day 150 Joint Response Assessment Report, the results of a Per-Protocol population should always be treated with caution, particularly in a randomized study with a no-treatment arm. Indeed, patients can be removed for post-treatment violations which can be related to treatment, the analysis becoming a non-randomized comparison. The PP analysis may be used just as supportive analysis.

A18. (Pages 44 & 46). Missing footnote. Please clarify whether the footnote "a" in Figures B5 and B6 refers to the stratified log rank test, as in the preceding figures.

Response. Yes. Footnotes are the same (EMEA CHMP Assessment Report)

A.19 (Page 45). Please clarify why the results for disease control rate (DCR) but not for progression-free survival (PFS) are different to those reported in the primary publication (Bellmunt et al., J Clinical Oncology 2009; 27: p. 4456). DCR values in the primary publication are 41.1% and 24.8% for the two study groups whereas in the MS (p. 45) DCR values of 55.1% and 27.1% are given.

Response: The results reported in the primary publication correspond to the results in the ITT population while those reported in the MS report correspond to the results in the evaluable population for efficacy.

The DCR values are expressed in several ways in the primary publication (Table 3, p 4458) and in the EMEA report (Table 22 and Table 23, p 49-50). To simplify the manufacturers submission (p 45) we expressed DCR as partial response (8.6%) plus stable disease (8.6% + 46.5% = 55.1% for vinflunine + BSC and 27.1% for BSC) consistent with Table 3, p4458 of the primary publication under "Overall response in evaluable patients" (n=185 / 85) and used by the EMEA to summarise efficacy in Table 22 (p49) of their report.

A20. (Pages 59 & 60). The MS reports the median overall survival as 7.9 months (95% CI 6.67 to 9.69 months). However, in the primary publication (Vaughn et al., Cancer, 2009; 115: p. 4113) the corresponding data are 8.2 months (95% CI 6.8 to 9.6 months). Please explain the discrepancy.

Response: The median overall survival (OS) in the primary publication (8.2 months) corresponds to the OS update performed after the final CSR for CA183001.

Again to simplify the MS, we chose to remain consistent with the EMEA report (application submitted in Feb 2008, median overall survival = 7.9 months, p55) rather than the later final publication by Vaughn et al (2009) when, with longer follow-up, the survival had improved slightly to 8.2 months.

A21. (Pages 59 & 60). The rate of disease control, duration of disease control, response duration, and progression-free survival are not reported in the primary publication (Vaughn et al.). Please clarify the source of these data.

Response: The rate of disease control, duration of disease control, response rate and progression-free survival are reported in the Clinical Study Report (CSR) of the CA 183001 study (CA001).

A22. (Page 124). The question "Were there any unexpected imbalances in drop-outs between groups?" is answered "yes". This appears inconsistent with the text, which states there were no differences in drop out rates. Please clarify.

Response: There is no difference in the drop-out rate between groups and the question "Were there any unexpected imbalances in drop-outs between groups?" should be answered "No". This was an error in the MS.

A23. The vesicant nature of vinflunine is not mentioned in the MS. Please explain whether there would be clinical, safety or cost implications of using a vesicant.

Response: A large number of cytotoxic agents in regular, routine use are classed as vesicants (The cytotoxic Handbook 4th edition page 133). Group 1 vesicants include anthracyclines, paclitaxel and all the vinca alkaloids (including vinflunine).

Vinflunine will only be used by centres that are experienced in the routine use of cytotoxic chemotherapy and we can reasonably expect that the risk of extravasation will be minimised. The best estimate regarding the likely or potential incidence of extravasation with the whole vinca class of drug is probably the National Patients Safety Agency Rapid Response Report Supplementary information from 2008 (NPSA/2008/RRR04, page 7). There is insufficient global experience with reported incidents of extravasation with vinflunine on the safety data base (0) but the overall incidence of extravasation with whole vinca alkaloid family is estimated to be 0.027% (NPSA report above). Given this relatively low incidence and general, routine use of vesicants in cancer treatment, we did not flag this as a separate cost in the MS. Naturally, remain vigilant to patient safety.

