New directions in the management of advanced pancreatic cancer: a review

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Complete surgical resection is the only potentially curative option for pancreatic cancer. However, most patients have advanced/metastatic disease at the time of diagnosis, or will relapse after surgery. Systemic chemotherapy is only palliative. Gemcitabine-based therapy is an acceptable standard for unresectable locally advanced/metastatic pancreatic cancer, but average median survival is only 6 months. The addition of other chemotherapies (including other antimetabolites, platinum, and topoisomerase I inhibitors) or targeted therapies (farnesyl transferase inhibitors, metalloproteinase inhibitors, cetuximab and bevacizumab) to gemcitabine has failed to improve outcome. The combination of gemcitabine and erlotinib, a small-molecule tyrosine kinase inhibitor of the human epidermal growth factor receptor, was recently approved by the US/European authorities for use in advanced disease. In a phase III trial, the combination demonstrated a significant improvement in overall survival compared with gemcitabine monotherapy. Positive efficacy results have also been observed in a phase III trial, favoring the addition of capecitabine to gemcitabine compared with gemcitabine alone. This review focuses on the recent developments in systemic treatment, and discusses how novel agents might be incorporated into future treatment strategies for pancreatic cancer. *Anti-Cancer Drugs* 19:435–446 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Worldwide, pancreatic cancer is the 13th most common form of cancer and the eighth most common cause of cancer-related death for both sexes combined [1]. Pancreatic cancer has a very poor prognosis, even when diagnosed at early stages, with overall 5-year survival rates of 20.3% for patients with localized disease and 8% for those with regionalized disease [2]

These poor figures reflect the inadequacy of existing treatment strategies, advanced stage at diagnosis (the majority of patients are diagnosed with advanced disease, and only 15–20% present with resectable tumors [3]), the inaccuracy of currently available staging studies to establish surgically curable patients, and the propensity of this disease to spread to distant sites at an early stage.

Most patients with pancreatic cancer have advanced/metastatic disease at the time of diagnosis. For these patients median survival is only approximately 6 months with gemcitabine-based therapy [2] Therefore, there is an urgent need for new and more effective therapies for patients with advanced/metastatic disease, and this review will focus on recent developments in the systemic treatment of advanced pancreatic cancer.

Neoadjuvant and adjuvant chemotherapy for pancreatic cancer

Complete resection is the only potentially curative option for patients with pancreatic cancer. Despite the availability of improved staging tools, improved supportive care, and improved surgical techniques, patient prognosis after resection of the primary tumor remains poor with a median survival of 13–15 months and 5-year survival of 15–20% [4–6].

Although the value of neoadjuvant therapy in pancreatic cancer has not been fully established, treatment with 5-fluorouracil (5-FU)-based chemoradiotherapy or gemcitabine (Gemzar)-based chemotherapy, may bring about tumor downstaging in a minority of patients with locally advanced disease, allowing for resection [7–11]. The benefit of neoadjuvant therapy in resectable and locally advanced pancreatic cancer needs to be better studied and evaluated in prospective randomized trials.

Adjuvant therapy in pancreatic cancer has been better studied than neoadjuvant strategies in patients with localized disease. The role of combined modality therapy in the adjuvant setting though remains controversial (Table 1) [12–17]. The Gastrointestinal Tumor Study Group conducted a multicenter randomized trial that

Table 1 Key trials of adjuvant therapy in resectable pancreatic cancer

Trial	Regimen	Number of patients	Median survival (months)
Gastrointestinal Tumor Study Group [12]	5-FU + 40 Gy radiation	21	20[a]
	Surgery alone	22	11
Gastrointestinal Tumor Study Group [13]	5-FU + 40 Gy radiation	30	18
European Organisation for Research and Treatment of Cancer [14]	5-FU + 40 Gy radiation	110	17.1
	Surgery alone	108	12.6
European Study Group for Pancreatic Cancer 1 Trial [15]	Chemotherapy	147	20.1
	No chemotherapy	142	15.5
	Chemoradiotherapy	145	15.9
	No chemoradiotherapy	144	17.9
CONKO-001 [16]	Gemcitabine	179	22.1
	Surgery alone	177	20.2
RTOG 9704 [17]	5-FU + 50.4 Gy radiation	270	16.7
	Gemcitabine + 5-FU + 50.4 Gy radiation	268	18.8[a]

5-FU, 5-fluorouracil.
[a]Statistically significant.

enrolled 43 patients over an 8-year period to either 5-FU and radiotherapy followed by additional chemotherapy with 5-FU for 2 years, or to no additional therapy after surgery. The median survival favored the treatment arm, 20 months compared with 11 months [12]. This trial has been criticized for its small sample size, the long time taken to enroll patients, and the low number of patients enrolled per participating institutions. A subsequent phase II trial from the same group, where all enrolled patients with surgically resected pancreatic cancer, however, were treated with the same schedule of 5-FU and radiotherapy, resulted in a similar median survival as the treatment arm from the original Gastrointestinal Tumor Study Group trial [13].

