

Palliative treatment of pancreatic cancer

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Despite numerous diagnostic possibilities the early diagnosis of pancreatic cancer is still an exemption. Only 10–15% of patients are diagnosed at a stage where the tumor is resectable. Thus, most patients are treated with a palliative intention at first diagnosis. Palliative treatment comprises different therapeutic modalities involving radiochemotherapy and conventional chemo-

therapy. Chemotherapy, in particular, has been challenged by several new concepts involving combination regimens and the addition of targeted therapies to conventional therapeutic regimens. This review offers a critical presentation of current concepts in the palliative treatment of pancreatic cancer, discussing the problems of each and pointing to the development of new therapeutic strategies.

KEY WORDS: chemotherapy, gemcitabine, pancreatic cancer, targeted therapies.

INTRODUCTION

Although there has been substantial progress in the development of innovative chemotherapies, a major breakthrough in the treatment of locally advanced or metastatic pancreatic cancer still evades researchers. Treating this set of patients always requires an interdisciplinary approach involving the primary care oncologist, the surgeon, the radiotherapist and the anesthesiologist. This review offers a critical presentation of current concepts in the palliative treatment of pancreatic cancer and points to the development of new therapeutic strategies.

Most malignant tumors of the exocrine pancreas are ductal adenocarcinomas. In addition to these is the far smaller number of cyst adenocarcinomas, acinar-cell-carcinomas, adenosquamous carcinomas, mucinous carcinomas and giant cell carcinomas. However, most available data and studies refer to ductal adenocarcinomas. During the last years there has been a substantial

improvement in the imaging techniques of the pancreas and we now know of a number of genetic defects and alterations (including activating mutations in the small G-protein Ras and inactivating mutations in tumor-suppressor genes such as DPC4/Smad4, p53, CDKN2 and BRCA2). In addition, a histopathological progression model for precursor lesions in the development of pancreatic cancer, the so-called PanIN (pancreatic intraepithelial neoplasia), has been established.

Despite numerous diagnostic possibilities and the above-mentioned molecular and pathological findings early diagnosis of this disease is still an exemption. In some cases the compression of the common bile duct by a small tumor with consecutive cholestasis can lead to the diagnosis of a resectable tumor. However, since other typical symptoms are missing during the early stages of this disease and since we do not have any sensitive or specific markers at hand that can help to identify patients at risk, most of these patients are diagnosed when a resection in curative intent is impossible. In most cases abdominal pain and weight loss are typical symptoms of advanced tumors. Two-thirds of the patients present with an impaired glucose tolerance or diabetes. In the USA more than 30 000 new cases are documented every year and, due to the poor prognosis, the number of deaths is almost the same. These numbers put pancreatic cancer at fourth place in the

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statistics of cancer-associated deaths in the USA.¹ Pancreatic cancer is a disease of the elderly, since the average age for the first diagnosis is for men when they are at the age of 67 and, for women, when they are 74.² The incidence of pancreatic cancer is increasing. The reasons for this phenomenon are not well understood. Risk factors for the development of pancreatic cancer that are reasonably well-documented are nicotine abuse, overweight and hereditary pancreatitis.³ The data are less homogeneous with respect to other factors.

PALLIATIVE THERAPY

The only way to actually cure patients with pancreatic cancer is the complete surgical removal of the tumor. However, only 10–15% of patients are diagnosed at a stage when the tumor is resectable. Thus, most patients are treated with a palliative intention at first diagnosis. This review therefore focuses on the possibilities and problems of palliative radiochemotherapy and chemotherapy in the treatment of pancreatic cancer and, since relevant data exist only for the ductal adenocarcinoma, the review will focus on this entity.

PALLIATIVE RADIOCHEMOTHERAPY

A palliative radiochemotherapy is a therapeutic option in patients with locally advanced unresectable tumors. In this setting radiation is the main therapeutic modality and the additional chemotherapy is meant to increase radio-sensitivity. In 1981 Moertel *et al.*⁴ showed in a three-armed trial with a total of 149 patients a significant increase in the overall survival of patients with locally advanced unresectable tumors (5.5 vs 10 months) by a combined radiochemotherapy with fluorouracil (5-FU), compared to radiotherapy alone.