Section B: Clarification on cost-effectiveness data

B1. (Page 69; section 6.2.1). The MS states that the population modelled consists of advanced or metastatic TCCU patients who failed a prior platinum-containing regimen. Bellmunt et al. 2009 describe the trial participants as patients with locally advanced or metastatic TCCU with documented progression after first-line platinum. Please confirm whether trial participants correspond to patients who stopped responding to a platinum-containing regimen?

Response: For the study L00070 in 302 P1, the inclusion criteria were the following:

"Patients with progressive disease who failed or progressed after first line platinum-containing chemotherapy for advanced or metastatic disease. First line chemotherapy was defined as receiving at least 2 cycles. Nevertheless, in case of clear evidence of progressive disease after the first cycle of previous chemotherapy patients were accepted and stratified as refractory patients".

So we can confirm that the eligible ITT population had stopped responding or had relapsed following platinum-containing chemotherapy. It is evident from Bellmunt et al (J Clin Oncol 2009; 27:4454-61) and the EMEA report that the 13 ineligible patients had not progressed and the EMEA considered this a legitimate reason for their exclusion.

B2. (Page 76; table B31). The hazard ratio for overall survival (OS) shown in the table is 0.70. The text states this is based on the data from study 302 for the eligible ITT patient population. However, in Figure B4 (page 40), the hazard ratio is shown as 0.78. Please confirm the actual value used in the model. If this differs from 0.78, please explain the reason for this discrepancy.

Response: In table B4 page 41 the OS results used are issued from the results of the clinical trial published in the Bellmunt article (Bellmunt et al 2009 J Clin Oncol 27:4454-61).

In page 76 table B31, we used the multivariate cox regression model which adjusted for significant prognostic factors at randomisation or baseline, including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin.

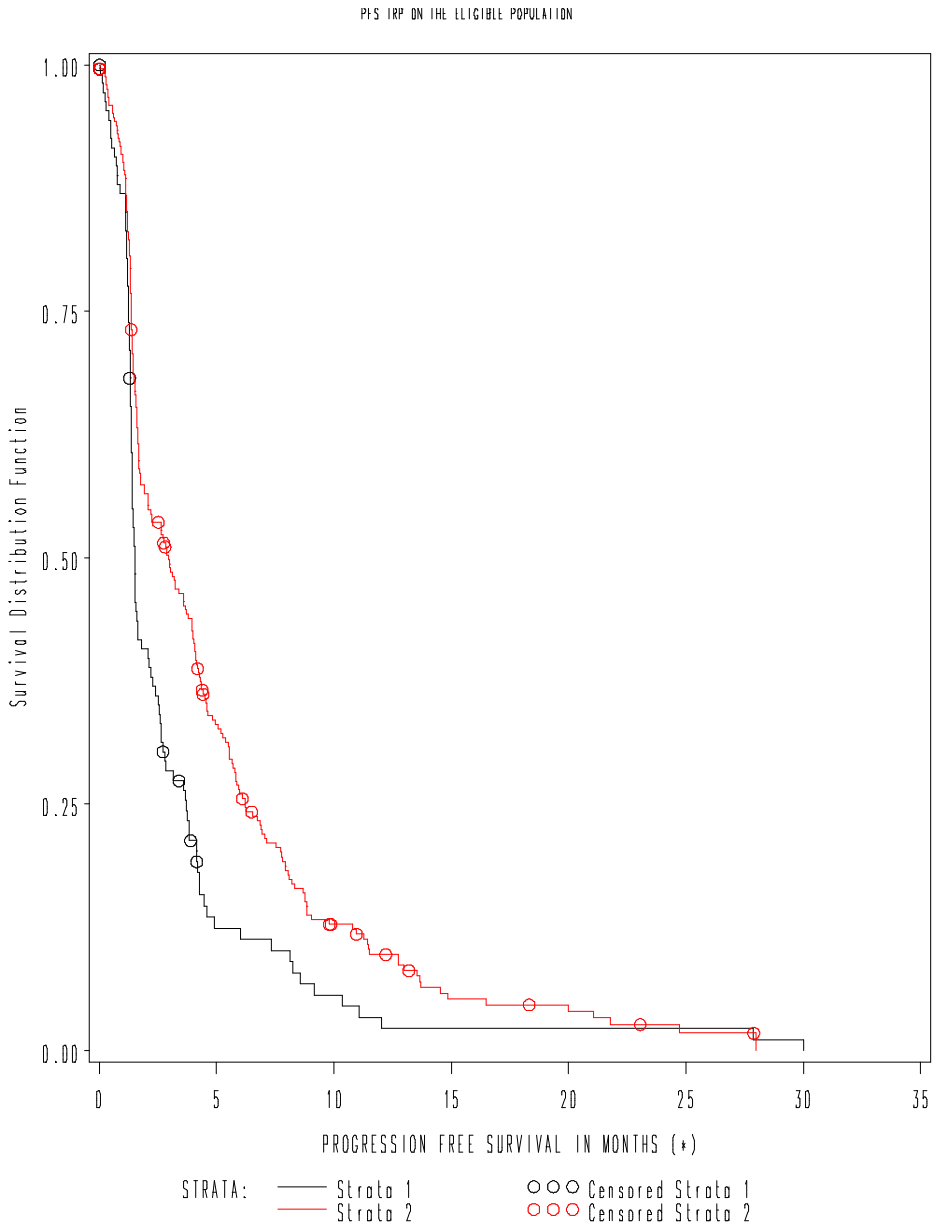
B3. (Page 76; table B31) The hazard ratio for progression-free survival (PFS) in the eligible ITT population shown in the table is 0.47. However, only the hazard ratio for the ITT population is provided in the clinical effectiveness section (Fig B6, p 46, HR 0.68). Please supply the equivalent PFS curve as that in figure B6 for the eligible ITT population.

