Systemic Therapy of Advanced Pancreatic Cancer: Has the Landscape Changed?

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Abstract: Limited progress has been made in the treatment of advanced pancreatic cancer. Gemcitabine was established as a standard of care after a randomized phase III study showed an improvement in clinical benefit response and overall survival over 5-flurouracil. Multiple phase III studies have been conducted to improve upon the response and survival established with single-agent gemcitabine. Combining different cytotoxic chemotherapy with gemcitabine failed to provide any meaningful survival advantage over gemcitabine monotherapy. A modest improvement in overall survival was noted when an epidermal growth factor receptor tyrosine kinase inhibitor (erlotinib) was added to gemcitabine. The landscape for the treatment of advanced pancreatic cancer changed with the introduction of the fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) regimen at the 2010 American Society of Clinical Oncology meeting. The phase III clinical trial showed an overall survival improvement in the gemcitabine group of 6.8 months compared to 11.1 months in the FOLFIRINOX arm ($P<.0001$). More interestingly, almost half of the patients in the FOLFIRINOX group were alive after 1 year, and the response rate was 31.6%. A new triplet chemotherapy regimen has emerged to replace the use of single-agent gemcitabine in a highly selected patient population. In this article, we will review the published data on first-line chemotherapy, with discussion of targeted agents for advanced pancreatic cancer and potential future directions.

Introduction

Pancreatic adenocarcinoma is a lethal cancer with 1-year and 5-year survival rates of 20% and 4%, respectively. In 2011, an estimated 37,170 patients were diagnosed with pancreatic cancer, and 33,370 patients died from the disease.[1] Surgical resection may offer a chance for cure if the tumor is detected early. However, more than 80% of patients with pancreatic cancer will present with an unresectable tumor due to distant metastases and/or local invasion of large vessels. Even in patients who undergo a curative surgical resection, more than 80% will eventually die of local and systemic recurrence.

Pancreatic carcinogenesis is a multistep pathway that results from accumulation of multiple mutations in oncogenes and tumor suppressor genes. The activation of the *KRAS* oncogene has been reported in more than 80–85% of patients, and inactivation of tumor suppressor genes—such as *p53*, *p16*, and *DPC4*—has been reported in more than 70% of the tumors.[2-4] These gene mutations and additional epigenetic events result in aberrant expression of critical proteins, such as the epidermal growth factor receptor (EGFR) and its ligands, vascular endothelial growth factor (VEGF), cyclooxygenase-2, survivin, NF-κB, Bcl-2, Bcl-xl, matrix metalloproteinases, and other key molecules. These molecular changes could be responsible for the de novo resistance of pancreatic cancer to anticancer drugs and radiation therapy.[5-7]

Palliative cytotoxic therapy is the main treatment modality in patients with advanced pancreatic cancer. The pivotal trial by Burris and colleagues in 1997 positioned single-agent gemcitabine as a standard of care.[8] This study compared fluorouracil (5-FU) to gemcitabine (Gemzar, Lilly) in 126 patients with metastatic or locally advanced pancreatic cancer. Results showed that gemcitabine was associated with a statistically significant improvement in the primary endpoint of clinical benefit response (defined as a composite of measurements of pain, performance status, and weight; *P*=.0022) and a 5-week improvement in median survival compared to 5-FU. However, the median survival for the gemcitabine arm was dismal at 5.65 months, with a 1-year survival rate of 18%. This article will examine the changing landscape in the systemic treatment of pancreatic cancer. Readers are referred to Almhanna and Kim[9] for discussion of second-line chemotherapy and to Lowery and O'Reilly[10] for discussion of molecular markers.

Combination Cytotoxic Therapies in Pancreatic Cancer

After the US Food and Drug Administration (FDA) approved gemcitabine for advanced pancreatic cancer, investigators quickly proceeded to test combinations of cytotoxic therapies based on a gemcitabine backbone. Between 1995 and 2012, many studies were undertaken in the phase III setting to test combinations with platinum compounds, fluoropyrimidines, antifolates, and topoisomerase I inhibitors (Table 1). Some of these combinations showed promising signals in the phase II setting based on objective response rates and/or time to progression. However, outcomes of most phase II trials could not be replicated in phase III trials.

Gemcitabine Plus Fluoropyrimidines

Gemcitabine and 5-FU combinations have been studied in multiple randomized trials using either bolus or infusional 5-FU.[11-13] The results were disappointing, with no improvement in response rate, time to progression, or survival. Improvement in progression-free survival (PFS) was shown in only 1 study, by Berlin and coworkers, which examined the bolus 5-FU in combination with gemcitabine.[11] PFS was improved by 1 month, but no increase in overall survival (OS) was observed. Use of a different administration schedule of 5-FU and modulation with leucovorin did not affect the clinical outcome in patients with advanced pancreatic cancer.

Two phase III trials conducted in Europe investigated whether the addition of capecitabine (Xeloda, Genentech) to gemcitabine would provide benefit over gemcitabine alone. Hermann and colleagues evaluated 319 patients with advanced pancreatic cancer who received gemcitabine 1,000 mg/m^2 on days 1 and 8 and capecitabine 1,300 mg/m^2/day given in 2 divided doses for 14 days of an every-3-week cycle. Median survival was 8.4 months in the capecitabine/gemcitabine arm versus 7.2 months in the gemcitabine arm, a difference that was not statistically significant (*P*=.234).[14] However, a subgroup analysis of patients with Karnofsky performance status of 90–100% showed improvement in OS (10.1 vs 7.4 months; *P*=.014). A British study by Cunningham and associates investigated the combination of capecitabine (1,660 mg/m^2 daily for 21 days in a 4-week schedule) plus the standard dose and schedule of gemcitabine versus gemcitabine monotherapy in 533 patients. The combination arm was associated with higher response rate (19.1 vs 12.4%) and improved PFS.[15] However, these improvements did not translate to increased OS (7.1 vs 6.2 months; hazard ratio [HR], 0.86; *P*=.08). Hematologic and skin toxicities were predictably higher in the doublet arm compared to the gemcitabine monotherapy arm. Grade 3/4 neutropenia was noted in 35% of the combination arm versus 22% in the control arm, and grade 3/4 hand-foot skin reaction was noted in 4% of the combination arm versus 0% in the control arm.

