NHS England

Evidence review: Gemcitabine plus capecitabine for adjuvant treatment in resected pancreatic cancer

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Prepared by: The NICE Medicines and Technologies Programme on behalf of NHS England Specialised Commissioning

The content of this evidence review was up-to-date in December 2017. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information

Key points

The prognosis for people with pancreatic cancer is poor, with average life expectancy on diagnosis just 4–6 months, a relative survival to 1 year of approximately 20%, and only 3% of people surviving for 5 years or longer. Because of the difficulty in getting an early diagnosis, only 4–10% of people with pancreatic cancer are eligible for potentially curative surgery. People who are able to have surgery to remove the tumour (resection) and then be given adjuvant chemotherapy, have up to a 30% chance of surviving for 5 years (NICE guideline final scope: Pancreatic cancer diagnosis and management in adults). A NICE guideline on pancreatic cancer diagnosis and management is in development, with an expected publication date of January 2018.

This evidence review looks at the efficacy and safety of gemcitabine and capecitabine for treating people who have had potentially curative surgery for pancreatic cancer. It is based on 1 open label randomised controlled trial that compared adjuvant treatment with gemcitabine plus capecitabine with gemcitabine alone in people who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resections in which no or only very few residual tumour cells are left). Although the study was generally well-conducted, it was open label and participants and study investigators knew which treatment had been allocated, which is a source of bias. However, the primary outcome of overall survival is unlikely to be influenced by bias.

Neither gemcitabine nor capecitabine are licensed for adjuvant treatment in people who have had pancreatic cancer resection, either as monotherapy or in combination and their use for this indication is off-label.

The evidence review concludes that, over a median follow-up of 43.2 months, gemcitabine plus capecitabine increased median overall survival by 2.5 months (from 25.5 months to 28.0 months) compared with gemcitabine alone. Overall survival was defined as the time from randomisation until death from any cause. Median time from surgery to randomisation was 64 days. There was no difference between the 2 treatment groups for relapse-free survival time.

The benefits for overall survival with combination treatment were found to be greater in people who had R0 resections compared with R1 resections. In people who had R0 resections, gemcitabine plus capecitabine increased median overall survival by 11.6 months compared with gemcitabine alone (from 27.9 months to 39.5 months). In people who had R1 resections, there was a 0.7 month difference between the 2 treatment groups for median overall survival (23.0 months in the gemcitabine group compared with 23.7 months in the gemcitabine plus capecitabine group).

Compared with gemcitabine alone, estimated overall survival at 5 years was found to be 12.5% higher with gemcitabine plus capecitabine (16.3% compared with 28.8%).

These results are only estimates as not all people still alive at the end of the study would have had 5 years of follow-up. The study ran for approximately 7.5 years but participants could be recruited to the study at any time during the first 6 years.

There was no difference between the 2 groups for treatment-related serious adverse events, although the study did not report how these were defined. There were more grade 3-4 adverse events of diarrhoea, neutropenia and hand-foot syndrome with the gemcitabine plus capecitabine combination compared with gemcitabine alone. However, there were fewer grade 3-4 adverse events of infection and other infestations (adverse event category not defined in the paper) with the gemcitabine plus capecitabine combination compared with gemcitabine alone. There was no difference between the treatment groups in terms of quality of life.

The benefit of the increase in overall survival time seen with the gemcitabine plus capecitabine combination needs to be balanced against the potential risk of an increase in adverse events compared with gemcitabine alone.

Contents

1. Introduction

Background and current guidance

Pancreatic cancer is the fifth leading cause of cancer death in the UK. On average, 23 people die each day from the disease. The symptoms of pancreatic cancer are non-specific. One survey found that 40% of people diagnosed with pancreatic cancer in England had visited their GP 3 or more times before the diagnosis was made. Fifty per cent of people are diagnosed as an emergency in the A and E system. Even after diagnosis of pancreatic cancer there is evidence from the National Cancer Intelligence Network of wide variation in practice throughout England (NICE guideline final scope: Pancreatic cancer: diagnosis and management in adults).

Common presenting symptoms of pancreatic cancers include jaundice (for tumours occurring in the head of the pancreas), abdominal pain, weight loss, steatorrhoea, and new-onset diabetes (ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up 2015).

The UK has one of the worst pancreatic cancer survival rates in Europe, with average life expectancy on diagnosis just 4–6 months and a relative survival to 1 year of approximately 20%. Only 3% of people survive for 5 years or longer. This figure has not improved much in over 40 years, and the more recent effects of increased surgery and adjuvant chemotherapy on survival outcomes are not yet established. Because of late diagnosis only 4–10% of people with pancreatic cancer are eligible for potentially curative surgery. People who are able to have surgery to remove the tumour and be given adjuvant chemotherapy have up to a 30% chance of surviving 5 years (NICE Guideline final scope: Pancreatic cancer: diagnosis and management in adults).

The purpose of this evidence review is to assess the effectiveness and safety of using gemcitabine and capecitabine in combination as adjuvant therapy following potentially curative surgery for pancreatic cancer compared with gemcitabine alone. Neither gemcitabine nor capecitabine are licensed for adjuvant treatment in people who have had pancreatic cancer resection, either as monotherapy or in combination.

A NICE guideline on pancreatic cancer diagnosis and management is in development, with an expected publication date of 31 January 2018. This NICE guideline will include recommendations on adjuvant treatment for people who have had pancreatic cancer resection.

NICE have published a number of guidance's relating to pancreatic cancer.

Product overview

Mode of action

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of 5-fluorouracil (summary of product characteristics [SPC]: **Xeloda**).

Gemcitabine, is a pyrimidine antimetabolite, it is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The

cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP (SPC: **Gemzar**).

Regulatory status

Neither gemcitabine nor capecitabine are licensed for adjuvant treatment in people who have had pancreatic cancer resection, either as monotherapy or in combination. Therefore use of either gemcitabine alone or gemcitabine plus capecitabine for this indication would be off-label. In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the patient and whether using gemcitabine and capecitabine is suitable outside their authorised indications. Supporting information and advice is also available from the GMC.

There are a number of generic preparations available for gemcitabine solution or powder for solution for infusion as well as the brand Gemzar. There are also a number of generic formulations available for capecitabine oral tablets and the brand Xeloda. Gemcitabine (Gemzar) is licensed for the treatment of locally advanced or metastatic adenocarcinoma of the pancreas. It is also licensed for the treatment of several other types of cancer as specified and outlined in the SPC. Capecitabine (Xeloda) is not licensed for the treatment of any stage of pancreatic cancer.

For full details of the licensed indications for gemcitabine solution or powder for solution for infusion and capecitabine oral tablets see the SPCs.

Dosing information

For dosing information for the licensed indications of gemcitabine and capecitabine refer to the SPCs. The dosage regimens in the SPC differ depending on the licensed indication. The dosage regimens used in the study discussed in this evidence review differ from the dosage regimens in the SPCs for the licensed indications.

In the study discussed in this evidence review (an open label randomised controlled trial, Neoptolemos et al. 2017) the doses of gemcitabine and capecitabine used in the study were: gemcitabine intravenous infusion 1000 mg/m^2 once a week for 3 of every 4 weeks (1 cycle) for 6 cycles (24 weeks) and oral capecitabine 1660 mg/m^2 daily for 21 days followed by 7 days' rest (1 cycle) for 6 cycles (24 weeks). The total daily dose of capecitabine is given in 2 divided doses (Xeloda).

Cost

There are a variety of generic preparations of gemcitabine solution for infusion and powder for solution for infusion available. The costs for the least expensive preparations listed in the BNF include the following:

- gemcitabine 200 mg/5 ml concentrate for solution for infusion £6.40 for 1 vial
- gemcitabine 1 gram/25 ml concentrate for solution for infusion £13.09 for 1 vial
- gemcitabine 2 gram/50 ml concentrate for solution for infusion £26.86 for 1 vial

Costs provided exclude VAT (BNF, November 2017).