However, the effectiveness of radiochemotherapy compared to chemotherapy alone in the palliative treatment of pancreatic cancer has been recently reviewed by the Cochrane Collaboration. A total of 50 studies with a total number of 7043 patients were analyzed. These showed that radiochemotherapy also improved 1-year survival (0 vs 58%, $P = 0.001$) when compared to the best supportive therapy (BSC) or radiotherapy alone. Nonetheless, the review concluded that there is not sufficient evidence to treat patients with locally advanced unresectable tumors with radiochemotherapy instead of chemotherapy alone, especially since radiochemotherapy is associated with a significant higher level of toxicity.⁵ In the American Society of Clinical Oncology (ASCO) 2006 Chauffert *et al.* presented a phase III study in which patients with locally

advanced unresectable tumors received conventional chemotherapy with gemcitabine compared to radiochemotherapy with 5-FU/Cisplatin (60 Gy, 5-FU 300 mg/m² 24 h day 1–5, Cisplatin 20 mg/m²/d day 1–5) followed by therapy with gemcitabine.⁶ Grade III/IV hematological and non-hematological toxicity was twice as high as in the chemotherapy-alone group. In addition, median survival in the radiochemotherapy group was with 8.5 months lower than in the gemcitabine-group (14.5 months).

PALLIATIVE CHEMOTHERAPY

Patients with locally advanced or metastatic pancreatic cancers profit in their quality of life and survival from the administration of chemotherapy compared to BSC.⁷ In phase-II studies median survival times of up to 8 months have been reported for 5-FU monotherapy.⁸ In a Cochrane analysis chemotherapy significantly reduced 1-year mortality (OR 0.37, 95% CI: 0.25–0.57) when compared to BSC. However, there was no significant reduction in the 1-year mortality when 5-FU monotherapy was compared to 5-FU containing combination therapies (OR 0.9, 95% CI 0.62–1.30).⁵

GEMCITABINE

After the study presented by Burris *et al.*⁹ gemcitabine was established as the gold-standard in the treatment of pancreatic cancer. This study showed a moderate increase in median survival when gemcitabine was compared with 5-FU monotherapy (5.7 vs 4.4 months, 1-year survival 18% vs 2%), but a significant improvement in a new parameter, the so-called 'clinical benefit response' (CBR; 23.8 vs 4.8%). CBR is a construct of a number of parameters including pain intensity, use of analgetics, functional impairment and change of bodyweight. Interestingly, the Cochrane analysis could not confirm a statistically significant difference between a non-gemcitabine therapy and gemcitabine in terms of 1-year mortality.⁵

A monotherapy with gemcitabine (Table 1) showed in several phase III trials a median survival of 5–6.5 months with a 1-year survival of about 11–25%. Studies with a higher proportion of patients with non-metastatic locally advanced tumors had even slightly higher survival rates. Common side-effects of a gemcitabine therapy are hematotoxicity (i.e., leucopenia and granulopenia), symptoms of a common flu or edema. On rare occasions gemcitabine can induce interstitial pneumonitis. Radiotherapy in patients pretreated with gemcitabine can induce severe skin and liver necrosis.

Table 1. Effectiveness of a gemcitabine monotherapy. Phase-III studies showing the results of the gemcitabine monotherapy arm of each respective study. TTP, time to progression

Author	Patients (n)	Progression free survival (months)	Survival (months)
Burris ⁹	126	2.7	5.3
van Cutsem ²⁰	688	3.6	6.1
Berlin ¹⁴	327	2.2	5.4
RochaLima ²⁹	350	3.0 (TTP)	6.6
Louvet, ¹⁷	313	3.7	7.1
Oettle ³³	552	3.3	6.3
Riess [abstract]	473	3.5	6.2
Moore ²⁴	284	3.6	5.9
Hermann [abstract]	319	4.0	7.3

Abstracts: Hermann *et al.*, Proc ASCO 2005, No. A4010; Riess *et al.*, Proc ASCO 2005, No. A4009.

EFFICACY OF GEMCITABINE: A QUESTION OF APPLICATION?