The EORTC conducted a phase III trial enrolling duodenal, distal common bile duct, periampullary, and pancreatic cancer patients undergoing curative surgical resection to either split course radiotherapy (40 Gy) and 5-FU (25 mg/kg, days 1–5, weeks 1 and 5) or no additional therapy. Although, there was no statistically significant benefit to postoperative therapy, there was a trend in improvement of median survival favoring the treatment arm for the subset of pancreatic cancer patients (17.1 vs. 12.6 months; $P = 0.099$) [14]. More recently, the largest randomized adjuvant trial reported to date (61 cancer centers, 11 countries) disputed the role of adjuvant chemoradiotherapy in pancreatic cancer [15]. This randomized phase III trial, with a 2×2 factorial design, suggested that adjuvant chemotherapy improved median survival (20.1 vs. 15.5 months in the chemotherapy and nonchemotherapy arms respectively; $P = 0.09$), whereas adjuvant chemoradiotherapy, consisting of split course radiotherapy (40 Gy) and bolus 5-FU as radiosensitizer had a deleterious effect on median survival (15.9 and 17.9 months in the chemoradiotherapy and no chemoradiotherapy arms, respectively; $P = 0.05$).

The role of gemcitabine in the adjuvant setting has recently been studied in a multicenter phase III trial [16]. The primary endpoint (disease-free survival) was longer in the treatment arm (13.4 vs. 6.9 months; $P < 0.001$). Median survival numerically favored the gemcitabine arm; 22.1 months, compared with 20.2 months in the observation arm ($P = 0.06$). Another trial, a US-based cooperative group study, RTOG 9704, [17] compared adjuvant chemotherapy with either 5-FU or gemcitabine in regard to overall survival (OS), locoregional disease control, distant disease control, and failure patterns. All patients received chemoradiation (5-FU and radiotherapy). A total of 533 patients were enrolled and 442 analyzed. The patients were stratified by tumor size ($<$ or $>$ 3 cm), nodal involvement, and surgical margins. For patients with pancreatic head tumors (380 patients) the median survival was superior for patients receiving gemcitabine as adjuvant therapy compared with those receiving 5-FU; 18.8 months compared with 16.7 months ($P = 0.047$). However, there were no statistically significant differences in median survivals when body and tail tumors were also included in the analyses ($n = 422$, $P = 0.2$) [17].

Management of advanced pancreatic cancer

Traditionally, 5-FU-based chemotherapy or chemoradiotherapy have been used in the treatment of locally advanced pancreatic cancer (Table 2) [18–21], but the value of radiotherapy in locally advanced disease is unclear. In a randomized trial, where patients were treated with weekly bolus 5-FU with or without radiotherapy, median survival was 8.2 and 8.3 months, respectively [20]. Furthermore, in a recently reported French trial, the combination of 5-FU with cisplatin and

Table 2 Phase III trials comparing chemoradiation, radiation, and chemotherapy in locally advanced unresectable pancreatic cancer

Trial	Regimen	Number of patients	Median survival (months)
Gastrointestinal Tumor Study Group [18]	5-FU + 60 Gy radiation	111	11.4[a]
	5-FU + 40 Gy radiation	117	8.4[a]
	60 Gy radiation alone	25	5.3
Gastrointestinal Tumor Study Group [19]	5-FU + SMF	22	9.7[a]
	SMF alone	21	7.4
Eastern Cooperative Oncology Group [20]	5-FU + 40 Gy radiation	47	8.2
	5-FU alone	44	8.3
FFCD-SFRO study [21]	5-FU + 60 Gy radiation + cisplatin	59	8.4
	Gemcitabine	60	14.3[a]

[a]Statistically significant.
5-FU, 5-fluorouracil; SMF, streptozocin, mitomycin, and 5-FU.

radiotherapy was found to be inferior to gemcitabine monotherapy for locally advanced disease [21].

Gemcitabine-based therapy is an acceptable treatment approach for both unresectable locally advanced and metastatic pancreatic cancer. In a phase III trial of patients with advanced disease, gemcitabine was found to be better than 5-FU in alleviating pain, functional impairment, and weight loss, and was also associated with a significantly longer median survival, leading to Food and Drug Administration (FDA) approval of gemcitabine in advanced pancreatic cancer [22].

The approved schedule of administration for gemcitabine is 1000 mg/m^2 over 30 min once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles consist of 30 min intravenous infusions for 3 consecutive weeks out of every 4 [23]. Gemcitabine toxicity (and perhaps efficacy) is, however, schedule dependent. Gemcitabine is a prodrug that is intracellularly converted to an active metabolite, and the rate at which this metabolite is incorporated into DNA depends on its concentration relative to unconverted prodrug [24]. Pharmacokinetic data from phase I trials suggest that these relative concentrations are optimal when gemcitabine is administered as a fixed-dose rate (FDR) infusion of 10 mg/m^2/min [25,26], implying that gemcitabine may be more effective when given as a FDR than as a standard infusion. In a randomized phase II trial, in which pancreatic cancer patients were treated with gemcitabine as a 2200 mg/m^2 standard rate infusion or 1500 mg/m^2 FDR infusion, there was a suggestion that the FDR infusion had superior efficacy, but at the cost of greater hematologic toxicity [27]. This trial was not powered for comparative analyses, but the data supported continued evaluation of the FDR infusion strategy with gemcitabine in pancreatic cancer patients.

