JOP. J Pancreas (Online) 2007; 8(2):166-176.

HIGHLIGHT ARTICLE - Slide Show

Pancreatic Cancer: Are We Moving Forward Yet?
Highlights from the Gastrointestinal Cancers Symposium. Orlando, FL, USA. January 20th, 2007

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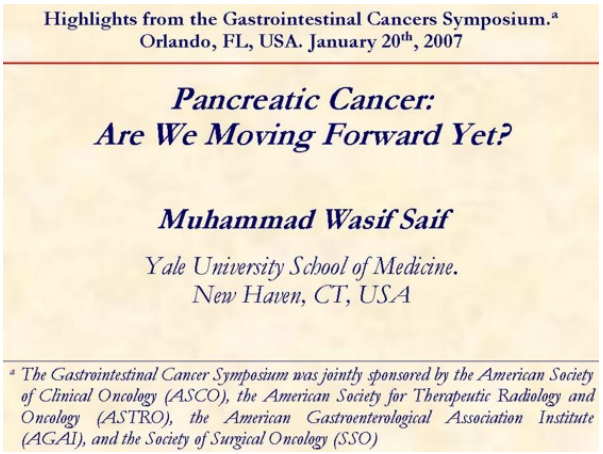
Summary

Survival for patients with pancreatic cancer remains abysmal. Standard treatment for resected and locally advanced disease usually consists of 5-fluorouracil (5-FU, either bolus or continuous infusion) and external beam radiation. However, recent studies have shown the role of gemcitabine either used alone or incorporated with 5-FU and external beam radiation in this setting. Gemcitabine and erlotinib (Tarceva®) are currently the only standard chemotherapeutic agents approved by FDA for the treatment of advanced pancreatic cancer. Combination chemo-therapy trials incorporating gemcitabine with other agents such as 5-FU, oxaliplatin, or capecitabine generally show improved outcomes in objective response rates but with little or no improvement in survival in phase III trials. In this article, the author summarizes the key studies in pancreatic cancer presented at the 2007 Gastrointestinal Cancers Symposium (Orlando, FL, USA; January, 2007). The studies discussed here include preliminary results of the Cancer and Leukemia Group B (CALGB) phase III trial of gemcitabine plus bevacizumab and activity of other targeted agents including sorafenib, cetuximab, retrospective and population-based studies evaluating the role of chemo-radiotherapy and radiotherapy, an analysis of 3,306 patients from the Surveillance, Epidemiology and End Results (SEER) database evaluating the predictive role of lymph nodes in survival following pancreatectomy and the assessment of novel agents, such as Genexol-PM® and S-1.



Targeted Agents

- Bevacizumab
- Cetuximab
- Sorafenib

CALGB 80303 (Preliminary Results)

A double-blind, placebo-controlled, randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in advanced pancreatic cancer [1]

- *Eligibility criteria*
  - No prior therapy for advanced disease
  - ECOG performance status of 0-2
  - No tumor invasion of adjacent organs
  - No bleeding risk

[1] Kindler HL, et al. 2007 Gastrointestinal Cancers Symposium; Abstract No: 108. [Link]

Preliminary results of the Cancer and Leukemia Group B (CALGB) 80303 study - which is a double-blind, placebo-controlled, randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in patients with advanced pancreatic cancer - were presented by Dr. Kindler [1].

CALGB 80303: Methods

- *Study design*
  - Patients received:
    - gemcitabine 1,000 mg/m^2 over 30 minutes on days 1, 8, 15 every 28 days
    - bevacizumab 10 mg/kg or placebo on days 1, 15 every 28 days
  - Restaging CT scan was done after 2 cycles
- *End points*
  - Primary endpoint was overall survival with stratification on:
    - ECOG performance status (0/1 or 2)
    - disease extent (locally advanced or metastatic)
    - prior external beam radiation (yes/no)
- *Statistics*
  - 90% power to detect a difference in median overall survival of 6 vs. 8.1 months

The patients were administered gemcitabine 1,000 mg/m^2 over 30 minutes on days 1, 8, 15 every 28 days, bevacizumab 10 mg/kg or placebo on day 1, 15 every 28 days. Restaging CT scan was done after two cycles.

CALGB 80303: Demographic Features

602 patients are currently valuable

	Gemcitabine + bevacizumab (n=302)	Gemcitabine + placebo (n=300)
Male/female ratio	58% / 42%	51% / 49%
Median age (years)	63.8	65.0
ECOG performance status 2	9%	9%
Prior radiation therapy	11%	11%
Stage IV	85%	84%

Demographic characteristics of both arms were well-balanced.

