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Rapid review

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer

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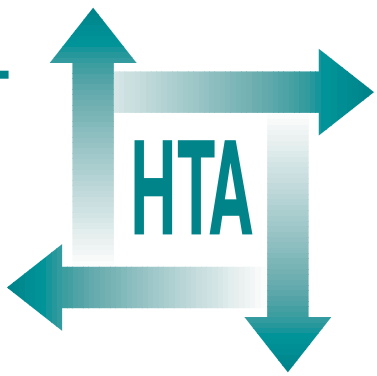
Health Technology Assessment
NHS R&D HTA Programme



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A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer

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The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

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Contents

List of abbreviations

ASCO	American Society of Clinical Oncology
AUC	area under the curve
BSC	best supportive care
CBR	clinical benefit response
CCTR	Cochrane Controlled Trials Register
CDDP	cisplatin*
CDSR	Cochrane Database of Systematic Reviews
CI	confidence interval
CR	complete response*
CRD	Centre for Reviews and Dissemination
CRIB	Current Research in Britain
DARE	Database of Abstracts of Reviews of Effectiveness
DRSI	disease-related symptom improvement
ESPAC	European Society for the Study of Pancreatic Cancer
FA	folinic acid*
FDA	Food and Drug Administration
5-FU	5-fluorouracil
G-CSF	granulocyte-colony stimulating factor*
GI	gastrointestinal
HEED	Health Economic Evaluation Database
IFN	interferon*
IL-2	interleukin-2*
LYG	life-year gained
MMC	mitomycin C
MR	minor response*
N/A	not available*
NHS EED	National Health Service Economic Evaluation Database
NS	not stated*
OHE	Office of Health Economics
PD	progressive disease*
PR	partial response*
PVI	protracted venous infusion
QALY	quality-adjusted life-year
QoL	quality of life
Q-TWiST	quality-adjusted time without symptoms or toxicity
RCT	randomised controlled trial
rhG-CSF	recombinant human granulocyte-colony stimulating factor*
RT	radiotherapy*
ScHARR	School of Health and Related Research
SD	stable disease*
SMSpaLAR	somatostatin analogue octreotide
TNM	tumour–node–metastasis
UFT	uracil-tegafur*

* Used only in tables and figures

Executive summary

Background

Pancreatic cancer is the eighth most common cancer in the UK and the sixth most common cause of cancer death; in 1998, 3198 men and 3364 women died from this condition. In an average health authority with a population of 500,000, there would be approximately 60 new cases of pancreatic cancer per year, based on the age and sex distribution of England and Wales. Over 75% of these patients are over 65 years of age.

The symptoms are wide ranging, but they may appear only towards the latter stage of the disease, so the vast majority of patients present with advanced disease. There are therefore rarely more than a few months between diagnosis and death, and palliative care is the best treatment that can be offered for the majority of sufferers. It is estimated that around 10–15% of patients diagnosed with pancreatic cancer currently receive palliative chemotherapy. This proportion is expected to rise and may increase to around 35% within the next few years.

5-Fluorouracil (5-FU) has been the standard chemotherapy used for pancreatic cancer in the UK over recent years, with evidence of a small survival advantage and improvement in quality of life (QoL) in a proportion of these patients. Gemcitabine is a relatively new chemotherapy drug; it inhibits DNA synthesis and is indicated for the treatment of adults with locally advanced or metastatic adenocarcinoma of the pancreas and for patients with 5-FU refractory pancreatic cancer.

Objectives

This review aimed to evaluate the clinical and cost-effectiveness of gemcitabine as first and second line therapy in the treatment of pancreatic cancer.

Methods

Systematic searches of clinical effectiveness, cost-effectiveness, and modelling in pancreatic cancer and gemcitabine were performed. The databases searched included: MEDLINE, EMBASE, Science Citation Index, Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database and the National Research Register. Web resources and industry submissions were also consulted. All HTA and related secondary research studies were included. Primary research studies were included if the authors had attempted to measure an outcome of importance.

A qualitative review was undertaken of all identified studies conducted on patients with a diagnosis of pancreatic adenocarcinoma, using gemcitabine alone or in combination with another drug. All Phase I studies were excluded.

Cost-effectiveness analyses were performed to estimate the marginal cost and marginal effectiveness of gemcitabine in comparison with standard therapy with 5-FU. The difference in mean survival was combined with the difference in the average cost of the interventions to calculate the cost per life-year gained (LYG). Costs were direct drug costs and health service costs. No QoL data were identified. However, given the significance of QoL for patients with pancreatic cancer, an illustration was provided, using quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis, of the potential impact of QoL on the cost per LYG results.

Results

Number and quality of studies, and direction of evidence of clinical effectiveness

A review of the published literature identified seven randomised controlled trials (RCTs). However, only one was a fully published RCT comparing gemcitabine with standard chemotherapy treatment (5-FU). No RCTs of gemcitabine versus best supportive care were located. Fifty-seven other studies were identified, of which 17 examined the use of gemcitabine alone.

No high-quality RCTs of gemcitabine as a second line treatment were identified.

Summary of benefits

There is a very poor evidence base by which to assess the efficacy of gemcitabine. The validity of the only RCT that compared gemcitabine with the standard treatment of 5-FU is open to question. In the control arm of this study the drug was administered as a bolus infusion. It is unlikely that bolus 5-FU alone would be used as standard practice in the UK. In other forms of gastrointestinal cancer therapy, bolus 5-FU alone would be considered to be inferior to other 5-FU regimens in terms of response rates and efficacy. These factors, in combination with the small patient sample included in the trial, mean that its results cannot be regarded as definitive.

From the available evidence it would appear that gemcitabine as a first line therapy offers similar survival to 5-FU-based regimens, but it is impossible to demonstrate conclusively its superiority in terms of either survival or QoL.

There is insufficient evidence to determine with any degree of certainty the benefit of gemcitabine as a second line therapy.

Costs

No published UK costings of gemcitabine were identified. The cost of 5-FU is dependent on the mode of its delivery. Two regimens currently used in the UK are considered: the De Gramont regimen (5-FU 400 mg/m^2 by bolus injection plus 400 mg/m^2 22-hour infusion, plus 200 mg/m^2 folinic acid 2-hour infusion for 2 days at 14-day intervals) for which an inpatient stay is generally required for its administration; and protracted venous infusion of 5-FU (300 mg/m^2 per day via an ambulatory pump), which allows the drug to be administered in the home setting. Although the drug cost of gemcitabine is more expensive that 5-FU this may be partly offset by lower administration costs, particularly in comparison with the De Gramont regimen. The cost of drug administration for protracted venous infusion 5-FU varies markedly according to local circumstances. For instance, the frequency of visits to the hospital for checking and flushing of the central line and pump may vary between once weekly and once every 6 weeks. This type of local variability will impact on the cost of 5-FU and, therefore, on the relative cost-effectiveness of gemcitabine.

Costs per life-year gained

Preliminary estimates of the cost of gemcitabine per LYG suggest that it may be below £20,000. However, the clinical evidence on which the analysis is based is poor and no published UK estimates of the cost of gemcitabine have been identified. The sensitivity analysis confirms that the cost per LYG is sensitive to assumptions on cost and survival. Given these uncertainties, it would be difficult to place too much weight on the findings. Further evidence is required before any definite conclusions can be drawn about cost-effectiveness.

Cost per quality-adjusted life-year

Given the significance of QoL for patients with pancreatic cancer an illustration has been provided, using Q-TWiST analysis of the potential impact of QoL adjustments on survival and the cost per LYG. No QoL data were identified, so the results of the analysis are purely illustrative. However, the analysis does demonstrate that the addition of a QoL adjustment is likely to reduce the survival gain. This would result in a cost per quality-adjusted life-year gained that is higher than the cost per LYG.

Conclusions

Need for further research

Gemcitabine as first line therapy

Until Phase II studies with existing or new drugs, alone or in combination, demonstrate significant improved benefit in pancreatic cancer, randomised studies are likely to be directed towards toxicity, QoL and any small survival benefits that may be obtained with gemcitabine alone compared with a modern 5-FU-based protocol or a combination of the two.

The evidence for QoL benefits of gemcitabine is particularly poor. There is widespread acknowledgement of the need for a RCT to confirm the survival benefits of gemcitabine and, particularly, to enable the collation of acceptable QoL data.

Gemcitabine as second line therapy

Further high-quality randomised trial evidence is required to determine fully the value of gemcitabine as a second line treatment.

Chapter 1

Background to the disease

Pancreatic cancer is the eighth most common cancer in the UK and the sixth most common cause of cancer death. One-year survival rates are in the order of 12% and less than 2% of patients survive to 5 years.[1] In 1998, 3198 men and 3364 women died from pancreatic cancer in the UK and it is estimated that about 7000 new diagnoses are made annually.[2]

The symptoms of pancreatic cancer are wide-ranging, and quality of life (QoL) can be greatly reduced by jaundice, nausea, weight loss, loss of appetite and severe pain; patients may also suffer from diabetes, diarrhoea and profound depression. These symptoms may appear only towards the latter stages of the illness, so the majority of patients present with advanced stage disease. As such, there are rarely more than a few months between diagnosis and death, and palliative care is the best that can be offered for the majority of sufferers.

Description of the underlying health problem

Epidemiology

Pancreatic cancer has an annual incidence rate of around 12 per 100,000 and a similar 11 per 100,000 mortality rate in England and Wales.[1] In 1997 there were an estimated 5730 people (2740 males and 2990 females) diagnosed with pancreatic cancer in England and Wales.[3] Of these, 4320 (1940 males and 2380 females) were in the over 65 years age group, accounting for 75% of all patients diagnosed with pancreatic cancer (*Figure 1*[4]).

In an average health authority with a population of 500,000, there would be approximately 60 new cases of pancreatic cancer per year, based on the age distribution in England and Wales.

The most consistent risk factor is smoking,[5] but diet[6] (particularly the lack of fruit and vegetables or excess alcohol) has also been implicated. Diabetes and pancreatitis are additional risk factors and a very small number of tumours have been shown to be familial.

The 1-year survival rates are generally low at around 12%[1] and survival to 5 years is extremely rare, at less than 3%.[1] Therefore, as a group, patients with pancreatic cancer have an extremely poor prognosis when considered within the context of other cancers. The disease often presents late, which contributes to the poor outlook. The stage of

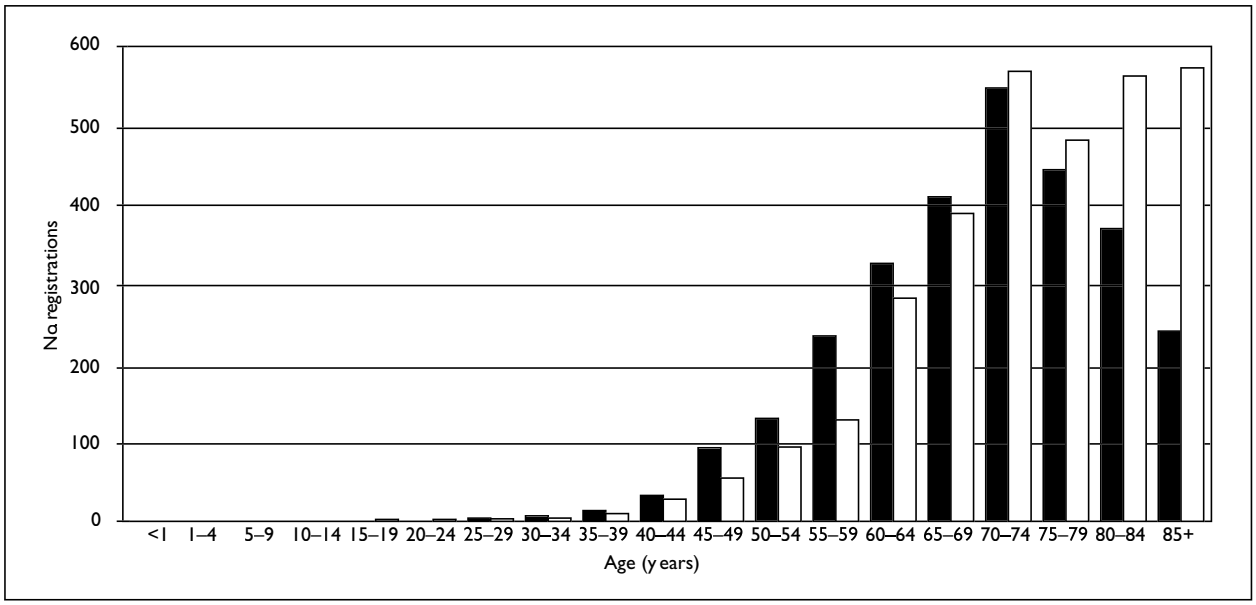


FIGURE 1 *National age/sex registrations for pancreatic cancer, 1994 (Source: Office for National Statistics[4]) (■, men; □, women)*

disease is determined by the tumour–node–metastasis (TNM) staging system, as shown below in *Table 1*[7]; although only US data are available, they show clearly that the highest proportion of patients are defined as having Stage IV tumours.

Currently, curative surgery is offered to only about 4% of the overall patient population.[1] Survival rates are highest in this patient group and some specialist centres attain 21% 5-year survival rates.[8] In the latter stages of the disease, palliative surgery, stenting, chemotherapy or radiotherapy can be used to relieve symptoms, but such treatments are purely palliative and outcomes remain poor.

Current service provision

The majority of patients diagnosed with pancreatic cancer receive no definitive treatment. Historically, curative surgery has been a hazardous procedure, commonly with perioperative 30-day mortality rates of over 10%. New guidance on the management of upper gastrointestinal (GI) cancers has recommended that surgery should be carried out only by specialists in cancer centres, where perioperative 30-day mortality rates should rarely exceed 5%.[9]

For the majority of those with late stage disease, the treatments offered are palliative. Although radiotherapy and chemoradiotherapy may both be considered for young, fit patients with inoperable localised disease, palliative treatment is largely based on best supportive care (BSC) or systemic chemotherapy to improve the patient's QoL. Other techniques used include the insertion of biliary stents and surgical bypasses.

The fact that over 75% of these patients are over 65 years of age[9] has important functional implications for the suitability of treatments available because individuals may be of poor performance status and have other co-existing illnesses. Active therapy may, therefore, be unsuitable and BSC is frequently the only treatment offered.

Bachmann presented data on treatment patterns for patients diagnosed with pancreatic cancer in the south and west of England and in South Wales between June 1996 and May 1997.[10] Based on data from 36 hospitals, 6% of patients underwent surgery, 7% received chemotherapy alone, and less than 5% had chemoradiotherapy or radiotherapy. The majority of patients, around 80%, received BSC.

The use of chemotherapy varies by geographical location and between different providers. No data are available to allow the accurate determination of the current proportion of patients receiving palliative chemotherapy on a national basis. It is likely to have increased since Bachmann's study,[10] but is estimated to be around 10–15% by a number of leading clinicians (Crellin A, Yorkshire Centre for Clinical Oncology, Cookridge Hospital, Leeds: personal communication, 2000). Eli Lilly have estimated the figure to be 24%, which is quoted in their submission.[11]

Following the introduction of new guidance on the management of upper GI cancers,[9] in which chemotherapy has been recommended as a consideration in both first line and adjuvant therapy, it is anticipated that an increasing percentage of patients will receive this in the next few years. The proportion of patients receiving chemotherapy may rise to around 35%. This is based on the assumption that 10–15% of patients may undergo surgical resection in the future. Of the remaining 85–90%, it is assumed that 40% will be suitable for palliative chemotherapy.

5-Fluorouracil (5-FU) has been the standard chemotherapy used for pancreatic cancer in the UK. There is evidence of a small survival advantage and an improvement in QoL in some patients.[12] 5-FU has been studied using a variety of doses and schedules, but the response rate rarely exceeds 20% and no consistent effect on disease-related symptoms or survival has been demonstrated.[13] Gemcitabine (Gemzar) is now used variably in

TABLE 1 *Stage of cancer at presentation (source: American College of Surgeons National Cancer Database[7])*

Stage	Definition (from TNM staging system)	Approximate % at diagnosis
I	No distant metastases or regional lymph nodes present; the tumour is either limited to the pancreas or has extended directly to the duodenum, bile duct or peripancreatic tissues	21
II	No distant metastases or regional lymph nodes present, but the tumour has extended directly to the stomach, spleen, colon or adjacent large blood vessels	10
III	Regional lymph node metastases are present but no distant metastases; tumour stage is immaterial	17
IV	Distant metastases present; tumour and lymph node stage are immaterial	52

the UK but there remains uncertainty about the role of chemotherapy in pancreatic cancer and the optimal regimen.

The number of patients currently receiving gemcitabine for pancreatic cancer is not known. Eli Lilly have estimated that 417 patients, 6% of those diagnosed, will receive gemcitabine in the UK in 2000.[11] This is derived from the assumptions that 24% of patients diagnosed with pancreatic cancer will receive chemotherapy and that 29% of these patients currently receive gemcitabine. It is not possible to check the reliability of this figure.

Description of intervention

Gemcitabine is a chemotherapy drug that inhibits DNA synthesis. It is a novel nucleoside analogue with a wide spectrum of activity against a variety of solid tumours. Although many clinical trials have evaluated gemcitabine in different regimens and doses, only one randomised controlled trial (RCT) has compared it with 5-FU as a first line treatment.[13] Based on the results of this trial, which showed improved clinical benefit and a median survival improvement, gemcitabine has been adopted in the USA as the standard palliative chemotherapy for advanced pancreatic cancer.[14]

Identification of patients

Patients should be identified by following the recommendations from the guidance in the management of upper GI cancers,[9] as detailed below.

Patients with jaundice, or those aged over 55 years who have pain or other symptoms that could be due to pancreatic cancer, should be assessed by abdominal ultrasound.[9] Those with dilated bile ducts and no evidence of gallstones, and any others considered likely to have pancreatic cancer on the basis of symptoms and ultrasound findings, should normally be referred for further assessment.

Further assessment of the tumour may involve spiral computed tomographic scanning, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and/or endoscopic retrograde cholangiopancreatography. When symptoms or imaging clearly show that the disease is metastatic or inoperable, or the patient is not sufficiently fit to undergo radical treatment, there may be no advantage in further assessment of the primary tumour. Such patients should be offered appropriate palliative treatment.

Criteria for treatment

Chemotherapy, including gemcitabine, should be administered only to patients with a reasonably good performance status. A decision to offer this agent should be based on the stage of the disease (if known), age, prognosis, performance status, liver function and haematological status, and a general assessment of the patient's well-being.

Intervention

The following descriptions have been taken from the 'summary of product characteristics', as listed in the electronic Medicines Compendium.[15]

Therapeutic classification

Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas, and for those with 5-FU refractory pancreatic cancer.

Dosage form and route

In adults, the recommended dose of gemcitabine is 1000 mg/m^2, administered by a 30-minute intravenous infusion. This should be repeated once weekly for up to 7 weeks, followed by a week of rest. Subsequent cycles should consist of infusions, once weekly, for 3 consecutive weeks out of every 4 weeks. A dose reduction is applied based on the degree of toxicity experienced by the patient.

Contraindications

Gemcitabine is contraindicated in those patients with a known hypersensitivity to the drug.

Warnings

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity. Gemcitabine can suppress bone marrow function, as manifested by leucopenia, thrombocytopenia and anaemia. However, myelosuppression is short lived, not usually resulting in dose reductions and only rarely causing discontinuation. Administration of this agent should be stopped at the first signs of any evidence of microangiopathic haemolytic anaemia, such as a rapidly falling haemoglobin level with concomitant thrombocytopenia or elevation of serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase, which may indicate development of the haemolytic uraemic syndrome. Renal failure may not be reversible, even with the discontinuation of therapy, and dialysis may be required.

Precautions

The status of patients receiving therapy with gemcitabine must be monitored closely and suitable laboratory facilities are required.

Treatment may be necessary for patients who are compromised by drug toxicity.

Therapy should be started cautiously in those with compromised bone marrow function. As with other oncolytics, the possibility of cumulative bone marrow suppression should be considered when using combination or sequential chemotherapy.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. The suspension or modification of therapy should be considered when drug-induced marrow depression is detected. Peripheral blood counts may continue to fall after gemcitabine is stopped.

Chapter 2

Effectiveness

Methods for reviewing effectiveness

Search strategy

The search strategy aimed to identify all publications relating to gemcitabine and pancreatic cancer. Keyword strategies were developed using key references retrieved through initial scoping searches. Search strategies did not include search terms or filters that would limit results to specific publication types or study designs. Date and language restrictions were not used. Searches of the following databases were undertaken: MEDLINE, EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Central Cochrane Controlled Trials Register (CENTRAL/CCTR), the NHS Centre for Reviews and Dissemination (CRD) databases (Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (NHS EED), HTA), and the Office of Health Economics (OHE) Health Economics Evaluation Database (HEED). A search of the last 6 months of PubMed was undertaken to identify recent studies not yet indexed on MEDLINE.

In addition to searches of electronic bibliographic databases, further sources were consulted to identify current research and grey literature. The National Research Register, Medical Research Council Clinical Trials Register, US National Institutes of Health Clinical Trials Register, and Current Research in Britain databases were searched. The publications lists and current research registers of health technology assessment and guideline-producing agencies, and funding and regulatory bodies were consulted. Industry submissions and the reference lists of included studies were handsearched and the Science Citation Index search facility was utilised.