There are also a variety of generic preparations of capecitabine available. The costs for the least expensive preparations listed in the BNF include the following:

- capecitabine 150 mg tablets cost £10.40 for 60 tablets
- capecitabine 300 mg tablets cost £39.99 for 30 tablets
- capecitabine 500 mg tablets cost £52.00 for 120 tablets

Costs provided exclude VAT (BNF, November 2017).

2. Summary of results

This evidence review is based on 1 open label randomised controlled trial which compared adjuvant treatment with gemcitabine plus capecitabine with gemcitabine alone in 730 people who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resections). The main outcome of the study was overall survival, defined as the time from randomisation until death from any cause. Relapse-free survival, which was defined as the minimum time from randomisation to date of local tumour recurrence, lymph node spread, distant metastases or death from any cause, was a secondary outcome. Participants in the study were followed-up for a median of 43.2 months. The study included people with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). Although the study was generally well-conducted, it was open label and participants and study investigators knew which treatment had been allocated, which is a source of bias. However, the primary outcome of overall survival is unlikely to be influenced by bias.

Compared with gemcitabine alone there was a statistically significant increase of 2.5 months in the median overall survival time with gemcitabine plus capecitabine. The median overall survival time was 25.5 months in the gemcitabine group compared with 28.0 months in the gemcitabine plus capecitabine group.

Gemcitabine plus capecitabine had a statistically significant treatment effect on overall survival in people who had negative resection margins (R0 resections). In people who had positive resection margins (R1 resections) gemcitabine plus capecitabine had no statistically significant treatment effect on overall survival. However, the study was powered for the primary outcome of overall survival for the whole group; while the analysis of the R0 and R1 resection subgroups was pre-specified, caution should be exercised when interpreting the results of these individual subgroups. In this study, positive resection margins (R1) were defined as any tumour cell within 1 millimetre of any surface of the specimen.

In people who had R0 resections, gemcitabine plus capecitabine increased median overall survival by 11.6 months compared with gemcitabine alone (from 27.9 months to 39.5 months). In people who had R1 resections, there was a 0.7 month difference between the 2 treatment groups for median overall survival (23.0 months in the gemcitabine group compared with 23.7 months in the gemcitabine plus capecitabine group).

Compared with gemcitabine alone, estimated overall survival at 5 years was found to be 12.5% higher with gemcitabine plus capecitabine (16.3% compared with 28.8%). These results are only estimates as not all people still alive at the end of the study would have had

5 years of follow-up. The study ran for approximately 7.5 years but participants could be recruited to the study at any time during the first 6 years.

There was no statistically significant difference between gemcitabine plus capecitabine and gemcitabine alone for median relapse-free survival time. So although an increase in overall survival was seen, no difference was seen in how long it took for the pancreatic cancer to relapse or progress in the people who were still alive. The median relapse-free survival time was 13.1 months in the gemcitabine group compared with 13.9 months in the gemcitabine plus capecitabine group. Three-year relapse-free survival was 20.9% in the gemcitabine group compared with 23.8% in the gemcitabine plus capecitabine group and 5 year relapse-free survival was 11.9% in the gemcitabine group compared with 18.6% in the gemcitabine plus capecitabine group.

Fourteen percent of participants in the gemcitabine group and 22% of participants in the gemcitabine plus capecitabine group stopped treatment early due to side-effects. There was no statistical significant difference between gemcitabine plus capecitabine and gemcitabine alone for the percentage of participants who had at least 1 treatment-related serious adverse event (26% in the gemcitabine group compared with 24% in the gemcitabine plus capecitabine group), although the study did not report how it defined treatment-related serious adverse events.

Adverse events were graded according to the National Cancer Institute common toxicity criteria, version 4.03. This grades adverse events on a scale of 1 to 5 with 4 being the most serious adverse event and 5 being death. Grade 3–4 adverse events were reported by 54% of participants in the gemcitabine group compared with 63% of participants in the gemcitabine plus capecitabine group. There was a statistically significant higher percentage of participants who had grade 3–4 adverse events of diarrhoea, neutropenia and hand-foot syndrome in the gemcitabine plus capecitabine group compared with the gemcitabine group. There was a statistically significant lower percentage of participants who had grade 3–4 adverse events of infection and other infestations (adverse event category not defined in the paper) in the gemcitabine plus capecitabine group compared with the gemcitabine group:

- Diarrhoea: 2% in the gemcitabine group compared with 5% in the gemcitabine plus capecitabine group
- Neutropenia: 24% in the gemcitabine group compared with 38% in the gemcitabine plus capecitabine group
- Hand-foot syndrome: No participants in the gemcitabine group compared with 7% in the gemcitabine plus capecitabine group
- Infections and other infestations: 7% in the gemcitabine group compared with 3% in the gemcitabine plus capecitabine group.

The benefit of the increase in overall survival time seen with the gemcitabine plus capecitabine combination needs to be balanced against the potential risk of an increase in adverse events compared with gemcitabine alone.

3. Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England's Policy Working Group for the topic (see the

literature search terms section for more information). The research questions for this evidence review are:

1. What is the evidence for the **clinical effectiveness** of gemcitabine and capecitabine in combination compared with gemcitabine alone as an adjuvant treatment for individuals who have had potentially curative surgery for pancreatic cancer?
2. What is the evidence for the **safety** of gemcitabine and capecitabine in combination compared with gemcitabine alone as an adjuvant treatment for individuals who have had potentially curative surgery for pancreatic cancer?
3. What is the evidence on the **cost effectiveness** of using gemcitabine and capecitabine in combination compared with gemcitabine alone as an adjuvant treatment for individuals who have had potentially curative surgery for pancreatic cancer?

The searches for evidence were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The NICE evidence summary: process guide (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the grade of evidence section for more information).

4. Summary of included studies

The evidence review includes 1 open label randomised controlled trial (Neoptolemos et al. 2017), which compared adjuvant treatment (given within 12 weeks of surgery) with gemcitabine plus capecitabine with adjuvant treatment with gemcitabine alone.

A summary of the included study is shown in table 1 (see the evidence summary tables for full details).

Table 1 Summary of included study

Study	Population	Intervention and comparison	Primary outcome
Neoptolemos et al. (2017) Open label randomised controlled trial conducted at 92 hospitals in England, Scotland, Wales, Germany, France and Sweden (76% of participants were from the UK)	730 adults (median age 65 years; 57% male) who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 and R1 resection)[a]	Adjuvant treatment (given within 12 weeks of surgery) with gemcitabine plus capecitabine compared with treatment with gemcitabine alone[b]	Overall survival, measured as the time from randomisation until death from any cause
[a] With histological confirmation and with no evidence of malignant ascites, liver or peritoneal metastasis, or spread to other distant abdominal, or extra-abdominal organs			

[b] The doses of gemcitabine and capecitabine used in the study were: gemcitabine intravenous infusion 1000 mg/m^2 once a week for 3 of every 4 weeks (1 cycle) for 6 cycles (24 weeks) and oral capecitabine 1660 mg/m^2 daily for 21 days followed by 7 days' rest (1 cycle) for 6 cycles (24 weeks). The total daily dose of capecitabine is given in 2 divided doses (Xeloda).

Details of the excluded studies are listed in the section on evidence selection.

5. Results

An overview of the results for clinical effectiveness and safety and tolerability can be found in the evidence summary tables.

Clinical effectiveness

Gemcitabine and capecitabine in combination compared with gemcitabine alone

The open label randomised controlled trial (Neoptolemos et al. 2017) compared adjuvant treatment with gemcitabine plus capecitabine with gemcitabine alone. It included 730 adults who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection) with histological confirmation and with no evidence of malignant ascites, liver or peritoneal metastasis, or spread to other distant abdominal, or extra-abdominal organs. The primary outcome was median overall survival time; secondary outcomes included median relapse-free survival time and quality of life. People who had previously had neo-adjuvant chemotherapy or other concomitant chemotherapy and those with pancreatic lymphoma, macroscopically remaining tumours (R2 resection) or tumour, node and metastasis (TNM) stage IV disease were excluded from the study. The median follow-up time in the study was 43.2 months (95% confidence interval [CI] 39.7 to 45.5 months). All 6 cycles of treatment were given to 239/366 (65%) of participants in the gemcitabine group and 195/364 (54%) of participants in the gemcitabine plus capecitabine group.

