Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background The ESPAC-3 trial showed that adjuvant gemcitabine is the standard of care based on similar survival to and less toxicity than adjuvant 5-fluorouracil/folinic acid in patients with resected pancreatic cancer. Other clinical trials have shown better survival and tumour response with gemcitabine and capecitabine than with gemcitabine alone in advanced or metastatic pancreatic cancer. We aimed to determine the efficacy and safety of gemcitabine and capecitabine compared with gemcitabine monotherapy for resected pancreatic cancer.

Methods We did a phase 3, two-group, open-label, multicentre, randomised clinical trial at 92 hospitals in England, Scotland, Wales, Germany, France, and Sweden. Eligible patients were aged 18 years or older and had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection). We randomly assigned patients (1:1) within 12 weeks of surgery to receive six cycles of either 1000 mg/m² gemcitabine alone administered once a week for three of every 4 weeks (one cycle) or with 1660 mg/m² oral capecitabine administered for 21 days followed by 7 days' rest (one cycle). Randomisation was based on a minimisation routine, and country was used as a stratification factor. The primary endpoint was overall survival, measured as the time from randomisation until death from any cause, and assessed in the intention-to-treat population. Toxicity was analysed in all patients who received trial treatment. This trial was registered with the EudraCT, number 2007-004299-38, and ISRCTN, number ISRCTN96397434.

Findings Of 732 patients enrolled, 730 were included in the final analysis. Of these, 366 were randomly assigned to receive gemcitabine and 364 to gemcitabine plus capecitabine. The Independent Data and Safety Monitoring Committee requested reporting of the results after there were 458 (95%) of a target of 480 deaths. The median overall survival for patients in the gemcitabine plus capecitabine group was 28·0 months (95% CI 23·5–31·5) compared with 25·5 months (22·7–27·9) in the gemcitabine group (hazard ratio 0·82 [95% CI 0·68–0·98], p=0·032). 608 grade 3–4 adverse events were reported by 226 of 359 patients in the gemcitabine plus capecitabine group compared with 481 grade 3–4 adverse events in 196 of 366 patients in the gemcitabine group.

Interpretation The adjuvant combination of gemcitabine and capecitabine should be the new standard of care following resection for pancreatic ductal adenocarcinoma.

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Introduction

In 2012, an estimated 338 000 new cases of pancreatic cancer were diagnosed worldwide and 331 000 people died from pancreatic cancer.[1] Pancreatic cancer is likely to become the second leading cause of cancer mortality in the near future because therapies for other cancers are becoming more advanced than those for pancreatic cancer and because the prevalence of pancreatic cancer is increasing globally.[1] In patients with advanced pancreatic cancer, 1 year survival has slightly improved because of the wider use of systemic chemotherapy[1] and, more recently, the use of combination chemotherapies,[2–5] including gemcitabine in combination with capecitabine[2] or nab-paclitaxel,[3] and a regimen comprising folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX).[5] Surgical techniques have also substantially improved, allowing more patients to undergo resection,[1] but 5 year survival with tumour removal alone is generally less than

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Research in context

Evidence before this study

In developing this trial, we undertook several systematic reviews and meta-analyses between March, 2006, and March, 2007, in both the advanced and adjuvant settings. We searched MEDLINE, OLDMEDLINE, CancerLit, Embase, ISI Web of Science, ISI Science and Technology Proceedings, current contents databases, trial registries, and conference proceedings, and results identified included randomised controlled trials involving patients with advanced or resected pancreatic cancer of chemotherapy, novel drugs, radiotherapy, chemoradiotherapy, and best supportive care. We were directly involved in the ESPAC-1plus, ESPAC-1, ESPAC-3(v1), and ESPAC-3(v2) adjuvant trials of resected pancreatic cancer. We were also directly involved in the GemCap trial which compared the combination of gemcitabine and capecitabine to gemcitabine alone in advanced and metastatic pancreatic cancer. In the adjuvant setting, the role of chemoradiotherapy was rejected by ESPAC-1plus, which had a pragmatic design comprising randomisation either to chemoradiotherapy plus chemotherapy or or to no chemoradiotherapy plus chemotherapy or alternatively to chemotherapy alone and no adjuvant treatment, and also a 2 × 2 factorial design of chemotherapy versus no chemotherapy and chemoradiotherapy versus no chemoradiotherapy. Although there was scepticism with respect to the efficacy of 5-fluoruracil and folinic acid used in these studies, comparison with the control groups of ESPAC-1plus, ESPAC-1, and ESPAC-3(v1) confirmed the superior survival value of this regimen compared with no chemotherapy. ESPAC-3(v2) showed that adjuvant gemcitabine was not superior to 5-fluoruracil and folinic acid for survival, and, hence, there was a wider choice of proven chemotherapies that could be used to enhance survival over single drugs. In ESPAC-4, we chose the combination of gemcitabine and capecitabine (an orally active 5-fluoruracil prodrug) to compare with gemcitabine, as the combination had a higher objective response, increased progression-free survival,and increased overall survival in a meta-analysis of the two randomised trials compared with gemcitabine monotherapy. Before this study, the evidence was that the best estimated 5 year survival after resection for pancreatic cancer was with adjuvant chemotherapy using either 5-fluorouracil plus folinic acid from ESPAC-1 (21·1% [95% CI 14·6–28·5]) and from ESPAC-3(v2) (15·9% [12·7–19·4]), or gemcitabine from ESPAC-3(v2) (17·5% [14·0–21·2]). For comparison, estimated 5 year survival with resection and no chemotherapy was 8·0% (3·8–14·1) and with chemoradiotherapy was 10·8% (6·1–17·0), as shown in ESPAC-1.

Added value of this study

In ESPAC-4, estimated 5 year survival confirmed the ESPAC-3(v2) estimates for gemcitabine. Survival favoured adjuvant gemcitabine plus capecitabine in most clinical subgroups, including patients with R1 resection margins. This was a pragmatic trial including all patients who had undergone resection for pancreatic ductal adenocarcinoma including WHO performance status 0, 1 and 2, R1 resection margins, and all patients irrespective of postoperative CA19-9 concentration. The improved survival results were achieved without any significant increase in overall toxicity and was manageable with protocol driven capecitabine dose reduction when required.

Implications of all the available evidence

The ESPAC-4 trial establishes the combination of gemcitabine and capecitabine as the treatment of choice in the adjuvant setting after resection for pancreatic ductal adenocarcinoma.

10%.[6–8] After resection, the use of adjuvant chemotherapy with either 5-fluorouracil plus folinic acid or gemcitabine doubled 5 year survival to around 16–21%.[6–10] The role of adjuvant chemoradiotherapy with or without systemic chemotherapy has been questioned, but systemic chemotherapy is generally accepted as the established standard of care.[1,6,7,11,12] Gemcitabine does not increase survival compared with 5-fluorouracil plus folinic acid in the adjuvant setting,[13] although gemcitabine has been the drug of choice because of a better safety profile than 5-fluorouracil plus folinic acid.[6–8,13]

We aimed to assess whether overall survival could be improved by using combination systemic chemotherapy in the adjuvant setting. For this, we chose to use gemcitabine and capecitabine because this combination has synergism between the intracellular metabolites of capecitabine and gemcitabine on thymidylate synthase involved in normal DNA synthesis. Clinical trials in the advanced setting have shown that this combination produces a better tumour response, improved progression free survival, and improved overall survival by meta-analysis compared with monotherapy, while maintaining an acceptable toxicity profile.[2,4]

Methods

Study design and patients

We did a phase 3, two-group, open-label, multicentre, randomised clinical trial at 92 hospitals in England, Scotland, Wales, Germany, France, and Sweden. Eligible patients were aged 18 years or older and had undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection)[14] 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. No restriction was placed on randomisation on the basis of postoperative carbohydrate antigen 19-9 (CA19-9) concentrations. Other specific inclusion criteria were full recovery from surgery, a WHO performance score of two or less, creatinine clearance of at least 50 mL/min, and a

life expectancy of more than 3 months. Patients who had previously had neo-adjuvant chemotherapy or other concomitant chemotherapy and with pancreatic lymphoma, macroscopically remaining tumours (R2 resection), or TNM stage IV disease[15] were excluded.