Preliminary scoping searches were completed in July 2000. Full searches of bibliographic databases, and of further current research and grey literature sources, were carried out in August 2000. Hand and citation searches were undertaken in November 2000. The search strategies and sources consulted are listed in appendix 1.

Inclusion and exclusion criteria

- Studies conducted on patients with a diagnosis of pancreatic adenocarcinoma were considered.
- Studies involving the administration of gemcitabine to patients with inoperable advanced (including locally advanced and metastatic) or relapsed disease, and as an adjuvant treatment for curatively resected pancreatic disease with no apparent residual disease, were considered.
- All studies that used gemcitabine alone or in combination with another drug were considered.
- All Phase I studies were excluded.

Data extraction strategy

Data were extracted by one reviewer, using standardised forms (appendix 2), and were checked by a second reviewer. All disagreements were resolved by discussion.

Quality assessment strategy

All publications were assessed according to the accepted hierarchy of evidence,[16] whereby meta-analyses of RCTs were taken to be the most authoritative form and uncontrolled observational studies the least authoritative. In addition, the Jadad scoring system was used to assess the quality of all RCTs and the resulting quality scores are listed (*Table 2*).

Data synthesis

Given the heterogeneity of the interventions evaluated and of the study population characteristics and outcome measures, we have not attempted to pool outcomes or conduct any form of meta-analysis. Instead, a qualitative analysis was undertaken.

Results

Quantity and quality of research available

Number of studies identified

The searches undertaken retrieved a total of 458 studies. These included seven RCTs, 57 Phase II studies and 33 Phase I studies. In addition, we identified one investigational new drug treatment study and two retrospective and four prospective clinical studies. All Phase I trials were excluded from this assessment.

Randomised controlled trials

Seven RCTs were identified.[13,17–22] The characteristics of their design are shown in *Table 2*. Two

studies compared the role of gemcitabine in the adjuvant setting in combination with both chemotherapeutic and immunotherapeutic drugs. One compared the effect of gemcitabine with that of bolus infusional 5-FU and another compared gemcitabine with 5-FU administered intra-arterially. Three further trials compared gemcitabine with metallomatrix proteinase inhibitors; two of these studies involved marimistat and one BAY12-9566.

The RCT published by Burris and colleagues in 1997[13] compared the effect of gemcitabine with 5-FU in patients with pathologically confirmed locally advanced or metastatic pancreatic cancer. No description of the method of randomisation was available and the investigation was single blind. Drop-outs and withdrawals were described.

Two trials were published by Lygidakis and co-workers.[19,20] These compared the use of neoadjuvant and adjuvant gemcitabine in combination with immunotherapy with surgery alone. The first examined the use of gemcitabine in the adjuvant setting.[19] No descriptions of randomisation and blinding were available, but the authors accounted for all withdrawals and drop-outs. The other study examined the use of a chemoimmunotherapy regimen involving gemcitabine as both a neoadjuvant and an adjuvant treatment.[20] No descriptions were available of the methods involved in randomisation and blinding, and there was no mention of withdrawals and drop-outs.

The remaining four studies were available only in summary form and, consequently, our assessment of quality was not necessarily fully representative of the actual study design owing to the limited methodological details available.

Two of these RCTs were conducted by British Biotech and compared the use of gemcitabine with the matrix metalloproteinase inhibitor marimistat. The results of the earliest of these trials (study 128) were published, in abstract, at the year 2000 annual meeting of the American Society of Clinical Oncology (ASCO), and further details are available from a company press release.[21] However, no details are provided about the methods used for randomisation, blinding, or withdrawals and drop-outs. The only details relating to the second study are available from a press release.[17] Again, no description of randomisation is available and there is no discussion about withdrawals and drop-outs. However, the study is described as double blind and placebo controlled.

A further RCT, conducted by Moore and colleagues,[22] compared gemcitabine with another matrix metalloproteinase inhibitor known as BAY12-9566. Again, the results of this study have been published only in abstract form, so full methodological details are not available. No information was given relating to randomisation and blinding, or to withdrawals and drop-outs.

The final RCT identified is currently ongoing and is being conducted by Cantore and co-workers.[18] Preliminary findings were, again, presented at ASCO 2000 and an abstract is available. Although drop-outs and withdrawals were described, no account of the methods of randomisation or blinding was supplied.

TABLE 2 *Description of RCTs identified*

Study	Was the study described as randomised?	Was the method used in randomisation considered appropriate?	Was the study described as double blind?	Was the method used for blinding considered appropriate?	Was there a description of withdrawals and drop-outs?	Jadad score
Burris *et al.*, 1997[13]	Yes	Not described	No	Not described	Yes	2
Lygidakis *et al.*, 1988[20]	No	Not described	No	Not described	Yes	1
Lygidakis *et al.*, 1988[19]	Yes	Not described	No	Not described	Yes	2
Cantore *et al.*,, 2000[18]	Yes	Not described	No	Not described	No	1
Moore *et al.*, 2000[22]	Yes	Not described	No	Not described	No	1
Rosemurgy *et al.*, 1999[21] (British Biotech study 128)	Yes	Not described	Yes	Not described	No	2
British Biotech, 2000 (study 193)[17]	Yes	Not described	Yes	Not described	No	2

Other identified studies

We also identified a total of 57 Phase II studies and seven of other design. Seventeen examined the use of gemcitabine alone.[23–39] A further 18 looked at the drug in combination with 5-FU.[40–57] Five studies combined gemcitabine with docetaxel,[58–62] four with platinum compounds,[63–66] two with mitomycin C (MMC),[67,68] and seven with other drugs in more complex combinations.[69–75] In addition, four examined the role of gemcitabine plus radiation,[76–79] and two used regimens in which gemcitabine was combined with hormonal treatments.[80,81]

The characteristics of all studies are given in appendix 3 (*Tables 3–12*). The key results from the studies are also given in appendix 3 (*Tables 13–22*).

Discussion of results

Survival

Gemcitabine as an adjuvant treatment

The evidence identified relating to the use of gemcitabine as an adjuvant treatment consists of two RCTs. Both were published by Lygidakis and colleagues and examined the use of gemcitabine as part of a combination chemoimmunotherapy regimen. In the first study,[19] involving 512 patients recruited between 1991 and 1998, those randomised to adjuvant chemotherapy achieved a better mean survival (32 months with curative intent and 16 months with palliative surgery) than those who received surgery alone (14 months with curative intent and 6.8 months with palliative surgery). In the second study[20] ($n = 26$), in which the chemoimmunotherapy was administered as both a neoadjuvant and an adjuvant treatment, there was a statistically significant difference in the number of patients with progressive disease and in survival. Three patients who received the multi-modality treatment compared with nine who received surgery alone had progressive disease ($p < 0.01$) and, at the time the study was written, all 14 patients in the chemoimmunotherapy group remained alive, compared with only six in the surgery alone group ($p < 0.01$).

A number of limitations affect these two studies. First, both obtained low Jadad scores; their results, therefore, can be considered to be of low quality. In addition, it was difficult to distinguish between the effects of the large number of different drugs administered and, consequently, to state definitively the value of gemcitabine in the adjuvant setting. As such, the evidence identified relating to this use of gemcitabine is limited.[20] In addition, no Phase II or other studies were identified that could further establish the effectiveness of this drug in the adjuvant setting.

Gemcitabine as a single agent therapy

The best available evidence relating to the use of gemcitabine as a first line therapy comes from Burris and co-workers.[13] This study compared the use of gemcitabine with 5-FU in 126 patients with locally advanced or metastatic pancreatic cancer. Patients randomised to gemcitabine had significantly better 1-year survival (18% versus 2%, $p = 0.0025$), significantly better median survival (5.65 versus 4.41 months, $p = 0.0025$), improved median progression-free survival (2.33 versus 0.92 months, $p = 0.0002$), and a longer time to treatment failure (2.04 versus 0.92 months, $p = 0.0004$). However, no difference was observed in partial tumour response rates between the two treatment arms.

Although this study did show a significant benefit for the use of gemcitabine in comparison with 5-FU, questions exist that cast doubt on the validity of its results. First, in the control arm, 5-FU was administered as a bolus infusion. This method has been shown to be suboptimal in other types of GI cancers[82] and, as such, may not be a valid control against which to evaluate gemcitabine. Other randomised studies that have compared the use of 5-FU against BSC for pancreatic cancer have used more clinically active regimens and have shown similar survival rates to that obtained by gemcitabine in the Burris trial.[12,83] It could therefore be surmised that, had 5-FU been given in a more active form, the comparatively significant benefit attributed to gemcitabine could have been reduced. Secondly, this particular trial obtained a low Jadad score. Finally, it can be criticised because of the small sample size involved. Only 126 individuals were included in the analysis; results based on such a small patient population cannot be regarded as definitive.

This, the best quality data available, fails adequately to prove the superiority of gemcitabine in first line treatment, so it is necessary to examine other data. The additional RCTs identified all assessed gemcitabine against experimental treatments, so their results are difficult to extrapolate into this argument. The published information relating to the two British Biotech RCTs is limited. Both of these trials were reasonably large, with study 128[21] recruiting 414 and study 193[17] 239 patients. Although we know that no significant difference in survival was observed between marimistat and gemcitabine, we have been unable to obtain any details of survival times in either arm. In addition,

the reports available consist of abstracts and press releases only and, as such, the information available is insufficient to enable us to comment on the effectiveness of gemcitabine.

In the abstract published by Moore and colleagues,[22] details are given of a randomised comparison of gemcitabine and BAY12-9566. In a trial involving 277 patients, gemcitabine proved to produce statistically significant better survival than BAY12-9566, with a median survival rate of 6.4 months compared with 3.2 ($p = 0.0001$) and a median progression-free survival of 3.54 months compared with 1.77 ($p = 0.012$). This median survival rate is broadly comparable with the 5.65 months obtained by Burris and co-workers.

Eli Lilly have suggested that BAY 12-9566 was used in this RCT at a dosage that was ineffectual. No response appeared to be seen in this arm and toxicity was minimal. It has been claimed by Eli Lilly,[11] therefore, that this trial was equivalent to gemcitabine against BSC. However, Phase I and II studies were conducted, prior to this RCT, to determine the active and optimum dose of BAY 12-9566.[84] The dosage determined by these earlier studies was used in this RCT. In addition, while BAY 12-9566 may have exerted no effect in this trial, it is also possible that it may have demonstrated a negative survival impact. It would therefore be inappropriate to extrapolate the results as a study of gemcitabine against BSC. It should also be noted that the abstract reports only the interim analysis, so further details are required before a full assessment of this RCT can be made.

One retrospective report of an investigational new drug treatment programme, published by Storniolo and colleagues, was identified.[33] This study had on open-label single-arm design and gathered data from 3023 patients with advanced pancreatic cancer treated at 823 centres. The data collected were used to assess several outcomes, but the number of observations for any given end-point varied according to the number of completed records returned by the investigators. As such, patient numbers vary according to the specific data point in question. Full details of the numbers assessed are listed in *Table 5*.

Storniolo and co-workers reported median survival to be 4.8 months (95% confidence interval (CI), 4.5 to 5.1), the probability of survival at 1 year to be 15%, and the median time to disease progression to be 2.7 months (95% CI, 2.6 to 2.7). Tumour response was assessed in 982 patients. Within this patient group, 1.4% achieved a complete response and 10.6% a partial response; there was an overall response rate of 12.0% (95% CI, 10.0 to 14.2).

All the remaining studies identified were of a Phase II or retrospective cohort design. Ten were published in abstract form,[23,25,26,28,30–32,34,36,39] so the available data are limited. In addition, they frequently included only very small numbers of participants, often reduced further by a failure to evaluate all patients. A large number of different outcomes were reported and, owing to the nature of study designs and differences in patient populations between studies, the results were not fully comparable. We have therefore not attempted to pool outcomes. However, from these studies, 1-year survival ranged between 4% and 26%, and median survival between 4 months and 8.8 months.

Although it would appear from this information that gemcitabine is a reasonable treatment method for patients with advanced pancreatic cancer, in the light of other available research it fails to prove an absolute advantage over other treatment options, such as 5-FU. In two RCTs[12,83] comparing 5-FU to BSC in patients with advanced pancreatic cancer, comparable results have been obtained. Glimelius and colleagues[12] and Palmer and co-workers[83] reported median survivals of 6 and 8.25 months, respectively, in patients receiving 5-FU-based chemotherapy, compared with 2.5 and 3.75 months in patients who received BSC. The administration of gemcitabine led to a median survival of 5.65 months in the Burris trial,[13] 6.4 months in the Moore trial,[22] and ranged between 4 months and 8.8 months in the other identified studies, so no distinct survival benefit of gemcitabine over other forms of chemotherapy can be claimed.

Gemcitabine in combination chemotherapy

A total of 36 Phase II studies were identified that had utilised gemcitabine in combination with another chemotherapeutic drug. 5-FU was the most frequent combination (used in 18 studies) and, with this regimen, 1-year survival was seen to range between 25% and 39.5%, and median survival between 4.4 months and 13 months. There were far fewer Phase II studies examining other gemcitabine combinations, and the results and outcomes are not consistently reported. All the study details are, however, presented in *Tables 6–10* and *16–20* (appendix 3).

Based on the results of the Phase II studies, it is impossible to assess fully the impact of gemcitabine

on survival as part of a combination chemotherapy regimen. Most of the results were published as abstracts and the data were inconsistently reported. In addition, the numbers of participants entering these studies were very small and the numbers evaluated were, frequently, even smaller. It was therefore very difficult to assess any trends that may exist in survival, median progression-free survival, or response rates. Although it would appear, from the limited details available, that the administration of such regimens is reasonable, further studies and randomised trials are necessary before the value of gemcitabine in combination chemotherapy can be properly ascertained.

Gemcitabine in chemoradiation

Only four Phase II studies[76–79] were identified that examined the role of gemcitabine in chemoradiation. All were published in abstract form. They reported different outcomes and were very small projects in terms of the numbers of patients enrolled and assessed. Full details of study designs and results are shown in *Tables 11* and *21* (appendix 3), but, based on the information available, there is insufficient evidence to assess the effect of gemcitabine on survival when administered as part of a chemoradiation regimen. Further, detailed, high-quality studies are required before this role can be fully determined.

Gemcitabine and hormonal treatment

Two Phase II studies[80,81] were identified that examined the efficacy of gemcitabine in combination with hormonal agents. Details are listed in *Tables 12* and *22* (appendix 3). Both of these studies are small and differ in the drugs used and outcomes assessed. As such, in our opinion, there is insufficient evidence to determine the role of gemcitabine in combination with hormonal agents

Gemcitabine as a second line treatment

Eight of the identified studies involved participants with relapsed disease.[27,29,35,38,40,46,68,79] None of the relevant studies was a high-quality RCT. Rothenberg and colleagues' trial[29] was the only one exclusively to involve individuals with relapsed disease and examined the effect of gemcitabine in patients with metastatic pancreatic cancer that had progressed despite the administration of 5-FU. This study demonstrated a median survival of 4 months and a 1-year survival of 4%. Only 74 patients were recruited, and, of these, only 63 were evaluated for clinical benefit response ((CBR) see 'Quality of life' section below) and 54 for response. The remaining studies all involved relapsed patients as only a small part of the patient cohort, so the extrapolation of their results to assess the effectiveness of gemcitabine as a second line treatment is difficult. Three involved the administration of gemcitabine alone,[27,35,38] two gemcitabine in combination with 5-FU,[40,46] one gemcitabine and MMC,[68] and one gemcitabine and radiotherapy.[79] Details and outcomes of these studies are all listed in the quality and results tables (*Tables 5, 6, 9, 11, 15, 16, 19* and *21* (appendix 3)).

Again, from these results, it would appear that gemcitabine is a reasonable option in second line treatment, but the small numbers involved and the Phase II designs fail to provide conclusive evidence for the use of this drug above and beyond any other form of chemotherapy in this setting. A high-quality randomised trial is required before its benefits and superiority to other regimens can be confirmed.

Quality of life

Gemcitabine as an adjuvant treatment

Neither of the two RCTs[19,20] identified assessed QoL after the administration of gemcitabine in the adjuvant setting. In the authors' opinion there is therefore currently insufficient evidence to advocate its use as an adjuvant treatment to improve QoL in patients with resectable pancreatic cancer.

Gemcitabine as a single agent therapy

Pancreatic cancer is a devastating disease with a particularly dismal prognosis, so the maintenance of QoL is the major goal of palliation. The Burris RCT[13] provided the best evidence in relation to the efficacy of gemcitabine in terms of improving this outcome in advanced pancreatic cancer patients.

Burris and co-workers[13] used CBR to attempt to determine the effect of gemcitabine on QoL. They demonstrated that it led to significantly more clinical benefit responders compared with those randomised to 5-FU (23.8% versus 4.8%, $p = 0.0022$).

However, the arguments used to criticise the study design should be reiterated. The 5-FU regimen might have been administered in a suboptimal manner, its potential benefits to QoL might not have been fully expressed and, with such a small sample size, the results of the study cannot be regarded as definitive.

It should also be noted that the method used to assess QoL (i.e. CBR) is not a validated tool. It is based on the assessment of four parameters: pain intensity (a daily assessment on a linear analogue scale), analgesic intake (assessed by consumption of morphine or its equivalent), Karnofsky performance status, and weight change

(a secondary parameter). In order for patients to be designated as clinical benefit responders they must show a significant and sustained 50% improvement in at least one of the three assessed parameters, with no deterioration in any of the others. If they remain stable in all parameters they are considered to be responders if they have not lost 7% of their body weight, and non-responders if there has been greater weight loss.

A number of criticisms of this technique have been made.[85–87] For example, the primary criteria for this response is based on patients' self-reports, the subjective nature of which could lead to a 'placebo effect'.[88] Furthermore, the CBR end-point requires follow-up to be long enough for a response to be observed. This is an issue for Burris and colleagues' study,[13] where the possibility remains that patients receiving 5-FU were removed from the study earlier than those on gemcitabine, so the results are not entirely reliable.

In an effort to overcome this criticism, Hoffman and Glimelius have attempted to calibrate the CBR outcome against the validated QoL tool, the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire-30.[89] In a total of 151 patients (53 with pancreatic cancer) they demonstrated that the CBR overestimated the beneficial effects in certain patients and underestimated them in others. They deemed that the overestimation was due to the fact that the CBR did not consider adequately the adverse effects of chemotherapy, while the underestimation occurred because the CBR level is dominated by pain assessment but alterations in other symptoms will also have a great impact on QoL. Despite these problems, however, they concluded that the CBR is a better surrogate marker for clinical benefit in pancreatic cancer than other methods such as objective response or performance status.

However, as the ability of the CBR for measuring the effectiveness of palliative chemotherapy is still contentious, the Burris trial has not proved conclusively the palliative benefit of gemcitabine. It therefore becomes necessary to assess other forms of evidence.

In the study conducted by Storniolo and co-workers,[33] no formal measurements of QoL in the patient population were undertaken by using a validated tool. However, a symptom benefit outcome was assessed by using a scale of disease-related symptom improvement (DRSI). This is similar in intent to CBR but is measured retrospectively, using data routinely collected by physicians during the course of a study. These patients were classified as DRSI responders if they experienced an improvement in one or more of a number of parameters without a concomitant fall in any of the others. The parameters were pain, analgesic class and Karnofsky performance status (=20 points). In addition, patients could be classed as responders if they showed stability in all three of these parameters but had an increase in weight of 7% or greater. A total of 18.4% of these patients had experienced DRSI by cycle 4 of the treatment schedule. However, the reliability of this increase is not without question. The value was determined retrospectively and patients were included in the assessment only if their records contained sufficient information. A large number of patients within the trial were therefore omitted from the DSRI calculation. However, again, the trend was for a small benefit attributable to the administration of gemcitabine that was consistent with the other information available.

Other identified evidence included six Phase II studies and one retrospective cohort study.[27–29,31,32,35,38] QoL is not a valid end-point for Phase II studies because the aim is to determine toxicity and anticancer activity. Despite this, a number of the Phase II trials also used CBR as an outcome measure and were able to add further background evidence concerning the efficiency of gemcitabine. The identified Phase II trials showed much higher CBR rates than those obtained in Burris and colleagues' study, ranging from 27% to 70%.

Although the limitations of the QoL tools used must be taken into account, it would still appear that gemcitabine has a slight positive impact on QoL in advanced pancreatic cancer patients, and is a reasonable option for improving this outcome in their palliative care. However, based on the available evidence, the value of gemcitabine in improving QoL, over and above other forms of treatment, remains inconclusive. Burris and co-workers' trial showed a significant benefit over 5-FU but, owing to cautions over the administration of 5-FU, this cannot be considered to be a definitive result. Further evidence in the form of the results of high-quality randomised trials is required to assess fully the benefit of gemcitabine over other forms of treatment in terms of patients' QoL.

Gemcitabine in combination chemotherapy

CBR rates ranging between 45% and 64% were reported in seven of the Phase II trials examining the combination of gemcitabine and 5-FU.[43,44,46,48,50,54,56] One study using gemcitabine and MMC showed a CBR rate of 60%,[67] while the

other combination regimens showed rates ranging between 38% and 78%.[63,69,70,72,75]

These results again demonstrate that such chemotherapy regimens may offer positive benefit regarding patients' QoL, but the available evidence cannot be relied upon as definitive. Further studies, involving more participants and of higher methodological quality, are required before its full impact on QoL can be assessed.

