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HIGHLIGHT ARTICLE

New Developments in the Treatment of Pancreatic Cancer

Highlights from the "44th ASCO Annual Meeting". Chicago, IL, USA. *May 30 - June 3, 2008*

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Summary

Pancreatic cancer remains a major therapeutic challenge in 2008. The annual incidence rate of pancreatic cancer is almost identical to the mortality rate; approximately 37,000 new cases are diagnosed each year in the United States, and approximately 33,000 patients die from this disease. Poor prognosis has been attributed to an inability to diagnose pancreatic cancer at an early stage. Majority of patients have advanced pancreatic cancer at the time of diagnosis. Advanced disease is associated with a dismal outcome, with a median survival of 3-6 months. The author summarizes the key studies presented at the 44th ASCO Annual Meeting, Chicago, IL, USA, May 30 - June 3, 2008. CONKO-001 study: final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine *vs*. observation in patients with resected pancreatic cancer. E4201 study: a randomized phase III study of gemcitabine in combination with radiation therapy *vs*. gemcitabine alone in patients with localized, unresectable pancreatic cancer. AViTA study: 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. CONKO-003 study: final results of a randomized trial in patients with gemcitabine-refractory pancreatic cancer.

Introduction

Pancreatic cancer remains a major therapeutic challenge in 2008. The annual incidence rate of pancreatic cancer is almost identical to the mortality rate; approximately 37,000 new cases are diagnosed each year in the United States, and approximately 33,000 patients die from this disease [1, 2]. Poor prognosis has been attributed to an inability to diagnose

Table 1. Key studies in pancreatic cancer presented at the Annual Meeting of ASCO 2008.

Abstract #	Author	Study	Title
LBA4504	Neuhaus *et al*. [3]	CONKO-001	Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine *vs*. observation in patients with resected pancreatic cancer
4506	Loehrer *et al*. [4]	E4201A	A randomized phase III study of gemcitabine in combination with radiation therapy *vs*. gemcitabine alone in patients with localized, unresectable pancreatic cancer
4507	Vervenne *et al*. [5]	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
4508	Pelzer *et al*. [6]	CONKO-003	A randomized trial in patients with gemcitabine-refractory pancreatic cancer: final results of the CONKO-003 study

Table 2. Final results of the CONKO-001 study.

	Gemcitabine	Observation	P value
Median disease free survival	13.4 months	6.9 months	<0.001
Median overall survival	22.8 months	20.2 months	0.005
1-year overall survival	72%	72.5%	Not reported
3-year overall survival	36.5%	19.5%	Not reported
5-year overall survival	21%	9.0%	Not reported

pancreatic cancer at an early stage. Majority of patients have advanced pancreatic cancer at the time of diagnosis. Advanced disease is associated with a dismal outcome, with a median survival of 3-6 months. Below is a summary of the data on pancreatic cancer presented at the 44th ASCO Annual Meeting', Chicago, IL, USA, May 30 - June 3, 2008 (Table 1).

Adjuvant Therapy of Pancreatic Cancer

A minority of patients (15-20%) present with resectable disease as pancreatic cancer tends to metastasize to regional lymph nodes early in the course of the disease and many patients have subclinical liver metastases at the time of diagnosis. Despite following curatively intended resection, prognosis of patients with pancreatic cancer is dismal. Whereas gemcitabine-based chemotherapy is standard in advanced pancreatic cancer, the role of adjuvant chemotherapy is still under discussion [7].

Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine *versus* observation in patients with resected pancreatic cancer so called the CONKO-001 were presented at the meeting [3].

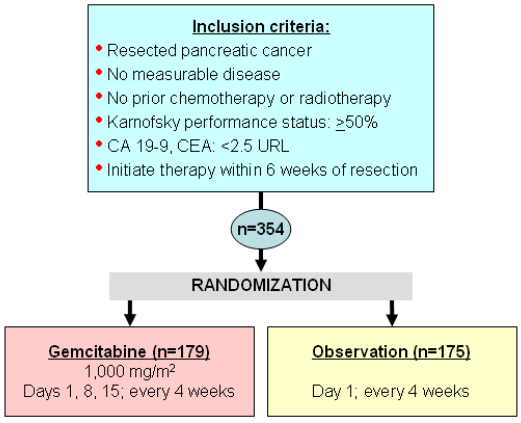

Figure 1. Study design CONKO-001: adjuvant chemotherapy in patients with resected pancreatic cancer.
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CONKO-001. A Multicenter Phase III Trial of Adjuvant Chemotherapy with Gemcitabine versus Observation in Patients with Resected Pancreatic Cancer

