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HIGHLIGHT ARTICLE

Novel Agents and Future Prospects in the Treatment of Pancreatic Adenocarcinoma

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Summary

Pancreatic adenocarcinoma is one of the most aggressive malignancies and the fourth leading cause of cancer-related mortality in the United States. The majority of patients are diagnosed at advanced stage with inoperable locally advanced tumors or metastatic disease, and palliative chemotherapy remains the best therapeutic option for these patients. Despite intensive clinical and pre-clinical research over the last few years, the combination of the anti-metabolite drug gemcitabine with the targeted agent erlotinib, is considered standard of care in the treatment of these patients, with only minimal or modest efficacy. Therefore, novel therapeutic approaches are currently under clinical investigation in an attempt to produce more definite results for this fatal disease. In this paper we summarize five most interesting research abstracts as presented at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting. In two studies, nimotuzumab, a monoclonal antibody against epidermal growth factor receptor (EGFR) (Abstract #4009) and bavituximab, a monoclonal antibody against phosphatidylserine (Abstract #4054) are tested in combination with gemcitabine in patients with advanced pancreatic cancer. Abstract #4012 is a study of gemcitabine with vismodegib, a novel hedgehog pathway inhibitor, whereas in Abstract #4035, toxicity and efficacy results of sunitinib in combination with gemcitabine in patients with pancreatic adenocarcinoma are presented. Lastly, safety results of pimasertib, a novel mitogen-activated protein kinase kinase (MEK) inhibitor, combined with the standard gemcitabine are presented in Abstract #4041.

What We Knew Before the 2013 ASCO Annual Meeting?

Pancreatic cancer is one of the most lethal malignancies with dismal prognosis and a mortality rate almost equal to its incidence [1]. Even though the only potentially curative treatment is surgical resection, the vast majority of patients present with advanced stage disease and palliative chemotherapy remains the treatment of choice in the management of these patients [2]. Single agent gemcitabine or the combination of gemcitabine with the epidermal growth factor receptor (EGFR) inhibitor erlotinib is considered standard of care in the treatment of advanced pancreatic adenocarcinoma with only modest efficacy, which indicates the need for better treatment options [3, 4]. Up to date, erlotinib remains the only biological agent approved for the treatment of advanced pancreatic cancer. More recently, the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) proved to be superior to single agent gemcitabine, and although associated with higher toxicity, it has been accepted as the preferred first line treatment in selected fit patients [5]. Thus, there is an imperative need for molecularly targeted agents with better tolerability, availability for chronic treatment and better selectivity to conventional chemotherapy, that will achieve long-term disease control while maintaining an acceptable toxicity profile. A variety of new agents, including monoclonal antibodies and tyrosine kinase inhibitors, are currently under extensive clinical investigation.

Keywords Adenocarcinoma; Antibodies, Monoclonal; gemcitabine; Molecular Targeted Therapy; Pancreatic Neoplasms

Abbreviations c-kit: proto oncogene protein c-kit; RET: proto oncogene proteins ret; FLT-3: FMS-like tyrosine kinase-3; K-*ras*: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MEK: mitogen-activated protein kinase kinase; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor

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What We Learnt at the 2013 ASCO Annual Meeting?

Monoclonal Antibodies in Combination with Gemcitabine in the Treatment of Advanced Pancreatic Cancer (Abstracts #4009 [6] and #4054 [7])

EGFR is a commonly expressed target in pancreatic cancer that is associated with cancer cell proliferation, metastasis, and induction of angiogenesis. It is expressed in 30% to 89% of pancreatic cancers and exposure of pancreatic cancer cell lines to gemcitabine resulted in increased activation of EGFR. Although, the simultaneous use of gemcitabine with an EGFR-targeting therapy seemed as a promising ground for research, the combination of cetuximab, a human-murine IgG1 chimeric antibody against EGFR, with gemcitabine failed to prove more effective than single agent gemcitabine [8].