Overall survival

Overall survival was defined as the time from randomisation until death from any cause. The median time from surgery to randomisation was 64 days. Participants still alive at the point of final analysis were censored at the date last seen alive. There was a statistically significant increased overall survival with gemcitabine plus capecitabine compared with gemcitabine alone. Gemcitabine plus capecitabine increased the median overall survival time by 2.5 months compared with gemcitabine alone. The median overall survival time was 25.5 months (95% confidence interval [CI] 22.7 to 27.9 months) in the gemcitabine group compared with 28.0 months (95% CI 23.5 to 31.5 months) in the gemcitabine plus capecitabine group (hazard ratio [HR] for death 0.82, 95% CI 0.68 to 0.98, p=0.032).

In the gemcitabine group 147/366 (40%) participants had negative resection margins (R0 status) and 219/366 (60%) had positive resection margins (R1 status). In the gemcitabine plus capecitabine group the proportions were 143/364 (39%) and 221/364 (61%) respectively. In this study, positive resection margins (R1) were defined as any tumour cell within 1 millimetre of any surface of the specimen. Gemcitabine plus capecitabine had a statistically significant treatment effect on overall survival in people who had negative resection margins (HR for death 0.68, 95% CI 0.49 to 0.93). In people who had positive resection margins gemcitabine plus capecitabine had no statistically significant treatment

effect on overall survival (HR for death 0.90, 95% CI 0.72 to 1.13). However, the study was powered for the primary outcome of overall survival for the whole group; while the analysis of the R0 and R1 subgroups was pre-specified, caution should be exercised when interpreting the results of these individual subgroups.

For the subgroup who had R0 status, gemcitabine plus capecitabine increased median overall survival by 11.6 months compared with gemcitabine alone. Median overall survival was 27.9 months (95% CI 23.8 to 34.6 months) in the gemcitabine group compared with 39.5 months (95% CI 32.0 to 58.0 months) in the gemcitabine plus capecitabine group. For the subgroup who had R1 status, median overall survival was 23.0 months (95% CI 21.6 to 26.2 months) in the gemcitabine group compared with 23.7 months (95% CI 20.7 to 27.1 months) in the gemcitabine plus capecitabine group.

Estimated overall survival (secondary outcome) at 12 months was 80·5% (95% CI 76.0% to 84.3%) in the gemcitabine group compared with 84.1% (95% CI 79.9% to 87.5%) in the gemcitabine plus capecitabine group and at 24 months it was 52.1% (95% CI 46.7% to 57.2%) in the gemcitabine group compared with 53·8% (95% CI 48.4% to 58.8%) in the gemcitabine plus capecitabine group.

Estimated overall survival at 5 years (secondary outcome) was 16.3% (95% CI 10.2% to 23.7%) in the gemcitabine group compared with 28.8% (95% CI 22.9% to 35.2%) in the gemcitabine plus capecitabine group (p=0.032).

Relapse-free survival

Relapse-free survival was defined as the minimum time from randomisation to date of local tumour recurrence, lymph node spread, distant metastases or death from any cause. In the gemcitabine group 286/366 (78%) had a relapse or died compared with 271/364 (74%) in the gemcitabine plus capecitabine group. There was no statistically significant difference between gemcitabine alone and gemcitabine plus capecitabine for median relapse-free survival time. The median relapse-free survival time was 13.1 months (95% CI 11.6 to 15.3 months) in the gemcitabine group compared with 13.9 months (95% CI 12.1 to 16.6) in the gemcitabine plus capecitabine group (HR for relapse or death 0.86, 95% CI 0.73 to 1.02, p=0.082).

Three-year relapse-free survival was 20.9% (95% CI 16.5% to 25.7%) compared with 23.8% (95% CI 19.2% to 28.6%) in the gemcitabine plus capecitabine group. Five-year relapse-free survival was 11.9% (95% CI 7.8% to 16.9%) in the gemcitabine group compared with 18.6% (95% CI 13.8% to 24.0%) in the gemcitabine plus capecitabine group.

Quality of life

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ) C-30, version 3. The figures reported in the study for the number of participants who completed the questionnaire were inconsistent. Quality of life questionnaires were completed by 665 participants, reported as 334 in the gemcitabine group and 321 in the gemcitabine plus capecitabine group. Questionnaires at 3, 6 and 12 months were completed by 496, 452 and 388 participants respectively. No statistically significant effect was shown on quality of life questionnaire results by treatment

group (HR –0.10, 95% CI –0.29 to 0.09, p=0.3). No further information was provided in the study on quality of life assessment scores.

Safety and tolerability

Adverse events

In Neoptolemos et al. (2017), 52/366 (14%) of participants in the gemcitabine group and 79/364 (22%) of participants in the gemcitabine plus capecitabine group stopped treatment before the end of the 6th cycle due to toxicity. No statistical analysis was provided for this outcome.

The safety analysis set in Neoptolemos et al. (2017) included 725 participants, 366 in the gemcitabine group and 359 in the gemcitabine plus capecitabine group. There was no statistical significant difference between gemcitabine alone and gemcitabine plus capecitabine for treatment-related serious adverse events (151 events reported in 94/366 [26%] participants in the gemcitabine group compared with 154 events reported by 86/359 [24%] participants in the gemcitabine plus capecitabine group [p>0.05]). The study does not report how it defined treatment-related serious adverse events.

Adverse events were graded according to the National Cancer Institute common toxicity criteria, version 4.03. This grades adverse events on a scale of 1 to 5 with 4 being the most serious adverse event and 5 being death.

There were 481 grade 3–4 adverse events reported by 196/366 (54%) participants in the gemcitabine group compared with 608 reported by 226/359 (63%) participants in the gemcitabine plus capecitabine group. There was no statistical analysis reported for this outcome.

There was a statistically significant higher percentage of participants who had grade 3–4 adverse events of diarrhoea, neutropenia and hand-foot syndrome in the gemcitabine plus capecitabine group compared with the gemcitabine group. There was a statistically significant lower percentage of participants who had grade 3-4 adverse events of infection and other infestations (adverse event category not defined in the paper) in the gemcitabine plus capecitabine group compared with the gemcitabine group.

- Diarrhoea: 6/366 (2%) in the gemcitabine group compared with 19/359 (5%) in the gemcitabine plus capecitabine group (p= 0.008)
- Neutropenia: 89/366 (24%) in the gemcitabine group compared with 137/359 (38%) in the gemcitabine plus capecitabine group (p= 0.0001)
- Hand-foot syndrome: No participants in the gemcitabine group compared with 26/359 (7%) participants in the gemcitabine plus capecitabine group (p<0.0001)
- Infections and other infestations: 24/366 (7%) in the gemcitabine group compared with 9/359 (3%) in the gemcitabine plus capecitabine group (p= 0.012).

The study authors reported that the rate of febrile neutropenia was low in both groups and that the grade 3–4 hand-foot syndrome events were generally manageable with appropriate capecitabine dose modification.

For the other grade 3–4 adverse events of anaemia, fatigue, fever, decreased lymphocyte count, platelets, thromboembolic events, decreased white blood cell count, acute kidney

injury, multi-organ failure, cardiac disorders and benign, malignant and unspecified neoplasms there was no statistically significant difference in percentage of participants who had these events between the 2 groups.

There were 6 grade 5 events; 5 in the gemcitabine group and 1 in the gemcitabine plus capecitabine group. These were 1 multi-organ failure, 1 cardiac disorders and 3 benign, malignant and unspecified neoplasms in the gemcitabine group and 1 infection or infestation in the gemcitabine plus capecitabine group.

Summary of product characteristics

Neither gemcitabine nor capecitabine are licensed for adjuvant treatment in people who have had pancreatic cancer resection, either as monotherapy or in combination. The adverse event information provided in the summaries of product characteristics (SPCs) is based on clinical trial data investigating gemcitabine and capecitabine for their licensed indications. The SPCs also provide information on adverse events for gemcitabine or capecitabine in combination with other chemotherapy for their licensed indications. The SPCs do not provide information on adverse events for gemcitabine combined with capecitabine.