Response: In table B6 p46 we used the PFS results issued from the clinical trial published in journal of clinical oncology (Bellmunt et al 2009 J Clin Oncol 27:4454-61)

In table B31 page 76 we used the multivariate cox regression model which adjusted for significant prognostic factors at randomisation or baseline, including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin

Table 1: Time related secondary endpoints in the eligible patients

	VFL + BSC	BSC	p-value
Number of patients	**249**	**108**	
PFS			
N events	225	102	
N censored	24	6	
Median (95% CI)	**3.0** (2.1-4.0)	**1.5** (1.4-2.1)	0.0003



B4. (Page 76; table B31). The mean values and standard errors for OS and PFS hazard ratios presented in this table do not match those in table B32 (p78). Please explain the reason for this discrepancy.

Response: To follow

B5. (Page 78; table B32). Please provide the source of the estimates (mean and SE) used for the risk of adverse events with vinflunine plus BSC. Please explain the differences between these values and those presented in Table B34 (page 86).

Response: To follow

B6. (Page 96; table B39). Please explain the methodology for calculating the cost for palliative radiation therapy and how the other costs shown in the table have been derived.

Response: Where available, all costs are based on the latest National Reference Costs for 2007/2008 which will be used as a basis for contract in 2009. As such, these should be regarded as 2009 costs. Where 2009 costs are not available, cost data from the nearest possible year have been reported and inflated where necessary. National Reference Costs, represent charges paid by those commissioning services (primary care trust) to those providing services (hospitals). All hospitals in England are required to report the costs of providing services. The National Reference Costs are then based on a weighted mean of costs of providing services. As such, these are expected to be provide a reasonable reflection of the cost of current care, taking into account significant variation across hospitals. The National Reference Costs form the tariff which acts as a basis for negotiation of contracts between purchasing and providing organisations. As such, these represent the actual charge that would be incurred when commissioning these services.

However, chemotherapy and radiotherapy were initially excluded from the list of case payments. Therefore discussion with clinical experts (oncologists, nurses and clinical coding specialists) have allowed to establish the appropriate codes to be used.