Gemcitabine in chemoradiation

Of the relevant four Phase II studies identified,[76–79] none used any validated QoL instrument. Only one[77] examined CBR, in which 50% of patients obtained such a response. This study recruited only 20 patients and is therefore unsuitable to assess the true impact of gemcitabine chemoradiation on QoL. Further high-quality randomised trial evidence is required.

Gemcitabine and hormonal treatment

Only one of the two studies identified[80,81] assessed the impact of gemcitabine in combination with hormonal agents on QoL.[81] It demonstrated a 47% improvement in the CBR rate when gemcitabine and tamoxifen were administered together. Unfortunately, in this trial only 17 patients were studied, too few to prove conclusively the benefits of these agents. Again, further high-quality randomised trial evidence is required.

Gemcitabine as a second line treatment

Rothenberg and colleagues[29] assessed the CBR in patients with metastatic pancreatic cancer refractory to 5-FU, demonstrating a rate of 27%. Of the other studies that included relapsed patients, the CBR rates ranged between 44% and 48%. Unfortunately these studies did not consist solely of relapsed patients; the majority had locally advanced or metastatic disease. These results are therefore not fully representative of the effect of gemcitabine as a second line treatment.

Although, based on this limited evidence, it would appear that second line gemcitabine may offer some benefit to relapsed patients, there are insufficient data to determine conclusively its full value. Further high-quality randomised trial evidence is required to determine the real value of gemcitabine as a second line treatment.

Clinical effect size

Owing to the limited number of studies, and their small size, poor quality and diversity of design, it is not appropriate to perform any meta-analyses to show clinical effect size. The most informative study was that published by Burris and colleagues,[13] which demonstrated a 16% 1-year survival advantage to gemcitabine over 5-FU. However, for the reasons discussed previously, this comparison has been heavily criticised and the results cannot be relied upon as definitive.

Adverse effects of intervention

We identified two studies that reviewed the safety and toxicity of gemcitabine.[90,91] Aapro and co-workers[90] reviewed data from 979 patients taking part in 22 completed clinical studies in which they received gemcitabine 800–1250 mg/m^2 on days 1, 8 and 15 every 28 days. Similarly, Tonato and colleagues[91] assessed the toxicity profile of this drug in 790 patients taking part in Phase II trials. There was some degree of overlap in the results reported because each group of authors made use of some of the same Phase II trials. Neither study was based solely on pancreatic cancer patients; both consisted of a cohort or individuals with a range of solid tumours.

Both these studies determined that haematological toxicity was mild (*Table 23*). Mucositis and alopecia were both rare, and nausea and vomiting both mild. Likewise, both studies demonstrated that transient rises in serum transaminases, mild proteinura and haematuria were common but rarely clinically significant. Renal failure of uncertain aetiology was reported in seven patients in the cohort assessed by Aapro and co-workers. In this study, 18.9% of patients were seen to experience transient 'flu-like symptoms', with mild fever reported in 37.3%. Peripheral oedema occurred in 20.3% of patients in the absence of cardiac, hepatic or renal failure.

Tonato and colleagues examined the toxicity profile according to age. The patient population was divided into two groups: patients aged less than 65 years (n = 549) and those older than 65 (n = 241). Toxicity was not seen to differ significantly between the two groups, with the exception of

TABLE 23 *Toxicities*

WHO toxicity	% in Aapro *et al.*, 1998[90]		% in Tonato *et al.*, 1995[91]	
	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	6.8	1.3	6.4	0.9
Leucopenia	8.6	0.7	8.1	0.5
Neutropenia	19.3	6.0	18.7	5.7
Thrombo-cytopenia	4.1	1.1	6.4	0.9

nausea and vomiting, which was lower in the older age group.

Both these reviews concluded that gemcitabine is well tolerated and has a mild toxicity profile.

Ongoing studies

Further high-quality studies are required before the effectiveness of gemcitabine can be determined. We identified a total of 11 ongoing RCTs, 23 Phase II studies and three of unclear design, all of which are listed in appendix 4 (*Tables 24–26*).

The most important study in relation to adjuvant treatment is that being conducted by the European Society for the Study of Pancreatic Cancer (ESPAC). This ESPAC3 trial compares the use of adjuvant gemcitabine or 5-FU and folinic acid with surgery alone. Recruitment commenced in 2000; consequently it will not report for a minimum of 5 years. However, when complete, it should provide the necessary information to determine the full role of gemcitabine in the adjuvant setting. There is also an ongoing trial in which the role of gemcitabine in adjuvant chemoradiation is being examined. One arm will involve 5-FU and radiotherapy, the other gemcitabine and radiotherapy. This will further the evaluation of the role of adjuvant chemoradiation in this disease, particularly in the light of the results of an earlier trial, ESPAC1.

Cantore and colleagues[18] have published the preliminary results of a trial comparing gemcitabine versus 5-FU and folinic acid versus intra-arterial 5-FU with folinic acid, epirubicin and carboplatin. Although the numbers of patients involved in this study are low, it should provide further evidence to allow a fuller assessment of the effectiveness of gemcitabine as a first line treatment. We are not aware of any other RCTs that compare gemcitabine with either BSC or 5-FU.

A number of RCTs will examine the use of gemcitabine in combination chemotherapy. The remaining ongoing RCTs identified are all comparing gemcitabine with experimental treatments.

Conclusion

There is a very poor evidence base by which to assess the efficacy of gemcitabine. The validity of the only RCT that compares this agent with the standard treatment of 5-FU has been questioned and, in combination with the small patient sample, its results cannot be regarded as definitive. In addition, owing to the experimental comparisons used and the limited results reported, it is exceedingly difficult to evaluate or validate the other relevant RCTs.

Although from the evidence available it would appear that gemcitabine offers similar survival to 5-FU-based regimens, it is impossible to demonstrate conclusively its superiority in terms of either survival or QoL. Further evidence is required before the full value of gemcitabine in pancreatic cancer can be assessed.

Chapter 3

Economic analysis

This section examines the cost-effectiveness of gemcitabine in pancreatic cancer. A review of the existing economic evidence is presented and an economic evaluation is undertaken.

Existing economic evidence

The search strategy defined in chapter 2 identified two articles on the economics of gemcitabine as first line therapy. One published economic evaluation of gemcitabine in pancreatic cancer was identified[92] and one reference indicated the existence of a cost-effectiveness analysis by an Italian group.[93] No published economic evaluations of gemcitabine as second line therapy for pancreatic cancer were identified.

In addition, an economic evaluation of gemcitabine in both first and second line treatment was included in the Eli Lilly submission to NICE.

Ragnarson-Tennvall and Wilking, 1997[92]

An economic evaluation was undertaken of the treatment of patients diagnosed with pancreatic cancer in Sweden. This study estimated the incremental cost per life-year gained (LYG) for gemcitabine by using a hypothetical analysis of gemcitabine and BSC versus BSC. The analysis synthesised the survival rates and resource use (inpatient and outpatient care) from Burris and colleagues' trial[13] with Swedish epidemiological data.

Using the trial results of an additional survival of 38 days (0.104 years), the incremental cost per LYG for gemcitabine was estimated to be kr. 132,286 (Swedish kroner). Based on current exchange rates, the cost per LYG was estimated to be around £14,000. One-way sensitivity analyses were presented, which indicated that the cost-effectiveness ratio varies between kr. 64,870 and kr. 234,361 (£6900–£24,800). This analysis showed the cost-effectiveness ratio to be particularly sensitive, in the upward direction, to any reductions in incremental survival from treatment with gemcitabine. The sensitivity analysis also indicated that costs per LYG are sensitive to assumptions about patients' needs for inpatient and outpatient care, and the required number of chemotherapy cycles.

The authors of this Swedish study concluded that gemcitabine may be a cost-effective treatment alternative for patients with pancreatic cancer. However, a number of issues must be noted:

- The analysis was not based on a RCT, but on data collected retrospectively.
- The study combined Swedish epidemiological data with US survival results. It may not be appropriate to combine data from two separate countries or, on that basis, to generalise with respect to results from a UK setting.
- The appropriateness of modelling LYGs on such a modest advantage in survival is questionable. The cost per LYG is sensitive to small changes in incremental survival. The sensitivity analysis demonstrates that that there is much greater risk at the top end of the range.
- The study does not take account of QoL.
- The authors concluded that further clinical studies and economic evaluations are required before any definite conclusions can be drawn about the cost-effectiveness of gemcitabine.

Trippoli and Messori, 1999[93]

Using the survival data from Burris and co-workers' trial[13] and cost data estimated from individual data on the use of resources and morbidity, preliminary data were presented, in abstract form, showing the incremental cost of gemcitabine to be less than $20,000 compared with 5-FU. Further information provided details of a preliminary estimate of cost per quality-adjusted life-year (QALY) analysis using the quality-adjusted time without symptoms or toxicity (Q-TWiST) approach (Messori A, Meta-analysis Study Group of Società Italiana di Farmacia Ospedaliera [Italian Society of Hospital Pharmacists]: personal communication, 2000). This work was not taken beyond the preliminary estimates owing to issues relating to the quality of the cost data.

The Italian evaluation used the Gompertz method[94] to derive area under the curve (AUC) survival estimates for cases and controls. This method, which requires the extrapolation of survival curves to infinity, resulted in a discounted (3% annual rate) estimate of survival gain for gemcitabine patients over 5-FU of 2.9 months. This estimate compares with a median (non-discounted) benefit, reported

by Burris and co-workers, of 1.24 months (38 days). An estimate of the incremental LYG is derived by subtracting the AUC for the 5-FU patients from the AUC for the gemcitabine patients.

The Q-TWiST method has been used in other cancer studies[95–98] and involves partitioning remaining lifetime into periods, with and without specified symptoms and toxicity, relapse time, and death. Health state utility values are then assigned to each of the defined health states (e.g. zero for death). Ideally, utility values are derived empirically by using time trade-off or other valuation techniques, although they are often assigned arbitrarily. Multiplying the state utility values by the duration of time patients spend in each state and aggregating the results enables the calculation of quality-adjusted survival time.

Although the Italian study does not give details of the Q-TWiST analysis used, there are earlier articles from the same research group[95,99] in which this technique has been applied in an alternative clinical setting. In this earlier analysis, a utility value of 1 was assigned to the survival period without symptoms and toxicity. An arbitrary value of 0.5 was assigned to toxicity and relapse periods. It is assumed that a similar approach was used for their analysis of gemcitabine. Based on the lack of QoL evidence in pancreatic cancer, it is not possible to assess the appropriateness of these utility values.

The incremental LYG was estimated to be 0.22 years. The use of Q-TWiST analysis, as detailed,[100] produced a quality-adjusted LYG of 0.20 years. Based on an incremental cost of $10,538 (£7500), the Italian analysis results in an estimated discounted cost per LYG of $48,000 (£33,500) and a cost per QALY of $52,000 (£36,800). No sensitivity analysis was presented. The authors argued that this result indicated that gemcitabine is cost-effective on the basis that $50,000–$80,000 is acceptable for cost per LYG and cost per QALY estimates.

Eli Lilly industry submission[11]

The unpublished industry submission received from Eli Lilly reviewed the Swedish study but made no reference to the Italian study. The submission also included an economic evaluation of first and second line treatment with gemcitabine for patients with pancreatic cancer. These evaluations are reviewed separately below.

Gemcitabine for first line treatment

Their economic evaluation for first line treatment compared gemcitabine with 5-FU using outcome and resource-use data made available to them from Burris and colleagues' trial.[13] Eli Lilly were involved as sponsors of that work and have access to data that were not available to the School of Health and Related Research (ScHARR) or to the Swedish and Italian teams. A hypothetical evaluation of gemcitabine compared with BSC was also presented.

Cost estimates

Their costing took an NHS perspective, with an 18-month time horizon. Drug costs and their administration were assumed to have been incurred in the first 12 months and were not discounted. Some costs of follow-up and monitoring beyond 12 months were discounted as 6%. The standard dose of 1000 mg/m^2 was assumed for gemcitabine, and 5-FU was assumed to have been delivered at the Burris trial rate of 600 mg/m^2 weekly. This regimen is not generally used in the UK and has been shown to be a suboptimal method of administration in other types of GI cancer.[82] It may therefore not be considered as an appropriate comparator. However, no other evidence currently exists.

Patient-specific dosage data were available to Eli Lilly from the trial data. Oncologists' visits were assumed to take place at the time of infusion. One GP visit per month was assumed while patients were receiving chemotherapy. After disease progression, two GP visits per month were assumed for symptomatic control and palliation. Costs for concomitant drugs were included, using assumptions about drug usage and British National Formulary prices, but only if the formulations are used in the UK. Gemcitabine was priced using a confidential figure reflecting the price to NHS hospitals. The British National Formulary price of 5-FU was used in their analysis. Hospitalisation data were available to, and used by, Eli Lilly to estimate resource use, using a health resource group casemix analysis and NHS reference costs.

They estimated a cost per patient of £3568 for gemcitabine and £1261 for 5-FU, a difference of £2300. The cost of gemcitabine itself accounted for almost half of the total cost incurred by patients using the drug. Gemcitabine was shown to be more expensive than 5-FU for all categories of resource use, although this may be a result of the longer survival and, therefore, longer treatment time for the patients receiving gemcitabine.

Outcomes

Three end-points were considered, including progression-free survival, CBR, and the primary

outcome of total survival time. Outcome results from Burris and co-workers' trial were used to derive estimates for these three variables. Kaplan–Meier survival curves were used to estimate the AUC and the 95% CI for mean survival. The discounting of benefits at 6% appears to have been calculated, although this was not clear from the table of results. Eli Lilly estimated an overall mean survival for gemcitabine patients of 6.79 months, compared with 4.52 months for 5-FU patients, an incremental benefit of 2.27 months (0.19 life-years). Based on the shape of the survival curves, this gave a figure considerably higher than the median difference of 1.24 months reported by Burris and colleagues[13] (*Table 27*). The mean survival gain for gemcitabine patients, as estimated by Eli Lilly, was 1.14 months longer than the median figure reported by Burris (an 83% increased difference). The incremental differences for progression-free survival and the CBR were reported at 1.39 months and 19% respectively.

Cost-effectiveness ratios

Eli Lilly presented a table of average and incremental cost-effectiveness ratios and rightly pointed out that it is only the incremental figures that should be used to inform policy. The central estimates of incremental cost per LYG and cost per CBR are both £12,200, while cost per progression-free LYG is £19,900. The cost per LYG figure is substantially lower than the estimate presented by Trippoli and Messori.[93] Eli Lilly also proffered an analysis using a scenario whereby 5-FU was administered by continuous infusion, as is sometimes the case in the UK. They assumed that the costs for 5-FU would increase by £1900 (a 50% increase) and that the outcome benefits would be the same as if drug administration had been by weekly infusion. Consequently, the incremental cost per LYG for gemcitabine was estimated to fall to £8,900.

A hypothetical analysis was also presented, comparing gemcitabine with BSC, in which BSC was assumed to cost nothing and to have the same benefits as 5-FU in the above analysis. The conservative estimate of the incremental cost per LYG was given as £18,900. Synthesising their own analysis with the results of a recent European trial comparing gemcitabine with BAY 12-9566, they produced a second estimate of the incremental cost per LYG for gemcitabine over BSC of £8650. Both these figures compare with the Swedish estimate of £14,000 per LYG.

TABLE 27 *Eli Lilly mean survival estimates and medians from Burris* et al., *1997*[13]

	Burris *et al.*, 1997[13] median (months)	Eli Lilly mean (months)
Gemcitabine	5.65	6.79
5-FU	4.41	4.52
Survival gain	1.24	2.27

Sensitivity analysis

The sensitivity analysis prepared by Eli Lilly indicated that the incremental cost per LYG is relatively robust, except when survival benefit is shortened. The 95% CI for survival results in costs per LYG varying from £10,000 to £25,300. This cost-effectiveness ratio is clearly more sensitive in the upward direction. The 95% CI for overall survival is likely to be overestimated owing to the influence of covariance. This does not alter the consequence that any reduction in the gemcitabine survival gain assumption would result in a proportionately greater increase in the cost-effectiveness ratio. There is a similar effect for cost per CBR, if the CBR gain assumption is varied, resulting in 95% CI estimates of £7500–£31,600 per CBR.

Discussion of first line therapy economic evaluation

Eli Lilly have presented a commendable economic evaluation for gemcitabine as first line therapy. Their costings are the most comprehensive seen to date and they have made good use of resource data made available to them from the pivotal trial. In terms of outcomes, their use of mean survival has resulted in a higher survival benefit estimate compared with that reported in Burris and colleagues' trial.[13]

A cost-effectiveness analysis was presented, which, Eli Lilly argue, indicates that first line treatment using gemcitabine is cost-effective compared with other NHS funded treatments. This may be the case, although the comparison of cost per LYG figures for gemcitabine with cost per QALY figures for other treatments is not a comparison of like with like. The assessment of QoL would almost certainly mean that the cost per QALY would be higher, possibly markedly higher, than costs per LYG. Eli Lilly indicated that increased toxicity from gemcitabine would reduce QoL, although they argued that this may be offset by the palliative effects of this agent. They also argued that some QoL aspects were reflected in the costs of treatment for adverse drug reactions and in the CBR measure. The current report has already noted that CBR is a non-validated and inadequate indicator of health related QoL. Given the

importance of QoL considerations in this clinical setting, in which survival time is short, it is unfortunate that the Eli Lilly report does not add to our knowledge of the QoL implications of gemcitabine.

As in the Swedish evaluation, the Eli Lilly analysis showed that the cost-effectiveness parameters are sensitive to reductions in survival and other outcome assumptions. The Eli Lilly survival assumptions were higher than the median figures reported in the trial and there is some doubt about the survival gains demonstrated in Burris and co-workers' trial (discussed earlier in the current report). These factors may mean that Eli Lilly's central cost per LYG estimate of £12,200 is a significant underestimate of the actual ratio.

Gemcitabine for second line treatment

Eli Lilly have presented a tentative economic evaluation of gemcitabine in second line therapy for pancreatic cancer, using data from a non-randomised single-arm study on patients who were refractory to 5-FU. The lack of a comparator arm means that only a partial economic evaluation was possible. The costing analysis employed the same methodology as for first line treatment and produced almost identical costs (total cost per patient £3234). The small reduction, compared with first line costs, is the result of shorter survival for the members of this patient group, who have more advanced disease.

Kaplan–Meier survival curves were again used to estimate mean survival outcome and CBR was once more used as a clinical outcome measure. Outcome gains were poorer for second line compared with first line treatment because of the more advanced nature of the disease. Discounted LYG was estimated at 5 months (6% discount rate). This measure is fairly meaningless in the absence of a comparator treatment, which means that the incremental survival benefits of gemcitabine cannot be identified. Eli Lilly argued that CBR is the more important outcome measure and that the incremental benefits can be measured by assuming that CBR is zero for BSC patients. The CBR was recorded as 27% for gemcitabine.

Eli Lilly reported average costs per LYG and per CBR of £7800 and £12,000, respectively. These figures should not be used to inform policy because they are average and not incremental costs. They argued that the cost per CBR can be regarded as incremental if it is assumed that the CBR benefits of BSC are zero. Their analysis also assumed that the costs of BSC are zero, so that their cost per CBR ratio is a conservative estimate, weighted against gemcitabine. Even if the simplifying assumptions behind their analysis are accepted, the implicit assumption is that CBR is a valid and meaningful outcome measure. These assertions have been questioned elsewhere in this report. Furthermore, there were no comparator figures with which to compare their cost per CBR estimate, although they pointed out that their estimate is lower than that from their analysis of first line treatment. Their sensitivity analysis indicated that costs per CBR are relatively insensitive to changes in input assumptions. Cost per LYG sensitivity analysis was not undertaken because of the lack of meaning of the average cost per LYG.

The second line therapy analysis presented by Eli Lilly is subject to the criticisms of their first line analysis. Again, QoL was not addressed and their analysis was not based on the results of a randomised blinded trial. Gelber[88] has published his concerns that the lack of randomisation and blinding in the original study[13] are important shortcomings. He has also argued that no survival benefits from gemcitabine in second line treatment have been demonstrated and criticises the use of the unvalidated CBR measure.

Summary of Eli Lilly evaluation

Eli Lilly have presented economic evaluations that indicate that gemcitabine may be cost-effective in relation to current first line treatments for pancreatic cancer. They have presented a detailed and comprehensive costing analysis. It is in the area of outcome benefits where most uncertainty exists. The lack of QoL information for patients with pancreatic cancer is an important drawback in their analyses, especially given the palliative nature of the treatment. In addition, their estimates of survival gains derive from single studies in which the survival gains from gemcitabine have been questioned. Their use of Kaplan–Meier and mean (as opposed to median) survival figures has meant higher survival gain estimates than would have accrued by using median figures as presented in Burris and co-workers' article. Sensitivity analysis, for first line therapy in particular, has shown cost-effectiveness ratios to be particularly sensitive to reductions in the survival and CBR gain assumptions. Until better evidence for survival and QoL gains is forthcoming (ideally from double-blind RCTs), the effectiveness and cost-effectiveness of gemcitabine in this clinical setting remains open to question.

Summary of existing economic evidence

In summary, the existing evidence suggests that the cost-effectiveness of gemcitabine may be in line

with currently available treatments but the quality of the evidence is poor.