The SPC for gemcitabine powder for solution for infusion (Gemzar) states that the most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST and ALT) and alkaline phosphatase, reported in approximately 60% of people; proteinuria and haematuria reported in approximately 50% of people; dyspnoea reported in 10–40% of people (with the highest incidence in people with lung cancer); and allergic skin rashes reported in approximately 25% of people and associated with itching in 10% of people.

The SPC for gemcitabine (Gemzar) also lists the following as very common (occurring in 1 in 10 or more people) adverse events: leucopenia (neutropenia grade 3 = 19.3%, grade 4 = 6%), thrombocytopenia, anaemia, dyspnoea (usually mild and passes rapidly without treatment), vomiting, nausea, elevation of liver transaminases (AST and ALT) and alkaline phosphatase, allergic skin rash, alopecia, haematuria, mild proteinuria, influenza-like symptoms, oedema or peripheral oedema-including facial oedema (oedema is usually reversible after stopping treatment).

The SPC for capecitabine oral tablets (Xeloda) states that the most commonly reported or clinically relevant treatment-related adverse drug reactions were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain and stomatitis), hand-foot syndrome, fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction in those with pre-existing compromised renal function, and thrombosis or embolism. This is based on data in people treated with capecitabine as either monotherapy or in combination with different chemotherapy regimens for its licensed indications.

The SPC also lists the following as very common (occurring in 1 in 10 or more people) adverse drug reactions for capecitabine when used as monotherapy (based on clinical trial data for its licensed indications): anorexia, diarrhoea, vomiting, nausea, stomatitis, abdominal pain, palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome), fatigue and asthenia. The SPC states that based on post-marketing experience, persistent or severe hand-foot syndrome can eventually lead to loss of fingerprints.

For information on contraindications, special warnings and precautions for use, interactions with other medicinal products and dosage information for the licensed indications for gemcitabine and capecitabine refer to the SPCs.

Medicines and Healthcare products Regulatory Agency (MHRA) advice

The MHRA issued a Drug Safety Update on capecitabine and the risk of severe skin reactions in January 2014. This highlighted that skin reactions associated with the use of capecitabine include hand-foot syndrome and dermatitis, which occur very commonly (in more than 1 in 10 people). Severe skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have also been very rarely reported during treatment with capecitabine. The Drug Safety Update reports that TEN and SJS are characterised by generalised tender erythematous maculae, progressing to blisters and denudation and commonly preceded by photophobia, symptoms of upper respiratory tract infection, and fever. People should be informed of the possibility of such reactions and informed to seek urgent medical advice should any symptoms of a severe skin reaction occur. The Drug Safety Update recommends that capecitabine should be permanently discontinued in people who have a severe skin reaction during treatment and that the reaction should be treated promptly.

6. Discussion

Evidence strengths and limitations

The evidence selection process identified 1 study for inclusion in this evidence review, Neoptolemos et al. (2017), an open label randomised controlled trial. The study population in Neoptolemos et al. (2017), included people with the indication and characteristics of interest. It also directly compared the intervention of interest with an intervention that is currently used in UK clinical practice for this indication (gemcitabine: off-label indication). Seventy-six percent of the study population were from the UK, therefore results are likely to be generalisable to a UK population. The study included key patient-orientated outcome measures including overall survival (primary outcome), relapse-free survival (secondary outcome) and adverse effects. An overview of the quality assessment of the outcome measures can be found in the grade of evidence table. The study was randomised using a minimisation method, including the resection margin (negative [R0] or positive [R1]) and country as stratification factors. However, the study was open label. Treatment allocation was not concealed to either participants or study investigators, which introduces a risk of bias. Although, the primary outcome of overall survival is unlikely to be influenced by bias.

The study showed a statistically significant increase in median overall survival time of 2.5 months with gemcitabine plus capecitabine compared with gemcitabine alone. However the upper limit of the 95% confidence intervals around the hazard ratio for death for gemcitabine plus capecitabine compared with gemcitabine alone was 0.98 (where 1 would indicate a non-significant difference).

The study population included people who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection) with histological confirmation and with no evidence of malignant ascites, liver or peritoneal metastasis, or spread to other distant abdominal, or extra-abdominal organs. People who had previously

had neo-adjuvant chemotherapy or other concomitant chemotherapy and those with pancreatic lymphoma, macroscopically remaining tumours (R2 resection) or tumour, node and metastasis (TNM) stage IV disease were excluded from the study. Consequently this study provides no data on the comparison of adjuvant gemcitabine alone with gemcitabine plus capecitabine for these groups of people. Inclusion criteria for the study also required participants to have a full recovery from surgery, a WHO performance score of 2 or less and a creatinine clearance of at least 50 mL/min.

Baseline characteristics including age, sex, country of origin, WHO status, smoking status, resection margin status, tumour grade, lymph nodes (negative or positive), maximum tumour size and tumour stage appeared well balanced between the 2 groups. Although no statistical analysis of differences between groups appear to have been undertaken.

The authors of the study commented that post-operative carbohydrate antigen 19-9 levels are an important independent predictor of survival. Post-operative carbohydrate antigen 19-9 (KU/L) levels were available for 341/366 participants in the gemcitabine group and 321/364 participants in the gemcitabine plus capecitabine group. Median post-operative levels were 20.5 KU/L (range 0.1 to 2448.3) in the gemcitabine group and 17.6 KU/L (range 0.6 to 8112.0) in the gemcitabine plus capecitabine group. Median results appear similar but the range of results in each group was broad.

Participants who relapsed received additional treatment with chemotherapy, chemoradiotherapy, surgery and other treatment as appropriate; 94/243 (39%) participants who relapsed in the gemcitabine group and 77/236 (33%) participants who relapsed in the gemcitabine plus capecitabine group received additional treatment. Thirty-eight participants in the gemcitabine group had capecitabine in some form as additional chemotherapy.

The efficacy analysis was based on the intention to treat population which included all participants in their initially randomised groups irrespective of any protocol deviations with the exception of 2 participants (1 from each group) who withdrew consent between randomisation and the start of therapy. Twenty-six participants were lost to follow-up in the gemcitabine group and 25 were lost to follow-up in the gemcitabine plus capecitabine group, the reasons for this were similar between the 2 groups. The study was powered to detect a difference between treatment groups for the primary outcome of overall survival. Overall survival data was also provided for pre-specified subgroups of participants including participants with negative and positive resection margins. However, caution should be exercised when interpreting the results of these individual subgroups.

Participants were reviewed every 3 months after surgery for 5 years, if they were alive at this point. The study provided estimated overall survival results at 5 years, however, these results are only estimates. The study ran for approximately 7.5 years but participants could be recruited to the study at any time during the first 6 years. The study design planned for each participant to have a minimum follow-up of 2 years. The median follow-up in the study was 43.2 months.

The specific method of follow-up (haematology, clinical chemistry, and use of a tumour marker) at each clinic visit was determined by each site because of wide variations in routine clinical practice. Adverse events were graded according to the National Cancer Institute

common toxicity criteria, version 4.03, which is a standardised classification and severity grading scale for adverse events in cancer therapy clinical trials and other oncology settings.

The Independent Data and Safety Monitoring Committee requested reporting of the results after there were 458 deaths (95% of the target).

Costs of treatment

No studies were identified during literature searches (see search strategy for full details) that compared the cost-effectiveness of using gemcitabine and capecitabine in combination compared with gemcitabine alone as an adjuvant treatment for individuals who have had potentially curative surgery for pancreatic cancer. The study included in this evidence review (Neoptolemos et al. 2017), did not include an outcome investigating cost-effectiveness.

The table shows the comparative costs of 6 cycles of gemcitabine plus capecitabine compared with gemcitabine alone, as used in the study. The costs are for the medicines only (excluding VAT) and do not include any local procurement discounts or any other potential costs incurred, such as additional treatment (for example, for adverse events), staffing costs or distribution costs.