Finally, clinical advisors have provided information on the frequency of resource used, such as the proportion of patients who receive first line chemotherapy and the specific regimen used.

Enclosed is a detailed document on the cost used for the model.

B.7 Please state when a reference for the current price of vinflunine, for example BNF / MIMS, will be available.

Response. Already available from March 2010 (PDF attached)

Pierre Fabre Response to Clarification Requests – Outstanding Answers 13/09/10

Section B: Clarification on cost-effectiveness data

Question B4 Page 76; table B31). The mean values and standard errors for OS and PFS hazard ratios presented in this table do not match those in table B32 (p78). Please explain the reason for this discrepancy

Response:

The hazard ratios used for VFL+BSC are reported in table B32: Estimates of OS for patients receiving vinflunine+BSC were calculated using the multivariate hazard ratio for vinflunine+BSC; an assumption of proportional hazards between events was maintained beyond trial duration (Figure B10b). Health outcomes for patients receiving VFL+BSC were calculated using multivariate hazard ratios for vinflunine (OS and PFS) from Study L007 IN 302 P1/Bellmunt (study 302). The hazard of experiencing an event (either disease progression or death) for patients receiving VFL+BSC was assumed to be proportional to the event hazard rates in the BSC group, based on findings from multivariate Cox regression analysis which adjusted for significant prognostic factors at randomization or baseline including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin. The effect of VFL+BSC on OS and PFS, respectively, was significant after adjusting for the five prognostic factors. A Weibull survival model was used to extrapolate PFS and OS for patients receiving BSC beyond the duration of follow-up in study 302 (i.e. 2.4 years). All analyses conducted using data from Study 302 were undertaken for the eligible patient population.

Question B5 Page 78; Table B32. Please provide the source of the estimates (mean and SE) used for the risk of adverse events with vinflunine plus BSC. Please explain the differences between these values and those presented in Table B34 (page 86).

Response:

- Severe adverse events (grades 3 and 4) in study 302 which could have an impact on HRQL were presented in Table 34.
- In the model (Table 32) or the economic evaluation (question 6.4.22), were identified medical-resource use for the management of constipation (grades 3 and 4) (20.2% [vinflunine+BSC], 0.9% [BSC]), febrile neutropenia (grades 3 and 4) resulting in hospitalization (5.2% [vinflunine+BSC], 0% [BSC]), and abdominal pain (grades 3 and 4) resulting in hospitalisation (1.2% [vinflunine+BSC], 0.7% [BSC]). Fatigue and injection-site reactions, while frequent in Study 302, were deemed not to involve additional utilisation of medical-care services and were not included.

Appendix: Number of papers excluded in the systematic literature review

A) n=22 Papers excluded because the trial did not meet primary endpoints **or** were preliminary studies
B) n= 8 Papers excluded because they are not second-line and did not meet endpoints **or** were preliminary studies
C) n= 23 Papers excluded because they are not second-line studies
D) n= 2 Papers excluded because they are not second-line studies and were chemo-radiotherapy

E) n= 5 Papers excluded because they were not clinical trials **or** were not in metastatic disease **or** were not chemotherapy studies
F) n= 21 Papers excluded because they are reviews
Total is 81 including comments.

Appendix: Papers (references) excluded in the systematic literature review

A) Papers excluded because the trial did not meet primary endpoints **or** were preliminary studies