Phosphorylation of gemcitabine induces the generation of its active metabolite gemcitabine-triphosphate. This time-dependent process, mediated by the deoxycytidine-kinase, might be positively influenced by prolonged infusion of gemcitabine. Therefore, a phase-II study used a prolonged infusion protocol ("fixed dose rate infusion" or FDR-infusion) of gemcitabine (10 mg/m²/min over 150 min). This mode of application showed an advantage for median survival by the FDR-infusion.¹⁰ However, it should be noted that this study used a much higher dose of gemcitabine than usual and hematotoxicity was significantly increased under this FDR protocol. Grade III/IV neutropenia was observed in 49% of the patients and grade III/IV thrombo- and leucopenia in 40% of them. In the ASCO 2006 a randomized phase III study was presented that compared a conventional application of gemcitabine (1000 mg/m² over 30 min) with a FDR-protocol (1500 mg/m² gemcitabine over 150 min).¹¹ The primary end-point of this study was to show an increase in median survival from 6 to 8 months. As expected the FRD protocol showed a higher rate of grade III/IV hematotoxicity when compared to gemcitabine alone, but also patient survival increased by 1 month for the FDR protocol (median/1-year survival: 4.9 months/17% for gemcitabine, 6 months/21% for FDR-gemcitabine). However, this effect was not statistically significant.

COMBINATION THERAPIES

There have been numerous attempts in phase II and III studies to improve the efficacy of palliative chemotherapy by using combination regimens, most of which were based on gemcitabine.¹² Unfortunately most studies

were unable to show an advantage for combination therapies when compared to gemcitabine alone (Table 2). These results are supported by the data presented by the Cochrane analysis, where 1-year mortality was analyzed (OR 0.88, 95%, CI 0.74–1.05).⁵

In one study there was a significant difference in survival for a combination of gemcitabine (1000 mg/m² per week × 3 every 4 weeks) and the oral fluoropyrimidine analog, capecitabine (1660 mg/m² for 21 days every 4 weeks) (GEM-CAP *vs* Gem: overall response rate (ORR): 14.2 *vs* 7.1%, median survival: 7.4 *vs* 6 months, 1-year-survival: 26 *vs* 19%).¹³ Before this study three other phase-III studies analyzing combination therapies showed no significant advantage for the combination of gemcitabine with a fluoropyrimidine (5-FU or capecitabine)^{14,15} or that the advantage was applicable to only a small subset of patients with a very good performance status.¹⁶ In addition, differences may also be caused by different doses of capecitabine in the various studies.

A subgroup analysis from the Cochrane data was able to show that the combination of gemcitabine with platin-analogs can reduce 6-month mortality (OR 0.59, 95% CI 0.43–0.81, *P* = 0.001). For example the combination of gemcitabine, here in a prolonged application, with oxaliplatin in contrast to conventional gemcitabine (GemOx; gemcitabine 1000 mg/m² over 100 min day 1, oxaliplatin 100 mg/m² day 2) was able to increase response rate (26.8 *vs* 17.3%) and progression-free survival (3.7 *vs* 2.3 months). However, this study failed to demonstrate an increase in overall survival, which might be the result of the relatively high number of second-line therapies applied in both arms of this study.¹⁷ Another comparison between conventional monotherapy with gemcitabine (1000 mg/m² over 30 min) with a gemcitabine/oxaliplatin regime showed an increase in median survival by about

Table 2. Median survival of combination chemotherapies in phase-III studies

Author	Intervention	Gemcitabine median survival in months	Combination median survival in months	P-value
Burris ⁹	Gem vs 5-FU	5.7	–	–
Berlin ¹⁴	Gem vs Gem + 5-FU	5.4	6.7	n.s.
Riess [abstract]	Gem vs Gem + 5-FU	6.2	5.85	n.s.
Hermann [abstract]	Gem vs Gem + Capecitabine	7.3	8.4	n.s.
Louvet ¹⁷	Gem vs GemOx	7.1	9.0	n.s.
Heinemann ¹⁸	Gem vs Gem/Cisplatin	6.0	7.6	n.s.
Rocha Lima ³⁴	Gem vs Gem/Irinotecan	6.6	6.3	n.s.
Abou-Alfa ³⁵	Gem vs Exatecan	6.2	6.7	n.s.
Oettle ³³	Gem vs Gem/Permetrexed	6.3	6.2	n.s.
Cunningham [abstract]	Gem vs Gem + Capecitabine	6.0	7.4	0.026
Van Cutsem ²⁰	Gem vs Gem + Tipifarnib	6.1	6.3	n.s.
Bramhall ²¹	Gem vs Gem + Marimastat	5.4	5.4	n.s.
Moore ²⁴	Gem vs Gem + Erlotinib	5.91	6.24	0.038

P < 0.05.

5-FU, 5-fluouracil.

Abstracts: Cunningham *et al.* ECCO 2005; No. A PS11; Hermann *et al.* Proc ASCO 2005; No. A4010; Riess *et al.* Proc ASCO 2005; No. A4009.