Ethical approval was provided by the Liverpool Adult Research Ethics Committee on March 4, 2008. Ethical approval was also obtained in each of the other participating countries. The study conformed to the principles of the International Conference on Harmonization on Good Clinical Practice, and was undertaken by the Liverpool Clinical and Cancer Research UK Trials Unit. All participants provided written informed consent before randomisation. The protocol is available online.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive gemcitabine or gemcitabine plus capecitabine within 12 weeks of surgery by trained authorised staff within the Liverpool Clinical and Cancer Trials Unit. Randomisation was based on a minimisation routine with a random element of 20% including the resection margin (negative or positive) and country was used as a stratification factor. Participants and study investigators were not masked to treatment allocation.

Procedures

Gemcitabine was delivered as a 1000 mg/m² intravenous infusion administered once a week for three of every 4 weeks (one cycle) for six cycles (24 weeks). Capecitabine was administered orally for 21 days followed by 7 days' rest (one cycle) for six cycles (24 weeks) at a daily dose of 1660 mg/m². Patients were reviewed every 3 months after surgery for 5 years if alive at this point. 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.

Outcomes

The primary endpoint was overall survival, measured as the time from randomisation until death from any cause. Patients still alive at the point of final analysis were censored at the date last seen alive. Secondary endpoints included survival estimates at 24 months, 5 year survival, and relapse-free survival measured as the minimum time from randomisation to date of local tumour recurrence, lymph node spread, distant metastases, or death from any cause. Toxicity was graded according to the National Cancer Institute common toxicity criteria, version 4.03. 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 5 year survival estimates were also calculated for the ESPAC-3 trial (version 2), which were not previously available at the time of publication.[13]

Statistical analysis

This trial was designed to detect a hazard ratio (HR) of 0·74 between the gemcitabine and gemcitabine plus capecitabine groups. With the use of a two-sided α level of 0·05, 480 events were required to obtain 90% power to detect a difference between treatment groups. We estimated that 480 events could be obtained by enrolling 722 patients (361 in each group) over a period of 6 years (reaching a maximum recruitment rate of 13 patients per month) and allowing each patient to have a minimum follow-up of 2 years. The sample size was inflated to account for patient withdrawals (10%) and patients who were lost to follow-up (5%) at the time of analysis.

We estimated overall survival using the Kaplan-Meier method. We analysed the primary endpoint with a stratified log-rank test,[16] with the treatment effect expressed as an HR (gemcitabine plus capecitabine *vs* gemcitabine) and 95% CI. Median and 5 year survival estimates are presented with 95% CIs. Further analyses were done by adjusting the treatment effect using multivariable regression techniques based on the Cox proportional hazard[17] model and using multiple imputation[18] based on chained equations to impute missing data of key prognostic covariates. 50 imputed datasets were used with variable estimates obtained with the use of Rubin's rules. Factors with a p value less than 0·25 using a univariate log-rank test were explored further in the multivariable setting using backward selection techniques based on Akaikes Information Criterion.[19] Assumptions of proportional hazards were assessed by assessment of the Schoenfeld residuals.[20]

The number of patients receiving treatment, the percentage of patients receiving treatment as per the protocol, and the range of total doses received are reported. The median follow-up was calculated with the reverse Kaplan-Meier method.[21] The number of patients experiencing at least one high-grade (3 or 4) toxic episode or serious adverse event is also reported as a percentage of the total number of patients in the safety set within each treatment group. Proportions were compared with Fisher's exact test with the significance level set at p values less than 0·05. Further comparisons of toxicity between treatment groups were done according to short-term acute toxicity, adverse long-term late effects, and mortality risk generated by a treatment programme (TAME) method guidelines.[22] Quality of life was assessed as a longitudinal covariate which was modelled jointly[23] with overall survival, in which both longitudinal and survival models were adjusted for key prognostic covariates.

All efficacy analyses were done in the intention-to-treat population retaining all patients in their initially randomised groups irrespective of any protocol deviations with the exception of patients who withdrew consent between randomisation and the start of therapy. Toxicity was analysed in all patients who received trial treatment according to the treatment they received.

For the **protocol** see https://www.lctu.org.uk/Public/SSES4_PROTOCOL.9-ESPAC-4_Protocol.pdf

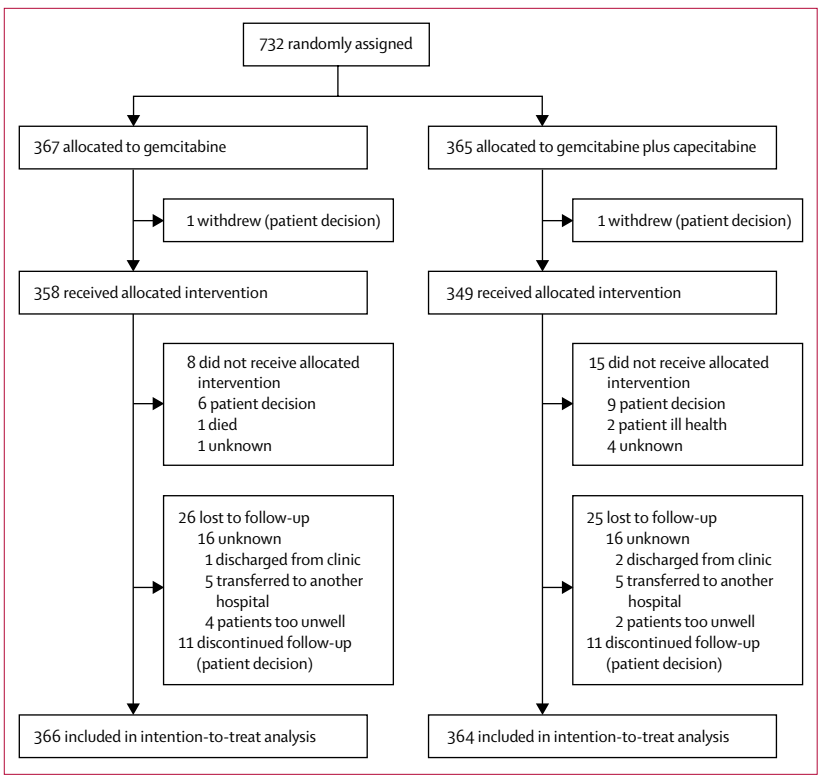

Figure 1: **Trial profile**

Interim analyses for efficacy were included after 100, 200, 300, and 400 deaths. Efficacy was determined with the use of Peto boundaries, and no adjustments to the final α level were required.[24] These analyses were undertaken by the Independent Safety and Data Monitoring Committee in a strictly controlled confidential manner. The Independent Safety and Data Monitoring Committee was also responsible for assessing the trial in terms of safety and had full access to all of the data throughout the course of the trial. Final decisions on the conduct of the trial were taken by the Trial Steering Committee, which received recommendations from the Independent Safety and Data Monitoring Committee and support from the Trial Management Group. All statistical analyses were done with SAS version 9.3 and Stata version 13.1. A two-sided significance level of p values less than 0·05 was used throughout. This trial was registered with the EudraCT, number 2007-004299-38, and ISRCTN, number ISRCTN96397434.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Following the decision of the Independent Data and Safety Monitoring Committee to recommended early publication, JPN, EEP, DHP, PG, and RJ had full access to all the data in the study from Dec 11, 2015. They take full responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author took the final responsibility for the decision to submit for publication.