Nimotuzumab is a humanized IgG1 monoclonal antibody against EGFR that mediates anti-tumor effects by its capacity to inhibit proliferation, survival and angiogenesis. It has demonstrated a unique toxicity profile, characterized by the absence of severe skin, renal and gastrointestinal mucosa toxicities commonly associated with EGFR-targeting therapy [9]. Strumberg *et. al*. (Abstract #4009 [6]) conducted a phase II, randomized, placebo-controlled study of gemcitabine with or without nimotuzumab in patients with advanced pancreatic cancer, aiming to test the efficacy and safety of the agent. A total of 192 patients (average age 63.6±10 years) were enrolled in the trial, in which overall survival was the primary endpoint, while progression free survival and safety were the secondary endpoints. Nimotuzumab was administered weekly at a dose of 400 mg and was well tolerated with no high grade toxicities reported. Skin toxicity (grade 1/2) was observed in 13% of patients. Although no statistically significant differences in median overall survival (6.0 months for gemcitabine-placebo *vs*. 8.7 months for gemcitabine-nimotuzumab; P=0.21) or progression free survival (3.7 months *vs*. 5.4 months P=0.06) were reported, the combination of gemcitabine and nimotuzumab managed to significantly improve the one-year overall survival (19.5% *vs*. 34.4%; P=0.034). A sub-analysis showed that in patients aged more than, or equal to, 62 years, both median overall survival (5.2 months *vs*. 8.8 months; P=0.034) and progression free survival (3.2 months *vs*. 5.5 months; P=0.0096) were significantly improved by the addition of nimotuzumab to gemcitabine (Table 1) [6]. Despite the fact that the results presented in the study were promising, especially in patients aged more than or equal to 62 years, further testing is needed in this regard.

Phosphatidylserine is an anionic phospholipid normally found on the internal surface of the cellular plasma membrane, including that of the vascular tissue. In the tumor microenvironment, several stress conditions and molecules induce phosphatidylserine exposure on the outer surface of the vascular endothelial cells [10]. Bavituximab is a chimeric IgG1 phosphatidylserine-targeting monoclonal antibody that promotes vascular destruction and triggers antitumor immune response [11]. In murine models of pancreatic cancer, bavituximab was able to inhibit tumor growth, reduce microvessel density, and enhance the antitumor and anti-metastatic activity of gemcitabine [10]. The results from a randomized, open-label, phase II study of gemcitabine with or without bavituximab in 70 patients (67 of whom received study treatment) with metastatic pancreatic adenocarcinoma were reported by Pandya *et al*. (Abstract #4054 [7]). Overall survival was the primary endpoint of the trial, while overall response rate and progression free survival were secondary endpoints. Thirty-three patients were randomized to receive single agent gemcitabine, while 34 patients received the combination of gemcitabine plus bavituximab. The monoclonal antibody was administered weekly at a dose of 3 mg/kg. Although the agent was well tolerated with only grade 1/2 toxicities reported, the combination of gemcitabine-bavituximab failed to show any statistically significant improvement in median overall survival (5.2 months for single agent gemcitabine *vs*. 5.6 months for gemcitabine-bavituximab), progression free survival (3.9 months *vs*. 3.7 months) or overall response rate (13% *vs*. 28%) (Table 2) [7]. In this study, the addition of bavituximab to gemcitabine resulted in only moderate efficacy with mild toxicity.

Table 1. Results of a phase II, randomized, placebo-controlled trial of nimotuzumab plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer (Abstract #4009 [6]).

	Gemcitabine plus placebo	Gemcitabine plus nimotuzumab	Hazard ratio	P value
Median overall survival	6.0 months	8.7 months	HR=0.83	0.21
- In patients aged ≥62 years	*5.2 months*	*8.8 months*	*HR=0.66*	*0.034*
Median progression free survival	3.7 months	5.4 months	HR=0.73	0.06
- In patients aged ≥62 years	*3.2 months*	*5.5 months*	*HR=0.55*	*0.0096*
1-year overall survival	19.5%	34.4%	HR=0.69	0.034
1-year progression free survival	9.5%	21.5%	HR=0.71	0.05

Table 2. Results of a randomized phase II trial of gemcitabine with or without bavituximab in patients with non-resectable stage IV pancreatic adenocarcinoma (Abstract #4054 [7]).