All three analyses[11,92,93] have a number of important caveats. They are all dependent on the outcome results from a single (Eli Lilly sponsored) trial. The generalisability of the trial's results are therefore unproven to date. The Swedish group acknowledged that their use of Burris and colleagues' results may not be appropriate, given that they used a different treatment comparator and considering the geographical contexts of the two studies. Burris and co-workers' patient group is also likely to have included a population with a different age structure and also a different status to the Swedish cohort in terms of disease stage and their experience of operative interventions.

Both the Swedish and the Eli Lilly analyses demonstrated the upward sensitivity of the cost per LYG ratio to decreases in incremental survival benefit from gemcitabine. The effectiveness review presented in chapter 2 casts some doubt on the survival benefits demonstrated by Burris and colleagues' trial. The questions concerning the method of administration of the 5-FU may mean that the survival gains from gemcitabine have been overestimated. As demonstrated by the sensitivity analysis, any reductions in survival benefits from those reported by Burris and colleagues would reduce significantly the cost-effectiveness of gemcitabine. Burris and co-workers' trial, however, remains the only, and therefore the best, evidence on survival benefit.

The evidence for the QoL benefit of gemcitabine is particularly poor. There is widespread acknowledgement of the need for a RCT to confirm the survival benefits of gemcitabine, particularly to enable the collation of acceptable QoL data.[87,88,92] Without better information, the cost-effectiveness of gemcitabine for first and second line treatment of pancreatic cancer remains in doubt.

Methods for economic analysis

An economic evaluation has been undertaken to compare the cost-effectiveness of first line treatment with gemcitabine with 5-FU. 5-FU has been used as a comparator because it is widely used in the UK and available evidence suggests that it is probably as effective as other drug regimens.[9] No evidence on which to base an evaluation of gemcitabine against BSC has been identified.

Given that the evidence concerning second line treatment relies solely on one Phase II trial, no economic evaluation has been undertaken.

Estimation of net benefits

Survival

In a RCT[13] comparing gemcitabine with the bolus administration of 5-FU, gemcitabine demonstrated a significantly improved CBR (23.8% versus 4.8%, $p = 0.0022$) and a median survival benefit of 1.24 months (5.65 versus 4.41, $p = 0.0025$).

The area under a survival curve indicates the overall survival time experienced by the cohort. Therefore, the area between the gemcitabine and 5-FU curves indicates the mean difference in survival experienced by the two groups. The survival gain, taken from the Eli Lilly industry submission,[11] estimated in this way was 2.27 months (6.79 versus 4.52).

ScHARR did not have access to the raw data on which this figure was calculated. However, our estimate, based on the same methodology, but using the published curves from Burris and colleagues' article, produced a figure close to the Eli Lilly value (appendix 5). The Eli Lilly value was used in the cost-effectiveness calculations.

Owing to the shape of the survival curves in Burris and co-workers' trial, the median survival, although a useful measure in assessing clinical efficacy, underestimates the AUC. In the economic analysis, the mean survival gain used in conjunction with the mean cost gives a better indication of the cost-effectiveness ratio.

As noted in the discussion of results in chapter 2, the survival benefits demonstrated by the RCT have been questioned. The 1-year survival rate in the 5-FU arm was unusually low, at 2%. The median survival for the 5-FU arm may also be considered to be low at 4.41 months (mean 4.52). In trials by Glimelius and colleagues[12] and by Palmer and co-workers[83] that compared combined 5-FU and other chemotherapy agents with BSC, the median survivals for 5-FU were 6.0 and 7.6 months respectively. In these trials, the median survival for BSC was 2.5 and 3.5 months respectively (mean 4.2 and 4.9).[12,83] These mean survivals for BSC are comparable with the 5-FU mean survival in Burris and colleagues' trial (*Figure 2*).

Effectiveness of different 5-FU regimens

The weekly bolus 5-FU regimen, as used in the Burris trial, is not generally used in the UK. However, a number of different 5-FU regimens are

used. The De Gramont regimen consists of 5-FU 400 mg/m^2 by bolus intravenous injection plus 400 mg/m^2 22-hour infusion plus high-dose folinic acid 200 mg/m^2 2-hour infusion for 2 days at 14-day intervals. A modified De Gramont regimen (5-FU/folinic acid), which allows the drug to be administered on an outpatient basis, is also used. The protracted venous infusion (PVI) regimen consists of 5-FU 300 mg/m^2 per day administered continually via an ambulatory pump. The Mayo regimen consists of 5-FU 425 mg/m^2 plus low-dose folinic acid 20 mg/m^2 by bolus injection, administered every 5 days and repeated at 28-day intervals.

There is strong evidence to show that, in other treatments of GI cancer, the use of bolus 5-FU alone would be considered inferior in terms of response rates and efficacy. Given the absence of evidence on the effectiveness of alternative 5-FU regimens, the mean survival gain of gemcitabine over 5-FU is assumed to be the same for the different regimens. However, this may well mean that the survival gains for gemcitabine are overstated.

Quality of life

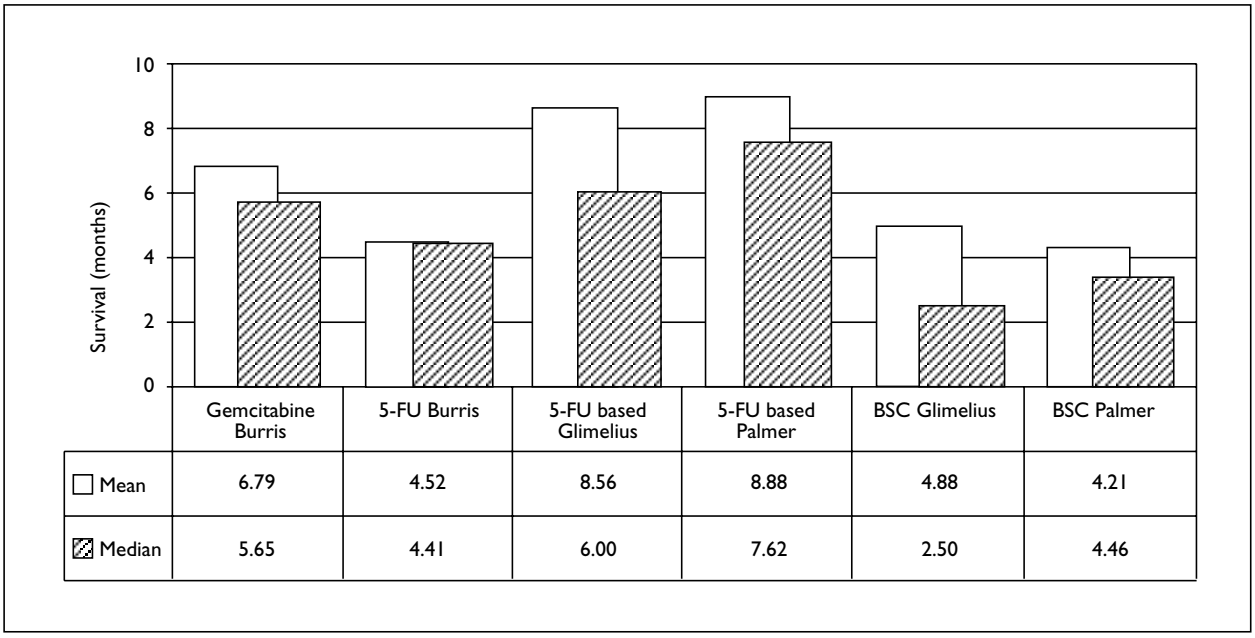
No QoL evidence has been identified that compares gemcitabine with 5-FU or with BSC by using validated QoL instruments. As discussed in the previous chapter, the use of CBR as presented in Burris and colleagues' trial has not been validated and caution should be exercised in the interpretation of this outcome measure.

However, given the significance of QoL for patients with pancreatic cancer, an illustration has been provided, using Q-TWiST analysis, of the potential impact of QoL adjustments on survival (appendix 6).

Estimation of net costs

No published UK costs for the use of gemcitabine in pancreatic cancer were identified. A value for the drug cost, based on a standard 1000 mg/m^2 dose for an assumed average patient of 1.8 m^2, has been obtained from the Leeds Cancer Centre (Crellin A, Yorkshire Centre for Clinical Oncology, Cookridge Hospital, Leeds: personal communication, 2000). It is assumed that gemcitabine is given by a 30-minute intravenous infusion, once weekly for 7 weeks out of 8, and then, for subsequent cycles, once weekly for 3 weeks out of every 4. It is also assumed that infusions are given on an outpatient basis. The cost of an outpatient visit is based on the national average cost of a medical oncology outpatient appointment of £109.[101] The costs for hospitalisations and concomitant medicines have been taken from Eli Lilly's data.

The cost of 5-FU is dependent on the type of delivery. Two regimens, both commonly used in the UK, are considered: the De Gramont regimen, which is the more expensive, having high inpatient and chemotherapy costs; and the PVI 5-FU regimen, which allows the drug to be administered in the home setting. Although, for the PVI 5-FU regimen, there are additional costs associated with the pump and the insertion of a central line, it offers the advantage of low numbers of inpatient and outpatient visits. The costs for the modified De Gramont regimen are similar to those for the PVI regimen; these are not considered separately.



	Gemcitabine Burris	5-FU Burris	5-FU based Glimelius	5-FU based Palmer	BSC Glimelius	BSC Palmer
Mean	6.79	4.52	8.56	8.88	4.88	4.21
Median	5.65	4.41	6.00	7.62	2.50	4.46

FIGURE 2 *Mean and median survival for gemcitabine and 5-FU in pancreatic cancer*

The mean treatment costs per month for PVI 5-FU and for the De Gramont regimen are taken from Ross and colleagues' publication.[102] Updated costs for chemotherapy and consumables have been obtained from the Royal Marsden Hospital (Cunningham D, Royal Marsden Hospital, Surrey: personal communication, 2000). Other costs, including concomitant medications and intravenous fluids, inpatient stays, outpatient visits, operations and the provision of a telephone helpline service, have been taken from Ross and co-workers' data[102] and inflated to year 2000 prices. Owing to the absence of data on nursing time to set up infusions and pharmacy costs, these were excluded from the article. In addition, general practitioner visits and travel expenses were not taken into account. Costs relating to investigations and tests have been omitted from our analysis because it was assumed that patients receiving gemcitabine or 5-FU would receive similar investigational procedures.

Monthly and total treatment costs, as estimated by ScHARR, are given in *Tables 28* and *29*. The total treatment costs were calculated by multiplying the cost per month by the treatment period.

It has been assumed that patients are treated until disease progression. Time to progression data were taken from the Eli Lilly submission.[11] ScHARR estimates of these figures, based on the published curves from Burris and colleagues' trial, produced values close to the Eli Lilly value.

NHS savings from use of gemcitabine

It is not possible to conclude from published data whether savings would accrue from the use of gemcitabine. Prolonged survival simply delays the costs of the eventual decline of a patient.

Estimation of cost-effectiveness

Estimation of cost per life-year gained

The mean survival gain for gemcitabine (2.27 months) was combined with the incremental cost of the gemcitabine over 5-FU to calculate a cost for gemcitabine per LYG (*Figure 3*).

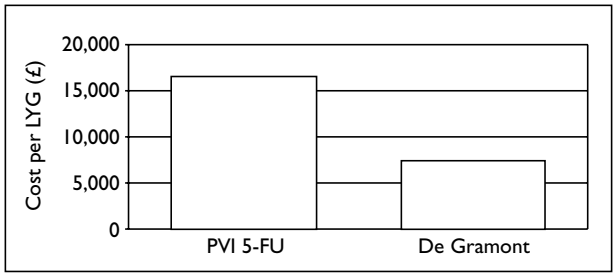


FIGURE 3 *Estimate of incremental cost per LYG of gemcitabine versus 5-FU*

TABLE 29 *Monthly treatment costs for gemcitabine*

	ScHARR (£)	Eli Lilly (£)
Total cost	1419.79	1219.59
Total cost excluding health professionals	1419.79	1157.75

Based on comparison with the PVI 5-FU regimen, the incremental cost of gemcitabine was estimated to be £16,543 per LYG. On using the De Gramont regimen, the corresponding figure is £7209.

Sensitivity analysis on cost per life-year gained

Costs

Cost of gemcitabine. The cost per month of gemcitabine from the Eli Lilly submission was lower than the cost estimate used in our analysis (*Table 29*). It was derived by dividing the cost per patient by the time to progression (3.93 months). The Eli Lilly figure included an estimate of visits to health professionals based on the unpublished evidence from Burris and colleagues' trial. We have excluded this cost because no estimate for it was identified for inclusion in our estimate of 5-FU costs. The Eli Lilly estimates for the cost of the drug and the infusion are lower and are based on individual dosage data from the Burris trial.

The ScHARR drug cost estimates were based on a standard 1000 mg/m^2 dose for an assumed average patient of body surface area 1.8 m^2, assuming that all patients are treated until disease progression.

TABLE 28 *Dose and cost of different drug regimens*

Regimen	Drugs in regimen	Dosage (mg/m^2)	Length of treatment (months)	Total treatment drug cost (£)
Gemcitabine	Gemcitabine	1000 (30-min infusion)	3.93	4839
De Gramont	5-FU 5-FU Folinic acid	400 (bolus injection) 400 (22-h infusion) 200 (2-h infusion)	1.78	3478
5-FU PVI	5-FU	300 (continuously every day)	1.78	1715

Substituting the Eli Lilly cost estimate for gemcitabine in the analysis reduces the incremental cost per LYG for gemcitabine against PVI 5-FU to £9468. The cost of visits to health professionals is not included in the 5-FU cost, so, if this is omitted from the calculation, the cost per LYG falls to £8527.

Cost of protracted venous infusion 5-fluorouracil. The cost per month of PVI 5-FU outlined in the Eli Lilly submission was higher than the cost estimate used in our analysis. A comparison of the costs is given in *Table 30*.

The key differences are that the Eli Lilly estimates were higher for infusions (pump and flushings) and operations, and lower for hospitalisations. The cost of checking and flushing of a central line/infusion pump will depend on the frequency of visits to the hospital. The Eli Lilly estimate assumed that this would involve a weekly visit. More typically, this occurs less frequently, once every 2 or 3 weeks for stable patients (Crellin A, Yorkshire Centre for Clinical Oncology, Cookridge Hospital, Leeds: personal communication, 2000). In one cancer centre where a helpline is available to support patients at home, it has been shown that visits to the hospital can be reduced to once every 6 weeks (Cunningham D, Royal Marsden Hospital, Surrey: personal communication, 2000). The Eli Lilly estimate assumed that central line insertion and removal would be undertaken during an inpatient stay; however, for many providers, this is undertaken as a day case procedure.

Substituting the Eli Lilly estimate of the cost of PVI 5-FU in the analysis changes the incremental cost per LYG for gemcitabine to £15,565. If the central line insertion and removal are assumed to be day case procedures, and the frequency of checking and flushing of the central line and pump is once every 6 weeks, not weekly, the cost per LYG is £20,361.

TABLE 30 *Monthly treatment costs for PVI 5-FU*

	ScHARR (£) (£/month)	Eli Lilly (£) (£/month)
Drug cost	123.00	130.46
Drug administration		
Infusion (incl. pump and flushings)	166.68	429.11
Hospitalisations	505.08	139.00
Visits to health professionals	N/A	71.51
Concomitant medications	18.53	23.74
Operations	148.29	271.28
Total	961.58	1065.10

N/A, not available

Treatment period. Despite changes in the assumptions concerning the costs of PVI 5-FU and gemcitabine in the above sensitivity analysis, the cost-effectiveness of gemcitabine remains within the levels of treatments currently used in the NHS. Discrepancies in costs of both PVI 5-FU and gemcitabine remain. A difference of £4720 between the total treatment costs of the two drugs would correspond to a cost per LYG greater than £25,000.

Survival

The survival gain for gemcitabine against 5-FU in Burris and co-workers' trial has been questioned. The following sensitivity analysis shows the impact on the cost per LYG if the survival difference is decreased.

The median survival reported in Burris and colleagues' trial is supported by the results of a number of further trials, including Moore and co-workers, who noted a median survival of 6.4 months.[22] However, there is some evidence to suggest that survival with gemcitabine may be lower than this. Storniolo and colleagues reported a 5.1-month median survival in a study of 2380 chemo-naive patients,[33] and Colucci and co-authors reported a 4.85-month median survival.[63] On reducing the mean survival gain for gemcitabine by the same proportion as the median survival (as in the Storniolo report), the cost per LYG increases further from £16,543 to £20,087. This assumes that the treatment period, based on the time to progression, is also reduced proportionally.

The cost per LYG results presented in *Figure 3* are based on the assumption that the PVI 5-FU survival will be the same as that for 5-FU from Burris and colleagues' trial. As noted in the discussion of results in chapter 2, this may understate the 5-FU survival benefit. There is no evidence to allow accurate identification of the survival benefits of PVI 5-FU against gemcitabine. In addition, anecdotal evidence to date suggests that the addition of folinic acid to the PVI 5-FU regimen of patients with pancreatic cancer may enhance the survival benefits with little additional cost (Crellin A, Yorkshire Centre for Clinical Oncology, Cookridge Hospital, Leeds: personal communication, 2000).

Within the Eli Lilly submission, the 95% CI for mean survival gain was presented. Based on this, the company presented a sensitivity analysis for the upper and lower 95% CIs. The base case cost per LYG was £12,206 and the upper and lower CI costs were £10,062 and £25,316 respectively. Given our higher estimate of the base case, this would increase the cost per LYG based on the lower CI to levels above £25,000.

Estimation of cost per quality-adjusted life-year gained

Given the significance of QoL for patients with pancreatic cancer, an illustration shows, by using Q-TWiST analysis, the potential impact of QoL adjustments on survival (appendix 6).

The Q-TWiST method compares treatments on the basis of quality-adjusted survival times. The overall survival of patients is divided into different health states, which, in turn, are weighted according to the QoL in each health state to derive a QALY estimate.[103] The three health states identified in Burris and co-workers' trial were: time in clinical benefit; time before progressive disease when not in clinical benefit; and time from disease progression to death. We followed the illustration used by Messori and colleagues in their articles on ovarian cancer,[95,99] assigning estimated utilities of 1.0, 0.5 and 0.5 to each of the health states respectively. Sensitivity analysis was undertaken on the utility variables to encompass a wide range of values of QoL because, clearly, these utilities are illustrative and have no empirical basis.

Based on Burris and co-workers' survival data, the mean LYG between patients treated with gemcitabine and those treated with 5-FU is 0.19 years. When using the costs of the PVI regimen, the cost per QALY is £16,543. On utilising the Q-TWiST methodology, with estimated values for the QoL utilities as given above, the QALYs gained are estimated at 0.148. This implies an incremental cost per QALY gained of £21,088.

Sensitivity analysis on cost per quality-adjusted life-year

QoL in different health states is unknown. Sensitivity analysis was used to explore the impact of changes in the utility scores on the cost per QALY (see appendix 6 for further details).

In the base case, time in clinical benefit, time before progressive disease when not in clinical benefit, and time from disease progression to death (relapse period) were assigned utilities of 1.0, 0.5 and 0.5 respectively. However, assuming that patients who are experiencing clinical benefit have perfect health (a utility score of 1) when they are receiving chemotherapy is unlikely. In addition, the time to disease progression and time from disease progression to death may have a higher or lower QoL than the assumption of 0.5.

A range of sensitivities were explored in terms of changes in the utility value of each health state independently and changes in the utility value of more than one health state at a time. In many cases this resulted in only small changes in the cost per QALY relative to the base case. The cost per QALY gained was relatively sensitive to assumptions about QoL in the relapse period, rising by 30% to £26,115 when the QoL in the period was reduced from 0.5 to 0.1.

The base case scenario assumes that the two drugs have the same utility in each health state. It seems reasonable, although not certain, that QoL would be similar for both drugs when patients are experiencing clinical benefit and during the period of disease progression until death. It is in the health state of time to progression when not in clinical benefit that there is most likelihood of differences in utility values. Trial data[13] showed that, although both drugs were well tolerated, patients treated with gemcitabine experienced more frequent and more severe toxicities than those treated with 5-FU, so it may be reasonable to expect that those treated with gemcitabine would have a lower QoL than if they were receiving chemotherapy. The cost per QALY was sensitive to changes in the utility of this health state. When the utilities for 5-FU were increased, or those for gemcitabine were decreased by 0.2, then the QALY gain reduced from 0.148 to 0.103, giving a cost per QALY of £30,460.

The utilities used in the sensitivity analysis are illustrative only and have no empirical basis. Further evidence on QoL is needed.

Conclusions

Preliminary estimates of the cost per LYG for gemcitabine as first line therapy suggest that it may be around £16,543. However, the clinical evidence on which the analysis is based is poor. Uncertainty relating to the evidence of effectiveness means that the cost-effectiveness analysis cannot be considered to be robust.

No published UK estimates of the cost of gemcitabine have been identified. The cost of 5-FU administration varies by regimen and also by provider for the same regimen. The cost difference between gemcitabine and 5-FU is therefore not known with certainty. The sensitivity analysis undertaken does however demonstrate that the cost per LYG remains within acceptable limits, despite changes to the cost assumptions.

The results of the analysis on cost per QALY gained are purely illustrative because no QoL data have been identified. However, the analysis demonstrates that the addition of a QoL adjustment is likely to result in a cost per QALY gained that is higher than the cost per LYG.

Impact on the NHS budget

The impact on the NHS budget would depend on:

- the number of patients with pancreatic cancer receiving chemotherapy
- the change in the market share of gemcitabine if a positive NICE recommendation is made.

