NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

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

23 July 2010

Contents

List of Tables

List of Figures

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Executive summary

The UK approved name, brand name, marketing status and principal pharmacological action of the proposed technology. The indication(s) and any restriction(s)

Vinflunine (Javlor®) is a novel treatment for adults with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen [Section 1.5]. Vinflunine was granted a Marketing Authorisation (MA) by the European Medicines Evaluation Agency (EMEA, now EMA) on 21 September 2009. Vinflunine is not yet marketed in the UK. This is a microtubule targeting chemotherapeutic agent of the vinca-alkaloid family (ATC code: L01CA05). Vinflunine treatment should be initiated under the responsibility of a physician qualified in the use of anticancer chemotherapy.

The recommended course of treatment. The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost price.

The recommended dose of vinflunine is 280-320 mg/m² administrated as a 20-minute intravenous infusion every 3 weeks. Vinflunine is supplied as individual vials containing 250 mg or 50 mg vinflunine at a concentration of 25mg/mL. The cost is £1062.50 for 250 mg vial, £212.50 for 50 mg. (section 1.10).

The main comparator

The licensed indication represents an unmet clinical need. There is currently no recognized therapy in second-line treatment for advanced and metastatic grade (Section 2.6).

Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison and/or mixed treatment comparison, or from non-randomised studies. The main clinical results of the RCTs and any relevant non-RCT evidence

The principle evidence for registration is a phase III, multinational, randomised clinical trial comparing vinflunine plus best supportive care (vinflunine+BSC) to supportive care alone (BSC) in patients with advanced TCCU who have progressed after a platinum-containing regimen (Study 302, Section 5).

Patients (n=370) were randomised in a ratio of 2:1 in favour of the treatment arm (253/117). Vinflunine demonstrated a 2.6-month survival advantage (6.9 vs. 4.3 months, HR 95% CI: 0.78 ; 95% CI 0.61-0.99 ; p=0.0403) in the eligible ITT population (n=357). Multivariate Cox analysis adjusting for prognostic factors confirmed a death reduction of 32% on the eligible ITT population (HR=0.68 [0.52-0.88], p=0.0035). Overall response rates (ORR), disease control, PFS were all statistically significant favouring vinflunine+BSC. These results confirmed earlier results from two phase II studies.

The mean number of administered courses was 4.2 [1-20]. More patients received at least one palliative radiotherapy in the BSC arm (4% in the study arm vs 24% in the control arm). No statistical difference was found between vinflunine+BSC and BSC in quality of life and change from baseline of the EORTC-QLQ-C30 global health status score.

Main grade 3-4 toxicities for vinflunine safety analysis (n=450) were neutropenia (55%) febrile neutropenia (6.7%), fatigue (16%), constipation (15%).

In relation to the economic evaluation, details of:

- *the type of economic evaluation and justification for the approach used*
- *the pivotal assumptions underlying the model/analysis*
- *the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.*

A cost-utility analysis based on the phase III clinical trial and its primary efficacy end points was performed from the NHS and Personal Social Services (PSS) perspective in accordance with the NICE HTA guidance [Sections 6.2.5, 6.2.6]. The hazard rates of experiencing disease progression or death for vinflunine+BSC and the proportional hazards assumption were used to describe the progression and survival curves of patients receiving VFL+BSC compared to BSC [Section 6.3.2]. A Weibull survival model was used to extrapolate PFS and OS for patients receiving BSC beyond the duration of the follow-up in the phase III pivotal trial (Section 6.3.7). The mean EORTC-QLQ-C30 score was converted into utility index using a published regression model (O'Leary 1995) (Section 6.4.9). Medical resource use during chemotherapy treatment plus best supportive care or best supportive care alone, before progression and after progression till death, were identified in the clinical trial database or provided by clinical advisors, and translated into costs using NHS or published references prices in the UK (Section 6.5.1). The chemotherapy cost includes the acquisition cost, as well as the administration in an outpatient setting, the premedication, monitoring and treatment of severe adverse events (Section 6.5.5).

Based on the Cox multivariate analysis in the eligible population, a mean dose of 287mg/m^2, a mean cycle cost of £2,337, a mean number of treatment cycles of 4.2 [1-20], pre-progression and post-progression cost of £580 and £1,253 per month respectively, vinflunine plus best supportive care allows an extended survival of 0.267 year with an incremental cost of £13,071 compared to best supportive care alone and an incremental cost-effectiveness ratio (ICER) of £48,894 per life year

gained (£ per LYG). In terms of survival adjusted to quality of life, the efficacy gain is 0.131, with an incremental cost-effectiveness ratio of £100,144 per quality adjusted life year gained (£ per QALY) (Section 6.7.6).

Table 1: Base-case cost-effectiveness results

	Vinflunine + BSC	BSC
Technology acquisition cost	9 485	0
Other costs	12 228	8 642
Total costs	21 714	8 642
Difference in total costs	N/A	13 072
LYG	0.898	0.630
LYG difference	N/A	0.267
QALYs	0.364	0.234
QALY difference	N/A	0.131
ICER	N/A	100 144

A fifth of the incremental cost of vinflunine plus best supportive care stems from the additional weeks spent in remission and extended life time, and therefore in supportive treatment before or after progression. Using a free (£0) chemotherapy acquisition cost, the incremental cost-effectiveness ratio would be very close to the maximum threshold (i.e. £27,478 per QALY) [Section 6.7.7].

Summary of Clinical results and Economic Analysis

The principle registration study (Study 302), was an extreme test of efficacy in patients with high tumour burden and a short expected survival (4.3 months). A survival advantage of 2.6 months represents a 60% gain and is a remarkable achievement for a new cancer drug. The indication for vinflunine is an unmet clinical need in a small patient population. Clinical guidelines or audit have never been extended to cover these patients. Consequently the core data set required for robust economic evaluation is absent. This economic model was robust but the absence of any data that reflects the efficiency and productivity of superior treatment in similar circumstances for other tumour areas (NSCLC, renal) disadvantaged vinflunine.

End of Life

In light of NICE social value judgements and the recent publication of “end-of-life” supplementary advice in health technology appraisals, different considerations should be stated: Vinflunine is a novel treatment option for a small population with an incurable illness and a 5-month life expectancy with no alternative treatment, increases survival by 2.6 months (incremental LYG is 3.2 months in the economic model) which represents a 150% life-expectancy gain, and is not licensed in other indications. Using the trial-based utility of 0.79 for an healthy individual of the same age, the additional weight that would need to be assigned to QALY benefits among patients treated with

vinflunine for this therapy to be cost-effective at a willingness-to-pay of £30,000/QALY is 2.06 (Section 6.10.5).

Table 2: Impact and QALY weights to be considered by the appraisal committee

	Vinflunine+BSC vs BSC
Incremental cost (£)	13 072
Incremental LYG	0.267
IQ (Max)	0.131
ICER (Max Q)	61 890
Relative weights (Max Q, £30 000)	2.06

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Vinflunine (Javlor®) is a cytotoxic drug for the management of malignant disease. ATC code L01CA05.

1.2 What is the principal mechanism of action of the technology?

Vinflunine suppresses microtubule treadmilling, leading to mitotic arrest and cell death (apoptosis). Vinflunine is distinguished from the other vinca-alkaloids in its relative binding affinity to tubulin, allowing higher intra-cellular concentrations with reduced neurotoxicity.

1.3 *Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).*

Vinflunine was granted a European Union Marketing Authorisation on 21st September 2009 (EU/1/09/550/001-0012).

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The main point of the discussion with the Competent Authority (EMEA) is described in the CHMP Assessment Report (EMEA/CHMP/370293/2009) pages 34-54 and relates to the use of the Modified ITT (described as eligible ITT in subsequent sections) survival analysis as the most valid and appropriate way to describe the efficacy of vinflunine in the pivotal phase III clinical trial, study 302. This discussion will be reviewed in detail in section 5.

Patients entering study 302 had to be considered fit enough to receive chemotherapy but willing to be randomised to receive BSC. These courageous patients were difficult to find and tended to be closer to the end of life compared to patients entering earlier phase II studies. Important and difficult factors affecting response to chemotherapy, such as poorer performance status, extensive disease (number of organs affected (41% > 3) and visceral involvement (74%)) and short duration of response to earlier chemotherapy (>82% relapse within 6 months), were common in the study population. Median survival in the control arm was only 4.3 months, confirming the end of life setting for this trial

population. Given the short survival of the control group, it is generally recognised that this was a difficult study design and represents a very severe test of the efficacy of Vinflunine.

Unfortunately, 13 ineligible patients that did not have progressive disease were entered into the study, 4 in the experimental arm and 9 in the control arm. These ineligible patients were not the intended study population and their survival was considerably longer than the eligible patients (13 months v 4.3 months) leading to a disproportionate effect on the statistical analysis. The Competent Authority recognised this confounding factor and accepted the use of the Modified ITT analysis of the eligible patient population to assess the efficacy of this treatment. The eligible patient population represents 98% of the patients in the active treatment arm and 92% of those in the control (BSC) arm. A Marketing Authorisation was issued.

As a cytotoxic agent, vinflunine should only be used under the responsibility of a physician qualified in the use of anticancer chemotherapy. Dose modification and adjustments are stated in section 4.2 in the SmPC.

What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Vinflunine is indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen.

1.5 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Several phase I studies are still ongoing to assess the recommended dose in special populations where this drug may offer important options:

Patients with chronic liver disease: Completed

Patients with Renal impairment: Ongoing

Elderly patients with cancer: Ongoing

There are no other studies in TCCU at the moment.

1.6 If the technology has not been launched, please supply the anticipated date of availability in the UK.

This innovative new product is licensed for an unmet clinical need but the current health economics of managing these patients is immature. The product was registered in September 2009 but will only be launched in September 2010 when appropriate preparation for health technology assessment (HTA) and local hospital adoption procedures has been performed.

1.7 Does the technology have regulatory approval outside the UK? If so, please provide details.

A European Union-wide Marketing Authorisation was granted by the EMEA on 21st September 2009.

1.8 *Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?*

This is an innovative treatment for an unmet clinical need and a potential good candidate to the "Innovation Pass". We intend to apply to include vinflunine for inclusion in this new process. *This process is currently suspended pending definition of the "New Cancer Drug Budget"*

A submission to the SMC and AWMSG is planned for August 2010. An eight week process for SMC is anticipated.

1.9 *For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.*

Table A1: Unit costs of technology being appraised

Pharmaceutical formulation	Concentrate for solution for infusion
Acquisition cost (excluding VAT)	£1,062.50 for a vial containing 250mg at 25mg/mL £212.50 for a vial containing 50mg at 25mg/mL
Method of administration	20-min intravenous infusion after reconstitution in 100mL saline
Doses	The standard dose of Vinflunine is 320mg/m^2 every three weeks. Patients with known pre-disposing factors for greater haematological toxicity should be initiated at 280mg/m^2 and may be later escalated. In the face of toxicity, the dose may be reduced to 250mg/m^2
Dosing frequency	Every 21 days
Average length of a course of treatment	3 cycles (9 weeks)
Average cost of a course of treatment	Assuming a BSA of 1.85m^2: 320 mg / m^2 would cost £2550 (592mg from 2 x 250 and 2 x 50mg vials) x 3 = £7,650 + VAT 280 mg / m^2 would cost £2337.50 (518mg from 2 x 250mg vials and 1 x 50mg vial) x 3 = £7,012.5 + VAT Average dose in the phase III was 287 mg/m2 and at BSA of 1.85 m2 would cost £2337.50 (530mg required from 2 x 250mg and 1 x 50mg vial). 3 Cycles would cost £7,012.5 plus VAT
Anticipated average interval between courses of treatments	One course of treatment, median of 3 cycles, mean number was 4.2 cycles.
Anticipated number of repeat courses of treatments	This treatment is to prolong survival at the end of life. Unlikely that a course of treatment will be repeated.
Dose adjustments	• Starting dose reduced to 280mg/m^2 in patients with performance status (PS) 0-1 who have had prior pelvic irradiation. In the absence of dose delay or reduction due to haematological toxicity, this may be increased to 320mg/m^2 for subsequent cycles. • In case of grade 4 neutropenia (ANC $<$ 500/mm^3) for more than 7 days or febrile neutropenia, of mucositis or constipation grade 2 $\geq$ 5 days or $\geq$ grade 3 any duration, or any other toxicity grade $\geq$ 3 (except Grade 3 vomiting or nausea), the dose must be adjusted to 280mg/m^2 (or 250mg/m^2 in case of a previous dose of 280mg/m^2), the treatment must be discontinued in case of a second (third) event.

1.10 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not Applicable.

1.11 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Vinflunine treatment should be initiated under the responsibility of a physician qualified in the use of anticancer chemotherapy. There are no additional tests beyond routine practice for Cytotoxic chemotherapy.

1.12 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Usual clinical practice for cytotoxic chemotherapy requires adequate monitoring of complete blood counts (CBC) prior to each cycle. As will most chemotherapy, both patients and staff must remain alert to signs and symptoms of infection and other toxicity during treatment and take appropriate measures when required.

1.13 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

To prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration. Prophylactic anti-emetics are routinely used in chemotherapy units to reduce the risk and incidence of nausea or vomiting.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

The underlying cause of cancer in the urothelial tract is prolonged chemical irritation caused through smoking or industrial exposure to solvents and chemical irritants. Most patients (70%) will be diagnosed with superficial bladder cancer while the remaining 30% will be invasive or metastatic bladder cancer. The majority of superficial tumours are managed with a sequence of surgery, radiotherapy and BCG and will never progress to more invasive disease.

Patients with invasive disease require more radical treatment. Radical cystectomy (removal of all or most of the bladder) is often accompanied with chemotherapy (neo adjuvant or adjuvant) to eliminate disease that may have already spread beyond the primary site. Unfortunately, many patients subsequently relapse with metastatic disease. As the disease has now spread beyond the original organ, systemic chemotherapy is often the best way to tackle the underlying disease.

Untreated, metastatic TCCU is associated with a median survival rarely exceeding 3 to 6 months. According to treatment guidelines, the most common recommendation is to use chemotherapy that contains cisplatin. Other drugs are added to supplement the activity of cisplatin. GC (gemcitabine and cisplatin), MVAC or accelerated MVAC (a combination of methotrexate, vinblastine, doxorubicin and cisplatin accelerated by use of GCSF) are the most used combination for first line use as adjuvant, neo-adjuvant and often used again for advanced disease (European Association of Urology Guidelines, 2004; Jakse et al 2004).

Patients that subsequently relapse after first line chemotherapy represent a difficult management challenge. Further deterioration in organ function (especially renal function), increasing tumour burden and developing resistance to existing drugs severely limits the treatment options available and a number of unproven cytotoxic agents have crept into regular practice.

Vinflunine is the first chemotherapeutic agent licensed for advanced transitional cell carcinoma of the urothelium (TCCU) after failure of a prior platinum-containing regimen. When tested in the extreme, end of life setting of study 302, vinflunine demonstrated a significant increase in survival of 2.6 months. This is a relative survival improvement of 60% compared to BSC and strongly suggests high activity and great clinical utility in this very difficult setting. Vinflunine has been licensed for use at any time after the failure of prior platinum containing treatment and longer periods of disease control, similar of greater than that seen in phase II studies.

2.2 How many patients are assumed to be eligible? How is this figure derived?

Cancer in the urothelial tract includes all cancer of the urinary tract excluding renal tumours. TCCU represents 90% of urothelial cancer. Estimates of the number of patients in England have been made from the published incidence rates by NYCRIS for 2007 according to Table A2 (updated to include

Wales). (Population of England 51.446 m from Office of National Statistics, www.statistics.gov.uk March 2010).

Transitional cell carcinomas of the urothelial tract (TCCU) are cancers that form in transitional cells in the lining of the bladder (90%), renal pelvis (9%), or ureter (1%). The majority (90%) of tumours in the urothelial tract are TCCU, other cell types being squamous, adenocarcinoma and other rare types. In England in 2007, the incidence of urothelial cancer is estimated to be 11,215 of which 10,094 will be TCCU (Based on 2007 NYCRIS incidence and mortality data). This represents 4.6% of all malignant sites (excluding non-melanoma skin). Mortality from TCCU is estimated to be 5,196 per year, representing 3.6% cancer mortality.

Table A2: Estimated Incidence and Mortality with TCCU in England and Wales

			Urothelial Cancer		TCCU (90% Urothelial)	
England and Wales	Crude Incidence*	Crude Mortality*	Incidence	Mortality	Incidence	Mortality
Renal Pelvis	1.5	0	817	-	735	-
Ureter	0.9	0.3	490	163	441	147
Bladder	19	9.5	10,343	5,172	9,309	4,655
Other urinary	0.4	0.3	218	163	196	147
Total	21.8	10.1	11,868	5,498	10,681	4,949

*Source NYCRIS 2007. Table updated to include Wales

Male: female ratio is 70:30. Bladder cancer is the most frequently occurring tumour of the urinary system, accounting for around 90% of cases. It is estimated that 70% of bladder cancer presents with non-invasive disease (Tis, Ta and T1). The remaining 30% have invasive or metastatic disease. Data is very limited and it is only estimated that 1500-2000 patients receive first line chemotherapy and that 50 % of these will be candidates for second line treatment (800-1000). Expert opinion is that these may be overestimates.

2.3 *Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.*

No single technology appraisal (STA) guidelines currently exist on therapy options in case of progression after 1st line chemotherapy for advanced disease.

Related interventional procedures No 287 (Feb 2009) Laparoscopic cystectomy.

Relate Clinical Guidelines: CSGUC, Improving outcomes in urological cancers, September 2002

2.4 *Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.*

The current specialist management of TCCU is performed with a Multi-Disciplinary Team (MDT) approach involving urologists, radiotherapists, oncologists and appropriate diagnostic and palliative care. There is currently no recognized therapy for patients with advanced and metastatic grade that relapse from earlier chemotherapy. In many cases, patients that relapse are relatively fit and request further therapy to extend life or address the underlying cause of symptoms. Repeated use of platinum containing chemotherapy is possible if the time to progression is long (12 months) and the patient's renal function remains adequate. Unfortunately, this is often not the case and a variety of other chemotherapy drugs have been adopted into local practice based on limited and uncontrolled phase II trial results. It is very reassuring that patients that relapse are not abandoned and NHS clinicians continue to seek treatment to reduce symptoms and extend survival but the agents available are limited by PCT or trust formularies. There is great local variation in the treatment patients receive and the most likely or optimum patient pathway is not well defined. The development of a new and proven treatment for patients at this stage of their disease will add structure and audit to management.

When patients are not fit for radical treatment they are treated with symptom-specific containment procedures. These are often delivered by a range of health care professionals in an inpatient, outpatient, community or home setting, i.e. acute admissions, community nurse specialists, the general practitioner, a dietician, a health visitor, and within hospice stays when necessary. Symptom specific treatment is inevitably patient initiated and coordinated through the GP practice. The complex range of symptoms at this stage of end of life treatment is always going to cause high anxiety for the patient and their carer(s). This can be very demanding on resources to the point of wastefulness. Having an active treatment programme that even extends to this late stage, can be more efficient than we sometimes think (re; renal and NSCLC).

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

As above, there is currently no consistent treatment pathway for patients that have progressive disease after platinum-based chemotherapy.

If patients receive further chemotherapy, the choice of which drug is subject to considerable inter- and intra-hospital variation.

When patients are closer to the end of life, care delivery is spread more widely across the NHS and there is considerable uncertainty and variability in the range, frequency and nature of support treatments individual patients receive. Experience from other tumour sites suggests that when a new treatment is introduced for a previously unmet clinical need, the NHS is unlikely to already have systems to track the complex array of consumption of these individual patients. Efforts were made to estimate the likely supportive care after a failure of a prior platinum-containing regimen and end-of-life treatment for the economic model [Section 6.5.1]. Given the complexity, this is very difficult and the health economic model created will severely disadvantage any new treatment for a previously unmet clinical need.

"Real World" data on patients with other tumours (renal cell) suggest that actual consumption of untreated patients (based on PBR data sets) is higher than estimated and consumption for treated patients that subsequently relapse is less. Due to the uncertainty of data on current treatment, the manufacturer has applied to be considered for the "Innovation Pass". The manufacturer is in

discussion with the NCRN and NCIN to discuss processes for the collection of real and robust health economic data for TCCU.

2.6 Please identify the main comparator(s) and justify their selection.

There is currently no standard therapy in patients with advanced transitional cell carcinoma of the urothelium whose disease has progressed after a prior platinum-containing chemotherapy. The licensed indication for vinflunine represents an unmet clinical need.

With no other recognised active treatment available to use as a control, the regulatory authorities considered Best Supportive Care (BSC) as an appropriate control for study 302.

There are a number of issues around using BSC as the control for the registration trial for new cancer treatments. Patients must be fit to receive chemotherapy but willing to accept randomisation to BSC with the obvious implications of this decision. As a result, patients were generally closer to the end of their life than most patients that fail after earlier platinum (e.g. phase II trial patients). This means that survival will be relatively short allowing the new drug little time to have an effect on a relatively high burden of disease. This design is a particularly stern test of efficacy for vinflunine. However, having demonstrated a significant survival benefit in such difficult circumstances, there is optimism that this could replace the "lucky-dip" chemotherapy that is often used for patients that are in generally good condition when they relapse after platinum, especially if their renal function is compromised.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In order to prevent and to treat severe constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7. Other clinical competencies for managing adverse reactions associated with cytotoxic chemotherapy are well established in chemotherapy units, for example the risk of emesis and neutropenic sepsis.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

In the economic model constructed for this submission and based on study 302, the pathway followed by patients that receive vinflunine is protocol driven and the resource for acquisition, reconstitution, blood tests and any support treatment or toxicity management can be measured or estimated with a reasonable degree of accuracy.

In existing clinical practice, a significant proportion of patients that relapse following earlier platinum based chemotherapy are treated with further courses of chemotherapy (30% of patients in the BSC arm of study 302 went on to receive chemotherapy). We were unable to find NHS estimate the real world cost of current practice. As a result, in the context of the economic model designed around study 302, the cost associated with the use of vinflunine is only compared to BSC. The cost of using

vinflunine (reconstitution, hospital visits, administration) appears as a "new" cost allocated only to the active treatment.

This represents a significant obstacle in the economic analysis of new, innovative treatment for a previously unmet clinical need. In similar, established indications such as 2nd line treatment for NSCLC, the acquisition and administration cost of any existing treatment (e.g. docetaxel), can offset the cost of new treatment it replaces. Innovative new drugs for unmet clinical need seem to be unfairly disadvantaged by the lack of real world data on what really happens at the moment.

BSC is symptom driven and not easily defined (see 2.5). Delivery is multi-focal and the overall cost and efficiency of patient driven demand is difficult to estimate. According to Guidance, the palliative treatment includes several specialists and community based services. Patients facing the end of active treatment have high anxiety levels and are likely to place high demand on community services. We have been unable to discern between protocol driven and unstructured BSC.

The combined effect of new treatment costs allocated only to vinflunine, the absence of any existing chemotherapy costs to offset these "new" costs and a poor understanding of the standard treatment NHS patients receive with supportive care, results in a health economic model that would make it impossible to demonstrate that vinflunine is cost effective, even if the cost of vinflunine was reduced to zero.

The proposed Innovation Pass would offer a mechanism to refine the understanding of the patient pathway and collect real world data on the economics of care and outcomes.

2.9 Does the technology require additional infrastructure to be put in place?

No additional infrastructure would be required for routine use of vinflunine or data monitoring for any Innovation Pass.

Existing NHS infrastructure has been created through the NCRN, NCIN and the cancer registries. Real world data for some tumour types, e.g. LUCADA and lung cancer, contributes to quality and equity of care and similar processes could be created for urinary cancer to support an Innovation Pass.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

The main cause of TCCU cancer is long-term exposure to chemical irritants from industry or smoking. The prevalence of these risk factors in some lower socio-economic groups introduces some inequality and regional variation.

The pivotal, open-label randomised multicentre phase III study 302 was performed in 83 sites from 21 countries (France, Denmark, Poland, Russia, Spain, Argentina, Canada, Serbia-Montenegro, Italy, United-Kingdom, Belgium, Finland, Greece, Netherlands, Bulgaria). The majority of patients with TCCU are males, between 50 to 75 years old (in the study 302, 79% and 81% respectively, see Section 5.3.3) with on average 64 years old.

The therapeutic added value and the tolerance of vinflunine are similar across the population with regards to age, gender, weight, and race.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

Extending median survival from 4.3 to 6.9 months in the extreme, end of life setting of a randomised clinical trial against BSC is a remarkable achievement for a new drug. This result in TCCU compares very favourably with the experience in, for instance, NSCLC. The only drug that extended median and one year survival v BSC in NSCLC, improved median survival from 21 to 28 weeks (1.6 months). However, the NICE approval of drugs for NSCLC in 2001 resulted in a dramatic improvement in data collection and audit of patient pathways (e.g. LUCADA). This has improved the speed and quality of referral and the same drugs that "only" gave 1.6 months improvement in end of life studies v BSC now deliver better outcomes and, 10 years on, contribute to dramatic improvements in 5 year survival when used as adjuvant to surgery or radiotherapy.

The clinical case for the approval of vinflunine for TCCU is strong and holds great promise for further improvement beyond these initial trial results. Understanding of the patient pathway in the NHS makes it impossible to demonstrate cost effectiveness at this stage. Reducing the drug cost to zero highlights the difficulty in building an economic model for a previously unmet clinical need. The whole UK patient population would then face discrimination in their access to this new treatment from a European perspective.

The description of the "Innovation Pass" requires that the NHS, NICE and the manufacturer work together to seek ways to provide treatment that is both clinically and cost effective for the NHS. These principles would be useful when defining the "New Cancer Drug Funding"

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Pierre Fabre proposes that vinflunine should be used to pilot the Innovation Pass / New Cancer Drug Fund.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

Remit/appraisal objective

To appraise the clinical and cost effectiveness of vinflunine monotherapy for the second line treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of prior platinum-containing chemotherapy.

Table A3: Decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen	Adults with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen	
Intervention	Chemotherapy	Chemotherapy	
Comparator(s)	No alternative treatment (BSC)	No alternative treatment (BSC)	
Outcomes	Overall Survival, Progression Free Survival, Response rates, adverse effects of treatment, Quality of Life	Overall Survival, Progression Free Survival, adverse effects of treatment, Quality of Life	No comparative data for response rate in this end of life population with a heavy tumour burden*
Economic analysis	Cost-utility analysis from the NHS and PSS perspective	Cost-utility analysis from the NHS and PSS perspective	
Subgroups to be considered	Not Applicable	Not Applicable	
Special considerations, including issues relating equity and equality	Not Applicable	Not Applicable	

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A systematic review of the literature was undertaken to identify published data on the clinical efficacy of vinflunine and potential comparator products in the treatment of patients with metastatic TCCU progressing after treatment with a platinum-based regimen. The search was designed to identify all clinical data published without any time constraints. The review was run several times between January 2009 and May 2010. To ensure completeness it was most recently performed on 17th May 2010.

The following bibliographic databases were searched for papers and abstracts: Cochrane Central Register of Controlled Trials (CENTRAL), CAB abstracts, BIOSIS previews using the Cochrane Library's online search facility; Index Medicus database (MEDLINE), including PUBMED®. Conference proceedings, including ASCO, ESMO, ESMO/ECCO, EAU, were searched 'by hand'. A flowchart of the systematic review is given in Figure B1.

The searches were carried out with a search strategy that was consistent with the functionality of each database, but all included terms related to TCCU, vinflunine and other potential comparator chemotherapies. The systematic review was limited to English-language publications and the strategies are detailed in Appendix 2, section 9.2.

Study selection

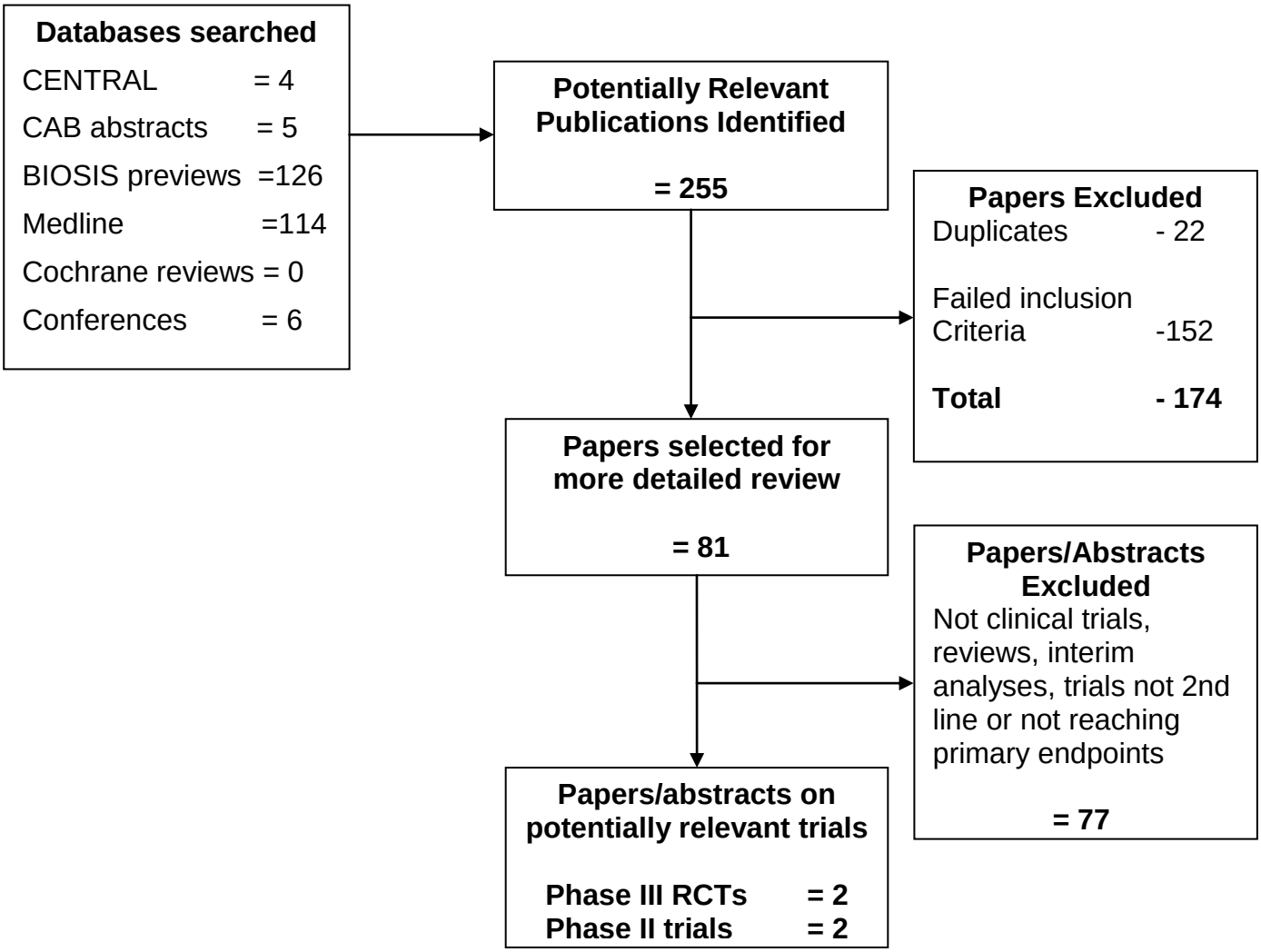
5.1.2 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table B1: Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: Patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) Interventions: vinflunine as a single agent or as part of a combination following prior platinum-based chemotherapy Outcomes: Objective response rate, Overall survival, progression free survival, time to treatment failure, safety Study design: Randomised controlled trials, phase II studies, systematic reviews, meta-analyses Language restrictions: trials reported in English
Exclusion criteria	Population: Non-metastatic or in situ TCCU Interventions: trials not involving vinflunine Outcomes: non-inferiority studies Study design: non-inferiority studies Language restrictions: non-English reports

A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure B1: Flowchart of systematic review to identify relevant trials.



5.1.3 *When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.*

One phase III RCT was identified. There were several interim reports in abstract form identified but were disregarded in favour of the final report published in Journal of Clinical Oncology (Bellmunt et al 2009) and one longer term follow-up presented at European Association of Urology meeting in April 2010 and published in abstract form (Culine et al 2010). Thus, there were two papers/abstracts on one phase III RCT identified (Figure B1).

Complete list of relevant RCTs

5.1.4 *Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.*

Table B2: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
L00070 IN 302 P1 (Study 302)	Vinflunine + Best Supportive Care (BSC)	BSC	Adults (n=370) with locally advanced or metastatic TCCU progressing after platinum-based chemotherapy PS ECOG/WHO 0 or 1	Bellmunt et al (2009) Culine et al (2010)

5.1.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Study 302 compares vinflunine plus BSC with BSC alone in a population of patients with advanced or metastatic disease who have relapsed after prior platinum-based chemotherapy for whom there was no alternative, evidence-based standard chemotherapy. The study 302 patient population represents a previously unmet clinical need. The regulatory authorities accepted that BSC was an appropriate control for registration. A European license was granted on 21st September 2009 (section 1.8).