Between 1997 and 2005 numerous attempts were made to improve on the efficacy observed with standard gemcitabine monotherapy in patients with advanced pancreatic cancer, but with little success. Phase III trials were undertaken with gemcitabine in combination with a range of chemotherapy agents. Unfortunately, combining gemcitabine with 5-FU, irinotecan (Campto), oxaliplatin (Eloxatin), pemetrexed (Alimta), and exatecan all failed to show superiority over gemcitabine monotherapy (Table 3) [28–38].

Combining FDR gemcitabine with oxaliplatin (GEMOX) did result in superior response rate, progression-free survival (PFS), 8-month survival rate, and clinical benefit response compared with patients receiving standard gemcitabine treatment, even though median survival was not statistically different between the two arms [30]. The positive results observed with GEMOX, however, may have been a positive effect of FDR gemcitabine over standard infusion gemcitabine, rather than as a result of the addition of oxaliplatin. Pooled analysis of the data from this and another randomized trial of gemcitabine and cisplatin versus gemcitabine alone, suggest that the combination of gemcitabine with a platinum analog significantly improves PFS and OS compared with gemcitabine monotherapy in patients with advanced pancreatic cancer [39]. Recent preliminary data from a phase III trial comparing gemcitabine versus gemcitabine FDR versus GEMOX, however, have once again failed to reveal a survival advantage for this combination [40].

Targeted therapies have also been investigated for advanced pancreatic cancer. Such agents show promise against other solid tumors, including non-small cell lung cancer (NSCLC) and colorectal cancer [41], but initial findings in pancreatic cancer patients were less encouraging (Table 3) [33–38]. The antitumor agents, marimastat and talomastat (BAY 12-9566), are inhibitors of matrix metalloproteinase, an enzyme that plays a key role in degradation of the extracellular matrix, and in angiogenesis [42]. In phase III trials, neither marimastat monotherapy nor marimastat with gemcitabine, improved OS compared with gemcitabine monotherapy [34,35]. Talomastat monotherapy had a negative impact on survival; in a phase III trial, median survival with this targeted agent was 3.74 months compared with 6.59 months for gemcitabine monotherapy [36].

Strategies that target *K-ras* were thought to have therapeutic potential in pancreatic cancer patients as *K-ras* mutations are observed in 75–100% of these tumors (the highest frequency of *K-ras* mutation among all human cancers) [3]. The farnesyl transferase enzyme *K-ras* regulator tipifarnib in combination with gemcitabine did not improve OS compared with gemcitabine monotherapy in a phase III trial [33]. Despite these early failures, recent developments for gemcitabine combination therapies do offer some hope for patients with advanced pancreatic cancer.

Recent advances in treatment strategy for advanced pancreatic cancer

On the basis of data from recent clinical trials in patients with advanced pancreatic cancer, there is now good reason to believe that efficacy of gemcitabine monotherapy can be bettered. Recent preliminary phase III trial data indicated a significant survival advantage with gemcitabine in combination with capecitabine (Xeloda) over gemcitabine monotherapy [43]. More significantly, in November 2005, another targeted agent, erlotinib (Tarceva), became the first agent to receive FDA approval in combination with gemcitabine for the treatment of advanced pancreatic cancer based on positive phase III trial data (Table 4) [43–47].

Table 3 Negative phase III trials (vs. gemcitabine monotherapy) in advanced pancreatic cancer