CALGB 80303: Efficacy

	Gemcitabine + bevacizumab (n=302)	Gemcitabine + placebo (n=300)
Median overall survival	5.7 months (95% CI: 4.8-5.9)	6.0 months (95% CI: 4.8-6.9)
Median progression free survival	4.8 months (95% CI: 4.2-5.3)	4.3 months (95% CI: 3.8-5.5)
Overall response rate	13.5%	10.3%
Stable disease	40.9%	33.6%

Median follow-up was 8.4 and 8.1 months for gemcitabine plus bevacizumab and gemcitabine plus placebo arms, respectively. As of August 2006, 377 patients (196 and 181 for each arm, respectively) have died (80% of total expected deaths at the planned final analysis).

CALGB 80303: Hematological Toxicity

518 patients are currently valuable for toxicity

	Gemcitabine + bevacizumab (n=264)	Gemcitabine + placebo (n=254)
Neutropenia	31%	29%
Anemia	5%	8%
Thrombocytopenia	12%	11%

Hematological (gemcitabine) toxicity was equal on both arms.

CALGB 80303: Toxicity

518 patients are currently valuable for toxicity

	Gemcitabine + bevacizumab (n=264)	Gemcitabine + placebo (n=254)
Hypertension	8%	2%
Perforation	0%	0%
Gastrointestinal bleed	3%	2%
Cardiovascular accident	1%	2%
Proteinuria	2%	1%
Venous thrombosis	9%	9%

Hypertension and proteinuria were more common on the bevacizumab arm compared to the placebo arm.

CALGB 80303: Conclusions

- The addition of bevacizumab to gemcitabine does not improve survival in advanced pancreatic cancer

This double-blind, placebo-controlled, randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in patients with advanced pancreatic cancer did not show any survival benefit of adding bevacizumab to gemcitabine.

Discussion

- More patients with ECOG performance status of 0 were enrolled in the phase II study [2] than in the phase III study (CALGB 80303)
- All patients had advanced pancreatic cancer in the phase III study
- 23% vs. 11% had radiation therapy (phase II vs. phase III study)

[2] Kindler HL, et al. J Clin Oncol 2005; 23:8033-40. [Link]

In spite the encouraging results of phase II study [2], the phase III study failed to show any benefit of adding bevacizumab to gemcitabine. The demographic characteristics of both arms were balanced. As well as, this was a well-powered study. Moreover, the study was rationale-based.

Which Dose of Bevacizumab ?

- Because there have been no dose-finding trials of bevacizumab in pancreatic cancer, the optimal dose of this agent for this disease remains unclear
- A 10 mg/kg dose was used in this trial. In contrary, a randomized phase II trial in colorectal cancer suggested that a dose of 5 mg/kg every 14 days was more effective than 10 mg/kg [3] and a randomized phase III trial in similar patient population confirmed the efficacy of the 5 mg/kg dose [3]. Another phase III study in colorectal cancer that used a 10 mg/kg dose in combination with oxaliplatin-based regimen revealed significant activity and tolerable toxicity [3]. In a randomized phase II trial in non-small-cell lung cancer, a dose of 15 mg/kg every 21 days was found to be more active than the 7.5 mg dose, associated with fewer episodes of significant bleeding at the higher dose [3]. The efficacy and safety of the 15 mg/kg bevacizumab dose in lung cancer has been confirmed in a randomized phase III trial [3].
- Whether an alternate efficacy might have been observed had Kindler et al. [2] - who arbitrarily chosen a higher dose than the 10 mg/kg used in this trial - cannot be definitively ascertained without additional study

[2] Kindler HL, et al. J Clin Oncol 2005; 23:8033-40. [Link]
[3] Saif MW. JOP. J Pancreas (Online) 2006; 7:163-73. [Link]

[2, 3]

Targeted Agents

- Bevacizumab
- Cetuximab
- Sorafenib

GEMOXCET Study

Cetuximab plus gemcitabine/oxaliplatin in 1st line advanced pancreatic cancer: a multicenter phase II study [4]

- **Eligibility criteria**
  - Histological or cytological diagnosis of advanced pancreatic adenocarcinoma
- **Primary endpoint**
  - Response according to RECIST
- **Treatment plan**
  - Cetuximab 400 mg/m^2 at first infusion followed by weekly 250 mg/m^2 combined with gemcitabine 1,000 mg/m^2 as a 100-minute infusion on day 1 and oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 2 every 2 weeks

[4] Kullmann F, et al. 2007 Gastrointestinal Cancers Symposium; Abstract No: 128. [Link]

Targeting the epidermal growth factor receptor pathway with agents such as cetuximab, a chimeric antibody, is an attractive therapeutic approach in the management of pancreatic cancer. [4]

GEMOXCET: Efficacy Results

64 patients are currently evaluable

Efficacy parameters	Results
Overall response rate	38%
Complete response	1 patient (1.6%)
Partial response	12 patients (18.8%)
Stable disease	24%
Median time to progression	155 days
6-month survival	54% (95% CI: 37-78%)

The addition of cetuximab to the combination of gemcitabine and oxaliplatin exhibited a high response rate of 38%, with a 54% 6-month survival.