5.1.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable

List of relevant non-RCTs

5.1.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

Table B3: List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
L00070 IN 202 P1 (Study 202) Phase II study	Vinflunine every 3 weeks at initial dose 320mg/m^2	TCCU after failure of platinum-containing regimen (n=51)	Efficacy and safety	Culine et al (2006)	Relevant patient diagnostic group, progressed after platinum regimen
CA 183001 (CA 001) Phase II study	Vinflunine every 3 weeks at initial dose 280mg/m^2 or 320mg/m^2	TCCU after failure of platinum-containing regimen (n=151)	Efficacy and safety	Vaughn et al (2009)	Relevant patient diagnostic group, progressed after platinum regimen

5.2 *Summary of methodology of relevant RCTs*

5.2.1 *As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.*

Methods

5.2.2 *Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.*

Table B4: Summary of methodology of the RCT study 302

Trial no. **(acronym)**	**L00070 IN 302 P1** **Study 302**
Location	Multicentre; 83 centres from 21 countries
Design	Open-label, randomised, interventional
Duration of study	3years 3months (May 2003-August 2006)
Method of randomisation	Patients randomised 2:1 by the Biometric department of Pierre Fabre and stratified according to investigational centre and to response to previous chemotherapy regimen strata (refractory vs non-refractory patients).
Method of blinding (care provider, patient and outcome assessor)	N/A
Intervention(s) (n =) and comparator(s) (n =)	Vinflunine + BSC n = 253 BSC = 117
Primary outcomes (including scoring methods and timings of assessments)	Overall survival; Study duration continued until the last patient withdrew from treatment. After withdrawal from the study treatment each patient was followed until death.
Secondary outcomes (including scoring methods and timings of assessments)	To compare patient benefit through a quality of life questionnaire (EORTC QLQ-C30) and clinical benefit parameters, performed before randomisation and at the end of cycles 1, 2, 4 and 6 To compare the safety profile in both arms. Maximum NCI-CTC grade or severity was reported by cycle and by patient. To assess response rate, time to response, response duration and progression free survival in patients treated with vinflunine plus best supportive care. Efficacy was determined according to the RECIST criteria. An Independent Review Panel was consulted in order to confirm all responses (and stabilisation if appropriate).
Duration of follow-up	Patients were followed-up until death. Median duration of follow-up at last report = 42 months

Treatment posology and duration

All patients in study 302 assigned to the vinflunine + BSC arm were initially treated with vinflunine 320 mg/m^2 every 21 days as a 20 minute infusion plus BSC. The protocol was amended to allow a lower starting dose (280 mg/m^2 plus BSC) in patients at greater risk of haematological toxicity. Patients assigned to the control arm were given BSC treatment according to the local standards of the study site (including palliative radiotherapy, antibiotics, analgesics, corticosteroids, transfusions).

In the study arm (vinflunine+BSC), patients were treated until disease progression in the absence of unacceptable toxicity, intercurrent illness or other reactions that, according to the investigator, would significantly affect the clinical status of the patient. Treatment was also withdrawn if requested by the patient.

In the control (BSC) arm, visits were recorded until there was an inability to meet the three-week schedule, progressive disease requiring systemic anti-neoplastic therapy or patient refusal.

Safety was assessed throughout the treatment period and before each administration according to NCI-CTC version 2.0 criteria.

Participants

5.2.3 *Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.*

The 302 study population consisted of adults (≥ 18years old) of both sexes with histologically confirmed locally advanced or metastatic TCCU and with documented progression following platinum-based chemotherapy and PS ECOG/WHO (Eastern Cooperative Oncology Group and World Health Organization) of 0 or 1. The inclusion and exclusion criteria are summarised in Table B5.

Table B5: Eligibility criteria in study 302

Inclusion Criteria	Exclusion Criteria
- Histologically confirmed locally advanced or metastatic TCCU - Documented progression following platinum-based chemotherapy for advanced or metastatic disease. First-line chemotherapy was defined as administration of at least 2 cycles. However, patients with clear evidence of disease progression after the first cycle of chemotherapy, were accepted as refractory patients and stratified - Previous systemic chemotherapy must have been terminated at least 30 days before randomisation, with complete resolution of any toxicities - Prior radiotherapy was allowed if it had affected <30% of the bone marrow, was completed at least 30 days before randomisation with complete resolution of any toxicities - Patients with measurable and / or non-measurable disease according to RECIST criteria, defined as follows: Measurable disease: lesions that can be accurately measured in at least one dimension, in non-irradiated patients: -evaluated by conventional scanner: larger diameter ≥ 20 mm -evaluated by spiral CT or magnetic resonance imaging (MRI), the largest diameter ≥ 10 mm Non-measurable disease: lesions in non-irradiated patients, whose greatest diameter is <20mm by conventional CT or <10mm by spiral CT or MRI and truly non-measurable lesions such as bone lesions, ascites, pleuritis / pericarditis, lymphangitis skin / lung - Age ≥ 18 years - PS (ECOG / WHO) 0 or 1, - Estimated life expectancy of at least 12 weeks, - Haematologic function (before initiation of treatment): • ANC ≥ 1.5 x 10^9/l • platelets ≥ 100 x 10^9/l - Liver function (before initiation of treatment): • Bilirubin ≤ 1.5 x ULN, • transaminases ≤ 2.5 x ULN (<5 x ULN only if liver metastases) - Renal (before initiation of treatment): creatinine clearance calculated ≥ 40 ml / min (Cockcroft and Gault) - Electrocardiogram (ECG) without significant changes with clinical consequences (during the 7 days preceding randomisation).	- TCCU with known brain metastases or leptomeningeal infringement. Initial cerebral assessment by CT or MRI was not required unless there was clinical suspicion CNS involvement - Peripheral neuropathy grade ≥ 2 according to NCI CTC (version 2.0) - Previous history of serious illness or medical condition or concomitant uncontrolled medical condition that could be exacerbated by treatment: -infection requiring antibiotics during the 2 weeks before the start of randomisation in the study, -uncontrolled cardiac arrhythmia, -unstable diabetes, -uncontrolled hypercalcaemia> 2.9mmol/l (or grade >1 according to NCI CTC Version 2.0) -patients with concomitant heart failure class III-IV New York Heart Association, patients with unstable angina, patients with myocardial infarction during the 6 months preceding randomisation and / or poorly controlled hypertension were excluded, - Patients who received more than one previous systemic chemotherapy for advanced or metastatic disease, - Patients who received an experimental treatment or other cancer during the 30 days preceding randomisation, - Patients with other cancers, except basal cell carcinoma treated adequately or carcinoma in situ of the cervix or cancer of incidental prostate cancer (stage Tla, Gleason score 6 antigen Prostate Specific <0.5 ng /mL) or other tumours with a disease-free interval ≥ 5 years - Pregnant or lactating women, - Adults of childbearing age not using a method of contraception during the study period and for 60 days after the last treatment, - Psychological, familial, sociological circumstances or geographical location that would not be compatible with protocol compliance and medical monitoring.

5.2.4 *Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.*

The patient populations in each arm of the trial were generally well matched across all parameters with the exception of performance status (PS), as highlighted in Table B6. The experimental arm, vinflunine plus BSC, had a higher proportion of poorer PS patients than the control, BSC, arm (71.5% versus 61.5%). Approximately 74% of patients in both arms had visceral organ involvement, which is a recognised indicator of poor prognosis (Bajorin et al 1999, Bellmunt et al 2010).

Table B6: Characteristics of participants in study 302

Study 302 Baseline characteristic	**Vinflunine + BSC**	**BSC**
n = 370	**n = 253**	**n = 117**
Median Age (Min - Max)	64.2 (37 - 86) years	64.2 (35 - 85) years
< 65 years [n, (%)]	135 (53.4)	60 (51.3)
≥ 65 years [n, (%)]	118 (46.6)	57 (48.7)
Gender		
Male [n, (%)]	197 (77.9)	95 (81.2)
Female [n, (%)]	56 (22.1)	22 (18.8)
ECOG PS		
0 [n, (%)]	**72 (28.5)**	**45 (38.5)**
1 [n, (%)]	**181 (71.5)**	**72 (61.5)**
Creatinine clearance [(n, (%)]		
> 60	134 (54.0)	69 (59.0)
40-60 (mL/min)	104 (41.9)	41 (35.0)
< 40	10 (4.0)	4 (3.4)
Missing	0 (0)	3 (2.6)
No. Organs involved [(n, (%)]		
1	62 (24.5)	31 (26.5)
2	87 (34.4)	39 (33.3)
≥ 3	104 (41.4)	47 (40.2)
Visceral involvement [(n, (%)]	187 (73.9)	87 (74.4)
Relapse/progression within 6 months of prior CTx*	82.4%	86.1%
Prior platinum regimen		
Cisplatin (no other plat.)	164 (64.8)	85 (72.6)
Carboplatin (no other plat.)	75 (29.6)	23 (19.7)
Other plat. combination	14 (5.6)	9 (7.7)

*based on 250 patients in the vinflunine + BSC and 108 patients in the BSC arm

Outcomes

5.2.5 *Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.*

The primary efficacy endpoint was overall survival (defined as the time elapsed between randomisation and death or last follow-up).

The secondary endpoints were:
Best confirmed complete responses (CR) and partial responses (PR), from the date of randomisation until the end of treatment:

- Objective response rate: total rate of CR and PR (calculated from the confirmed best response recorded from the date of randomisation until the end of treatment).
- Time to onset of response: time until first CR or PR for patients with a confirmed response.
- Duration of response: calculated in responders (ie confirmed CR and PR) from the date on which the criteria of CR or PR were met for the first time until the date of disease progression or death from any cause (whichever comes first).
- Duration of stable disease (SD) calculated as the time between the date of randomisation and documentation of progression or death from any cause.
- Rate of disease control: the total rate of CR plus PR plus SD rate.
- Duration of disease control: Calculated in SD, CR and PR patients as the period between the date of randomisation and documentation of progression or death from any cause.
- Progression-free survival (PFS): calculated from the date of randomisation to the date of progression or death from any cause (whichever comes first).

The duration of response, stable disease, disease control the duration of the disease were censored at the time of the introduction of any new treatment.

Other criteria

- Quality of life (QoL): according to the primary parameters of EORTC QoL questionnaire (QLQ-C30). The secondary QoL parameters included the 14 other scales: the 5 functional scales and the 9 scales of "symptoms".
- Response in terms of clinical benefit: the main criterion of clinical benefit was defined as an improvement in the three months following the first dose of study medication or the first visit of at least one of the following parameters, performance score, weight, current intensity of pain compared to baseline and without prior or concomitant deterioration of another parameter

Evaluation Criteria: Independent review committee (IRC)
The objective of the IRC was to independently assess patient responses and progression-free survival. The IRC assessed tumour responses and progression using radiographs and clinical data from randomised patients. Tumour responses were assessed according to RECIST criteria for each patient

until disease progression or until May 31, 2007 (closing date).

A contract research organisation (Synarc) performed the Independent radiological and clinical assessments.

Statistical analysis and definition of study groups

5.2.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Primary Hypothesis

The objective of the protocol was to show significant survival superiority in the vinflunine + BSC arm versus the BSC only arm. The sensitivity analyses for the primary efficacy parameter included :

- overall survival analysed in the per protocol population.
- overall survival censored at the time (start date) of further chemotherapy in the randomised population and in the statistical analysis plan per protocol population.

The estimation of the number of events was based on the following clinical hypotheses :

- the median survival time for vinflunine + BSC arm is 6 months.
- the median survival time for BSC arm is 4 months.

Calculating the number of subjects:

For a total of 364 subjects randomized 2:1 in the vinflunine + BSC and BSC treatment groups, a total of 290 deaths were required to reject the null hypothesis that the risks of death (λ) were similar between the 2 groups:

$H_0: \lambda_{BSC} / \lambda_{vinflunine} = 1$

- With a power of 90% and a significance threshold of 5% bilaterally, using the log-rank test.
- The following assumptions were made:
  - Overall survival time followed the exponential law,
  - Median overall survival was 6 months for the vinflunine + BSC arm and 4 months for the BSC arm (von der Maase H, 2000, Sternberg CN, 1988), which corresponds to vinflunine, with a reduced risk of death of 1 / 3 under the alternative hypothesis (ie, relative risk of death [A / B] = 2 / 3)
  - Constant recruitment rates over 24 months
  - A follow-up time of 6 months after randomisation of the last topic
  - 10% of subjects would be lost to follow-up.

For patients who had not died, survival duration was censored at the date of last news if the patient was lost to follow-up or reached the time point of analysis without a known record of death. For patients who received secondary chemotherapy, survival duration was censored at the start date of the secondary chemotherapy.

A Cox multivariate analysis on survival was performed in order to take into account prognostic factors (treatment group, alkaline phosphatase (< median, ≥ median), haemoglobin (< median, ≥ median), visceral metastases (yes, no), WHO PS (0, ≥1), radiotherapy of the pelvis (yes, no), and the presence of lymph nodes (yes, no)). Survival information was collected approximately every 6 weeks during the first 6 months and then every 2 months until death.

Secondary Objectives

Secondary objectives were to compare patient benefit through a quality of life questionnaire (EORTC QLQ-C30) and clinical benefit parameters, to compare the safety profile in both arms and to assess response rate (according to RECIST). The Independent Review Committee (IRC) reviewed tumour assessments with CR and PR, time to response, response duration and progression free survival.

Statistical methods for categorical variables: the $\chi 2$ test was performed to compare proportions or replaced by Fisher exact test if the expected frequency in one cell of the contingency table was less than 5. The 95% CI for proportions was computed following the exact method.

Statistical method for ordinal variables: comparison between treatment arms was provided for ordinal data using the non-parametric Wilcoxon rank sum test.

Statistical method for continuous variables: the distribution of quantitative data was examined by the Kolmogorov-Smirnov test in order to test for normality. In case of Gaussian distribution, the comparison between treatment arms was made with a Student t-test. In case of non-Gaussian distribution, a non-parametric Wilcoxon test was performed.

Statistical methods for time to event data: Kaplan-Meier curves and life tables by treatment arm were used to describe time dependent parameters. Confidence intervals on the median were calculated using the reflection method. Stratified Log rank tests were performed to compare the two arms for overall survival. Multivariate analyses were performed to take into account the prognostic factors. A stratified Cox proportional hazard model was applied to the data.

Statistical methods for Quality of Life data: data was analysed with a mixed effect model with change from baseline as the response. The most suitable covariance structure was chosen according to Akaike's Information Criterion and Schwartz Bayesian Criterion between unstructured, compound symmetric and autoregressive of order 1.

Populations analysed

1) Intent to treat population (ITT): all randomised patients whether treated or not were analysed in the group they were assigned by randomisation.
2) Eligible ITT patients were an ITT population that excluded 13 patients who were randomised but did not meet the eligibility criteria at baseline. These protocol violations were not treatment related.
3) Per protocol population: patients that were eligible and treated in the arm assigned by randomisation.
4) Evaluable for response: patients that were eligible, evaluable and treated in the arm assigned by randomisation.
5) Evaluable for safety: included all treated patients, in the treatment arm they actually received.

6) Evaluable for quality of life: included patients who completed (more than two thirds of the questions) one questionnaire within 14 days prior to randomisation and at least one questionnaire during study period at least 21 days after the beginning of study treatment or first visit for patients in BSC group. Patients were analysed in the group they were assigned by randomisation.

Table B7: Populations analysed for efficacy (study 302)

	Populations analysed in study 302	
	vinflunine+BSC	BSC
Randomised patients (ITT population)	253 (100.0%)	117 (100.0%)
Eligible ITT population	249 (98.4%)	108 (92.3%)
Per-protocol population	248 (98.0%)	117 (100.0%)
Population evaluable for response according to investigator	215 (85.0%)	93 (79.5%)
Population evaluable for response according to IRP/IRRC/IRC	185 (73.1%)	85 (72.6%)

Efficacy Analysis

Primary efficacy analyses for overall survival were performed on the whole randomised population using a log-rank test and a multivariate analysis using a Cox proportional hazards model, on the pre-planned per-protocol populations and on the eligible ITT population. Secondary end point analyses were performed on the whole randomised ITT population and on the response evaluable population.

5.2.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

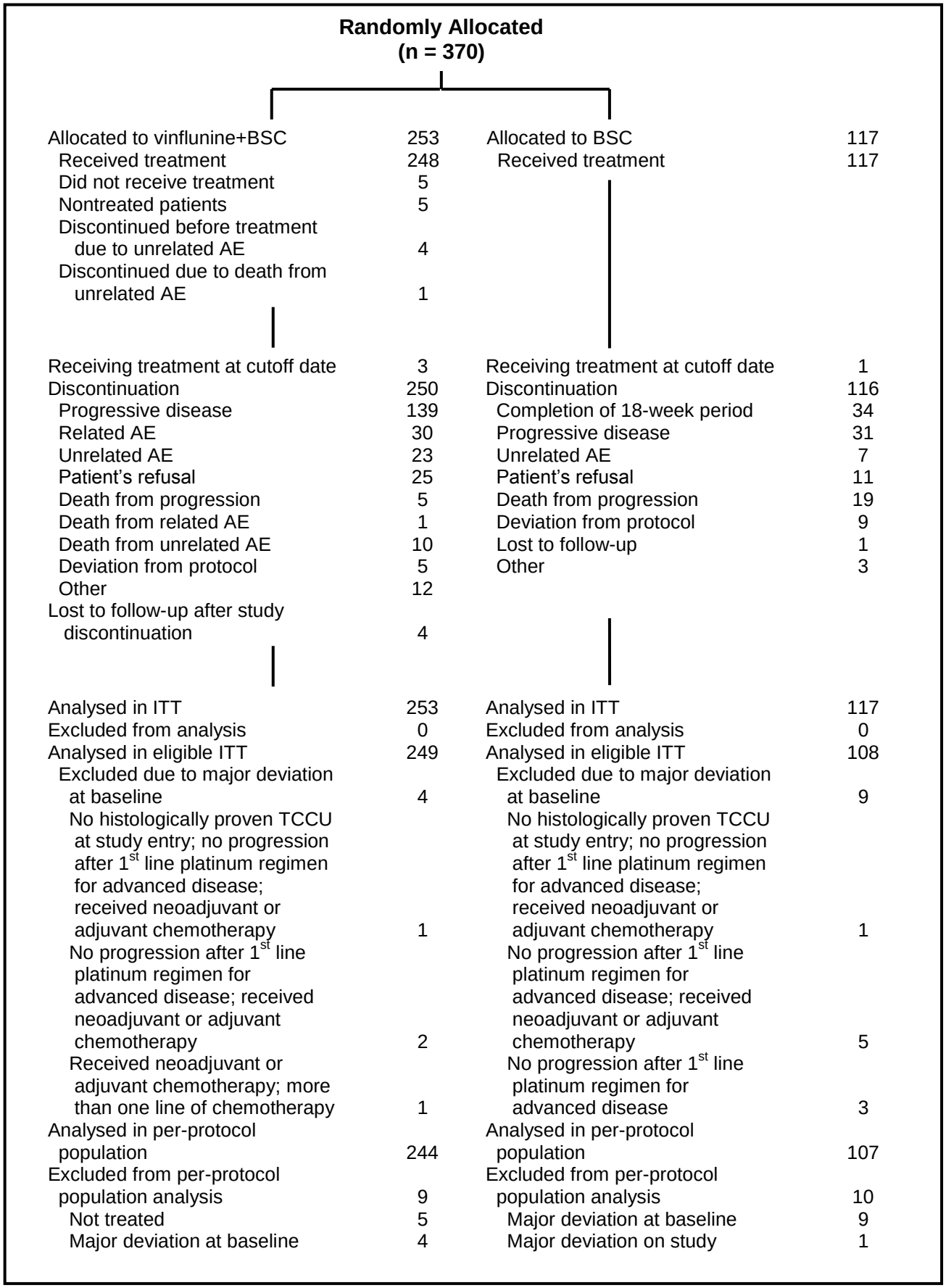
Major clinical deviations from the eligibility criteria were observed in the ITT population for 13 patients who had at least one major protocol violation. Exclusion of these 13 patients defines the eligible ITT sub-group that was analysed post-hoc. This eligible ITT group corresponds to the population targeted by the protocol. The overall survival analysis of these 357 patients is acceptable as being a comparison of randomly assigned groups because the violations cannot be a result of treatment. The CHMP assessment report (EMEA/H/C/000983) also considered that the eligible ITT population was the most relevant for the efficacy analysis as it most closely reflects the population intended for treatment.

Pre-planned efficacy analyses were performed, based on blinded assessment by an Independent Review Panel (IRP), on patients with partial or complete responses or long stabilizations (lasting at least 4 cycles). Also, an Independent Review Committee (IRC) evaluated study-related images and a subset of selected, prospectively defined clinical information for all patients who were randomized.

Participant flow

5.2.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure B2: Consort Diagram Study 302



Critical appraisal of relevant RCTs

5.2.9 *The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.*

- *Was the method used to generate random allocations adequate?*

Yes, the Biometric department of Pierre Fabre Medicament performed randomisation. Patients were randomised 2:1, Vinflunine + BSC versus BSC. Patient randomisation was limited to stratification by study site and whether a patient was refractory to prior chemotherapy (defined as progression within the first 2 cycles of a prior platinum-containing regimen). The baseline patient demographics were well balanced between the two arms, with the exception of PS (Table B6).

- *Was the allocation adequately concealed?*

This was an open-label study.

- *Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?*

The eligibility criteria for this RCT and the comparison to BSC selected a patient population with aggressive disease and short term predicted survival. As shown in Table B6, the groups were evenly matched for all parameters except PS which was an important first-line prognostic factor (Bellmunt et al 2009). There was an imbalance of 10% for PS favouring the control arm.

- *Were the care providers, participants 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)?*
-

This was an open-label study, but the independent review committee (IRC) were blinded, thereby minimising the potential for bias from the analysis of the evaluable population..

- *Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?*
-

The drop-out rate was evenly balanced between both arms.

- *Is there any evidence to suggest that the authors measured more outcomes than they reported?*

No, the publication of study 302 (Bellmunt et al., 2009) is consistent with the protocol.

- *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, an ITT analysis was completed. A further ITT analysis was carried out on the population of randomised patients that excluded the 13 ineligible patients with protocol violations at baseline unrelated to treatment. Of the study population, 9/117 (7.69%) patients were excluded from the BSC arm and 4/253 (1.58%) from the vinflunine + BSC arm (see 5.3.7 and Figure B2). This group is referred to as the eligible ITT population.

5.2.10 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

Please see Appendix 3, section 9.

5.2.11 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

There was only one RCT identified.

5.3 Results of the relevant RCTs

5.3.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. ***If there is more than one RCT, tabulate the responses.***

5.3.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

5.3.3 For each outcome for each included RCT, the following information should be provided.

- *The unit of measurement.*
- *The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.*
- *A 95% confidence interval.*
- *Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.*
- *When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.*
- *Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.*
- *Discuss and justify definitions of any clinically important differences.*
- *Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.*

Efficacy Results

Definitions of the different populations analysed (as above)

- ITT population: all randomised patients.
- Eligible ITT population; the ITT population minus 13 ineligible patients that did not meet the inclusion criteria at base line (as described in 5.3.7 and in the Consort diagram, Fig. B2).
- Per-protocol population (eligible and treated)
- Total evaluable for response: eligible patients who received a minimum of 2 cycles during 42 days of treatment.

Primary endpoint (OS)

The main objective of the study was to demonstrate superiority of Vinflunine + BSC over BSC in terms of survival on the basis of the statistical hypothesis that the median survival in the vinflunine + BSC group would be 6 months (Culine et al., 2006) versus a median survival of 4 months in the BSC group (von der Maase et al., 2006).

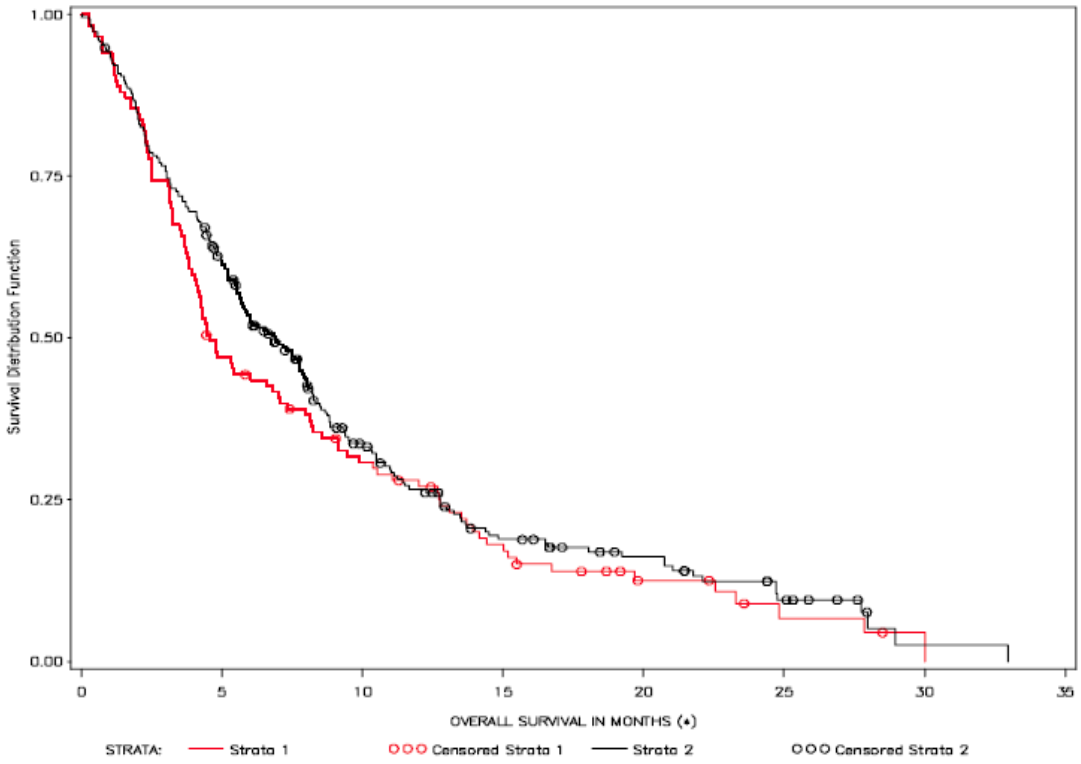
Table B8: Summary of OS results for the ITT and eligible ITT populations

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 (5.7-8.0)	4.3 (3.8-5.4)	0.013	0.74 (0.59-0.94)

Overall survival in the ITT population

In the ITT population, the goal of achieving at least a two month median survival advantage for vinflunine + BSC over BSC was reached (6.9 months versus 4.6 months) and the risk of death was reduced by 12%. As summarised in the Table B8 and Figure B3, the log-rank test was not statistically significant.

Figure B3: Overall survival. All randomised (ITT) patients



	VFL + BSC N = 253	BSC N = 117
No. of events	204	103
No. censored (%)	49 (19.4)	14 (12.0)
Overall survival in months:		
Median (95% CI)	6.9 (5.7, 8.0)	4.6 (4.1, 7.0)
Hazard ratio (95% CI)	0.88 (0.69, 1.12)	
p value[a]	0.2868	

a: Stratified log rank test; CSR VFL 302 Table 34

Planned Multivariate Analysis

The pre-specified multivariate analysis conducted on the ITT population showed that vinflunine had a statistically significant (p = 0.036) affect on overall survival when pre-determined prognostic factors were considered: PS, visceral invasion, alkaline phosphatase, haemoglobin and prior pelvic irradiation.

In this model, vinflunine reduces the risk of mortality by 23% versus BSC, with a relative risk of 0.77 (CI 95%: 0.61-0.98) (Table B9).

Table B9: Multivariate analysis of overall survival using a Cox proportional hazards model

Randomisation Variables[a]	Relative Risk (CI 95%)	*P* Value [b]
Treatment group	0.772 (0.61, 0.98)	0.0360
Alkaline phosphatase	0.624 (0.50, 0.79)	< 0.0001
Haemoglobin	0.660 (0.52, 0.84)	0.0007
Visceral metastases	0.635 (0.48, 0.84)	0.0013
WHO PS	0.482 (0.37, 0.63)	< 0.0001
Pelvic irradiation	0.742 (0.56, 0.99)	0.0425

a : This analysis used the following prognostic factors (at study entry): treatment group, alkaline phosphatase (<median, ≥median), haemoglobin (<median, ≥median), visceral metastases (yes, no), WHO PS (0, ≥ 1), pelvic radiotherapy (yes, no).
b : p value Chi-square of Wald - CSR 302 vinflunine

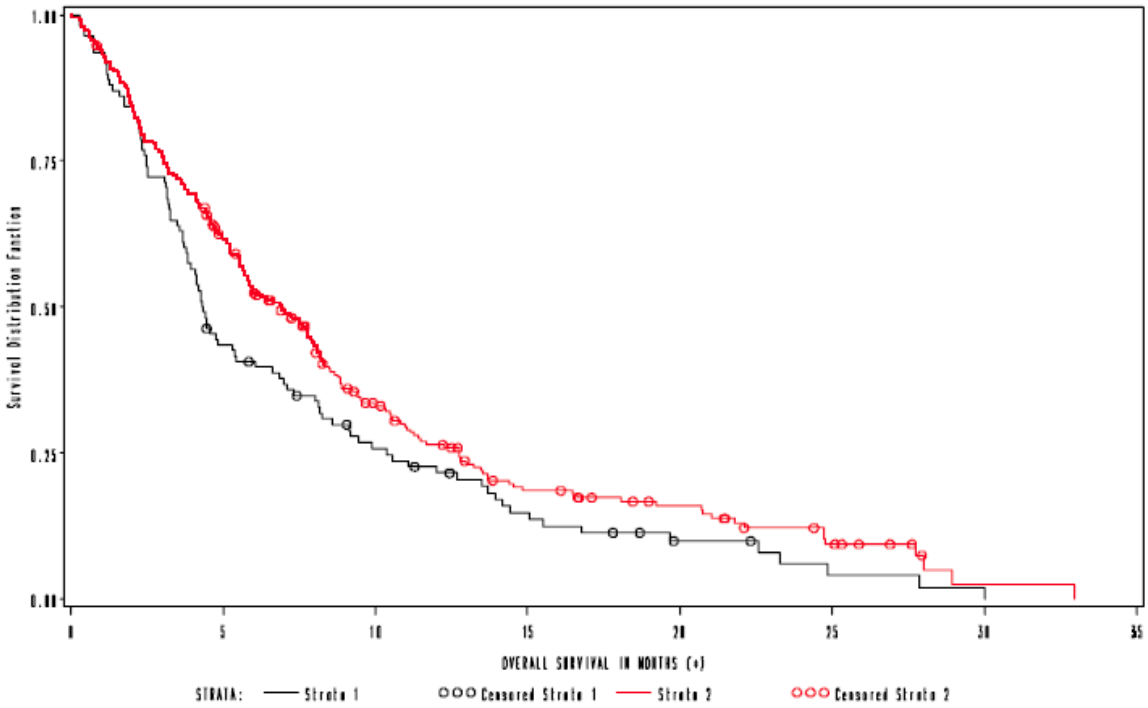
Plausible explanations for the difference in statistical significance between the ITT population log-rank test and the multivariate analysis were sought by examining some limitations of the trial; this included the imbalance between PS which favoured the BSC arm. Study 302 was not initially stratified by PS but only by study site and refractoriness to prior platinum-based therapy. A multivariate analysis (Table B9) using a Cox proportional hazards model adjusted for pre-specified prognostic factors (Bellmunt et al., 2009, Bajorin et al., 1999)showed that vinflunine reduced the risk of death by 23%. This and all of the other prognostic variables showed significant differences between the two study arms.

Overall survival in the eligible ITT population:

Evidence of anti-cancer activity and therapeutic benefit in these patients, with a very short life expectancy (~4 months), may be affected by any difference in clinical criteria governing study eligibility.

In the eligible ITT population, a median survival advantage of 2.6 months was observed in the vinflunine + BSC group (6.9 month v 4.3months for BSC) and the risk of mortality was reduced by 22% as summarised in Table B8 and Figure B4.

Figure B4: Overall survival in the eligible ITT population



	VFL+BSC (N=249)	BSC (N=108)
No. of events	202	98
No of censored (%)	47 (18.9)	10 (9.3)
Median in months (95% CI)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
Hazard ratio (95% CI)	0.78 (0.61, 0.99)	
p value[a]	0.0403	

a: Stratified log rank test ; CSR VFL 302 Additional efficacy analysis Table 10

To confirm these positive findings and to verify that the potential imbalances in prognostic factors resulting from the exclusion of some patients from the eligible ITT group does not call into question the treatment effects on overall survival, an extended Cox multivariate analysis was carried out on the eligible ITT population. This takes into account the adjusted prognostic factors pre-specified by the protocol and is summarised in Table B10.

The data show that potential imbalances in prognostic factors caused by the exclusion of 13 ineligible patients did not impact on the treatment effect seen in the eligible ITT population.

To examine the consistency of results, the same approach was used in the ITT population and it was again shown that the treatment had a significant impact on overall survival (Table B10).

Table B10: Summary of results on overall survival

	Median overall survival *(months)*		HR (CI 95 %) p value	
	vinflunine + BSC	BSC	Stratified log-rank test	Extended multivariate analysis
ITT	6.9	4.6	0.88 (0.69 – 1.12) p = *0.2868*	0.74 (0.57 – 0.96) p = *0.0221*
Eligible ITT population	6.9	4.3	0.78 (0.61 – 0.99) p = *0.0403*	0.68 (0.52 – 0.88) p = *0.0035*

Long Term Follow-up

These data were confirmed in a long term follow-up reported at the European Association of Urology meeting on 17th April 2010 (Culine et al., 2010; median duration of follow-up: 42 months). In the whole ITT population the objective of the 2 month median survival advantage favouring vinflunine + BSC was achieved, (6.9 versus. 4.6 months, HR 95%CI: 0.88 [0.70-1.10]) but not statistically significant (p=0.26), while the planned multivariate analysis adjusting for prognostic factors still showed a statistically significant effect of vinflunine on OS (p=0.025) with risk of death reduced by 23% versus BSC (HR: 0.77 [0.61 – 0.97]). In the eligible ITT population OS was significantly longer for vinflunine + BSC: 6.9 versus 4.3 mo, (HR: 0.78 [0.61 – 0.96]; p=0.02)]. This update confirms that the median survival difference previously observed in the original publication of the data is maintained with long term follow-up. These findings were additionally supported by a sensitivity analysis that considered all censured data as events in the vinflunine + BSC arm: a difference >2 months in median survivals has always been observed. ORR, disease control, PFS were all statistically significant favouring vinflunine + BSC (p=0.006, p=0.002, p=0.001, respectively).