See Online for appendix

Results

Between Nov 10, 2008, and Sept 11, 2014, 732 patients were randomly assigned. The target was 722 patients, but the extra 10 patients were recruited for pragmatic reasons. At the time of recruitment termination, there were patients at different sites still considering joining the trial. If they wished to join the trial, we allowed them to do so for ethical reasons. The data cutoff date was March 9, 2016. 367 patients were randomly assigned to receive gemcitabine alone and 365 were randomly assigned to receive gemcitabine plus capecitabine (figure 1). Two patients were excluded from the full analysis set as they withdrew consent between randomisation and starting therapy (one in each group). The Independent Data and Safety Monitoring Committee recommended early publication based on a clear signal of efficacy, and this was accepted on Dec 11, 2015, by the Trial Steering Committee. Demographic and pathological details of the patients by group are shown in table 1. Eight patients who had stage IV pancreatic tumours but had complete surgical clearance and were anxious to join the trial were enrolled in the study.

The median follow-up time was 43·2 months (95% CI 39·7–45·5). The median overall survival time was 25·5 months (22·7–27·9) in the gemcitabine group and 28·0 months (23·5–31·5) in the gemcitabine plus capecitabine (HR 0·82 [95% CI 0·68–0·98], p=0·032), favouring the gemcitabine plus capecitabine group (figure 2). Estimated overall survival was 80·5% (95% CI 76·0–84·3) at 12 months and 52·1% (46·7–57·2) at 24 months in the gemcitabine group and 84·1% (79·9–87·5) at 12 months and 53·8% (48·4–58·8) at 24 months in the gemcitabine plus capecitabine group. The median overall survival for patients in the gemcitabine group who had positive resection margins (R1 status) was 23·0 months (95% CI 21·6–26·2) and in patients who had negative resection margins (R0 status) was 27·9 months (23·8–34·6). Median overall survival for patients in the gemcitabine plus capecitabine group was 23·7 months (20·7–27·1) in patients with R1 status and 39·5 months (32·0–58·0) in patients with R0 status ($\chi^2_{1df,trend}$=14·83, p=0·0001; figure 2). Sensitivity analyses done in the per-protocol population did not differ significantly from the primary analysis of the intention-to-treat population.

Univariate survival analyses showed that smoking, preoperative, and postoperative CA19-9 concentrations, preoperative C-reactive protein concentrations, resection margin status, tumour grade, lymph nodes status, maximum tumour size, tumour stage, venous resection, and local invasion were all associated with survival (p<0·05; table 2) but not performance status (appendix).

	Gemcitabine (n=366)	Gemcitabine plus capecitabine (n=364)	Total participants (n=730)
Sex			
Male	212 (58%)	202 (55%)	414 (57%)
Female	154 (42%)	162 (45%)	316 (43%)
Age (years)	65 (37–80)	65 (39–81)	65 (37–81)
WHO status			
0	158 (43%)	150 (41%)	308 (42%)
1	199 (54%)	202 (55%)	401 (55%)
2	9 (2%)	12 (3%)	21 (3%)
Smoking status			
Never	151 (41%)	146 (40%)	297 (41%)
Past	136 (37%)	148 (41%)	284 (39%)
Present	62 (17%)	61 (17%)	123 (17%)
Unknown	17 (5%)	9 (2%)	26 (4%)
Concurrent conditions			
None	82 (22%)	106 (29%)	188 (26%)
Yes	280 (77%)	257 (71%)	537 (74%)
Unknown	4 (1%)	1 (<1%)	5 (1%)
Diabetes			
No	266 (73%)	272 (75%)	538 (74%)
Non-insulin-dependent	52 (14%)	45 (12%)	97 (13%)
Insulin-dependent	47 (13%)	46 (13%)	93 (13%)
Unknown	1 (<1%)	1 (<1%)	2 (<1%)
Preoperative carbohydrate antigen 19-9 (KU/L)			
Number of patients with measurements	234	224	458
Median	142·5 (0·9–10 761·0)	154·5 (0·8–76 549·0)	150·5 (0·8–76 549·0)
Postoperative carbohydrate antigen 19-9 (KU/L)			
Number of patients with measurements	341	321	662
Median	20·5 (0·1–2448·3)	17·6 (0·6–8112·0)	18·7 (0·1–8112·0)
Preoperative C-reactive protein (mg/L)			
Number of patients with measurements	275	271	546
Median	8·0 (0·1–343·0)	8·0 (0·3–190·0)	8·0 (0·1–343·0)

(Table 1 continues in next column)

	Gemcitabine (n=366)	Gemcitabine plus capecitabine (n=364)	Total participants (n=730)
(Continued from previous column)			
Postoperative C-reactive protein (mg/L)			
Number of patients with measurements	344	348	692
Median	5·0 (0·1–345·0)	5·0 (0·0–296·0)	5·0 (0·0–345·0)
Time from surgery to randomisation (days)			
Median	65 (23–111)	64 (21–111)	64 (21–111)
Hospital stay (days)			
Number of patients with measurements	363	357	720
Median	12 (1–89)	12 (3–58)	12 (1–89)
Resection margin status			
Number of patients with negative status	147 (40%)	143 (39%)	290 (40%)
Number of patients with positive status	219 (60%)	221 (61%)	440 (60%)
Country			
France	12 (3%)	12 (3%)	24 (3%)
Germany	34 (10%)	33 (9%)	67 (9%)
Sweden	40 (11%)	43 (12%)	83 (11%)
England	257 (70%)	254 (70%)	511 (70%)
Scotland	12 (3%)	9 (2%)	21 (3%)
Wales	11 (3%)	13 (4%)	24 (3%)
Tumour grade			
Well differentiated	30 (8%)	32 (9%)	62 (8%)
Moderately differentiated	192 (52%)	175 (48%)	367 (50%)
Poorly differentiated	140 (38%)	147 (40%)	287 (39%)
Undifferentiated	2 (1%)	2 (1%)	4 (1%)
Unknown	2 (1%)	8 (2%)	10 (1%)
Lymph nodes			
Negative	67 (18%)	76 (21%)	143 (20%)
Positive	299 (82%)	288 (79%)	587 (80%)
Maximum tumour size (mm)			
Number of patients with measurements	361	352	713
Median	30 (0–110)	30 (6–105)	30 (0–110)

(Table 1 continues on next page)

	Gemcitabine (n=366)	Gemcitabine plus capecitabine (n=364)	Total participants (n=730)
(Continued from previous page)			
Tumour stage			
I	7 (2%)	15 (4%)	22 (3%)
II	29 (8%)	20 (5%)	49 (7%)
III	325 (89%)	326 (90%)	651 (89%)
IV	5 (1%)	3 (1%)	8 (1%)
Surgery			
Whipple resection	188 (51%)	182 (50%)	370 (51%)
Total pancreatectomy	27 (7%)	22 (6%)	49 (7%)
Pylorous-preserving resection	122 (33%)	129 (35%)	251 (34%)
Distal pancreatectomy	29 (8%)	31 (9%)	60 (8%)
Venous resection			
No	298 (81%)	323 (89%)	621 (85%)
Yes	63 (17%)	39 (11%)	102 (14%)
Unknown	5 (1%)	2 (1%)	7 (1%)
Extent of resection			
Standard	289 (79%)	279 (77%)	568 (78%)
Radical	53 (14%)	56 (15%)	109 (15%)
Extended lymphadenectomy	18 (5%)	28 (8%)	46 (6%)
Unknown	6 (2%)	1 (<1%)	7 (1%)
Cholecystectomy			
No	78 (21%)	90 (25%)	168 (23%)
No, already excised	18 (5%)	16 (4%)	34 (5%)
Yes	270 (74%)	257 (71%)	527 (72%)
Unknown	0	1 (<1%)	1 (<1%)
Local invasion			
No	189 (52%)	189 (52%)	378 (52%)
Yes	176 (48%)	173 (48%)	349 (48%)
Unknown	1 (0%)	2 (1%)	3 (<1%)
Postoperative complications			
No	271 (74%)	250 (69%)	521 (71%)
Yes	93 (25%)	113 (31%)	206 (28%)
Unknown	2 (1%)	1 (<1%)	3 (<1%)

(Table 1 continues in next column)

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Data are n (%) or median (range).