GEMOXCET: Toxicities

Frequency of grade 3-4 toxicities

Leucopenia	10%
Anemia	15%
Thrombocytopenia	12%
Diarrhea	7%
Nausea	17%
Infection	16%
Allergy	6%
Cetuximab-attributable skin reactions	5%

The addition of cetuximab to the gemcitabine plus oxaliplatin regimen was well tolerated.

GEMOXCET: Conclusion

- Addition of cetuximab to gemcitabine plus oxaliplatin is well tolerated and exhibits a high response rate
- Further evaluation in a phase III trial is warranted

Addition of cetuximab to gemcitabine plus oxaliplatin is well tolerated and showed a high response rate. Further evaluation in a phase III trial is warranted.

Targeted Agents

- Bevacizumab
- Cetuximab
- Sorafenib

Sorafenib plus Gemcitabine for Advanced Pancreatic Cancer

A phase II study [5]

- Rationale
  - Sorafenib is an inhibitor of Raf-1 kinase and vascular endothelial growth factor receptor-2
  - Sorafenib inhibits proliferation in pancreatic cancer cell lines
  - Sorafenib has anti-tumor activity in pancreatic cancer xenograft models

[5] Wallace JA, et al. 2007 Gastrointestinal Cancers Symposium; Abstract No: 137. [Link]

Sorafenib is a small molecular that inhibit Raf kinase, PDGF (platelet-derived growth factor) and VEGF (vascular endothelial growth factor) receptor kinase. With its potent inhibitory effects against Raf-1 kinase and vascular endothelial growth factor receptor-2, sorafenib is a novel oral anticancer agent targeting signal transduction and angiogenic pathways. [5]

Sorafenib plus Gemcitabine for Advanced Pancreatic Cancer

- Experimental design
  - Eligible patients had no prior chemotherapy, measurable disease, normal organ function, ECOG performance status of 0-1
  - Patients received gemcitabine 1,000 mg/m^2 over 30 minutes at days 1, 8, 15 every 28 days, and sorafenib 400 mg orally twice daily at days 1-28
  - CT scans were obtained every 2 cycles

Sorafenib is administered continuously, whereas gemcitabine is given at 1,000 mg/m^2 weekly at days 1, 8, 15 every 4 weeks.

Sorafenib plus Gemcitabine: Efficacy Results

17 patients are currently valuable

Response rate	0
Stable disease	23%
Median overall survival	4 months
Median progression free survival	3.2 months
6-month survival	23%

Gemcitabine plus sorafenib showed no objective responses.

Sorafenib plus Gemcitabine: Toxicity

Frequency of grade 3-4 toxicities

Neutropenia	29%
Thrombocytopenia	6%
Thrombosis	18%
Fatigue	18%
Rash	12%
Nausea	12%
Hypertension	6%
Hand-foot syndrome	6%
Diarrhea	6%
Gastrointestinal bleeding	6%

No episode of neutropenic fever was observed.

Sorafenib plus Gemcitabine: Conclusion

- Gemcitabine plus sorafenib is inactive in patients with advanced pancreatic cancer

Although the combination was well tolerated, gemcitabine plus sorafenib is inactive in advanced pancreatic cancer.

Adjuvant Treatment of Pancreatic Cancer

The role of:

- Radiotherapy
- Chemo-radiotherapy

Adjuvant Therapy for Pancreatic Cancer

Background

- No universally accepted standard approach
- Standards of care vary depending on which side of the Atlantic you are on:
  - North America: chemo-radiotherapy followed by chemotherapy (GITSG study [6])
  - Europe (ESPAC-1 [7] and CONKO [8] studies): chemotherapy alone
- This has led to significant controversy about the role of adjuvant radiotherapy in these patients

[6] Cancer 1987; 59:2006-10. [Link]
[7] Neoptolemos JP, et al. Lancet 2001; 358:1576-85. [Link]
[8] Oettle H, et al. JAMA 2007; 297:267-77. [Link]

Early studies, such GITSG [6] have shown a benefit of adjuvant chemo-radiotherapy after surgical resection of pancreatic cancer. However, recent trials, such as ESPAC-1 [7] and CONKO [8] have shown a benefit of adjuvant chemotherapy while showing a negative effect with the addition of radiotherapy. This has led to significant controversy about the role of adjuvant radiotherapy in these patients.