Characteristics of Ineligible Patients

The protocol for study 302 specified a patient population with advanced or metastatic disease that was progressing. The expected survival for this population is expected to be short and the use of BSC as the control is justified. Thirteen patients were ineligible and were not representative of this target study population. The reasons for ineligibility are summarised in Table B11.

Table B11: Ineligible patients at study entry

Patient Number	Protocol violation	Treatment	Survival (months)	Status at cut off November2006
Patients with 3 protocol violations				
550543	(2) (3) (4)	vinflunine	15.7	Lost to follow-up
550202	(2) (3) (4)	BSC	4.8	Deceased
Patients with 2 protocol violations				
050419	(1) (4)	vinflunine	5.5	Alive
060601	(3) (4)	BSC	13.1	Deceased
110206	(3) (4)	BSC	19.2	Alive
130101	(3) (4)	BSC	15.2	Deceased
520704	(3) (4)	BSC	12.7	Deceased
550243	(3) (4)	vinflunine	2.6	Deceased
550301	(3) (4)	vinflunine	5.7	Deceased
600401	(3) (4)	BSC	15.5	Alive
Patients with1 protocol violation				
030206	(3)	BSC	12.7	Deceased
110504	(3)	BSC	23.6	Alive
550644	(3)	BSC	28.5	Alive

(1) More than one line of chemotherapy (1 patient vinflunine)
(2) Not histologically proven advanced or metastatic transitional cell carcinoma of the urothelium at study entry (2 pts: 1 BSC 1 vinflunine).
(3) No progression after first line platinum-based chemotherapy for treatment of advanced disease (12 pts: 9 BSC, 3 vinflunine)
(4) Patient had received neoadjuvant or adjuvant chemotherapy (10 pts: 6 BSC, 4 vinflunine)

Impact of ineligible patients

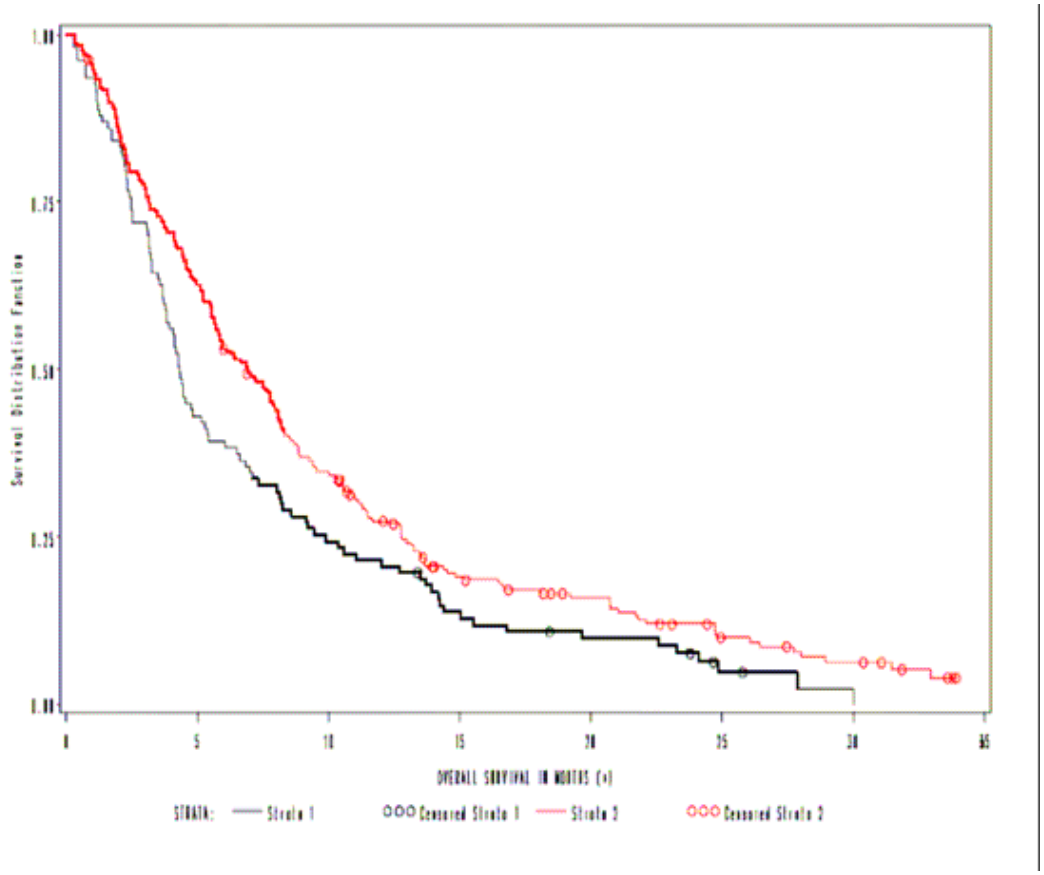
The median survival of 13.1 months observed in 13 ineligible patients is clearly different and falls outside the confidence intervals observed in the eligible ITT population (Table B11).

The fact that the proportion of ineligible was higher in the BSC group, may explain why the treatment effect did not reach statistical significance in the primary analysis ITT population (stratified log rank test).

Per Protocol Analysis

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 month advantage favouring vinflunine + BSC (6.9 month versus 4.3 months), with a reduction in risk of death by 26% HR 0.74 (95% CI: 0.59, 0.94). This difference was statistically significant (p = 0.0130).

Figure B5: Overall survival, per protocol population study 302



	VFL+BSC (N=244)	BSC (N=107)
No. of events	216	102
No of censored (%)	28 (11.5)	5 (4.7)
Median in months (95% CI)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
Hazard ratio (95% CI)	0.74 (0.59, 0.94)	
p value[a]	0.0130	

Results on secondary endpoints

All of the secondary endpoint analyses demonstrated statistically significant differences in favour of patients treated with vinflunine + BSC and confirmed the clinical benefits previously observed in two Phase II studies.

Response rate:

According to the IRC, the overall and objective response rates in the vinflunine + BSC arm were 8.6% (95% CI: 5.0 -13.7) among evaluable patients (n = 185) and 0% in the BSC alone arm (see Table B12).

Table B12: Response rates of evaluable patients

Response Rates: Evaluable Patients	VFL + BSC	BSC
Investigator Best Overall Response, N (%)	**N= 215**	**N= 93**
CR	0 (0)	0 (0)
PR	28 (13.0)	0 (0)
SD	106 (49.3)	21 (22.6)
PD	81 (37.7)	72 (77.4)
ORR, % (95% CI)	13.0 (8.8, 18.3)	0 (0)
IRC Best Overall Response, N (%)	**N= 185**	**N= 85**
CR	0 (0)	0 (0)
PR	16 (8.6)	0 (0)
SD	86 (46.5)	23 (27.1)
PD	83 (44.9)	62 (72.9)
ORR, % (95% CI)	8.6 (5.0, 13.7)	0 (0)

The median time from randomisation to the first response was 2.1 months in the vinflunine + BSC group (n = 16 responders) and was comparable for the ITT and evaluable populations.

In the evaluable population the median duration of response was 7.4 months in the vinflunine + BSC group.

The median durations of stable disease in the evaluable population were comparable to those observed for the ITT population: 5.4 months (95% CI: 4.6-6.1) in the vinflunine + BSC arm versus 4.2 months (95% CI: 3.8-4.9) in BSC arm.

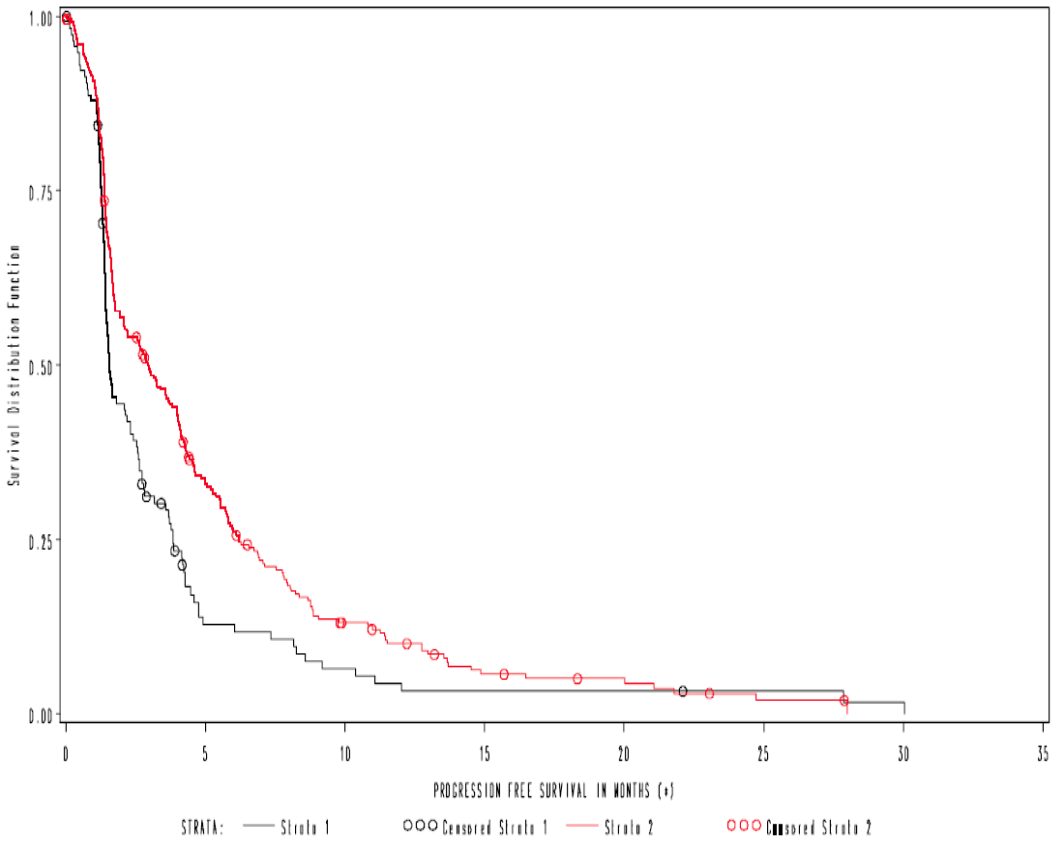
Disease control rate (DCR):

According to the IRC, the rate of disease control (CR + PR + SD) among evaluable patients was significantly higher in the vinflunine + BSC arm than in the BSC group (55.1% versus 27.1%, p <0.0001) (Table B12) and the median duration of disease control in the randomised population was significantly longer (p = 0.0233) in the vinflunine + BSC group than in the BSC group (5.7 months - 95% CI 5.0 to 6.3 months - versus 4.2 months - 95% CI 3.8 to 4.9 months).

Progression Free Survival (PFS):

The PFS was significantly longer (HR = 0.68, CI 95%: 0,54-0,86, p = 0.0012) in the vinflunine + BSC group than in the BSC arm (3.0 months [CI 95%: 2,1 - 4.0 months] versus 1.5 months [95% CI: 1.4 to 2.3 months] (Figure B6).

Figure B6: Progression Free Survival (IRC) in the ITT population



	VFL+BSC (N=253)	BSC (N=117)
No. of events	228	107
No. censored (%)	25 (9.9)	10 (8.6)
PFS in months		
Median (95% CI)	3.0 (2.1, 4.0)	1.5 (1.4, 2.3)
Hazard ratio (95% CI)	0.68 (0.54, 0.86)	
p value[a]	< 0.0012	

Clinical benefit and quality of life:

The EORTC QLQ-C30 questionnaire was completed at study entry, at the end of cycles 1, 2, 4, and 6 for the vinflunine + BSC arm and at entry and on days 21, 42, 84 and 126 for the BSC arm. The compliance at study entry was 91.3% in the vinflunine + BSC arm and 90.6% in the BSC arm.

Compliance at the end of cycle 6/day126 was 58.4% in the vinflunine + BSC arm and 53.7% in the BSC arm. There were no statistically significant differences in overall score EORTC QLQ-C30 between the two groups compared to the condition of patients entering the study (p = 0.658).

Initially there was a greater number of patients with intolerable pain requiring chronic treatment with morphine in the vinflunine + BSC group than in the BSC arm (23.3% versus 17.1%).

During the study fewer patients required radiotherapy for symptom control in the vinflunine + BSC (4%) than in the BSC group (23.9%) demonstrating a positive impact of vinflunine on symptomatology.

Overall, even in a poor prognosis population, vinflunine had no deleterious effect on Quality of Life. Considering clinical benefit and quality of life, there was no statistically significant difference between groups.

The clinical benefit parameter is a composite which takes into account the parameters evaluated during the period from randomisation to each cycle/21 days: PS (WHO scale), weight and intensity of pain (measured by the pain questionnaire deMcGill-Merlzack) and the incidence of symptomatic radiation referred to above. The response rate of clinical benefit in the evaluable population was 9.4% in the vinflunine + BSC arm and 7.6% in the BSC arm (p = 0.6066).

Conclusion

The objective in the Phase III trial (study 302) of a median survival advantage of 2 months for the vinflunine + BSC arm was achieved. In the eligible ITT population, (i.e. that which accurately represents the target population of patients with advanced or metastatic TCCU who had progressed following platinum-based first-line treatment), there was a survival advantage of 2.6 months, representing a 60% improvement in survival. The risk of death in this group was significantly reduced by 22% (p = 0.0403, HR 0.78; 95% CI: 0.61 - 0.99).
These results were confirmed by multivariate analysis conducted on the eligible population (p = 0.0035) (HR: 0.68, CI 95%: 0,52-0,88) and the ITT population (p = 0.0221) (HR 0.74, CI 95%: 0,57-0,96) and in a long term follow-up analysis.

The secondary efficacy endpoints, progression-free survival, response rate and overall rate of disease control, which are important in this end of life context, were all statistically significant in favour of vinflunine + BSC.

The efficacy results of study 302 are summarised in Table B13.

This randomised study confirmed and extended the results of two phase II trials.

Table B13: Summary of efficacy results

	Number of patients (%)	
	vinflunine+BSC (N=253)	BSC (N=117)
ORR (ITT) N (%) (95% CI)	16 (6.3) (3.7 ; 10.1)	0
ORR (IRC) evaluable patients N (%) (95% CI)	N = 185 16 (8.6) (5.0 ; 13.7)	N = 85 0
Disease control rate (%) (IRC) (95% CI) *p*	(41.1) (35.0 ; 47.4) *p = 0.0024*	(24.8) (17.3 ; 33.6)
Response duration (IRC) months (95% CI)	7.4 (4.5 ; 17.0)	-
Disease control duration (IRC) months (95%CI) *p*	5.7 (5.0 ; 6.3) *p = 0.0233*	4.2 (3.8 ; 4.9)
PFS months (IRC) (95% CI) *p*	3.0 (2.1 ; 4.0) *p = 0.0012*	1.5 (1.4 ; 2.3)
Overall survival months (95% CI) Randomised population *p*	N = 253 6.9 (5.7 ; 8.0) *p = 0.2868*	N = 117 4.6 (4.1 ; 7.0)
Overall survival months (95% CI) Eligible ITT population *p*	N = 249 6.9 (5.7 ; 8.0) *p = 0.0403*	N = 108 4.3 (3.8 ; 5.4)

5.4 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.4.1 The following steps should be used as a minimum when presenting a meta-analysis.

- *Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.*
- *Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).*
- *Provide an adequate description of the methods of statistical combination and justify their choice.*
- *Undertake sensitivity analysis when appropriate.*
- *Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).*

5.4.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

There was only one RCT identified, a meta-analysis is therefore not possible.

5.4.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

5.5 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.5.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

The treatment of advanced or metastatic TCCU patients who have failed prior treatment containing a platinum salt is an unmet clinical need that has been the subject of empirical testing with a number of agents in phase II settings. The systematic search for evidence described in sections 5.1.1 to 5.1.7 established that prior to the vinflunine phase II trials. No other agent has demonstrated clinically relevant efficacy with a positive risk / benefit balance that warranted further testing in a phase III study. The single RCT (study 302), which tested vinflunine in a relevant disease setting, employed BSC as a control and there are no identifiable studies with which indirect or mixed treatment comparisons may be made.

5.5.2 *Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.*

5.5.3 *Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.*

5.5.4 *For the selected trials, provide a summary of the data used in the analysis.*

5.5.5 *Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.*

5.5.6 *Please present the results of the analysis.*

5.5.7 *Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.*

5.5.8 *If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.*

5.5.9 *Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.*

5.6 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.6.1 *If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.*

The systematic review described in sections 5.1 to 5.6 were designed to identify all evidence for efficacy and safety of vinflunine in the treatment of TCCU as well as potential comparators in all clinical trial and non-trial settings. This review identified two reports of non-RCT evidence for vinflunine (both were phase II studies; Table B14) and a number of phase II studies with other agents. The studies with other agents were excluded on the basis that they did not meet the inclusion criteria described in 5.1-5.6 and Appendix 9.

Table B14: Non-RCTs

Study	Objective	Administration	Patient No	Diagnosis	End-points
L00070 IN 202 P1 (study 202) Phase II multicenter open-label, nonrandomised trial, in 2nd line	Efficacy and safety	Vinflunine every 3 weeks Initial dose : 350mg/m^2 (1st 6 patients) 320 mg/m^2	n = 58	TCCU after failure of a prior platinum-containing regimen	Primary end-point : ORR Secondary: Response duration, disease control, progression-free-survival, overall survival
CA 183001 (CA 001) Phase II multicenter open-label, nonrandomised trial, in 2nd line	Efficacy and safety	Vinflunine every 3 weeks Initial dose : 320 or 280 mg/m^2	n = 151	TCCU after failure of a prior platinum-containing regimen	Primary : Response rates Secondary: Response duration, time to response, disease control, progression-free-survival, overall survival

5.8.2 *Summary of methodology of relevant non-RCTs*

The methodology employed in the two identified non-RCT studies, study 202 and study CA 001, is summarised in Table B15.

Table B15: Summary of methodology for non-RCTs

Trial no. (acronym)	**L00070 IN 202 P1 (Study 202)**	**CA 183001 (CA 001)**
Location	International multicentre; 16 European centres	International, multicentre 60 centres from 12 countries, most sites in the USA
Design	Open-label, non-comparative, interventional, phase II in patients with advanced TCC of the bladder who had received one previous line of platinum-based chemotherapy.	Open-label, non-comparative, interventional, phase II in patients with advanced transitional cell urothelial cancer not suitable for regional/local therapy and had progressed within 12 months of ≥ 2 cycles of platinum-based chemotherapy.
Duration of study	1year 9 months (November 2000-September 2002)	2 year 4 months (January 2005 and April 2007).
Method of randomisation	N/A	N/A
Method of blinding	N/A	N/A
Intervention(s) (n =)	Vinflunine (n= 58) 350mg/m^2 or 320mg/m^2 3 weekly	Vinflunine (n= 151) 280 – 320mg/m^2 3 weekly
Primary outcomes (including scoring methods and timings of assessments)	Efficacy as second-line therapy in advanced TCCU (response rates). Response was assessed using WHO criteria after two cycles. Patients with progressive disease stopped, stable disease had 2 cycles more and were reassessed. Treatment could be continued according to investigators opinion or until progression, toxicity or patient preference.	To confirm anti-cancer activity and to define ORR in patients not candidates for cystectomy. Responses were defined by the IRRC and were measured in patients receiving at least one cycle of treatment using CT or MRI within 4 weeks of study entry and repeated every 6 weeks.
Secondary outcomes (including scoring methods and timings of assessments)	Duration of response, PFS, OS, assessment of tolerance associated with treatment Assessments as above	Duration of response, time to response, disease control rate, PFS, OS and safety profile. Assessed as above
Duration of follow-up	All lesions were regularly assessed beyond the end of the study until progression or start of another treatment	Responses were assessed every six weeks. Median duration of follow-up = 11.9 months

TITLE: Phase II Study of IV Vinflunine in second-line treatment in patients with advanced transitional cell bladder cancer. (study 202)

The study design is summarised in Table B15.

Description of treatment groups and posology

Vinflunine was administered at 350 mg/m² every three weeks in the first 6 patients. A preliminary safety evaluation, performed programme-wide across all ongoing phase II trials, led to a dose reduction to 320mg/m^2 3 weekly. Fifty-one patients were treated at this dose and one patient died before receiving any treatment. All patients who received at least one cycle of treatment were evaluable for safety. The efficacy analyses were confined to the 51 patients treated at 320mg/m^2.

Treatment was discontinued for:

- Disease progression
- Unacceptable toxicity
- Intercurrent illness or other reasons deemed by the investigator to significantly affect the patient's clinical condition if treatment was continued
- Patient requests that they leave the study

Table B16: Dose of vinflunine in study 202

Initial dose	Number of patients			
	Entered	Treated	Eligible	Evaluable
350 mg/m^2	6	6 (100%)	5 (83.3%)	3 (50%)
320 mg/m^2	52*	51 (98.1%)	50 (96.2%)	47 (90.4%)

*One patient died before receiving treatment

Table B17: Study 202 Eligibility criteria

Inclusion criteria	Exclusion Criteria
- Transitional cell carcinoma (TCCU) of the bladder confirmed by histology, - Patients with refractory or progressive disease, progressed after first line platinum-based chemotherapy for advanced or metastatic disease, or patients with disease progression after chemotherapy with platinum-based adjuvant or neo-adjuvant therapy - Any systemic chemotherapy or radiotherapy must have been terminated 30 days before administration of study medication and the patient must have recovered from all adverse events - At least one lesion not previously irradiated and measured in two dimensions by CT or MRI; measurements must have been performed < 28 days before the first day of administration of study medication - Age ≥ 18 years - Karnofsky index (KPS) ≥ 80% - Estimated life expectancy of at least 12 weeks - Appropriate marrow, liver and kidney function: • ANC ≥ 2.0 x 10^9/L, platelets ≥ 100 x 10^9/L • Bilirubin ≤ 1.5 x upper limit of normal (ULN). Transaminases ≤ 2.5 x ULN, unless the increase was due liver involvement • Creatinine clearance calculated (≥ 40 ml / min); Cockcroft and Gault formula • Normal ECG (within 7 days preceding administration of study drug)	- Bladder cancer other than transitional cell (adenocarcinoma, squamous cell carcinoma or other) - Patients with transitional cell carcinoma not originating in the bladder - Presence of metastasis (s) brain (s) or breach leptomeningeal. The CT was not required to exclude this possibility, except in cases of clinical suspicion of central nervous system (CNS) involvement - Pleural effusion / ascites or bone metastases as the only evaluable lesions, - Other serious diseases or conditions including : • Peripheral neuropathy of NCI CTC grade ≥ 2 • Uncontrolled active infection • Any medical condition that may be exacerbated by treatment or could not be controlled: heart failure class III-IV New York Heart Association (NYHA), or unstable angina or a history of myocardial infarction in the previous six months and / or unmanageable hypertension - Concurrent administration of other anticancer or experimental treatment - Patients who received more than one previous systemic chemotherapy containing a platinum salt or patients who received an experimental drug within 30 days preceding the first day of administration of study medication - Other cancers except skin cancer or basal cell cancers of the cervix in situ treated adequately or any other with an interval cancer in remission less than 5 years - Psychological, sociological or family does not allow medical monitoring and compliance of study protocol. - Pregnancy or breastfeeding. - Women of childbearing age must agree to use adequate contraception throughout the period and for 60 days after the last dose of treatment - Patients requiring systemic steroids (except for an antiemetic)

Calculating the number of subjects required:

The multi-step procedure for sample size described by Fleming for Phase II clinical studies was used.

Under this procedure, a cohort of 50 evaluable patients was planned.

Fifty-eight patients were included in the study and 57 patients were treated and analyzed, 51 of whom received the recommended dose (RD) of 320mg/m^2.

Principals Tested

Efficacy was determined according to WHO criteria. An independent committee has validated the responses and long-term stabilisation of disease (for at least two successive evaluations). Tumour assessments were performed every two cycles.

The objective response rate was determined in the ITT and evaluable patient populations. The decision rules were based on the multi-step procedure for a sample devised by Fleming.

The safety profile was evaluated by clinical examination and vital signs, Karnofsky index, blood count, serum biochemistry, tolerability and adverse events using the common toxicity criteria NCI (version 2.0).

Statistical tests used

The duration of response among patients with an objective response, progression-free survival and overall survival were evaluated by the Kaplan-Meier method

Results

The demographic and baseline characteristics of patients included in the analysis of the ITT population treated at the 320 mg/m² dose level are summarised in Table B18.

The analysis of efficacy results is limited to patients treated at 320 mg/m², the population at 350 mg/m² was too small to justify a separate analysis.

All patients included in the study had disease progression after treatment with prior platinum and a high percentage of poor prognosis criteria (49% of visceral invasion and 61% extension in ≥ 2 sites) (Table B18).

Before entering the study, prior therapy included surgery, radiotherapy, or local bladder instillations of either chemotherapy or BCG and all patients had received systemic platinum-based chemotherapy as summarised in Table B19.

Table B18: Patient characteristics study 202

Number of Patients	51
Initial vinflunine dose	320 mg/m²
Body Surface Area (m²)	
Median	1.9
Confidence Interval	1.3-2.4
Age (years)	
Median	63
Confidence Interval	42-81
>65	19 (37.3)
50-65	28 (54.9)
35-49	4 (7.8)
Karnofsky index	N (%)
100 %	12 (23.5)
90 %	16 (31.4)
80 %	22 (43.1)
70 %	1 (2.0)
Male	41 (80.4)
Female	10 (19.6)
Number of organs involved:	
1	20 (39.2)
2	19 (37.3)
≥3	12 (23.5)
Sites:	
Lung only	7 (13.7)
Liver only	6 (11.8)
Bone only	1 (2.0)
Lymph nodes	34 (66.7)
Skin	2 (3.9)
Soft tissue	8 (15.7)
Lung+Liver	9 (17.6)
Lung+Bone	1 (2.0)
Liver+Bone	2 (3.9)
Other organs	12 (23.5)

Table B19: Prior chemotherapy

Number of patients = 51 (100%)		
M-VAC or CMV	Neo-adjuvant Adjuvant Advanced All	1 (2.0) 8 (15.7) 13 (25.5) 22 (43.1)
Gemcitabine/platinum	Neo-adjuvant Adjuvant Advanced All	1 (2.0) 7 (13.7) 17 (33.3) 25 (49.0)
Others	Neo-adjuvant Adjuvant Advanced All	- - 4 (7.8) 4 (7.8)

Response rates (primary endpoint) and disease control are summarised in Table B20.

Table B20: Response Rate and Disease Control rate

	ITT	Evaluable
Number of patients	51	47
Complete response (CR)	-	-
Partial response (PR)	9 (18%)	8 (17%)
Objective Response Rate (OR)	9 (18%)	8 (17%)
95% CI	8.4 – 30.9%	7.7 – 30.8%
Stable disease (SD)	25 (49%)	25 (53%)
Disease control (OR+SD)	34 (67%)	33 (70%)
Progressive Disease (PD)	14 (27%)	14 (30%)
Non evaluable	3 (6%)	NA

After an independent external review, an ORR of 18% (95% CI 8.4 to 30.9) was observed in the ITT and 17% (95% CI 7.7 to 30.8) in the evaluable patient groups Disease control was achieved in 67% and 70% of ITT and evaluable patients respectively.

Patients were stratified according to the time to relapse after their prior platinum-based chemotherapy and the response rates are summarised in Table B21.

Table B21: Response rates according to the time to relapse after prior platinum-based chemotherapy, study 202

	Response rates (n = 51)		
Time to relapse:	**< 3 months**	**3 - 12 months**	**≥ 12 months**
Number of patients (%)	19 (100%)	24 (100%)	8 (100%)
Complete response	-	-	-
Partial response	2 (10.5)	6 (25.0%)	1 (12.5%)
Stable disease	9 (47.4%)	11 (45.8%)	5 (62.5%)
Disease Control rate	11 (57.9%)	17 (70.8%)	6 (75.0%)
Progressive Disease	6 (31.6%)	6 (25.0%)	2 (25.0%)
Non evaluable	2 (10.5%)	1 (4.2%)	-

Result of secondary endpoints

- Median duration of response

The median duration of response was 9.1 months (95% CI 4.2 to 15.0)

- Median progression-free survival

The median progression-free survival was 3 months (95% CI2.4 to 3.8).

- Median overall survival

The median overall survival was 6.6 months (95% CI 4.8 to 7.6).

Conclusion

This Phase II open label study in patients with advanced transitional cell bladder cancer resistant or refractory to prior platinum-based chemotherapy evaluated the efficacy and safety of vinflunine as second line treatment.

Response rates of 18% in the ITT population and 17% in the evaluable population were observed. Disease control was observed in 67% of patients. The median progression-free survival was three months and median overall survival was 6.6 months. These results place vinflunine among the most active drugs in this therapeutic context.

The effectiveness of vinflunine in this Phase II with the associated acceptable tolerance in these patients for whom there was no standard treatment option led to the decision to continue clinical development for TCCU.

TITLE:Phase II study of intravenous (IV) Vinflunine in patients with advanced or metastatic transitional cell carcinoma of the urothelium, Study CA 001.

The study design is summarised in Table B15.

Description of treatment groups and posology

Of the 175 patients enrolled, 151 were treated with vinflunine. The majority of untreated patients did not meet eligibility criteria between the selection and initiation of treatment and 4 untreated patients died before starting treatment.

Of the 151 patients, 5 patients (3.3%) were still being treated at the database lock (3 had stable disease assessed by the investigator and 2 were partial responders).

The median duration of follow-up was 11.9 months (95% CI 9.6-13.0).

Vinflunine was administered every 3 weeks by infusion over 15 to 20 minutes. Based on initial experience with the tolerability of vinflunine and its partial renal clearance, patients with a KPS of 80-90% or CrCl between 20mL/min and 60mL/min or prior pelvic irradiation or who were ≥75 years old received an initial dose of 280 mg/m^2, which was escalated in cycle 2 to 320 mg/m^2 if well tolerated. Other patients received an initial dose of 320 mg/m^2, which could be reduced to 280 or 250 mg/m^2 in subsequent cycles in the presence of grade 3 or 4 toxicity.

The median duration of treatment was 9 weeks with a maximum of approximately 16 months. The median number of cycles was 3 and the maximum 21.

The inclusion and exclusion criteria are summarised in Table B22.

Calculating the number of subjects required

The primary objective of this study was to define the objective response rate. The sample size of 150 was predetermined to achieve a desired CI width around the estimated ORR of 15%. The exact two sided 95% CI would extend to a maximum width of 12% with a lower limit ≥ 10%.

Primary endpoints

The primary efficacy endpoint was ORR, defined as the percentage of patients achieving a CR or PR, determined by an independent response review committee (IRRC). The response was determined using the modified WHO criteria. Tumour assessments were made every two cycles until the

Table B22: Eligibility criteria for study CA 001

Inclusion Criteria	Exclusion criteria
- Adults ≥ 18 years - Advanced or metastatic TCCU confirmed by histology (bladder, kidney, renal pelvis or ureter) - At study entry, patients were not to be candidates for local treatment with surgery or radiotherapy - Patients must have received at least 2 cycles of chemotherapy containing cisplatin at a dose of at least 60 mg/m^2 or carboplatin in a dose corresponding to an AUC 4 - Evidence of the disease by at least one lesion measurable in two dimensions - Patients with refractory or progressive disease occurring within 12 months of at least 2 cycles of platinum based chemotherapy. - KPS > 80% - Patients must have recovered from side effects of previous treatment. - A period of 2 weeks must have elapsed between the last dose of chemotherapy (6 weeks for nitroso-ureas, mitomycin C and liposomal doxorubicin) and the start of study treatment. Following an amendment, a period of 4 weeks was required from the last dose of chemotherapy, immunotherapy and radiotherapy	- Women of childbearing age not using an authorised method of contraceptive - Pregnant or breastfeeding women - Sexually fertile men not prepared to use contraception during the study - Patients with non-transitional cell carcinoma of the urothelial tract - other cancer except skin cancer or basal cell cancers of the prostate (T1a or T1b, Gleason score <6, PSA <0.5 ng.mL) or cancer of the cervix or other cancer with an interval of remission less than 5 years - Patients who have discontinued treatment due to platinum toxicity reasons only - Patients who received more than one line of prior chemotherapy - Presence of brain metastases or leptomeningeal damage. The CT was not required to exclude this possibility, except in cases of clinical suspicion of CNS involvement, - Peripheral neuropathy grade> 2, changed to grade> 3 in Amendment 10 - prior radiotherapy to ≥30% of bone marrow - An uncontrolled medical condition, recent major abdominal surgery, or an active infection that could prevent patients from receiving treatment under the protocol - absolute neutrophil count <1500/mm^3 or platelets <100000/mm^3 - Inadequate liver function defined as bilirubin> 1.5 times the ULN or transaminase> 2 times the normal value (> 5 times normal in cases of liver metastases) - Inadequate renal function defined as CrCl <40 mL/min, or <20 mL/min in Amendment 5 (Cockcroft-Gault), for Canada and Sweden, the creatinine clearance could not be below 40 mL/min - Heart failure class III-IV New York Heart Association (NYHA), or unstable angina or a history of myocardial infarction in the previous six months and / or hypertension - Psychological, sociological or family does not allow medical monitoring or compliance with protocol. - Patients with hypersensitivity to vinca alkaloids - Patients requiring treatment with ketoconazole, itraconazole, ritonavir, amprenavir and indinavir - Concomitant administration of another treatment with immunotherapy, corticosteroids, chemotherapy, radiotherapy, hormone therapy or other experimental treatment

implementation of an amendment which stipulated tumour assessments every six weeks. The primary analysis of response rates was conducted on the ITT population and the secondary analysis on the

population of evaluable patients. The response rate was analysed on the basis of investigator assessment and an IRRC. PFS was calculated on the basis of IRRC evaluation and that of the investigator. The safety assessments were made using the common toxicity criteria (CTC) of the National Cancer Institute (NCI) version 2.0.

Statistical tests used

The duration of objective responses, PFS and OS were evaluated by the Kaplan-Meier method.

Results

The baseline patient characteristics are summarised in Table B23.