Table 1: **Baseline characteristics**

Postoperative CA19-9 concentration and maximum tumour size were included in the multivariable Cox proportional hazards model under non-linear transformations. The stratification factors of resection margin and country were forced inclusions as main effects in the model. Multiple imputation was used to correct for missing data for postoperative CA19-9 concentration (n=68), maximum tumour size (n=15), and tumour grade (n=3). A model based on 730 patients (446 deaths) identified resection margin status, postoperative CA19-9 concentrations, tumour grade, lymph node status, and maximum tumour size as significant independent factors of overall survival (table 2). Gemcitabine and capecitabine had a statistically significant treatment effect compared with gemcitabine alone (HR 0·79 [95% CI 0·66–0·96], p=0·016). Assessment of Schoenfeld's residuals did not identify any covariates that violated the proportional hazards assumption. Median postoperative CA19-9 concentrations were 17·7 KU/L (9·0–44·0) in the resection margin-negative group and 20·0 KU/L (9·0–63·5) in the resection margin-positive groups (p=0·11 unpaired *t* test on the log-transformed data).

For comparison with the CONKO-01[8] and JASPAC-1[25] trials, we further analysed survival data using cutoff points for postoperative CA19-9 concentrations of more than 92·5 KU/L and more than 37 KU/L. 68 (9%) patients in our study had missing postoperative CA19-9 values. 549 (83%) patients had postoperative CA19-9 concentrations of 92·5 KU/L or lower with a median survival of 29·6 months (26·6–32·1) and 5-year survival of 24·9% (20·0–31·0). 113 (17%) patients had CA19-9 concentrations higher than 92·5 KU/L with a median survival of 13·1 months (10·8–16·2) and 5 year survival was not obtained. 452 (68%) of 662 patients had a CA19-9 concentration of 37 KU/L or lower with a median survival of 31·8 months (29·5–38·0) and a 5 year survival of 25·6% (20·0–32·8) and 210 (32%) patients had postoperative CA19-9 concentrations of more than 37 KU/L with median survival of 16·0 months (14·1–17·9) and 5 year survival of 14·9% (0·10–22·6). Comparisons of postoperative CA19.9 by treatment arms for ESPAC-4, CONKO-001, and JASPAC01 are shown in table 3.

557 (76%) patients had a relapse or died. Of these, 286 (78%) were in the gemcitabine group, and 271 (74%)

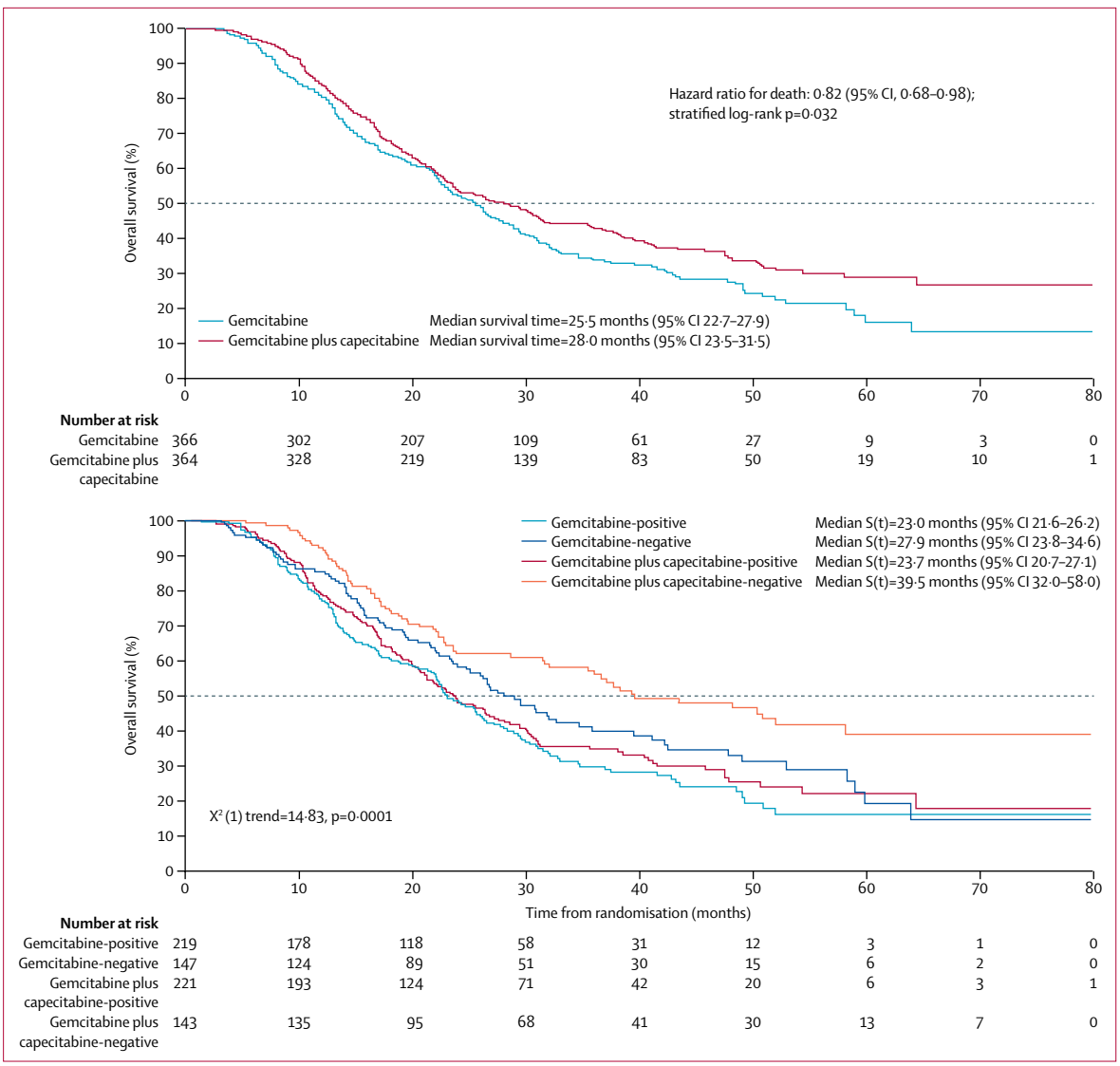

Figure 2: **Kaplan Meier plots for overall survival (A) and for overall survival by resection margin status and treatment group (B)**

were in the gemcitabine plus capecitabine group. The median relapse-free survival was 13·1 months (11·6–15·3) in the gemcitabine group and 13·9 months (12·1–16·6) in the gemcitabine and capecitabine group (HR 0·86, 95% CI 0·73–1·02, p=0·082; appendix). 3 year relapse-free survival was 20·9% (16·5–25·7) and 5 year relapse-free survival was 11·9% (7·8–16·9) for the gemcitabine group, whereas for the gemcitabine plus capecitabine group, 3 year relapse-free survival was 23·8% (19·2–28·6) and 5 year relapse-free survival was 18·6% (13·8–24·0; appendix). 479 (66%) of 730 patients had tumour recurrence, of whom 243 (66%) were in the gemcitabine group and 236 (65%) were in the gemcitabine plus capecitabine group. 78 (11%) patients died without radiological evidence of tumour recurrence. Specific sites of tumour recurrence at relapse are given in table 4.