Adjuvant Radiation Therapy in Surgically Resected Pancreatic Cancer

A study on survival benefit [9]

- **Objective**
  - To determine if adjuvant radiation therapy improves overall survival in patients with resected pancreatic cancer
- **Study design**
  - Population-based study

[9] Greco JA, et al. 2007 Gastrointestinal Cancers Symposium; Abstract No: 109. [Link]

The primary aim of this population-based study was to determine if adjuvant radiotherapy improves overall survival in patients with resected pancreatic cancer [9].

Adjuvant Radiation Therapy in Surgically Resected Pancreatic Cancer: Methods

- **Methods**
  - Using the Surveillance, Epidemiology, and End Results (SEER) registry, all patient records from 1973-2003 with surgically resected pancreatic adenocarcinoma were queried
- **Exclusion criteria**
  - Patients with stage 3 or 4 disease, preoperative or intraoperative radiation therapy, multiple primary malignancies, or incomplete tumor grading, staging, radiation, or demographic data were excluded
- **Statistics**
  - Kaplan-Meier methods and the log-rank test were used for survival data. A Cox regression model was tested with gender, race, tumor grade, age over 60 years, stage, and radiation as covariates

Using the Surveillance, Epidemiology, and End Results (SEER) registry, all patient records from 1973-2003 with surgically resected pancreatic adenocarcinoma were queried.

Adjuvant Radiation Therapy in Surgically Resected Pancreatic Cancer: Results

- 2,636 patients with resected pancreatic cancer were included in analysis
- 1,123 received adjuvant radiotherapy and 1,513 did not
- With a mean follow-up of 19 months, median overall survival for the patients receiving radiotherapy was 18 months compared to 11 months for the group that did not (P<0.01)
- Additionally, Cox regression demonstrated that patients who received adjuvant radiotherapy had a significant increase in overall survival when compared to patients who received no adjuvant radiotherapy (HR=0.57; 95% CI: 0.52-0.63; P<0.01)
- Independent significant factors leading to decreased survival included race other than black compared to white (P<0.01), moderately (P<0.01) and poorly differentiated (P<0.01) histology, age greater than 60 years (P<0.01) and increased stage of tumor (P<0.01)

The data demonstrated that patients who received adjuvant radiation therapy had a statistically significant increase in overall survival when compared to patients who received no adjuvant radiation therapy.

Adjuvant Radiation Therapy in Surgically Resected Pancreatic Cancer: Conclusions

- These data suggest a survival benefit for the addition of radiotherapy following surgical resection of pancreatic cancer
- Radiotherapy was an independent predictor of survival in this model after adjusting for the effects of gender, race, tumor grade, age and stage

These data suggest a survival benefit for the addition of radiotherapy following surgical resection of pancreatic adenocarcinoma.

Adjuvant Treatment of Pancreatic Cancer

The role of:

- Radiotherapy
- Chemo-radiotherapy

Adjuvant Radiation and Chemotherapy for Pancreatic Adenocarcinoma

The Mayo Clinic Experience [10]

- **Objective**
  - To determine prognostic factors and the impact of adjuvant radiotherapy and chemotherapy on overall survival in patients after resection of pancreatic adenocarcinoma

[10] Corsini MM, et al. 2007 Gastrointestinal Cancers Symposium; Abstract No: 110. [Link]

The study aimed to determine the impact of adjuvant radiotherapy and chemotherapy on overall survival in patients after resection of pancreatic adenocarcinoma [10].

The Mayo Clinic Experience

- **Methods**
  - Retrospective review of 472 consecutively treated patients who underwent complete resection with negative margins (R0), for (T1-3N0-1M0) invasive adenocarcinoma of the pancreas from 1975 to 2005 at the Mayo Clinic, Rochester, MN, USA
- **Inclusion criteria**
  - Included metastatic or unresectable disease at the time of surgery, positive surgical margins, and indolent tumor types such as islet cell tumors and mucinous cystadenocarcinomas
- **Treatment**
  - Median radiotherapy dose was 50.4 Gy in 28 fractions. 98% of patients receiving radiotherapy received concurrent 5-FU based chemotherapy
- **Statistics**
  - The Kaplan-Meier method was used to estimate overall survival

A retrospective review of 472 consecutively treated patients who underwent complete resection with negative margins (R0), for (T1-3N0-1M0) invasive adenocarcinoma of the pancreas from 1975 to 2005 at the Mayo Clinic, Rochester, MN, USA was performed.