Table B23: Baseline characteristics for study CA 001

Characteristic	Total, n= 151 (%)
Age, y	
Median	66
Range	31-83
<65	70 (46.4)
≥65	81 (53.8)
≥75	26 (17.2)
Sex	
Male	121 (80.1)
Female	30 (19.9)
Race	
White	130 (86.1)
Black	5 (3.3)
Asian	16 (10.6)
Karnofsky PS	
100%	47 (31.1
90%	56 (37.1)
80%	48 (31.8)
Renal impairment	
CrCl 20-60mL/min	61 (40.4)
Disease location	
Bladder	106 (70.2)
Other urinary locations	45 (29.8)
Pts with ≥1 target lesion	140 (92.7)
No. Target lesions (IRRC)	
1	44 (29.1)
2	44 (29.1)
3	26 (17.2)
4	14 (9.3)
≥5	12 (7.9)
Pts with target lesions (IRRC)*	140 (92.7)
Liver	76 (50.3)
Lung	39 (25.8)
Bladder	7 (4.6)
Adrenal	3 (2.0)
Kidney	1 (0.7)
Spleen	1 (0.7)
Lymph nodes & others**	90 (59.6)
Pts without target lesions	11 (7.3)

* Patients may have disease in > 1 site

** Other lesions may include visceral disease

Efficacy results

Primary endpoint

In the ITT population the main criterion, namely response rate assessed by an independent panel was 14.6% with 95% CI from 9.4% to 21.2%.

Response rates in different subgroups of patients, including those who had a visceral invasion and renal insufficiency, were comparable to those observed in the overall population.

Secondary endpoints

- Response time:

The time to onset of response was 1.4 months (95% CI = 1.18 months to 2.96 months).

- Median duration of response:

The median duration of response was 6 months (95% CI = 5.42 to 9.46 months)

- Duration of stabilization:

The median duration of stable disease was 4 months (95% CI = 3.48 to 4.67 months) for the 42% of patients whose best response was stable disease

- Rate of disease control:

The rate of disease control was 57% (95% CI = 48.7% to 65%) for the ITT patients and 61% (95% CI = 51.7% to 69%) for evaluable patients

- Duration of disease control:

The median duration of disease control was 4.6 months (CI 95% = 4.1 months to 5.5 months)

- Median progression-free survival

The median progression-free survival was 2.8 months (95% CI = 2.56 to 3.84 months)

- Median overall survival

The median overall survival was 7.9 months (95% CI = 6.67 to 9.69 months).

Conclusion

The results of this study confirm the efficacy of vinflunine monotherapy in patients with advanced transitional cell urothelial cancer after failure of prior platinum-based chemotherapy.

The response rate analysed by the IRRC was 14.6% (95% CI: 9.4% - 21.2%) with a median duration of response 6 months (95% CI 5.4-9.5). Responses were observed in patients with unfavourable prognostic features (poor performance status, renal disease and refractory visceral invasion) as summarised in Table B24.

Rates of disease control, duration of stable disease, PFS and OS were also all favourable as summarised in Table B25.

Table B24: Response rates in the ITT population subgroups, study CA 001

	Subgroups	Number of responders/ patients	RR % (95% CI)
Age	<65	5/70	7.1 (2.4 – 15.9)
	≥65	17/81	21.0 (12.7 – 31.5)
Gender	Men	16/121	13.2 (7.8 – 20.6)
	Women	6/30	20.0 (7.7 – 38.6)
	>50	6/28	21.4 (8.3 – 41.0)
	≤50	0/2	0.0 (0.0 – 84.2)
Race	Asian	1/16	6.3 (0.2 – 30.2)
	Caucasian	20/130	15.4 (9.7 – 22.8)
	Others	1/5	20.0 (0.5 – 71.6)
Karnofsky	90-100	17/103	16.5 (9.9 – 25.1)
	80	5/48	10.4 (3.5 – 22.7)
Creatinine clearance (mL/min)	≥60	14/90	15.6 (8.8 – 24.7)
	<60	8/61	13.1 (5.8 –24.2)
Time from prior chemotherapy and progressive disease (months)	<3	9/81	11.1 (5.2 – 20.0)
	≥3	13/70	18.6 (10.3 – 29.7)
Time from relapse or progression after a first line chemotherapy and first VFL administration (months)	<1	7/73	9.6 (3.9 – 18.8)
	≥1	15/78	19.2 (11.2 – 29.7)
Prior chemotherapy with vinca-alkaloids	Yes	1/4	25.0 (0.6 – 80.6)
	No	21/147	14.3 (9.1 – 21.0)
Prior chemotherapy with taxane	Yes	4/28	14.3 (4.0 – 32.7)
	No	18/123	14.6 (8.9 – 22.1)
Prior platinum-containing regimen	Yes	14/95	14.7 (8.3 – 23.5)
	No	8/56	14.3 (6.4 – 26.2)
Stage	Metastatic	13/97	13.4 (7.3 – 21.8)
	Neo-adjuvant/adjuvant	9/54	16.7 (7.9 – 29.3)
Visceral involvement	Yes	7/74	9.5 (3.9 – 18.5)
	Others	15/77	19.5 (11.3 – 30.1)
Number of organs involved	1	16/85	18.8 (11.2 – 28.8)
	2	3/41	7.3 (1.5 – 19.9)
	≥3	2/14	14.3 (1.8 – 42.8)
	missing	1/11	9.1 (0.2 – 41.3)
Initial dose mg/m^2	280	17/111	15.3 (9.2 – 23.4)
	320	5/40	12.5 (4.2 – 26.8)
Country	USA	14/92	15.2 (8.6 – 24.2)
	Others	8/59	13.6 (6.0 – 25.0)
Neoadjuvant without platinum	Yes	3/22	13.6 (2.9 – 34.9)
	No	19/129	14.7 (9.1 – 22.0)

Table B25: Efficacy results, study CA 001

Best Response – IRRC : all patients	**n = 151**
Response rate % (Partial response), n (%)	22 (14.6)
Stable disease, n (%)	64 (42.4)
Progressive disease, n (%)	49 (32.5)
Non evaluable, n (%)	16 (10.6)
Response duration (IRRC), n = 22 Median (95% CI), months	6 (5.42 - 9.46)
Progression-free-survival, n = 151 Median (95% CI), months	2.8 (2.56 - 3.84)
Overall survival, n = 151 Median (95% CI), months	7.9 (6.67 - 9.69)

General conclusions on the efficacy data for vinflunine from three trials

The efficacy of vinflunine is supported by data from two Phase II and one phase III trial on a total of 450 patients treated for advanced or metastatic transitional cell carcinoma of the urothelium. The efficacy data are summarised in Table B26.

The results demonstrate the value of therapeutic vinflunine on improving overall survival of patients with advanced or metastatic TCCU who progress following platinum-based chemotherapy.

The efficacy of vinflunine with regard to survival was confirmed by:

- Consistency of efficacy parameters between the Phase II and Phase III trials.
- Longer, statistically significant overall survival in the vinflunine + BSC group in the eligible ITT population of study 302 (p = 0.0403, HR = 0.78, [CI 95%: 0.61-0.99]). This population accurately reflects that targeted by the protocol.
- The statistically significant (p = 0.036) effect of treatment with vinflunine on overall survival demonstrated by the pre-specified multivariate Cox analysis of the ITT population in the phase III trial (study 302). In this model, vinflunine reduced the mortality risk by 23% versus BSC, with a relative risk of 0.77 (CI 95%: 0.61-0.98),

Any delay in the progression of cancer is a direct benefit to patients because progression is inevitably accompanied by serious morbidity ultimately resulting in death.

In this population of advanced and heavily pre-treated patients, vinflunine gave reproducible response rates between the different studies, notably achieving control of disease and symptoms in 40 to 60% of patients. In the phase III study, which confirmed the results of the phase II trials, all efficacy parameters were statistically significantly better in patients treated with vinflunine: rate of disease control (p = 0.0024), progression-free survival (p = 0.0012).

Table B26: Summary of efficacy results in the 3 studies

Results	vinflunine 202 (n = 51)	CA 001 (n = 151)	Study 302 (vinflunine + BSC) (n = 253)	Study 302 (BSC) (n = 117)
Number of treated patients	51 (100)	151 (100)	248 (98.0)	117 (100.0)
ORR* N (%) (95% CI)	9 (17.6) (8.4, 30.9)	22 (14.6) (9.4, 21.2)	16 (6.3) (3.7, 10.1)	0
Evaluable patients ORR* N (%) (95% CI) *p*	N = 47 8 (17.0) (7.6, 30.8)	N = 132 21 (15.9) (10.1, 23.3)	N = 185 16 (8.6) (5.0, 13.7) *p = 0.00063*	N = 85 0
Disease control rate (%)* (95% CI)* *p*	(66.7) (52.1, 79.2)	86 (56.9) (48.7, 65.0)	104 (41.1) (35.0, 47.4) *p = 0.0024*	29 (24.8) (17.3, 33.6)
Response duration months (95% CI)	9.1 (4.2, 15.0)	6.0 (5.4, 9.5)	7.4 (4.5, 17.0)	-
Disease control duration* (95% CI) *p*	-	4.6 (4.1,5.5)	5.7 (5.0, 6.3) *p = 0.0233*	4.2 (3.8, 4.9)
PFS months (ITT population) 95 % CI *p*	3.0 NA	2.8 (2.6, 3.8)	3.0 (2.1, 4.0) *p = 0.0012*	1.5 (1.4, 2.3)
Overall survival months (ITT population) (95% CI) *p*	NA	NA	6.9 (5.7, 8.0) *p = 0.2868*	4.6 (4.1, 7.0)
Overall survival months (eligible ITT patients) (95% CI) *p*	6.6 (4.8, 7.6) NA	7.9 (6.7, 9.7) NA	6.9 (5.7, 8.0) *p* = 0.0403	4.3 (3.8, 5.4)

*IRC Independent review Committee

5.7 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.7.1 *If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.*

Not applicable

5.7.2 *Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.*

5.7.3 *Give a brief overview of the safety of the technology in relation to the decision problem.*

Summary of the safety profile of vinflunine.

Four hundred fifty (450) patients with TCCU treated with vinflunine monotherapy were included in the Phase II and Phase III trials.

Table B27 summarizes the number of patients and the number of cycles evaluated for tolerance in these patients

Table B27: Numbers of patients analysed for tolerance, by study

Study number	Abbreviation	Number of patients	Number of cycles
L0070 IN 202 P1	study 202	51	197
CA 183-001	CA 001	151	577
L00070 IN 302 EP1	study 302	248	1048
Total	vinflunine TCCU	450	1822
BSC		117	NA

As part of the comprehensive assessment of tolerance to vinflunine therapy, categories of predictable adverse events associated with the use of vinca alkaloids and, more specifically, vinflunine have been identified (Table B28).

Table B28: Overview of adverse events attributable to treatment with vinflunine from the three studies; 202, CA 001 and 302.

Number of patients (%)	450 (100%)	
NCI CTC version 2.0 Grading	Any grade	Grade 3/4
Febrile neutropenia	30 (6.7)	30 (6.7)
Arrhythmias	8 (1.8)	2 (0.4)
Myocardial infarction/Ischaemia	4 (0.9)	4 (0.9)
SIADH	0	0
Abdominal pain	95 (21.1)	21 (4.7)
Constipation	247 (54.9)	69 (15.3)
Diarrhoea	58 (12.9)	4 (0.9)
Ileus	14 (3.1)	12 (2.7)
Intestinal obstruction	2 (0.4)	1 (0.2)
Nausea	184 (40.9)	13 (2.9)
Stomatitis/Mucositis	122 (27.1)	12 (2.7)
Vomiting	123 (27.3)	13 (2.9)
Infusion site reactions	124 (27.6)	2 (0.4)
Extravasation	3 (0.7)	0
Asthenia / fatigue	249 (55.3)	71 (15.8)
Immediate hypersensitivity	10 (2.2)	1 (0.2)
Infection with severe neutropenia	21 (4.7)	19 (4.2)
Myalgia	74 (16.4)	14 (3.1)
Peripheral motor neuropathy	3 (0.7)	0
Peripheral sensory neuropathy	51 (11.3)	4 (0.9)
Hepatic dysfunction	5 (1.1)	5 (1.1)

Overall, the adverse events most frequently observed with vinflunine were neutropenia, anaemia, constipation, fatigue and asthenia.

The principal toxicity was neutropenia.

Neutropenia is usually of short duration, rarely exceeding 5 days. The protocols for study 202, CA 001 and study 302 specified that G-CSF could be used in cases of severe neutropenia to reduce the risk of febrile neutropenia. Febrile neutropenia or infection associated with severe neutropenia was reported in 6.7% and 4.7% of patients respectively.

Of the 6 toxic deaths related to treatment (1.3% of the treated population), 4 were related to myelotoxicity (0.9%).

Neutropenia and anaemia are side effects that oncologists are familiar with and used to managing. Effective protocols for managing chemotherapy-associated haematological toxicities are in place in oncology centres/units and include the use of growth factors and transfusions. Close monitoring of haematologic parameters is necessary during treatment and is a well established component of chemotherapy protocols.

Table B29: Haematological side effects

	Vinflunine: 445 pts TCCU 2nd line		Topotecan IV : 620 pts* SCLC 2nd line		Topotecan IV : 518 pts* SCLC 2nd line	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Anaemia	93	17	99	33	100	42
Leucopenia	85	45	99	81	100	88
Neutropenia	80	55	97	92	98	97
Thrombocytopenia	54	5	95	53	95	44
Febrile neutropenia	6.7	6.7	NA	NA	NA	NA
	N° pts	%	N° pts	%	N° pts	%
Death	4	< 1 %	15	2.4	8	1.5

*EPAR

Constipation is a common and dose limiting, side effect, but, because it is predictable, prophylactic measures are recommended in the Summary of Product Characteristics (SPC) to avoid or minimise its impact. Grades 3 to 4 were observed in 15% of patients but resulted in withdrawal from treatment in just 2%. None of the patients underwent surgery, all episodes were reversible and recurrence was rare after the implementation of specific measures.

The use of laxatives is now recommended from day 1 to day 5 or 7 of vinflunine administration to reduce the risk of constipation. This is especially important in patients at increased risk such as those suffering from chronic constipation, patients with grade ≥ 1 after their 1st administration of vinflunine, patients with peritoneal carcinomatosis, abdominal masses, prior major abdominopelvic surgery or patients receiving concomitant treatment with opioids.

Although the incidence of myocardial infarction is rare, given that the ischemic events are a class effect, special attention should be given to patients with a history of ischemic heart disease.

Overall, for the population of advanced or metastatic TCCU patients treated 2nd line after platinum-based therapy the safety profile of vinflunine is predictable, acceptable and manageable by prophylactic and therapeutic measures. Consequently, treatment-related deaths and discontinuation rates are low.

Many adverse reactions frequently associated with cytotoxic chemotherapy that are undesirable for patients (eg alopecia) or potentially dose-limiting and / or life-threatening (eg diarrhoea, neurotoxicity, pulmonary toxicity, nephrotoxicity, hepatotoxicity) are not characteristic of treatment with vinflunine.

In conclusion, vinflunine has an acceptable and well characterised safety profile, allowing it to be generally well tolerated by patients. This is particularly important considering the target population who are most likely to have been treated intensively with a range of different therapeutic modalities.

5.8 Interpretation of clinical evidence

5.8.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The principle findings from the clinical evidence are that for patients with advanced or metastatic TCCU who have failed a first-line platinum-based chemotherapy regimen, survival can be improved by a median of 2.6 months (95% CI: 5.7-8.0; study 302). In this late stage patient presentation, a median survival of 4.3 months (95% CI: 3.8-5.4) was observed with BSC alone, the survival

advantage seen with vinflunine represents a 60% improvement. This provides a foundation to explore longer term advantages for patients with earlier stage disease.

Vinflunine was well tolerated with a dose limiting toxicity of constipation. This is increasingly well managed using appropriate prophylaxis. The relative incidence of neutropenia with vinflunine is comparable to other cytotoxic agents and specialist oncology units are vigilant to symptoms of infection and subsequent management of this toxicity. The reported incidence of renal toxicity was low with vinflunine and this is significant in patients with diminishing renal function.

The quality of life experienced by patients treated with vinflunine was not compromised over those who had BSC and the observed trend was for an improvement with time from administration (study 302).

5.8.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The seminal licensing study (study 302) focussed on a specific patient population who were willing to accept randomisation to BSC as the management plan for their disease. This had consequences on key prognostic factors (PS, high tumour burden) and short expected survival. Such extreme patient characteristics represent a severe test of efficacy for a new drug. The strength of Study 302 is that any improvement in survival in patients in this end of life setting is a good indication that the agent is active and a candidate for use in earlier stages of disease with longer survival ambitions. The weakness of study 302 was that randomisation to BSC meant that fitter patients at an earlier disease stage were ineligible.

5.8.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence base from Study 302 is very specific to the decision problem. Prior to this evidence there was uncertainty regarding the relevance of further chemotherapy for this patient population. This evidence provides a basis for improving management for selected patients. Patients treated within the vinflunine licensed indication are likely to benefit from treatment providing the referral pathways to oncologists can be optimised (c.f. NSCLC management and referral patterns following NICE approval of new treatment in 2001).

5.8.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Key prognostic factors affecting clinical benefit were identified as PS, visceral involvement and anaemia. Continued monitoring of these key prognostic factors after platinum based chemotherapy will ensure the timely initiation of vinflunine at the first signs of progression. The adoption of vinflunine will provide good reason for continued monitoring and discussion of metastatic patients through the multidisciplinary team (MDT).

Patients with advanced or metastatic TCCU who have failed a platinum-based chemotherapy regimen who remain under the care of an oncologist are often considered for further systemic chemotherapy. Patients relapsing after >12 months may be re-challenged with platinum based chemotherapy. The majority of patients appear to relapse in less than 12 months (Table B21, von der Maase et al., 2000) and may receive an alternative chemotherapy regimen. The choice of agent may depend on what is available in the hospital and based on activity seen in other tumour types. The availability of vinflunine provides the first evidence-based treatment for post-platinum chemotherapy regimens.

The evidence from phase II studies conducted in a range of indications in patients for whom there are limited therapeutic options have informed the dose of vinflunine recommended in the SPC. The RD is modified in the SPC based on prognostic factors that predispose patients to specific toxicity, e.g. prior pelvic radiotherapy and lower PS.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic search was conducted to identify published reports on the cost-effectiveness of vinflunine in the treatment of patients with advanced transitional cell carcinoma of the urothelium (metastatic bladder cancer). Searches were conducted using OVID and the Medline and Embase databases. No restrictions were applied to publication date within these searches. All databases were accessed and searched on November 1, 2008 and repeated on July 22, 2010. Search strategies and findings are included in Appendix 9.10. Published reports were considered relevant to the decision problem addressed in this economic evaluation only if: (a) the study referred to vinflunine; (b) the study population related to adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen; and (c) the study was an economic evaluation. Search terms included "carcinoma, transitional cell" or "urinary bladder neoplasms", "urethral neoplasms" or "metastatic bladder cancer" or "transitional cell carcinoma of the urothelium", *and* "economic" or "costs and cost analysis", *and* "vinflunine". This search yielded no pertinent studies. Consequently, no published cost-effectiveness evaluations were deemed relevant to the decision problem considered in this economic evaluation.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Not Applicable

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

Not applicable.

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

6.2 De novo analysis

Patients

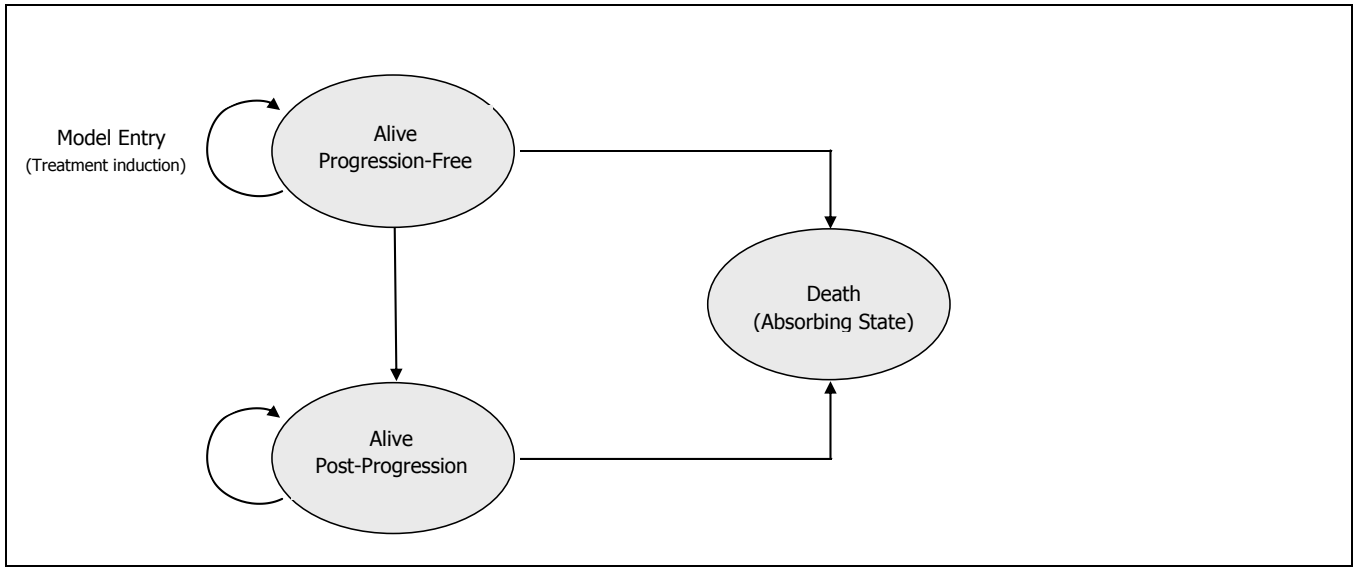
6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The population included in this economic evaluation is adult patients with advanced or metastatic transitional cell carcinoma of the urothelium who have failed a prior platinum-containing regimen (Sections 1.5 and 2.2) and directly reflects the population of the phase III study 302. This population is within the licensed indication for vinflunine (section 2).

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure B7: Model health states



6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The analytic model that was used projects expected clinical and economic outcomes for patients with advanced transitional cell carcinoma of the urothelium who have failed a prior platinum-based regimen, who are assumed alternatively to receive vinflunine+BSC vs BSC as second-line therapy. The modelling approach is similar to state-transition (Markov) models that are commonly used to estimate incremental cost-effectiveness of cancer therapies. The modelling approach may be labelled as a "partitioned-survival" model. Use of a model structure based on progression-free survival (PFS) and overall survival (OS) health states is consistent with clinical outcomes employed in oncology trials, and specifically with those employed in Study 302. As patients are usually treated until disease progression, differences in costs and potentially health related quality of life (HRQL) between pre- and post-progression health states should be expected. Presence or absence of disease progression has

been reported to be a key determinant of health-state utility (Bremner et al., 2007, Nafees et al., 2008, Wittenberg et al., 2005).

The model is characterized by three mutually exclusive health states ("Alive Pre-Progression", "Alive Post-Progression", and "Dead"). The model is similar to a Markov cohort model, with states defined based on vital status, and for patients remaining alive, disease progression. However, unlike a Markov model in which transitions between health states are modelled explicitly using transition probabilities, the model employed in this economic evaluation 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. Transition probabilities are not employed, but estimates of OS and PFS are consistent with those observed in Study 302 without the assumptions that would be required to obtain such consistency within the framework of a Markov cohort model. Similar methods have been employed in other UK-based evaluations of the cost-effectiveness of oncology interventions (e.g., lapatinib [NICE Technology Appraisal in development] and bevacizumab [NICE TA 178]).

In the model, treatment is assumed to be administered in cycles of 21 days (i.e., every 3 weeks), until disease progression, major toxicity or other reason for therapy discontinuation, or death (if occurring prior to progression). Following therapy initiation, patients are assumed to be in an "Alive Pre-Progression" health state, and to be at risk of disease progression and/or death over time. In reality, patients have already experienced disease progression on prior therapy at the point of entry into the model, but on initiating further treatment as they enter the model, they are considered to be progression-free from the perspective of this (second) line of treatment. Patients who experience disease progression are assumed to discontinue therapy. Those who discontinue therapy are assumed to transition to an "Alive Post-Progression" health state (i.e., palliative care only) and to reside in that state until death (a "capture" or "absorbing" state).

While residing in a particular health state, patients are assigned a corresponding cost of care as well as health-state preference weight (i.e. utility value), both of which are assumed to depend upon disease status.

6.2.4 Please define what the health states in the model are meant to capture.

Model states are meant to capture differences in HRQL and costs for pre- and post-progression health states in this patient population. As treatment is indicated until disease progression, presence or absence of disease progression is assumed to be a key determinant of HRQL and medical resource utilization.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model captures the key aspects of advanced transitional cell carcinoma of the urothelium, namely, the health effects, the clinical benefits and economic impacts of therapy, and outcomes associated with progressive disease.

Discussions with clinical consultants and review of available evidence suggested there would be minimal value in including additional measures of disease status, such as "stable disease", "complete

response", and/or "partial response"--which also were assessed among patients in Study 302 either as "events" or disease states in the model. The principal measures of the benefit of vinflunine therapy in this patient population have been deemed to be PFS and OS. According to the Study 302 report, there were no differences in HRQL between patients who were randomized to receive vinflunine+BSC versus BSC. Ascertaining whether "duration of disease control" (i.e., time from date of randomization until documentation of progression or death among patients who are stable or responders) was longer, on average, for patients receiving vinflunine+BSC (vs those receiving BSC) would have required additional analyses of trial data, adjusting for the proportion of patients with stable disease or partial response by treatment. At the time of model development, however, there was no evidence in support of an expected increase in HRQL and/or reduced healthcare utilization among patients with advanced transitional cell carcinoma of the urothelium who are responders versus those with stable disease or those who experience progression. Increasing the complexity of the model (i.e., number of states and events) was deemed to be inadvisable if assumed benefits could not be supported by an acceptable level of evidence. It should be noted that two recent NICE appraisals - namely, that of lapatinib in advanced or metastatic breast cancer (NICE lapatinib assessment [TA under development]), and assessment of bevacizumab, sorafenib tosylate, sunitinib, and temsirolimus in the treatment of renal cell carcinoma (NICE TA 178) - accepted simple models that considered survival benefits only. The latter appraisal suggests that a "simple model … is appropriate given the decision problem and the data available". For all of the above-described reasons, the cost-effectiveness of vinflunine was evaluated solely based on expected impacts on OS and PFS.

HRQL impacts associated with side effects of chemotherapy were not included (section 6.4.8 and 6.4.12).

The baseline risk of disease progression for patients receiving BSC was assumed to be represented by the empirical distribution of PFS time in study 302. BSC was assumed to reflect underlying disease progression among patients with advanced transitional cell carcinoma of the urothelium who have failed a prior platinum-based chemotherapy (Section 2.1).

6.2.6 *Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.*

Table B30: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	5 years	Per reference case (Lifetime)	NICE 2008
Cycle length	Daily	Consistent with model design	Section 6.2.2, 6.2.6
Half-cycle correction	No	Survival ascertained daily	NICE 2008
Measure of health effects	QALYs	Per reference case	NICE 2008
Discount rate	Annual rate of 3.5% on both costs and health effects	Per reference case	NICE 2008
Perspective on costs	NHS and PPS	Per reference case	NICE 2008

QALYs=Quality-adjusted life-years; NHS=National Health Service; PSS=Personal Social Services

Technology

6.2.7 *Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?*

The technology under evaluation, vinflunine, is implemented within the economic evaluation within its marketing authorization [Sections 1.3 and 1.5]. Vinflunine is indicated as monotherapy for the treatment of adult patients with advanced or metastatic advanced transitional cell carcinoma of the urothelium after failure of a prior platinum-containing regimen [Section 1.5]. In adult patients with an ECOG PS score of 0 and without previous irradiation to the pelvic area, the recommended dose of vinflunine is 320 mg/m² once every 3 weeks [Section 1.10]. For patients with ECOG PS of 1 and PS 0 with previous irradiation, the recommended dose is 280 mg/m² for the first cycle, escalated to 320 mg/m² in the absence of any haematological toxicity causing treatment delay or dose reduction. In the economic evaluation, the mean dose assumed for patients receiving vinflunine was assumed to be 287 mg/m^2, which was the mean dose among patients who received vinflunine in Study 302. In the economic evaluation, vinflunine therapy was assumed to continue until disease progression, therapy discontinuation, or death.

6.2.8 *Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.*

- *The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).*
- *The robustness and plausibility of the endpoint on which the rule is based.*
- *Whether the 'response' criteria defined in the rule can be reasonably achieved.*
- *The appropriateness and robustness of the time at which response is measured.*

- *Whether the rule can be incorporated into routine clinical practice.*
- *Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.*
- *Issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

In the economic evaluation, vinflunine therapy is assumed to continue until (secondary) disease progression, other reasons for discontinuation (e.g. unacceptable toxicity) or death. Patients who experience disease progression and discontinue vinflunine therapy are assumed thereafter to receive BSC, consistent with the absence of other evidence-based second-line therapies indicated for the treatment of this condition in the UK. Best efforts were employed based on clinical interviews and review of the published literature to estimate medical resource utilization for patients receiving BSC (section 6.5.1).

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

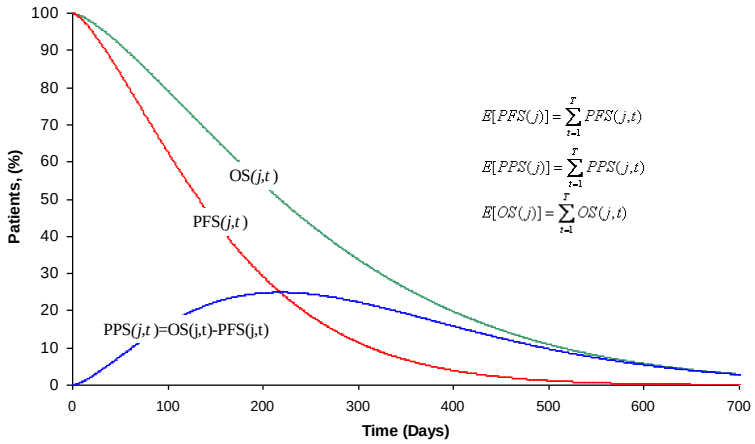
6.3.1 Please demonstrate how the clinical data were implemented into the model.

The model is very similar to a state-transition (Markov) model with states defined based on vital status, and for those remaining alive, disease progression. However, unlike a Markov cohort model, in which transitions between states are modelled explicitly, the model calculates the proportion of patients in each treatment group that are expected to reside in each of the states, based on the estimated survival functions for PFS and OS. Rather than estimating transition probabilities (i.e., from alive/pre-progression to alive/post-progression or death, and from post-progression to death) for use within the model, an area-under-the-curve (AUC) analysis is used to estimate mean time prior to disease progression and mean survival alive. The difference between the two curves provides a direct estimate of the mean time alive following disease progression. This approach permits direct use (and modelling, as necessary) of PFS and OS data from Study 302 without the assumptions that would be required to obtain such consistency within the framework of a Markov cohort model with explicit transition probabilities.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

To calculate measures of effectiveness, the proportion of patients receiving each treatment strategy (j) that are expected to be alive at each time (t) (i.e., overall survival, [*OS(j,t)*]), and alive and progression-free at each time (i.e., progression-free survival, [*PFS(j,t)*]), are generated by the model. In the model, time *t* represents days since initiation of therapy. For each strategy, the proportion of patients alive and post-progression at each time (post-progression survival, [*PPS(j,t)*]) is calculated by subtracting *PFS*(*j,t)* from *OS(j,t)*.

Figure B8: Schematic of approach for estimating time in model health states.



Expected (i.e., mean) PFLYs, PPLYs, and overall LYs for each strategy, (*E[PFS(j)]*, *E[PPS(j)]*, and *E[OS(j)]*, respectively) are calculated as the sum of *PFS(j,t)*, *PPS(j,t)*, and *OS(j,t)* over the modelling timeframe, *T*, as follows:

$$E[PFS\ (j)] = \sum_{t=1}^{T} PFS\ (j,t) \qquad (1)$$

$$E[PPS\ (j)] = \sum_{t=1}^{T} PPS\ (j,t) \qquad (2)$$

$$E[OS\ (j)] = \sum_{t=1}^{T} OS\ (j,t) \qquad (3)$$

Thus, for any given strategy, E[PFS(j)] and E[OS(j)] equal the area under the curves represented by PFS(j,t) and OS(j,t), while E[PPS(j)] represents the area between the PFS(j) and OS(j) curves, as shown in Figure B8.