Table 2 Cost of gemcitabine plus capecitabine compared to gemcitabine alone

Treatment	Approximate cost for 6 cycles of treatment[c]
Gemcitabine plus capecitabine[a,b]	£811.00
Gemcitabine alone[a,b]	£483.00

[a] Costs based on the doses of gemcitabine and capecitabine used in the Neoptolemos et al. (2017) study: gemcitabine intravenous infusion 1000 mg/m^2 once a week for 3 of every 4 weeks (1 cycle) for 6 cycles (24 weeks) and oral capecitabine 1660 mg/m^2 daily for 21 days followed by 7 days' rest (1 cycle) for 6 cycles (24 weeks). This is an off-label indication for gemcitabine and capecitabine. For dosage information for the licensed indications for gemcitabine and capecitabine refer to the SPC.

[b] Costs based on the least expensive generic preparations listed in BNF, November 2017.

[c] Based on an average Body Surface Area of 1.79 m^2 (Sacco JJ et al. 2010). Single dose for gemcitabine calculated as 1790 mg using 2 gram/50 ml concentrate for solution for infusion (listed in the BNF as £26.86 for 1 vial, wastage included in the cost calculated above). Daily dose for capecitabine calculated as 2971.4 mg (cost above based on a dose of 1500 mg twice a day using 500 mg tablets listed in the BNF as £52.00 for 120 tablets).

7. Conclusion

The conclusion of this evidence review is based on results from 1 open label randomised controlled trial which compared adjuvant gemcitabine plus capecitabine to gemcitabine alone in a population of people who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection). Although the study was generally well-conducted, it was open label and participants and study investigators knew which treatment had been allocated, which is a source of bias. However, the primary outcome of overall survival is unlikely to be influenced by bias.

Adjuvant gemcitabine plus capecitabine extended overall survival time compared with adjuvant gemcitabine alone. However, there was no difference between the 2 treatment groups for relapse-free survival time. There was an increase in some grade 3-4 adverse

events with the gemcitabine plus capecitabine combination. Combination treatment was not found to adversely affect quality of life compared with gemcitabine alone.

Compared with gemcitabine alone, gemcitabine plus capecitabine increased median overall survival time by 2.5 months (from 25.5 months to 28.0 months). Overall survival was defined as the time from randomisation until death from any cause. Median time from surgery to randomisation was 64 days.

In people who had negative resection margins after surgery (R0 status) gemcitabine plus capecitabine was shown to have a statistically significant treatment effect on overall survival compared with gemcitabine alone. However, in those who had positive resection margins after surgery (R1 status), gemcitabine plus capecitabine was not shown to have a statistically significant treatment effect on overall survival compared with gemcitabine alone. However, the study was powered for the primary outcome of overall survival for the whole group; while the analysis of the R0 and R1 subgroups was pre-specified, caution should be exercised when interpreting the results of these individual subgroups.

Compared with gemcitabine alone, gemcitabine plus capecitabine increased median overall survival time by 11.6 months in people who had R0 resections (from 27.9 months to 39.5 months). In people who had R1 resections, median overall survival was 23.0 months in the gemcitabine group compared with 23.7 months in the gemcitabine plus capecitabine group; a difference of 0.7 months.

Compared with gemcitabine alone, estimated overall survival at 5 years was found to be 12.5% higher with gemcitabine plus capecitabine (16.3% compared with 28.8%).This is only an estimate as study participants still alive at the end of the study will not all have had 5 years of follow-up. The median follow-up time was 43.2 months.

There was no difference between the 2 groups for treatment-related serious adverse events, although the study did not report how these were defined. There were more grade 3-4 adverse events of diarrhoea, neutropenia and hand-foot syndrome with the gemcitabine plus capecitabine combination compared with gemcitabine alone. However, there were fewer grade 3–4 adverse events of infection and other infestations (adverse event category not defined in the paper) with the gemcitabine plus capecitabine combination compared with gemcitabine alone, and the authors of the study reported that the rate of febrile neutropenia was low in both groups. The study authors also reported that the grade 3–4 hand-foot syndrome events were generally manageable with appropriate capecitabine dose modification.

In conclusion, the benefit of the increase in overall survival time seen with gemcitabine plus capecitabine needs to be balanced against the potential risk of an increase in adverse events compared with gemcitabine alone.

8. Evidence summary table

Gemcitabine and capecitabine in combination compared with gemcitabine alone for adjuvant treatment in people who have had potentially curative surgery for pancreatic cancer							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 1: Neoptolemos et. al 2017							
P1, open label randomised controlled trial conducted at 92 hospitals in England, Scotland, Wales, Germany, France and Sweden (76% of participants were from the UK)	730 adults aged 18 years or older who had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection) with histological confirmation and with no evidence of malignant ascites, liver or peritoneal metastasis, or spread to other distant abdominal, or extra-abdominal organs. A clear CT scan of the chest, abdomen, and pelvis was required within 3 months before randomisation. Other inclusion criteria included: full recovery from surgery, a WHO performance score of 2 or less, creatinine clearance of at least	Participants were randomised 1:1 to receive either gemcitabine alone or gemcitabine plus capecitabine within 12 weeks of surgery. Participants and study investigators were not masked to treatment allocation. The doses of gemcitabine and capecitabine used in study were: gemcitabine intravenous infusion 1000 mg/m^2 once a week for 3 of every 4 weeks (1 cycle) for 6 cycles (24 weeks) and oral capecitabine 1660 mg/m^2 daily for 21 days followed by 7 days' rest (1 cycle) for 6 cycles (24 weeks). All 6 cycles of treatment were given to 239/366	Primary Clinical effectiveness	Overall survival, measured as the time from randomisation until death from any cause. Participants still alive at the point of final analysis were censored at the date last seen alive.	The median follow-up time was 43.2 months (95% confidence interval [CI] 39.7 to 45.5 months). The median overall survival time was 25.5 months (95% CI 22.7 to 27.9 months) in the gemcitabine group compared with 28.0 months (95% CI 23.5 to 31.5 months) in the gemcitabine plus capecitabine group (hazard ratio for death [HR] 0.82, 95% CI 0.68 to 0.98, p=0.032). Gemcitabine plus capecitabine had a statistically significant treatment effect on overall survival in people who had negative resection margins (HR for death 0.68, 95% CI 0.49 to 0.93). In people who had positive resection margins gemcitabine plus capecitabine had no statistically significant treatment effect on overall survival (HR for death 0.90, 95% CI 0.72 to 1.13). For the subgroup who had negative resection margins, median overall survival was 27.9 months (95% CI 23.8 to 34.6 months) in the gemcitabine group compared with 39.5 months (95% CI 32.0 to	8/10 The research questions, aims, design and methods are clearly stated and described. The results are generalisable to a UK population. The study population focuses on people with the indication and characteristics of interest. The comparator is an intervention that is currently used in UK clinical practice for this indication (gemcitabine: off-label indication). The study was a	Direct study focusing on people with the indication and characteristics of interest