Gemcitabine and Platinum Compounds

The rationale for the cytotoxic combination of gemcitabine and platinum compounds was based on preclinical evidence of synergistic activity. In vitro studies showed that the combination of gemcitabine with cisplatin increased the concentration of platinum-DNA adduct formation and inhibited DNA excision repair processes to a much greater extent than gemcitabine alone,[16] with similar synergistic activity in preclinical studies in xenograft animal models. Phase II trials showed response rates of 11–26%, with median survival times ranging from 7.1–8.2 months.[17,18] Subsequently, multiple phase III trials were conducted to confirm the efficacy of the platinum and gemcitabine doublet.

Table 1. Selected Phase III Trials in Advanced Pancreatic Cancer

Study	N	Drug Combination	RR (%)	TTP/ PFS	Median Survival (months)	1-Year Survival (%)
Berlin et al[11]	326	Gemcitabine vs Gemcitabine + 5-FU	5.6 6.9	2.2 3.4	5.4 6.7	18 18
Riess et al[13]	466	Gemcitabine vs Gemcitabine + infusional 5-FU	7 5	3.5 3.5	6.2 5.8	22 21
Hermann et al[14]	319	Gemcitabine vs Gemcitabine + capecitabine	7.8 10.0	3.9 4.3	7.2 8.4	30 32
Cunningham et al[15]	533	Gemcitabine vs Gemcitabine + capecitabine	12.4 19.1	3.8 5.3	6.2 7.1	22 24
Rocha Lima et al[67]	342	Gemcitabine vs Gemcitabine + irinotecan	4.4 16.1	3 3.5	6.6 6.3	22 21
Abou-Alfa et al[68]	349	Gemcitabine vs Gemcitabine + exatecan	5.1 6.8	3.8 3.7	6.2 6.7	21 23
Oettle et al[69]	565	Gemcitabine vs Gemcitabine + pemetrexed	7.1 14.8	3.3 3.9	6.3 6.2	20 21
Colluci et al[20]	400	Gemcitabine vs Gemcitabine + cisplatin	10.1 12.9	3.9 3.8	8.3 7.2	34 31
Heinemann et al[19]	195	Gemcitabine vs Gemcitabine + cisplatin	8.2 10.2	3.1 5.3	6.0 7.5	25 25
Louvet et al[22]	313	Gemcitabine vs Gemcitabine + oxaliplatin	17.3 26.8	3.7 5.8	7.1 9.0	28 35
Poplin et al[23]	832	Gemcitabine vs Gemcitabine + oxaliplatin	6 9	2.6 2.7	4.9 6.2	16 21
Conroy et al[28]	342	Gemcitabine vs Oxaliplatin + irinotecan + 5-FU + leucovorin	9.4 31.6	3.3 6.4	6.8 11.1	20.6 48.4

5-FU=fluorouracil; N=number of patients; NA=data not available; PFS=progression-free survival; RR=response rate; TTP=time to tumor progression.

A study by Heinemann and coworkers of 198 patients comparing gemcitabine plus cisplatin with gemcitabine alone showed improvement in the time to tumor progression by nearly 2 months in the doublet arm, although there was no significant survival advantage.[19] A larger Italian study by Collucci and associates (N=400) showed no improvement in time to tumor progression and no survival advantage for cisplatin/gemcitabine over gemcitabine.[20] The median OS was 8.3 months in the gemcitabine arm versus 7.2 months in the cisplatin/gemcitabine arm, with no difference in objective response rates.[20] Hematologic toxicity was significantly higher in the combination group, although it was tolerable in most patients. The authors concluded that the gemcitabine and cisplatin combination was not appropriate for most patients with advanced pancreatic cancer due to increased toxicities.

With the increasing use of third-generation platinums, oxaliplatin has been tested in pancreatic cancer alone and in combination with gemcitabine. A study of the oxaliplatin/gemcitabine combination in 64 patients showed a median survival of 9.2 months, with a 36% 1-year survival rate. There was also an impressive 40% clinical benefit response rate in these patients.[21] These findings quickly led to 2 large, phase III trials. The European study conducted by the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) and the Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) enrolled 326 patients,[22] and a study conducted by the Eastern Cooperative Oncology Group (ECOG) in the United States had 832 patients.[23]

The study by Louvet and colleagues randomly assigned patients to receive either standard-dose gemcitabine alone or in combination with oxaliplatin (GEMOX).[21] The GEMOX regimen consisted of gemcitabine 1,000 mg/m^2 by fixed dose rate on day 1 and oxaliplatin 100 mg/m^2 on day 2 every 2 weeks. Patients in the GEMOX arm achieved a superior response rate (26.8 vs 17.3%), greater improvement in PFS (5.8 vs 3.7 months) and higher

clinical benefit response (38.2 vs 26.9%). There was no significant improvement, however, in the primary endpoint of OS (9.0 vs 7.1 months; *P*=.13).[22]

ECOG 6201 was a 3-arm study that included standard dose and schedule gemcitabine, gemcitabine by fixed dose rate, and GEMOX. The study posed the question of whether the schedule of administration of gemcitabine would impact its efficacy based on the results of the previously described randomized phase II study. The ECOG study, which was probably a more definitive study than that conducted by GERCOR and GISCAD, showed no significant difference in rates of median survival, which were 5 months, 6 months, and 5.9 months for standard gemcitabine, fixed dose rate gemcitabine, and GEMOX, respectively.[23] There was a noticeable increase in hematologic toxicity for gemcitabine by the fixed dose rate infusion compared to the standard dose and schedule of gemcitabine. Hence, the promise suggested by early exciting data for gemcitabine by fixed dose rate, as well as for GEMOX combination therapy, did not materialize.