Discounted expected PFLYs, PPLYs and overall LYs (*E[PFS(j)]'*, and *E[PPS(j)', E[OS(j)]'*, respectively), given the annual discount rate for effectiveness measures (r_e), are calculated as follows:

$$E[PFS\ (j)]' = \sum_{t=1}^{T} \frac{PFS\ (j,t)}{(1 + r_e / 365)^{t-1}} \qquad (4)$$

$$E[PPS\ (j)]' = \sum_{t=1}^{T} \frac{PPS\ (j,t)}{(1 + r_e / 365)^{t-1}} \qquad (5)$$

$$E[OS\ (j)]' = \sum_{t=1}^{T} \frac{OS\ (j,t)}{(1 + r_e / 365)^{t-1}} \qquad (6)$$

Expected QALYs for each treatment, E[QALY(j)], are calculated by multiplying *E[PFS(j)]* and *E[PPS(j)]* by corresponding estimates of utility for pre- and post-progression survival time ($U_{PFS}(j)$ and $U_{PPS}(j)$, respectively) and summing, i.e.:

$$E[QALY\ (j)] = E[PFS\ (j)] \times U_{PFS}\ (j) + E[PPS\ (j)] \times U_{PPS}\ (j) \qquad (7)$$

Discounted expected QALYs for each strategy (*E[QALY(j)'*) are calculated as follows:

$$E[QALY\ (j)] = E[PFS\ (j)]' \times U_{PFS}\ (j) + E[PPS\ (j)]' \times U_{PPS}\ (j) \qquad (8)$$

The model thus assumes that utilities are invariant with respect to time since therapy initiation, and are conditional only on progression status. Post-progression utility is assumed to be proportional to pre-progression utility, and is estimated by multiplying pre-progression utility by one minus the estimated percentage reduction in utility associated with progression, as follows:

$$U_{PPS}\ (j) = U_{PPS}\ (j) \times \%\Delta_{PFS}^{PPS}$$

The model also calculates the expected difference between strategies in these outcomes, e.g.:

$$\Delta E[QALY\ ]_{1vs\,2} = E[QALY\ (1) - E[QALY\ (2)] \qquad (9)$$

Where j=1 represents the VFL+BSC strategy and j=2, BSC strategy

Health outcomes for patients receiving BSC were based on time-to-event data (PFS and OS) from Study 302. Statistical analyses were undertaken using SAS statistical software Version 9.1 (SAS Institute Inc., North Carolina). Health outcomes for patients receiving vinflunine+BSC were calculated using multivariate hazard ratios for vinflunine (OS and PFS) from Study 302 . The hazard of experiencing an event (either disease progression or death) for patients receiving vinflunine+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 randomisation or baseline, including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin. The effect of vinflunine+BSC on OS and PFS, respectively, was significant after adjusting for the five prognostic factors. Differences observed between the two treatment arms could not be explained by imbalances in the distribution of prognostic factors between the two treatment arms in the eligible patient population. The Cox model proportional hazards assumption was investigated with the test of Grambsch and Therneau; the global test did not indicate a violation of the proportional hazards assumption (EMEA/CHMP/370293/2009). All analyses conducted using data from study 302 were undertaken for the eligible ITT patient population. The hazard ratios for vinflunine+BSC are reported in Table B31.

Table B31: Relative hazard ratios for vinflunine versus BSC

Parameter	Value	Source
vinflunine (vs BSC): Hazard ratio (mean, SE)		
Overall survival	0.70 (0.11)	Study 302
Progression-free survival	0.47 (0.54)	Study 302

Figures B9a and B9b show estimates of PFS and OS for patients receiving vinflunine+BSC and BSC employed in the model up to days 912 (OS) and 284 (PFS) (end of BSC in study 302).

Figure B9a: Overall survival by treatment

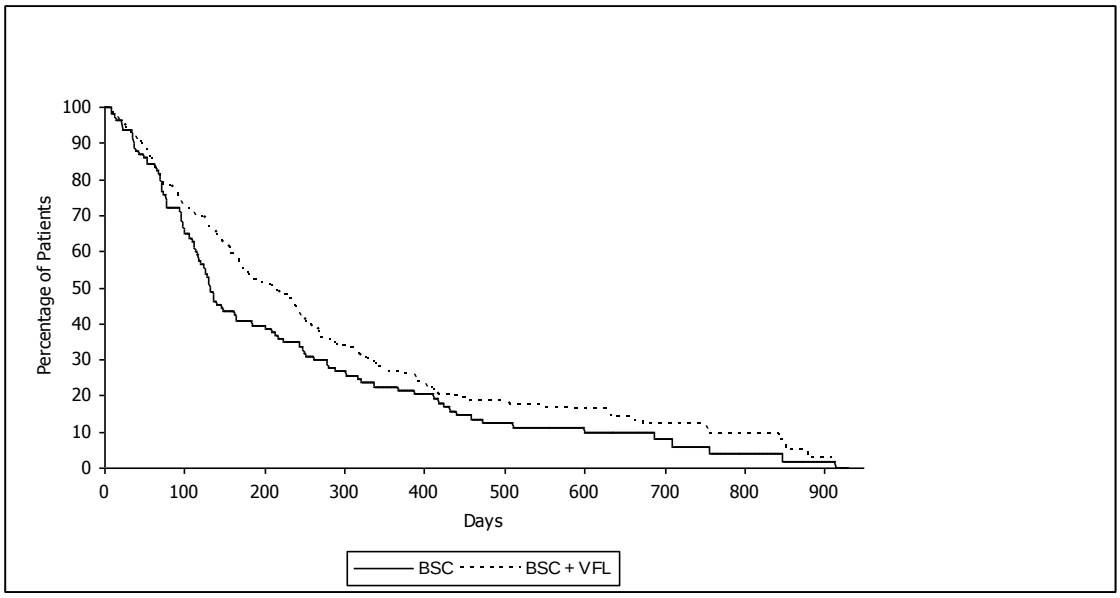
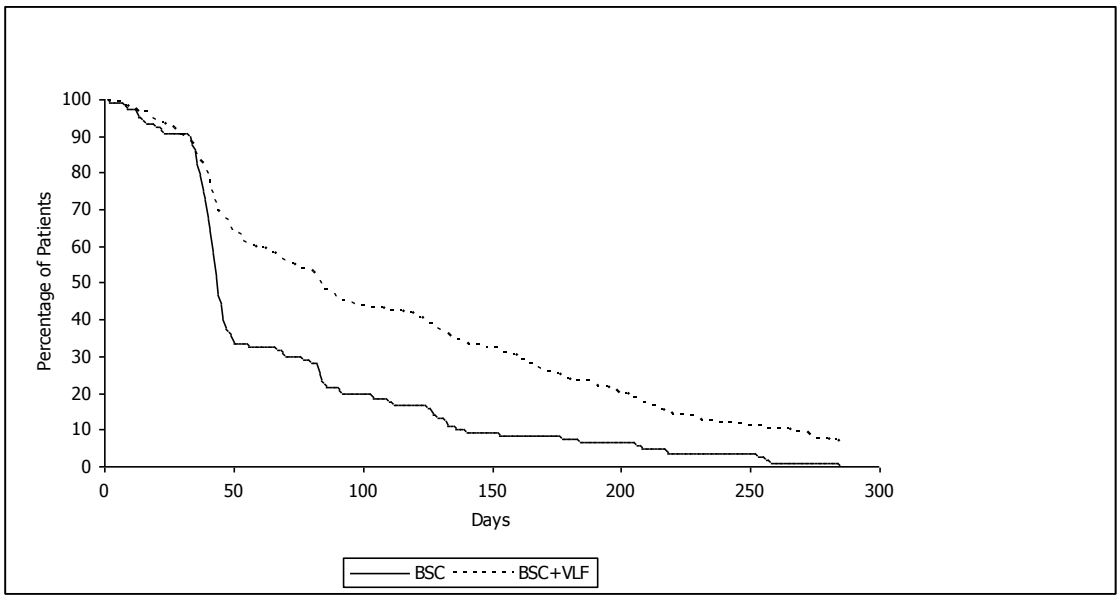


Figure B9b: Progression free survival by treatment



See Section 6.3.7 for methods employed in extrapolating OS and PFS up to five years.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Risk of disease progression and death among patients receiving vinflunine+BSC were shown to vary over time in study 302; survival probabilities are assumed to be time-dependent in this evaluation.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate outcome measures were linked to final outcomes (QALYs). The expected number of QALYs were estimated using a two-stage process. First, mean time spent in pre- and post-progression health states (i.e., pre-progression survival and post-progression survival, respectively) were estimated by the model. Mean time pre- and post-progression was assumed to be dependent upon treatment, and was estimated using data from the study 302.

Utility weights were assumed to differ according to patient's disease status (i.e., whether they have experienced disease progression or not). Time in pre- and post-progression health states, respectively, were weighted by the corresponding utility value. Utility values assigned to patients in the pre-progression health state were based on data from study 302, and mapped as reported in Section 6.1.4; estimates assigned to patients post-progression were based on a study reported by van den Hout et al (2006), as noted in Section 6.4.9.

The relationship between disease progression and overall survival in patients with advanced bladder cancer has been established elsewhere (Vieweg et al., 1999, Herr 2000).

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- *the criteria for selecting the experts*
- *the number of experts approached*
- *the number of experts who participated*
- *declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought*
- *the background information provided and its consistency with the totality of the evidence provided in the submission*
- *the method used to collect the opinions*
- *the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*
- *the questions asked*
- *whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).*

Not applicable. Expert opinion was not used to inform any of the clinical parameter values employed by the model.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B32: Variable list, values, distribution, source

Parameter	Value	Distribution	SE	Source
VFL, cost per vial (£)	1062.5	Lognormal	-	Sect. 6.5.5
VFL, vial size (mg)	250	n/a	-	Sect. 6.5.5
VFL, (mg per m2) per cycle	287	Lognormal	1,8	Sect. 6.5.5
VFL, average body surface (m2)	1.85	-	-	Sect. 6.5.5
VFL, cycles per year	17.4	n/a	-	-
VFL, dose delay [calibration] (days)	14	n/a	-	Sect. 6.5.5
VFL, cost administration, first cycle (£)	208	Lognormal	52	Sect. 6.5.5
VFL, cost administration, subsequent cycles (£)	154	Lognormal	39	Sect. 6.5.5
VFL, risk adverse events (%)				
Constipation (Grade 3 and 4)	20.2	Beta	?	Sect 5.9
Febrile neutropenia w hosp (Grades 3 and 4)	5.2	Beta	?	Sect 5.9
Abdominal pain w hosp (Grades 3 and 4)	1.2	Beta	?	Sect 5.9
VFL, monitoring cost (per month)	5.2	Lognormal	1.3	Sect. 6.5.5
VFL, cost palliative RT, pre-progresssion (per mo.)(£)	5.2	Lognormal	1.3	Sect 6.5.1
VFL, cost palliative RT, post-progresssion (per mo.)(£)	46.0	Lognormal	11.5	Sect 6.5.1
VFL, cost palliative CT, post-progresssion (per mo.)(£)	41.0	Lognormal	10.3	Sect 6.5.1
VFL, OS, hazard ratio (vs BSC)	0.69	Lognormal	0.08	Sect. 6.3.2
VFL, PFS, hazard ratio (vs BSC)	0.47	Lognormal	0.05	Sect. 6.3.2
BSC, incidence adverse events (%)				
Constipation (Grade 3 and 4)	0.9	Lognormal	0.23	Sect 5.9
Febrile neutropenia w hospitalisation (Grades 3 and 4)	0	Lognormal	0	Sect 5.9
Abdominal pain w hosp (Grades 3 and 4)	0.70	Beta	0.18	Sect 5.9
BSC, palliative RT, pre-progresssion (per mo.)(£)	116	Lognormal	29	Sect 6.5.6
BSC, palliative RT, post-progresssion (per mo.)(£)	31	Lognormal	7.8	Sect 6.5.6
BSC, palliative CT, post-progresssion (per mo.)(£)	46,0	Lognormal	11.5	Sect 6.5.6
Both therapies, cost side effects				
Constipation (Grade 3 and 4)	39	Lognormal	7	Sect. 6.5.7
Febrile neutropenia (Grades 3 and 4)	3 538	Lognormal	885	Sect. 6.5.7
Abdominal pain (Grades 3 and 4)	577	Lognormal	139	Sect. 6.5.7
Both treatments, other cost pre-progression	580	Lognormal	145	Sect. 6.5.6
Both treatments, other post pre-progression	1 253	Lognormal	313	Sect. 6.5.6
Both treatments, health-state utilities				
Pre-progression	0.65	Beta	0.01	Sect. 6.4.9
Post-progression (% reduction)	61,0	Beta	15.3	Sect. 6.4.9
Discount rate (%)				-
Effects	3.5	n/a	-	-
Cost	3.5	n/a	-	-

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Yes. 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). Because most patients were dead by the end of the trial, and consistent with estimates of life expectancy in this patient population, it may be argued that such extrapolation would not have been necessary. The model time horizon was extended up to 5 years (beyond the point at which <1% of all patients were estimated to be dead (i.e. 3.8 years) to appropriately reflect a lifetime time horizon as recommended for the reference case. A time horizon of 5 years also permits a longer window of observation suitable for sensitivity analyses.

Using regression methods, a stratified Weibull survival function was fitted to patient-level failure time data for patients receiving BSC in Study 302 (scale=0.9308, shape=1.0743) (Appendix 9.11). Figure B10a shows the empirical and modelled data for patients receiving BSC. In the economic evaluation, Kaplan-Meier OS data for BSC patients were employed up to day 912 (last observation for BSC in study 302), and Weibull projections were employed for OS between day 913 and 5 years. Estimates of OS for patients receiving vinflunine+BSC were calculated using the multivariate hazard ratio for vinflunine+BSC (section 6.3.2); an assumption of proportional hazards between events was maintained beyond trial duration (Figure B10b).

Figure B10a: Observed and estimated overall survival for patients receiving BSC

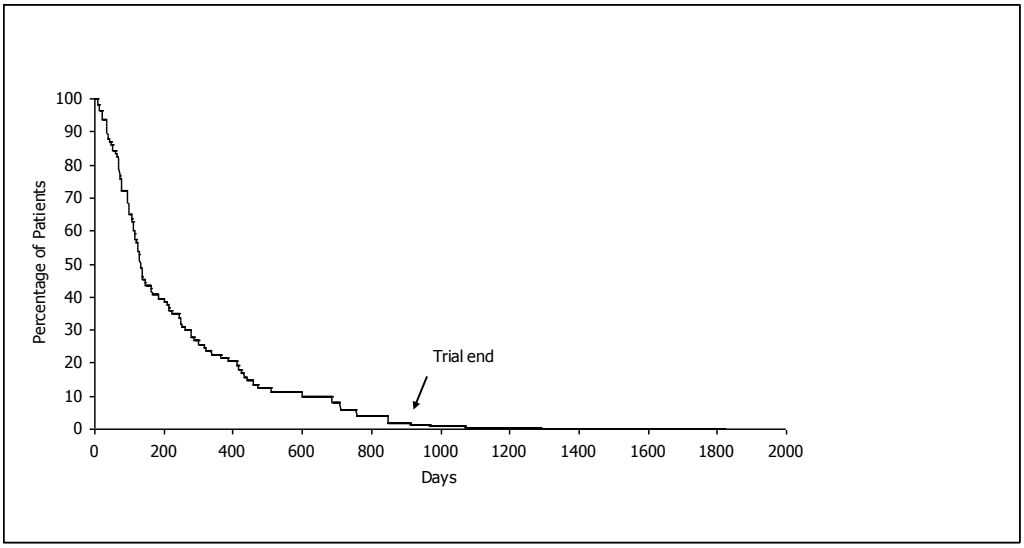
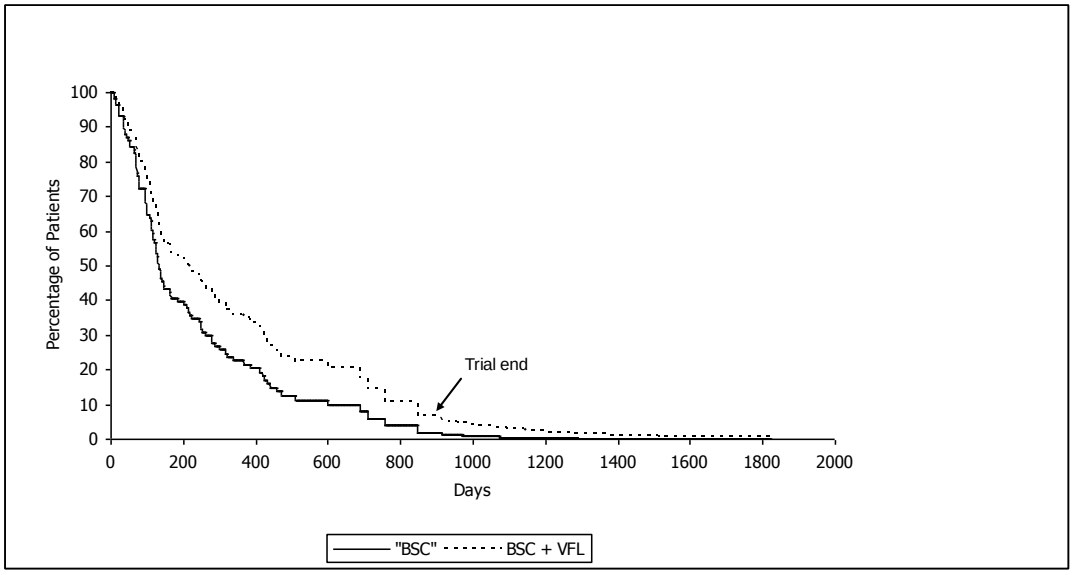


Figure B10b: Observed and estimated overall survival by treatment



The same methodology was employed to extrapolate PFS beyond the duration of follow-up in Study 302 (day 285), up to 5 years. A stratified Weibull survivor function was employed to fit a curve to patient-level failure time data (PFS) for patients receiving BSC in Study 302 (scale=0.7400, shape=1.3513) (Appendix 9.11). Figure B10c shows the empirical and modelled data for patients receiving BSC. In the economic evaluation, Kaplan-Meier data on PFS were employed up to day 284 (last observation for PFS for BSC in Study 302), and PFS estimates derived from Weibull projections were employed thereafter. Estimates of PFS for patients receiving vinflunine were calculated using the multivariate hazard ratio for vinflunine+BSC (Figure B10d) (section 6.3.2); an assumption of proportional hazards between events was maintained beyond trial duration.

Figure B10c: Observed and estimated PFS for patients receiving BSC

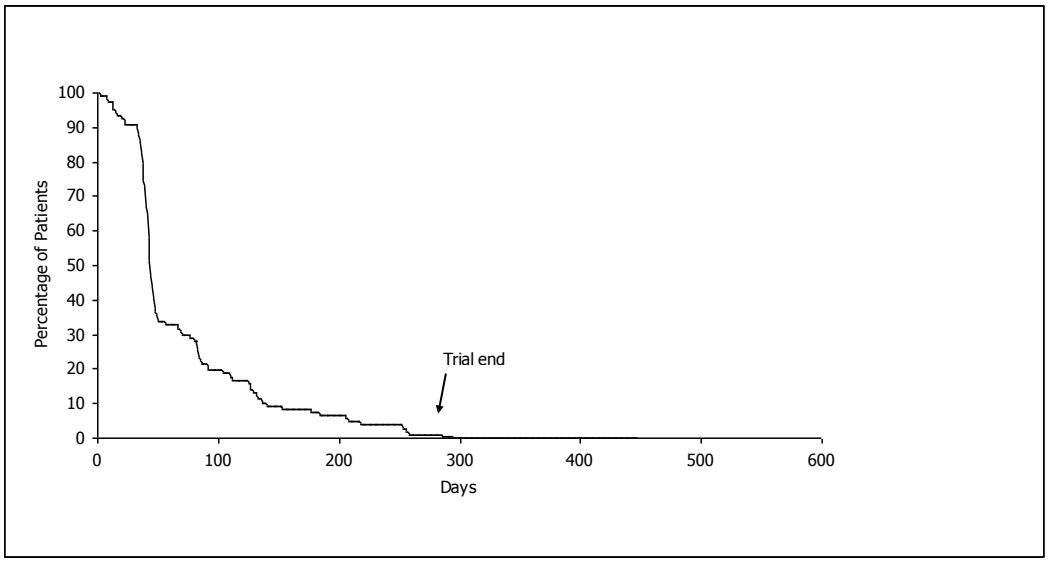
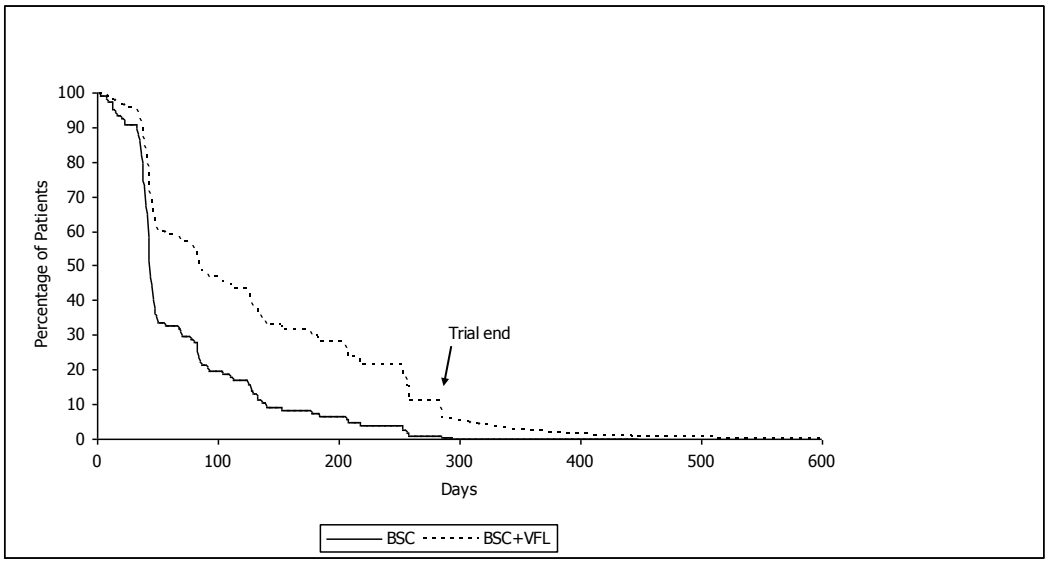


Figure B10d: Observed and estimated PFS by treatment



6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumptions employed in the *de novo* economic model in addition to those mentioned in Section 6.3 include:

1. Impact of adverse events on health-state utilities is assumed to be captured by the reported mean value for the EORTC QLQ-C30 global health status score for patients in the pre-progression health state.
2. An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.
3. Price of vinflunine is assumed £1062.5 per 250-mg vial.
4. Dosage of vinflunine is assumed to be equal to the mean reported dose in study 302 (287 mg/m2). As the actual (vs planned) dose was employed, use of relative dose intensity is not warranted.
5. Patient's average body surface area is assumed to be equal to the mean reported BSA (1.85 /m^2) in Study 302.
6. Vinflunine is assumed to be administered as a 20-min IV infusion in an outpatient setting.
7. Vial wastage is assumed to be zero in the base case analysis (i.e., vinflunine vials are assumed not to be discarded).
8. As planned versus actual days of treatment may differ due to early discontinuation or missed dosages, model calibration was undertaken to ensure that the number of vinflunine cycles in the model is consistent with the number of treatment days (cycles) (i.e., mean [range]: 4.2 [1-20]) in Study 302.
9. For monitoring, patients receiving vinflunine require complete blood counts (CBC) prior to each administration (cycle) (i.e., every 21 days); constipation prophylaxis is also initiated with each therapy cycle.
10. Health care utilization associated with BSC for patients in pre- and post-progression health states does not vary by treatment and amount of time spent in these states.

11. Use of palliative radiotherapy pre- and post-progression is dependent on treatment; the additional cost associated with such therapy is included in the analyses.

    Use of palliative chemotherapy for patients who experience disease progression is dependent on prior therapy; additional cost associated with such therapies is included in the analyses.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Patients with advanced transitional cell carcinoma of the urothelium failing a prior platinum-containing regimen suffer from a variety of symptoms that impair health-related quality of life (HRQL). Patients most often have a urinary bladder *in situ* and experience a moderate degree of abdominal pain and haematuria (personal communication, Dr. H. von der Maase, Dr. A. Glass). Systemic symptoms may include weakness, anorexia, fatigue, insomnia, and depression. Depending on the metastatic site(s) involved, patients may experience local (pelvic) or distal (limbs) bone pain, with an increased risk of bone fracture(s) and limitations in motion. Other symptoms include lower back pain (sacral plexus involvement), nausea (liver), shortness of breath due to compressed airways and/or endobronchial disease (lung and/or mediastinal lymphs), urinary obstruction, and sexual dysfunction (genitourinary tract). Patients may differ, however, with respect to the incidence and extent of their symptoms. Some younger patients may be asymptomatic, while others with advanced age often have severely impaired health status and may be deemed ineligible to receive further chemotherapy.

Review of the published literature yielded no reports on HRQL in patients with advanced transitional cell carcinoma of the urothelium initiating second-line therapy. Worthy of mention, however, are reported decreases in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) questionnaire (Aaronson 1984) domain scores for global quality of life, physical, emotional, role, and social functioning, pain, fatigue, and insomnia at study entry among patients with advanced transitional cell carcinoma of the urothelium participating in a randomised controlled trial of first-line chemotherapies (Roychowdhury 2003).

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As the disease progresses into its terminal stage, all of the above-described symptoms are likely to worsen (personal communication, Dr. H. von der Maase, Dr. A. Glass). Most often, fatigue, weakness, nausea associated with terminal disease, and pain prevent age-appropriate functional performance and social interaction. The patient is progressively confined to home or bed, and if ambulatory, requires multiple rests during the day. Decreased physical functioning and social interaction lead to further physical limitations and isolation, and the patient often becomes depressed and his/her health status rapidly declines. Increased use of narcotics is frequently associated with constipation, vomiting, excessive somnolence, and increased risk of falls. Often problematic although not common to all patients are acute exacerbations of underlying symptoms requiring emergency treatment and/or hospitalization (e.g., severe dyspnea due to mediastinal/lung involvement, which often leads to anxiety and hyperventilation). Review of published literature yielded no reports on HRQL among patients failing first- or second-line therapies.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- *Method of elicitation.*
- *Method of valuation.*
- *Point when measurements were made.*
- *Consistency with reference case.*
- *Appropriateness for cost-effectiveness analysis.*
- *Results with confidence intervals.*

The EQ-5D questionnaire was not administered to patients participating in study 302 (Bellmunt et al., 2009). A search of published estimates of utilities (EQ-5D or other) for model-specified health states (pre- and post-progression, respectively) in this patient population yielded no data (see Section 6.4.5 below).

HRQL was assessed in study 302 using the EORTC Quality of Life-Core 30 (QLQ-C30) questionnaire (Aaronson 1993). Among patients randomised to receive vinflunine plus best supportive care (vinflunine+BSC) in this trial, the questionnaire was administered at baseline, at the end of the first, second, fourth, and six cycles of chemotherapy, and at the end of the study period; among patients randomised to BSC only, it was administered at baseline and on days 21, 42, 84 and 126. The EORTC QLQ-C30 was not collected beyond week 18; HRQL data therefore were available only for the treatment period (i.e., pre-progression). In the eligible study population, a total of 189 (76%) patients randomised to receive vinflunine+BSC, and 78 (72%) patients randomized to receive BSC, were evaluable for HRQL. Change from baseline in the EORTC QLQ-C30 global health status score did not differ significantly between the two treatment groups (p=0.658, repeated-measures analyses).

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- *Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.*

- *Details of the methodology used.*
- *Details of validation of the mapping technique.*

Mapping algorithms are not available for the EORTC QLQ-C30 questionnaire. HRQL data from study 302 were transformed to health-state utilities for pre-progression patients (i.e., on treatment) using response values for the EORTC QLQ-C30 questionnaire item #30 ("How would you rate your overall quality of life during the past week"?) (scale, 0-100) in conjunction with a published regression model relating this measure to utility values from a time-trade-off analysis in a sample of US cancer patients and their relatives (O'Leary et al., 1995). As pre-progression HRQL did not differ significantly between the two treatment arms in study 302, pre-progression health-state utility values were assumed to be independent of treatment and time since therapy initiation.

A two-step process was employed for estimation. First, responses to item #30 of the EORTC QLQ-C30 were pooled across treatment groups; values were subsequently converted to a 0-to-1 range. Second, assessment-level estimates of health-state utilities were derived using published information (O'Leary 1995) on the functional relationship between rating scale values and time-trade-off utilities:

$T = 1.18 \times R$ for $R \leq 0.85$

$T = 1.00 \times R$ for $R \geq 0.85$

Where T=time trade-off utility and R=rating scale value.

Derivation of the above-described functional specification ("plateau") is reported by O'Leary et al., along with two alternative specifications (i.e., "linear" and "power", respectively). The authors investigated these relationships in two populations: 124 cancer patients who were asked to evaluate their current state of health, and 102 relatives and close friends who were asked to evaluate health-state scenarios. Patients were interviewed on one occasion. The interview included the Quality of Life Index (QLI), a time-trade-off utility question, and a rating scale value question (further details are reported in the publication). Patients also were asked to rate their functional status using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale, to fill out a brief HRQL questionnaire consisting of five 10-cm visual analogue scales, and to provide socio-demographic information. Relatives and close friends also were interviewed on one occasion. These interviews included 9 time-trade-off questions that involved 8 health-state scenarios; one of the questions was repeated at random to assess reliability. After the repeated time-trade-off question, respondents were asked to rate the same randomly selected health state using the rating scale question from the patient interview. All rating scale values were normalized to a 0-to-1 scale by dividing by 100. Three functional relationships between rating scale values and time-trade-off utilities were modelled--an unrestricted linear model, a power function, and a plateau relationship each fit to both the patient and the relative/close friends' data. The proportion of variance (R^2) in time-trade-off utilities explained by the rating scale was 0.31 for the "linear" model, 0.29 for the "power" model, and 0.29 for the "plateau" model in the sample of cancer patients; among relatives and close friends, the corresponding proportions were 0.59, 0.58, and 0.58. The authors recognize that while none of the models could sufficiently explain the relationship between time trade-off patient's rating scale value and the patient's time trade-off utility value for his/her current health state, explained variance was almost twice as high for both the "plateau" and "power" regression models among relatives and close friends than for patients (see details in publication). The authors conclude that the plateau model may provide

an appropriate basis for adjustment of rating scale values for health-state scenarios when direct elicitation of time-trade-off utilities is infeasible.

The "plateau" functional specification from relatives and close friends of cancer patients by O'Leary et al. (1995) was used to derive assessment-level utility values for patients in study 302. A mean utility value was subsequently obtained by calculating the mean utility score for each patient across all assessments, excluding the last assessment, and subsequently calculating the mean (SE) across all patients, irrespective of treatment assignment; values were weighted by the number of assessments. The last assessment was excluded as it was expected that it would reflect the impact of disease progression among some patients. Findings from analyses including and excluding the last assessments, respectively, are reported in the Table B33 below.

Table B33: Quality of Life and derived utility estimates among patients from study 302

		QLQ-C30 (Q30)	Utility
	Patients Evaluable* for Quality of Life	Mean (SE)	Mean (SE)
Last assessment included	267	52.9 (0.2)	0.61 (0.013)
Last assessment excluded	217	55.7 (1.3)	0.65 (0.014)

* Per Study L007 IN 302 criteria

We note that the derived value of 0.65 is consistent with utility values reported for patients with other advanced cancers (e.g., advanced breast cancer [0.63]) (Tengs & Wallace, 2000, de Knonig et al., 1991), recurrent metastatic breast cancer [0.59] (Tengs & Wallace 2000, Hutton et al., 1996), second-line treatment of advanced renal cell carcinoma [0.60] [NICE TA 178], metastatic colorectal cancer [0.60] [NICE TA118], and hormone refractory metastatic prostate cancer [0.54] [NICE TA101])

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A systematic search was conducted to identify published reports providing information on HRQL among patients with advanced transitional cell carcinoma of the urothelium (metastatic bladder cancer). The search was conducted using the OVID, Medline, and Embase databases. No restrictions were applied to publication date within searches. Search strategies and findings are included in Appendix 9.12. Search terms included "carcinoma, transitional cell" or "urinary bladder neoplasms", "urethral neoplasms" or "metastatic bladder cancer" or "transitional cell carcinoma of the urothelium", *and* "health-related quality of life" or "quality of life".

The search yielded 182 (Medline) and 38 (Embase) reports, for which abstracts were reviewed. Publications were only considered relevant to the decision problem addressed in this economic evaluation if: (a) the study population consisted of adult patients with advanced or metastatic transitional cell carcinoma of the urothelium initiating second-line therapy; and (b) the study reported

HRQL data for patients pre- or post-progression. Ten published reports were identified as potentially relevant for this review. These reports were reviewed by two independent reviewers. Results of this review suggested that there are no published HRQL data for patients with advanced transitional cell carcinoma of the urothelium pre- and post-progression that are relevant to the decision problem considered in this economic evaluation.

One trial-based cost-utility analysis (Robinson 2004) was identified during this review which reported estimates of differences in HRQL among patients with advanced metastatic bladder cancer randomized to first-line chemotherapy (i.e. gemcitabine/cisplatin [GC] or methotrexate/ vinblastine/doxorubicin/cisplatin [MVAC]). At study entry, and in separate analyses conducted by Rowchowdhury et al. (2003), lower EORTC QLQ-C30 scores for global quality of life, physical, emotional, role, and social functioning, pain, fatigue, and insomnia were reported across all patients. Utility values for pre- and post-progression health states were not reported (a difference in utility of 0.43 is reported during treatment in favour of patients receiving MVAC only; the corresponding gain over the remaining lifetime was 0.13).

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

Not Applicable

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Adverse events associated with vinflunine most frequently include fatigue, constipation, abdominal pain, and neutropenia.

Table B34: Adverse event incidence (grade 3-4) study 302

Adverse event	Incidence of grade 3-4 in study 302	
	Vinflunine + BSC	BSC
Fatigue	19.7%	19.6%
Constipation	16.4%	0.9%
Abdominal pain	4.1%	6.5%
Neutropenia	50.4%	0.9%
Febrile neutropenia	6.1%	0%

Presence of fatigue is consistent with reports of most common physical symptoms associated with cancer and cancer treatment (Carelle et al., 2002). Fatigue impacts patients' capacity for daily activities and work, and is associated with loss of interest in social and sexual interaction (Carelle et al., 2002).