1. J Clin Oncol. 2010 Mar 10;28(8):1373-9. Epub 2010 Feb 8. Phase II study of sunitinib in patients with metastatic urothelial cancer. Gallagher DJ, et al
2. Phase 2 trial of sorafenib in patients with advanced urothelial cancer: a trial of the Eastern Cooperative Oncology Group. Dreicer R, et al.
3. Cancer. 2009 Feb 1;115(3):517-23. Phase 1/2 study of intravenous paclitaxel and oral cyclophosphamide in pretreated metastatic urothelial bladder cancer patients. Di Lorenzo G, et al.
4. Invest New Drugs. 2007 Apr;25(2):181-5. Epub 2006 Sep 16. A phase II study of PS-341 (Bortezomib) in advanced or metastatic urothelial cancer. Gomez-Abuin G, et al.
5. Am J Clin Oncol. 2006 Feb;29(1):3-7. A phase I dose finding study of cisplatin, gemcitabine, and weekly docetaxel for patients with advanced transitional cell cancer. Tinker A, et al.
6. Am J Clin Oncol. 2005 Apr;28(2):109-13. A phase II trial of sequential chemotherapy with docetaxel and methotrexate followed by gemcitabine and cisplatin for metastatic urothelial cancer. Artz A, et al.
7. Urol Oncol. 2004 Sep-Oct;22(5):393-7. A multi-institutional phase II trial of gemcitabine plus paclitaxel in patients with locally advanced or metastatic urothelial cancer. Kaufman DS, et al.
8. J Clin Oncol. 2002 Feb 15;20(4):937-40. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. Vaughn DJ, et al.
9. Cancer Invest. 2002;20(5-6):673-85. Feasibility trial of methotrexate-paclitaxel as a second line therapy in advanced urothelial cancer. Bellmunt J, et al.
10. Comment in: Cancer Invest. 2002;20(5-6):855-6.
11. Eur J Cancer. 2001 Nov;37(17):2212-5. A feasibility study of carboplatin with fixed dose of gemcitabine in "unfit" patients with advanced bladder cancer. Bellmunt J, et al.
12. Ann Oncol. 2001 Oct;12(10):1417-22. Combination chemotherapy with gemcitabine and ifosfamide as second-line treatment in metastatic urothelial cancer. A phase II trial conducted by the Hellenic Cooperative Oncology Group. Pectasides D,et al.
13. J Clin Oncol. 2001 Jun 15;19(12):3018-24. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. Meluch AA, et al.
14. J Urol. 2001 Jan;165(1):67-71. Docetaxel and ifosfamide as second line treatment for patients with advanced or metastatic urothelial cancer after failure of platinum chemotherapy: a phase 2 study. Krege S, et al.
15. Ann Oncol. 2000 Nov;11(11):1391-4. Phase II EORTC trial with 5-fluorouracil, cisplatin and interferon-alpha as second-line treatment of advanced transitional cell cancer of the urothelial tract. De Mulder PH, et al.
16. Jpn J Clin Oncol. 1999 Apr;29(4):204-8. Long-term follow-up results of a Pilot Phase II study of multidrug chemotherapy (MVP-CAB) in patients with advanced urothelial cancer. Gohji K, et al.

17. Br J Cancer. 1997;75(4):606-7. Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter. Papamichael D, et al.
18. Invest New Drugs. 1997;15(2):157-63. Phase II trial of oral piritrexim in advanced, previously treated transitional cell cancer of bladder. Khorsand M, et al.
19. Ann Oncol. 1995 Oct;6(8):836-7. A phase II study of 5-fluorouracil and high dose folinic acid in cisplatin-refractory metastatic bladder cancer. Huan SD, et al.
20. Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. Pollera CF, et al.
21. Clin Oncol (R Coll Radiol). 1993;5(1):25-9. A phase II study of epirubicin in advanced transitional cell bladder cancer. The Yorkshire Urological Cancer Research Group. Jones WG, et al.
22. Invest New Drugs. 1992 Nov;10(4):317-21. Phase II trial of pirarubicin in the treatment of advanced bladder cancer. Mahjoubi M, et al.

B) Papers excluded because they are not second-line and did not meet endpoints **or** were preliminary studies