In contrast to the results of E6201, a pooled analysis of 2 randomized studies suggested that there might be a benefit from the use of gemcitabine plus a platinum agent over gemcitabine alone in patients with advanced pancreatic cancer. The pooled analysis among 503 evaluable patients showed an improvement in PFS (median, 5.5 months vs 3.5 months, respectively; HR, 1.56; *P*=.013) and OS (median, 8.3 months vs 6.7 months, respectively; HR, 1.23; *P*=.031).[24] However, the conclusion of this meta-analysis must be considered against the many large failed randomized phase III studies.

Other Gemcitabine-Based Cytotoxic Combinations

Other gemcitabine-based chemotherapy combinations are listed in Table 1. These agents include the DNA topoisomerase inhibitors irinotecan and exatecan, the thymidylate synthase inhibitor pemetrexed, and other platinum analogs. None of the phase III trials using a combination of gemcitabine doublets showed improvement in OS. However, other combination regimens have gained interest among clinicians.

The gemcitabine, docetaxel, and capecitabine (GTX) regimen was developed based on preclinical work by Fine and colleagues.[25,26] A retrospective analysis of 35 patients showed impressive results, with 9% of patients achieving a complete remission and 31% achieving a partial response.[25] In a prospective phase II trial, which is available only in abstract form, 21.9% of patients achieved a partial response, and 41% had stable disease.[26] The median OS of 14.5 months was impressive; however, there are currently no phase III data to support the use of this combination.

Another combination that has gained interest is nab-paclitaxel (Abraxane, Celgene) with gemcitabine. Overexpression of secreted protein acidic and rich in cysteine (SPARC) has been noted in pancreatic tumors and their stroma. Nab-paclitaxel has shown clinical activity in patients who overexpress SPARC because it binds to the albumin portion of the paclitaxel. Because paclitaxel has affinity to the protein receptor gp60 in the blood vessel wall, it is delivered to the tumor site at a high concentration (as are other cytotoxic agents). In a phase I/II trial of 44 patients, median OS among patients receiving a combination of gemcitabine and nab-paclitaxel was 12.2 months, which is almost double the historical control of gemcitabine alone. A confirmed overall response rate was achieved in 50% of patients treated, and the disease control rate (complete response, partial response, and stable disease for 16 weeks or longer according to Response Evaluation Criteria In Solid Tumors [RECIST] criteria) was 68%.[27] A phase III trial comparing the combination of gemcitabine and nab-paclitaxel against single-agent gemcitabine is ongoing. In 2009, nab-paclitaxel was given orphan status for the treatment of advanced pancreatic cancer, and the National Comprehensive Cancer Network (NCCN) included use of gemcitabine plus nab-paclitaxel as a category 2B recommendation.

Changing Landscape With FOLFIRINOX Chemotherapy

The landscape for the treatment of advanced pancreatic cancer changed with a report of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) chemotherapy first presented at the 2010 American Society of Clinical Oncology (ASCO) meeting.[28] This phase III trial randomly assigned 342 patients with ECOG performance status of 0 or 1 to receive FOLFIRINOX chemotherapy or standard gemcitabine chemotherapy. The FOLFIRINOX regimen was comprised of oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and 5-FU 400 mg/m^2 as bolus followed by 2,400 mg/m^2 as continuous infusion over 46 hours every 2 weeks. The primary endpoint of the study was OS. At a median follow-up of 27 months, OS was 11.1 months in the FOLFIRINOX arm compared to 6.8 months in the gemcitabine arm (*P*<.0001).[28] More interestingly, almost half the patients in the FOLFIRINOX group were alive after 1 year, and the response rate was 31.6%—the highest rate seen in phase III pancreatic cancer trials.

As expected, patients in the FOLFIRINOX group experienced more grade 3/4 adverse events, such as febrile neutropenia (5.4% vs 1.2%), thrombocytopenia (9.1% vs 3.6%), diarrhea (13% vs 2%), and sensory neuropathy (9% vs 0%) than patients in the gemcitabine group. However, quality of life assessment showed that 69% of

Table 2. Selected Phase III Trials in Advanced Pancreatic Cancer Using Targeted Agents

Study	N	Regimen	RR (%)	TTP/PFS (months)	Median Survival (months)	1-Year Survival (%)
Van Cutsem et al[30]	688	Gemcitabine vs Gemcitabine + tipifarnib	8 6	3.6 3.7	6.0 6.5	24 27
Moore et al[33]	277	Gemcitabine vs Gemcitabine + BAY 12-9566	NA	3.5 1.7	6.5 3.7	25 10
Bramhall et al[34]	414	Gemcitabine vs Gemcitabine + marimastat	26 3	3.8 1.9	5.6 3.8	19 16
Bramhall et al[35]	239	Gemcitabine vs Gemcitabine + marimastat	11 16	NA	5.5 5.5	17 18
Moore et al[38]	569	Gemcitabine vs Gemcitabine + erlotinib	8 8.6	3.6 3.8	5.9 6.2	17 23
Kindler et al[50]	535	Gemcitabine vs Gemcitabine + bevacizumab	10 13	2.9 3.8	5.9 5.8	NA
Philip et al[41]	745	Gemcitabine vs Gemcitabine + cetuximab	14 12	3.0 3.4	5.9 6.3	NA
Van Cutsem et al[51]	607	Gemcitabine + erlotinib vs Gemcitabine + erlotinib + bevacizumab	8.6 13.5	3.6 4.6	6.0 7.1	NA NA
Kindler et al[53]	632	Gemcitabine vs Gemcitabine + axitinib	2 5	4.4 4.4	8.3 8.5	NA

N=number of patients; NA=data not available; PFS=progression-free survival; RR=response rate; TTP=time to tumor progression.

patients in the FOLFIRINOX group had no decrease in the Global Health Status and Quality of Life scale at 6 months after therapy, compared to only 34% of the gemcitabine group. This finding signals that the adverse events associated with cancer progression have a higher impact on quality of life compared to the adverse events associated with chemotherapy in patients with advanced pancreatic cancer.