The incidence of pancreatic cancer is not changing dramatically. For men, it has been declining at 3–4% every 5 years since the mid-1970s, while the incidence for women increased slightly until the end of the 1980s and has subsequently plateaued. The number of patients diagnosed with this cancer is therefore not expected to change dramatically.

The introduction of guidance on the diagnosis and treatment of upper GI cancers[9] is anticipated to increase the number of patients who will be referred to specialist oncologists. This will raise the number who are considered for chemotherapy. Within the next few years the proportion of patients receiving chemotherapy may rise to around 35%. This is based on the assumption that 10–15% of patients may undergo resection in the future. Of the remaining 85–90% it is assumed that only 40% will be suitable for palliative chemotherapy.

If there is a positive NICE recommendation, the market share of gemcitabine is likely to increase. It is unlikely that this drug would achieve a 100% market share, and any changes are likely to be gradual, occurring over a number of years. In the company submission, Eli Lilly assumed a market share of gemcitabine of 55% by 2002. They provided no indication of their expectation of market share beyond that date.

Eli Lilly suggested that the impact on the NHS budget would be likely to be in the order of £330,000–£640,000 per annum. They gave an upper ceiling of £2 million per annum by 2002, based on the assumption that all patients with locally advanced or metastatic disease (estimated to be 71% of all patients) receive chemotherapy.

The Eli Lilly estimates take account only of the drug costs and the medications used to treat side-effects. This is not unreasonable, given that this is the only resource that will directly impact on the NHS budget. However, it should be noted that other resource use will also change, including costs relating to chemotherapy infusions, hospitalisation and visits to and by health professionals (e.g. Macmillan nurses). In particular, the use of gemcitabine requires an outpatient visit (or in some instances a day case visit) once a week for 7 weeks out of 8 and then for 3 weeks out of every 4. Continuous infusion regimens require fewer hospital visits, which may allow a greater throughput of patients within existing facilities.

The cost estimates provided by Eli Lilly are considered to be reasonable, although the suggestion that the use of gemcitabine may go some way to addressing regional inequality in survival[11] should be viewed with caution.

Chapter 4

Factors relevant to the NHS

Geographical variability in availability of gemcitabine

The availability of gemcitabine currently varies according to geographical location within the UK. Some centres and units have funding for gemcitabine, while this has been refused at some hospitals, including a number of specialist centres.[11]

Chapter 5
Discussion

Gemcitabine for first line treatment of pancreatic cancer

Quality of the evidence

Evidence for the effectiveness of gemcitabine for the first line treatment of pancreatic cancer is limited. One RCT exists, published by Burris and colleagues in 1997,[13] which compares the effect of gemcitabine with that of 5-FU in patients with pathologically confirmed, locally advanced or metastatic pancreatic cancer. This study does show a statistically significant survival benefit for the use of gemcitabine compared with 5-FU, although there are questions that cast doubt on the validity of its results. The median survival gain from Burris and co-workers' trial was 1.24 months (mean 2.27). This is a relatively small gain, although it should be noted that, for patients with a short remaining lifetime, particularly those who are younger, this period of time is often considered to be extremely valuable.

The limitations of the trial have been outlined in chapter 2. Burris and colleagues' trial[13] includes only 126 participants; results based on such a small sample cannot be regarded as definitive. In the control arm, the 5-FU was administered as a bolus infusion. There is little direct evidence to suggest that different 5-FU schedules are any better or worse than each other in pancreatic cancer. However, there is very strong evidence to show that, in other areas of GI cancer therapy, bolus 5-FU alone would be considered to be inferior in terms of response rates and efficacy. It is difficult to imagine bolus 5-FU alone being used in current practice in the UK, either within trials or as standard practice; it therefore cannot be considered to be a suitable comparator. Indeed, the results of Glimelius and co-workers,[12] in terms of survival and equivalent toxicity, would support the suboptimal nature of the 5-FU in Burris and colleagues' trial.

No evidence on QoL was identified. The use of CBR as a proxy measure for QoL in Burris and co-workers' trial suggests that gemcitabine may offer benefit, but CBR has not been validated and its clinical relevance must be interpreted with caution. Gemcitabine was reviewed and approved by the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee in 1995. However, in 1996, Gelber, a member of this Committee, highlighted ongoing concern over the ability of CBR to capture adequately patients' assessment of QoL, and stated that, "it is not clear whether the current criteria for Clinical Benefit Response is indeed acceptable to the FDA".[88] Despite this, however, gemcitabine is the standard treatment for pancreatic cancer in the USA, and indeed in many European counties.

Quality of life issue

QoL is an important issue. Pancreatic cancer is a serious disease with a profound impact on QoL. Severe pain is a common symptom. It also causes jaundice, weight loss, poor appetite, vomiting, general GI problems and diabetes.[9] The role of chemotherapy in pancreatic cancer and its impact on QoL is not clear cut. Benefits in terms of survival time and the alleviation of symptoms may be outweighed by the cost of toxicity and deterioration in QoL.[104]

There is some evidence to support the role of chemotherapy in advanced pancreatic cancer. In 1996, Glimelius and colleagues reported on 90 patients with advanced pancreatic and biliary cancer who were randomised to receive chemotherapy (5-FU, leucovorin with or without etoposide) plus BSC or BSC alone.[12] Overall survival was significantly longer in the chemotherapy group (median 6 versus 2.5 months, $p < 0.01$). In addition, the patients in the chemotherapy group had better emotional functioning together with improved performance in role functioning, better appetite and less pain. Overall QoL-adjusted survival was 4 months in the chemotherapy group and 1 month in the BSC group. These authors concluded that chemotherapy can add to both quantity and quality of life in advanced pancreatic cancer.

Toxicity

Gemcitabine as a first line therapy has been shown to be well tolerated and to have a mild toxicity profile. In Burris and co-workers' trial it was shown to have a more frequent and more severe toxicity profile than 5-FU. This, once again, may point to the possibility that a suboptimal dose of 5-FU was delivered because the toxicity of bolus 5-FU would

generally be expected to be similar to that relating to gemcitabine.

Treatment costs

The drug cost of gemcitabine is more expensive than 5-FU, but overall costs are partly offset by simplicity of drug administration. No inpatient admission is required, as in the case of the De Gramont regimen. Costs relating to pump and central line insertion and removal, as required for PVI 5-FU, are avoided, as are the potential complications arising from the use of central venous catheters. In addition, some cancer centres and/or units may not have the infrastructure necessary to support PVI 5-FU schedules. One major advantage of continuous infusion regimens is the potential to reduce the number of hospital visits per patient, which is beneficial to both patients and providers.

Preliminary estimates of the cost per LYG suggest that gemcitabine should not be dismissed, because it is a potentially cost-effective treatment for pancreatic cancer. However, these results are sensitive to survival assumptions; small changes in survival produce cost per LYG values well above the level achieved by currently available treatments. It should be noted that the introduction of a QoL adjustment to survival is likely to diminish gemcitabine's survival advantage, resulting in a cost per QALY that is higher than the cost per LYG.

Gemcitabine for second line treatment of pancreatic cancer

Only one Phase II trial (by Rothenberg and colleagues[29]) has used gemcitabine solely as a second line treatment. Although this demonstrated a median survival of 4 months and a 1-year survival of 4%, no additional evidence is available to support this trial. Phase II trials alone should not form the basis of the establishment of standard therapy.

Other applications of gemcitabine

A trial conducted by the European Society for the Study of Pancreatic Cancer (ESPAC3) began recruiting in 2000. This study will compare the use of adjuvant gemcitabine or 5-FU and folinic acid with surgery alone.

The use of gemcitabine as part of a combination chemotherapy regimen appears to offer a possible way forward. Evidence to date comprises only Phase II studies. These have been presented as abstracts, the results are inconsistently reported, and the numbers of participants entering the studies are very small. It would appear from the limited details available that the administration of such regimens is reasonable. Further studies and randomised trials should be conducted before the value of gemcitabine in combination chemotherapy is assessed.

Need for further research

The prognosis for pancreatic cancer patients remains poor. For those with an unsatisfactory performance status the emphasis should remain on symptom control and involvement of a palliative care team. For patients with a good performance status, chemotherapy may offer benefit. However, no chemotherapy drugs have yet demonstrated response rates higher than 20%. Gemcitabine offers, at best, a small increase in survival over 5-FU. Further RCTs are required.

Until Phase II studies with existing or new drugs, alone or in combination, demonstrate significantly improved activity in pancreatic cancer, randomised studies are likely to be directed towards looking at toxicity, QoL, and any small survival benefits that may be obtained with gemcitabine alone compared with a modern 5-FU-based protocol or a combination of the two.

Evidence for QoL benefits of gemcitabine is particularly poor. There is almost universal acknowledgement of the need for a double-blind RCT to confirm the survival benefits of this agent, particularly to enable the collation of acceptable QoL data.[87,88,92]

Chapter 6

Conclusions

Gemcitabine has not been shown conclusively to be superior to 5-FU in terms of survival or QoL. There is, however, no evidence to suggest that gemcitabine is worse that 5-FU. Preliminary estimates of the cost per LYG for gemcitabine as first line therapy suggest that this agent should not be dismissed, but these results are not robust. Further evidence on survival, QoL and cost is required before any definite conclusions can be drawn about cost-effectiveness. Additional research is required in the form of a RCT to confirm the survival benefits of gemcitabine compared with a modern 5-FU-based protocol and to provide good QoL data.

The evidence for the use of gemcitabine as second line therapy is inconclusive. Further confirmation from high-quality randomised trials is required. In addition, further evidence in the form of the results of RCTs is also required concerning the use of gemcitabine as adjuvant treatment and in combination therapy.

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Appendix 1

Search strategy

MEDLINE (OVID BIOMED 1966–)

1 gemcitabine.af.
2 103882 84 4.rn.
3 difluorodeoxycytidine.tw.
4 difluorocytidine.tw.
5 gemzar.tw.
6 ly 188011.tw.
7 ly188011.tw.
8 dfdc$.tw.
9 or/1–8
10 Pancreatic neoplasms/
11 exp Pancreas/
12 Pancreatic diseases/
13 11 or 12
14 Neoplasms/
15 Digestive system neoplasms/
16 Carcinoma/
17 Adenocarcinoma/
18 or/14–17
19 13 and 18
20 (pancrea$ adj5 (cancer$ or neoplasm$ or neoplasia$ or carcinoma$ or tumor$ or tumour$ or adenocarcinoma$)).tw.
21 10 or 19 or 20
22 9 and 21

EMBASE (OVID BIOMED 1980–)

1 exp Pancreas tumor/
2 (neoplas$ or tumor$ or malignan$ or cancer or carcinoma or adenocarcinoma).hw.
3 Pancreas disease/
4 exp pancreas/
5 3 or 4
6 2 and 5
7 (pancrea$ adj5 (cancer$ or neoplasm$ or neoplasia$ or carcinoma$ or tumor$ or tumour$ or adenocarcinoma$)).tw.
8 1 or 6 or 7
9 gemcitabine.af.
10 gemzar.af.
11 103882 84 4.rn.
12 ly 188011.af.
13 ly188011.af.
14 dfdc$.af.
15 difluorocytidine.af.
16 difluorodeoxycytidine.af.
17 or/9–16
18 8 and 17

Science Citation Index (Web of Science 1981–)

Topic = ((gemcitabine or gemzar or difluorodeoxycytidine or difluorocytidine or ly 188011 or ly188011 or dfdc*) and pancrea*); DocType=All document types; Language=All languages; Databases= SCI-EXPANDED, SSCI, A&HCI; Timespan=All Years;

Cochrane Library (CDSR and CENTRAL/CCTR) (2000 Issue 3)

#1 GEMCITABINE
#2 GEMZAR
#3 DIFLUORODEOXYCYTIDINE
#4 DIFLUOROCYTIDINE
#5 DFDC*
#6 ((((#1 or #2) or #3) or #4) or #5)
#7 PANCREA*
#8 #6 and #7

NHS CRD DARE, NHS EED and HTA (complete databases)

gemcitabine or difluorodeoxycytidine or difluorocytidine or gemzar or dfdc$ or 103882(w)84 or ly188011 or ly(w)188011/All fields AND pancrea$/All fields

PubMed (last 180 days from 31 August 2000)

#11 Search #9 and #10 Limits: 180 days
#10 Search pancrea* Limits: 180 days
#9 Search #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 Limits: 180 days
#8 Search dfdc* Limits: 180 days
#7 Search ly188011 Limits: 180 days
#6 Search ly 188011 Limits: 180 days
#5 Search gemzar Limits: 180 days
#4 Search difluorocytidine Limits: 180 days
#3 Search difluorodeoxycytidine Limits: 180 days

#2 Search 103883 84 4 Limits: 180 days
#1 Search gemcitabine Limits: 180 days

OHE HEED (complete database)

Search terms

gemcitabine
difluorodeoxycytidine
difluorocytidine
gemzar
dfdc*
103882 84 4
ly188011
ly(w)188011

Fields searched

Abstract
All data
Article title
Book title
Drug names
Keywords
Technology assessed

Other sources consulted

AÉTMIS (Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé)
AHFMR (Alberta Heritage Foundation for Medical Research)
AHRQ (Agency for Healthcare Research and Quality)
Alberta Clinical Guidelines Programme
ARIF (Aggressive Research Intelligence Facility)
CancerGuide: finding clinical trials on the Internet
CancerWEB
CCOHTA (Canadian Co-ordinating Office for Health Technology Assessment)
CCT (Current Controlled Trials)
CenterWatch trials register
Centre for Clinical Effectiveness, Monash University
Centre for Health Economics, York University
CPG Infobase (Canadian Medical Association, Clinical Guidelines Programme)
Current Research in Britain
DTB (*Drug and Therapeutics Bulletin*)
eGuidelines
EMEA (European Agency for the Evaluation of Medicinal Products)
FDA (Food and Drug Administration)
Harvard CUA (Cost–utility analysis) database
HERC (Health Economics Research Centre), Oxford University
HERG (Health Economics Research Group), Brunel University
HERU (Health Economics Research Unit), Aberdeen University
HSRU (Health Services Research Unit), Aberdeen University
HSRU (Health Services Research Unit), Oxford University
HSTAT (Health Services/Technology Assessment Text, US National Library of Medicine)
IHE (Institute of Health Economics), Alberta
INAHTA (International Network of Agencies for Health Technology Assessment) Clearing House
Manitoba Guidelines and Statements
MRC (Medical Research Council) Funded Projects Database
MSAC (Medical Services Advisory Committee), Australia
MTRAC (Midland Therapeutic Review and Advisory Committee)
National Guideline Clearinghouse
NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
NCI (National Cancer Institute)
NHMRC (National Health and Medical Research Council), Australia
NHS Centre for Reviews and Dissemination, York University
NHS R&D Programmes
NIH (National Institutes of Health) Consensus Development Programme
NIH Clinical Trials database (ClinicalTrials.gov)
North of England Guidelines, University of Newcastle
NRR (National Research Register)
SBU (Swedish Council for Health Technology Assessment)
SHPIC (Scottish Health Purchasing Intelligence Consortium)
SIGN (Scottish Intercollegiate Guidelines Network)
Therapeutics Initiative (Vancouver)
TRIP (Turning Research into Practice) database
Wales, Health Evidence Bulletins
Wessex DEC (Development and Evaluation Committee) reports
West Midlands DES (Development and Evaluation Service) reports

Appendix 2

Data extraction form

Section 1: Study information

Unique study identifier:

First authors:

Title:

Publication date:

Year of data:

Final publication: Y/N

Funding source:
Government Pharmaceutical Private Unfunded Unclear

Outcome	**Yes (time stated)**	**Yes but no time stated**	**Not given**	**Definition/ indication as stated in article**	**Value**
Median survival (months)					
Survival at time point					
Surgery					
Clinical benefit response					
Median progression-free survival (months)					
Time to treatment failure (months)					
Partial response rate					
Symptomatic response rate					
Objective response rate					
Overall response rate					

Section 2: study design and conduct

Randomisation before treatment?

Yes No Unclear

Please indicate the degree of concealment according to the following criteria:

A: adequate
B: possibly adequate
C: clearly inadequate
D: not randomised

	Description	Degree of concealment
Details of method of randomisation		
Inclusion criteria for participants		
Exclusion criteria for participants		

If RCT, complete Jadad scoring system.

Jadad scoring

Give a score of 1 point for each "yes" or 0 points for "no".

1. Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)? ☐
2. Was the study described as double blind? ☐
3. Was there a description of withdrawals and drop-outs? ☐

Give 1 additional point if the method to generate the sequence of randomisation was described and if it was appropriate (table of random numbers, computer generated etc.).

Deduct 1 point if this method was inappropriate (patients allocated alternately, according to date of birth, hospital number etc.).

Give 1 point if the method of double blinding was described and was appropriate (identical placebo, active placebo, dummy etc.).

Deduct 1 point if the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet versus injection with no double dummy).

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and reasons for each withdrawal must be stated. If there were no withdrawals it should also be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Overall Jadad score:

Section 3: study details

Single site Multicentre

Duration of follow-up:

Planned recruitment (number of patients):

Number eligible:

Number randomised:

Number completing trial:

Recruitment period:
Start Finish Not stated

Number analysed:

Section 4: participants

Inclusion criteria

Did all patients have a diagnosis of pancreatic carcinoma?
Yes No

If NO, are outcome data available separately for patients with pancreatic carcinoma?
Yes No

If NO, contact authors?

Did all patients have a pathologically confirmed diagnosis of pancreatic carcinoma
Yes No

If NO, is outcome available separately for patients in whom pathological diagnosis was made?
Yes No

If NO, contact authors?

Participants	Total	Control	Treatment 1	Treatment 2	Treatment 3
Number randomised					
Number with pancreatic cancer					
Number with histo-logical confirmation					
Mean/median age					
Age range					
Patients undergoing biliary stenting					
Surgical treatment for pancreatic cancer					
Disease extent	**Total**	**Control**	**Treatment 1**	**Treatment 2**	**Treatment 3**
Locally advanced					
Metastatic					
Relapsed					

Section 5: interventions

Details of regimen used	Control	Treatment 1	Treatment 2	Treatment 3
Drug/s				
Dose/s				
Schedule				
RT dose				

Co-interventions

Was any co-intervention used prior to stated drug therapy?
Yes No Not stated

If YES, please give details:

Was any concomitant therapeutic drug therapy used?
Yes No Not stated

If YES, please give details:

Was any drug used post-intervention?
Yes No Not stated

If YES, please give details:

Section 6: toxicity

Outcome	**Scale used**	**%/# patients and severity for control**	**%/# patients and severity for treatment 1**	**%/# patients and severity for treatment 2**	**%/# patients and severity for treatment 3**
Laboratory					
Haematological					
Anaemia					
Leucopenia					
Neutropenia					
Thrombocytopenia					
Hepatic					
ALT					
AST					
Alkaline phosphatase					
Bilirubin					
Renal					
Proteinuria					
Haematuria					
BUN					
Creatinine					
Non-laboratory					
Nausea and vomiting					
Pain					
Fever					
Rash					
Dyspnoea					
Constipation					
Diarrhoea					
Haemorrhage					
Infection					
Alopecia					
Stomatitis					
Somnolence					
Paraesthesias					
Other					

Were causes of death given?
Yes No

If YES, please give details of cause and number per treatment group:

Cause of death	Control	Treatment 1	Treatment 2
Treatment related			
Malignancy related			
Other			

Section 7: quality of life

Method used to calculate quality of life scores?