	Gemcitabine alone	Gemcitabine plus bavituximab
Median overall survival	5.2 months	5.6 months
Median progression free survival	3.9 months	3.7 months
Overall response rate	13%	28%

Vismodegib, a Hedgehog Pathway Inhibitor, in Patients with Metastatic Pancreatic Cancer (Abstract #4012 [12])

Hedgehog signaling pathway plays a significant role in the development of pancreatic gland during embryonic development. Although the pathway is physiologically under inhibition, it is frequently reactivated during pancreatic carcinogenesis [13]. Indeed, intrinsic mutations in the hedgehog pathway and paracrine or autocrine activation through overexpression of the hedgehog ligands could lead to abnormal pathway signaling and result in tumorigenesis or maintenance of existing tumors [14, 15]. Several studies support that hedgehog-secreted signaling proteins are over-expressed in both the stroma and cancer stem cells, leading to the formation of a dense desmoplastic stroma that surrounds cancer cells and blocks drug delivery, and even participate in the maintenance of cancer stem cells which may be involved in metastasis [16, 17]. For this reason, the hedgehog pathway seems as an interesting target for inhibition in patients with pancreatic adeno-carcinoma.

Vismodegib (GDC-0449) is an orally administrable molecule that acts as a selective hedgehog pathway inhibitor that blocks hedgehog signaling by binding to smoothened (SMO), a key component of hedgehog pathway, and inhibiting activation of downstream hedgehog target genes. In human tumor cell xenograft models, including colorectal cancer and pancreatic carcinoma, vismodegib presented antitumor activity via blockade of the hedgehog pathway [18]. Catenacci *et al*. (Abstract #4012 [12]) presented the results of a phase IB/randomized phase II placebo-controlled study of vismodegib in combination with gemcitabine in patients with stage IV pancreatic cancer. In the phase IB study, seven patients were included, none of whom presented severe toxicity. In the phase II study, 106 patients were enrolled, of whom 53 patients were randomized to receive gemcitabine-placebo and 53 patients received the combination of gemcitabine-vismodegib. The primary endpoint of the study was progression free survival. Vismodegib was administered orally at a dose of 150 mg daily. No statistically significant differences in response, median progression free survival (4.0 months for gemcitabine-vismodegib *vs*. 2.5 months for gemcitabine-placebo; P=0.30) or overall survival (6.9 months *vs*. 6.1 months; P=0.84) were reported between single agent gemcitabine and the combination of gemcitabine with vismodegib (Table 3). Hematological toxicity (myelosuppression), hyponatremia, asthenia and elevated glucose levels in blood were the most frequently reported grade 3/4 toxicities, equally observed in both groups (Table 4) [12]. The addition of vismodegib to standard gemcitabine failed to improve progression free survival, response or overall survival in patients with metastatic pancreatic cancer.

Table 4. Toxicity comparison of gemcitabine plus vismodegib *vs*. gemcitabine plus placebo (Abstract #4012 [12]).

Grade 3/4 adverse events	Gemcitabine plus vismodegib	Gemcitabine plus placebo
Neutropenia	32%	28%
Lymphopenia	4%	15%
Thrombocytopenia	9%	11%
Anemia	9%	23%
Hyponatremia	4%	15%
Fatigue	13%	8%
Hyperglycemia	23%	19%
Elevated ALT	13%	9%
Hyperbilirubinemia	11%	6%
Nausea	11%	11%

Pimasertib, a MEK 1/2 Inhibitor, Plus Gemcitabine in Patients with Metastatic Pancreatic Adenocarcinoma (Abstract #4041 [19])

Ras-Raf-MEK-extracellular signal-regulated kinase (ERK) pathway is one of the most significant intracellular signaling pathways that regulates a

Table 3. Efficacy comparison of gemcitabine plus vismodegib *vs*. gemcitabine plus placebo (Abstract #4012 [12]).