The Mayo Clinic Experience: Results (I)

Treatment	No. of cases	Mean no. of adverse prognostic factors
No adjuvant radiotherapy	180	1.0
Adjuvant radiotherapy	246	1.2
Adjuvant CT-RT + CT	28	1.4
Adjuvant CT only	9	1.6

CT: chemotherapy
CT-RT: concurrent chemo-radiotherapy

The Mayo Clinic Experience: Results (II)

- Overall survival -

Treatment	Median (95% CI) years	2 years	5 years
No adjuvant radiotherapy	1.6 (1.2-1.8)	39%	17%
Adjuvant radiotherapy	2.1 (1.6-2.6)	50%	28%
Adjuvant CT-RT + CT	2.9 (1.4-6.9)	61%	34%
Adjuvant CT only	1.1 (0.4-1.8)	15%	0

CT: chemotherapy
CT-RT: concurrent chemo-radiotherapy

Median follow-up was 2.7 years in surviving patients. Median overall survival for patients receiving adjuvant concurrent chemo-radiotherapy was 2.1 years *vs.* 1.6 years for those not receiving adjuvant radiotherapy (P=0.001).

The Mayo Clinic Experience: Conclusions

- *Addition of adjuvant concurrent chemo-radiotherapy improves overall survival after R0 resection for invasive adenocarcinoma of the pancreas*

This large, single institution retrospective study series suggests that the addition of adjuvant chemo-radiotherapy improves overall survival after R0 resection for invasive adenocarcinoma of the pancreas.

Discussion

- ***Positive points:***
  - *Large study*
  - *Long follow-up*

Prediction of Survival Following Pancreatic Cancer Surgery by Lymph Node Ratio

Lymph Node Ratio Predicts Survival Following Pancreatic Cancer Surgery

A study based on SEER database [11]

- ***Background*** *Lymph node (LN) status is an important prognostic factor following curative pancreaticoduodenectomy. Studies on other malignancies suggest that the actual number of LNs evaluated and the ratio of metastatic to examined lymph nodes (LNR) may be more powerful predictors of survival.*
- ***Aim*** *To investigate the impact of total LN count and LNR on outcome after pancreatectomy.*
- ***Methods*** *The Surveillance, Epidemiology and End Results (SEER) database was used to identify 3,306 patients who underwent pancreatectomy for pancreatic adenocarcinoma between 1988-2003. The effect of total LN count and LNR on survival was examined using univariate and multivariate analyses*

[11] Pawlik TM, et al. 2007 Gastrointestinal Cancers Symposium; Abstract No: 111. [Link]

For predicting survival after pancreatic cancer surgery, the ratio of metastatic to examined nodes might be more accurate than the absolute number of metastatic nodes sampled. Pawlik *et al.* [11] reported that the number of lymph nodes examined was also predictive of survival in an analysis of 3,306 patients from the Surveillance, Epidemiology and End Results (SEER) database.

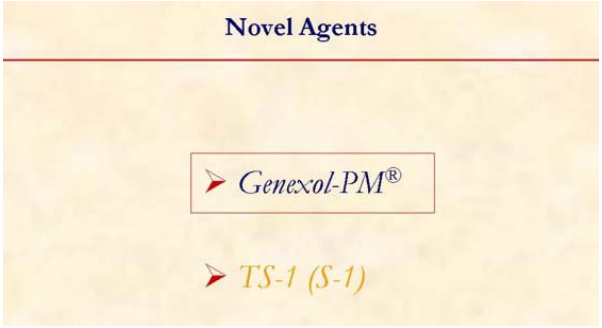
Lymph Node Ratio Predicts Survival Following Pancreatic Cancer Surgery

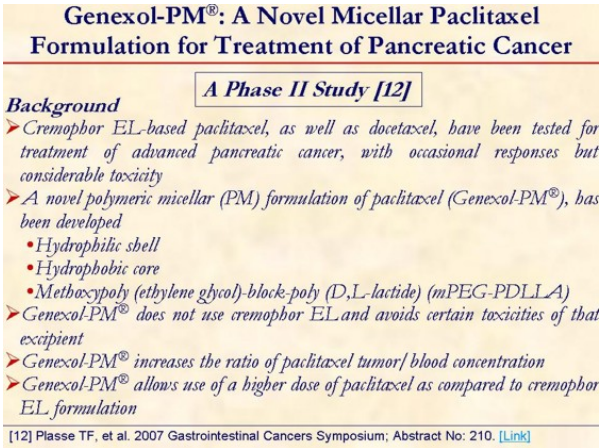
- ***Results***
  - *Patients with metastatic nodal disease had significantly worse survival than those with node negative disease (P<0.001)*
  - *Five-year survival was less than 15% for those who had fewer than a dozen lymph nodes examined versus 30% for those who had a dozen or more lymph nodes examined (P<0.001)*
- ***Conclusion***
  - *After pancreaticoduodenectomy, LNR may be a better predictor of survival and should be considered when stratifying patients in future clinical trials*
  - *Among the node negative patients, survival could be prognostically stratified based on the number of lymph nodes examined*

• Median number of LNs examined was 6; 677 (20%) patients had zero LNs examined.