23. Invest New Drugs. 2010 Feb 27. [Epub ahead of print] A phase II trial of sorafenib in first-line metastatic urothelial cancer: a study of the PMH Phase II Consortium. Sridhar SS, et al.
24. Ann Oncol. 2009 Jun;20(6):1074-9. Epub 2009 Jan 23. A phase II trial of cisplatin (C), gemcitabine (G) and gefitinib for advanced urothelial tract carcinoma: results of Cancer and Leukemia Group B (CALGB) 90102. Philips GK, et al.
25. Cancer. 2008 Jun 15;112(12):2671-5. Phase 2 trial of pemetrexed disodium and gemcitabine in advanced urothelial cancer (E4802): a trial of the Eastern Cooperative Oncology Group. Dreicer R, et al.
26. BJU Int. 2008 Jan;101(1):20-5. Epub 2007 Oct 8. A phase II trial of cisplatin, fixed dose-rate gemcitabine and gefitinib for advanced urothelial tract carcinoma: results of the Cancer and Leukaemia Group B 90102. Philips GK, et al.
27. Urol Oncol. 2003 May-Jun;21(3):185-9. Phase II trial of cisplatin, 5-fluorouracil, and interferon-alpha-2B as first line treatment of advanced urothelial cancer. Bazarbashi S, et al.
28. J Clin Oncol. 2002 Mar 1;20(5):1361-7. Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. Siefker-Radtke AO, et al.
29. Ann Oncol. 2002 Feb;13(2):243-50. Weekly chemotherapy with docetaxel, gemcitabine and cisplatin in advanced transitional cell urothelial cancer: a phase II trial. Pectasides D, et al.
30. Br J Cancer. 2002 Feb 1;86(3):326-30. Phase II multicentre study of docetaxel plus cisplatin in patients with advanced urothelial cancer. Garcia del Muro X, et al.

C) Papers excluded because they are not second-line studies

31. J Clin Oncol. 2009 Nov 20;27(33):5634-9. Epub 2009 Sep 28. Randomized phase II/III trial assessing gemcitabine/ carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. De Santis M, et al.
32. Ann Oncol. 2007 Aug;18(8):1359-62. Gemcitabine and oxaliplatin combination: a multicenter phase II trial in unfit patients with locally advanced or metastatic urothelial cancer. Carles J, et al.
33. Eur Urol. 2005 Aug;48(2):246-51. Phase II trial of weekly paclitaxel and carboplatin chemotherapy in patients with advanced transitional cell cancer. Johannsen M, et al.
34. J Chemother. 2005 Aug;17(4):441-8. Methotrexate-paclitaxel-epirubicin-carboplatin (M-TEC) combination chemotherapy in patients with advanced bladder cancer: an open label phase II study. Tsavaris N, et al.
35. Erratum in: J Chemother. 2005 Oct;17(5):following 573. Kopteridis, P [corrected to Kopterides, P].
36. Br J Cancer. 2004 Aug 31;91(5):844-9. A phase I/II study of gemcitabine and fractionated cisplatin in an outpatient setting using a 21-day schedule in patients with advanced and metastatic bladder cancer. Hussain SA, et al.
37. Urol Oncol. 2002 Nov-Dec;7(6):235-7. Pilot study of sequentially applied doublets in poor-prognosis metastatic urothelial cancer. Williams D, Millikan R.
38. J Clin Oncol. 2001 May 15;19(10):2638-46. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human

granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. Sternberg CN, et al.
39. J Urol. 2000 Nov;164(5):1538-42. Phase II study of paclitaxel and cisplatin for advanced urothelial cancer. Burch PA, et al.
40. J Clin Oncol. 2000 Sep;18(17):3068-77. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. von der Maase H, et al.
41. Comment in: J Clin Oncol. 2001 Feb 15;19(4):1229-31.
42. J Clin Oncol. 2000 May;18(9):1921-7. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. Kaufman D, et al.
43. J Clin Oncol. 1999 Sep;17(9):2876-81. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. Moore MJ, et al.
44. Br J Cancer. 1998 Oct;78(8):1067-75. A randomized trial comparing methotrexate and vinblastine (MV) with cisplatin, methotrexate and vinblastine (CMV) in advanced transitional cell carcinoma: results and a report on prognostic factors in a Medical Research Council study. MRC Advanced Bladder Cancer Working Party. Mead GM, et al.
45. J Clin Oncol. 1998 Oct;16(10):3392-7. Docetaxel and cisplatin in metastatic urothelial cancer: a phase II study. SengelÃ¸v L, et al.
46. Br J Cancer. 1998 Aug;78(3):370-4. Paclitaxel and carboplatin in patients with metastatic urothelial cancer: results of a phase II trial. Zielinski CC, et al.
47. Jpn J Clin Oncol. 1998 Aug;28(8):497-501. Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese Urothelial Cancer Research Group. Kuroda M, et al.
48. Gan To Kagaku Ryoho. 1998 Jul;25(8):1179-87. [Effect of UFT on treatment of urological cancer--effect of UFT on treatment of invasive bladder cancer and advanced prostate cancer. Ibaraki Urological Cancer Chemotherapy Study Group] [Article in Japanese] Uchida K, et al.
49. Am J Clin Oncol. 1997 Aug;20(4):327-30. Continuous-infusion 5-fluorouracil and cisplatin for advanced/recurrent transitional cell cancer of the bladder: a Southwest Oncology Group trial. Kish JA, et al.
50. Am J Clin Oncol. 1997 Jun;20(3):319-21. A phase II trial of cisplatin and interferon alpha 2b in patients with advanced bladder cancer. Parnis FX, et al.
51. Ann Oncol. 1997 Apr;8(4):373-8. 5-Fluorouracil, interferon-alpha-2b and cisplatin (FAP) for advanced urothelial cancer. A phase II study. Hellenic Co-operative Oncology Group. Kosmidis PA, et al.
52. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. Petrioli R, et al.
53. Cancer. 1994 Apr 1;73(7):1932-6. Carboplatin, methotrexate, and vinblastine in the treatment of patients with advanced urothelial cancer. A phase II trial. Boccardo F, et al.

D) Papers excluded because they are not second-line studies and were chemo-radiotherapy
54. Int J Radiat Oncol Biol Phys. 2009 Apr 1;73(5):1425-31. Epub 2008 Nov 25. Accelerated radiotherapy, carbogen, and nicotinamide (ARCON) in the treatment of advanced bladder cancer: mature results of a Phase II nonrandomized study. Hoskin P, et al.
55. Radiother Oncol. 2009 Apr;91(1):120-5. Epub 2008 Nov 5. Carbogen and nicotinamide in locally advanced bladder cancer: early results of a phase-III randomized trial. Hoskin PJ, et al.

E) Papers excluded because they were not clinical trials **or** were not in metastatic disease **or** were not chemotherapy studies
56. Hinyokika Kiyo. 2006 Feb;52(2):99-105. Angiotensin-II combined intra-arterial chemotherapy for locally advanced bladder cancer: a case series study at a single institution. Shimabukuro T, et al.
57. Eur Urol. 2004 Feb;45(2):176-81. Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990-2000 in Japan. Nishiyama H, et al.

58. BMC Cancer. 2008 Feb 29;8:65. Comparative study of the radiosensitizing and cell cycle effects of vinflunine and vinorelbine, in vitro. Simoens C, et al.
59. Urol Oncol. 2002 Jul-Aug;7(4):159-66. Higher antitumor activity of vinflunine than vinorelbine against an orthotopic murine model of transitional cell carcinoma of the bladder. Bonfil RD, et al.
60. Eur J Cancer. 1999 Mar;35(3):512-20. Superior in vivo experimental antitumour activity of vinflunine, relative to vinorelbine, in a panel of human tumour xenografts. Hill BT, et al.