	Gemcitabine plus vismodegib	Gemcitabine plus placebo	Hazard ratio	P value
Median progression free survival	4.0 months	2.5 months	HR=0.81	0.30
Median overall survival	6.9 months	6.1 months	HR=1.04	0.84
Response:				
- Complete response	0%	2%		
- Partial response	8%	11%		
- Stable disease	51%	38%		

Table 5. Toxicity of gemcitabine plus pimasertib in metastatic pancreatic adenocarcinoma (Abstract #4041 [19]).

Grade 3/4 adverse events	Gemcitabine plus pimasertib
Neutropenia	32%
Thrombocytopenia	25%
Asthenia	19%
Dyspnea	9%
Transaminitis	9%
Anemia	8%
Diarrhea	6%
Pulmonary embolism	6%
Pulmonary sepsis	6%

wide range of cellular processes including proliferation, survival, and motility. Dysregulation of the pathway is correlated with the pathogenesis of various human cancer types. V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (K-*ras*), one isoform of ras, is a small GTPase that is found to be mutated and constantly active in the vast majority of pancreatic adenocarcinomas [20], and thus, inhibition of this particular pathway at a level downstream of K-*ras* remains a field of great interest. In that direction, mitogen-activated protein kinase kinase (MEK) serves as an appealing target.

Verslype *et al*. (Abstract #4041 [19]) presented the results of a dose-escalation study of gemcitabine in combination with pimasertib, a highly potent ATP noncompetitive inhibitor of MEK1 and MEK2, in 53 patients with metastatic pancreatic adenocarcinoma. All of the patients enrolled in the study had a good performance status (PS=0-1) and a median age of 61 years. Two dosing schedules were investigated. In the first schedule, pimasertib was administered orally once a day for 5 days followed by a 2-day break, whereas in the second schedule, the agent was administered twice a day continuously along with the standard dose of gemcitabine. Maximum tolerated doses were set at 120 mg for first schedule and 75 mg for second schedule. Two dose-limiting toxicities were observed, both in the second schedule, including one incident of grade 3 confusion with ataxia and disorientation (at 60 mg twice-daily) and one incident of grade 4 suicidal ideation (at 75 mg twice-daily). The recommended phase II dose was set at 60 mg twice-daily. The most common adverse events included fatigue, ocular (serous retinal detachment) and skin toxicities, nausea, diarrhea and peripheral edema, whereas neutropenia, thrombocytopenia and asthenia were the most frequently observed grade 3/4 toxicities (Table 5). Ten patients presented partial response and 13 patients had stable disease for 3 months or more [19]. Further testing of the agent is warranted.

Randomized Phase II Trial of Gemcitabine With or Without Sunitinib in Advanced Pancreatic Cancer (Abstract #4035 [21])

Sunitinib is a multi-target inhibitor of several receptor tyrosine kinases (RTKs) relevant to tumor angiogenesis, including vascular endothelial growth factor (VEGF)1,2,3 receptors and platelet-derived growth factor (PDGF) receptors as well as proto oncogene proteins c-kit (c-kit), FMS-like tyrosine kinase 3 (FLT-3) and proto oncogene proteins ret (RET) receptors. The antitumor activity of sunitinib is mainly attributed to its ability to inhibit tumor angiogenesis. This novel agent has been shown to sensitize pancreatic cancer to the cytotoxic effects of ionizing radiation [22] and, when administered in combination with metronomic gemcitabine, improved survival in an orthotopic model of pancreatic cancer [23]. More recently, in pancreatic cancer cell lines, sunitinib was able to inhibit cancer cell proliferation and induce apoptosis, leading to a reduction in local tumor growth and intratumoral proliferative activity. In this study however, only modest additive effects were observed when sunitinib was administered in combination with gemcitabine [24].

The results of a prospective randomized phase II study of gemcitabine with or without sunitinib in 113 patients with advanced pancreatic adenocarcinoma were presented by Richly *et al*. (Abstract #4035 [21]). Sunitinib was administered at a dose of 50 mg daily for 2 weeks followed by a 1-week break. The primary endpoint of the study was progression free survival, while time to progression, overall survival, overall response rate and toxicity were secondary endpoints. The combination of gemcitabine-sunitinib failed to significantly improve progression free survival (13.3 weeks for gemcitabine *vs*. 11.6 weeks for gemcitabine-sunitinib; P=0.74), 6-month progression free survival rate (26.8% *vs*. 25.0%), overall response

Table 6. Results of a phase II, randomized trial with gemcitabine *vs*. gemcitabine plus sunitinib in advanced pancreatic cancer (Abstract #4035 [21]).