Of the 2,629 patients who had LNs examined, 1,068 (41%) had no LN metastases (N0) and 1,561 (59%) had metastatic nodal disease (N1). Median survival was 12 months and 5-year survival was 15%.

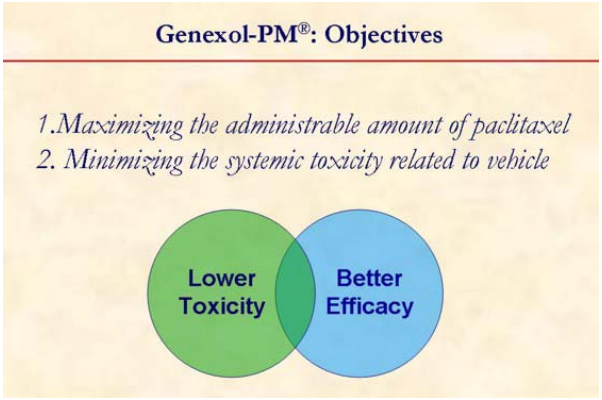
- On multivariate analysis, prognostic factors included tumor stage, grade, tumor size greater than 2 cm, number of LNs examined, LNR, and N1 disease (all P<0.05). Specifically, 5-year survival of patients with N1 disease (7%) was worse compared with patients who had N0 disease (18%) (P<0.001).
- Patients with N0 disease could be further prognostically stratified based on the number of LNs evaluated (5-year survival: 15% in less than 12 LNs vs. 30% in 12 or more LNs; P<0.001).
- Even after adjusting for other competing risk factors, an increase in LNR was correlated with decreased survival (HR=2.5, P<0.001).
- As the LNR increased median survival decreased (LNR 0: 17 months; LNR greater than 0 to 0.2: 16 months; LNR greater than 0.2 to 0.4: 13 months; LNR greater than 0.4: 10 months; P<0.001).

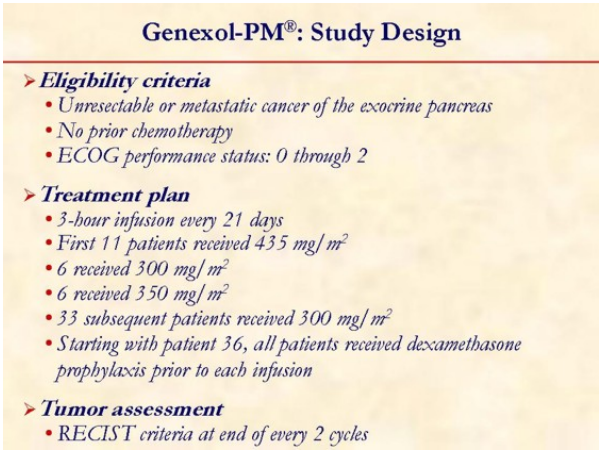




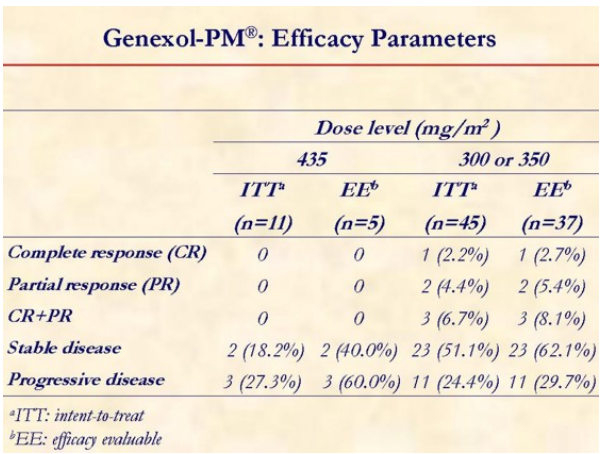
Genexol-PM® is a novel micellar formulation of paclitaxel in a low molecular weight biodegradable synthetic polymer [12]. Substitution of cremophor EL by patented bioabsorbable polymer results in changes in pharmacokinetic behavior of paclitaxel:

- higher maximally tolerated dose value;
- lower toxicity.





Patients with measurable disease, ECOG PS less than or equal to 2, no prior chemotherapy, and adequate organ function received 3-hour infusion of Genexol-PM® every 21 days.



	Dose level (mg/m²)			
	435		300 or 350	
	ITT[a] (n=11)	EE[b] (n=5)	ITT[a] (n=45)	EE[b] (n=37)
Complete response (CR)	0	0	1 (2.2%)	1 (2.7%)
Partial response (PR)	0	0	2 (4.4%)	2 (5.4%)
CR+PR	0	0	3 (6.7%)	3 (8.1%)
Stable disease	2 (18.2%)	2 (40.0%)	23 (51.1%)	23 (62.1%)
Progressive disease	3 (27.3%)	3 (60.0%)	11 (24.4%)	11 (29.7%)

[a]ITT: intent-to-treat
[b]EE: efficacy evaluable

The results are promising and comparable to single agent gemcitabine.