Agent class	Regimen	Phase	Results (vs. gemcitabine monotherapy)
Chemotherapy	Gemcitabine + 5-FU [28]	III	OS: 6.7 months (vs. 5.4; $P=0.09$) PFS: 3.4 months (vs. 2.2; $P=0.022$) RR: 9.9% (vs. 5.6%)
	Gemcitabine + irinotecan [29]	III	OS: 6.3 months (vs. 6.6; $P=0.789$) One-year survival: 21% (vs. 22%) TTP: 3.5 months (vs. 3; $P=0.352$) RR: 16.1 (vs. 4.4%; $P<0.001$)
	Gemcitabine + oxaliplatin [30]	III	OS: 9 months (vs. 7.1; $P=0.13$) PFS: 5.8 months (vs. 3.7; $P=0.04$) RR: 26.8% (vs. 17.3%; $P=0.04$)
	Gemcitabine + pemetrexed [31]	III	OS: 6.2 months (vs. 6.3; $P=0.848$) One-year survival: 21.4% (vs. 20.1%; $P=0.718$) PFS: 3.9 months (vs. 3.3; $P=0.11$) TTF: 3 months (vs. 2.2; $P=0.268$) RR: 14.8% (vs. 7.1%; $P=0.004$)
	Gemcitabine + exatecan [32]	III	OS: 6.7 months (vs. 6.2; $P=0.52$) TTP: 3.7 months (vs. 3.8; $P=0.22$) RR: 6.9% (vs. 5.2%)
Ras-farnesyl transferase inhibitor	Gemcitabine + tipifarnib [33]	III	OS: 193 days (vs. 182; $P=0.75$) One-year survival: 27% (vs. 24%) PFS: 112 days (vs. 109 days) RR: 6% (vs. 8%)
Matrix metalloproteinase inhibitor	Marimastat [34]	III	OS: 105–125 days (vs. 167; $P=0.19$) One-year survival: 14–20% (vs. 19%) PFS 115 g, 56–59 days (vs. 115; $P=0.0001$) TTP: 59–64 days (vs. 84; $P=0.80$) RR: 3% (vs. 26%)
	Gemcitabine + marimastat [35]	III	OS: 165.5 days (vs. 164; $P=0.95$) One-year survival: 18% (vs. 17%) PFS: 92.5 days (vs. 96; $P=0.68$) TTP: 107 days (vs. 89; $P=0.70$) RR: 11% (vs. 16%)
	Talomastat [36]	III	OS: 3.74 months (vs. 6.59; $P<0.001$) One-year survival: 10% (vs. 25%) PFS: 1.68 months (vs. 3.5; $P<0.001$) RR: <1% (vs. 5%)
EGFR inhibitor	Cetuximab [37]	III	OS: 6.5 months (vs. 6; $P=0.14$) PFS: 3.5 months (vs. 3; $P=0.058$) RR: 7% (vs. 7%)
VEGF inhibitor	Bevacizumab [38]	III	OS: 5.8 months (vs. 6.1; $P=0.78$) PFS: 4.9 months (vs. 4.9; $P=0.99$) RR: 11 vs. 10%

EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil; OS, overall survival; PFS, progression-free survival; RR, response rate; TTF, time to treatment failure; TTP, time to progression; VEGF, vascular endothelial growth factor.

Erlotinib

Erlotinib is a small-molecule tyrosine kinase inhibitor (TKI) of the human epidermal growth factor receptor (EGFR), which has been approved in the US and EU for the treatment of recurrent NSCLC, following the failure of at least one prior chemotherapy regimen [44,48]. EGFR is dysregulated in many tumor types [49] and elevated in 40–65% of pancreatic tumors [50–53]. Elevated EGFR is associated with increased tumor size, late clinical stage, poor prognosis, and reduced sensitivity to chemotherapy, making it an attractive target for therapy [54,55]. EGFR signaling is central to tumorigenesis and disease progression (Fig. 1) [56]. In response to the binding of a ligand (such as epidermal growth factor), the receptor activates an intrinsic tyrosine kinase activity, leading to receptor phosphorylation and the initiation of downstream signaling pathways including the MAPK and phosphatidylinositol-3-OH kinase (PI3K/Akt)-mediated pathways. This affects gene transcription and protein translation, stimulating tumor-cell proliferation, migration, adhesion, and angiogenesis, and inhibiting apoptosis [57,58].

Erlotinib blocks the intrinsic tyrosine kinase activity of EGFR and preclinical data show that, in pancreatic cell lines, erlotinib prevents receptor activation, and inhibits downstream signal transduction and cell proliferation [59]. In primary pancreatic cancer xenografts it also enhances gemcitabine-induced apoptosis [59]. Phase Ib clinical trial data in patients with unresectable pancreatic carcinoma were also encouraging; erlotinib in combination with gemcitabine showed a high rate of disease stabilization and acceptable toxicity profile [60]. As a result of these preclinical and early clinical data, a phase III study of erlotinib was initiated.

PA.3 was a multicenter, randomized, double-blind, placebo-controlled phase III clinical study of erlotinib in combination with gemcitabine, in patients with locally advanced or metastatic pancreatic adenocarcinoma. The trial met its primary endpoint, with the combination regimen being the first gemcitabine combination to demonstrate a statistically significant survival advantage over gemcitabine monotherapy [44,45] and the regimen was consequently approved for locally advanced, unresectable, or metastatic disease in the US and for metastatic disease in the EU [44,48].

Table 4 Results of key trials of erlotinib, capecitabine, bevacizumab, and cetuximab in advanced pancreatic cancer

Agent class	Regimen	Phase	Results
Chemotherapy	Capecitabine + gemcitabine [43]	III (vs. gemcitabine)	OS = 7.4 months (vs. 6; HR = 0.8, $P = 0.026$)[a] RR = 14 vs. 7% ($P = 0.008$)[a]
VEGF inhibitor	Bevacizumab + gemcitabine [46]	II	OS = 8.8 months PFS = 5.4 months RR = 21%
EGFR inhibitor	Cetuximab + gemcitabine [47]	II	OS = 7.1 months PFS = 3.8 months RR = 12%
EGFR inhibitor	Erlotinib + gemcitabine [45]	III (vs. gemcitabine)	OS = 6.4 months (vs. 6; HR = 0.81, $P = 0.028$) PFS = 3.8 months (vs. 3.5; HR = 0.76, $P = 0.006$) RR = 8.6 vs. 7.9%