Study Design. A prospective, open, multicenter, controlled phase III study was designed to evaluate the efficacy and toxicity of gemcitabine in pancreatic cancer patients after complete (R0 or R1) resection (Figure 1). After stratification for R0/R1, nodal tumor involvement and tumor stage patients were randomized to receive either gemcitabine (1 g/m^2 days 1, 8, and 15 every 4 weeks) for 6 months or observation. Objectives. Primary study endpoint was disease free survival; secondary endpoints included overall survival and toxicity. The study was powered to detect a significant difference in disease free survival with 90% probability at a significance level of 0.05 on all eligible patients. Results. The results of this study were recently published in JAMA 2007 showing that postoperative gemcitabine is well tolerated and significantly delays the development of recurrent disease after

Table 3. Subgroup analyses of the CONKO-001 study.

Gemcitabine *vs.* observation	P value	Hazard ratio
R0 resection	0.018	0.74
R1 resection	0.088	0.62
N- disease	Not reported	0.57
N+ disease	Not reported	0.80
T1-2	0.120	0.58
T3-4	0.018	0.74

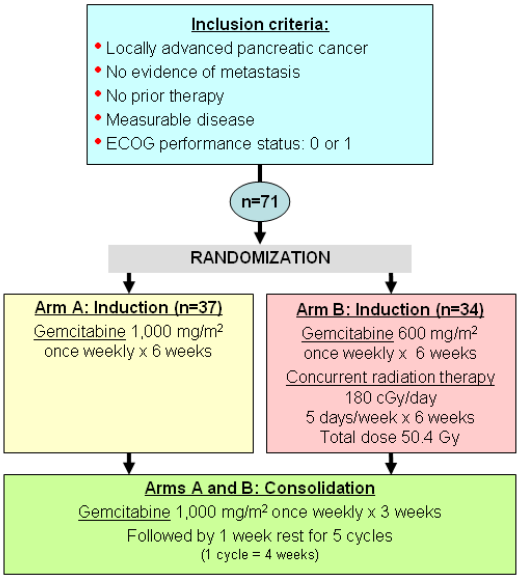

Figure 2. Study design of E4201: gemcitabine in combination with radiation therapy in locally advanced pancreatic cancer.

complete resection of pancreatic cancer. At this meeting, 3-year and 5-year overall survival was presented (Table 2). Subgroup analyses also presented at the meeting demonstrate significant increased disease free survival for gemcitabine in all subgroups of stratification as shown in Table 3.

In summary, adjuvant treatment with gemcitabine for 6 months significantly increases disease free survival and overall survival compared with observation alone.

Locally Advanced Pancreatic Cancer

Surgery is often contraindicated by vascular invasion, making the pancreatic cancer unresectable. Neoadjuvant chemo-radiation has theoretical advantages; however, true pathological down-staging is rare with current treatment (1-5%) [8]. Unfortunately, most succumb with distant metastases. Chemo-radiation therapy has shown to be associated with improved overall survival as well as better pain control. A recent French study (FFCD-SFRO: Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique) showed improved overall survival with gemcitabine *vs*. chemo-radiation using 5-FU and cisplatin [9]. The first study that compared gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with locally advanced pancreatic cancer was presented at the meeting (E4201 study) [4].

E4201. A Randomized Phase III Study of Gemcitabine in Combination with Radiation Therapy versus Gemcitabine Alone in Patients with Localized, Unresectable Pancreatic Cancer

Study Design. Patients with histologically proven, locally advanced pancreatic cancer, Eastern Cooperative Oncology Group (ECOG) performance status less than 2, without prior chemotherapy or radiation therapy were enrolled onto this study as outlined in Figure 2. Objectives. With a planned sample size of 316 eligible patients, the trial was designed to have an 88% power to detect a 50% improvement in median overall survival from 8 to 12 months (one-sided log-rank test; significance level P=0.025). Results. From April 2003 to December 2005, 71 patients were enrolled but 69 only were evaluable. The study was closed

Table 4. Preliminary results of the E4201 study.

	Gemcitabine alone (n=37)	Gem plus radiation therapy (n=34)	P value
Objective response rate	5%	6%	Not reported
Partial response	5%	6%	Not reported
Stable disease	35%	68%	Not reported
Median progression free survival	6.7 months	6.0 months	0.50
Median overall survival	9.2 months	11.0 months	0.034
6-month survival	76%	74%	Not reported
18-month survival	11%	29%	Not reported
24- month survival	4%	12%	Not reported

Table 5. Summary of evolution of chemotherapy in advanced pancreatic cancer.