Gemcitabine and capecitabine in combination compared with gemcitabine alone for adjuvant treatment in people who have had potentially curative surgery for pancreatic cancer							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
	50 mL/min and a life expectancy of more than 3 months. People who had previously had neo-adjuvant chemotherapy or other concomitant chemotherapy and those with pancreatic lymphoma, macroscopically remaining tumours (R2 resection) or tumour, node and metastasis (TNM) stage IV disease were excluded. 732 adults were randomised and 730 were included in the efficacy analysis (intention to treat population); 366 randomised to gemcitabine (median age 65 years [range 37 to 80 years], 58% male; 89% tumour stage 3) and 364 randomised to gemcitabine plus capecitabine (median age 65 years [range 39 to 81 years], 55% male; 90% tumour stage 3). In the gemcitabine group 147/366 (40%)	(65%) participants in the gemcitabine group and 195/364 (54%) participants in the gemcitabine plus capecitabine group. Participants were reviewed every 3 months after surgery for up-to 5 years. The specific method of follow-up (haematology, clinical chemistry, and use of a tumour marker) at each clinic visit was determined by each site because of wide variations in routine clinical practice.			58.0 months) in the gemcitabine plus capecitabine group. For the subgroup who had positive resection margins, median overall survival was 23.0 months (95% CI 21.6 to 26.2 months) in the gemcitabine group compared with 23.7 months (95% CI 20.7 to 27.1 months) in the gemcitabine plus capecitabine group.	randomised controlled trial, however it was open label. Participants and study investigators were not masked to treatment allocation, which may have introduced a high risk of bias.	
			Secondary Clinical effectiveness	Estimated overall survival at 12 and 24 months	Estimated overall survival at 12 months was 80.5% (95% CI 76.0% to 84.3%) in the gemcitabine group compared with 84.1% (95% CI 79.9% to 87.5%) in the gemcitabine plus capecitabine group. Estimated overall survival at 24 months was 52.1% (95% CI 46.7% to 57.2%) in the gemcitabine group compared with 53.8% (95% CI 48.4% to 58.8%) in the gemcitabine plus capecitabine group.		
			Secondary Clinical effectiveness	Estimated overall survival at 5 years	Estimated overall survival at 5 years was 16.3% (95% CI 10.2% to 23.7%) in the gemcitabine group compared with 28.8% (95% CI 22.9% to 35.2%) in the gemcitabine plus capecitabine group (p=0.032).		
			Secondary Clinical effectiveness	Relapse-free survival (measured as the minimum time from randomisation to date of local tumour	The median relapse-free survival time was 13.1 months (95% CI 11.6 to 15.3 months) in the gemcitabine group compared with 13.9 months (95% CI 12.1 to 16.6 months) in the gemcitabine plus capecitabine group (HR for relapse or death 0.86, 95% CI 0.73 to 1.02, p=0.082).		

Gemcitabine and capecitabine in combination compared with gemcitabine alone for adjuvant treatment in people who have had potentially curative surgery for pancreatic cancer							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
	participants had negative resection margins (R0 status) and 219/366 (60%) had positive resection margins (R1 status); in the gemcitabine plus capecitabine group the percentages were 143/364 (39%) and 221/364 (61%) respectively. Median time from surgery to randomisation was 65 days in the gemcitabine group and 64 days in the gemcitabine plus capecitabine group. 725 adults were included in the safety analysis (366 in the gemcitabine group and 359 in the gemcitabine plus capecitabine group).			recurrence, lymph node spread, distant metastases or death from any cause)	286/366 (78%) participants in the gemcitabine group and 271/364 (74%) participants in the gemcitabine plus capecitabine group had a relapse or died. Three year relapse-free survival was 20.9% (95% CI 16.5% to 25.7%) in the gemcitabine group compared with 23.8% (95% CI 19.2% to 28.6%) in the gemcitabine plus capecitabine group. Five year relapse-free survival was 11.9% (95% CI 7.8% to 16.9%) in the gemcitabine group compared with 18.6% (95% CI 13.8% to 24.0%) in the gemcitabine plus capecitabine group.		
			Secondary Clinical effectiveness	Quality of life assessed using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ) C-30, version 3	Quality of life questionnaires were completed by 665 participants (reported as 334 in the gemcitabine group and 321 in the gemcitabine plus capecitabine group). No statistically significant effect was shown on quality of life questionnaire results by treatment group (HR –0.10, 95% CI –0.29 to 0.09, p=0.3). However, the figures reported in the study for the number of participants who completed the questionnaire were inconsistent.		
			Secondary Safety	Percentage of participants who stopped treatment before end of 6th cycle due to toxicity	52/366 (14%) of participants in the gemcitabine group and 79/364 (22%) of participants in the gemcitabine plus capecitabine group stopped treatment before the end of the 6th cycle due to toxicity. No		

Gemcitabine and capecitabine in combination compared with gemcitabine alone for adjuvant treatment in people who have had potentially curative surgery for pancreatic cancer							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
					statistical analysis was provided for this outcome.		
			Secondary Safety	Adverse events The number of participants with treatment-related serious adverse events was reported. Toxicity was graded according to the National Cancer Institute common toxicity criteria, version 4.03 which grades adverse events on a scale of 1 to 5 with 4 being the most serious adverse event and 5 being death.	There were 151 treatment-related serious adverse events reported in 94/366 (26%) participants in the gemcitabine group compared with 154 reported by 86/359 (24%) participants in the gemcitabine plus capecitabine group (p>0.05). The study did not report how it defined serious treatment-related adverse events. There were 481 grade 3-4 adverse events reported by 196/366 (54%) participants in the gemcitabine group compared with 608 reported by 226/359 (63%) participants in the gemcitabine plus capecitabine group. There was no statistical analysis reported for this outcome. There was a statistically significant higher percentage of participants who had grade 3-4 adverse events of diarrhoea, neutropenia and hand-foot syndrome in the gemcitabine plus capecitabine group compared with the gemcitabine group. There was a statistically significant lower percentage of participants who had grade 3-4 adverse events of infection and other infestations in the gemcitabine plus capecitabine group compared with the gemcitabine group. Diarrhoea: 6/366 (2%) in the gemcitabine group compared with 19/359 (5%) in the		

Gemcitabine and capecitabine in combination compared with gemcitabine alone for adjuvant treatment in people who have had potentially curative surgery for pancreatic cancer							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
					gemcitabine plus capecitabine group (p= 0.008) Neutropenia: 89/366 (24%) in the gemcitabine group compared with 137/359 (38%) in the gemcitabine plus capecitabine group (p= 0.0001) Hand-foot syndrome: No participants in the gemcitabine group compared with 26/359 (7%) participants in the gemcitabine plus capecitabine group (p<0.0001) Infections and other infestations: 24/366 (7%) in the gemcitabine group compared with 9/359 (3%) in the gemcitabine plus capecitabine group (p= 0.012) For the other grade 3-4 adverse events of anaemia, fatigue, fever, decreased lymphocyte count, platelets, thromboembolic events, decreased white blood cell count, acute kidney injury, multi-organ failure, cardiac disorders and benign, malignant and unspecified neoplasms there was no statistically significant difference between the 2 groups. There were 6 grade 5 events, 5 in the gemcitabine group and 1 in the gemcitabine plus capecitabine group.		
Critical appraisal summary This randomised controlled trial had clearly stated and well defined outcome measures. It directly compared the intervention of interest with an intervention currently used in UK clinical practice for this indication. The majority of the study population were from the UK (76%) and the study population included people with the indication and characteristics of interest.							

Gemcitabine and capecitabine in combination compared with gemcitabine alone for adjuvant treatment in people who have had potentially curative surgery for pancreatic cancer							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
The study was randomised using a minimisation method, the resection margin (negative or positive) and country were used as stratification factors. The study was open label; participants and study investigators were not masked to treatment allocation and so there was a high risk of bias. The efficacy analysis was based on an intention to treat population and included all participants in their initially randomised groups irrespective of any protocol deviations with the exception of participants who withdrew consent between randomisation and the start of therapy (2 participants withdrew consent, one from each group). Twenty-six participants were lost to follow up in the gemcitabine group and 25 were lost to follow-up in the gemcitabine plus capecitabine group, the reasons for this were similar between the 2 groups. The Independent Data and Safety Monitoring Committee requested reporting of the results after there were 458 (95%) of a target of 480 deaths. The study was powered for the primary outcome of overall survival for the whole group. Overall survival data was also provided for pre-specified subgroups of participants including participants with negative and positive resection margins. However caution should be exercised when interpreting the results of these individual subgroups. The specific method of follow-up (haematology, clinical chemistry and use of a tumour marker) at each clinic visit was determined at each site because of wide variations in routine clinical practice. Participants who relapsed received additional treatment with chemotherapy, chemoradiotherapy, surgery and other treatment as appropriate (94 out of 243 participants who relapsed in the gemcitabine group and 77 out of 236 participants who relapsed in the gemcitabine plus capecitabine group received additional treatment). Of the 243 participants in the gemcitabine group who relapsed, 38 had capecitabine in some form as additional chemotherapy. For the quality of life outcome, the figures reported in the study for the number of participants who completed the questionnaire were inconsistent.							