1 month in the GemOx-arm. However, the difference did not reach statistical significance.¹¹ In addition, the patients in the GemOx arm had a higher amount of grade III nausea/emesis and neuropathy, the latter a known side effect of oxaliplatin therapy. An analysis that pooled the data from the GemOx study with that from a German phase-III trial could, at least for the pooled data, show a statistically significant difference in the overall survival for patients who were treated with a first-line combination therapy containing platinum-analog. Patients with a good performance status, that is, a Karnofsky index of 90–100%, profited the most from a combination therapy.¹⁸ Recently Reni *et al.* reported on a combination therapy consisting of gemcitabine, cisplatin, epirubicin and 5-FU that could improve progression free survival when compared with a monotherapy (60 vs 28%). However, each arm of this study contained only about 50 patients.¹⁹

Since the available data do not support a significant effect on survival for combination therapies, a weekly monotherapy with gemcitabine 1000 mg/m² remains the standard in the treatment of locally advanced or metastatic pancreatic cancer. Nonetheless, the phase-III studies presented support an increase in survival by combination therapies (i.e., regimens containing platinum), especially for patients with a good performance status (Eastern Cooperative Oncology Group [ECOG] grade 0 or 1). Thus, the use of combination therapies for this subset of patients seems to be justified even outside clinical trials. Although progress in the

treatment of pancreatic cancer is small, the prognosis of patients with metastatic pancreatic cancer is improving over the years.

“TARGETED THERAPY”

Many trials have tested numerous combinations of various agents in the treatment of pancreatic cancer. Therefore, a significant improvement in prognosis by adding more chemotherapeutic agents is unlikely, or is likely to be accompanied by much higher toxicity.¹⁹ A combination of conventional chemotherapies with targeted therapy therefore seems to be the only way to go. The concept underlying the idea of targeted therapies is the specific and selective alteration of molecular targets that sustain tumor growth or metabolism. Among other attempts, randomized trials have tried to inhibit the small G-proteins Ras by farnesyl-transferase inhibitors and to inhibit different matrix metalloproteases.^{20,21} The combination of the farnesyl-transferase inhibitor, tipifarnib or the matrix metalloprotease inhibitor, marimastat with gemcitabine had no effect on survival when compared to standard mono-therapy.

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITION

The epidermal growth factor receptor (EGFR) and its ligands are over-expressed in more than 50% of pancreatic cancers. However, blocking the EGFR by treatment with the chimerical antibody cetuximab in

combination with gemcitabine did not lead to a significant increase in the tumor response and progression, and on overall survival.^{22,23} However, a recent phase III study was able to show a significant increase in progression-free survival (3.55 vs 3.75 months) and overall survival (5.91 vs 6.24 months) by a combination of erlotinib, a small molecule inhibitor of the receptor tyrosine kinase activity of the EGFR, and gemcitabine (hazard ratio 0.82, $P = 0.038$).²⁴ Taken the high patient numbers into account (284 or 285 patients per arm) these small differences are enough to reach statistical significance. Therefore, these data were the basis for the Food and Drug Administration approval of the erlotinib and gemcitabine combination for treating metastatic pancreatic cancer. Nonetheless, the combination therapy had a significant higher rate of grade III/IV toxicities (rash and diarrhea). A subgroup analysis was able to show that patients who developed a grade II skin reaction (rash) had an improved median survival under combination therapy compared to patients with no skin reaction (10.5 vs 5.3 months). Another noteworthy aspect was the improved effectiveness in patients with impaired performance status (ECOG 2). However, up to now it is not clear from a clinical point of view how relevant this difference actually is. The difference for overall survival is approximately 2 weeks; for progression-free survival: approximately 8 days.

INHIBITION OF ANGIOGENESIS

In the treatment of colorectal cancer, the combination of a conventional chemotherapy (irinotecan/5-FU/leucovorin protocol) with an antibody directed against the vascular endothelial growth factor (VEGF), bevacizumab, was able to significantly increase median survival.²⁵ An analogous study investigating a combination of gemcitabine and bevacizumab in the USA (CALGB 80303) was stopped after an interim analysis made an increase in overall survival, the primary endpoint, by the combination therapy unlikely.²⁶ The promising data from the phase-II study could obviously not be reproduced (median survival 8.8 months, 1-year survival 29%)²⁷ in a phase-III trial. There, the patients who profited most developed early hypertension greater than grade II.