94 (39%) of 243 patients in the gemcitabine group with relapse and 77 (33%) of 236 patients in the gemcitabine plus capecitabine group with relapse received additional treatment. In the gemcitabine group, additional treatment comprised chemotherapy in 77 (32%) patients, chemo-radiotherapy in 10 (4%) patients, surgery in 12 (5%) patients, and other treatment in 5 (2%) patients, with some patients having multiple treatments. Additional treatment in the gemcitabine plus capecitabine group comprised chemotherapy in 72 (31%) patients, chemoradiotherapy in 10 (4%) patients, surgery in 8 (3%) patients, and other treatment in 5 (2%) patients. Of the 243 patients in the gemcitabine group who relapsed, 38 (16%) patients had capecitabine in some form as additional chemotherapy.

Estimated 5 year survival was compared between the randomised groups across the ESPAC-1,[7] ESPAC-3(v2),[13]

	HR (95% CI)	Log-rank χ^2	p value
Univariate Cox proportional hazards models			
Sex			
Male	1	..	..
Female	0·85 (0·71–1·03)	2·83	0·092
Age (years)	1·00 (0·99–1·01)	0·14	0·708
WHO status			
0	1	..	..
1	1·13 (0·94–1·37)	1·68	0·194
2	1·31 (0·73–2·34)	0·81	0·369
Smoking status			
Never	1	..	..
Past	1·05 (0·85–1·29)	0·20	0·654
Present	1·38 (1·07–1·78)	5·97	0·015
Diabetes			
No	1	..	..
Non-insulin-dependent	0·95 (0·72–1·26)	0·12	0·726
Insulin-dependent	1·03 (0·78–1·37)	0·06	0·813
Preoperative carbohydrate antigen 19-9 (KU/L)*	1·07 (1·01–1·14)	5·36	0·021
Postoperative carbohydrate antigen 19-9 (KU/L)†	1·36 (1·28–1·45)	91·6	<0·0001
Preoperative C-reactive protein (mg/L)*	1·09 (1·01–1·19)	4·89	0·027
Postoperative C-reactive protein (mg/L)*	0·98 (0·93–1·04)	0·31	0·577
Resection margin			
Negative	1	..	
Positive	1·51 (1·24–1·83)	17·4	<0·0001
Country			
England	1	..	..
France	1·08 (0·66–1·76)	0·10	0·755
Germany	0·75 (0·52–1·09)	2·30	0·129
Sweden	0·78 (0·57–1·05)	2·76	0·096
Scotland	0·69 (0·37–1·29)	1·34	0·247
Wales	1·09 (0·67–1·78)	0·13	0·718
Tumour grade			
Well	1	..	..
Moderate	1·41 (0·96–2·08)	3·02	0·082
Poorly	2·35 (1·59–3·46)	18·5	<0·0001
Undifferentiated	0·67 (0·09–4·91)	0·16	0·692
Unknown	1·12 (0·39–3·18)	0·04	0·837
Lymph nodes			
Negative	1	..	..
Positive	2·36 (1·78–3·11)	36·4	<0·0001
Maximum tumour size (mm)‡	1·12 (1·06–1·18)	16·4	<0·0001
Tumour stage			
I or II	1	..	..
III or IV	1·60 (1·13–2·25)	7·02	0·008
Venous resection			
No	1	..	..
Yes	1·30 (1·01–1·67)	4·11	0·042
Local invasion			
No	1	..	..
Yes	1·32 (1·10–1·58)	8·62	0·003
Treatment§			
Gemcitabine	1	..	..
Gemcitabine plus capecitabine	0·82 (0·68–0·98)	4·61	0·032
Multivariate Cox proportional hazards models			
Treatment			
Gemcitabine	1	..	..
Gemcitabine plus capecitabine	0·79 (0·66–0·96)	5·76	0·016
Resection margin			
Negative	1	..	..
Positive	1·27 (1·04–1·55)	5·40	0·020
Country			
England	1	..	..
France	1·89 (1·10–3·23)	5·36	0·021
Germany	0·83 (0·57–1·20)	0·97	0·324
Sweden	0·85 (0·63–1·15)	1·09	0·297
Scotland	0·65 (0·34–1·24)	1·71	0·191
Wales	1·13 (0·68–1·89)	0·24	0·625
Postoperative carbohydrate antigen 19-9 (KU/L)†	1·24 (1·17–1·33)	43·27	<0·0001
Tumour grade			
Well	1	..	..
Moderate	1·65 (1·08–2·52)	5·45	0·020
Poor	2·58 (1·68–3·97)	18·86	<0·0001

(Table 2 continues in next column)

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(Table 2 continues on next page)

	HR (95% CI)	Log-rank χ^2	p value
(Continued from previous page)			
Undifferentiated	1·05 (0·34–3·24)	0·01	0·926
Unknown	1·24 (0·16–9·28)	0·04	0·836
Lymph nodes			
Negative	1	..	..
Positive	1·74 (1·30–2·33)	14·14	<0·0001
Maximum tumour size (mm)‡	1·12 (1·04–1·21)	8·73	0·003

HR=Hazard ratio. *Log transformation applied. †Log transformation applied: log (carbohydrate antigen 19-9 + 1). ‡Square root transformation applied: χ^2 (max tumour size + 0·5). §Adjusted for stratification factors, resection margin, and country.

Table 2: **Analysis of efficacy**

and ESPAC-4 adjuvant treatment trials (appendix). In the ESPAC-1 trial, estimated 5 year survival was 21·1% (95% CI 14·6–28·5) for the chemotherapy group (5-fluorouracil plus folinic acid), 8·0% (3·8–14·1) in the no chemotherapy group, and 10·8% (6·1–17·0) in the group randomised to chemoradiotherapy.[7] In the ESPAC-3(v2) trial, estimated 5 year survival was 17·5% (14·0–21·2) for patients in the gemcitabine group and 15·9% (12·7–19·4) for patients in the 5-fluorouracil plus folinic acid group. In the ESPAC-4 trial, estimated 5 year survival was 16·3% (10·2–23·7) for patients randomised to gemcitabine, and 28·8% (22·9–35·2) for patients randomised to gemcitabine plus capecitabine. Adjuvant gemcitabine plus capecitabine favoured survival in most clinical subgroups (figure 3).

1877 cycles of gemcitabine were given to 365 (100%) patients in the gemcitabine group, and 1724 cycles of gemcitabine plus capecitabine were given to 361 (98%) patients in the gemcitabine plus capecitabine group. One (<1%) patient in the gemcitabine group, and six (2%) patients in the gemcitabine plus capecitabine group did not start treatment. All six cycles of treatment were given to 239 (65%) patients in the gemcitabine group and to 195 (54%) in the gemcitabine plus capecitabine group.

The median dose intensity was 93% (5–104) of the planned protocol for the gemcitabine group, and 83% (5–114) for gemcitabine and 78% (0·8–100) for capecitabine in the gemcitabine plus capecitabine group. The median cumulative dose of gemcitabine was 16750 mg/m² in the gemcitabine group, and 15000 mg/m² in the gemcitabine plus capecitabine group. The median cumulative dose of capecitabine was 162680 mg/m². 458 (63%) patients died, 239 (65%) of 366 patients in the gemcitabine group and 219 (60%) of 364 patients in the gemcitabine plus capecitabine group. 127 (35%) of 366 patients in the gemcitabine group stopped treatment before the end of the sixth cycle due to toxicity in 52 (41%), disease progression in 32 (25%), patient decision in 13 (10%),