The trial was highly selective and enrolled only patients with metastatic disease who had a good performance status (ECOG 0 and 1) and normal bilirubin level. The study excluded patients with a high bilirubin level because of the increased risk of irinotecan-induced toxicity. Therefore, only 14% of patients had a biliary stent. A recent meta-analysis of advanced pancreatic cancer patients has shown that platinum/gemcitabine and capecitabine/gemcitabine combinations are beneficial in the subset of patients who have good performance status.[29] The HRs were just 0.85 and 0.91. The FOLFIRINOX regimen had an HR of 0.57, and its use has been supported by a randomized clinical study.[28] Therefore, FOLFIRINOX should be strongly considered as a first-line option for patients with metastatic pancreatic cancer who are younger than 76 years and who have a good performance status (ECOG 0 or 1), no cardiac ischemia, and normal or nearly normal bilirubin levels.

Targeted Agents in the Treatment of Pancreatic Cancer

The promise of improving outcome with a conventional cytotoxic therapy combination was diminished with the successive negative reports of large phase III trials—until the FOLFIRINOX data in 2010—and focus shifted to incorporating targeted drugs into the therapy of pancreatic cancer (Table 2). Once again, all of the trials used gemcitabine as the backbone chemotherapy. Most of the trials, which used targeted agents either as monotherapy or in combination with gemcitabine, failed to show clinical benefit over gemcitabine monotherapy. One exception was the gemcitabine and erlotinib (Tarceva Genentech/OSI Pharmaceuticals) combination.

Among the first agents to be tested in pancreatic cancer was the farnesyltransferase inhibitor tipifarnib (R11577), which inhibits the posttranslational farnesylation of the KRAS oncoprotein. The high frequency of activating *KRAS* mutations in pancreatic cancer prompted the urgency to test the drug in this setting. Unfortunately, a large phase III trial showed no clinical benefit when tipifarnib was added to gemcitabine.[30] Another farnesyltransferase inhibitor, SCH66336, was tested in a phase II study and did not show improvement over gemcitabine.[31] The National Cancer Institute of Canada investigated another novel agent,

BAY 12-9566, an inhibitor of the matrix metalloproteinase that contributes to tumor invasion and metastases. BAY 12-9566 was compared to gemcitabine in a phase III trial evaluating efficacy. Interestingly, the results showed superiority of gemcitabine over BAY 12-9566 in regard to survival (6.59 months vs 3.74 months), PFS, and quality of life.[32,33] Another matrix metalloproteinase inhibitor, CAS 154039-60-8 (Marimastat, British Biotech), was studied as both a single agent and in combination with gemcitabine. Neither regimen showed any additional benefit over gemcitabine monotherapy.[34,35] After the initial failures of these targeted agents, the focus shifted to other classes of drugs that have already shown activity in other tumor types, such as EGFR blockers and inhibitors of the VEGF and insulin growth factor pathways.

EGFR Blockade

Pancreatic cancers overexpress EGFR in a significant proportion of patients with a poor prognosis.[36,37] In 2005, investigators from the National Cancer Institute of Canada reported the first phase III clinical trial of EGFR tyrosine kinase blockade combined with gemcitabine that improved survival over single-agent gemcitabine. The trial randomized 569 patients with locally advanced and metastatic pancreatic adenocarcinoma to receive gemcitabine combined with either erlotinib or placebo.[38] The addition of erlotinib resulted in a modest improvement in median survival (from 5.9 months to 6.4 months) that was statistically significant (HR=0.81; *P*=.025). The 1-year survival rate improved from 17% to 24%, and there was also an improvement in PFS.[38] The combination arm experienced greater erlotinib-related adverse events, such as skin rash (72% vs 29%), diarrhea (56% vs 41%), and stomatitis (23% vs 14%). The presence of a skin rash was associated with a higher likelihood of achieving disease control. The median survival for patients with a rash of grade 2 or higher was 10.5 months, with 1-year survival rates of 43%. As in lung cancer and colorectal cancer, skin rash can predict which pancreatic cancer patients might benefit from EGFR blockade therapy.

Although the improvement of gemcitabine plus erlotinib over single-agent gemcitabine was very modest, these data are the first to show a statistically significant difference in the primary endpoint of survival. Although different subanalyses of EGFR status and mutation did not identify which patients would benefit from erlotinib therapy, simple skin rash was predictive of better clinical outcome. This study subsequently formed the basis of the FDA's approval of erlotinib in combination with gemcitabine in patients with advanced pancreatic cancer.