Constipation was frequent among patients receiving vinflunine in Study 302, but was successfully managed with adequate prophylaxis (personal communication Dr. H. von der Maase). Moderate-to-severe cases were noted to result in abdominal pain, which at times led to nausea and vomiting resulting in hospitalization. Abdominal pain as a result of toxicity of vinflunine was primarily due to constipation. The SPC recommends the use of laxatives and dietary measures including oral hydration from day 1 to 5 or 7 of each vinflunine administration to prevent constipation for all patients.s

Quality-of-life data used in cost-effectiveness analysis

6.4.9 *Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.*

Utility values employed in this economic evaluation are reported in Table B35. Methods of derivation of values for the pre-progression health state are reported in Section 6.4.4. Post-progression utility values for patients with advanced transitional cell carcinoma of the urothelium were not available either from Study 302 or from the published literature [Sections 6.4.5]. A utility value was therefore used from a study by van den Hout et al (2006) reporting EQ-5D values in a sample of 1270 terminally ill cancer patients with painful bone metastases or poor-prognosis non-small-cell lung cancer. In that study, the EQ-5D questionnaire was administered weekly for the first quarter and monthly thereafter (bone study) or biweekly (lung study), and valuation was undertaken using UK-based tariffs reported by Dolan (1997). The mean (SD) EQ-5D value of 0.25 (0.32) that the authors report over the last 6 months of life was employed in this economic evaluation. In the economic evaluation, disease progression therefore was assumed to confer a decline of 61% in mean utility (versus pre-progression value) (i.e., 0.25 represents a 61% reduction from the pre-progression value of 0.65). It should be noted that a value of 0.25 is consistent with values reported for patients in terminal/palliative cancer states (e.g., terminal metastatic breast cancer [0.25] [Launois et al., 1996], and [0.29] [de Koning et al., 1991]), terminal liver cancer [0.20] [Mangtani et al., 1995], and colorectal cancer [0.24] [NICE TA 100]).

Table B35: Utility values employed in economic evaluation

Health State	Utility value Mean [SE]	Reference in Submission	Justification
Pre-progression	0.65 (0.014)	Section 6.4.4	EQ-5D not collected in L007 IN 302 & no published data
Post-Progression	0.25 (0.009)	Section 6.4.9	EQ-5D not collected in L007 IN 302 & no published data

6.4.10 *If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:*

Not Applicable. Expert opinion was not used to inform any of the utility values employed by the model.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

As discussed in Section 6.4.1, patients failing platinum-based regimens (in the pre-progression health state in our model) are likely to experience some degree of abdominal pain and haematuria. Patients may also experience weakness, anorexia, fatigue, insomnia, and depression. Organ-specific symptoms related to metastatic involvement of selected sites may include local or distal bone pain and limitations in movement, lower back pain (sacral plexus involvement), nausea (liver), shortness of breath due to compressed airways and/or endobronchial disease (lung and/or mediastinal lymph nodes), and urinary obstruction and sexual dysfunction (genitourinary tract). For patients receiving chemotherapy and experiencing side effects, the expected impacts are described in Section 6.4.8.

Patients in the post-progression health state are likely to experience worsening of any symptoms experienced in the pre-progression health state. Increasing levels of fatigue, weakness, nausea associated with terminal disease, and pain prevent age-appropriate functional performance and social interaction. The patient is progressively confined to home or bed, and if ambulatory, requires multiple rests during the day. Decreased physical functioning and social interaction lead to further physical limitations and isolation, and the patient often becomes depressed and his/her health status rapidly declines. Increased use of narcotics is frequently associated with constipation, vomiting, excessive somnolence, and falls. Often problematic although not common to all patients are acute exacerbations of underlying symptoms requiring emergency treatment and/or hospitalization (e.g. severe dyspnoea due to mediastinal/lung involvement, which often leads to anxiety and hyperventilation).

There were no data on post-progression resource consumption, or on the differences in consumption between patients treated with vinflunine plus BSC and those receiving just BSC. Any estimates were applied equally to all patients.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Disutilities are not available from Study 302 for patients who experienced adverse effects while receiving vinflunine. Moreover, incorporating such disutility values into the model would have required a number of assumptions about the duration and severity of adverse effects, as well as their co-dependent or independent impact on total disutility. Also, adverse events were presumably captured in the responses of patients receiving vinflunine to the global health status question (Item #30) of the EORTC QLQ-C30, which was used to obtain utility values for the pre-progression state in this economic evaluation.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

All patients were assumed to be in a pre-progression health state at model entry (i.e., baseline, see Section 6.4.9). No quality-of-life events were taken from the baseline.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant over time within each health state.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Values in Sections 6.4.3 and 6.4.8 have not been amended.

Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.4.16 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Targeted reviews of published literature yielded no data on medical-resource use and costs of care for patients with advanced transitional cell carcinoma of the urothelium who failed prior platinum-containing regimens [Section 6.5.3]. Methods of resource identification, measurement, and valuation performed by the York Health Economics consortium in the UK included targeted reviews of published literature, interviews with clinical experts (i.e., oncologists, nurses and clinical coding specialists), and data from the National Schedule of Reference Costs, which includes case payments used when commissioning services in the UK. Estimation of use of palliative radiotherapy (pre- and post-progression) and chemotherapy (post-progression) was supplemented with analyses of data from Study 302. Clinical advisors provided information on the frequency of resource use. Based on discussions with these experts, it became apparent that there are significant differences in the care of patients with advanced bladder cancer across the UK. Clinicians found it difficult to provide estimates of typical resource use, emphasizing that care is tailored to the needs of individual patients, and that urothelial cancer does not lend itself easily to identifying a typical care pathway. Where differences were observed, the research team sought to establish an estimate of typical resource use and clarify this with clinical advisors.

Cost data (excluding drug cost) were largely derived from National Reference Costs, which represent charges paid by those commissioning services (primary care trust) to those providing services (hospitals). This approach was favoured over attempts to generate a bottom-up estimate of cost for each of the components listed in the tables. Health Technology Assessments conducted by NICE are increasingly reliant on National Reference Costs, as are commissioners and providers of care. As such, these were deemed to be the most suitable source of data where there were multiple options available.

Where available, all costs were based on the latest National Reference Costs for 2007/08, which will be used as a basis for contracts in 2009. Where 2009 costs were not available, cost data from the nearest possible year are reported and inflated where necessary.

Pre-progression. Best supportive care pre-progression was assumed not to vary by treatment (based on expert opinion), and included home visits by a general practitioner (1 per month), a community nurse specialist (4 per month), a health visitor (1 per month), and a dietician (1 per month), as well as one follow-up visit with an oncologist each month. Nurse, health visitor, and dietician visit unit costs were estimated to be £82, £60, and £40, respectively, based on hourly rates reported by Curtis et al. (2007), plus travel expenses. The cost of an outpatient oncologist follow-up visit was £91 (NHS HRG TNCKFUSS 800 [Consultant led follow-up outpatient]).

The cost of palliative radiotherapy also was included, consistent with findings from Study 302, wherein 3.3% of vinflunine+BSC patients, and 22.2% of those receiving BSC, received palliative radiotherapy. Mean total radiation dose was lower among patients receiving vinflunine+BSC (16.2 Gys vs 26.9 Gys for those receiving BSC alone). Mean dose per fraction was assumed to be 4 Gys, based on expert recommendations. Unit costs for radiation services were £246 for dosimetry, based on a weighted average of NHS HRG codes SC1Z, SB3Z, SB4Z, SB5z and SB6Z (Define volume for radiation therapy), and £96 for NHS HRG code SC22Z (Deliver a fraction of therapy on a megavoltage machine).

With respect to chemotherapy, there is currently no standard second-line treatment in the UK for patients with advanced TCCU whose disease has progressed after a prior platinum-containing regimen. A proportion of patients are offered second line chemotherapy according to institutional practices, clinician experience with other drugs and drug availability within the hospital. As no normal practice could be defined, alternative chemotherapy as 2nd line treatment was not included in the economic model.

Anticipated use of vinflunine and associated estimates of cost of administration and monitoring are summarized in section 6.5.5.

Post-progression. Best supportive care post-progression was assumed not to vary by treatment (based on expert opinion), and included home visits by a general practitioner (1 per month), a community nurse specialist (4 per month), and a health visitor (1 per month), as well as one non-consultant-led follow-up visit each month, hospice care services, and pain medication (morphine sulphate, 1 ml daily). GP, dietician, health visitor, and nurse visit unit costs were estimated to be £61, £60, £40 and £82, respectively, based on hourly rates reported by Curtis et al., plus travel expenses. The cost of a non-consultant-led follow-up visit was estimated to be £63 (NHS HRG TNCKFUSS 800). Utilization and cost of hospice services were based on data from a published survey (Remak et al 2004) of 17 breast cancer specialists, as data specific to metastatic bladder cancer were not available. In that survey, 70% of patients were estimated to receive hospice care (30% day visits, and 40% averaged five overnight stays); corresponding average monthly cost was estimated to be £551.

Costs of palliative radiation and chemotherapy were also included, consistent with findings from study 302, wherein 22% of vinflunine+BSC patients, and 16% of BSC patients, received palliative radiotherapy following disease progression. Mean total radiation dose was 23.5 Gys for both therapies. Average dose per fraction was assumed to be 4 Gys. Unit costs of palliative radiotherapy services are reported above (pre-progression). There are no standard third-line (palliative) chemotherapeutic agents in the UK. In the model, 29.0% of vinflunine+BSC patients, and 34.2% of those receiving BSC, were assumed to receive palliative chemotherapy, based on findings from Study 302. Based on expert opinion, patients were assumed to receive two cycles of gemcitabine (single agent, 7-day course NHS HRG SB02Z) (50% of patients), methotrexate, carboplatin, vinblastine ("MVCarbo", 21-day course, NHS HRG SB02Z), (33% of patients), and docetaxel (75 mg, 21 day

course, NHS HRG SB02Z) (17% of patients), consistent with regimens employed as palliative therapies in Study 302. The cost of outpatient chemotherapy procurement and delivery was assumed to be £346 for NHS HRG SB02Z (same for all therapies).

Summaries of estimates of resource utilisation and unit costs associated with pre- and post-progression health states are provided in Tables B36a and B36b below.

Table B36a: Resource utilisation, by health state

Parameter	Value	Source
Pre-Progression: Best Supportive Care		
General practitionner home consultation/ month	1	Expert opinion
Community nurse specialist visit / week	4	Expert opinion
Health home visitor / month	1	Expert opinion
Dietician / month	1	Expert opinion
Consultant led (oncologist) visit/ month	1	Expert opinion
Palliative radiation therapy:		
Percentage of patients (VFL/BSC)	3.3 / 22.2	Analyses / Study Data[1]
# Courses (mean)		
VFL	1,2	Analyses / Study Data[1]
BSC	2,0	Analyses / Study Data[1]
Total dose (mean) (Gys)		
VFL	16,2	Analyses / Study Data[1]
BSC	26,9	Analyses / Study Data[1]
Dose per fraction (mean) (Gys)	4	Expert opinion
Post-Progression: Best Supportive Care		
Consultation general practitionner / month	1	Expert opinion
Community nurse specialist / month	4	Expert opinion
Health visitor / month	1	Expert opinion
Dietician / month	1	Expert opinion
Hospice care	(see footnote)[2]	Remak, 2004
Non-consultant (oncologist) visit / month	1	Expert opinion
Pain medication (morphine sulfate 1ml daily) / month	30	Expert opinion
Palliative radiation therapy:		
Percentage of patients (VFL/BSC)	22.1 / 15.7	Analyses / Study Data[1]
# Courses (mean) (VFL and BSC)	1,9	Analyses / Study Data[1]
Total dose (mean) (Gys) (VFL and BSC)	23,5	Analyses / Study Data[1]
Dose per fraction (mean) (Gys)	4	Expert opinion
Palliative chemotherapy:		
Percentage of patients (VFL/BSC)	29.0% / 34.2%	Analyses / Study Data[1]
Gemcitabine single agent / 7 days	50%	Analyses / Study Data[1]
Methotrexate, vinblasting, carboplatin ("Mvcarbo") / 21 days	33%	Analyses / Study Data[1]
Docetaxel (75 mg / 21 days)	17%	Analyses / Study Data[1]
Number of cycles	2	Expert Opinion

[1] Study L007 IN 302 P1/Bellmunt

[2] Assumed 30% of patients, day visits, 40% five overnight stays

Cost of palliative radiation therapy and chemotherapy adjusted per month in PFS and PPS in clinical trial

PFS (VFL/BSC) (LYs) =0.36/0.18

PPS (VFL /BSC) (LYs) =0.41/0.43

Table B36b: Unit cost (pre- and post-progression)

Parameter	Value	Source
General practitionner home consultation	£61	Curtis 2007
Community nurse specialist visit	£82	Curtis 2007
Health visitor visit	£40	Curtis 2007
Dietician visit	£60	Curtis 2007
Consultant (oncology) led follow-up visit	£91	NHS HRG TNCKFUSFF 800
Not consultant (oncology) follow-up visit	£63	NHS HRG TNCKFUSFF 800
Radiation:		
Dosimetry/planning (outpatient) / course	£246	NHS weighted HRG SB1Z, SB3Z, SB4Z, SB5Z, SB6Z
Per fraction (outpatient)	£96	NHS HRG SC22Z
Hospice care / month	£551	Remak 2004
Morphine sulfate 1 ml prefilled syringe	£5	BNF, vs. 57
Gemcitabine single agent	£346	NHS HRG SB02Z
Methotrexate, carboplastin, vinblastin	£346	NHS HRG SB02Z
Docetaxel	£346	NHS HRG SB02Z

BNF=British National Formulary

6.4.17 *Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.*

NHS reference costs are appropriate for costing the intervention being appraised [Section 6.5.1].

Resource identification, measurement and valuation studies

6.4.18 *Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:*

- *country of study*
- *date of study*
- *applicability to UK clinical practice*
- *cost valuations used in study*
- *costs for use in economic analysis*
- *technology costs.*

Whilst principles of systematic reviewing were employed, a full systematic search was not undertaken for identification of resource use. The search included recognized sources of high-quality evidence, including Medline HMIC, PsycINFO, and CINAHL. Searches were restricted to English language papers. No search filters for study design were included, and studies from outside the UK were also included, although reviewed for relevance to UK settings. Search findings were reviewed for relevance, sifting the findings by title, abstract, and finally full articles. In addition, hand searching of known relevant sources (e.g., HTA reports of cancer treatments) was also conducted. The primary intention of the searches was to identify evidence on resource use associated with best supportive care in the UK. Unit costs applied to resources were derived from commonly used sources, in particular the NHS Reference Costs and the Unit Costs of Health and Social Care maintained by the PSSRU at the University of Kent.

One trial-based cost-utility analysis (Robinson 2004) was identified during this review, which reported estimates of costs of care among patients with advanced metastatic bladder cancer randomised to first-line chemotherapy (i.e., GC or MVAC) in the UK. Mean total cost per patient (excluding chemotherapy and administration) were £2,406 [MVAC] and £3,739 [GC] over a median follow-up of approximately 19 months (2009 price levels). Because more than 30% of patients were alive at trial termination (von der Maase 2000), and costs were not reported separately for pre- and post-progression health states, the study was deemed not directly applicable to this evaluation. Another study (Avristcher 2006) reporting cost of terminal care among patients with urinary bladder cancer was identified; the study was US-based and not limited to patients with advanced disease.

6.4.19 *If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:*

- *the criteria for selecting the experts*
- *the number of experts approached*
- *the number of experts who participated*
- *declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought*
- *the background information provided and its consistency with the totality of the evidence provided in the submission*
- *the method used to collect the opinions*
- *the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*
- *the questions asked*
- *whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).*

As search findings provided insufficient evidence on resource use, interviews of expert advisors (i.e. oncologists, nurses and clinical coding specialists) provided assumptions upon which estimates of resource use and cost were based. Where expert opinion has been used in this evaluation, this is clearly stated throughout. Due to the variable nature of best supportive care in different settings, these estimates are inevitably based on estimates of average practice. Variability in clinical practice and costs is addressed through sensitivity analyses.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

6.4.20 *Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.*

Table B37: Cost of treatment

Items	Intervention	Reference in Submission	Comparator	Reference in Submission
Technology Cost	£1062.5 (250 mg vial)	Sections 1.9 and 1.10	0	VFL is add-on to BSC
Mean cost of technology treatment	£2337.5 per cycle	Table 6.5.5a	N/A	-
Administration Cost	£208 first cycle	Table 6.5.5a	N/A	-
	£154 subs. cycles	Table 6.5.5a		
Monitoring cost (CBC)	£3.18 per cycle	Table 6.5.5a	N/A	-
Constipation prophylaxis	£0.7 per cycle	Table 6.5.5a	N/A	-
Total	£2549 first cycle	-	N/A	-
	£2495 subs. cycles			

CBC = complete blood count

Table B38 provides detailed estimates and assumptions concerning resource utilization and unit costs employed in estimating the cost of chemotherapy. The assumed mean dosage of vinflunine was 287 mg/m^2, based on the mean dose in Study 302 ; mean body surface area was assumed to be 1.85 m^2. A cost of £1062.5 per vial (250 mg) was employed. Drug wastage was not factored into the reference case, but was examined in sensitivity analyses. The acquisition drug cost of BSC was assumed to be zero, as vinflunine is assumed to be administered in addition to BSC. Vinflunine was assumed to be administered once every 21 days, by means of a 20-minute infusion consistent with prescribing information. As treatment delays and interruptions were reported during the trial and are expected in clinical practice, the number of treatment cycles projected by the model (based on progression-free survival) was calibrated to match the mean number of cycles in study 302 (i.e. 4.2). In that study, the most common reasons for treatment delays were administrative or driven by patients' requests and/or convenience (66%), followed by non-study drug-related adverse events (12%), and drug-related haematological (10%) and non-haematological toxicities (11%).

In the model, vinflunine was assumed to be administered in the outpatient setting, consistent with findings from Study 302 and expectations as to the likely setting of use in the UK. Note that the Reference Costs schedule includes payments for drug procurement as well as drug delivery, but data for vinflunine is obviously not available. Discussions with clinical coding experts and clinical advisors allowed the research team to establish the appropriate codes to be used, although it should be acknowledged that there is some uncertainty within certain hospitals about the appropriate use of chemotherapy codes. A cost of IV administration of £208 was assumed for the first cycle of

treatment, based on NHS Healthcare Resource Group (HRG) code SB14Z (Outpatient first attendance, delivery); the corresponding estimate for subsequent cycles was £154 (HRG code SB15Z [Outpatient second and subsequent attendances]). Monitoring costs for complete blood counts (CBC) prior to administration of each cycle of chemotherapy also were included, consistent with prescribing information. Cost of constipation prophylaxis (one week of laxatives therapy) also was assumed with each cycle of chemotherapy, consistent with expert recommendations (personal communication, Dr. H. von der Maase) and the 61% observed risk of constipation in study 302 among patients receiving vinflunine+BSC.

Table B38: Estimates of utilisation and cost associated with chemotherapy

Parameter	Value	Source
Chemotherapy		
VFL dose per patient per cycle	287 mg/m2	Analyses / L007 IN 302 P1
VFL cost (250 mg vial)	£1062.5	Section 1.9 and 1.10
Body surface area (BSA) (mean) (m2)	1,85	Analyses / L007 IN 302 P1
VFL administration setting (Outpatient)	100%	Assumption & L007 IN 302 P1
Vial wastage	0%	Assumption
VFL outpatient delivery cost		
First attendance	£208	NHS HRG SB14Z
Second and subsequent attendances	£154	NHS HRG SB15Z
Mean delay between cycles (days)	14	Analyses / Model Calibration
CBC (per cycle)	£3.18	NHS DAP823
Laxative: bisacodyl (5mg, 20 tablet pack) (per cycle)	£0.7	BNF vs. 57

CBC = complete blood count

Health-state costs

6.4.21 *Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.*

Table B39: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in Submission
Pre-progression (per month)	General practitionner home consultation	£61	Section 6.5.1
	Community nurse specialist home visit	£329	
	Health home visitor	£40	
	Dietician home visit	£60	
	Oncologist follow-up visit	£91	
	Total BSC	£580	
	Palliative radiation therapy (VFL/BSC)	£5.2 / £116	
	Total	£585 / £696	
Post-progression (per month)	General practitionner home consultation	£61	Section 6.5.1
	Community nurse specialist home visit	£329	
	Health home visitor	£40	
	Dietician home visit	£60	
	Non-consultant oncologist follow-up visit	£63	
	Hospice care	£551	
	Pain medication	£150	
	Total BSC	£1 253	
	Palliative radiation therapy (VFL/BSC)	£46 / £31	
	Palliative chemotherapy (VFL/BSC)	£41 / £46	
	Total	£1340 / £1330	

*Cost of palliative radiation therapy and chemotherapy adjusted per month in PFS and PPS in study L007 IN 302
PFS (VFL/BSC) (LYs) = 0.36 / 0.18
PPS (VFL /BSC) (LYs) = 0.41 / 0.43

Adverse-event costs

6.4.22 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Medical-resource use and unit costs were identified 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 hospitalization (1.2% [vinflunine+BSC], 0.7% [BSC] [Section 5.9]). Fatigue and injection-site reactions, while frequent in Study 302 , were deemed not to involve additional utilization of medical-care services and were not included.

Clinical management of constipation was assumed to include one GP consultation and use of laxatives (Bisacodyl 5 mg, 20 unit pack). The cost of a GP visit was estimated to be £38, based on hourly rates reported by Curtis (2007) the cost of a Bisacodyl pack was assumed to be £0.65. Cost of hospitalization for febrile neutropenia was assumed to be £3538, based on a weighted average of unit costs for elective and non-elective admissions for febrile neutropenia (NHS HRG TEI PA45_Z, TEI_S_ PA45_Z, and TEI_L_ PA45_Z). Corresponding hospitalization cost for abdominal pain was estimated to be £557, based on the weighted average of cost for elective and non-elective admissions

for abdominal pain (NHS HRG TEI PA29_Z, TEI_S_ PA29_Z, and TEI_L_ PA29_Z). Table B40 summarises unit cost for the management of adverse events included in the model.

Table B40: List of adverse events and summary of costs included in the economic model

Adverse events*	Items	Value	Source	Reference in submission
Constipation	General practitioner consultation Bisacodyl (5 mg, 20 tablet pack) Total	£38 £0.7 £39	Curtis 2007 BNF vs. 57	Section 5.9
Febrile neutropenia with hospitalisation	Elective & non-elective inpatient	£3 538	NHS weighted, HRG TEI PA45_Z, TEI_S_ PA45_Z, and TEI L PA45 Z	Section 5.9
Abdominal pain with hospitalisation	Elective & non-elective inpatient	$551	NHS weighted, HRG TEI PA29_Z, TEI_S_ PA29_Z, and TEI_L_ PA29_Z	Section 5.9

*Grade 3 and Grade 4 only

Miscellaneous costs

6.4.23 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs were considered.

6.5 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.5.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Results from scenario analysis are provided below (section 6.7.9) and reflect structural sensitivity analyses. The use of hazard ratios (OS and PFS) for vinflunine in the economic evaluation is based on an assumption of the proportionality of hazards. The validity of this assumption was examined using the test of Grambsch and Therneau; the global test did not reveal a violation of the proportionality assumption (EMEA/CHMP/370293/2009). Alternative analytical scenarios employed to estimate PFS and OS for vinflunine+BSC and BSC included: (a) use of trial-based Kaplan-Meier estimates of survival (OS and PFS) for patients receiving vinflunine+BSC and BSC over the duration of follow-up in the trial (i.e., 2.4 years); and (b) use of modelled data obtained by fitting a gamma survivor function to patient-level failure time (PFS and OS) data. A gamma survivor function was selected based on examination of goodness-of-fit of alternative survivor functions; model parameters and figures depicting observed versus modelled data are reported in Appendix 9.14.

6.5.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Variables subjected to sensitivity analysis are listed in Section 6.3.6. In addition, two alternative analytical scenarios with respect to estimated OS and PFS by treatment also were included (section 6.6.1 and 6.7.9). Omitted variables included vial size and risk of side effects (addressed in PSA only).

In deterministic sensitivity analyses, parameter values were varied based on available alternative estimates. When data were unavailable, values were obtained multiplying the base case value for each variable by a factor of 0.5 and 1.5, respectively.

6.5.3 *Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).*

Yes. PSA was undertaken based on 1000 random iterations for the incremental comparison of vinflunine+BSC with BSC. Assumed distributions, means, and standard errors for the selected variables are presented in section 6.3.6.

Risks of adverse events and health-state utilities were sampled assuming a beta distribution; all other parameters were sampled assuming a log-normal or normal distribution. As input parameters, the model employs the mean (μ = basecase estimate) and standard error (σ = standard error of basecase estimate). Information was extremely limited or lacking to inform distributional assumptions underlying parameter values for estimates of medical resource use and unit cost; distributions were selected based on published recommendations (Briggs 2000).

Standard errors (SEs) for the vinflunine hazard ratios (OS and PFS) were derived from corresponding 95% confidence intervals. As standard errors for estimates of medical resource use were not available from study experts or NHS reference unit costs, values were assumed to be 25% of the base-case value. The same assumption was employed to estimate SEs for the risks of side effects.

6.6 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.6.1 *For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.*

Table B41: Summary of model results compared with clinical data

Outcome	Kaplan Meier Result	Model Result
Overall survival (LYs)		
Vinflunine + BSC	0.792	0.925
BSC	0.636	0.644
Difference	0.156	0.281
Incremental progression-free LYs (yrs)		
Vinflunine + BSC	0.368	0.348
BSC	0.188	0.188
Difference	0.180	0.160

Results reported on undiscounted basis

Differences between trial-based versus modelled outcomes can be explained by the following factors: (1) use of different time horizon (2.4 years in the trial vs 5 years in the model); (2) use of multivariate-adjusted hazard ratio for the effectiveness of vinflunine; and (3) extrapolation beyond the duration of follow-up in the trial.

6.6.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

A sample (n=150 first observations) of the estimated proportion of the cohort in various health states over time (ie., daily) is provided in Appendix 9.15 for each treatment group.

6.6.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Expected QALYs for each treatment group are calculated by multiplying expected pre- and post-progression survival time by corresponding estimates of pre- and post-progression health-state utility and summing [Section 6.3.4]. The model thus assumes that utilities are invariant with respect to time since therapy initiation, and that they are conditional only upon whether disease progression has occurred. Use of Markov trace is not applicable.

6.6.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table B42: Clinical outcomes and cost, by treatment

Outcome	LYs	QALYs	Cost (£)
Vinflunine + BSC			
Overall survival (undiscounted)	0,925	0,373	-
Overall survival (discounted)	0,898	0,364	21 714
Progression-free survival (undiscounted)	0,348	0,227	-
Progression-free survival (discounted)	0,345	0,224	12 830
Post-progression survival (undiscounted)	0,577	0,146	-
Post-progression survival (discounted)	0,553	0,140	8 884
BSC			
Overall survival (undiscounted)	0,644	0,238	-
Overall survival (discounted)	0,630	0,234	8 642
Progression-free survival (undiscounted)	0,188	0,122	-
Progression-free survival (discounted)	0,187	0,121	1 564
Post-progression survival (undiscounted)	0,456	0,116	-
Post-progression survival (discounted)	0,443	0,112	7 078

LY= Life Year; QALY=Quality Ajusted Life Years

6.6.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Breakdown of QALY gain by health state, Table B43a

Table B43a: Summary of QALY gain by health state

Outcome	QALY (VFL+BSC)	QALY (BSC)	Increment	Absolute Increment	Relative Increment
Progression-free survival (undiscounted)	0.227	0.122	0.104	0.104	77.4%
Progression-free survival (discounted)	0.224	0.121	0.103	0.103	78.8%
Post-progression survival (undiscounted)	0.144	0.114	0.030	0.030	22.3%
Post-progression survival (discounted)	0.138	0.111	0.027	0.027	20.9%
Overall survival (undiscounted)	0.373	0.238	0.135	0.135	-
Overall survival (discounted)	0.364	0.234	0.131	0.131	-

Breakdown of costs gain by health state, Table B43b.

Table B43b: Summary of costs by health state

Outcome	Cost (VFL+BSC)	Cost (BSC)	Increment	Absolute Increment	Relative Increment
Pre-progression					
Chemotherapy	9 485	0	9 485	9485	72,6%
Chemotherapy administration	701	0	701	701	5,4%
Monitoring	21	0	21	21	0,2%
Adverse events	199	4	194	194	1,5%
Other	2 423	1 560	863	863	6,6%
Post-progression	8 884	7 078	1 807	1807	13,8%
Total	21 714	8 642	13 072	13072	-

Breakdown of costs from model

Requested information is contained in Table 43b, above.

Base-case analysis

6.6.6 *Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.*

Table B44: Base case analysis

Technologies	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£/per incremental QALY)
BSC	8 642	0.630	0.234	-	-	-	-
VFL + BSC	21 714	0.898	0.364	13 071	0.267	0.131	100 144

Cost, LYs and QALYs are reported on discounted basis

Sensitivity analyses

6.6.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Table B45: Findings from deterministic sensitivity analyses

Scenario number - Description	Incremental Cost Per QALY Gained (£)	? Basecase
Basecase	100 144	-
VFL price (250 mg vial) (£):		
# 1 =0	27 478	-72 666
# 2 =200	41 156	-58 988
# 3 =400	54 835	-45 309
VFL vial wastage		
# 4 =297 mg/m^2 (two 250 mg + one 50 mg vials)	102 676	2 532
# 5 =based on assumed distribution of BSA (mean=1.85, sd=0.9)	121 095	20 951
Body Surface Area		
# 6 1.75 m^2	96 216	-3 928
# 7 1.80 m^2	98 180	-1 964
Number of cycles of therapy		
# 8 Three (recommended number of cycles)	70 233	-29 911
VFL cost of outpatient administration		
# 9 =0.5 x basecase	97 457	-2 687
# 10 =1.5 x basecase	102 830	2 686
Model time horizon		
# 11 Trial-based (2.4 years)	88 236	-11 908
Risk of adverse events (VFL and comparator) (%)		
# 12 =0.5 x basecase	99 400	-744
# 13 =1.5 x basecase	100 888	744
Cost of adverse events (VFL+BSC and BSC)(£)		
# 14 0.5 x basecase	99 400	-744
# 15 1.5 x basecase	100 188	44
Cost of BSC per mo. PFS (VFL+BSC and BSC) (£)		
# 16 0.5 x basecase	95 924	-4 220
# 17 1.5 x basecase	104 364	4 220
Cost of BSC per mo. PPS (VFL+BSC and BSC)(£)		
# 18 0.5 x basecase	93 862	-6 282
# 19 1.5 x basecase	106 426	6 282
Cost of palliative RT (VFL+BSC and BSC) (£) / per mo. PPS and PPS		
# 20 0.5 x basecase	100 521	377
# 21 1.5 x basecase	99 765	-379
Cost of palliative CT (VFL+BSC and BSC) (£) /per mo. PPS		
# 22 0.5 x basecase	100 040	-104
# 23 1.5 x basecase	100 247	103
Health-state utility PFS (VFL+BSC and BSC)		
# 24 =0.7	76 054	-24 090
# 25 =0.5	106 474	6 330
# 26 =0.4	133 094	32 950
Health-state utility, PPS reduction (VFL+BSC and BSC)(%)		
# 27 =20	81 904	-18 240
# 28 =30	85 712	-14 432
# 29 =40	89 891	-10 253
# 30 =50	94 498	-5 646
Discount rate (costs and effects) (%)		
# 31 =5	100 815	671

Note that this Table B45 states that the average dose was 297mg/m^2. This is a typographical error; the actual mean dose was 287mg/m^2.

6.6.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results of PSA for vinflunine+BSC versus BSC are presented as a cost-effectiveness plan (Figure B11a) and cost-effectiveness acceptability curve (Figure B11b). Findings are also summarized in tabular format in Tables B46a and B46b, respectively.