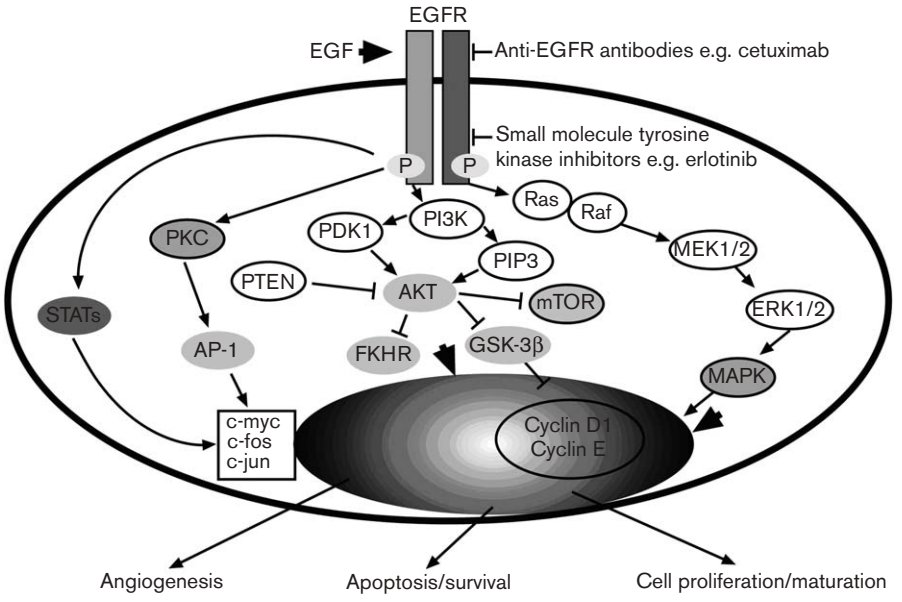
[a]Preliminary data.
EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, response rate; VEGF, vascular endothelial growth factor.

Median OS in PA.3 was 6.4 months in the erlotinib and gemcitabine arm and 6 months for gemcitabine alone. This median value of OS may underrepresent the survival advantage of the combination regimen, as the survival curves are in close proximity at this point. The areas under the curves are, however, significantly different and the hazard ratio (HR) is 0.81 ($P = 0.028$) representing a 19% decrease in the risk of death with erlotinib and gemcitabine throughout the duration of the trial. One-year OS was 23.8% for erlotinib and gemcitabine arm versus 19.4% for gemcitabine alone. An exploratory analysis by pretreatment characteristics found that a survival benefit, as evidenced by HR less than 1, was observed across most patient subpopulations. A significant improvement in median PFS was also observed in the gemcitabine and erlotinib arm; 3.8 versus 3.5 months in the gemcitabine monotherapy arm (HR = 0.76, $P = 0.006$). Tumor response rates were 8.6 and 7.9%, respectively.

Treatment was generally well tolerated with the incidence of adverse events broadly similar in both arms of PA.3 [45]. Patients who received erlotinib and gemcitabine experienced higher frequencies of rash, diarrhea, infection, and stomatitis, but these were generally grade 1 or 2 in severity.

On the basis of the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire C30, there was no significant difference between the treatment arms in terms of global quality

Fig. 1



Schematic representation of epidermal growth factor receptor signal transduction and its downstream effects [56] (reprinted with permission from *Clinical Cancer Research*).

of life or in the individual domains with the exception of worse diarrhea change scores in the erlotinib and gemcitabine arm ($P < 0.001$) [45].

Findings with other tumor types, particularly NSCLC, indicate that certain patient populations may derive greater benefit from molecular-targeted agents than others. For NSCLC, there is some retrospective evidence from subset analyses that patient characteristics such as prior smoking history, sex, adenocarcinoma or bronchioalveolar tumor histology, and Asian ethnicity may all be linked to treatment outcome with erlotinib and another EGFR TKI gefitinib (Iressa) [61–64]. It is not clear whether such factors are prognostic of disease outcome or predictive of treatment effect. Such characteristics are likely to be linked to molecular differences in EGFR or its associated signaling pathways, but these differences have not yet been clearly identified. Relationships between expression of EGFR, pMAPK, and pAkt and response to EGFR TKIs also remain to be firmly established as results have been contradictory [65–72], but there is some evidence that amplification of the *EGFR* gene may be linked to a higher likelihood of response and extended survival for patients with NSCLC [73,74]. Recent findings also suggest that somatic mutations in the EGFR tyrosine kinase domain may predict for good response to erlotinib and gefitinib treatment [66,73,75–79], whereas *K-ras* mutations may be associated with poor clinical outcome for these patients [66,73].