Another approach to targeting the EGFR signaling axis is with monoclonal antibodies that interfere with ligand binding to the receptor. Cetuximab (Erbitux, Bristol-Myers Squibb) is a chimeric immunoglobulin G1 monoclonal antibody with high affinity to the extracellular domain of EGFR. Preclinical data demonstrated both antiproliferative and antiangiogenic activity in human xenograft models.[39] A phase II study by Xiong and coworkers demonstrated that cetuximab in combination with gemcitabine resulted in a 76% disease control rate (12% partial response and 63% stable disease) in 41 patients with advanced pancreatic cancer. The median time to disease progression was 3.8 months, and median survival was 7.1 months.[40] The main toxicities noted were acne-like rash (88%), asthenia (85%), gastrointestinal complaints (61%), and myelosuppression (51%). These promising preliminary data prompted the Southwest Oncology Group (SWOG) to enroll 745 patients with advanced pancreatic cancer to test this regimen in a phase III setting. The results were disappointing, as the addition of cetuximab to gemcitabine did not improve OS (6.3 months vs 5.9 months) in patients with advanced pancreatic cancer.[41]

Other agents under investigation that target the EGFR pathway include gefitinib (Iressa, AstraZeneca) and lapatinib (Tykerb, GlaxoSmithKline), which have shown variable results in phase I and II clinical trials. Gefitinib is a tyrosine kinase inhibitor that interferes with adenosine 5'-triphosphate binding of the intracellular kinase domain of the epidermal growth factor receptor. A small trial of gemcitabine and gefitinib in advanced pancreatic cancer patients (N=53) showed modest results, with a median PFS of 4.1 months and a median survival of 7.3 months.[42] Six patients had a response to therapy, and 12 patients had disease stabilization. Lapatinib is a dual tyrosine kinase inhibitor that reversibly binds to both EGFR and HER2-neu. The drug was evaluated in a phase I study that enrolled 16 patients with metastatic pancreatic cancer. Median survival and median time to progression in this study were 10 months and 7 months, respectively.[43] A phase II study of lapatinib and gemcitabine in untreated metastatic pancreatic cancer was initiated. Accrual was terminated when a planned analysis at 6 months showed lack of efficacy. Among the 29 patients who had been enrolled, median survival was 4 months (95% confidence interval, 3.0–5.0 months).[44]

VEGF Blockade

VEGF is critical in the growth and angiogenesis of cells in many types of cancer, including pancreatic cancer. Inhibition of VEGF has resulted in dose-dependent growth inhibition of the tumor.[45-47] Bevacizumab (Avastin, Genentech) is a humanized monoclonal antibody against VEGF that has synergistic tumoricidal activity when combined with gemcitabine.[48] Hence, bevacizumab in combination with gemcitabine was tested for safety and

Table 3. Selected Phase II Trials in Advanced Pancreatic Cancer Using Targeted Agents

Study	N	Regimen	RR %	PFS/TTP (months)	Median OS (months)	1-Year Survival
Lersch et al[31]	63	SCH 66336 vs Gemcitabine	6 3.3	23% vs 31%*	3.3 4.4	NA
Xiong et al[40]	41	Cetuximab + gemcitabine	12	3.8	7.1	12
Fountzilla et al[42]	53	Gefitinib + gemcitabine	11	4.1	7.3	27
Safran et al[44]	29	Lapatinib + gemcitabine	10	NA	4.0	NA
Kindler et al[49]	52	Bevacizumab + gemcitabine	21	5.4	8.8	77†
Spano et al[52]	103	Axitinib + gemcitabine vs Gemcitabine	7 3	4.2 3.7	6.5 5.9	36.8 23.5
Wallace et al[55]	17	Sorafenib + gemcitabine	0	3.2	4.0	
Javle et al[62]	58	Gemcitabine + MK-0646 vs Gemcitabine + erlotinib + MK-0646 vs Gemcitabine + erlotinib	20 25 10	4.25‡ 2 2	12 7.5 6.5	NA
Kindler et al[643]	125	Gemcitabine + conatumumab vs Gemcitabine + AMG 479 vs Gemcitabine + placebo	0 3 5	3.9 5.1 2.1	7.5 7.3 6.2	59.7† 56.6 50.1

*Percentage of patients who achieved PFS at 3 months.

†Percentage of patients who achieved PFS at 6 months.

‡Outcome converted from weeks.

N=number of patients; NA=data not available; PFS=progression-free survival; RR=response rate; TTP=time to tumor progression.

efficacy in pancreatic cancer patients. In a phase II study by Kindler and colleagues, the combination showed a 67% disease control rate (21% partial response and 46% stable disease) in 52 patients with advanced pancreatic cancer. The median PFS was 5.4 months, and the median survival was 8.8 months.[49] However, due to the potential for vascular toxicity associated with bevacizumab, the study excluded patients with a history of bleeding and clotting problems and those taking daily nonsteroidal anti-inflammatory agents. The study, therefore, selected only favorable patients in this phase II setting. Significant grade 3/4 toxicities associated with therapy included hypertension (19%), thrombosis (13%), and visceral perforation (8%). The results of this phase II study led to the development of the Cancer and Leukemia Group B 80303 phase III trial, which compared gemcitabine plus bevacizumab versus gemcitabine alone. The study failed to show improvement in outcome; median OS was 5.8 months for gemcitabine plus bevacizumab compared to 5.9 months for single-agent gemcitabine.[50] The randomized phase III AVITA (A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial to Evaluate the Efficacy and Safety of Adding Bevacizumab to Erlotinib and Gemcitabine in Patients With Metastatic Pancreatic Cancer) study of 607 patients with metastatic pancreatic cancer explored the addition of bevacizumab to the gemcitabine plus erlotinib combination. This trial was a negative study, as it did not meet its endpoint of increased OS (which was 6 months in the placebo arm vs 7.1 months in the bevacizumab arm). There was, however, a significant improvement in PFS with the addition of bevacizumab.[51]

Axitinib (Inlyta, Pfizer), a small-molecule multitargeted agent with high potency and selectivity against VEGFRs 1–3 and other kinases (PDGFRβ, c-KIT), has been tested in pancreatic cancer. A randomized phase II study by Spano and associates enrolled 103 patients with locally advanced or metastatic pancreatic cancer.[52] The results are promising, showing a median OS of 6.9 months in the gemcitabine plus axitinib arm compared to 5.6 months in the gemcitabine-alone arm. Based on these data, a double-blind, randomised phase III study was conducted. A total of 632 patients were enrolled in the study with 1:1 randomization. The results were disappointing; median OS was 8.5 months for the gemcitabine plus axitinib arm versus 8.3 months for the gemcitabine plus placebo arm (HR, 1.014; 95% confidence interval, 0.86–1.309; *P*=.5436).[53]