	CONKO-001			JASPAC 01			ESPAC-4				HR (gemcitabine plus capecitabine *vs* gemcitabine)
	Gemcitabine			Gemcitabine			Gemcitabine		Gemcitabine plus capecitabine		
	Number of patients	Median survival	5 year overall survival	Number of patients	Median survival	5 year overall survival	Number of patients	Median survival	5 year overall survival	Number of patients	Median survival	5 year overall survival	
CA19-9≤92·5 KU/L	179 (100%)	22·8 (18·5–27·2)	20·7% (14·7–26·6)	..	..	..	279 (84%)	28·6 (26·2–31·9)	18·4% (11·9–28·4)	270 (84%)	31·0 (25·5–39·5)	30·7% (24·1–39·0)	0·87 (0·70–1·08); p=0·207
CA19-9>92·5 KU/L	0	..	..	..	..	..	62 (16%)	12·2 (9·3–14·9)	..	51 (16%)	16·6 (12·1–22·3)	..	0·62 (0·44–0·88); p=0·007
HR for CA19-9 >92·5 KU/L *vs* CA19-9 ≤92·5 KU/L	..	..	..	..	..	..	3·5 (2·546–4·807); p<0·0001	..	..	2·48 (1·73–3·547); p<0·0001	..	..	..
CA19-9≤37 KU/L	..	..	..	146 (77%)	..	..	227 (67%)	29·9 (27·1–34·6)	16·1% (9·0–28·6)	225 (70%)	37·7 (30·4–47·7)	33·2% (25·8–42·6)	0·81 (0·63–1·04); p=0·096
CA19-9>37 KU/L	..	..	..	44 (23%)	..	..	114 (33%)	14·7 (13·2–17·2)	14·8% (9·6–25·4)	96 (30%)	17·1 (14·5–22·0)	15·9% (8·9–28·4)	0·78 (0·60–1·04); p=0·086
HR for CA19-9>37 KU/L *vs* CA19-9≤37 KU/L	..	..	..	..	..	..	2·17 (1·653–2·835); p<0·0001	..	..	2·36 (1·756–3·172); p<0·0001	..	..	..

Data are n (%) or survival (95% CI), unless otherwise specified. CA19-9=carbohydrate antigen 19-9. HR=hazard ratio.

Table 3: **Comparisons of postoperative CA19-9 levels on survival of ESPAC-4 with the CONKO-01 and JASPAC-1 trials**

	Gemcitabine (n=366)	Gemcitabine plus capecitabine (n=364)	Total (n=730)	p value*
Disease relapse	243 (66%)	236 (65%)	479 (66%)	0·715
Site of relapse				
Local	129 (53%)	109 (46%)	238 (50%)	0·156
Liver	106 (44%)	92 (39%)	198 (41%)	0·348
Other intra-abdominal	46 (19%)	63 (27%)	109 (23%)	0·055
Lung	23 (9%)	29 (12%)	52 (11%)	0·398
Bone	7 (3%)	6 (3%)	13 (3%)	1·000
Unknown	4 (2%)	5 (2%)	9 (2%)	0·965
Death without recurrence	43 (12%)	35 (10%)	78 (11%)	0·416

Table 4: **Pattern of disease relapse**

death in three (2%), treatment never started in 1 (1%), lack of efficacy in 1 (1%), various other reasons in 11 (9%), and unknown reasons in 14 (11%). 169 (46%) of 364 patients in the gemcitabine plus capecitabine group stopped treatment before the end of the sixth cycle because of toxicity in 79 (47%), disease progression in 17 (10%), patient decision in 21 (12%), death in 4 (2%), treatment never started in three (2%), various other reasons in 7 (4%), and unknown reasons in 38 (22%).

725 (99%) patients were in the safety set and were analysed for adverse events. Of these, 366 received gemcitabine alone, and 359 received gemcitabine plus capecitabine (table 5). 180 (25%) of the 725 patients reported 305 treatment-related serious adverse events. 94 (26%) patients of the 366 who received gemcitabine had 151 events, and 86 (24%) of the 359 patients who received gemcitabine plus capecitabine had 154 events (p>0·05). There were 608 grade 3–4 events reported by 226 of 359 patients in the gemcitabine with capecitabine group compared with 481 grade 3–4 events in 196 of 366 patients in the gemcitabine group. The mean expected high-grade acute adverse event (within 30 days of treatment completion) was 0·89 in the gemcitabine group and 1·2 in the gemcitabine plus capecitabine group.[23] The corresponding high-grade late adverse event (after 30 days of treatment completion) was 0·3 in the gemcitabine group and 0·4 in the gemcitabine plus capecitabine group.[23]

Quality-of-life questionnaires were completed by 665 patients, 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 patients, respectively. Joint modelling included an intercept term for treatment group but not a time-by-treatment interaction as this did not improve the overall model fit. The results showed no significant effect in the longitudinal estimate of quality of life by treatment group (HR –0·10, 95% CI –0·29 to 0·09, p=0·3).

Discussion

This study has shown that survival with adjuvant chemotherapy with gemcitabine plus capecitabine significantly increased overall survival compared with gemcitabine alone after resection for pancreatic cancer. This occurred with an acceptable level of toxicity as predicted from the previous phase 3 trial in the advanced and metastatic setting.[3] Grade 3 or 4 neutropenia was more common in the gemcitabine plus capecitabine group (38%) than in the gemcitabine group (24%), but the rate of febrile neutropenia was low in both groups and there were fewer other infective manifestations in the gemcitabine plus capecitabine group (3%) compared with the gemcitabine group alone (7%). As expected, more grade 3 and 4 diarrhoea events occurred with gemcitabine plus capecitabine (5%) than with gemcitabine alone (2%). The only grade 3 and 4 hand-foot syndrome events occurred with the combination chemotherapy, but this only affected 7% of patients and was generally manageable with appropriate capecitabine dose modification.

The improvement in overall survival with systemic chemotherapy with 5-fluorouracil plus folinic acid shown in the ESPAC-1 trial represented a step change in survival after resection for pancreatic cancer, doubling the estimated 5 year survival to 21·1% (95% CI 14·6–28·5) compared with 8·0% (3·8–14·1) for surgery alone or 10·8% (6·1–17·0) for chemoradiotherapy.[6,7] The ESPAC-3 trial was important in showing that gemcitabine was not superior to 5-fluorouracil plus folinic acid and so pointed to the potential combination use of gemcitabine with 5-fluorouracil plus folinic acid.[13] The CONKO-001 trial[8] estimated a 5 year overall survival of 20·7% (14·7–26·6) in patients who received gemcitabine, which was slightly better than that estimated for gemcitabine in ESPAC-4. Similarly, the estimated 5 year overall survival in the control group of the CONKO-001 trial (no adjuvant chemotherapy) of 10·4% (5·9–15·0) was also slightly better than that estimated in the no chemotherapy groups of ESPAC-1[6,7] and ESPAC-3(v1).[9] These results need to be considered in the context of the inclusion criteria of CONKO-001, which specified that no patient with a postoperative CA19-9 concentration greater than 2·5 times the upper limit (92·5 KU/L) would be included.[8] As shown in both the ESPAC-3(v2)[13] and ESPAC-4 trials, the concentration of postoperative blood CA19-9 is a powerful independent predictor of survival (table 2). The quartile of patients with the highest postoperative blood CA19-9 concentrations had significantly lower overall survival than the other quartiles but still with significant survival benefit from adjuvant chemotherapy (appendix).

In ESPAC-4, 113 (17%) patients had postoperative CA19-9 concentrations higher than 92·5 KU/L with a median survival of 13·1 (10·8–16·2) months compared with those with a CA19-9 concentration of 92·5 KU/L or lower and a median survival of 29·6 (26·6–32·1) months. Other differences relating to independent prognostic variables between CONKO-001 and ESPAC-4 were tumour grade 3 (36% *vs* 40%, respectively), and lymph node positivity (68% *vs* 80%, respectively). Resection

margin positivity in CONKO-001 used the TNM system general definition of microscopic residual tumour, compared with the ESPAC-4 definition of any tumour cell within 1 mm of any surface of the specimen and this might account for some of the difference in the proportion of R1 cases reported in the two studies (17% *vs* 60% respectively). Overall, the patients in the ESPAC-4 trial appear to have had worse independent prognostic variables than those in CONKO-001, which makes the survival results of ESPAC-4 even more notable.