Genexol-PM®: Toxicity

	Dose level (mg/m²)				Overall	
	435 (n=11)		300 or 350 (n=45)		(n=56)	
	Any	≥grade 3	Any	≥grade 3	Any	≥grade 3
Neutropenia	6 (54.5%)	5 (45.5%)	18 (40.0%)	14 (31.1%)	24 (42.9%)	19 (33.9%)
Diarrhea	1 (9.1%)	0	16 (35.6%)	2 (4.4%)	17 (30.4%)	2 (3.6%)
Nausea	6 (54.5%)	1 (9.1%)	17 (37.8%)	2 (4.4%)	23 (41.1%)	3 (5.4%)
Vomiting	6 (54.5%)	0	17 (37.8%)	2 (4.4%)	23 (41.1%)	2 (3.6%)
Fatigue	1 (9.1%)	0	20 (44.4%)	8 (17.8%)	21 (37.5%)	8 (14.3%)
Hypersensitivity	1 (9.1%)	0	12 (26.7%)	4 (8.9%)	13 (23.2%)	4 (7.1%)
Arthralgia	1 (9.1%)	0	10 (22.2%)	0	11 (19.6%)	0
Dysgeusia	0	0	11 (24.4%)	0	11 (19.6%)	0
Neuropathy	4 (36.4%)	3 (27.3%)	26 (57.8%)	6 (13.3%)	30 (53.6%)	9 (16.1%)
Alopecia[a]	0	NA	23 (51.1%)	NA	23 (41.1%)	NA

NA: not applicable

Toxicities were generally those expected with paclitaxel and were manageable with standard supportive measures.

Genexol-PM®: Conclusions

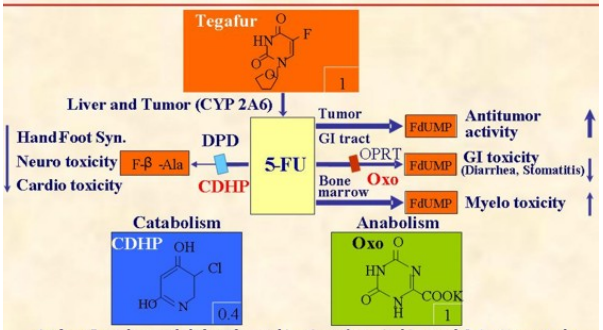
- Micellar paclitaxel at a dose of 300 mg/m² every 3 weeks was well-tolerated
- Common toxicities at 300-350 mg/m² of Genexol-PM® are qualitatively similar to 175 mg/m² of cremophor EL-based paclitaxel
- As compared to historical data, time to progression is similar to single agent gemcitabine but estimated median survival seems to be longer
  - Many patients were still alive and, therefore, censored for survival. But the lower end of the 95% confidence interval of the current study is similar to median survival reported for single agent gemcitabine
  - Several patients received subsequent therapy with gemcitabine and other agents
- Overall survival and other efficacy parameters show reasonable efficacy (compared to historical controls), suggesting further study of micellar paclitaxel for the treatment of pancreatic cancer

Genexol-PM® was generally well-tolerated in patients with advanced pancreatic cancer and resulted in progression-free survival similar to that seen historically with gemcitabine. Further evaluation of this agent in combination with gemcitabine is warranted.

Novel Agents

- Genexol-PM®
- TS-1 (S-1)

S-1: An Oral Fluoropyrimidine



A phase I study revealed that the combination of gemcitabine and S-1 appears to be feasible and effective against advanced pancreatic cancer [13]

[13] Ueno H, et al. Oncology 2005; 69:421-7. [Link]

S-1 is a new oral formulation consisting of 1 M tegafur, 0.4 M gimeracil and 1 M oteracil potassium. S-1 was developed by the scientific theory of both potentiating antitumor activity of 5-fluorouracil (5-FU) and reducing gastrointestinal toxicity induced by 5-FU. A phase I study previously published [13] revealed that the combination of gemcitabine and S-1 appears to be feasible and effective against advanced pancreatic cancer.