What relevance these observations will have on the use of erlotinib in pancreatic cancer is unclear. Levels of EGFR expression were not found to impact on outcome in the PA.3 trial, but *EGFR* mutation status and amplification were not studied [45]. The relevance of *EGFR* mutations in pancreatic cancer is currently undefined. The analysis of *K-ras* mutations was also beyond the scope of this trial, but may be of critical importance for future studies, bearing in mind its adverse association with survival in NSCLC patients and the high levels observed in pancreatic cancer [3]. The impact of treatment with erlotinib and its relationship to the presence or absence of *K-ras* mutations on survival remains unclear. It is interesting to speculate that the efficacy of the gemcitabine and erlotinib regimen may be augmented by the addition of a farnesyl transferase inhibitor such as tipifarnib.

Phase II trials of erlotinib monotherapy have recently been reported or are currently under way in patients with advanced pancreatic cancer who have previously been treated with prior gemcitabine-based chemotherapy for advanced disease. Efficacy results recently reported in one study were disappointing [80]. In this phase II trial 13 patients were enrolled. Time to progression was only 1 month and no responses were observed. Clinical outcome in future studies should correlate EGFR status (based on immunohistochemistry and gene amplification) as well as EGFR and *K-ras* mutations [81], and it is hoped that results will address the relevance of these markers in the treatment of pancreatic cancer.

Generally, we should not automatically assume that observations made in NSCLC will hold true in pancreatic cancer due to the differences in disease course for NSCLC and pancreatic cancer, and/or fundamental differences in tumor histology. This is highlighted by the failure of two phase III trials of erlotinib in combination with standard chemotherapy in NSCLC [82,83]. In one of these trials, TRIBUTE, erlotinib was combined with a gemcitabine-containing regimen, but failed to significantly increase efficacy over chemotherapy alone (except for a subgroup of never smokers). This is in sharp contrast to the positive results of PA.3.

One characteristic that does appear to correlate with prolonged survival with erlotinib, in both NSCLC and pancreatic cancer patients, is the presence of moderate-to-severe rash. This association was observed in BR.21 and PA.3 and has also been seen in trials of erlotinib and other EGFR-targeted agents, including cetuximab, in NSCLC [84]. For PA.3, this association is not explained by gemcitabine-related rash (there was no correlation between grade 1 rash and survival) or by patients who stay on treatment longer being at greater risk for rash, as the analysis was adjusted for this potential bias and this type of rash tends to occur in early stages of treatment. Rather, the observation may be as a result of variability in drug absorption or metabolism, the ability to generate a rash predicting for a more immunocompetent individual, or a pharmacogenetic basis that is seen in both germ line and tumor cells [45]. The relevance of rash is being investigated in a number of phase II trials of gemcitabine and erlotinib [81]; however, it is worth noting that rash is a purely treatment emergent effect, and making any prognostic judgment based on its presence/absence is currently inadvisable.

A better understanding of key cellular alterations that drive the cancer cell survival and/or the patient characteristics that predict for their presence will, no doubt, allow for a more individualized approach to treatment for pancreatic cancer, potentially leading to improved efficacy and patient survival and also aiding in the rational development of new combination regimens.

Cetuximab

Cetuximab, an anti-EGFR monoclonal antibody, blocks the extracellular domain of EGFR, preventing ligand-dependent or independent activation and downstream signaling [85]. It is approved in combination with irinotecan for the treatment of EGFR-expressing, meta-

static colorectal cancer in patients who are refractory to irinotecan-based chemotherapy in the US and the EU, and as monotherapy for patients with EGFR-expressing metastatic colorectal cancer intolerant to irinotecan-based chemotherapy in the US. It is also approved for locally or regionally advanced head and neck squamous cell carcinoma in combination with radiation therapy in the EU and the US and metastatic or recurrent head and neck squamous cell carcinoma that is refractory to platinum-based therapy in the US [86,87].

Preclinical studies indicate that cetuximab inhibits tumor growth, regression, and metastasis in pancreatic cancer mouse xenografts, effects that are enhanced by adding gemcitabine [88]. Phase II data for cetuximab and gemcitabine in chemotherapy-naive patients with advanced EGFR-positive pancreatic cancer were encouraging (Table 4) [47]. Median OS for patients treated with this regimen was 7.1 months, median time to progression was 3.8 months, and 1-year PFS and OS rates were 12 and 31.7%, respectively. Twelve percent of patients achieved a partial response, and 63.4% had stable disease (SD). The combination was generally well tolerated [47].

An open-label, randomized phase III trial comparing cetuximab and gemcitabine with gemcitabine alone in patients with advanced pancreatic cancer was subsequently initiated, and conducted by the Southwest Oncology Group. More than 700 patients were enrolled in centers throughout the US and Canada. Unfortunately, recently reported data indicate that this study failed to demonstrate a clinically significant advantage of the addition of cetuximab to gemcitabine for OS, PFS, and response [37]. Other cetuximab-based combination therapies, however, continue to be investigated for advanced pancreatic cancer (Table 5) [81].