MULTI-TARGETING

Multi-targeting-strategies (i.e., the inhibition of more than one signaling pathway by combining the inhibitors of VEGF and EGFR signaling) could present promising results in the treatment of colorectal cancer. These data and the disappointing results from the first studies

using targeted therapies induced the investigation of multi-targeting concepts in the treatment of pancreatic cancer. These concepts are under investigation in current studies.²⁶ However, one of the remaining problems for the improvement of any molecular therapy is the non-existence of any parameters that are able to predict a response, or an effect on survival of a given targeted therapy. Up to the present only retrospectively evaluated parameters such as a skin rash or elevated blood pressure have been noted. These are insufficient substitutes for the need for predictive information.

PALLIATIVE SECOND-LINE CHEMOTHERAPY

After the progress of the disease under palliative first-line therapy (which in most cases contains gemcitabine) the regular administration of a second-line therapy is not well established. However, there is an increasing body of evidence that up to 45% of the patients profit from a second-line therapy in respect to disease control.^{28,29} In a recent study patients were treated with a combination of 5-FU and oxaliplatin compared to BSC. An interim analysis of 45 patients of this study could show a significant benefit for median survival for the 5-FU/oxaliplatin group (21 vs 10 weeks).³⁰ Unfortunately, this randomized study was stopped due to slow patient recruitment, since most patients wanted to receive a palliative second-line therapy. Similar numbers for survival were described for his combination by Tsavaris.²⁸ In addition, perimetrexed or the fluoropyrimidine S1 were reported to reach a median survival of 20 weeks in the second-line therapy of pancreatic cancer.^{31,32} Ulrich-Pur *et al.* even reported median survival rates of 6.5 months under a second-line combination therapy with raltitrexed and irinotecan.²⁹ Nonetheless, larger studies confirming these results are missing to date.

CONCLUSION

Although there are a few studies showing the superiority of combination therapy in the treatment of locally advanced or metastatic pancreatic cancer, gemcitabine remains the standard therapy in palliative treatment. Median survival for patients with metastatic pancreatic cancer is slightly more than 6 months. Whether the addition of biologicals (mainly VEGF antagonists or EGFR inhibitors) can improve survival not only statistically but in a clinically relevant fashion is under investigation in current studies. Second-line therapies, after the failure of a first-line therapy, are probably effective; however, a standard for second-line therapies has not yet been established. Second-line therapies

should therefore be performed in controlled studies. One of the major goals in the treatment of patients with unresectable pancreatic cancer should be the improvement and the preservation of the quality of life of these patients.