	Gemcitabine	Gemcitabine plus sunitinib	P value
Median progression free survival	13.3 weeks	11.6 weeks	0.74
6-month progression free survival rate	26.8%	25.0%	-
Overall response rate	6.1%	7.1%	-
Median time to progression	14.0 weeks	18.0 weeks	0.60
Median overall survival	36.7 weeks	30.4 weeks	0.44

rate (6.1% *vs*. 7.1%), overall survival (36.7 weeks *vs*. 30.4 weeks; P=0.44) or time to progression (14.0 weeks *vs*. 18.0 weeks; P=0.60) compared to single agent gemcitabine (Table 6). In 78.8% of patients treated with gemcitabine-sunitinib and in 72.2% of patients treated with gemcitabine alone, at least one grade 3/4 adverse event was reported [21]. In this study, the combination of gemcitabine plus sunitinib showed only minimal efficacy.

Discussion

Despite the intensive pre-clinical and clinical research over the last few years in the field of novel agents for the treatment of advanced pancreatic cancer, this effort has not resulted yet to clinically meaningful interventions, and therefore, pancreatic cancer remains a significant challenge for clinical doctors and patients. Up to date, the EGFR inhibitor erlotinib remains the only biological agent that has demonstrated a small, but significant, added benefit to single agent gemcitabine. However, numerous new agents, including monoclonal antibodies and tyrosine kinase inhibitors, are currently being tested in an attempt to achieve better response, while maintaining a safe toxicity profile. In this year's ASCO Annual Meeting, the results from various studies investigating several novel agents in combination with standard gemcitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma, have been presented. Although some of these results were promising, the majority of these studies were negative.

Two monoclonal antibodies were tested in combination with gemcitabine in patients with advanced pancreatic cancer. Nimotuzumab, an anti-EGFR monoclonal antibody, managed to significantly improve the 1-year overall survival, although it failed to improve median overall survival and progression free survival in patients enrolled in the trial. However, specifically in patients aged more than, or equal to, 62 years, the addition of nimotuzumab to gemcitabine resulted in overall survival and progression free survival benefit compared to single agent gemcitabine with only mild toxicity [6]. Further testing of this agent is certainly needed. Bavituximab, another monoclonal antibody against phosphatidylserine, was well tolerated when combined with gemcitabine in patients with metastatic pancreatic adenocarcinoma, but showed only moderate efficacy in terms of overall survival and overall response rate [7]. A hedgehog pathway inhibitor, vismodegib, was also investigated along with gemcitabine in pancreatic cancer patients. Once again, the results for this agent were dismal and vismodegib failed to significantly improve response, progression free survival or overall survival. However, the agent was well tolerated with no significant added toxicity to single agent gemcitabine [12]. In addition, the results of a phase II study of sunitinib, a multi-target inhibitor of VEGF receptor (VEGFR)1,2,3, PDGF receptor (PDGFR), as well as c-KIT, FLT-3 and RET receptors, in combination with standard gemcitabine were presented. Although toxicities between both groups were similar, the addition of sunitinib was not able to improve progression free survival, overall response rate, overall survival or time to progression compared to gemcitabine alone [21]. Lastly, the results of a dose-escalation safety run-in study of pimasertib, a MEK 1/2 inhibitor, combined with gemcitabine were also presented. The maximum tolerated doses were defined for both dosing schedules and the recommended phase II dose was set at 60 mg twice daily. Promising results in terms of disease response were also reported for this agent [19]. Further testing is needed in this regard.

So far, little progress has been made in the field of targeted agents in the treatment of advanced pancreatic adenocarcinoma, although several agents are currently under investigation. More clinical trials along with the encouragement of patients to participate in these studies are required in order to produce more definite results for this fatal disease.

Conflicts of interest The authors have no conflicts to disclose

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