Pre-1996	Many drugs tested, nothing worked
1996	Gemcitabine is FDA approved
1996-2005	No drug or drug combination better than gemcitabine
2005	Gemcitabine-erlotinib is FDA approved
2005	Gemcitabine-capecitabine is better than gemcitabine?
2006	Gemcitabine plus oxaliplatin and fixed-dose rate gemcitabine are not better than gemcitabine (30 minutes)
2006	Gemcitabine plus bevacizumab no benefit
2007	Gemcitabine plus cetuximab no benefit

early because of slow accrual. The summary of the results are described in Table 4. Toxicity. Although tolerable, gemcitabine in combination with radiation therapy for locally advanced pancreatic cancer was more myelosuppressive, and also associated with considerable gastrointestinal toxicity and fatigue.

In summary, addition of radiation therapy to gemcitabine significantly improves overall survival (P=0.034) and triples the survival rate at 24 months for patients with locally advanced pancreatic cancer.

First-Line Treatment of Advanced Pancreatic Cancer

Little progress has been made on the treatment of advanced pancreatic cancer. Gemcitabine has been an acceptable standard for more than a decade. The benefit of single-agent gemcitabine in advanced and metastatic pancreatic cancer is small [10]. Adding other chemotherapy agents to gemcitabine did not result in meaningful improvement in survival. The randomized trials studying the addition of molecular targeting agents (cetuximab, bevacizumab, farnesyl transferase inhibitors and metalloproteinase inhibitors) to gemcitabine compared with gemcitabine alone have been disappointing [2]. A small gain in median survival by adding erlotinib to gemcitabine has recently been reported [11] (Table 5).

In the phase III, overall survival trial of erlotinib plus gemcitabine *vs*. gemcitabine the hazard ratio was 0.82 (95% CI: 0.69-0.99; P=0.0328) [11]. The phase II bevacizumab with gemcitabine trial showed a 21% response rate with a median overall survival of 8.8 months [12]. Therefore, a phase III randomized, double-blind, placebo controlled, multicenter study was conducted to evaluate the efficacy and safety of adding bevacizumab to erlotinib and gemcitabine in patients with metastatic pancreatic cancer (AViTA study) [5].

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 Design. The study design is shown in Figure 3. Objectives. The primary endpoint was overall survival, and the secondary endpoints included response, progression free survival, safety, and tolerability. Results. As of March 2007, 454 patients (233/221) had

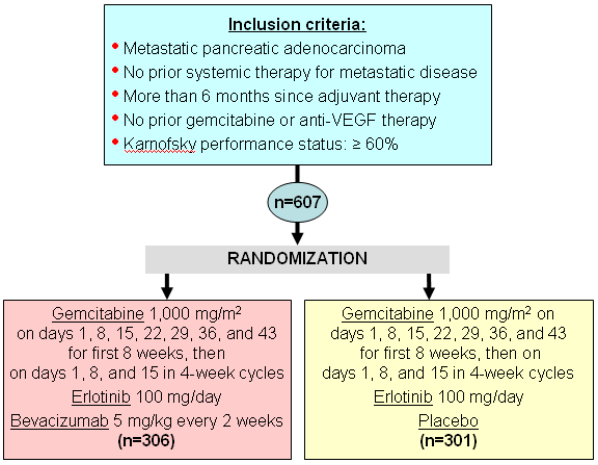

Figure 3. Study design of AViTA: addition of bevacizumab to erlotinib and gemcitabine in advanced pancreatic cancer.

Table 6. Results of the AViTA study.

	Gemcitabine plus erlotinib, plus:		P value
	Placebo (n=301)	Bevacizumab (n=306)	
Objective response rate	8.6%	13.5%	Not reported
Complete response	0	0.7%	Not reported
Partial response	8.6%	12.8%	Not reported
Stable disease	45.2%	49.2%	Not reported
Median progression free survival	3.6 months	4.6 months	0.0002
Median overall survival	6.0 months	7.1 months	0.2087

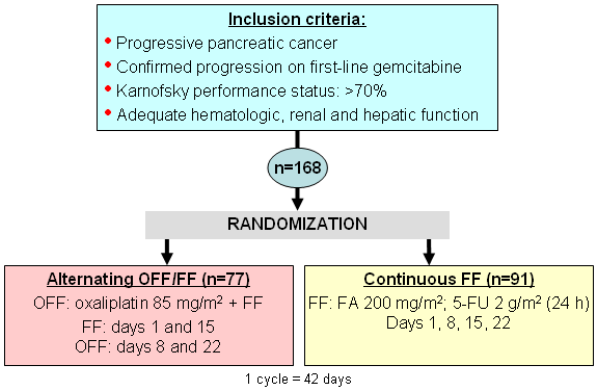

Figure 4. Study design of CONKO-003: patients with gemcitabine refractory pancreatic cancer.