Sorafenib (Nexavar, Onyx Pharmaceuticals/Bayer HealthCare Pharmaceuticals) is an orally active multikinase inhibitor with activity against VEGF, platelet-derived growth factor receptor, RAF, and RET kinases. It has a dual effect on tumor cells, and inhibits cellular proliferation and tumor angiogenesis. Sorafenib has been

tested in phase I and II trials in patients with advanced pancreatic cancer. In a phase I trial of 23 patients with advanced pancreatic cancer treated with sorafenib, 56% showed evidence of disease stabilization.[54] Later, a phase II study in chemotherapy-naïve patients with advanced pancreatic cancer examined sorafenib in combination with gemcitabine. Among the 17 patients who were evaluated in the first stage of the trial, none had any objective response. Median OS was 4.0 months, and median PFS was 3.2 months.[55]

IGFR Blockade

Human insulin-like growth factor–1 receptor (IGF-1R) is a transmembrane receptor tyrosine kinase that is involved in cellular growth and proliferation in normal tissues. Overexpression has been implicated in tumorigenesis and protection of cells from apoptosis.[56] In vitro studies have shown increased expression and activation of IGF-1R in pancreatic cell lines, which has contributed to the resistance of these cells to apoptosis. Treatment of these cell lines with IGF-1R neutralizing antibodies led to reduced cancer cell proliferation, reduced vascularization, and rapid apoptosis.[56-59] Furthermore, there is preclinical evidence of cross talk between the EGFR and IGF-1R signaling pathways, which may explain the acquired resistance to anti-EGFR drugs.[60] These preclinical studies helped in identifying IGR-1R blockade as a potential target for pancreatic cancer treatment and led to several clinical trials.

Promising antitumor activity was noted in a phase I study of MK-0646, a humanized monoclonal antibody against IGF-1R in combination with gemcitabine with or without erlotinib. A partial response was reported in 6 of 28 patients enrolled (21.4%).[61] The phase I results led to a 3-arm study comparing MK-0646 with gemcitabine (Arm A), MK-0646 with gemcitabine and erlotinib (Arm B), and gemcitabine with erlotinib (Arm C). Results of the study were presented at the 2011 ASCO meeting. In Arms A, B, and C, median PFS was 17 weeks, 8 weeks, and 8 weeks, respectively (P=.0425), and OS was 48 weeks, 30 weeks, and 26 weeks, respectively (P=.4).[62] The SWOG S0727 has explored the combination of gemcitabine plus erlotinib plus IMC-A12 (Cixutumumab, ImClone Systems Inc), another fully human IgG1 monoclonal antibody directed against IGF-1R versus gemcitabine plus erlotinib as first-line treatment in patients with metastatic pancreatic cancer.[63] The phase II study showed that the addition of cixutumumab to gemcitabine and erlotinib did not improve OS.

Kindler and colleagues presented a placebo-controlled, randomized phase II study introducing the monoclonal antibodies conatumumab (Amgen), a death receptor 5 agonist, and AMG 479 (Ganitumab, Amgen), an insulin-like growth factor receptor 1 antagonist.[64] In this study, 125 patients were randomized to receive conatumumab plus gemcitabine, AMG 479 plus gemcitabine, or gemcitabine plus placebo. There appeared to be a trend towards increased PFS with the addition of ganitumab to gemcitabine. A phase III study of ganitumab is ongoing, using 2 different doses compared to gemcitabine alone, with the goal of accruing 825 patients.[65]

Future Directions

The results with FOLFIRINOX are impressive, with an improvement in OS that is 3 months longer than that seen with gemcitabine alone. The use of FOLFIRINOX as a backbone chemotherapy instead of gemcitabine makes sense based on the phase III trial. As stated above, however, toxicity is a concern with this regimen, making it difficult to use in pancreatic cancer. Current large studies in pancreatic cancer are still using gemcitabine as a backbone, despite the impressive results of FOLFIRINOX. The FOLFIRINOX trial has provided evidence that gemcitabine does not have to be the backbone chemotherapy in pancreatic cancer.[66] Investigators should be encouraged to explore the use of non–gemcitabine-based backbone chemotherapy, such as FOLFOX or FOLFIRI, in future studies. Similar to colon cancer studies, it is much easier to add targeted agents to FOLFOX or FOLFIRI compared to FOLFIRINOX. Also, sequential treatment of FOLFOX followed by FOLFIRI in pancreatic cancer may provide similar outcomes compared to FOLFIRINOX, with reduced toxicity as well.

Currently, large numbers of targeted agents are being developed by pharmaceutical companies and other drug discovery laboratories. Since only a small incremental benefit is to be expected with most agents tested for pancreatic cancer, new research paradigms are needed to match the influx of new drugs with the limited number of patients going on clinical trials. There is a need for better tumor response monitoring and innovative strategies to demonstrate the biologic effects of targeted therapies. Molecular markers with potential therapeutic implications are desperately needed. The existence of multiple and complex gene mutations in tumors from patients with advanced pancreatic cancer dictates the need to develop rational drug combinations to target multiple pathways. It also underscores the need to support translational research and encourage accrual on clinical trials, and highlights the urgency to develop more intelligent clinical trial designs and the incorporation of genomics and other related technologies to select patients and predict outcomes.