The ESPAC-4 trial has shown a further step change in overall survival with gemcitabine plus capecitabine, with an estimated 5 year overall survival of 28·8% (22·9–35·2) compared with 16·3% (10·2–23·7) with gemcitabine, and also compared with 15·9% (12·7–19·4) with 5-fluorouracil plus folinic acid in the ESPAC-1 trial.[7]

Capecitabine is an orally active, tumour-selective, fluoropyrimidine carbamate providing prolonged fluorouracil exposure at lower peak concentrations. We have shown that the improvements in tumour response and disease control observed with gemcitabine plus capecitabine in advanced pancreatic cancer[3] can translate into a clear effect in the adjuvant setting. The JASPAC-1 pancreas cancer adjuvant trial has also shown superior survival with S-1, an orally active fluoropyrimidine compared with gemcitabine.[25] Estimated overall 5 year survival was 44·1% (36·9–51·1)% in the S-1 group and 24·4% (18·6–30·8) in the gemcitabine group.[25] The JASPAC-1 trial was undertaken in a group of patients with favourable prognostic features compared with the ESPAC trials. In the JASPAC-1 trial, 69% of the patients had a performance status of 0 compared with 42% in ESPAC-4, and 37% had an N0 status compared with only 20% in ESPAC-4.[25] The definition of R1 in JASPAC-1 was the microscopic presence of tumour cells at the surface of the resection margin and was present in 13% of specimens compared with 60% in ESPAC-4, where the definition was any tumour cell within 1 mm of any surface of the specimen and may account for some, but certainly not all, of the discrepancy.[15] In JASPAC-1, 99 (26%) of the 377 patients included in the analysis had a CA19-9 concentration greater than the upper limit of normal (37 KU/L) compared with 32% in the ESPAC-4 trial. The higher survival figures for gemcitabine in this trial compared with either ESPAC-3(v2) or ESPAC-4 might be accounted at least partly for by the inclusion of patients with better prognostic features in JASPAC-1. Lymph node status, performance status, and resection margin status are all independent significant survival factors shown in both ESPAC-3(v2) and ESPAC-4 (table 2, appendix). Europeans had higher toxicity with S-1 than Asians at equivalent doses because of differences in metabolism, so the findings of JASPAC-1 will be limited by ethnic considerations and trials of S-1 are required to assess its efficacy in whites.[25]

Despite a greater intensity of adverse survival factors in ESPAC-4, the median relapse-free survival was

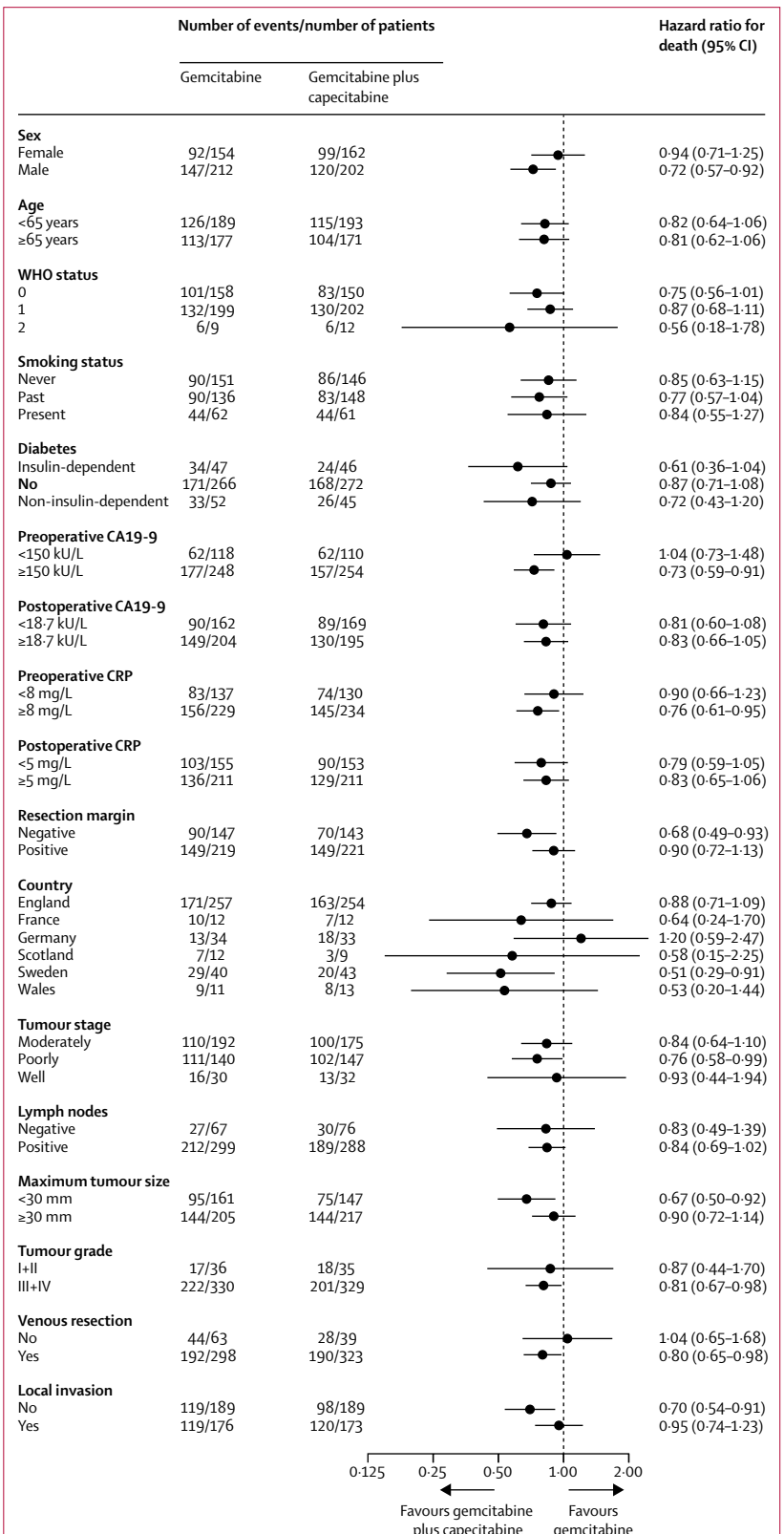

Figure 3: **Forest plot of the treatment effect on overall survival in prespecified subgroups**

	Gemcitabine (n=366)			Gemcitabine plus capecitabine (n=359)			p value grade 1–2	p value grade 3–4
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5		
Anaemia	213 (58%)	14 (4%)	0	201 (56%)	8 (2%)	0	0·549	0·279
Diarrhoea	151 (41%)	6 (2%)	0	161 (45%)	19 (5%)	0	0·331	0·008
Fatigue	241 (66%)	19 (5%)	0	230 (64%)	20 (6%)	0	0·641	0·870
Fever	74 (20%)	6 (2%)	0	62 (17%)	6 (2%)	0	0·342	1·000
Infection and infestations, other	56 (15%)	24 (7%)	0	37 (10%)	9 (3%)	1 (<1%)	0·046	0·012
Lymphocyte count decreased	100 (27%)	11 (3%)	0	78 (22%)	9 (3%)	0	0·085	0·821
Neutropenia	147 (40%)	89 (24%)	0	175 (49%)	137 (38%)	0	0·021	0·0001
Hand-foot syndrome	8 (2%)	0	0	111 (31%)	26 (7%)	0	<0·0001	<0·0001
Platelets	87 (24%)	7 (2%)	0	104 (29%)	8 (2%)	0	0·129	0·800
Thromboembolic events	7 (2%)	9 (2%)	0	16 (4%)	8 (2%)	0	0·058	1·000
White blood cell count decreased	136 (37%)	28 (8%)	0	141 (39%)	37 (10%)	0	0·593	0·242
Acute kidney injury	4 (1%)	2 (1%)	0	1 (<1%)	0	0	0·373	0·499
Multi-organ failure	0	0	1 (<1%)	0	0	0	NA	NA
Cardiac disorders	4 (1%)	1 (<1%)	1 (<1%)	3 (1%)	0	0	1·000	1·000
Benign, malignant, and unspecified neoplasms (including cysts and polyps), other	1 (<1%)	0	3 (1%)	0	1 (<1%)	0	1·000	0·495

Fisher's exact test was used to show statistically significant differences between the two groups. NA=not applicable.