Figure B11a: PSA on differences (vinflunine+BSC) vs BSC in cost and QALYs

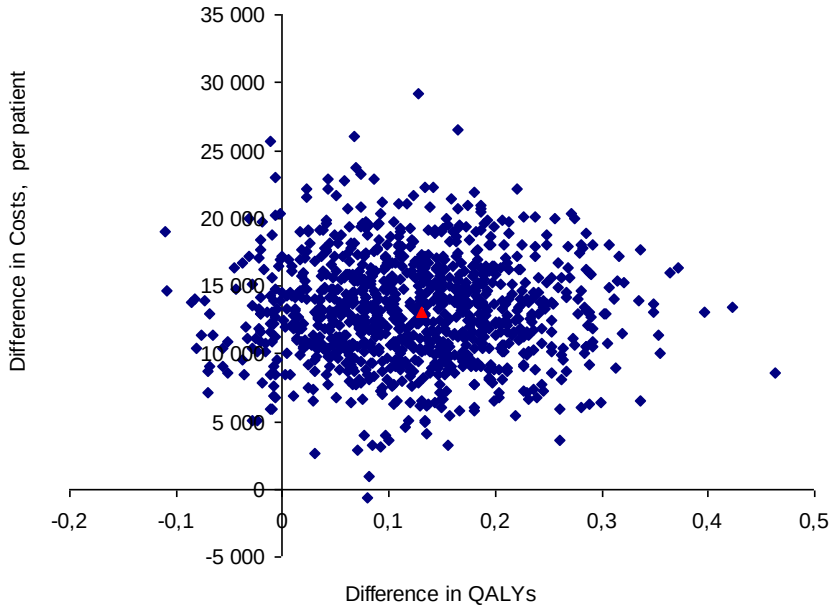


Table B46a: PSA summary (vinflunine vs BSC)

Cost-Effectiveness Ceiling Ratio (£)	Value
Number of Simulations	1000
NE quadrant (Cost>0, QALYs>0)	92,0%
SE quadrant (Cost<0, QALYs≥0, or Costs=0, QALYs>0; dominant)	0,1%
SW quadrant (Cost<0, QALYs<0)	0,0%
NW quadrant (Cost>0, QALYs≤0 or Cost=0, QALYs<0 ; dominated)	7,9%
Confidence Interval for dQALY	(-0.029, 0.291)
Confidence Interval for dCost	(5,977, 20,791)
Confidence Interval for ICER	(32,288, Dominated)

Figure B11b: Cost-effectiveness acceptability curve of VFL+BSC (vs BSC)

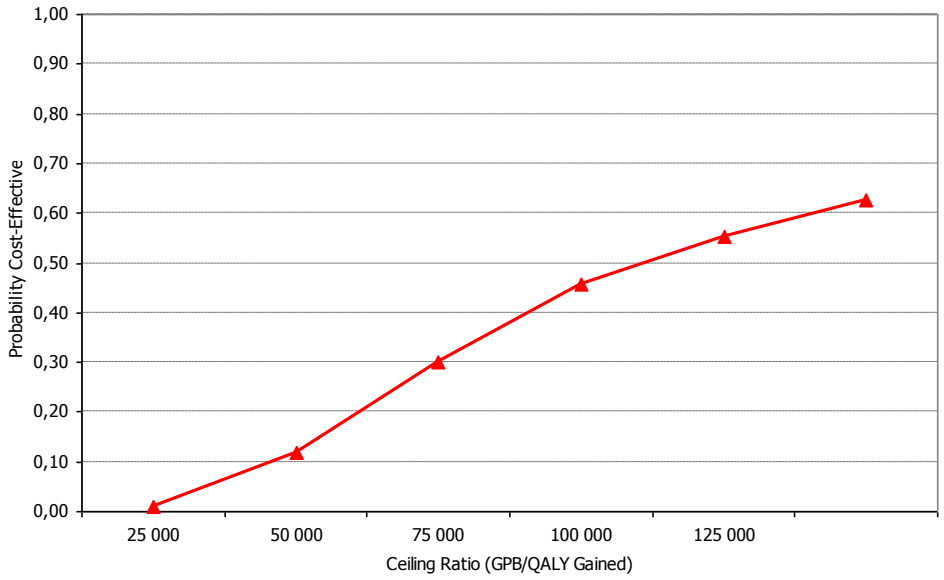


Table B46b: Percentage of simulations in which intervention is preferred

Cost-Effectiveness Ceiling Ratio (£/QALY)	Vinflunine + BSC
25 000	1,1
50 000	11,7
75 000	29,9
100 000	45,6
125 000	55,4
150 000	62,6

6.6.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Results from scenario analysis are provided below and reflect structural sensitivity analyses. No alternative model specifications were tested as model with states defined based on PFS and OS is consistent with clinical outcomes employed in oncology trials of treatments for advanced disease and endpoints in the vinflunine Study 302. As patients are usually treated until disease progression, differences in costs and potentially HRQL between pre- and post-progression health states should be expected. Presence or absence of disease progression has been reported to be a key determinant of health-state utility (Bremner 2007, Nafees 2008, Wittenberg 2005). Furthermore, partitioned survival models have been used in numerous prior technology assessments of cancer therapies. While we could have developed a model that included response to therapy, there was no evidence at the time of model development in support of differences in health-state utilities and/or cost of care for responders and non-responders in this patient population

Table B47: Findings from scenario analyses

Scenario number - Description		Incremental Cost Per QALY Gained (£)	∆ Basecase
Base case		100 144	
Effectiveness (OS & PFS) (VFL=BSC and BSC)			
# 1	= Kaplan-Meier estimates (trial-duration)	104 751	4 607
# 2	=Gamma modelled projections (5 years)	103 370	3 226

6.6.10 What were the main findings of each of the sensitivity analyses?

In deterministic sensitivity analyses, the incremental cost-effectiveness ratio (ICER) for vinflunine+BSC versus BSC alone ranged from £27 478 per QALY gained to £133 094 per QALY gained. The ratio was most sensitive to changes in health-state utilities (in particular, the assumed reduction associated with disease progression), the acquisition cost of vinflunine, the assumed number of cycles with vinflunine, and wastage assumptions based on assumed distribution of patient's BSA. Findings were overall stable with respect to changes in other model parameters and assumptions.

In PSA, the 95% CI for the difference (vinflunine+BSC minus BSC) in QALYs ranged from -0.029 to 0.291; the corresponding estimate for the difference in cost ranged from -£5977 to £20791. Accordingly, the lower bound of 95% CI for the ICER was £32,288 per QALY gained whereas the upper bound was dominated (vinflunine was dominated by BSC). At a threshold ceiling ratio of £30,000 per QALY gained, the probability that vinflunine+BSC is cost-effective versus BSC alone is 0.06

6.6.11 What are the key drivers of the cost-effectiveness results?

Key drivers of cost-effectiveness are the incremental efficacy of vinflunine (OS and PFS), the assumed acquisition cost of vinflunine, the number of cycles of therapy, and health-state utilities assigned to patients in pre- and post-progression health states.

6.7 Validation

6.7.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

A summary of tests of the model's internal consistency and corresponding findings is provided in Table B48.

Table B48: Summary of tests of model internal consistency

#	Test	Expected Effect	Observed Effect	Actions Taken
1	Set Utility to 1 and Utility reduction to 0	QALYs (BSC)=Lys(BSC), QALYs (VFL)=Lys(VFL)	As expected	None required
2	Set Cox HR to 1	QALYs(BSC)=QALYs(VFL)	As expected	None required
3	Set VFL acquisition and administration costs to 0, HR to 1, AE incidence and Costs to 0	No difference between VFL and BSC in terms of costs and effects	As expected	None required
4	Set incidence and AE costs VFL and BSC to same value	AE Costs(BSC) = AE Costs(VFL)	As expected	None required
5	Set BSC acquisition costs to VFL	Med Cost(BSC)= Med Costs(VFL)	As expected	None required
6	Set AE incidence to 0 and Costs to 100	AE Costs(BSC) = AE Costs(VFL) =0	As expected	None required
7	Set AE Costs to 100, and incidence to 0	AE Costs(BSC) = AE Costs(VFL) =0	As expected	None required
8	Set Time Horizon to 21+14-1=34 days	Admin Costs(VFL) = cAdminVFL_first=208	As expected	None required
9	All utilities = 0	QALY gain = 0	As expected	None required
10	Set discount rates for costs to 0%	Discounted Costs equal undicounted costs	As expected	None required
11	Set discount rates for health outcomes to 0%	Discounted benefits equal undiscounted benefits	As expected	None required
12	Set discount rates for benefits to 0%, set utilities to 1, utility reduction to 0, Cox HR to 1	Incremental QALY =0	As expected	None required
13	Set PercRxWasted to 10%	(Cost of acquisitions when PercRxWasted=10%)=(Cost of Acquisition when PercRxWasted=0%)*1.1	As expected	None required
14	Set RDI_Dose_VFLVFLStg to 0.75	(Cost of acquisitions when RDI_Dose_VFLVFLStg=0.75 should equal (Cost of ARDI_Dose_VFLVFLStg=1)*0.75	As expected	None required
15	Set Time Horizon to Day 912 (last BSC observation) (OS)	OS projections BSC basecase=Trial-based	As expected	None required
16	Set Time Horizon to Day 285 (last BSC observation)(PFS)	PFS projections BSC basecase=Trial-based	As expected	None required
16	Examine Pre and post progression LYs	PFLYs + PPLYs= LYs	As expected	None required
17	Examine Pre and post progression QALYs	PFUtil*PFLYs+PFUtil*PPUtilReduction*PPLYs=QALYs	As expected	None required
18	Set mean BSA=0	Acquisition Cost=0	As expected	None required

6.8 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.8.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Analysis of patient subgroups was not undertaken.

6.8.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable

6.8.3 Please describe how the statistical analysis was undertaken.

Not applicable

6.8.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Not applicable.

6.8.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Obvious subgroups were not considered.

6.9 Interpretation of economic evidence

6.9.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no published data relating to the decision problem considered in this economic evaluation, precluding comparisons of findings.

6.9.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes.

6.9.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths of the evaluation include:

(1) A clinically appropriate model structure using most available data from study 302 in either the base case or sensitivity analyses.
(2) Complete data (OS and PFS) for most patients participating in study 302.
(3) Use of transparent methodology and requirement of few assumptions regarding estimated clinical efficacy of vinflunine.
(4) Analyses addressed alternative scenarios with respect to estimated clinical efficacy of vinflunine using: (a) trial-based data (Kaplan-Meier estimates of OS and PFS for BSC and multivariate-adjusted hazard ratios for vinflunine [reference case]); (b) trial-based data (Kaplan-Meier estimates of OS and PFS for both treatment arms [scenario analyses]); (c) modelled data (gamma projections of OS and PFS for both treatment arms) (scenario analyses).
(5) Extensive deterministic and probabilistic sensitivity analyses given data availability.

Weaknesses of the evaluation include:

(1) Estimates of the effectiveness of vinflunine+BSC versus BSC alone in patients with advanced transitional cell carcinoma of the urothelium were based on data from a single Phase III randomized controlled clinical trial.
(2) Information on EQ-5D utilities was not available from study 302; need to estimate pre-progression utilities using EORTC QLQ-C30 scores from trial, employing published values for a different population of terminally ill patients in post-progression health state.
(3) Lack of data on medical-resource utilization (BSC pre- and post-progression) among patients with advanced transitional cell carcinoma of the urothelium in the UK and elsewhere; estimation based on expert opinion.
(4) Extremely limited reporting of data on resource use and costs, which necessitated that standard errors and distributional assumptions employed in PSA be based on assumption.
(5) Failure to differentiate between BSC resource consumption for patients treated with or without vinflunine as this may be different.

6.9.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Analyses presented within this submission are broad and cover key areas of uncertainty. This is similar to the introduction of other chemotherapies for unmet clinical needs (e.g. NSCLC, renal). Audit during a phase of managed introduction would make this analysis more robust. Key areas to cover would include:

(1) Audit patient profiles (prognostic factors) and outcomes with vinflunine in routine clinical practice.
(2) Collection of EQ-5D utilities in patients treated in routine clinical practice.
(3) Characterization of medical-resource utilization (BSC pre- and post-progression) in the population of interest.

6.10.5 *Additional Considerations: Eligibility of vinflunine for consideration of application of the end-of-life supplementary advice in health technology appraisals.*

In light of NICE Social Value Judgments and the recent publication of end-of-life supplementary advice in health technology appraisals (NICE 2009), PFM considers that vinflunine is a life-extending therapy for patients with short life expectancy, which is licensed for an indication (i.e., treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelium who have failed a prior platinum-containing regimen) affecting small numbers of patients with an incurable illness. The ICER for vinflunine in the UK is in excess of the upper end of the range normally approved by the Appraisal Committee, using the reference case outlined in the 2008 "Guide to Methods of Technology Appraisal" (NICE 2008). Therefore, PFM believes vinflunine in its current indication meets section 2 criteria of NICE's supplementary advice as follows:

1) <u>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</u>

Life expectancy in the population indicated for vinflunine treatment is less than 24 months; median survival rarely exceeds 3 to 6 months [Section 2.1].

2) <u>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.</u>

Vinflunine demonstrated a 2.6-month survival advantage (6.9 months in the vinflunine+BSC arm vs 4.3 months in the BSC arm, p=0.0403) in the eligible population [Section 5]. The eligible patient population represents the actual transitional cell carcinoma of the urothelium population targeted by the protocol (all randomized patients excluding those with clinically significant protocol violations at baseline: vinflunine+BSC: 4 patients, BSC: 9 patients). Risk of death was reduced by 22% in the vinflunine+ BSC arm versus the BSC arm: HR of 0.78 (95%CI: 0.61, 0.99).

Multivariate analysis of OS including pre-specified prognostic factors confirmed the significant effect of the treatment arm of survival (HR 0.69 [95% CI: 0.54, 0.88]), this difference being statistically significant (p=0.0027). The Cox model proportional hazards assumption was investigated with the test of Grambsch and Therneau as performed for the Cox model in the eligible population; the global test did not show a deviance from the proportional hazards assumption.

3) No alternative treatment with comparable benefits is available through the NHS

There is currently no standard therapy in patients with advanced transitional cell carcinoma of the urothelium whose disease has progressed after or during a prior platinum-containing regimen. These patients have a median survival of approximately 4 months and a poor prognosis. No randomised controlled trials have been conducted for single agent treatment of transitional cell carcinoma of the urothelium. Phase II studies have been conducted in small populations of patients (< 60) that show response rates ranging from 0% with bortezomib to 11%, 23% and 29% with gemcitabine. The eligibility criteria for these phase II studies were varied and they were not all second-line studies. None of them generated hypotheses with sufficient confidence for testing in phase III studies. Vinflunine provides a novel treatment option for patients with this condition.

4) The treatment is licensed or otherwise indicated for small patient populations

Vinflunine is indicated for the treatment of adult patients with advanced transitional cell carcinoma of the urothelium who have failed a prior platinum-containing regimen. It is estimated that 30-40% of metastatic patients with bladder cancer receive first line chemotherapy (2 000-3 000 patients in the UK) and that 40-50% of these will be candidates for second line treatment (800-1 500) [Section 2.2].

5) Impact of giving greater weight to QALYs achieved in later stages of terminal diseases, using assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age, and; magnitude of 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.

A utility weight of 0.79 was employed in additional analyses reflecting an assumption that the extended patient's survival period would be experienced at the full quality of life anticipated for a healthy individual of the same age, and following the methodology proposed by NICE in previous NICE appraisals of end of life therapies (NICE 2009). The utility assumption of 0.79 was based on the trial-based gender-weighted average of the UK population norms for the EQ-5D among persons 55-64 years of age (males [0.78], females [0.81] reported in a nationally representative survey of 3,395 men and women age 18 years or older in the UK (Kind 1999).

Calculation of QALY weights were undertaken as per NICE supplemental advice as follows:

Table B49: Impact and QALY weights to be considered by the appraisal committee

Parameter	Value
Incremental cost	13 071
Incremental LYG	0.267
Incremental QALYs (Original)	0.131
ICER (Original)	100 144
IQ (Max)	0.211
ICER (Max Q)	
Relative weights	
Original Q (£20 000)	5.01
Original Q (£30 000)	3.34
Max Q (£20 000)	3.09
Max Q (£30 000)	2.06

The additional weight (Max Q scenario) that would need to be assigned to QALY benefits among patients treated with vinflunine for this therapy to be cost-effective at a willingness to pay of £30,000/QALY is 2.06. Based on available information, the Committee has "*de facto* accepted a highest weight of 1.7 (relative to a pre- end-of-life threshold of £30,000 per QALY gained, noting that this is 2.5 relative to a pre end-of-life threshold of £20,000 per QALY gained)" (NICE 2009).

6) Estimates of the extension of life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival; assumptions used in the reference case economic modelling are plausible, objective and robust.

See number 3 above. The Cox analysis is considered an appropriate methodology to adjust for imbalances in baseline prognostic factors between treatment arms. Findings from this analysis are therefore considered to be reflective of the true survival benefit of vinflunine, and were used to form the reference case for the economic evaluation.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

This indication for vinflunine in TCCU is currently an unmet clinical need. The majority of data available on incidence, histology, mortality and treatment is centred on surgical management (BAUS 2009). Data after relapse from surgical interventions and BSC are limited. The number of patients that are candidates for treatment with vinflunine has been estimated and projected from regional cancer registry data (NYCRIS) and informal discussion with oncologists in this field. Estimates and assumptions have been stated. The manufacturer remains open to any additional data sources for England and Wales and any discussion on assumptions made (Appendix 9.15).

The majority of incident patients have early stage disease (Appendix 9.16) and are managed by surgeons over an extended period. Survival with advanced or metastatic disease is relatively short and mortality statistics have been assumed to be a more representative surrogate on which to base estimates of the number of patients that are candidates for chemotherapy for advanced disease.

The use of 1st line chemotherapy in advanced or metastatic disease is limited due to deterioration performance status and co-morbidity. It is estimated that approximately 30% of such patients receive first line chemotherapy (1500-2000 patients in England and Wales). The estimated use/potential for vinflunine is that half of patients that have received 1st line chemotherapy will be candidates for 2nd line treatment. It is estimated that 800-1000 patients are candidates for second line treatment (Appendix 9.15).

The number of patients in England and Wales that are candidates for vinflunine is estimated as follows (Table C1):

Table C1: Estimated number of patients

ENGLAND AND WALES	**2010**	**2011**	**2012**	**2013**	**2014**
Incidence	10,681	10,361	10,050	9,748	9,456
Mortality	4,949	4,800	4,656	4,516	4,381
1st line treatment rate	30%	30%	32%	34%	36%
1st line patient number	1,485	1,440	1,490	1,536	1,577
2nd line treatment rate	50%	50%	53%	56%	60%
2nd line patient estimate	**742**	**720**	**790**	**860**	**946**

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

There are currently no other agents licensed in the UK for patients with advanced or metastatic TCCU after failure of a platinum-containing regimen.

Management guidelines (NICE (2002), BAUS, BUG, and SIGN (2005)) advocates MDT management. Consideration of chemotherapy is suggested as part of the MDT management of selected/fit patients with advanced or metastatic disease. "Platinum containing" is suggested but the regimens are not stipulated.

Patients that relapse >12 months after platinum appear to be re-treated with the same regimen used earlier but this may be a minority of patients (see Table B21). Patients relapsing earlier than 12 months or are unsuitable for further platinum (usually deteriorating renal function) receive other drugs, often single agent chemotherapy. In the absence of a licensed agent, the choice of chemotherapy is made from the available range of drugs within the hospital based on activity in other tumour types (e.g. docetaxel, paclitaxel, gemcitabine, pemetrexed). There is inter- and intra-institutional variation in the choice of these alternative agents.

Disease management guidelines (NICE, BAUS, BUG, SIGN) did not extend to 2nd line chemotherapy as no treatment licensed treatment was available at that time. (This process has only just started with the European Association of Urology Guidelines, 2010 edition; Stenzl et al 2010). As a consequence, robust and uniform data on the current use and outcome from 2nd line chemotherapy has not been collected and the manufacturer was unable to include this in the economic model.

7.3 What assumption(s) were made about market share (when relevant)?

The uptake of a new cancer drugs by the NHS still requires local business plans, adoption procedures and commissioner support. Local priority setting and procedures may delay the uptake, even with positive NICE Guidance. The general rate of uptake of new cancer drugs by the NHS has also been reported to be amongst the lowest in Europe (Wilking et al., 2009). The manufacturer made the following assumptions (Table C2) in terms of uptake of vinflunine in advanced or metastatic TCCU over the 5 next years.

Table C2: Estimated Clinical Need and Uptake

	2010	2011	2012	2013	2014
Therapeutic Need (Est Patients)	742	720	790	860	946
Estimated Vinflunine Uptake					
With +ve NICE Guidance	5	108	197	301	426
With -ve NICE Guidance	5	14	39	86	142
"Market" Share					
With +ve NICE Guidance	1%	15%	25%	35%	45%
With -ve NICE Guidance	1%	2%	5%	10%	15%

A large proportion of patients that are candidates for vinflunine would continue to receive chemotherapy with other unlicensed agents.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The average treatment cost per patient, including the chemotherapy acquisition, its administration in an outpatient setting with a mean number of treatment cycles of 4.2, the premedication and monitoring, and hospitalizations in case of severe adverse events, is £10 406 (Section 6.5.5). The chemotherapy acquisition cost, the administration with the premedication and the monitoring, the treatment of severe adverse events represent 91.1% of the treatment cost, 7.5% and 1.9% respectively.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Cost data are derived from National Reference Costs, which represent charges paid by those commissioning services (primary care trust) to those providing services (hospitals).

7.6 Were there any estimates of resource savings? If so, what were they?

None could be assumed due to data limitations on the current resource demands these patients place on the NHS. A conservative assumption of non-difference of medical and paramedical care between patients receiving a chemotherapy treatment and patients with supportive care alone was done. This means that extended survival attracts additional assumed support costs at a similar rate to patients in terminal care.

There is considerable uncertainty regarding the health resource consumption for cancer patients during BSC.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Vinflunine is an active and useful drug that has demonstrated an important survival gain for even the most advanced, end of life patients with TCCU. The uptake in hospitals depends upon the policy decision made by NICE through this process.

Positive NICE Appraisal removes important barriers but access to vinflunine by the intended patient group will still be subject to regional variation for at least the first 5 years. The absence of positive NICE Appraisal would be a major limiting factor affecting access in England and Wales.

The "New Cancer Drug Budget" could be a useful way to accelerate access to important new drugs for smaller patient populations with a previously unmet clinical need and provide a basis for the collection of real resource utilisation data for these patients.

The uptake of vinflunine has been forecast in these three scenarios as follows (Table C3):

Table C3: Estimated Number of Patients Treated in 5 years (Assumptions as 7.1)

Patient Numbers	2010	2011	2012	2013	2014
With +ve NICE Guidance	5	108	197	301	426
With -ve NICE Guidance	5	14	39	86	142
With New Cancer Drug Funding	5	324	395	473	520

The total cost of treatment (Section 6.5.5) including drug acquisition, hospital and side-effect management costs is estimated as follows (Table C4):

Table C4: Estimated Total Cost of Treatment

Total Cost (Section 6.5.5)	2010	2011	2012	2013	2014
With +ve NICE Guidance	52,030	1,123,860	2,054,316	3,131,901	4,431,095
With -ve NICE Guidance	52,030	149,848	410,863	894,829	1,477,032

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

We already know from progress made in other tumours such as NSCLC, that patients receiving palliative chemotherapy live longer, consume supportive health resources at a lower rate during treatment and despite earlier concerns, this is actually proved itself to be good value for money. Improved data collection and audit (LUCADA is magnificent) allowed us to track the impact of new technology, not only the new drugs but also the way medical practice adapted to exploit it fully. So drugs that seemed to offer 1.6 months additional survival (v BSC) are used more effectively and contribute to markedly improved long term survival rates for some patient groups (15% absolute increase in 5 year survival). As second line treatment has already become established (e.g. docetaxel), new and alternative 2nd line treatments can be meaningfully appraised because they are "replacement" and not "new" costs.

Limited evidence in renal cancer also suggests that patients treated with appropriate new chemotherapy consume health resources at a lower rate than untreated patients (James 2009).

The fundamental issue with the economic model presented in this submission is the absence of real data on how these patients are currently managed. Without the existing real cost base we have no way to track reduced consumption of health resources elsewhere in the system. Additional survival suddenly becomes a liability rather than the primary goal of treatment. Survival will not improve as treatment stagnates, not only in TCCU but for any other rare tumour type when new treatment becomes available for a previously unmet clinical need.

We know that a significant number of patients relapsing after earlier platinum based chemotherapy go on to receive further chemotherapy but nobody can quantify it for inclusion in a model. We also know that patients that receive further chemotherapy have quicker and easier access to other palliative treatments and place fewer demands on the primary care team.

As with NSCLC, these efficiency gains can only become clear when we have audited best practice and implemented it consistently across the NHS. Better treatment and longer survival will cost more but the absence of real economic or resource data causes this to be overestimated compared to areas where these data are known.

There has to be a better way to manage the introduction of new cancer drugs. This is not a challenge to the appraisal process or the use of QALY, but a simple observation that new drugs are severely disadvantage by the fact that they have not previously existed and we have not been collecting the data for the last few years.

End of Life

In light of NICE social value judgements and the recent publication of "end-of-life" supplementary advice in health technology appraisals, different considerations should be stated: Vinflunine is a novel treatment option for a small population with an incurable illness and a 4.3-month life expectancy with no alternative treatment, increases survival by 2.6 months (and the incremental LYG is 3.2 months in the economic model) which represents a 60% improvement in overall survival, and is not licensed in other indications. Using the trial-based utility for an healthy individual of the same age of 0.79, the additional weight that would need to be assigned to QALY benefits among patients treated with vinflunine for this therapy to be cost-effective at a willingness-to-pay of £30,000/QALY is 2.06 (Section 6.10.5).

The concept of an innovation pass recognised that the economic data for new treatment for a previously unmet clinical need might be "immature". This programme is suspended but the new cancer drug budget could adopt principles for a logical and structured approach to the managed entry of new cancer treatment. A commitment to collect the relevant data through collaboration with NCRN/NCIN for a period before final NICE appraisal could remove the current data desert and help us to value new, active and innovative drugs more effectively.

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Please use a recognised referencing style, such as Harvard or Vancouver.

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9 Appendices

9.1 Appendix 1

9.1.1 SPC as a separate document.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

The databases searched were the Cochrane Central Register of Controlled Trials (CENTRAL), CAB abstracts and BIOSIS previews using the DIMDI (https://portal.dimdi.de/websearch/servlet/FlowController/Search) online search facility; Index Medicus database (MEDLINE) using PUBMED (http://www.ncbi.nlm.nih.gov/pubmed/); Conference proceedings, including ASCO, ESMO, ESMO/ECCO, EAU, were searched 'by hand' at the individual organizations websites.

9.2.2 The date on which the search was conducted.

Databases were searched on 17/05/2010

9.2.3 The date span of the search.

There were no time constraints on the searches of databases except conference proceedings which were limited to 2007 onwards.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). The data abstraction strategy

Using the search term "vinflunine" the following results were obtained from the DIMDI resource:

Database	N° papers	Comments	Papers meeting inclusion criteria
CENTRAL	4	3 excluded as they were interim reports of the same phase III trial	1
CAB abstracts	5	All excluded failed to meet inclusion criteria	0
BIOSIS previews	126	All titles scanned to identify papers potentially meeting inclusion criteria. All excluded except 2 which refer to eligible phase II trials with vinflunine	2

The following results were obtained from Medline using Pubmed:
The search term "vinflunine" identified 114 papers which were largely on the preclinical data and mode of action. The search was repeated using the Boolean expression "vinflunine AND (bladder OR tccu OR transitional OR urothel*)" which identified a subset of 23 potentially relevant papers. The abstracts of these were then scanned to see if they met the inclusion criteria. This identified 4 papers, three of them were the same two phase II and one phase III trials that were identified in the above Table. The fourth paper was a reanalysis of the phase III trial found by the same search which had been done to try to establish prognostic factors. Data from this paper will be included in the discussion on clinical evidence but was excluded from the systematic review as it does not identify a unique relevant trial or impact on the overall safety and efficacy described by the primary analysis of the trial. Thus 111 papers were excluded from the systematic review.
To identify trials of potential comparative agents Medline was searched (limited to titles) using the Boolean term "(advanced OR metastatic) AND (bladder OR transitional OR tccu OR urothel*) AND cancer AND (trial OR study OR clinical)". This identified 130 papers which were then scanned for their potential relevance. A subset of 58 papers was selected for closer scrutiny of the abstracts. This process failed to identify any additional vinflunine trials but did reveal a number of phase II studies with other agents in advanced bladder cancer. However, these were all excluded because they did not meet the inclusion criteria; examples included first-line studies, selection of patients unfit for platinum, failure to meet primary endpoints, combination with concurrent radiotherapy, neo/adjuvant chemotherapy trials.
Review of conference proceedings using the relevant organisation websites (ASCO, ESMO, ESMO/ECCO, EAU going back to 2007 identified 6 abstracts, 5 of these were interim analyses of the previously identified vinflunine studies and were therefore excluded but one was longer term follow-up of the phase III vinflunine study and was therefore included.

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

N/A

9.2.6 The inclusion and exclusion criteria.

The inclusion criteria in the systematic review carried out to identify relevant clinical trials were:
Advanced or metastatic transitional cell carcinoma of the urothelial tract (metastatic bladder cancer).
Phase II trials in which the experimental agent was used alone or as part of a combination following treatment with a platinum-based regimen and met their primary endpoints.
Phase III RCTs in which the experimental agent was used alone or as part of a combination following treatment with a platinum-based regimen.

9.2.7 The data abstraction strategy

See 9.2.4

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: **Study 302**		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	2:1 randomisation, assigned by Biometrics Department of Pierre Fabre and stratified by study site and refractoriness to prior chemotherapy	Yes
Was the concealment of treatment allocation adequate?	Open-label study	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline demographics were tabulated and compared. They were well balanced with the exception of PS which was biased in favour of the BSC arm by 10%	Yes
Were the care providers, participants 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)?	Open-label study but the assessors (IRC) were blinded minimising the risk of bias for responses	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No differences in drop-out rates, all patients accounted for in study report	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, all outcomes were reported.	Yes
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 an ITT analysis was conducted on all randomised patients. A further analysis was conducted on an ITT basis after removing 13 ineligible patients.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for section 5.5 (Indirect and mixed treatment comparisons)

Not applicable for the reasons described in section 5.5.1: There were no identifiable studies from which indirect or mixed comparisons could be made.

9.4.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

9.4.2 *The date on which the search was conducted.*

9.4.3 *The date span of the search.*

9.4.4 *The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

9.4.5 *Details of any additional searches (for example, searches of company databases [include a description of each database]).*

9.4.6 *The inclusion and exclusion criteria*.

9.4.7 *The data abstraction strategy.*

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.5 (Indirect and mixed treatment comparisons)

9.5.1 *A suggested format for the quality assessment of RCT(s) is shown below.*

Not applicable for the reasons described in section 5.5.1: There were no identifiable studies from which indirect or mixed comparisons could be made.

9.6 Appendix 6: Search strategy for section 5.6 (Non-RCT evidence)

The following information should be provided.

9.6.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

See Appendix 2.

The systematic review described in sections 5.1.1 to 5.1.7 and Appendix 2 were designed to identify all evidence for efficacy and safety of vinflunine in the treatment of TCCU as well as potential comparators in all clinical trial and non-trial settings.

9.6.2 *The date on which the search was conducted.*

17th May 2010 (Appendix 2)

9.6.3 *The date span of the search.*

As Appendix 2

9.6.4 *The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

As Appendix 2

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A Appendix 2

9.6.6 The inclusion and exclusion criteria.

As Appendix 2

9.6.7 The data abstraction strategy.

As Appendix 2, but focused on non-comparative studies and non-interventional studies.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Study ID or acronym	**Study 202**		**Study CA 001**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
How were responses assessed?	By independent panel	Yes	By independent panel	Yes
Were there any unexpected drop-outs? If so, were they explained or adjusted for?	No, all patients were accounted for. 1 Patient died before being treated. 6 patients excluded from analysis of efficacy as they were treated at a different dose.	Yes	No, all patients were accounted for.	
Were appropriate patients studied?	All patients met the inclusion criteria	Yes	All patients met the inclusion criteria	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, all outcome data were reported	Yes	No, all outcome data were reported	Yes
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 and this was appropriate. All patients treated at same starting dose were accounted for.	Yes	Yes and this was appropriate. All treated patients were accounted for.	Yes

9.8 Appendix 8: Search strategy for section 5.7 (Adverse events)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *The Cochrane Library.*

The systematic review described in sections 5.1.1 to 5.1.7 and Appendix 2 were designed to identify all evidence for efficacy and safety of vinflunine in the treatment of TCCU as well as potential comparators in all clinical trial and non-trial settings. Additional data were obtained from the company core data.

9.8.2 The date on which the search was conducted.

See 9.8.1

9.8.3 The date span of the search.

See 9.8.1

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See 9.8.1

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The company core data set of adverse events for the three studies, 202, 302 and CA 001 were examined.

9.8.6 The inclusion and exclusion criteria.

See 9.8.1

9.8.7 The data abstraction strategy.

See 9.8.1

9.9 Appendix 9: Quality assessment of adverse event data in section 5.7 (Adverse events)

9.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

See Appendix 7

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *EconLIT*
- *NHS EED.*

The databases searched were Medline and Embase using OVID

9.10.2 The date on which the search was conducted.

November 1st 2008 and repeated for completeness on July 22nd, 2010. On the latter date, the numbers of citations differed from those found in November 2008 at each search step (see Figures below), but the final outcome was the same. That is, no published cost-effectiveness evaluations were deemed relevant to the decision problem considered in this economic evaluation.

9.10.3 The date span of the search.

No restrictions were applied to publication date within these searches.