Conclusion

It has been more than a decade since gemcitabine was shown to have a benefit in advanced pancreatic cancer patients. The vast majority of gemcitabine-based combinations have failed to add any survival advantage over gemcitabine alone. Adding novel targeted agents to gemcitabine was disappointing as well. The recent FOLFIRINOX data have changed the landscape for patients with advanced pancreatic cancer with a good performance status and normal bilirubin levels. FOLFIRINOX should be strongly considered as the new standard of care for these patients. Still, there is little doubt that all newly diagnosed patients with pancreatic cancer must be considered for experimental therapies.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*. 2011;61:212-236.
2. Almoguera C, Shibata D, Forrester K, et al. Most human carcinomas of the exocrine pancreas contain mutant cK-ras genes. *Cell*. 1988;53:549-554.
3. Grünewald K, Lyons J, Fröhlich A, et al. High frequency of Ki-ras codon 12 mutations in pancreatic adenocarcinomas. *Int J Cancer*. 1989;43:1037-1041.
4. Rozenblum E, Schutte M, Goggins M, et al. Tumor-suppressive pathways in pancreatic carcinoma. *Cancer Res*. 1997;57:1731-1734.
5. Garcea G, Neal CP, Pattenden CJ, Steward WP, Berry DP. Molecular prognostic markers in pancreatic cancer: a systematic review. *Eur J Cancer*. 2005;41:2213-2236.
6. Ghaneh P, Kawesha A, Evans JD, Neoptolemos JP. Molecular prognostic markers in pancreatic cancer. *J Hepatobiliary Pancreat Surg*. 2002;9:1-11.
7. Plath T, Peters M, Detjen K, et al. Overexpression of pRB in human pancreatic carcinoma cells: function in chemotherapy-induced apoptosis. *J Natl Cancer Inst*. 2002;94:129-142.
8. 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;15:2403-2413.
9. Almhanna K, Kim R. Second-line therapy for gemcitabine-refractory pancreatic cancer: is there a standard? *Oncology* (Williston Park). 2008;22:1176-1183; discussion 1190, 1192, 1196.
10. Lowery MA, O'Reilly EM. Pancreatic cancer: the role of molecular markers in diagnosis and management. *Clin Adv Hematol Oncol*. 2011;9:900-908.
11. 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;20:3270-3275.
12. Di Costanzo F, Carlini P, Doni L, et al. Gemcitabine with or without continuous infusion 5-FU in advanced pancreatic cancer: a randomised phase II trial of the Italian oncology group for clinical research (GOIRC). *Br J Cancer*. 2005;93:185-189.
13. Reiss H, Helm A, Niedergethmann M, et al. A randomized, prospective, multicenter, phase III trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2005;23(suppl 16): Abstract LBA4009.
14. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol*. 2007;25:2212-2217.
15. 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;27:5513-5518.
16. van Moorsel CJ, Pinedo HM, Veerman G, et al. Mechanisms of synergism between cisplatin and gemcitabine in ovarian and non-small-cell lung cancer cell lines. *Br J Cancer*. 1999;80:981-990.
17. Heinemann V, Wilke H, Mergenthaler HG, et al. Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer. *Ann Oncol*. 2000;11:1399-1403.
18. Philip PA, Zalupski MM, Vaitkevicius VK, et al. Phase II study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. *Cancer*. 2001;92:569-577.
19. 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;24:3946-3952.
20. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol*. 2010;28:1645-1651.
21. Louvet C, André T, Lledo G, et al. Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study. *J Clin Oncol*. 2002;20:1512-1518.
22. 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;23:3509-3516.
23. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009;27:3778-3785.
24. Heinemann V, Labianca R, Hinke A, Louvet C. Increased survival using platinum analog combined with gemcitabine as compared to single-agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study. *Ann Oncol*. 2007;18:1652-1659.
25. Fine RL, Fogelman DR, Schreibman SM, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother Pharmacol*. 2008;61:167-175.
26. Fine R, Moorer G, Sherman W, et al. Phase II trial of GTX chemotherapy in metastatic pancreatic cancer. *J Clin Oncol* (ASCO Annual Meeting Proceedings Post-Meeting Edition). 2009;27(suppl 15): Abstract 4623.
27. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol*. 2011;29:4548-4554.
28. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817-1825.
29. Heinemann V, Boeck S, Hinke A et al Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer*. 2008;8:82.
30. 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;22:1430-1438.
31. Lersch C, van Cutsem E, Amado R, et al. Randomized phase II study of SCH 66336 and gemcitabine in the treatment of metastatic adenocarcinoma of the pancreas. *Proc Am Soc Clin Oncol*. 2001;20: Abstract 608.
32. Erlichman C, Adjei AA, Alberts SR, et al. Phase I study of the matrix metal loproteinase inhibitor, BAY 12–9566. *Ann Oncol*. 2001;12:389-395.
33. Moore MJ, Hamm J, Dancey J, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2003;21:3296-3302.
34. Bramhall SR, Rosemurgy A, Brown PD, et al. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J Clin Oncol*. 2001;19:3447-3455.
35. Bramhall SR, Schulz J, Nemunaitis J, et al. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer*. 2002;87:161-167.
36. Dong M, Nio Y, Guo KJ, Tamura K, Tian YL, Dong YT. Epidermal growth factor and its receptor as prognostic indicators in Chinese patients with pancreatic cancer. *Anticancer Res*. 1998;18:4613-4619.
37. Uegaki K, Nio Y, Inoue Y, et al. Clinicopathological significance of epidermal growth factor and its receptor in human pancreatic cancer. *Anticancer Res*. 1997;17:3841-3847.
38. Moore MJ, Goldstein D, Hamm J, et al. 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;25:1960-1966.
39. Overholser JP, Prewett MC, Hooper AT, et al. Epidermal growth factor receptor blockade by antibody IMC-C225 inhibits growth of a human pancreatic carcinoma xenograft in nude mice. *Cancer*. 2000;89:74-82.