Table 5 Ongoing clinical trials with erlotinib, capecitabine, bevacizumab, and cetuximab in patients with advanced pancreatic cancer [81]

Regimen	Phase	Indication
Capecitabine + gemcitabine + erlotinib	I	Advanced disease
Erlotinib + gemcitabine + bevacizumab + capecitabine	I-II	Advanced disease
Gemcitabine + bevacizumab + erlotinib	II	Locally advanced or metastatic disease
Genistein + gemcitabine + erlotinib	II	Advanced or metastatic disease
Gemcitabine + capecitabine + bevacizumab	II	Metastatic or unresectable disease
Bevacizumab + gemcitabine + 5-FU	II	Advanced disease
Bevacizumab + gemcitabine + oxaliplatin	II	Metastatic disease
Gemcitabine + cisplatin + bevacizumab	II	Metastatic disease
Capecitabine + docetaxel	II	Recurrent or progressive metastatic disease
Cetuximab + gemcitabine + oxaliplatin	II	Advanced or metastatic disease
Ixabepilone + cetuximab	II	Metastatic disease
Cetuximab + bevacizumab ± gemcitabine	II (randomized)	Advanced or metastatic disease
Bevacizumab + gemcitabine + cetuximab/erlotinib	II (randomized)	Advanced disease
Irinotecan + docetaxel ± cetuximab	II (randomized)	Metastatic disease
Erlotinib + gemcitabine + bevacizumab vs. erlotinib + gemcitabine	III	Metastatic disease
Erlotinib + capecitabine followed gemcitabine vs. erlotinib + gemcitabine followed by capecitabine	III	Metastatic disease

5-FU, 5-fluorouracil.

Bevacizumab

Bevacizumab is a recombinant, humanized IgG1 monoclonal antibody. In the US and the EU it is approved for use in combination with intravenous 5-FU-based chemotherapy for the first-line treatment of patients with metastatic colorectal cancer, and also, in combination with carboplatin and paclitaxel, for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic nonsquamous, NSCLC [89,90]. Bevacizumab selectively binds to vascular endothelial growth factor (VEGF), inhibiting its interaction with VEGF receptors, VEGFR-1 and VEGFR-2, on the surface of endothelial cells. The VEGF pathway is central to angiogenesis (new vessel generation) and maintaining established vasculature, both essential for tumor growth and development.

VEGF and its receptors (VEGFR-1, VEGFR-2, and VEGFR-3) are overexpressed in pancreatic cancer, promoting pancreatic cancer growth through paracrine angiogenic and autocrine mitogenic pathways [91], and correlating with advanced stage, liver metastases, postoperative recurrence, and decreased survival in patients and animal models [91–94].

Results from a phase II trial of bevacizumab and gemcitabine in advanced pancreatic cancer suggested that this is an active and well-tolerated combination (Table 4) [46]. Fifty-two patients were enrolled and of these, 11 (21%) had confirmed partial responses and 24 (46%) had SD. Median survival was 8.8 months and median PFS was 5.4 months. The 6-month survival rate was 77% [46]. Subsequently, a phase III trial of bevacizumab and gemcitabine in advanced pancreatic cancer was initiated [81]. Unfortunately, on the basis of an interim analysis, this trial was terminated early [95]. Analysis of the available data found no significant differences between OS ($P = 0.78$, HR = 1.03) or PFS ($P = 0.99$, HR = 1.0) for the gemcitabine (OS = 6.1 months, PFS = 4.7 months) or gemcitabine and bevacizumab arms (OS = 5.8 months, PFS = 4.9 months) [38]. Despite recently reported negative trials, a number of phase II and phase III studies are underway in advanced pancreatic cancer that include bevacizumab and cetuximab in combination with different agents (Table 5) [81].

Perhaps the most eagerly anticipated trial is the phase III (AVITA) study. This is comparing gemcitabine alone with

a combination of bevacuzimab, erlotinib, and gemcitabine. This strategy has considerable potential for the treatment of advanced pancreatic cancer through the simultaneous targeting of both EGFR and VEGF, as there is known synergy and interaction between the pathways. Inhibiting EGFR decreases VEGF expression in cell lines, and also decreases endothelial migration, and microvessel density in pancreatic and other cancer xenograft models [96,97]. A phase I/II study and a randomized phase II study of bevacizumab and erlotinib in NSCLC have found acceptable tolerability and evidence of activity [98,99], and this combination is now being investigated in various other solid tumors [81].

Capecitabine

Capecitabine is an orally administered fluoropyrimidine that is metabolized in both the liver and tumor cells into 5-FU, resulting in high intratumoral 5-FU concentrations [100]. In the US and the EU, capecitabine is approved for use as a first-line monotherapy in patients with metastatic colorectal cancer, and as second-line therapy alone or in combination with docetaxel, in patients with metastatic breast cancer who are resistant to or unsuitable for paclitaxel/anthracycline-containing regimens [101,102]. It is also approved as an adjuvant treatment for patients after surgery of stage III colon cancer and first line, in combination with a platinum-based regimen, for advanced gastric cancer [102].

In a phase II trial, capecitabine monotherapy for metastatic pancreatic cancer resulted in an overall response rate of 9.5%, whereas 41% of the patients experienced SD [103]. In a second study, capecitabine combined with gemcitabine was also active and well tolerated, with a response rate of 18.9 and 42% of patients experiencing SD [100]. Similarly, capecitabine and oxaliplatin seemed to be an effective regimen, based on preliminary results of a phase II trial in patients with metastatic pancreatic cancer [104].