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategy (Section 6.1.1) (Medline)

Search History (13 searches) (Click to close) — View Saved

# ▲	Searches	Results	Search Type	Actions
1	exp Carcinoma, Transitional Cell/ or exp Urinary Bladder Neoplasms/ or metastatic bladder cancer.mp.	15956	Advanced	Display More ≫
2	exp Urethral Neoplasms/ or exp Urinary Bladder Neoplasms/ or exp Carcinoma, Transitional Cell/ or transitional cell cancer of the urothelium.mp.	16338	Advanced	Display More ≫
3	1 or 2	16343	Advanced	Display More ≫
4	limit 3 to yr="2000 -Current"	11982	Advanced	Display More ≫
5	costs.mp. or exp "Costs and Cost Analysis"/	113105	Advanced	Display More ≫
6	4 and 5	92	Advanced	Display More ≫
7	economics.mp. or exp Economics/	205293	Advanced	Display More ≫
8	4 and 7	81	Advanced	Display More ≫
9	vinflunine.mp.	96	Advanced	Display More ≫
10	4 and 9	11	Advanced	Display More ≫
11	10 and 5	0	Advanced	Delete Save
12	7 and 10	0	Advanced	Delete Save
13	**8 or 6**	**109**	**Advanced**	Display More ≫

Remove Selected | Save Selected | Combine selections with: And | Or

Save Search History

Search strategy (Section 6.1.1) (Embase)

Search History (17 searches) (Click to close) — View Saved — CONTRACT

# ▲	Searches	Results	Search Type	Actions
1	exp bladder cancer/ or metastatic bladder cancer.mp.	15669	Advanced	Display More ≫
2	exp transitional cell carcinoma/ or exp bladder cancer/ or exp urinary tract tumor/ or transitional cell cancer of the urothelium.mp. or exp urethra cancer/	44793	Advanced	Display More ≫
3	exp "cost"/ or costs.mp.	127251	Advanced	Display More ≫
4	economics.mp. or economics/ or exp health economics/	204147	Advanced	Display More ≫
5	1 or 2	44795	Advanced	Display More ≫
6	4 or 3	227471	Advanced	Display More ≫
7	6 and 5	1132	Advanced	Display More ≫
8	limit 7 to (human and english language)	1030	Advanced	Display More ≫
9	metastatic.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	59609	Advanced	Display More ≫
10	8 and 9	103	Advanced	Display More ≫
11	bladder.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	52706	Advanced	Display More ≫
12	urothelium.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	2608	Advanced	Display More ≫
13	11 or 12	53420	Advanced	Display More ≫
14	13 and 10	16	Advanced	Display More ≫
15	from 14 keep 1-16	16	Advanced	Display More ≫
16	vinflunine.mp. or exp vinflunine/	249	Advanced	Display More ≫
17	**16 and 14**	**0**	**Advanced**	Delete Save

Remove Selected | Save Selected | Combine selections with: And Or

Save Search History

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

	Study name	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?		
9. Were details of the design and results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		
13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		

17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		
25. Was an explanation given if cost or benefits were not discounted?		
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		
27. Was the approach to sensitivity analysis described?		
28. Was the choice of variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?		
32. Were major outcomes presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?		
34. Did conclusions follow from the data reported?		
35. Were conclusions accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?		
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

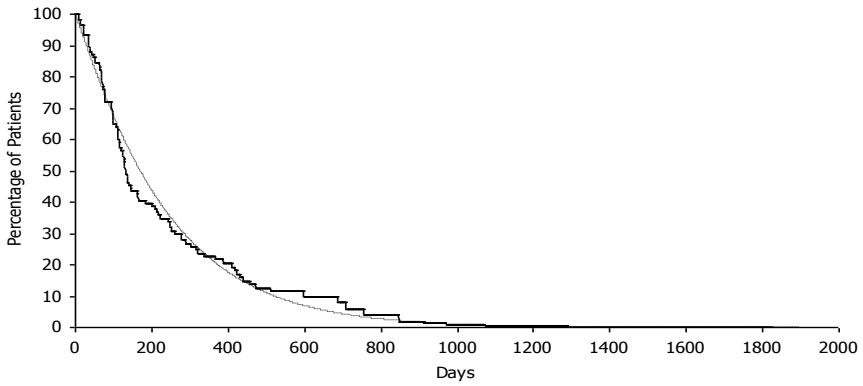
Appendix 9.11. Stratified Weibull: Parameter Estimates (Section 6.4.15)

Table. OS and PFS: Stratified Weibull model parameters

	PFS		OS	
	Estimate	**SE**	**Estimate**	**SE**
BSC				
Intercept	4.337	0.0759	5.4764	0.0968
Scale	0.7400	0.0514	0.9308	0.0727
Weibull Scale	76.48	8.5634	238.9812	23.1219
Survival function parameters				
λ	0.013076	0.000992	0.004184	0.000405
γ	1.351351	0.001464	1.074345	0.000405
VFL				
Intercept	4.914900	0.0628	5.714200	154.1687
Scale	0.925200	0.0446	0.923300	0.051700
Weibull Scale	136.307600	8.563400	303.138800	19.842700
Survival function parameters				
λ	0.007336		0.003299	
γ	1.080847	0.055556	1.083072	0.078739

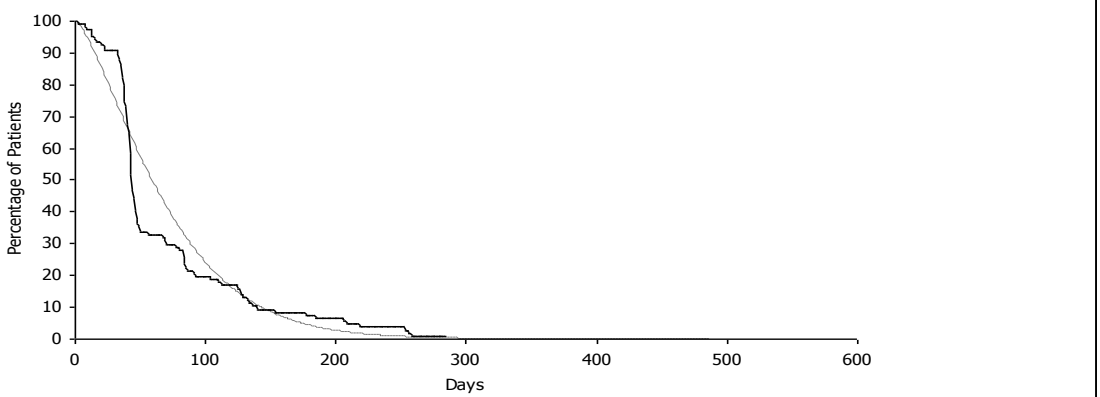
γ =1/scale. λ =exp(-Intercept - Estimate $_{L+C\ vs\ C\text{-}only}$).

Figure 1. Observed and estimated (Weibull) OS (BSC)



Weibull projections used in model from days 914 to 1825 only

Figure 2. Observed and estimated (Weibull) PFS (BSC)



Weibull projections used in model from days 285 to 421 only

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *NHS Economic Evaluation Database (NHS EED)*
- *EconLIT.*

The search was conducted using the OVID, Medline, and Embase databases.

9.12.2 The date on which the search was conducted.

Response

9.12.3 The date span of the search.

No restrictions were applied to publication date within searches.

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Appendix 9.12. Search strategy (Section 6.4.5) (Medline)

Search History (12 searches) (Click to close) View Saved

#	Searches	Results	Search Type	Actions
1	exp Carcinoma, Transitional Cell/ or exp Urinary Bladder Neoplasms/ or metastatic bladder cancer.mp.	15956	Advanced	Display More ≫
2	exp Urethral Neoplasms/ or exp Urinary Bladder Neoplasms/ or exp Carcinoma, Transitional Cell/ or transitional cell cancer of the urothelium.mp.	16338	Advanced	Display More ≫
3	1 or 2	16343	Advanced	Display More ≫
4	limit 3 to yr="2000 -Current"	11982	Advanced	Display More ≫
5	health status.mp. or exp Health Status/	70692	Advanced	Display More ≫
6	4 and 5	36	Advanced	Display More ≫
7	exp "Outcome Assessment (Health Care)"/ or exp "Quality of Life"/ or exp Health Status/ or health related quality of life.mp.	476972	Advanced	Display More ≫
8	4 and 7	1422	Advanced	Display More ≫
9	quality of life.mp. or exp "Quality of Life"/	89574	Advanced	Display More ≫
10	4 and 9	296	Advanced	Display More ≫
11	exp "Quality of Life"/ or health related quality of life.mp.	62281	Advanced	Display More ≫
12	**11 and 4**	**182**	**Advanced**	Display More ≫

Remove Selected | Save Selected | Combine selections with: And Or

Save Search History

CONTRACT

Appendix 9.12 (Cont.). Search strategy (Section 6.4.5) (Embase)

Search History (23 searches) (Click to close) — View Saved

	# ▲	Searches	Results	Search Type	Actions
☐	1	exp bladder cancer/ or metastatic bladder cancer.mp.	15618	Advanced	Display More ≫
☐	2	exp transitional cell carcinoma/ or exp bladder cancer/ or exp urinary tract tumor/ or transitional cell cancer of the urothelium.mp. or exp urethra cancer/	44649	Advanced	Display More ≫
☐	3	health status.mp. or exp health status/	47872	Advanced	Display More ≫
☐	4	[limit 8 to yr="2000 -Current"]	0	Advanced	Delete Save
☐	5	exp bladder cancer/ or metastatic bladder cancer.mp.	15618	Advanced	Display More ≫
☐	6	exp transitional cell carcinoma/ or exp bladder cancer/ or exp urinary tract tumor/ or transitional cell cancer of the urothelium.mp. or exp urethra cancer/	44649	Advanced	Display More ≫
☐	7	health status.mp. or exp health status/	47872	Advanced	Display More ≫
☐	8	health related quality of life.mp. or exp "quality of life"/	98268	Advanced	Display More ≫
☐	9	quality of life.mp. or exp "quality of life"/	108047	Advanced	Display More ≫
☐	10	5 or 6	44651	Advanced	Display More ≫
☐	11	8 or 7 or 9	146883	Advanced	Display More ≫
☐	12	10 and 11	1248	Advanced	Display More ≫
☐	13	limit 12 to yr="2000 -Current"	1098	Advanced	Display More ≫
☐	14	limit 13 to english language	981	Advanced	Display More ≫
☐	15	limit 14 to human	956	Advanced	Display More ≫
☐	16	metastatic.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	59409	Advanced	Display More ≫
☐	17	16 and 15	171	Advanced	Display More ≫
☐	18	from 17 keep 1-171	171	Advanced	Display More ≫
☐	19	bladder.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	52555	Advanced	Display More ≫
☐	20	urothelium.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	2600	Advanced	Display More ≫
☐	21	20 or 19	53269	Advanced	Display More ≫
☐	**22**	**21 and 18**	**38**	**Advanced**	Display More ≫
☐	23	from 22 keep 1-38	38	Advanced	Display More ≫

Remove Selected | Save Selected | Combine selections with: AND OR

Save Search History

9.12.5 *Details of any additional searches (for example, searches of company databases [include a description of each database*]).

9.12.6 The inclusion and exclusion criteria.

Publications were only considered relevant to the decision problem addressed in this economic evaluation if: (a) the study population consisted of adult patients with advanced or metastatic transitional cell carcinoma of the urothelium initiating second-line therapy; and (b) the study reported HRQL data for patients pre- or post-progression.

9.12.7 The data abstraction strategy.

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*
- *NHS EED*
- *EconLIT.*

9.13.2 The date on which the search was conducted.

9.13.3 The date span of the search.

9.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Appendix 9.13. Search strategy (Section 6.5.3)

Search History (22 searches) (Click to close) View Saved

#	Searches	Results	Search Type	Actions
1	exp bladder cancer/ or metastatic bladder cancer.mp.	16538	Advanced	Display More ≫
2	exp bladder cancer/ or exp urinary tract carcinoma/ or exp transitional cell carcinoma/ or transitional cell cancer of the urothelium.mp. or exp urethra cancer/	18830	Advanced	Display More ≫
3	1 or 2	18833	Advanced	Display More ≫
4	limit 3 to (human and english language and yr="2000 - 2009")	12669	Advanced	Display More ≫
5	exp "cost"/ or costs.mp.	134938	Advanced	Display More ≫
6	economics.mp. or exp economics/ or exp health economics/	220815	Advanced	Display More ≫
7	4 and 5	204	Advanced	Display More ≫
8	4 and 6	373	Advanced	Display More ≫
9	7 or 8	392	Advanced	Display More ≫
10	metastatic.mp.	63364	Advanced	Display More ≫
11	bladder/ or bladder.mp.	55578	Advanced	Display More ≫
12	urothelium.mp.	2748	Advanced	Display More ≫
13	9 and 10	18	Advanced	Display More ≫
14	11 or 12	56324	Advanced	Display More ≫
15	13 and 14	16	Advanced	Display More ≫
16	exp health care utilization/ or resource utilization.mp.	23005	Advanced	Display More ≫
17	4 and 16	20	Advanced	Display More ≫
18	9 or 17	401	Advanced	Display More ≫
19	10 and 18	18	Advanced	Display More ≫
20	13 or 19	18	Advanced	Display More ≫
21	14 and 19	16	Advanced	Display More ≫
22	11 and 21	16	Advanced	Display More ≫

Search History (13 searches) (Click to close) View Saved

	# ▲	Searches	Results	Search Type	Actions
	1	exp Carcinoma, Transitional Cell/ or exp Urinary Bladder Neoplasms/ or metastatic bladder cancer.mp.	16829	Advanced	Display More >>
	2	limit 1 to yr="2000 - 2009"	12512	Advanced	Display More >>
	3	exp Urethral Neoplasms/ or exp Urinary Bladder Neoplasms/ or exp Carcinoma, Transitional Cell/ or transitional cell cancer of the urothelium.mp.	17228	Advanced	Display More >>
	4	limit 3 to yr="2000 - 2009"	12789	Advanced	Display More >>
	5	2 or 4	12793	Advanced	Display More >>
	6	costs.mp. or exp "Costs and Cost Analysis"/	119854	Advanced	Display More >>
	7	5 and 6	106	Advanced	Display More >>
	8	economics.mp. or exp Economics/	215557	Advanced	Display More >>
	9	5 and 8	93	Advanced	Display More >>
	10	7 or 9	125	Advanced	Display More >>
	11	exp Health Care Costs/ or exp Health Resources/ or resource utilization.mp.	34762	Advanced	Display More >>
	12	5 and 11	24	Advanced	Display More >>
	13	10 or 12	127	Advanced	Display More >>

Remove Selected | Combine selections with: And Or

Save Search History

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

9.13.6 The inclusion and exclusion criteria.

9.13.7 The data abstraction strategy.

Appendix 9.14. Gamma Parameter Estimates (Section 6.4.17)

Table. OS and PFS: Gamma model parameters

	PFS		OS	
	Estimate	**SE**	**Estimate**	**SE**
BSC				
Intercept	4.049	0.0982	5.1205	0.1722
Scale	0.7489	0.0517	1.038	0.084
Shape	0.2285	0.1763	0.2638	0.2807
k =Shape^-2	19.1526		14.3698	
α	0.004487	0.000441	0.007205	0.001241
γ	1.335292	3.376602	0.963391	4.033600
VFL				
Intercept	4.545400	0.091000	5.530300	0.4791
Scale	0.975700	0.047300	1.021200	0.071600
Shape	0.205200	0.139800	0.5932	0.185100
k =Shape^-2	23.7490		2.8418	
α	0.009480	0.000863	0.004447	
γ	1.024905	3.320110	0.979240	0.082256
γ =1/scale. α =exp(-Intercept * Y).				

Figure 1. Observed and estimated (Gamma) OS (BSC)

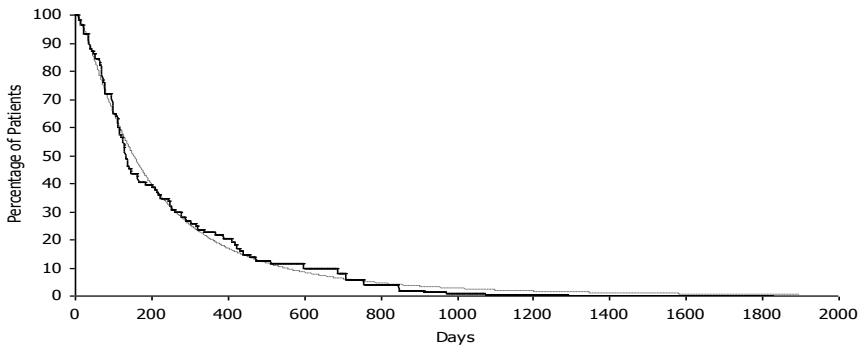
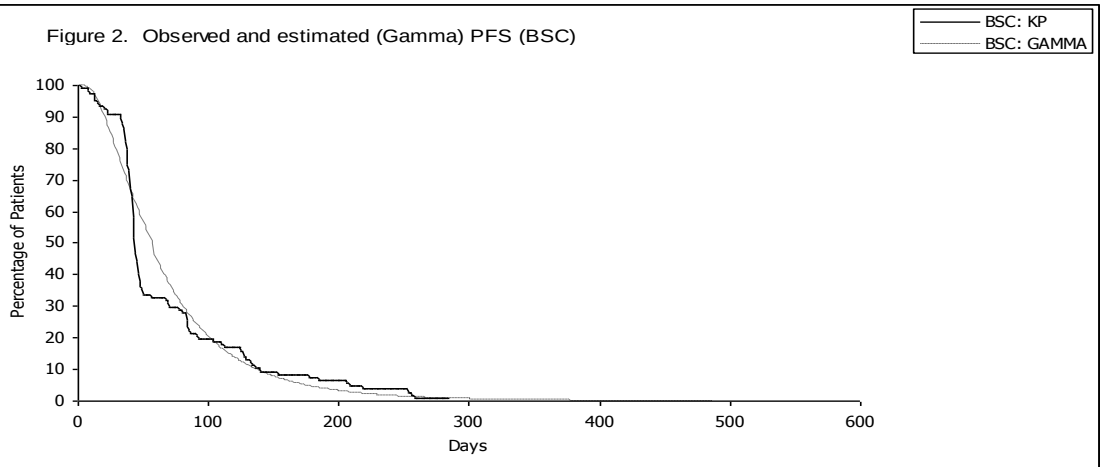


Figure 2. Observed and estimated (Gamma) PFS (BSC)



Appendix 9.15. Patient "Trace" (First 100 days only) (Section 6.5.2)

	VFL + BSC			BSC		
Days	**OS Undisc**	**PFS Undisc**	**PPS Undisc**	**OS Undisc**	**PFS Undisc**	**PPS Undisc**
0	100.00	100.00	-	100.00	100.00	-
1	100.00	99.56	0.44	100.00	99.07	0.93
2	100.00	99.56	0.44	100.00	99.07	0.93
3	100.00	99.56	0.44	100.00	99.07	0.93
4	100.00	99.56	0.44	100.00	99.07	0.93
5	100.00	99.56	0.44	100.00	99.07	0.93
6	100.00	99.56	0.44	100.00	99.07	0.93
7	100.00	99.12	0.88	100.00	98.13	1.87
8	98.72	98.67	0.05	98.15	97.20	0.95
9	98.72	98.67	0.05	98.15	97.20	0.95
10	98.72	98.67	0.05	98.15	97.20	0.95
11	98.72	98.67	0.05	98.15	97.20	0.95
12	98.07	97.78	0.30	97.22	95.33	1.90
13	97.43	97.78	0.00	96.30	95.33	0.97
14	97.43	97.32	0.11	96.30	94.39	1.90
15	97.43	96.87	0.56	96.30	93.46	2.84
16	97.43	96.87	0.56	96.30	93.46	2.84
17	97.43	96.87	0.56	96.30	93.46	2.84
18	97.43	96.87	0.56	96.30	93.46	2.84
19	97.43	96.41	1.02	96.30	92.52	3.77
20	97.43	96.41	1.02	96.30	92.52	3.77
21	95.48	95.95	0.00	93.52	91.59	1.93
22	95.48	95.49	0.00	93.52	90.65	2.86
23	95.48	95.49	0.00	93.52	90.65	2.86
24	95.48	95.49	0.00	93.52	90.65	2.86
25	95.48	95.49	0.00	93.52	90.65	2.86
26	95.48	95.49	0.00	93.52	90.65	2.86
27	95.48	95.49	0.00	93.52	90.65	2.86
28	95.48	95.49	0.00	93.52	90.65	2.86
29	95.48	95.49	0.00	93.52	90.65	2.86
30	95.48	95.49	0.00	93.52	90.65	2.86
31	95.48	95.49	0.00	93.52	90.65	2.86
32	95.48	95.03	0.45	93.52	89.72	3.80
33	94.83	94.09	0.73	92.59	87.85	4.74
34	94.17	93.15	1.03	91.67	85.98	5.69
35	92.86	91.22	1.63	89.81	82.24	7.57
36	92.19	89.75	2.45	88.89	79.44	9.45
37	91.53	87.23	4.31	87.96	74.77	13.20
38	91.53	86.19	5.34	87.96	72.90	15.07
39	91.53	83.01	8.52	87.96	67.29	20.67
40	91.53	81.37	10.16	87.96	64.49	23.48
41	90.86	77.38	13.49	87.04	57.94	29.09
42	90.86	73.14	17.72	87.04	51.40	35.64
43	90.86	69.94	20.93	87.04	46.73	40.31
44	90.86	67.93	22.93	87.04	43.93	43.11
45	90.86	65.15	25.71	87.04	40.19	46.85
46	90.86	62.97	27.89	87.04	37.38	49.65
47	90.20	62.23	27.97	86.11	36.45	49.66
48	90.20	61.47	28.72	86.11	35.51	50.60
49	90.20	59.93	30.27	86.11	33.64	52.47
50	90.20	59.93	30.27	86.11	33.64	52.47
51	90.20	59.93	30.27	86.11	33.64	52.47
52	88.85	59.93	28.92	84.26	33.64	50.61

Appendix 9.15 (Cont.). Patient "Trace" (First 100 days only) (Section 6.5.2)

	VFL + BSC (Cont.)			BSC (Cont.)		
Days	OS Undisc	PFS Undisc	PPS Undisc	OS Undisc	PFS Undisc	PPS Undisc
53	88.85	59.93	28.92	84.26	33.64	50.61
54	88.85	59.93	28.92	84.26	33.64	50.61
55	88.85	59.14	29.71	84.26	32.71	51.55
56	88.85	59.14	29.71	84.26	32.71	51.55
57	88.85	59.14	29.71	84.26	32.71	51.55
58	88.85	59.14	29.71	84.26	32.71	51.55
59	88.85	59.14	29.71	84.26	32.71	51.55
60	88.85	59.14	29.71	84.26	32.71	51.55
61	88.18	59.14	29.04	83.33	32.71	50.62
62	88.18	59.14	29.04	83.33	32.71	50.62
63	87.50	59.14	28.36	82.41	32.71	49.70
64	87.50	59.14	28.36	82.41	32.71	49.70
65	87.50	59.14	28.36	82.41	32.71	49.70
66	86.82	58.34	28.48	81.48	31.78	49.71
67	86.14	58.34	27.80	80.56	31.78	48.78
68	85.46	57.53	27.93	79.63	30.84	48.79
69	84.77	56.70	28.07	78.70	29.91	48.80
70	83.39	56.70	26.68	76.85	29.91	46.95
71	83.39	56.70	26.68	76.85	29.91	46.95
72	82.69	56.70	25.99	75.93	29.91	46.02
73	82.69	56.70	25.99	75.93	29.91	46.02
74	82.69	56.70	25.99	75.93	29.91	46.02
75	81.30	56.70	24.59	74.07	29.91	44.17
76	79.89	55.86	24.02	72.22	28.97	43.25
77	79.89	55.86	24.02	72.22	28.97	43.25
78	79.89	55.86	24.02	72.22	28.97	43.25
79	79.89	55.01	24.88	72.22	28.04	44.18
80	79.89	55.01	24.88	72.22	28.04	44.18
81	79.89	55.01	24.88	72.22	28.04	44.18
82	79.89	52.35	27.54	72.22	25.23	46.99
83	79.89	50.49	29.40	72.22	23.36	48.86
84	79.89	49.53	30.36	72.22	22.43	49.79
85	79.89	48.55	31.34	72.22	21.50	50.73
86	79.89	48.55	31.34	72.22	21.50	50.73
87	79.89	48.55	31.34	72.22	21.50	50.73
88	79.89	48.55	31.34	72.22	21.50	50.73
89	79.89	48.55	31.34	72.22	21.50	50.73
90	79.89	47.55	32.34	72.22	20.56	51.66
91	79.89	46.52	33.37	72.22	19.63	52.60
92	79.89	46.52	33.37	72.22	19.63	52.60
93	79.18	46.52	32.66	71.30	19.63	51.67
94	78.47	46.52	31.95	70.37	19.63	50.74
95	77.04	46.52	30.52	68.52	19.63	48.89
96	76.32	46.52	29.80	67.59	19.63	47.97
97	75.60	46.52	29.08	66.67	19.63	47.04
98	74.87	46.52	28.35	65.74	19.63	46.11
99	74.14	46.52	27.62	64.81	19.63	45.19
100	74.14	46.52	27.62	64.81	19.63	45.19

Population of the UK by country

	Population (thousands)	Percentage of total UK population
England	51,446	84
Wales	2,993	5
Scotland	5,169	8
Northern Ireland	1,775	3

Appendix 9.16 Population and estimated patient numbers

Crude Incidence and Mortality for Urinary Tract Cancer (NYCRIS 2007)

NYCRIS 2007	Crude Incidence	Crude Mortality
Urinary Tract (C64-C68)	35.3	16.4
C64 Kidney (Not included)	13.6	6.4
C65 Renal Pelvis	1.5	0
C66 Ureter	0.9	0.3
C67 Bladder	19	9.5
C68 Other urinary	0.4	0.3
Urinary Tract (Excl Kidney)	21.8	10.1

Projected Number of Patients
Assumption is TCCU is 90% all cases

England and Wales	All Urinary Tract		TCCU	
	Incidence	Mortality	Incidence	Mortality
C65 Renal Pelvis	817	-	735	-
C66 Ureter	490	163	441	147
C67 Bladder	10,343	5,172	9,309	4,655
C68 Other urinary	218	163	196	147
Total	11,868	5,498	10,681	4,949

Vinflunine Forecast					
Uptake			Jul-10		
ENGLAND AND WALES	**2010**	**2011**	**2012**	**2013**	**2014**
Incidence	10,681	10,361	10,050	9,748	9,456
Mortality	4,949	4,800	4,656	4,516	4,381
1st line	30%	30%	32%	34%	36%
1st Pts	1,485	1,440	1,490	1,536	1,577
2nd line	50%	50%	53%	56%	60%
2nd line Pts	742	720	790	860	946
Uptake Estimates for Vinflunine					
With +ve NICE Guidance	0%	15%	25%	35%	45%
With -ve NICE Guidance	0%	2%	5%	10%	15%
With New Cancer Drug Funding	0%	45%	50%	55%	55%
Patient Numbers					
With +ve NICE Guidance	5	108	197	301	426
With -ve NICE Guidance	5	14	39	86	142
With New Cancer Drug Funding	5	324	395	473	520

Assumptions

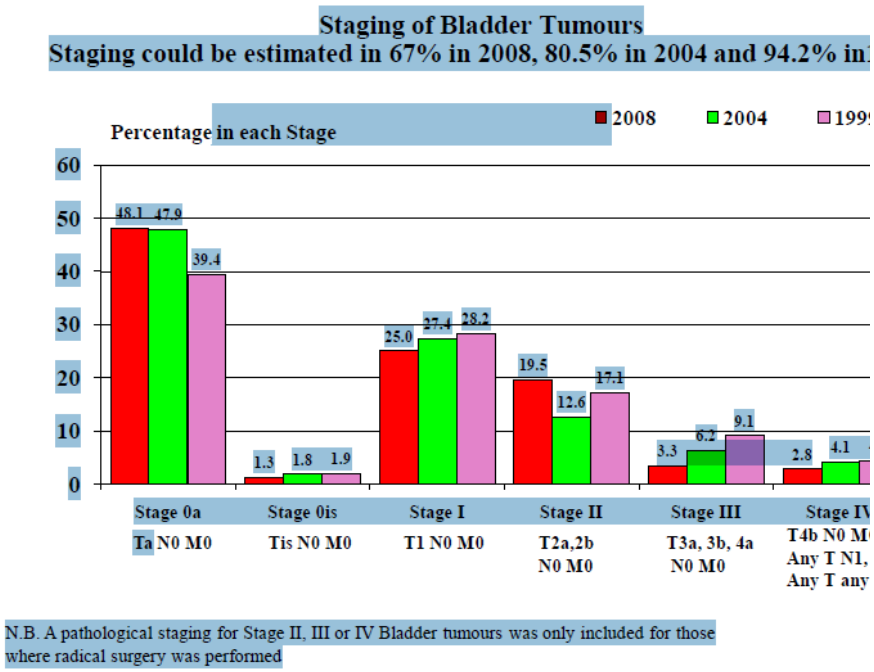
Incidence and mortality continue to decline at 3% per year
Mortality rate used as surrogate for patients relapsing after curative (surgical, XRT) treatments
Estimated 1st line chemotherapy (platinum based) for 30% patients
1st line chemotherapy will increase as more available treatment (MDT referral patterns)
50% patients that receive 1st line are fit to receive 2nd line chemotherapy at relapse
2nd line treatment will increase with observed benefits, audit and MDT working

Trends
Incidence and mortality will continue to decline at about 3% per year (NYCRIS).
Treatment rate for first and second line will increase as new treatment service becomes established and MDT referral patterns are established.

Assumption: New Cancer Drug Funding
The aim to include the target patient population as quickly and efficiently as possible and monitor clinical outcome. Associated audit of economic resource and confirmation of clinical outcome would lead to NICE Appraisal after a designated time period.

Appendix 9.16. Factors affecting Product Uptake in the NHS
Limited or absent data on current

Chart 26

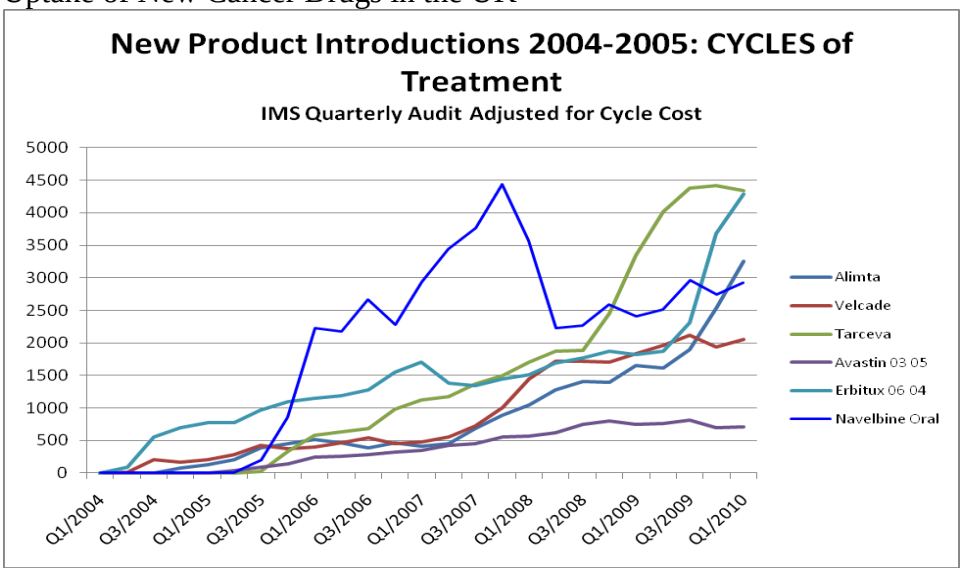


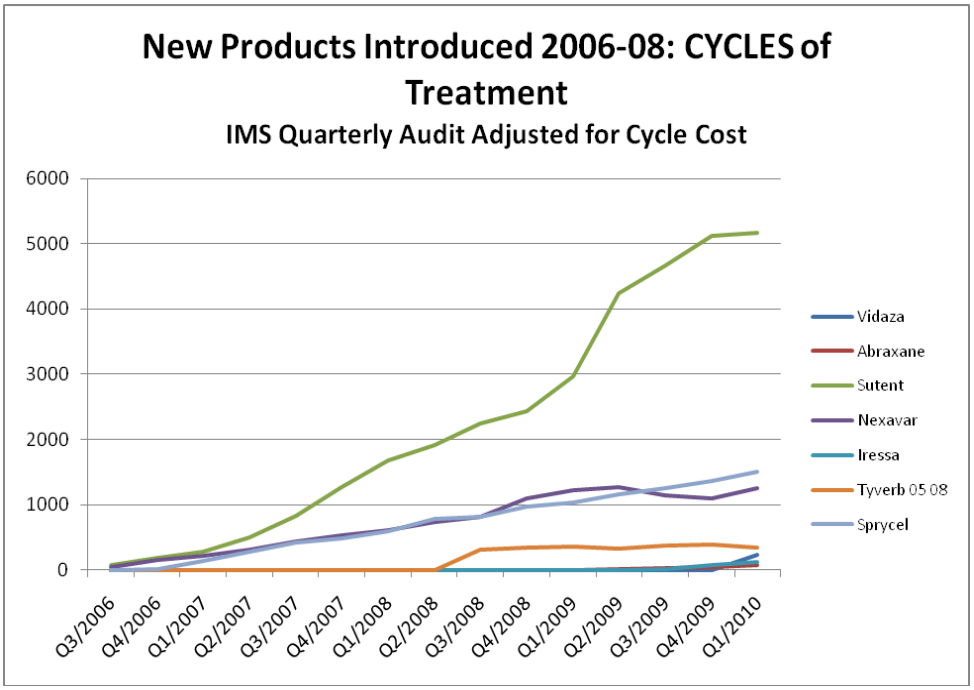
N.B. A pathological staging for Stage II, III or IV Bladder tumours was only included for those where radical surgery was performed

Source: BAUS
http://www.baus.org.uk/Resources/BAUS/Documents/PDF%20Documents/Data%20and%20Audit/2008finalanalyses.pdf

No staging, histology, incidence or pathway data could be found for the target population for vinflunine

Uptake of New Cancer Drugs in the UK





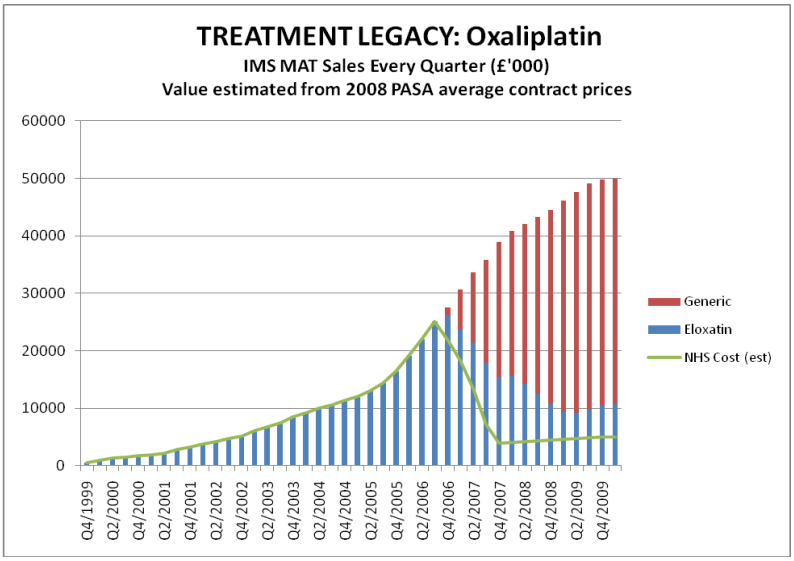
Source: IMS HPAI Audit. Cycles of treatment calculated from the MIMS price March 2010.

Uptake of new cancer drugs into the UK requires local approval and associated adjustment of referral pathways. This is hard to achieve. Adoption patterns are similar in the two time periods but the last two years are very slow.

Treatment Legacy

Many active chemotherapy drugs are first licensed in the advanced disease setting. Adoption into routine clinical practice allows the manufacturer to explore combined modality approaches to be developed with curative intent. At the end of the exclusivity period, the established use of that drug is met with generics at reduced cost to the health service.

Delayed adoption into licensed use threatens this development pattern.



10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain

information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not

provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the

confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).