9. Grade of evidence table

Gemcitabine and capecitabine in combination compared with gemcitabine alone for adjuvant treatment in people who have had potentially curative surgery for pancreatic cancer					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Neoptolemos et al. 2017	8	Direct	B	Overall survival (OS) is a measure of how long from the start of treatment people are expected to live. It is not restricted to deaths that are disease-related; deaths of any cause are accounted for. The median (a particular way of measuring the average) OS was 25.5 months in the gemcitabine group. The result provides an estimate of the true value of OS of the treatment. The probability that the true value is contained within the range of 22.7 – 27.9 months is 95%. The median OS was 28.0 months in the gemcitabine plus capecitabine group. The probability that the true value is contained within the range of 23.5 – 31.5 months is 95%. The results mean that people having gemcitabine plus capecitabine instead of gemcitabine alone after potentially curative surgery for pancreatic cancer could expect to live on average for an extra 2.5 months.

					In people who had negative resection margins after surgery (this means no cancer cells were seen at the outer edge of the tissue that was removed and suggests that all of the tumour was removed) gemcitabine plus capecitabine was shown to have a significant treatment effect on OS compared with gemcitabine alone. However, in those who had positive resection margins after surgery (some cancer cells were seen at the outer edge of the tissue that was removed suggesting that some of the tumour was left behind), gemcitabine plus capecitabine was not shown to have a significant treatment effect on OS compared with gemcitabine alone. Caution should be exercised when looking at the results for these subgroups of people with negative and positive resection margins as the study was powered (a way of planning how many participants or events need to be in a study to show a difference between 2 treatments) for the outcome of overall survival for the whole group. In people who had negative resection margins after surgery, gemcitabine plus capecitabine increased median OS by 11.6 months compared with gemcitabine alone. Median OS was 27.9 months in the gemcitabine group compared with 39.5 months in the gemcitabine plus capecitabine group. In people who had positive resection margins after surgery, median OS was 23.0 months in the gemcitabine group compared with 23.7 months in the gemcitabine plus capecitabine group. At 12 months an estimated 80.5% of people in the gemcitabine group and 84.1% in the gemcitabine plus capecitabine group were still alive. At 24 months an estimated 52.1% of people in the gemcitabine group and 53·8% in the gemcitabine plus capecitabine group were still alive. At 5 years an estimated 16.3% of people in the gemcitabine group and 28.8% in the gemcitabine plus capecitabine group were still alive. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The study ran for approximately 7.5 years but participants could be recruited to the study at any time during the first 6 years. The median follow-up time (the time a person was in the study from study entry until they died or if they were still alive the study ended) was 43.2 months.
Relapse free survival	Neoptolemos et al. 2017	8	Direct	B	Relapse free survival (or progression free survival) is a measure of how long from the start of treatment people can expect to remain both alive and free of disease relapse or progression. The median relapse free survival was 13.1 months in the gemcitabine group. The result provides an estimate of the true value of relapse free survival of the treatment. The probability that the true value is contained within the range of 11.6 – 15.3 months is 95%. The median relapse free survival was 13.9 months in the gemcitabine plus capecitabine group. The probability that the true value is contained within the range of 12.1 – 16.6 months is 95%.

					The results mean that people taking gemcitabine plus capecitabine instead of gemcitabine alone after potentially curative surgery for pancreatic cancer can expect no difference in how long they live without disease relapse or progression. At 3 years 20.9% of people in the gemcitabine group and 23.8% in the gemcitabine plus capecitabine group were still alive and had not had disease relapse or progression. At 5 years 11.9% of people in the gemcitabine group and 18.6% in the gemcitabine plus capecitabine group were still alive and had not had disease relapse or progression. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months.
Adverse effects	Neoptolemos et al. 2017	8	Direct	B	There was no difference between gemcitabine alone and gemcitabine plus capecitabine for treatment-related serious adverse events: 151 events reported by 26% of people in the gemcitabine group compared with 154 events reported by 24% of people in the gemcitabine plus capecitabine group. The study did not report how it defined treatment-related serious adverse events. Adverse events were graded according to the National Cancer Institute common toxicity criteria, which grades adverse events on a scale of 1 to 5 with 4 being the most serious adverse event and 5 being death. There were 481 grade 3-4 adverse events reported by 54% people in the gemcitabine group compared with 608 events reported by 63% people in the gemcitabine plus capecitabine group. Frequencies of grade 3-4 adverse events were also presented by symptom or system type. There was a higher percentage of people who had grade 3-4 adverse events of diarrhoea, neutropenia (a low level of neutrophils, a type of white blood cell), and hand-foot syndrome (a skin reaction) in the gemcitabine plus capecitabine group compared with the gemcitabine group. There was a lower percentage of people who had grade 3-4 adverse events of infection and other infestations (adverse event category not defined in the paper) in the gemcitabine plus capecitabine group compared with the gemcitabine group: • Diarrhoea: 2% in the gemcitabine group compared with 5% in the gemcitabine plus capecitabine group • Neutropenia: 24% in the gemcitabine group compared with 38% in the gemcitabine plus capecitabine group • Hand-foot syndrome: No people in the gemcitabine group compared with 7% people in the gemcitabine plus capecitabine group • Infections and other infestations: 7% in the gemcitabine group compared with 3% in the gemcitabine plus capecitabine group. For the other grade 3-4 adverse events of anaemia, fatigue, fever, decreased lymphocyte count (a type of white blood cell), platelets, thromboembolic events (blood clots), decreased white blood cell count, acute kidney injury, multi-organ

					failure, cardiac disorders and benign, malignant and unspecified neoplasms there was no difference in the percentage of people who had these events between the 2 groups. There were 6 grade 5 events (death due to an adverse event); 5 in the gemcitabine group and 1 in the gemcitabine plus capecitabine group. These results mean that if people had gemcitabine plus capecitabine instead of gemcitabine alone: • the percentage of people who have a grade 3-4 adverse event of diarrhoea could rise from 2% (2 in 100 people) to 5% (5 in 100 people) • the percentage of people who have a grade 3-4 adverse event of neutropenia could rise from 24% (24 in 100 people) to 38% (38 in 100 people) • the percentage of people who have a grade 3-4 adverse event of hand-foot syndrome could rise from 0 to 7% (7 in 100 people) • the percentage of people who have a grade 3-4 adverse event of infections and other infestations could fall from 7% (7 in 100 people) to 3% (3 in 100 people) This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 725 adults in the safety analysis with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months.
Percentage of participants who stopped treatment before end of 6th cycle due to toxicity	Neoptolemos et al. 2017	8	Direct	B	This outcome considered how many people had to stop taking their treatment before completing the full 6 cycles of chemotherapy because of side-effects, 14% of people in the gemcitabine group and 22% of people in the gemcitabine plus capecitabine group stopped treatment early due to side-effects. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months.
Quality of life	Neoptolemos et al. 2017	8	Direct	B	Quality of life was assessed using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ). This questionnaire asks questions about how symptoms or side-effects impact on a variety of aspects of daily living, family life and social activities and asks questions about how people feel and their mood.

					There was no difference on quality of life questionnaire results by treatment group. The results mean that people taking gemcitabine plus capecitabine instead of gemcitabine alone after potentially curative surgery for pancreatic cancer can expect no difference in their quality of life. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months. The figures reported in the study, for the number of people who completed the questionnaire were inconsistent. The study did not report the questionnaire results from each group.