FF: 5-FU 2 g/m^2 (24 h) plus FA 200 mg/m^2 (30 min) on days 1, 8, 15, and 22

OFF: FF plus oxaliplatin 85 mg/m^2, days 8 and 22

FA: folinic acid or leucovorin

died. Efficacy results are summarized in Table 6. Toxicity. No clinically relevant difference observed in grade 3-4 adverse events between the two arms (Table 7).

In summary, the study showed that the triple combination with two biologics combined with gemcitabine significantly improved progression free survival (P=0.0002), but not overall survival (P=0.2087), compared to gemcitabine plus erlotinib.

Second-Line Treatment of Advanced Pancreatic Cancer

Current data set on treatment options in second-line setting after gemcitabine failure is scattered and scant. A recently published editorial [13] highlighted that there is no consensus about second-line therapy after disease progression while receiving gemcitabine, but 5-FU-based regimens are considered. Randomized second line studies in advanced pancreatic cancer are very rare. At this meeting, the results of the CONKO-003 study were presented [6].

CONKO-003. A Randomized Trial in Patients with Gemcitabine Refractory Pancreatic Cancer

Study Design. This study randomized 165 patients to FF (5-FU 2 g/m^2 (24 h) plus folinic acid or leucovorin (FA) 200 mg/m^2 (30 min) on days 1, 8, 15, and 22) or OFF (FF plus oxaliplatin 85 mg/m^2, days 8 and 22) (Figure 4). Objectives. The primary endpoint was overall survival and secondary endpoints were disease free survival and toxicity. Results. The results presented at the meeting are

Table 7. Toxicity summary of the AViTA study: frequency of grade 3-4 adverse events.

	Gemcitabine + Erlotinib + Placebo (n=287)	Gemcitabine + Erlotinb + Bevacizumab (n=296)
Neutropenia	17%	21%
Thrombocytopenia	7%	8%
Rash	3%	8%
Arterial thromboembolism	3%	3%
Hypertension	1%	3%
Abdominal pain	1%	3%
Proteinuria	0	2%

Table 8. Efficacy results of the CONKO-003 study.

	OFF/FF (n=76)	FF (n=84)	P value
Median progression free survival	13 weeks	9 weeks	0.012
Median overall survival	20 weeks	13 weeks	0.014

FF: 5-FU 2 g/m^2 (24 h) plus folinic acid or leucovorin 200 mg/m^2 (30 min) on days 1, 8, 15, and 22
OFF: FF plus oxaliplatin 85 mg/m^2, days 8 and 22

summarized in Tables 8 and 9. The study indicated that alternating OFF/FF and continuous FF are feasible and tolerable regimens as second-line treatment of advanced pancreatic cancer after gemcitabine failure. OFF/FF results in significantly longer progression free survival (P=0.012) and overall survival (P=0.014) *vs*. FF. OFF/FF also results in substantially greater clinical benefit in patients with poor prognostic features (Table 10).
The authors suggested that OFF/FF should be considered standard second-line treatment in patients who progress on gemcitabine.

Keywords Adenocarcinoma; Carcinoma, Pancreatic Ductal; Fluorouracil; gemcitabine; oxaliplatin; Pancreatic Neoplasms; Radiotherapy; Salvage Therapy; Treatment Failure
Abbreviations CONKO: Charité Onkologie; FA: folinic acid or leucovorin

Conflict of interest The author has no potential conflicts of interest

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Table 9. Toxicity summary of the CONKO-003 study: grade 3-4 adverse events.

	OFF/FF (n=76)	FF (n=84)
Anemia	3	2
Thrombocytopenia	1	0
Neurologic	3	0
Nausea	1	3
Diarrhea	1	0

FF: 5-FU 2 g/m^2 (24 h) plus folinic acid or leucovorin 200 mg/m^2 (30 min) on days 1, 8, 15, and 22
OFF: FF plus oxaliplatin 85 mg/m^2, days 8 and 22

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Table 10. Benefit of OFF/FF in poor prognostic patients with advanced pancreatic cancer.

	Median progression free survival (months)		P value
	OFF/FF (n=76)	FF (n=84)	
Stage:			0.311
- IVa (M0)	13	13	
- IVb (M1)	13	8	
Karnofski performance status:			0.012
- 90-100%	14	10	
- 70-80%	11	7	

FF: 5-FU 2 g/m^2 (24 h) plus folinic acid or leucovorin 200 mg/m^2 (30 min) on days 1, 8, 15, and 22
OFF: FF plus oxaliplatin 85 mg/m^2, days 8 and 22

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