Who assessed quality of life?
Patient Doctor More than one individual
Details:

Outcome	Scale used	Control	Treatment 1	Treatment 2	Treatment 3
Global QoL					
Analgesic consumption					
Pain intensity					
Global pain					
Performance status					
Clinical benefit response					

Section 8: drop-outs and withdrawals

Are numbers and reasons for drop-out and withdrawals described?
Yes No

	Control	Treatment 1	Treatment 2	Treatment 3
Number originally randomised				
Number of losses to follow-up at end of treatment period				
Number analysed				
Reason 1				
Reason 2				
Reason 3				

Appendix 3

Tables 3–22

TABLE 3 *Gemcitabine as an adjuvant treatment (RCT)*

Reference	Study type	Overall Jadad score	Interventions	Participants	No. entered (evaluated)	Results
Lygidakis *et al.*, 1998[19]	RCT No description of method of randomisation used No description of blinding and none appears to have been carried out Withdrawals and drop-outs described	1	A = curative surgery alone B = curative surgery and gemcitabine (1000 mg/m^2), carboplatin (200 mg/m^2), mitoxantrone (0.2 g/kg) and immunotherapy (1 ml IL-2 and 0.5 ml γ-IFN) followed by 5-day transsplenic and 5-day transtumoral immunotherapy course with the same agents; this course was repeated at 2-month intervals during first postoperative year and every 3 months thereafter C = palliative surgery alone D = palliative surgery and the same drug regimen as in A	512 patients with pancreatic cancer	A = 106 (106) B = 168 (168) C = 103 (103) D = 135 (135)	***Mean survival (months)*** A = 14 B = 32 C = 6.8 D = 16
Lygidakis *et al.*, 1998[20]	RCT No description of method of randomisation No description of blinding and none appears to have been carried out No description of withdrawals or drop-outs	2	A = lipiodol (10 ml), 58% urografin (2 ml) suspended with docetaxel (100 mg/m^2), gemcitabine (1000 mg/m^2) and carboplatin (200 mg/m^2) via catheter in the superior mesenteric artery; catheter then repositioned in the splenic artery and a 10-day course of immunotherapy was administered using proleukin (1 ml 18 × 10^6) suspended in lipiodol (1.5 ml) and urografin (0.5 ml) for 10 consecutive days; further immunotherapy for 10 days commencing 20 days after subtotal pancreatectomy B = surgery alone	26 patients with histologically confirmed resectable pancreatic cancer	A = 14 (14) B = 12 (12)	***CR (no. patients)*** A = 11 B = 3 ***PD (no. patients)*** A = 3 B = 9 p <0.01 ***Survival (no. patients)*** A = 14 B = 6 p < 0.01

IL-2, interleukin-2; IFN, interferon; CR, complete response; PD, progressive disease

TABLE 4 *Gemcitabine as a single agent therapy (RCT)*

Reference	Study type	Overall Jadad score	Interventions	Participants	No. entered (evaluated)	Results
Burris *et al.*, 1997[13]	RCT No description of method of randomisation Treatment was single blind as study drug was not blinded to investigator because a rash was a potential side-effect of both 5-FU and gemcitabine Nos and reasons for drop-outs and withdrawals were stated	2	A = gemcitabine (1000 mg/m^2) weekly for 7 weeks then 1 week rest; then once weekly for 3 weeks out of every 4 B = 5-FU (600 mg/m^2 i.v. bolus) once weekly; one cycle every 4 weeks	126 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	126 (126)	***Median survival (months)*** A = 5.65 B = 4.41 *p* = 0.0025 ***1-year survival (%)*** A = 18 B = 2 *p* = 0.0025 ***Median progression-free survival (months)*** A = 2.33 B = 0.92 *p* = 0.0002 ***Time to treatment failure (months)*** A = 2.04 B = 0.92 ***CBR (%)*** A = 23.8 B = 4.8 *p* = 0.0022
Cantore *et al.*, 2000[18] [Abstract only]	RCT No description of method of randomisation No description of method of blinding Drop-outs and withdrawals described	1	A = gemcitabine (1000 mg/m^2) weekly for 7 weeks and 1 week rest; then weekly for 3 out of every 4 weeks B = 5-FU (400 mg/m^2) and FA (20 mg/m^2) on days 1–5 every 4 weeks for 6 cycles C = 5-FU (100 mg/m^2), FA (100 mg/m^2), epirubicin (60 mg/m^2) and carboplatin (300 mg/m^2) infused intra-arterially every 3 weeks for 6 cycles	106 patients with unresectable pancreatic cancer	A = 35 (31) B = 34 (31) C = 37 (35)	Preliminary report Results not yet reported
Moore *et al.*, 2000[22] [Abstract only]	RCT No description of method of randomisation No description of method of blinding No description of drop-outs and withdrawals	1	A = gemcitabine (1000 mg/m^2) weekly for 7 out of 8 weeks and then weekly for 3 out of every 4 weeks B = BAY12-9566 (80 mg p.o.) continuously	277 patients with pancreatic cancer	277 (277)	***Median survival (months)*** A = 6.4 B = 3.2 *p* = 0.0001 ***Median progression-free survival (months)*** A = 3.54 B = 1.77 *p* = 0.012
Rosemurgy *et al.*, 1999[21] [Abstract; British Biotech press release only]	RCT No description of method of randomisation used No description of blinding No description of withdrawals or drop-outs	2	A = gemcitabine (1000 mg/m^2 per day) weekly for 7 weeks and 1 week rest; then weekly for 3 weeks out of every 4 B = marimistat (5 mg/day) b.d. C = marimistat (10 mg/day) b.d. D = marimistat (25 mg/day) b.d.	414 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	414 (A = 104, B = 105, C = 102, D = 103)	No significant difference in survival ***Median survival (days)*** A = 167 B = 110.5 C = 105 D = 125

continued

TABLE 4 contd *Gemcitabine as a single agent therapy (RCT)*

Reference	Study type	Overall Jadad score	Interventions	Participants	No. entered (evaluated)	Results
British Biotech, 2000[17] [Press release only]	RCT No description of method of randomisation Double blind and placebo controlled No description of withdrawals or drop-outs	2	A = gemcitabine (1000 mg/m^2) and placebo (10 mg p.o. b.d.) B = gemcitabine (1000 mg/m^2) and marimistat (10 mg p.o. b.d.)	239 patients with pathologically confirmed pancreatic cancer	239 (239 but no info. about nos in each arm)	No significant difference in survival No significant difference in QoL

FA, folinic acid

TABLE 5 *Additional reports: gemcitabine as a single agent therapy*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Aykan *et al.*, 2000[23] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) weekly for 7 weeks and 1 week rest; then for 3 weeks out of every 4 until relapse or intolerable toxicity	14 patients with locally advanced or metastatic pancreatic cancer	14 (14)	Median survival = 6 months PR = 1 patient CR = 1 patient Overall response rate = 14%
Carmichael *et al.*, 1996[37]	Phase II	Gemcitabine (800 mg/m^2 or 1000 mg/m^2) once a week for 3 weeks followed by 1 week rest Dose increased by up to 20% if no toxicity	34 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	34 (32)	Median survival = 6.3 months Improvement in performance status = 17% Improvement in analgesic requirement = 7.4% Improvement in pain score = 28.6% Improvement in nausea = 27.3%
Casper *et al.*, 1994[24]	Phase II	Gemcitabine (800 mg/m^2 per week) for 3 weeks then 1 week rest Dose reduced for myelosuppression and escalated in absence of toxicity	44 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	44 (44)	Median survival = 5.6 months 1-year survival = 23% Median progression-free survival = 4 months Overall response rate = 11%
Casper *et al.*, 1991[25] [Abstract only]	Multicentre Phase II	Gemcitabine (800 mg/m^2 i.v.) weekly for 3 weeks every 28 days	43 patients with locally advanced or metastatic pancreatic cancer	43 (39)	PR = 13% SD = 38% MR = 8%
Crino *et al.*, 1997[26] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) once a week for 7 weeks and 1 week rest; then once weekly for 3 weeks out of every 4	24 patients with locally advanced or metastatic pancreatic cancer	24 (24)	PR = 16% SD = 41% PD = 41%

continued

TABLE 5 contd *Additional reports: gemcitabine as a single agent therapy*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Eickhoff *et al.*, 2000[39] [Abstract only]	Retrospective cohort study	A = gemcitabine (1000 mg/m^2 on days 1 and 8 every 3 weeks B = 5-FU (500 mg/m^2) and α-IFN (6×10^6 i.u.); 1 cycle every 6 weeks	65 patients with inoperable pancreatic carcinoma	A = 32 B = 33 (30 evaluated for CBR in each group; objective response evaluated in 28 patients in A and 30 in B)	***Overall survival (%)*** A = 23 B = 28 ***Median survival (months)*** A = 8.5 B = 10.2 ***CR (no.)*** A = 1 B = 4 ***PR (no.)*** A = 5 B = 4 ***Overall response (%)*** A = 21 B = 26
Klein *et al.*, 2000[38]	Retrospective cohort study	A = gemcitabine (1000 mg/m^2) weekly for 3 weeks out of every 4 B = 2 dose schedules of 5-FU and leucovorin (low-dose leucovorin 20 mg/m^2 i.v. bolus and 5-FU 370 mg/m^2 for 5 consecutive days every 28 days; or leucovorin 200 mg/m^2 and 5-FU 900 mg/m^2 every 2 weeks)	82 patients with pathologically confirmed advanced, metastatic or relapsed pancreatic cancer	A = 35 B = 47 (60 evaluated for objective response, 22 for toxicity, 85 for CBR, and 82 for survival)	***1-year survival (%)*** A = 23 B = 32 ***CBR (%)*** A = 48 B = 19 ***Objective response (%)*** A = 9 B = 4
Kurtz *et al.*, 1999[27]	Multicentre Phase II	Gemcitabine (800–1000 mg/m^2) weekly for 3 out of every 4 weeks	74 patients with surgically unresectable, metastatic or relapsed pancreatic cancer	74 (varies according to outcome)	Overall survival = 5 months CBR = 48% Progression-free survival = 2.5 months PR = 2 patients SD = 18 patients PD = 24 patients
Petrovic *et al.*, 1998[28] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) weekly for 7 weeks and 1 week rest; then once weekly for 3 weeks out of every 4	54 patients with pancreatic cancer	54 (11)	Median survival = 6.65 months 1-year survival = 26% CBR = 33%
Rothenberg *et al.*, 1996[29]	Multicentre Phase II	Gemcitabine (1000 mg/m^2) weekly for 7 weeks and 1 week rest; then for 3 weeks out of every 4	74 patients with metastatic pancreatic cancer that was refractory to and had progressed despite the administration of 5-FU	74 (63 evaluable for CBR and 54 for response)	Median survival = 4 months 1-year survival = 4% CBR = 27% PR = 11% SD= 30%
Roznowski and Ramlau, 1999[30] [English abstract only]	Phase II	Gemcitabine (1000 mg/m^2) weekly for 7 weeks and 1 week rest; then weekly for 3 weeks out of every 4	12 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	12 (12)	Median survival = 21 weeks Time to treatment failure = 15.7 weeks PR = 10% SD = 50%
Scheithauer *et al.*, 1999[31] [Abstract only]	Phase II	Gemcitabine (2200 mg/m^2) every 2 weeks for 6 months	38 patients with metastatic pancreatic cancer	38 (28)	Median survival >6.5 months CBR = 35% Median progression-free survival = 4.5 months Objective response rate = 28%

continued

TABLE 5 contd *Additional reports: gemcitabine as a single agent therapy*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Spagnuolo *et al.*, 1999[32] [Abstract only]	Phase II	Gemcitabine (1500 mg/m^2) every 28 days delivered in 30 min through superselective arterial or coeliac infusion	10 patients with locally advanced or metastatic pancreatic cancer	10 (10)	CBR = 7 patients PR = 2 patients MR= 4 patients
Storniolo *et al.*, 1999[33]	Retrospective investigational new drug study	Gemcitabine (1000 mg/m^2) once weekly for 7 weeks and 1 week rest; then once weekly for 3 weeks out of every 4 until disease progression or unacceptable toxicity	3023 patients with pathologically confirmed pancreatic cancer	3023 (varied for any given end-point based on no. of completed records returned by the investi-gators: 2015 for dosage, 2380 for survival, 2012 for disease progression, 982 for tumour response, 1694 for symptom benefit and 2140 for discontin-uation data)	Median survival = 4.8 months 6-month survival = 41% 9-month survival = 22% 1-year survival = 15% Median time to disease progression = 2.7 months PR = 10.6% CR = 1.4% Overall response rate = 12.0% DRSI = 18.4%
Tempero *et al.*, 1999[34] [Abstract only]	Randomised Phase II	A = gemcitabine (2200 mg/m^2) over a standard 30 min infusion weekly for 3 weeks out of every 4 B = gemcitabine (1500 mg/m^2) at a rate of 10 mg/m^2 per min weekly for 3 weeks out of every 4	93 patients with pathological confirmation of pancreatic cancer	93 (67)	***Median survival (months)*** A = 4.7 B = 6.1 ***1-year survival (%)*** A = 0 B = 23 ***Time to treatment failure (months)*** A = 1.9 B = 2.2 ***Objective response rate*** (%) A = 2.7 B = 16.6
Ulrich-Pur *et al.*, 2000[35]	Phase II	Gemcitabine (2200 mg/m^2) on days 1 and 15 repeated every 4 weeks; continued for patients achieving objective response or SD until 6 courses completed	43 patients with pathologically confirmed metastatic or relapsed pancreatic cancer	43 (43 evaluable overall and 36 for CBR)	Median survival = 8.8 months 1-year survival = 26.3% CBR = 44% Median progression-free survival = 5.3 months PR = 8 patients CR = 1 patient SD = 42% Overall response rate = 21%
Weissman and Ludwig, 1999[36] [Abstract only]	Phase II	Gemcitabine (1200 mg/m^2) as a 3-min infusion into intra-arterial catheter (coeliac artery for pancreatic cancer) or hepatic artery for cholangiocarcinoma; 1 cycle every 4 weeks	15 patients with inoperable pancreatic cancer	15 (15)	Median survival = 5.5 months CR = 2 patients SD = 4 patients

PR, partial response; CR, complete response; SD, stable disease; MR, minor response; PD, progressive disease; CBR, clinical benefit response

TABLE 6 *Additional reports: gemcitabine and 5-FU*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Anchisi *et al.*, 2000[40] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2 on days 1 and 8) and continuous infusion 5-FU (200 mg/m^2 per day on days 1 to 15); 1 cycle every 3 weeks	19 patients with pathologically confirmed locally advanced, metastatic or relapsed pancreatic cancer	19 (17)	Median survival = 21 weeks PR = 25% SD = 25% Overall response rate = 31%
Berlin *et al.*, 2000[41]	Phase II	Gemcitabine (1000 mg/m^2) and 5-FU (600 mg/m^2 i.v. bolus) weekly for 3 weeks out of every 4; protocol complete after 8 4-week cycles	37 patients with metastatic pancreatic cancer	37 (36)	Median survival = 4.4 months 1-year survival = 8.6 months PR = 14%
Borner *et al.*, 1998[42] [Abstract only]	Phase II ongoing	Gemcitabine (1000 mg/m^2) and continuous infusion 5-FU (200 mg/m^2) weekly for 3 weeks every 28 days	14 patients with locally advanced or metastatic pancreatic cancer	14 (12)	PR = 25% MR = 25% SD = 33% PD = 17%
Cascinu *et al.*, 1999[43]	Multicentre Phase II	Gemcitabine (1000 mg/m^2) and 5-FU (600 mg/m^2) weekly for 3 weeks out of every 4	54 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	54 (54)	Median survival = 7 months CBR = 51% PR = 2 patients SD = 34 patients
Cortes-Funes *et al.*, 1998[44] [Abstract only]	Phase I–II	Gemcitabine at 5 different dose levels (700, 800, 900, 1000, 1100 mg/m^2) and 5-FU (200 mg/m^2 per day) weekly for 3 weeks out of every 4	26 patients with pancreatic cancer	26 (24 overall; 20 CBR)	Overall survival = 10.4 months CBR = 55% PR = 3 patients CR = 1 patients Overall response rate = 16%
de Gusmao *et al.*, 1998[45] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2 per day) and 5-FU (500 mg/m^2 per day) weekly for 3 weeks; 1 cycle every 4 weeks for a maximum of 8 cycles	12 patients with pancreatic cancer (+2 with advanced biliary tract carcinoma)	14 (14)	Median survival = 13 months Objective response = 6 patients
Hidalgo *et al.*, 1999[46]	Phase I–II	Gemcitabine (700 mg/m^2) weekly for 3 weeks out of every 4 (dose escalated by 100 mg/m^2 in successive cohorts of patients to a maximum of 6 cycles) and 5-FU (200 mg/m^2)	26 patients with pathologically confirmed locally advanced, metastatic or relapsed pancreatic cancer	26 (26 overall; 22 CBR)	1-year survival = 39.5% CBR = 45% Median progression-free survival = 7.4 months PR = 4 patients CR = 1 patient Improvement of disease symptoms = 10 patients
Jovtis *et al.*, 1999[47] [Abstract only]	Multicentre Phase II	Gemcitabine (1000 mg/m^2), 5-FU (600 mg/m^2) and leucovorin (25 mg/m^2) weekly for 3 weeks out of every 4	18 patients with locally advanced or metastatic pancreatic cancer	18 (18)	Median survival = 11 months PR = 4 patients SD = 11 patients
Lencioni *et al.*, 2000[48] [Abstract only]	Phase I–II	Gemcitabine (1000 mg/m^2 i.v.), leucovorin (250 mg/m^2 i.v.) and 5-FU (3 doses of 1400, 2000 and 2600 mg/m^2) weekly for 3 weeks out of every 4	22 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	22 (21 evaluable for response and 16 for CBR)	CBR 9/16 patients PR = 1 patient Objective response = 1 patient SD = 11 patients

continued

TABLE 6 contd *Additional reports: gemcitabine and 5-FU*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Louvet *et al.*, 1999[49] [Abstract only]	Multicentre Phase II ongoing	FOLFUGEM: Leucovorin 400 mg/m^2 2-h i.v. infusion, followed by 5-FU 400 mg/m^2 bolus and 3000 mg/m^2 48-h infusion (first 24 patients) or 2000 mg/m^2 (remaining 24 patients) Gemcitabine day 3 after 5-FU infusion, at dose 1000 mg/m^2 (cycles 1 and 2), then increased to 1250 mg/m^2 (cycles 3 and 4) and to 1500 mg/m^2 (cycle 5 and following cycles) when toxicity was <WHO grade 3 Treatment administered every 2 weeks (or delayed to every 3 weeks if non-adequate haematological parameters) until progression in metastatic disease (30 patients), or for 6 courses followed by chemoradiation in locally advanced disease (18 patients)	48 patients with locally advanced or metastatic pancreatic cancer	48 (48)	1-year survival = 38% Median progression-free survival = 4.5 months
Matano *et al.*, 2000[50]	Phase II	Gemcitabine (1000 mg/m^2) days 1, 8 and 15 and 5-FU (500 mg/m^2) days 1–5; 1 cycle every 28 days with a 50% dose reduction if haematological toxicity	11 patients with pathologically confirmed metastatic pancreatic cancer	11 (11)	CBR = 64% Median progression-free survival = 26.8 weeks
Oettle *et al.*, 1999[51] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2), 5-FU (750 mg/m^2) and FA (200 mg/m^2) days 1, 8, 15 and 22, followed by a break of 2 weeks	17 patients with pancreatic cancer	17 (17)	Median progression-free survival = 7.5+ months
Pastorelli *et al.*, 2000[57] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2 i.v.) and 5-FU (600 mg/m^2 i.v.) days 1, 8 and 15, every 28 days	24 patients with advanced pancreatic cancer	24 (24 for toxicity and 22 for response)	Median survival = 7.5 months PR = 13% SD = 22.4%
Polyzos *et al.*, 2000[52] [Abstract only]	Phase II	Gemcitabine (750 mg/m^2) days 1 and 8, 5-FU (350 mg/m^2) days 1, 2, 3, 7 and 8, and leucovorin (350 mg/m^2) days 1, 2, 3, 7 and 8; 1 cycle every 4 weeks	40 patients with locally advanced or metastatic pancreatic cancer	40 (40)	1-year survival = 25% Median progression-free survival = 5 months Objective response rate = 20% SD = 38% PD = 43%
Riedel *et al.*, 2000[53] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) and 5-FU (2000 mg/m^2) weekly for 3 weeks then 1 week rest	15 patients with metastatic pancreatic cancer	15 (15)	1-year survival = 36% PR = 14% SD = 50% PD = 36%
Rodriguez-Lescure *et al.*, 1999[54] [Abstract only]	Phase I–II	Gemcitabine (800, 1000, 1200 and 1400 mg/m^2) and 5-FU (3 g/m^2) weekly for 3 weeks every 28 days	23 patients with pancreatic cancer	23 (21)	Median survival = 22 weeks CBR = 57% Median progression-free survival = 12 weeks PR = 3 patients CR = 1 patient SD = 33% Overall response rate = 19%
Shulman *et al.*, 2000[55] [Abstract only]	Phase II	Gemcitabine (600 mg/m^2) days 1, 8 and 15 and 5-FU (200 mg/m^2) daily for 21 days; 1 cycle every 28 days	15 patients with pathologically confirmed pancreatic cancer	15 (?)	Median survival = 8 months Median progression-free survival = 3 months PR = 13% SD = 40% PD = 40%

continued

TABLE 6 contd *Additional reports: gemcitabine and 5-FU*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Tarantini *et al.*, 1999[56] [Abstract only]	Phase I–II ongoing	A = gemcitabine (1000 mg/m^2) and 5-FU (1000 mg/m^2) days 1, 8 and 15, every 4 weeks B = gemcitabine (1000 mg/m^2) and 5-FU (2000 mg/m^2 24-h continuous infusion) days 1, 8 and 15 every 4 weeks C = gemcitabine (1200 mg/m^2) and 5-FU (2250 mg/m^2 i.v. 24-h continuous infusion) days 1, 8 and 15 every 4 weeks	17 patients with metastatic pancreatic cancer	17 (17 evaluable for toxicity and 14 for response)	CBR = 58.8% PR = 28.6%