10. Literature search terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with pancreatic cancer who have undergone potentially curative surgery (including R0 and R1 resections) and receiving adjuvant chemotherapy
I – Intervention Which intervention, treatment or approach should be used?	Adjuvant chemotherapy using gemcitabine and capecitabine (starting within 3 months of surgery)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Adjuvant chemotherapy using gemcitabine alone (starting within 3 months of surgery)
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term	Critical to decision-making: • Overall survival • Time to progression

outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	• Progression free survival • Overall response rate • Disease control rate • Adverse events • Quality of life • Cost-effectiveness
Assumptions / limits applied to search	
Exclusions: • Patients who have not had potentially curative surgery for pancreatic cancer • Abstracts • Conference papers • Papers published greater than 10 years ago • Non-English language papers	

11. Search strategy

Database: MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily, MEDLINE and Versions(R)

Platform: Ovid

Version: 1950 - date

Search date: 24th October 2017

Number of results retrieved: 87

Search strategy:

1 Capecitabine/ (3911)
2 capecitabine.tw. (5665)
3 capecitabin.tw. (24)
4 capecitabina.tw. (5)
5 xeloda.tw. (293)
6 ecansya.tw. (0)
7 apecitab.tw. (0)
8 "ro 09 1978".tw. (2)
9 "ro09 1978".tw. (2)
10 "ro 091978".tw. (0)
11 "ro091978".tw. (0)
12 or/1-11 (6386)
13 gemcitabine.tw. (14154)
14 gemzar.tw. (239)
15 difluorodeoxycytidine.tw. (270)
16 gemcite.tw. (3)
17 gemcitabin.tw. (74)
18 gemcitabina.tw. (5)
19 "ly 188011".tw. (8)
20 "ly188011".tw. (11)
21 or/13-20 (14279)
22 exp "Pancreatic Neoplasms"/ (70706)
23 pancrea*.tw. (269377)
24 or/22-23 (282024)
25 Chemotherapy, Adjuvant/ (38138)
26 adjuvant.tw. (125043)
27 adjunct.tw. (41322)
28 surg*.tw. (1745062)
29 resect*.tw. (321265)
30 postoperative.tw. (419002)
31 "post-operative".tw. (53183)
32 perioperative.tw. (78718)
33 "peri-operative".tw. (5744)
34 or/25-33 (2162595)
35 12 and 21 and 24 and 34 (110)
36 limit 35 to (english language and yr="2007 -Current") (90)
37 limit 36 to congresses (3)
38 36 not 37 (87)

Database: Embase
Platform: Ovid

Version: 1974 – 23rd October 2017
Search date: 24th October 2017
Number of results retrieved: 617
Search strategy:
1 Capecitabine/ (24064)
2 capecitabine.tw. (9926)
3 capecitabin.tw. (80)
4 capecitabina.tw. (10)
5 xeloda.tw. (2200)
6 ecansya.tw. (0)
7 apecitab.tw. (0)
8 "ro 09 1978".tw. (7)
9 "ro09 1978".tw. (2)
10 "ro 091978".tw. (1)
11 "ro091978".tw. (0)
12 or/1-11 (24813)
13 gemcitabine/ (47016)
14 gemcitabine.tw. (22630)
15 gemzar.tw. (1978)
16 difluorodeoxycytidine.tw. (286)
17 gemcite.tw. (6)
18 gemcitabin.tw. (192)
19 gemcitabina.tw. (10)
20 "ly 188011".tw. (42)
21 "ly188011".tw. (12)
22 or/13-21 (48511)
23 exp pancreas cancer/ (83694)
24 pancrea*.tw. (340874)
25 or/23-24 (357731)
26 adjuvant therapy/ (51957)
27 adjuvant chemotherapy/ (37267)
28 cancer adjuvant therapy/ (51950)
29 adjuvant.tw. (170384)
30 adjunct.tw. (50094)
31 surg*.tw. (2195248)
32 resect*.tw. (422141)
33 postoperative.tw. (517142)
34 "post-operative".tw. (92897)
35 perioperative.tw. (104370)
36 "peri-operative".tw. (11362)
37 or/26-36 (2721300)
38 12 and 22 and 25 and 37 (915)
39 limit 38 to (english language and yr="2007 -Current") (797)
40 limit 39 to (conference abstract or conference paper or "conference review") (180)
41 39 not 40 (617)
Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – 10 of 12, October 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 9 of 12, September 2017
HTA – 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 24th October 2017

Number of results retrieved: CDSR – 0; DARE – 0; CENTRAL – 18; HTA – 0; NHS EED – 0.
Search strategy:

ID	Search
#1	[mh ^Capecitabine]
#2	capecitabine:ti,ab
#3	capecitabin:ti,ab
#4	capecitabina:ti,ab
#5	xeloda:ti,ab
#6	ecansya:ti,ab
#7	apecitab:ti,ab
#8	"ro 09 1978":ti,ab
#9	"ro09 1978":ti,ab
#10	"ro 091978":ti,ab
#11	ro091978:ti,ab
#12	{or #1-#11}
#13	gemcitabine:ti,ab
#14	gemzar:ti,ab
#15	difluorodeoxycytidine:ti,ab
#16	gemcite:ti,ab
#17	"ly 188011":ti,ab
#18	ly188011:ti,ab
#19	{or #13-#18}
#20	[mh "Pancreatic Neoplasms"]
#21	pancrea*:ti,ab
#22	{or #20-#21}
#23	[mh ^"Chemotherapy, Adjuvant"]
#24	adjuvant:ti,ab
#25	adjunct:ti,ab
#26	surg*:ti,ab
#27	resect*:ti,ab
#28	postoperative:ti,ab
#29	"post-operative":ti,ab
#30	perioperative:ti,ab
#31	"peri-operative":ti,ab
#32	{or #23-#31}
#33	#12 and #19 and #22 and #32 Publication Year from 2007 to 2017

Clinicaltrials.gov searches
Search date: 25th October 2017
Number of results retrieved: 31
Search strategy and link to results page:
Condition field: pancreas OR pancreatic
Intervention field: (capecitabine OR xeloda OR ecansya OR apecitab OR (ro 09 1978) OR (ro09 1978) OR (ro 091978) OR (ro091978)) AND (gemcitabine OR difluorodeoxycytidine OR gemcite OR ly 188011)
Other terms: adjuvant OR adjunct OR surgery OR surgical OR surgically OR resectable OR resected OR resection OR postoperative OR (post-operative) OR perioperative OR (peri-operative)
Limited to: phase 2, 3 or 4
31 results
Note that the keywords: gemzar; gemcitabin; gemcitabina; LY 188011; capecitabin; capecitabina picked up by clinicaltrials.gov's in-built thesaurus mapping.
Clinicaltrialsregister.eu searches
Search date: 25th October 2017
Number of results retrieved: 16
Search strategy and link to results page:

(capecitabine OR capecitabin OR capecitabina OR xeloda OR ecansya OR apecitab OR (ro 09 1978) OR (ro09 1978) OR (ro 091978) OR (ro091978))
AND
(gemcitabine OR gemzar OR difluorodeoxycytidine OR gemcite OR gemcitabin OR (ly 188011) OR ly 188011 OR gemcitabina)
AND
(pancreas OR pancreatic)
AND
(adjuvant OR adjunct OR surgery OR surgical OR surgically OR resectable OR resected OR resection OR postoperative OR (post-operative) OR perioperative OR (peri-operative))
Limited to phase 2, 3 or 4

12. Evidence selection

The literature search identified 616 references (see search strategy for full details). These references were screened using their titles and abstracts, and the following were excluded: studies that did not meet the scope in terms of population, intervention, comparator or outcomes, general reviews of pancreatic cancer, and abstracts and conference reports. Four references were obtained and assessed for relevance. Of these, 1 reference (open label randomised controlled trial) is included in the evidence summary. The remaining references were excluded and are listed in the following table.

Study reference	Reason for exclusion
Xu J B, Jiang B, Chen Y et al. (2017) Optimal adjuvant chemotherapy for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis Oncotarget 8: 81419-29	Systematic review and network meta-analysis which included 14 studies. Only 1 of these 14 studies included gemcitabine plus capecitabine as an intervention (Neoptolemos et. al 2017, which has been included in this evidence review)
Deplanque G and Demartines N (2017) Pancreatic cancer: are more chemotherapy and surgery needed? The Lancet 389: 985–86	Not a relevant study (review and comment on Neoptolemos et. al 2017, which has been included in this evidence review)
Weinberg B A, Wang H, Yang X et al. (2014) Maintenance therapy with capecitabine in patients with resected pancreatic adenocarcinoma after adjuvant therapy: a retrospective cohort study Gastrointestinal Cancer Research 7: 91–97	Poor relevance against search terms (did not meet the scope in terms of intervention or comparator)

13. References

Neoptolemos JP, Palmer DH, Ghaneh P et al. (2017). Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, openlabel, randomised, phase 3 trial. The Lancet 389: 1011–24

Sacco JJ, Botten J, Macbeth F et al. (2010) The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. PLoS ONE 5 (1): e8933. doi:10.1371/journal.pone.0008933