F) Papers excluded because they are reviews

61. Crit Rev Oncol Hematol. 2003 Aug;47(2):171-9. Is there standard chemotherapy for metastatic bladder cancer? Quality of life and medical resources utilization based on largest to date randomized trial. Lehmann J, Retz M, StÃ¶ckle M.
62. Lancet Oncol. 2010 May 25. [Epub ahead of print] Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Sonpavde G, et al.
63. J Clin Oncol. 2010 May 1;28(13):e205-7; author reply e208. Epub 2010 Feb 16. Suggestions for regulatory agency approval of second-line systemic therapy for metastatic transitional cell carcinoma. Sonpavde G, et al.
64. Comment on: J Clin Oncol. 2009 Sep 20;27(27):4454-61. *{NB comment only}*
65. Bull Cancer. 2010;97 Suppl Cancer de la vessie:27-33. [Treatment strategies for metastatic patients in bladder cancer] [Article in French] ThÃ(c)odore C.
66. Curr Opin Urol. 2009 Sep;19(5):533-9. Second-line therapy in bladder cancer. Bachner M, De Santis M.
67. Curr Treat Options Oncol. 2009 Aug;10(3-4):256-66. Epub 2009 Apr 29. Systemic therapy of advanced urothelial cancer. Vaishampayan U.
68. Cancer. 2008 Sep 15;113(6):1284-93. Advanced bladder cancer: status of first-line chemotherapy and the search for active agents in the second-line setting. Gallagher DJ, Milowsky MI, Bajorin DF.
69. Comment in: Cancer. 2008 Sep 15;113(6):1275-7.
70. Semin Oncol. 2008 Jun;35(3 Suppl 3):S34-43. Clinical activity of vinflunine in transitional cell carcinoma of the urothelium and other solid tumors. Bellmunt J, Delgado FM, George C.
71. Expert Opin Investig Drugs. 2008 Apr;17(4):583-91. Vinflunine: clinical perspectives of an emerging anticancer agent. Yun-San Yip A, Yuen-Yuen Ong E, Chow LW.
72. Clin Cancer Res. 2008 Mar 15;14(6):1625-32. Vinflunine: a new microtubule inhibitor agent. Bennouna J, Delord JP, Campone M, Nguyen L.
73. Curr Opin Support Palliat Care. 2007 Oct;1(3):180-6. The evolving role of chemotherapy in advanced urothelial cancer. CalabrÃ² F, Sternberg CN.
74. Curr Opin Urol. 2007 Sep;17(5):363-8. New developments in first- and second-line chemotherapy for transitional cell, squamous cell and adenocarcinoma of the bladder. De Santis M, Bachner M.
75. Therapy of metastatic bladder carcinoma. Iaffaioli RV, Milano A, Caponigro F.
76. Ann Oncol. 2007 May;18(5):835-43. Epub 2006 Oct 3. New agents for treatment of advanced transitional cell carcinoma. Perabo FG, MÃ¼ller SC.
77. Comment in: Ann Oncol. 2007 Jun;18(6):1118.
78. Semin Oncol. 2007 Apr;34(2):135-44. Chemotherapy for metastatic or unresectable bladder cancer. Bellmunt J, Albiol S.
79. Expert Opin Investig Drugs. 2005 Oct;14(10):1259-67. Vinflunine: a novel antitubulin agent in solid malignancies. Bennouna J, Campone M, Delord JP, Pinel MC.
80. Ann Pharm Fr. 2005 Jan;63(1):28-34. [Vinflunine: a new anti-cancer fluorinated agent derived from Vinca-alkaloids] [Article in French] Jacquesy JC, Jouannetaud MP.
81. Crit Rev Oncol Hematol. 2003 Jun 27;46 Suppl:S105-15. Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. Sternberg CN, Vogelzang NJ.

7.2 Appendix 2: Differences in parameter values

Table 18: Differences in parameter inputsTable 18 shows the errors found by the ERG concerning the discrepancies between the reported parameter values and those used in the MS model.

Table 18: Differences in parameter inputs

Variable name	MS Table B32	Model
VFL, cost per vial	Lognormal	No
VFL, dose delay [calibration] (days)	n/a, mean = NR	Normal, mean = 3.5
VFL, risk of AE:		
Constipation	SE= NR	SE= 5.05%
Febrile neutropenia	SE= NR	SE= 1.30%
Abdominal pain	SE= NR	SE= 0.30%
BSC, incidence of AE:		
Constipation	Lognormal	Beta
Both therapies, cost side effects		
Constipation	SE= 7	SE= 9.75
Abdominal pain	mean = 577	mean = 557
VFL, OS, HR	SE= 0.0877	SE= 0.08
VFL, PFS, HR	SE= 0.0582	SE = 0.05

NR - not reported