TABLE 7 *Additional reports: gemcitabine and docetaxel*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Androulakis *et al.*, 1999[58] [Abstract only]	Multicentre Phase II	Gemcitabine (1000 mg/m^2) days 1 and 8, docetaxel (100 mg/m^2) day 8 and G-CSF (150 igr/m^2 s.c.) days 1–15; 1 cycle every 3 weeks	56 patients with locally advanced or metastatic pancreatic cancer	56 (43 for response and 56 for toxicity)	Median survival = 8 months 1-year survival = 32% Median progression-free survival = 3 months Time to treatment failure = 9 months
Cascinu *et al.*, 1999[59]	Phase I–II	A = (Phase I) gemcitabine (1000 mg/m^2) and docetaxel (70 mg/m^2); dose escalation of docetaxel if no dose limiting toxicities occurred in 1 of 3 or 2 of 6 patients B = (Phase II) gemcitabine (1000 mg/m^2 once weekly for 2 consecutive weeks every 3 weeks) and docetaxel (70 mg/m^2) once in week 2	27 patients with pathologically confirmed locally advanced, metastatic cancer	27 (27)	Median survival = 5.4 months Median progression-free survival = 3 months
Clark *et al.*, 2000[60] [Abstract only]	Phase II	Gemcitabine (600 mg/m^2) days 1, 8 and 15, and docetaxel (60 mg/m^2) day 1; 1 cycle every 28 days	34 patients with metastatic pancreatic cancer	34 (24)	PR = 1 patient CR = 1 patient Objective response rate = 8%
Jacobs *et al.*, 2000[61] [Abstract only]	Phase I–II	A = gemcitabine (800 mg/m^2) days 1, 8 and 15 and docetaxel (75 mg/m^2) day 1; 1 cycle every 28 days B = gemcitabine (1000 mg/m^2) days 1 and 8 or docetaxel (40 mg/m^2) days 1 and 8; 1 cycle every 21 days	29 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	29 (25)	Median survival = not yet reached Time to treatment failure = 5.25 months PR = 28% MR or SD = 40%
Kakolyris *et al.*, 1999[62] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) days 1 and 8, docetaxel (100 mg/m^2) day 8, every 3 weeks and rhG-CSF (150 igr/m^2 d_9–d_{15})	38 patients with pancreatic cancer	38 (38 for toxicity and 27 for response)	Median survival = 7 months 1-year survival = 22% Time to progression = 7 months PR = 7.4% SD = 33.3% PD = 59%

G-CSF, granulocyte-colony stimulating factor; rhG-CSF, recombinant human granulocyte-colony stimulating factor

TABLE 8 *Additional reports: gemcitabine and platinum compounds*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Colucci *et al.*, 1998[63] [Abstract only]	Randomised Phase II	A = gemcitabine (1000 mg/m^2) weekly for 7 weeks out of 8 and then weekly for 3 weeks out of every 4 B = gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) weekly for 7 weeks out of 8, and then weekly for 3 weeks out of every 4	103 patients with advanced pancreatic cancer	A = 51 (30) B = 52 (32)	***CBR (%)*** A = 45 (10/22) B = 38 (9/24) ***Overall response rate (%)*** A = 10 B = 31
Heinemann *et al.*, 1997[64] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) days 1, 8 and 15, and cisplatin (50 mg/m^2) days 1 and 15; 1 cycle every 28 days	41 patients with locally advanced or metastatic pancreatic cancer	41 (37)	Median survival = 8.6 months PR = 2 patients CR = 1 patient SD = 18 patients
Heinemann *et al.*, 1999[65] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) days 1 and 15, and cisplatin (50 mg/m^2) days 1 and 15	41 patients with locally advanced or metastatic pancreatic cancer	41 (35)	Median survival = 8.3 months 1-year survival = 28% Median progression-free survival = 4.3 months PR = 3 patients CR = 1 patient SD = 6 patients Overall response rate = 11.5%
Philip *et al.*, 1999[66] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) days 1, 8 and 15, and cisplatin (50 mg/m^2) days 1 and 15; 1 cycle every 28 days	27 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer	27 (22 evaluable for response; 26 for toxicity)	Median survival = 7.4 months Median progression-free survival = 6.2 months PR = 6 patients CR = 2 patients Overall response rate = 36.4%

TABLE 9 *Additional reports: gemcitabine and MMC*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Bazin *et al.*, 1999[67] [Abstract only]	Phase I–II	A = gemcitabine (1000 mg/m^2) days 1, 8 and 15, and MMC (5–10 mg/m^2) day 1, with a 2-week rest between cycles B = gemcitabine (1000 mg/m^2) days 1, 8, 21 and 29, and MMC (8 mg/m^2) day 1, with a 2-week rest between cycles	25 patients with pancreatic cancer	25 (23 for toxicity and 21 for efficacy)	CBR = 60% Objective response rate = 38%
Klapdor *et al.*, 1999[68]	Phase II	MMC (10–15 mg/m^2) day 1 and gemcitabine (800 mg/m^2) days 1, 8 and 15; 1 cycle every 3 weeks	28 patients with locally advanced, metastatic or relapsed pancreatic cancer	28 (28)	Median survival = 9 months Median progression-free survival = 7.5 months PR = 43% CR = 3% SD = 11% PD = 18%

TABLE 10 *Additional reports: gemcitabine and other chemotherapy combinations*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
De Castro *et al.*, 2000[69] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) days 1, 8 and 15, leucovorin (250 mg/m^2 i.v.) day 1, oral (leucovorin (7.5 mg/12 h) days 2–14, and UFT (390 mg/m^2) in 2 doses days 1–14; 1 course every 28 days, minimum 3 courses	42 patients with locally advanced, or metastatic pancreatic cancer	42 (38)	CBR = 47% PR = 16% SD = 39% PD = 45%

continued

TABLE 10 contd *Additional reports: gemcitabine and other chemotherapy combinations*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Feliu *et al.,* 1999[70] [Abstract only]	Phase II ongoing	Gemcitabine (1500 mg/m^2) days 1 and 14, i.v. leucovorin (250 mg/m^2 i.v.) day 1, oral leucovorin every 12 h days 2–15, and UFT (390 mg/m^2 per day days 1–14; 1 cycle every 28 days, minimum 3 cycles	25 patients with locally advanced or metastatic pancreatic cancer	25 (22)	Median survival = 8 months CBR = 59% Time to treatment failure = 6 months PR = 14% SD = 54% PD = 32%
Jacobs *et al.,* 1999[71] [Abstract only]	Phase II	Gemcitabine (800 mg/m^2) days 1, 8 and 15, and taxotere (75 mg/m^2) day 1	12 patients with pathologically confirmed locally advanced or metastatic pancreatic cancer)	12 (9)	Median progression-free survival = 2 months PR = 3 patients (33%) SD = 2 patients (22%)
Raderer *et al.,* 1998[72] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) days 1, 8 and 15, epirubicin (60 mg/m^2) day 1, and G-CSF (5 μg/kg per day s.c.) days 2–6; 1 course every 5 weeks	55 patients with pancreatic cancer	55 (47)	CBR = 40% Time to treatment failure = 3.6 months SD = 40% Objective response rate = 19%
Reni *et al.,* 1999[73] [Abstract only]	4 consecutive prospective clinical trials	A = 5-FU (600 mg/m^2) days 1, 8, 29 and 36, adriamycin (30 mg/m^2) days 1 and 29, and MMC (10 mg/m^2) day 1 B = epirubicin (50 mg/m^2) day 1, and 5-FU (1 g/m^2) days 1–5 C = as B but with cisplatin (50 mg/m^2) day 1 D = cisplatin 40 mg/m^2 and epirubicin (40 mg/m^2) day 1, 4-FU (200 mg/m^2) daily, and gemcitabine (600 mg/m^2) days 1–8	114 patients with pathologically confirmed metastatic pancreatic cancer	A = 22 (22) B = 44 (44) C = 22 (22) D = 29 (29)	***Median survival (months)*** A = 5 B = 5 C = 7 D = 6.5+ ***1-year survival (%)*** A = 9 B = 9 C = 5 D = 27? ***6-Month progression-free survival (%)*** A = 5 B = 10 C = 29 D = 42? ***Time to treatment failure (months)*** A = 2 B = 2.5 C = 2.5 D = 5 ***PR (%)*** A = 9 B = 2.5 C = 13.5 D = 62
Stathopoulos *et al.,* 2000[74] [Abstract only]	Phase II	Gemcitabine (900 mg/m^2) days 1 and 8, and irinotecan (300 mg/m^2) day 8; every 3 weeks	28 patients with pancreatic cancer	28 (28 evaluable for toxicity; 20 for response)	Median survival not yet reached Time to treatment failure = 30 weeks
Villa and Reni 1999[75] [Abstract only]	Phase II study	Cisplatin (40 mg/m^2) day 1, epirubicin (40 mg/m^2) day 1, and gemcitabine (600 mg/m^2) days 1 and 8, every 4 weeks; and 5-FU (200 mg/m^2 per day) daily	49 patients with metastatic pancreatic cancer	49 (43 for response; 22 for CBR)	1-year survival = 40% Median survival = 9.4 months PR = 89% MR = 8% PD = 9% SD = 14% CBR = 78%

UFT, uracil-tegafur

TABLE 11 *Additional reports: gemcitabine in chemoradiation*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Antonisse *et al.*, 1999[76] [Abstract only]	Phase II	Gemcitabine (300 mg/m^2 days 1, 8 and 15, and 1000 mg/m^2 weekly from day 22), and RT to the macroscopic tumour in 3 fractions on days 1, 8 and 15	21 patients with pancreatic cancer	21 (21)	Median survival = 16.2 months Reduction in CA19.9 = 82% Palliation of pain = 72% Reduction in analgesic consumption = 73%
Epelbaum *et al.*, 2000[77] [Abstract only]	Phase II	Gemcitabine (1000 mg/m^2) once weekly for 7 weeks; those who demonstrated a CBR went on to gemcitabine (400 mg/m^2) weekly for 3 weeks every 28 days for 2 cycles delivered concurrently with 50.4 Gy RT in 1.8 Gy daily fractions; gemcitabine re-escalated to 1000 mg/m^2 after RT as maintenance therapy	20 patients with locally advanced pancreatic cancer	20 (20)	Median survival = 12 months CBR = 10 (50%) PR = 20%
Reyes-Vidal *et al.*, 2000[78] [Abstract only]	Phase II	Gemcitabine (200, 225, 300 and 325 mg/m^2) for 5 weeks 4–8 hours prior to RT; RT (4500 cGy) through 3 fields in 25 fractions over 5 weeks	14 patients with pancreatic cancer	14 (14)	PR = 6 patients CR = 2 patients SD = 6 patients
Wilkowski *et al.*, 2000[79] [Abstract only]	Phase II	Gemcitabine (300 mg/m^2) on RT days 1, 15 and 29, 5-FU (350 mg/m^2) on each RT day; and RT in 1.8 Gy fractions up to 45 Gy	13 patients with locally advanced or relapsed pancreatic cancer	13	Surgery offered subsequently to 5 patients and 4 achieved a complete resection CA19.9 levels declined in 77% Downstaging in 7/10 primarily unresectable patients

RT, radiotherapy

TABLE 12 *Additional reports: gemcitabine and hormonal treatment*

Reference	Study type	Interventions	Participants	No. entered (evaluated)	Results
Caillouette *et al.*, 1999[80] [Abstract only]	Phase I–II	SMSpaLAR (160 mg i.m.) every 2 weeks for 4 injections and then monthly, and gemcitabine (1000 mg/m^2 i.v.) weekly for 3 weeks and then 1 week rest	19 patients with locally advanced or metastatic pancreatic cancer	19 (14)	Median survival = 18 weeks PR = 1 patient
Tomao *et al.*, 1998[81] [Abstract only]	Phase II	Gemcitabine (dosage not stated but administered once a week for 7 weeks then 1 week rest), and tamoxifen (daily continuously)	17 patients with metastatic pancreatic cancer	17 (17)	CBR = 8 patients PR = 1 patient SD = 9 patients

SMSpaLAR, somatostatin analogue octreotide

TABLE 13 *Gemcitabine as an adjuvant treatment (RCT)*

Reference	No. entered (evaluated)	Median survival (months)	CR (%)
Lygidakis *et al.*, 1998[19]	512 (512)	14 32 6.8 16	
Lygidakis *et al.*, 1998[20]	26 (26)		78 25

TABLE 14 *Gemcitabine as a single agent therapy (RCT)*

Reference	No. entered (evaluated)	Median survival (months)	1-year survival (%)	Median progression-free survival (months)	PR (%)	CBR (%)
Burris *et al.*, 1998[13]	126 (126)	5.65 4.41	18 2	2.33 0.92	5.4 0.0	23.8 4.8
Moore *et al.*, 2000[22] [Abstract only]	277 (277)	6.4 3.2		3.54 1.77		
Rosemurgy *et al.*, 1999[21] [Abstract; British Biotech press release only]	414 (414)					
British Biotech 2000[17] [Press release only]	239 (239)					

TABLE 15 *Additional reports: gemcitabine alone as a single agent therapy*

Reference	No. entered (evaluated)	Median survival (months)	1-year survival (%)	Median progression-free survival (months)	PR (%)	CR (%)	SD (%)	PD (%)	Objective/ overall response rate (%)	CBR (%)
Aykan *et al.*, 2000[23] [Abstract only]	14 (14)	6			7	7			14	
Carmichael *et al.*, 1996[37]	34 (32)	6.3								
Casper *et al.*, 1994[24]	44 (44)	5.6	23	4					11	
Casper *et al.*, 1991[25] [Abstract only]	43 (39)				13		38			
Crino *et al.*, 1997[26] [Abstract only]	24 (24)				16		41	41		
Eickhoff *et al.*, 2000[39] [Abstract only]	65 (65; 60 CBR)				5	1			21	
Klein *et al.*, 2000[38]	82 ([a])		23						9	48
Kurtz *et al.*, 1999[27]	74 ([a])			2.5	8		75		12	48
Petrovic *et al.*, 1998[28] [Abstract only]	54 (11)	6.65	26							33
Rothenberg *et al.*, 1996[29]	74 (63 CBR; 54 response)	4	4		11		30			27
Roznowski and Ramalu, 1999[30] [English abstract only]	12 (12)	5.25			10		50			
Scheithauer *et al.*, 1999[31] [Abstract only]	38 (28)	>6.5		4.5					28	35
Spagnuolo *et al.*, 1999[32] [Abstract only]	10 (10)				20					70
Storniolo *et al.*, 1999[33]	3023 ([a])	4.8	15	2.7	10.6	1.4			12	
Tempero *et al.*, 1999[34] [Abstract only]	93 (67)	4.7 6.1	0 23						2.7 16.6	
Ulrich-Pur *et al.*, 1999[35]	43 (43; 36 CBR)	8.8	26.3	5.3	18.6	2.3	42		21	44
Weissman and Ludwig, [Abstract only] 1999[36]	15 (15)	5.5				13	27			

[a] *No. evaluated varies according to outcome*

TABLE 16 *Additional reports: gemcitabine and 5-FU*

Reference	No. entered (evaluated)	Median survival (months)	1-year survival (%)	Median progression-free survival (months)	PR (%)	CR (%)	SD (%)	PD (%)	Objective/ overall response rate (%)	CBR (%)
Anchisi *et al.*, 2000[40] [Abstract only]	19 (17)	5.25			25		25		31	
Berlin *et al.*, 2000[41]	37 (36)	4.4			14					
Borner *et al.*, 1998[42] [Abstract only]	14 (12)				25		33	17		
Cascinu *et al.*, 1999[43]	54 (54)	7			4		63			51
Cortes-Funes *et al.*, 1998[44] [Abstract only]	26 (24; 20 CBR)				13	4			16	55
De Gusmao *et al.*, 1998[45] [Abstract only]	14 (14)	13							50	
Hidalgo *et al.*, 1999[46]	26 (26; 22 CBR)		39.5	7.4	15	4				45
Jovtis *et al.*, 1999[47] [Abstract only]	18 (18)	11			22		61			
Lencioni *et al.*, 2000[48] [Abstract only]	22 (21; 16 CBR)				5		52			56
Louvet *et al.*, 1999[49] [Abstract only]	48 (48)		38	4.5						
Matano *et al.*, 2000[50]	11 (11)			26.8						64
Oettle *et al.*, 1999[51] [Abstract only]	17 (17)			>7.5						
Pastorelli *et al.*, 2000[57] [Abstract only]	24 (22)	7.5			13		22.4			
Polyzos *et al.*, 2000[52]	40 (40)		25	5			38	43	20	
Riedel *et al.*, 2000[53] [Abstract only]	15 (15)		36		14		50	36		
Rodriguez-Lescure *et al.*, 1999[54] [Abstract only]	23 (21)	5.5		3	14	5	33		19	57
Shulman *et al.*, 2000[55] [Abstract only]	15 (?)	8		3	13		40	40		
Tarantini *et al.*, 1999[56] [Abstract only]	17 (14)				29					59

TABLE 17 *Additional reports: gemcitabine and docetaxel*

Reference	No. entered (evaluated)	Median survival (months)	1-year survival (%)	Median progression-free survival (months)	PR (%)	CR (%)	SD (%)	Objective/ overall response rate (%)
Androulakis *et al.*, 1999[58] [Abstract only]	56 (43)	8	32	3				
Cascinu *et al.*, 1999[59]	27 (27)	5.4		3				
Clark *et al.*, 2000[60] [Abstract only]	34 (24)				4	4		8
Jacobs *et al.*, 2000[61] [Abstract only]	29 (25)				28		40	
Kakolyris *et al.*, 1999[62] [Abstract only]	38 (27)	7	22					

TABLE 18 *Additional reports: gemcitabine and platinum compounds*

Reference	No. entered (evaluated)	Median survival (months)	1-year survival (%)	Median progression-free survival (months)	PR (%)	CR (%)	SD (%)	Objective/ overall response rate (%)	CBR (%)
Colucci *et al.*, 1999[63] [Abstract only]	103 (A = 30; B = 32)							A = 10 B = 31	A = 45 B = 38
Heinemann *et al.*, 1997[64] [Abstract only]	41 (37)	8.6			5	3	49		
Heinemann *et al.*, 1999[65] [Abstract only]	41 (35)	8.3	28	4.3	9	3	17	11.5	
Philip *et al.*, 1999[66] [Abstract only]	27 (22)	7.4		6.2	27	9		36.4	

TABLE 19 *Additional reports: gemcitabine and MMC*

Reference	No. entered (evaluated)	Median survival (months)	Median progression-free survival (months)	PR (%)	CR (%)	SD (%)	PD (%)	Objective/ overall response rate (%)	CBR (%)
Bazin *et al.*, 1999[67] [Abstract only]	25 (21)							38	60
Klapdor *et al.*, 1999[68] [Abstract only]	28 (28)	9	7.5	43	3	11	18		

TABLE 20 *Additional reports: gemcitabine and other chemotherapy combinations*

Reference	No. entered (evaluated)	Median survival (months)	1-year survival (%)	Median progression-free survival (months)	PR (%)	SD (%)	PD (%)	Objective/ overall response rate (%)	CBR (%)
de Castro *et al.*, 2000[69] [Abstract only]	42 (38)				16	39	45		47
Feliu *et al.*, 1999[70] [Abstract only]	25 (22)	8			14	54	32		59
Jacobs *et al.*, 1999[71] [Abstract only]	12 (9)	2			33	22			
Raderer *et al.*, 1998[72] [Abstract only]	55 (47)					40		19	40
Reni *et al.*, 1999[73] [Abstract only]	114 (114)	5 5 7 >6.5	9 9 9 27		9 2.5 13.5 62				
Stathopoulos *et al.*, 2000[74] [Abstract only]	28 (20)								
Villa and Reni, 1999[75] [Abstract only]	49 (43; 22 for CBR)	9.4	40	>9.4	89	14	9		78

TABLE 21 *Additional reports: gemcitabine in chemoradiation*

Reference	No. entered (evaluated)	Median survival (months)	PR (%)	CR (%)	SD (%)	CBR (%)
Antonisse *et al.*, 1999[76] [Abstract only]	21 (21)	16.2				
Epelbaum *et al.*, 2000[77] [Abstract only]	20 (20)	12	20			50
Reyes-Vidal *et al.*, 2000[78] [Abstract only]	14 (14)		43	14	43	
Wilkowski *et al.*, 2000[79] [Abstract only]	13					

TABLE 22 *Additional reports: gemcitabine and hormonal treatment*

Reference	No. entered (evaluated)	Median survival (months)	PR (%)	SD (%)	CBR (%)
Caillouette *et al.*, 1999[80] [Abstract only]	19 (14)	4.5	7		
Tomao *et al.*, 1998[81] [Abstract only]	17 (17)		6	53	47

Appendix 4

Tables 24–26

TABLE 24 *Ongoing studies: RCTs*

Title	Interventions	Expected accrual	Status
European study of pancreatic cancer – adjuvant chemotherapies in operable pancreatic cancer	A = 5-FU/FA B = gemcitabine C = surgery alone	990	Open
Phase III study of adjuvant fluorouracil chemoradiation preceded and followed by fluorouracil or gemcitabine in patients with resected pancreatic adenocarcinoma	A = chemoradiation + 5-FU B = chemoradiation and gemcitabine	330	Open
Phase III randomised study of gemcitabine with or without 5-FU in patients with advanced pancreatic adenocarcinoma	A = gemcitabine B = gemcitabine + 5-FU	320	Closed
Phase III randomised study of weekly intravenous P-30 protein plus daily oral tamoxifen vs. weekly intravenous gemcitabine for advanced pancreatic cancer	A = gemcitabine B = tamoxifen, P-30 protein	150	Closed
Randomised, double blind, placebo controlled multicentre study of CI-994 capsules plus gemcitabine infusion versus placebo capsules plus gemcitabine infusion in the treatment of patients with advanced pancreatic cancer	A = gemcitabine + CI994 capsules B = gemcitabine + placebo capsules	172	Open
Phase III randomised study of gemcitabine with or without R115777 in patients with advanced pancreatic cancer	A = gemcitabine B = gemcitabine + R115777	660	Open
Phase III randomised study of oral nitrocamptothecin versus gemcitabine in chemotherapy naive patients with unresectable locally advanced or metastatic adenocarcinoma of the pancreas	A = oral nitrocamptothecin B = gemcitabine	994	Open
Phase III randomised study of oral nitrocamptothecin versus most appropriate chemotherapy in patients with recurrent or refractory adenocarcinoma of the pancreas	A = oral nitrocamptothecin B = other chemotherapy	400	Open
Phase III study of gemcitabine versus intensive pancreatic proteolytic enzyme therapy with ancillary nutritional support in patients with Stage II, III or IV adenocarcinoma of the pancreas	A = gemcitabine B = pancreatic proteolytic enzyme therapy	72–90	Open
93311L/0008	A = ZD9331 B = gemcitabine	300	Open
EMD 121974-004	A = gemcitabine + EMD 121974 B = gemcitabine	60	Open