40. 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;22:2610-2616.
41. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group–directed intergroup trial S0205. *J Clin Oncol*. 2010;28:3605-3610.
42. Fountzilas G, Bobos M, Kalogera-Fountzila A, et al. Gemcitabine combined with gefitinib in patients with inoperable or metastatic pancreatic cancer: a phase II study of the Hellenic Cooperative Oncology Group with biomarker evaluation. *Cancer Invest*. 2008;26:784-793.
43. Safran H, Miner T, Resnick M, et al. Lapatinib/gemcitabine and lapatinib/gemcitabine/oxaliplatin: a phase I study for advanced pancreaticobiliary cancer. *Am J Clin Oncol*. 2008;31:140-144.
44. Safran H, Miner T, Bahary N, et al. Lapatinib and gemcitabine for metastatic pancreatic cancer: a phase II study. *Am J Clin Oncol*. 2011;34:50-52
45. Baker CH, Solorzano CC, Fidler IJ. Blockade of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling for therapy of metastatic human pancreatic cancer. *Cancer Res*. 2002;62:1996-2003.
46. Bockhorn M, Tsuzuki Y, Xu L, Frilling A, Broelsch CE, Fukumura D. Differential vascular and transcriptional responses to anti-vascular endothelial growth factor antibody in orthotopic human pancreatic cancer xenografts. *Clin Cancer Res*. 2003;9:4221-4226.
47. Solorzano CC, Baker CH, Bruns CJ, et al. Inhibition of growth and metastasis of human pancreatic cancer growing in nude mice by PTK 787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases. *Cancer Biother Radiopharm*. 2001;16:359-370.
48. Bruns CJ, Shrader M, Harbison MT, et al. Effect of the vascular endothelial growth factor receptor−2 antibody DC101 plus gemcitabine on growth, metastasis and angiogenesis of human pancreatic cancer growing orthotopically in nude mice. *Int J Cancer*. 2002;102:101-108.
49. 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;23:8033-8040.
50. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol*. 2010;28:3617-3622.
51. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2009;27:2231-2237.
52. Spano JP, Chodkiewicz C, Maurel J, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet*. 2008;371:2101-2108.
53. Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol*. 2011;12:256-262.
54. Siu LL, Awada A, Takimoto CH, et al. Phase I trial of sorafenib and gemcitabine in advanced solid tumors with an expanded cohort in advanced pancreatic cancer. *Clin Cancer Res*. 2006;12:144-151.
55. Wallace JA, Locker G, Nattam S, et al. Sorafenib (S) plus gemcitabine (G) for advanced pancreatic cancer (PC): a phase II trial of the University of Chicago Phase II Consortium. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2007;25(suppl 18): Abstract 4608
56. Resnicoff M, Abraham D, Yutanawiboonchai W, et al. The insulin-like growth factor I receptor protects tumor cells from apoptosis in vivo. *Cancer Res*. 1995;55:2463-2469.
57. Bergmann U, Funatomi H, Yokoyama M, Beger HG, Korc M. Insulin-like growth factor I overexpression in human pancreatic cancer: evidence for autocrine and paracrine roles. *Cancer Res*. 1995;55:2007-2011.
58. Tomizawa M, Shinozaki F, Sugiyama T, Yamamoto S, Sueishi M, Yoshida T. Insulin-like growth factor-I receptor in proliferation and motility of pancreatic cancer. *World J Gastroenterol*. 2010;16:1854-1858.
59. Moser C, Schachtschneider P, Lang SA, et al. Inhibition of insulin-like growth factor-I receptor (IGF-IR) using NVP-AEW541, a small molecule kinase inhibitor, reduces orthotopic pancreatic cancer growth and angiogenesis. *Eur J Cancer*. 2008;44:1577-1586.
60. van der Veeken J, Oliveira S, Schiffelers RM, et al. Crosstalk between epidermal growth factor receptor-and insulin-like growth factor-1 receptor signaling: implications for cancer therapy. *Curr Cancer Drug Targets*. 2009;9:748-760.
61. Javle MM, Shroff RT, Vardhachary G, et al. Phase I study of MK-0646, a humanized monoclonal antibody against IGF-1R in combination with gemcitabine or gemcitabine plus erlotinib (E) for advanced previously untreated pancreatic cancer. Paper presented at: 2010 Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, Florida.
62. Javle MM, Varadhachary GR, et al. Randomized phase II study of gemcitabine (G) plus anti-IGF-1R antibody MK-0646, G plus erlotinib (E) plus MK-0646 and G plus E for advanced pancreatic cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29(suppl): Abstract 4026.
63. Philip PA, Goldman BH, Ramanathan RK, et al. SWOG S0727: a randomized phase II trial of combination gemcitabine plus erlotinib plus IMC-A12 (cixutumumab) versus gemcitabine plus erlotinib as first-line treatment in patients (pts) with metastatic pancreatic cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2010;28(suppl 15): Abstract TPS223.
64. Kindler HL, Richards DA, Stephenson J, et al. A placebo-controlled, randomized phase II study of conatumumab (C) or AMG 479 (A) or placebo (P) plus gemcitabine (G) in patients (pts) with metastatic pancreatic cancer (mPC). *J Clin Oncol* (ASCO Annual Meeting Abstract). 2010;28(suppl 15): Abstract 4035.
65. ClinicalTrials.gov. GAMMA - Gemcitabine and AMG 479 in Metastatic Adenocarcinoma of the Pancreas. http://clinicaltrials.gov/ct2/show/NCT01231347?term=AMG+479+%28Ganitumab%29&rank=4. Identifier: NCT01231347.
66. Kim R. FOLFIRINOX: a new standard treatment for advanced pancreatic cancer? *Lancet Oncol*. 2011;12:8-9.
67. 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;22:3776-3783.
68. 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;24:4441-4447.
69. 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;16:1639-1645.