REFERENCES

- Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics. *CA Cancer J Clin* 2006; **56**: 106–30.
- Arbeitsgemeinschaft bevoelkerungsbezogener Krebsregister in Deutschland. Krebs in Deutschland. *Häufigkeit und Trends*. Saarbrücken: 2002; 32–6.
- Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. *Br J Cancer* 2005; **93**: 1310–5.
- Moertel CG, Frytak S, Hahn RG *et al*. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil. Gastrointestinal Tumor Study Group. *Cancer* 1981; **48**: 1705–10.
- Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. *Cochrane Database Syst Rev* 2006; **3**: CD002093.
- Chauffert B, Mornex F, Bonnetain F *et al*. Phase III trial comparing initial chemoradiotherapy (intermittent cisplatin and infusional 5-FU) followed by gemcitabine vs. gemcitabine alone in patients with locally advanced non metastatic pancreatic cancer: A FFCO-SFRO study. *J Clin Oncol* (2006 ASCO Annual Meeting Proceedings) 2006; **24**: Abs A4008.
- Glimelius B, Hoffman K, Sjoden PO *et al*. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996; **7**: 593–600.
- Lutz MP, Koniger M, Mucic R *et al*. A phase II study of weekly 24-h infusion of high-dose 5-fluorouracil in advanced pancreatic cancer. *Z Gastroenterol* 1999; **37**: 993–7.
- Burris HA 3rd, Moore MJ, Andersen J *et al*. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403–13.
- Tempero M, Plunkett W, Ruiz Van Haperen V *et al*. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2003; **21**: 3402–8.
- Poplin E, Levy DE, Berlin J *et al*. Phase III trial of gemcitabine (30-minute infusion) versus gemcitabine (fixed-dose-rate infusion[FDR]) versus gemcitabine + oxaliplatin [GEMOX] in patients with advanced pancreatic cancer (E6201) *J Clin Oncol* (2006 ASCO Annual Meeting Proceedings) 2006; **24**: Abs LBA4004.
- Petty RD, Nicolson MC, Skaria S, Sinclair TS, Samuel LM, Koruth M. A phase II study of mitomycin C, cisplatin and protracted infusional 5-fluorouracil in advanced pancreatic carcinoma: efficacy and low toxicity. *Ann Oncol* 2003; **14**: 1100–5.
- Cunningham D, Chau I, Stocken D *et al*. Neoptolemos phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. *2005 European Journal of Cancer Supplements* 2005; **3**: Abs PS114.
- Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002; **20**: 3270–5.
- Riess H, Helm A, Niedergethmann M *et al*. A randomised, prospective, multicenter, phase iii trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs. gemcitabine alone in patients with advanced pancreatic cancer. *J Clin Oncol* (2005 ASCO Annual Meeting Proceedings) 2005; **23**: Abs LBA4009.
- Herrmann R, Bodoky G, Ruhstaller T *et al*. Gemcitabine (G) plus capecitabine (C) versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG). *J Clin Oncol* (2005 ASCO Annual Meeting Proceedings) 2005; **23**: Abs A4010.
- Louvet C, Labianca R, Hammel P *et al*. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005; **23**: 3509–16.
- Heinemann V, Quietzsch D, Gieseler F *et al*. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006; **24**: 3946–52.
- Reni M, Cordio S, Milandri C *et al*. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005; **6**: 369–76.
- Van Cutsem E, van de Velde H, Karasek P *et al*. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 2004; **22**: 1430–8.
- Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JA. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J Clin Oncol* 2001; **19**: 3447–55.
- Xiong HQ, Rosenberg A, LoBuglio A *et al*. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial. *J Clin Oncol* 2004; **22**: 2610–6.
- Philip PA, Benedetti J, Fenoglio-Preiser C *et al*. Phase III study of gemcitabine (G) plus cetuximab (C) versus gemcitabine in patients (pts) with locally advanced or metastatic pancreatic adenocarcinoma (PC): SWOG S0205 study. *J Clin Oncol* (2007 ASCO Annual Meeting Proceedings) 2007; **25**: Abs LBA4509.
- Moore MJ, Goldstein D, Hamm J *et al*. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960–6.
- Hurwitz H, Fehrenbacher L, Novotny W *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335–42.
- Kindler K, Bylow A, Hochster HS *et al*. A randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis. *J Clin Oncol* (2006 ASCO Annual Meeting Proceedings) 2006; **24**: No. 18S Abs A4040.
- Kindler HL, Friberg G, Singh DA *et al*. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2005; **23**: 8033–40.
- Tsavaris N, Kosmas C, Skopelitis H *et al*. Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in

- gemcitabine-pretreated advanced pancreatic cancer: a phase II study. *Invest New Drugs* 2005; 23: 369–75.
- 29 Ulrich-Pur H, Raderer M, Verena Kornek G *et al.* Irinotecan plus raltitrexed *vs* raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. *Br J Cancer* 2003; 88: 1180–4.
 - 30 Oettle H, Pelzer U, Stieler J *et al.* Oxaliplatin/folinic acid/5-fluorouracil [(24h) (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine-refractory advanced pancreatic cancer (CONKO 003). *J Clin Oncol* (2005 ASCO Annual Meeting Proceedings) 2005; 23: Abs A4031.
 - 31 Boeck S, Weigang-Koehler K, Fuchs M *et al.* Second-line therapy with pemetrexed after gemcitabine failure in patients with unresectable locally advanced or metastatic pancreatic cancer: A multicenter phase II trial. *J Clin Oncol* (2006 ASCO Annual Meeting Proceedings) 2006; 24: Abs A4124.
 - 32 Sudo K, Yamaguchi T, Ishihara T, Nakamura K, Saisho H. Phase II study of S-1 in patients with gemcitabine resistant advanced pancreatic carcinoma. *J Clin Oncol* (2006 ASCO Annual Meeting Proceedings) 2006; 24: Abs A14070.
 - 33 Oettle H, Richards D, Ramanathan RK *et al.* A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol* 2005; 16: 1639–45.
 - 34 Rocha Lima CM, Green MR, Rotche R *et al.* Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004; 22: 3776–83.
 - 35 Abou-Alfa GK, Letourneau R, Harker G *et al.* Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol* 2006; 24: 4441–7.