TABLE 25 *Ongoing studies: Phase II*

Title	Interventions	Expected accrual	Status
Phase I/II study of concurrent prolonged gemcitabine infusion and external beam radiation for the treatment of locally advanced pancreatic cancer	Gemcitabine and dose-escalation RT	12–24	Closed
Phase II randomised study of gemcitabine vs. immunotherapy with cytoimplant as first line therapy in patients with unresectable, locally advanced or metastatic pancreatic cancer	A = gemcitabine B = cytoimplant	150	Closed
Phase II randomised study of SCH 66336 versus gemcitabine in patients with metastatic adenocarcinoma of the pancreas	A = gemcitabine B = SCH 66336	60	Closed

continued

TABLE 25 contd *Ongoing studies: Phase II*

Title	Interventions	Expected accrual	Status
Phase II study of cetuximab and gemcitabine in patients with locally advanced, metastatic or recurrent adenocarcinoma of the pancreas	Cetuximab and gemcitabine	40	Closed
Phase II study of 5-FU, LV calcium and gemcitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma	5-FU, leucovorin and gemcitabine	14–80	Closed
Phase II study of gemcitabine and docetaxel in patients with locally advanced or metastatic adenocarcinoma of the pancreas	Gemcitabine and docetaxel	33	Closed
Phase II study of gemcitabine and doxorubicin in patients with recurrent or refractory pancreatic cancer	Gemcitabine and doxorubicin	14–40	Closed
Phase II study of gemcitabine combined with radiation therapy in patients with locoregional adenocarcinoma of the pancreas	Gemcitabine and RT	40	Closed
Phase I/II study of gemcitabine and cisplatin followed by combined chemoradiation and/or surgical resection in patients with locally advanced pancreatic cancer	Gemcitabine and CDDP	Phase I = 15–36 Phase II = 14–25	Open
Phase I/II study of gemcitabine plus oxaliplatin in patients with refractory locally advanced or metastatic pancreatic carcinoma	Gemcitabine and oxaliplatin	20–40	Open
Phase II randomised study of docetaxel and gemcitabine versus docetaxel and cisplatin in metastatic or locoregionally advanced pancreatic carcinoma	A = docetaxel B = gemcitabine plus docetaxel	82	Open
Phase II study of gemcitabine and oxilaplatin in patients with locally advanced or metastatic pancreatic carcinoma	Gemcitabine and oxaliplatin	66	Open
Phase II study of gemcitabine and trastuzumab (herceptin) in patients with metastatic pancreatic cancer and overexpression of HER2-Neuq	Gemcitabine and trastuzumab	41	Open
Phase II study of gemcitabine, cisplatin and fluorouracil in patients with unresectable Stage III or IV pancreatic adenocarcinoma	Gemcitabine, CDDP and 5-FU	30	Open
A Phase II randomised study of an investigation of new medication vs. intravenous 5-FU in patients with pancreatic cancer whose disease has progressed following treatment with gemcitabine HCl treatment	A = oral investigational medication B = 5-FU	NS	NS
A Phase II randomised study comparing the safety and efficacy of avicine to avicine administered with gemcitabine in patients with pancreatic cancer	A = avicine B = avicine + gemcitabine	NS	NS
Gemcitabine and tomudex treatment in pancreatic cancer	Gemcitabine and tomudex	40	Open
Phase I/II study to investigate the use of gemcitabine in combination with raltitrexed in locally advanced metastatic adenocarcinoma of the pancreas	Gemcitabine and raltitrexed	30	Open
A Phase I/II study of gemcitabine and escalating doses of cisplatin in patients with inoperable pancreatic carcinoma	Gemcitabine and CDDP	44	Open
A randomised Phase II trial of neoadjuvant therapy for patients with resectable pancreatic cancer; gemcitabine alone versus gemcitabine combined with cisplatin versus gemcitabine with radiotherapy	A = gemcitabine B = gemcitabine + CDDP C = gemcitabine + RT	NS	Open
Phase II study to evaluate the feasibility and efficacy of combining gemcitabine with flutamide in advanced pancreatic cancer	Gemcitabine and flutamide	14–25	Open
A Phase II randomised open-label study of SCH 66336 and an active reference agent gemcitabine in patients with adenocarcinoma of the pancreas	SCH 66336 and gemcitabine	30	Open
A Phase II trial of gemcitabine, herceptin and radiation for regionally confined adenocarcinoma of the pancreas	Gemcitabine and herceptin	NS	Open

CDDP, cisplatin; NS, not stated

TABLE 26 *Ongoing studies: design unclear from details available*

Title	Interventions	Expected accrual	Status
Combination therapy in the treatment of patients with advanced pancreatic cancer	A = gemcitabine B = gemcitabine + investigational oral medication	NS	NS
Study for patients with a histologic diagnosis of pancreatic cancer	A = drug/gemcitabine B = drug/placebo	NS	NS
Investigation medication for the treatment of advanced pancreatic cancer	A = drug/gemcitabine B = gemcitabine	NS	NS

Appendix 5

Derivation of area under the curve

Calculation of survival gains as the area between the curves

The area under a survival curve indicates the overall survival time experienced by the cohort. Therefore, the area between the gemcitabine and 5-FU curves indicates the difference in survival experienced by the two groups (*Figure 4*). To calculate the area accurately, data points needed to be extrapolated from the graphs. The Kaplan–Meier product-limit estimator was used to estimate the mean (*Figure 5*); this was then verified by using the trapezoidal rule (*Figure 6*) to define errors.

In the first method, the mean survival time is calculated by multiplying the difference in each time step by the proportion of patients still alive. Data points are extrapolated at each step.

In the second method, data points are extrapolated from the graph at very small time steps. The area is then calculated using the trapezoidal rule, a simple numerical integration technique.

These methods were used to calculate the difference in mean overall survival (months) and mean time to progression (months) for the gemcitabine and 5-FU curves. The results, compared with the median values from the Burris trial,[13] are given in *Tables 31* and *32*.

Inter-rater reliability was within 1%, with no difference according to the method used. Although simple, these methods give a better indication of the difference in the survival experience of the two groups than a measure of the proportion surviving to a given point or the median survival time.

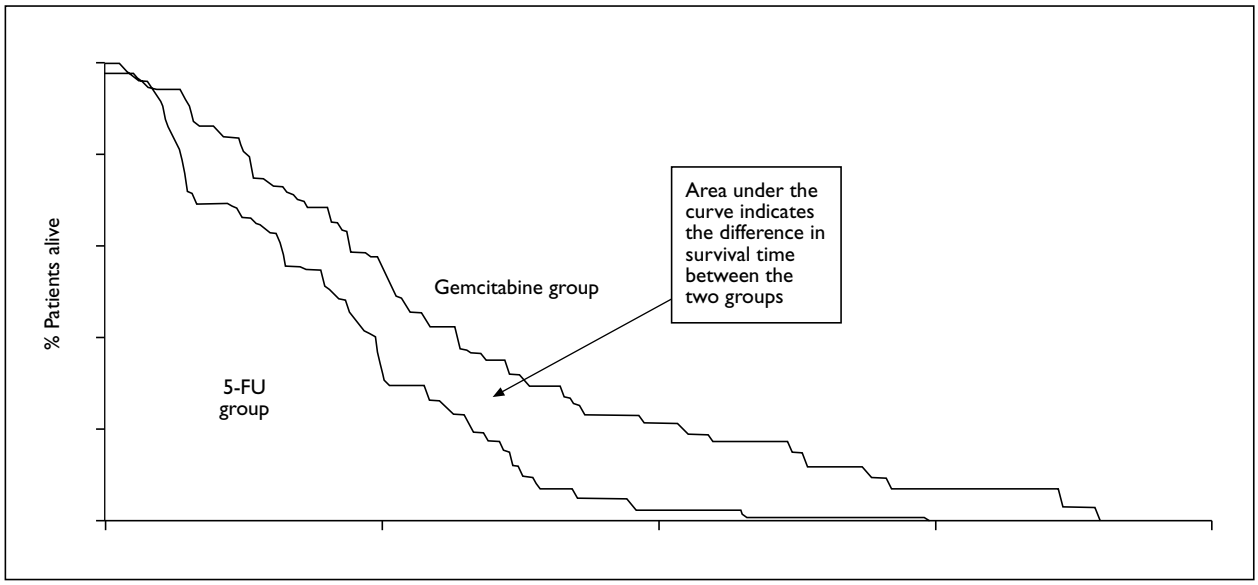

FIGURE 4 *Area under the curve*

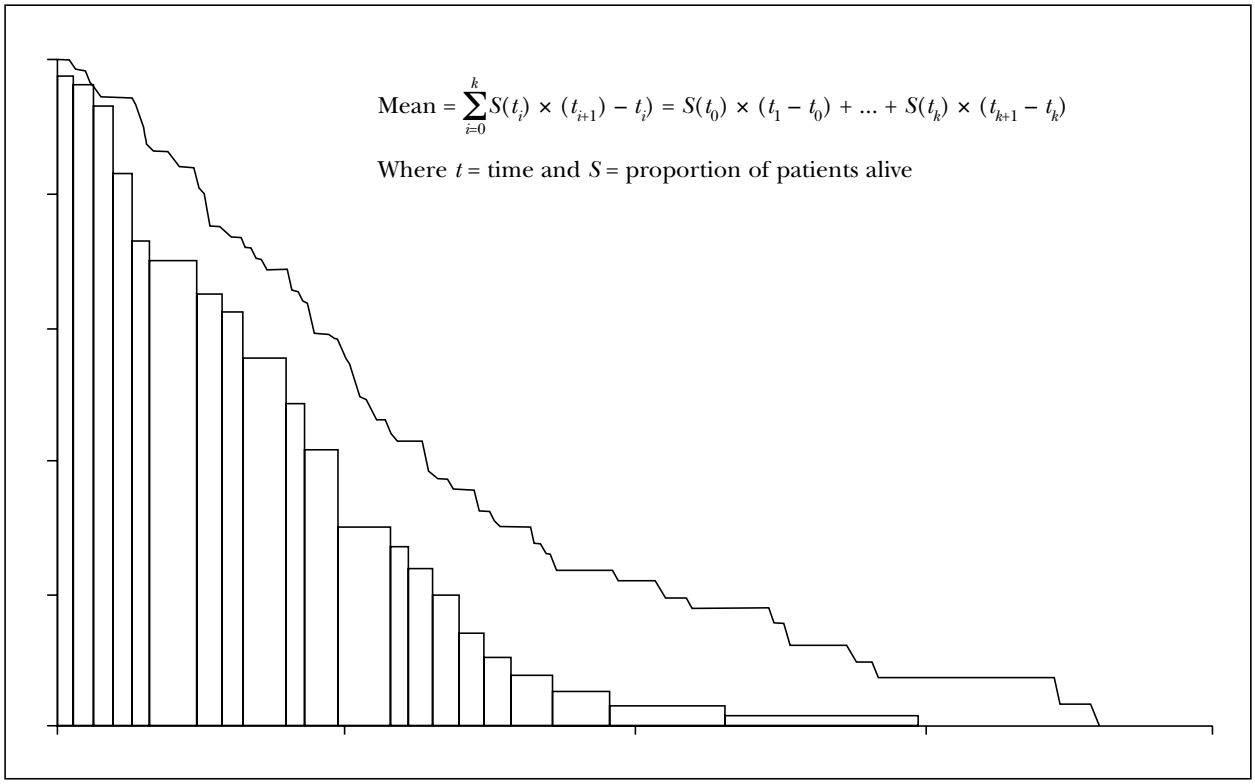

FIGURE 5 *Kaplan–Meier product limit estimator*

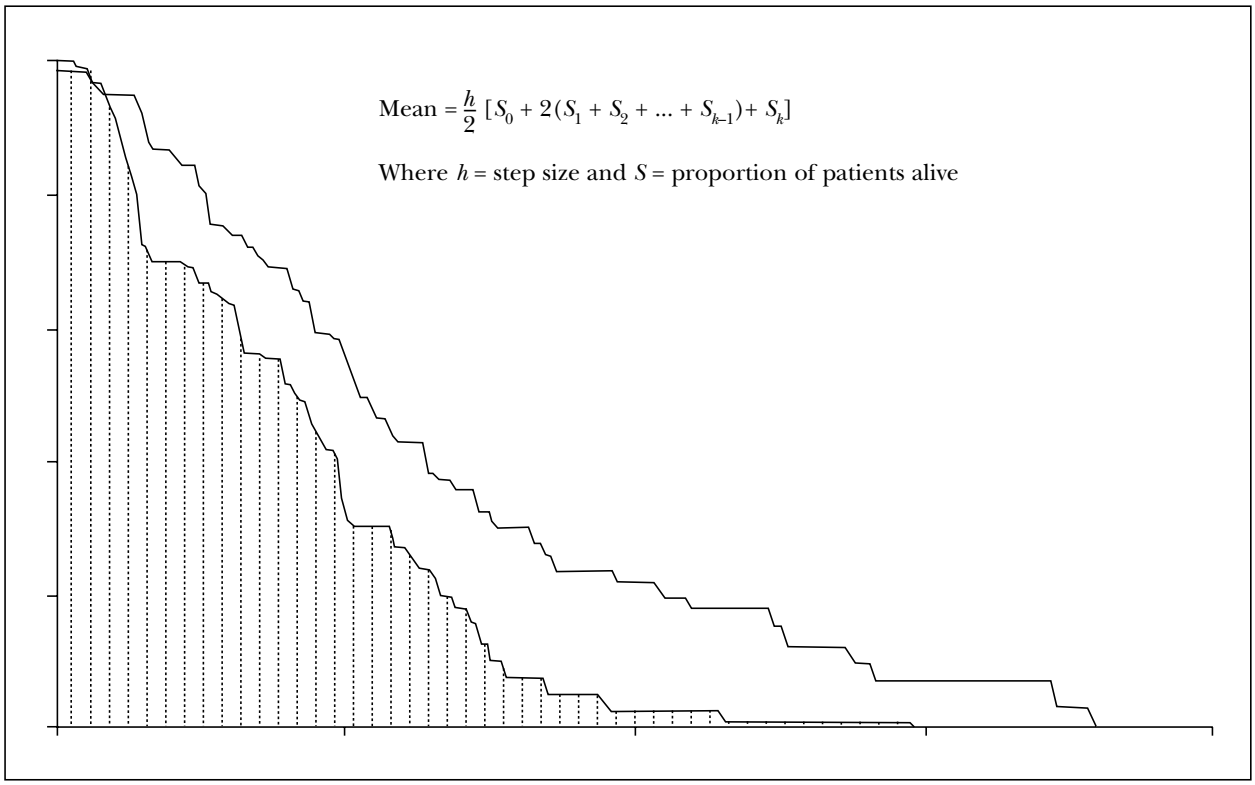

FIGURE 6 *Trapezoidal rule*

TABLE 31 *Mean overall survival (months) for gemcitabine and 5-FU calculated by Kaplan–Meier and trapezoidal methods*

	Method 1: Kaplan–Meier	**Method 2: trapezoidal**	**Burris *et al.*, 1997[13] (median)**
Gemcitabine	6.734	6.744	5.650
5-FU	4.345	4.351	4.410

TABLE 32 *Mean time to progression (months) for gemcitabine and 5-FU calculated by Kaplan–Meier and trapezoidal methods*

	Method 1: Kaplan–Meier	**Method 2: trapezoidal**	**Burris *et al.*, 1997[13] (median)**
Gemcitabine	3.930	3.930	2.330
5-FU	2.083	2.099	0.920

Appendix 6

Use of Q-TWiST analysis

Q-TWiST methodology

The Q-TWiST method is a technique that has been used frequently for evaluating survival in terms of both duration and quality of life, particularly in oncology. The method divides overall survival into different health states. The components normally used are: (1) survival time without symptoms and without toxicity, denoted as TWiST; (2) survival time with treatment-induced toxicity, denoted as TOX; and (3) survival after relapse, denoted as REL. Therefore, overall survival = TWiST + TOX + REL.

If QoL has not been recorded in the trial, then the TWiST component is usually characterised by a normal level of QoL, or a utility score equal to 1. Both TOX and REL correspond to a compromised QoL and are therefore assigned a utility score equal to 0.5.

In the article by Burris and colleagues,[13] the data did not conform to the standard Q-TWiST health states, so alternative progressive health states were considered, which could be derived from the data and were also clinically meaningful. Overall survival graphs were given for patients receiving both drugs and also corresponding time to progression graphs. Within the article, clinical benefit was reported as another end-point, stating the percentage of patients achieving clinical benefit and its median duration for patients in both arms of the trial.

This gives three health states:
A: time in clinical benefit
B: time to disease progression when not in clinical benefit
C: time from disease progression to death.

The three health states for the gemcitabine arm are shown in *Figure 7* and those for the 5-FU arm in *Figure 8*.

Sensitivity analysis

Below are a series of scenarios relating to *Table 33* when the utility scores for the different health states are varied across feasible ranges.

- Scenario 1 is the default scenario.
- Scenario 2 shows the difference when the QoL is reduced at the time when the patient is experiencing clinical benefit (A).
- Scenarios 3–6 show the effect of increasing and decreasing the utility scores for time to progression when not in clinical benefit (B) and the time from disease progression to death (C).
- Scenarios 7–11 show variations in combinations of health state utility scores.
- Scenarios 12–15 show variations in utility scores between the different drug regimens.

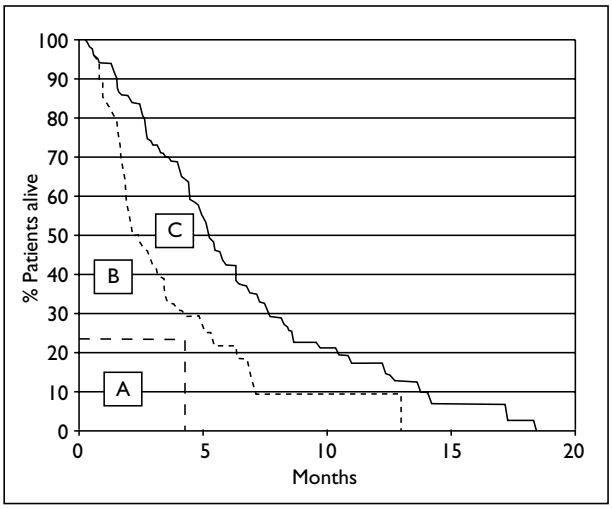

FIGURE 7 *The 3 health states in the gemcitabine arm (—, gemcitabine survival; - - -, gemcitabine time to PD; – –, CBR)*

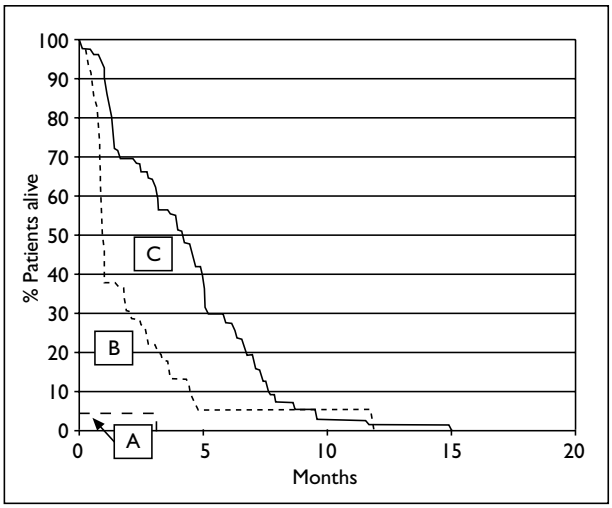

FIGURE 8 *The 3 health states in the 5-FU arm (—, 5-FU survival; - - -, 5-FU time to PD; – –, CBR)*

TABLE 33 *Sensitivity analysis*

Scenario	Time in clinical benefit	Time to disease progression when not in clinical benefit	Time from disease progression to death	QALY gained	Cost per QALY (£)
1	1.0	0.5	0.5	0.148	21,088
2	0.7	0.5	0.5	0.116	26,952
3	1.0	0.7	0.5	0.150	20,804
4	1.0	0.3	0.5	0.146	21,379
5	1.0	0.5	0.6	0.155	20,119
6	1.0	0.5	0.1	0.120	26,115
7	1.0	0.7	0.6	0.157	19,861
8	1.0	0.7	0.1	0.122	25,682
9	1.0	0.3	0.6	0.153	20,384
10	1.0	0.3	0.1	0.118	26,563
11	0.7	0.3	0.1	0.085	36,593
12				0.196	15,960
Gemcitabine	1.0	0.7	0.5		
5-FU	1.0	0.7	0.5		
13				0.103	30,460
Gemcitabine	1.0	0.5	0.5		
5-FU	1.0	0.5	0.5		
14				0.194	16,126
Gemcitabine	1.0	0.5	0.5		
5-FU	1.0	0.3	0.5		
15				0.101	31,071
Gemcitabine	1.0	0.3	0.5		
5-FU	1.0	0.5	0.5		

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We look forward to hearing from you.

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