***Table 5*: Grade 1–5 adverse events with gemcitabine alone and gemcitabine plus capecitabine**

13·1 months in the gemcitabine monotherapy group compared with 11·3 and 13·4 months respectively in the JASPAC-1[25] and CONKO-001[8] studies. This might be because of the high median dose intensity of gemcitabine delivered in the monotherapy group comprising 93% of the planned protocol in ESPAC-4, compared with a median of 84% and 86% in the gemcitabine groups in the JASPAC-1[25] and CONKO-001[8] studies respectively. In the JASPAC-1 trial, 149 (78%) patients had a relapse in the gemcitabine group and 123 (66%) had a relapse in the S-1 group.[25] In ESPAC-4, 243 (66%) patients had a relapse in the gemcitabine group compared with 236 (65%) patients in the combination group. Despite the similarities between the JASPAC-1 and ESPAC-4 trials in overall relapse, major differences were found in the frequency of tumour site recurrences, including local site recurrence (26% *vs* 53%), and liver metastases (26% *vs* 44%, respectively) in each of the respective gemcitabine groups. The reason for such discrepancies is unclear.

The proportion of patients who had salvage therapy in ESPAC-4 was relatively low; 94 (39%) of 243 patients in the gemcitabine group with relapse and 77 (33%) of 236 patients in the gemcitabine plus capecitabine group with relapse received additional treatment. In the JASPAC-1 trial, 79 (42%) of 190 patients in the gemcitabine group stopped treatment before completion compared with 127 (35%) of 366 patients in the ESPAC-4 trial, but only 52 (28%) of 187 patients that started S-1 in JASPAC-1 stopped treatment before completion compared with 169 (46%) patients in the combination group of ESPAC-4.[25] Nevertheless, 127 (69%) of the patients in the gemcitabine group of JASPAC-1 received second-line therapy (83 had S-1 based treatment) and 105 of 187 patients in the S-1 group (70 had gemcitabine based treatment).[25] Numerous factors should be considered among these and other trials in comprehending these differences including the distribution of adverse prognostic factors, the total dose intensity of per protocol therapy administered, the cumulative toxicity and fatigue, and other factors that might affect the ability to deliver second-line salvage therapy.

Patients with R0 resections in ESPAC-4 had better survival than those with R1 resection margins, but a substantial survival benefit with adjuvant chemotherapy was still observed in those with R1 resection margins (figure 1). Adjuvant gemcitabine plus erlotinib did not improve survival in patients with R0 pancreatic cancer resections (CONKO-005).[26] Further progress might be achieved through other combinations that have shown activity in advanced pancreatic cancer, with ongoing trials including the use of nab-paclitaxel plus gemcitabine,[3] FOLFIRINOX,[5] 5-fluorouracil folinic acid, oxaliplatin and irinotecan (FOLFOXIRI),[27] and gemcitabine, cisplatin, epirubicin, and capecitabine in stage I to II pancreatic cancers (PACT-15).[28] The RTOG 0848 adjuvant phase 3 trial (NCT01013649) aims to determine the survival benefit for fluoropyrimidine-based chemoradiotherapy after 5 months recurrence free survival from the start of adjuvant chemotherapy using either gemcitabine-based chemotherapy or non-gemcitabine based chemotherapy, such as modified FOLFIRINOX. Additional traction might be gained by the further assessment of therapeutic predictive response markers such as the human equilibrative nucleotide

transporter 1 and carboxylesterase 2 in selecting the optimum treatment regimens.[29,30] However in patients with resected pancreatic cancer, the results of ESPAC-4 indicate that adjuvant gemcitabine plus capecitabine is the new standard of care.

Contributors

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Declaration of interests

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References

1 Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. *Nat Rev Dis Primers* 2016; **2:** 16022.

2 Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; **27:** 5513–18.

3 Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369:** 1691–703.

4 Sultana A, Tudur Smith C, Cunningham D, et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007; **25:** 2607–15.

5 Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364:** 1817–25.

6 Neoptolemos JP, Dunn JA, Moffitt DD, et al, for the members of the European Study Group for Pancreatic Cancer (ESPAC). ESPAC-1: A European, randomized controlled study of adjuvant chemoradiation and chemotherapy in resectable pancreatic cancer. *Lancet* 2001; **358:** 1576–85.

7 Neoptolemos JP, Stocken DD, Friess H, et al, for the members of the European Study Group for Pancreatic Cancer (ESPAC). A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350:** 1200–10.

8 Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013; **310:** 1473–81.

9 Neoptolemos JP, Stocken DD, Tudur Smith C, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer* 2009; **100:** 246–50.

10 Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol* 2014; **32:** 504–12.

11 Liao WC, Chien KL, Lin YL, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Lancet Oncol* 2013; **14:** 1095–103.

12 Neoptolemos JP, T Cox. Bayesian analysis unravels pancreas cancer adjuvant therapy. *Lancet Oncol* 2013; **14:** 1034–35.

13 Neoptolemos JP, Stocken DD, Bassi C, et al, European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304:** 1073–81.

14 Campbell F, Smith RA, Whelan P, et al. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathology* 2009; **55:** 277–83.

15 Sobin LH, Gospodarowicz, MK, Wittekind C, eds. TNM classification of malignant tumours 7th edn. UICC 7th edn 2009. Oxford: Wiley-Blackwell, 2010.

16 Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc Ser A Stat Soc* 1972; **135:** 185–207.

17 Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **34:** 187–220.

18 White IR, Royston, P, Wood, AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011; **30:** 377–99.

19 Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr* 1974; **19:** 716–23.

20 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; **69:** 239–41.

21 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Contr Clin Trials* 1996; **17:** 343–46.

22 Trotti A, Pajak TF, Gwede CK, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. *Lancet Oncol* 2007; **8:** 613–24.

23 Henderson R, Diggle P, Dobson A. Joint modelling of longitudinal measurements and event time data. *Biostatistics* 2000; **1:** 465–80.

24 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977; **35:** 1–39.

25 Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet* 2016: **388:** 248–57.

26 Sinn M, Liersch T, Gellert K, et al. CONKO-005: Adjuvant therapy in R0 resected pancreatic cancer patients with gemcitabine plus erlotinib versus gemcitabine for 24 weeks—a prospective randomized phase III study. *J Clin Oncol* 2015; **33** (suppl)**:** abstr 4007.

27 Vivaldi C, Caparello C, Musettini G, et al. First-line treatment with FOLFOXIRI for advanced pancreatic cancer in clinical practice: patients' outcome and analysis of prognostic factors. *Int J Cancer* 2016; published online April 2. DOI:10.1002/ijc.30125.

28 Reni M, Cereda S, Rognone A, et al. A randomized phase II trial of two different 4-drug combinations in advanced pancreatic adenocarcinoma: cisplatin, capecitabine, gemcitabine plus either epirubicin or docetaxel (PEXG or PDXG regimen). *Cancer Chemother Pharmacol* 2012; **69:** 115–23.

29 Greenhalf W, Ghaneh P, Neoptolemos JP, et al, European Study Group for Pancreatic Cancer. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 Trial. *J Natl Cancer Inst* 2014; **106:** djt347.

30 Capello M, Lee M, Wang H, et al. Carboxylesterase 2 as a determinant of response to irinotecan and neoadjuvant FOLFIRINOX therapy in pancreatic ductal adenocarcinoma. *J Natl Cancer Inst* 2015; **107:** djv132.