Phase III data for capecitabine in combination with gemcitabine are contradictory. A Swiss phase II trial, which enrolled 319 patients with advanced pancreatic cancer, did not observe a statistically significant difference in OS between patients treated with gemcitabine and capecitabine and those treated with gemcitabine monotherapy [105]. However, preliminary data from another phase III trial of gemcitabine versus gemcitabine and capecitabine in patients with advanced pancreatic cancer are more encouraging (Table 4) [43]. In this trial, OS with gemcitabine and capecitabine was significantly improved over gemcitabine alone (HR = 0.80; 95% confidence interval: 0.65–0.98; $P = 0.026$). The median survival for gemcitabine and gemcitabine plus capecitabine was 6 and 7.4 months, respectively, and 1-year survival rates were 19 and 26%. A significant difference was also found in the response rates; 7% in the gemcitabine arm and 14% with gemcitabine plus capecitabine ($P = 0.008$). In addition, levels of toxicity were acceptable [43]. The final data from this study have not yet been reported but are expected by the end of 2007.

Future treatment strategies for advanced pancreatic cancer

Given the positive data observed in phase III trials, gemcitabine, erlotinib, and capecitabine are likely to form the foundation for future treatment strategies for advanced pancreatic cancer, and novel combinations of these agents are under investigation in range of ongoing studies (Table 5). The complex biology and genetic changes associated with the disease, however, provide a rationale for the investigation of new agents and new regimens.

Intriguing data have been observed with PEFG (gemcitabine plus cisplatin, epirubicin, and 5-FU). Phase III trial data have been published showing significantly better response rate and 4-month PFS for this combination over gemcitabine monotherapy [106]. This trial was, however, not powered to detect differences in OS and a larger confirmatory trial will be needed to determine the clinical relevance of these findings.

Promising results have also been observed with folfirinox (5-FU/leucovorin, irinotecan, and oxaliplatin) in patients with metastatic pancreatic cancer. Interim results from a randomized phase II trial of folfirinox versus gemcitabine, indicate that response rate was greater than 30% in the experimental arm, and that toxicity was manageable [107]. On the basis of these interim results, the trial is continuing as a phase III study.

A wide range of molecular-targeted agents that interact with pathways that are crucial to cell survival are also being studied in pancreatic cancer. These include agents that target poly ADP-ribose polymerase, histone deacetylase, Src/Abl kinases, and mammalian target of rapamycin, among others [81]. A complete list of molecularly targeted therapies that are currently in clinical development for pancreatic cancer is provided in Table 6 [81].

Conclusion

Improvements over gemcitabine monotherapy in patients with advanced pancreatic cancer have been modest. During the last decade, a wide range of therapeutic additions failed to improve prognosis over gemcitabine alone. Erlotinib and gemcitabine, however, received approval from the FDA for locally advanced or metastatic pancreatic cancer in 2005. The results from the PA.3 trial suggest that gemcitabine and erlotinib represents a step forward in the management of this disease, but defining

Table 6 Molecular-targeted agents in clinical development for advanced pancreatic cancer [81]

Agent	Target	Regimen	Indication	Phase
KU-0059436	PARP	+ Gemcitabine	Advanced disease	I
MGCD0103	HDAC	+ Gemcitabine	Locally advanced or metastatic disease	I/II
Valatinib	VEGF	+ Gemcitabine	Advanced disease	I/II
AZD0530	Src/Abl	+ Gemcitabine	Locally advanced or metastatic disease	I/II
Celecoxib	Cox-2	+ Gemcitabine	Metastatic disease	II
Dasatinib	Src/Abl	Monotherapy	Metastatic diseases	II
Everloimus	mTOR	Monotherapy (2nd-line)	Metastatic diseases	II
Imatinib	Abl	+ Gemcitabine	Locally advanced or metastatic disease	II
ISIS-2503	Ha-*Ras*	+ Gemcitabine	Advanced or metastatic disease	II
Lapatinib	EGFR/HER2	+ Gemcitabine	Metastatic disease	II
Triapine (3-AP)	Ribonucleotide reductase	+ Gemcitabine	Locally advanced disease	II
Sorafenib	RAF kinase	± Gemcitabine	Metastatic disease	II (randomized)
Sunitinib	PDGFR/VEGFR	Monotherapy (2nd-line)	Metastatic disease	II
Vandetanib	VEGFR2/EGFR	Monotherapy (2nd-line)	Advanced or metastatic disease	II
WX-671	UPA	± Gemcitabine	Locally advanced disease	II (randomized)
Axitinib	VEGFR	± Gemcitabine	Advanced disease	III

Cox-2, cycloxygenase-2; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; PARP, poly ADP-ribose polymerase; PDGFR, platelet-derived growth factor receptor; UPA, urokinase plasminogen activator; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

subsets of patients that benefit from this two-drug combination will be important. It is hoped that newer molecular-targeted agents that address cancer cell survival will take us to the next level in the management of pancreatic cancer.

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