Gemcitabine and S-1 Combination Therapy in Patients with Advanced Pancreatic Cancer

A Multicenter Phase II Study [14]

- **Eligibility criteria**
  - Patients with histologically or cytologically proven pancreatic adenocarcinoma with at least one measurable metastatic lesion were eligible for the study
  - No previous treatment for pancreatic cancer except surgery
  - Age ≥20 and ≤74 years
  - ECOG performance status of 0 or 1
  - Adequate organ function
- **Treatment plan**
  - Gemcitabine was given intravenously at a dose of 1,000 mg/m² over 30 min on days 1 and 8, and S-1 was given orally at a dose of 40 mg/m² twice daily from day 1 to day 14, repeated every 3 weeks

[14] Ueno H, et al. 2007 Gastrointestinal Cancers Symposium; Abstract No: 148. [Link]

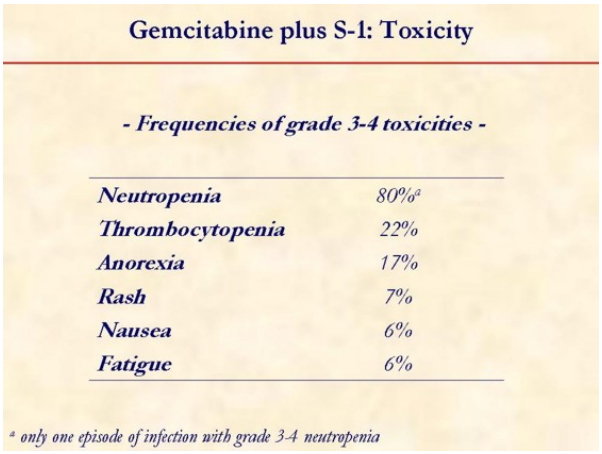
The phase I study previously published [13] led to a multicenter phase II study which was recently presented at the Gastrointestinal Cancers Symposium, 2007 [14].

Gemcitabine plus S-1: Efficacy

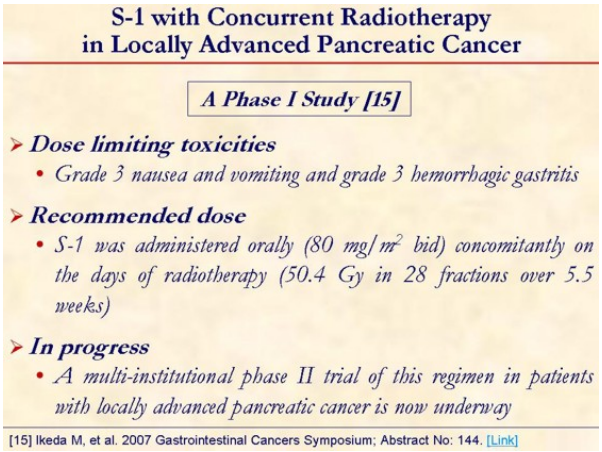
55 patients are currently valuable

Partial response	44%
Overall response rate	44%
Stable disease	48%
Median progression-free survival	5.9 months
Median overall survival	10.1 months
1-year survival rate	33%

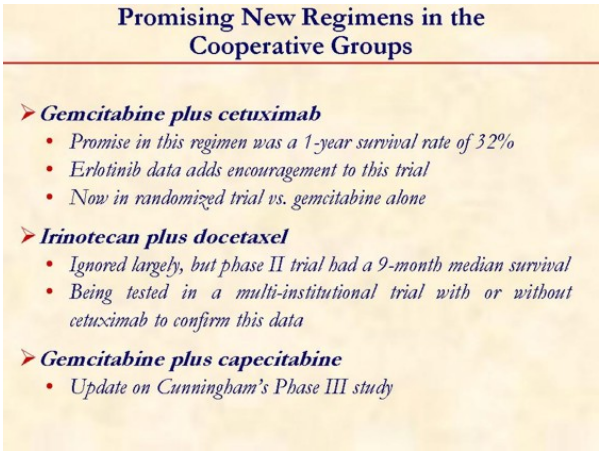
Gemcitabine plus S-1 therapy showed a high response rate (44%).

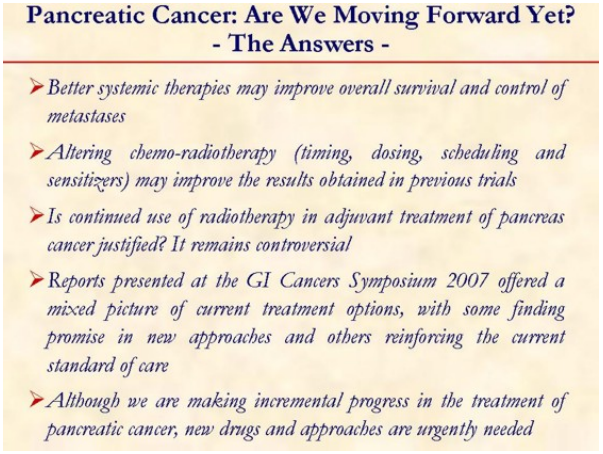


Gemcitabine plus S-1 regimen has acceptable toxicity profile in patients with advanced pancreatic cancer.



A phase I study investigated the maximum-tolerated dose of S-1 based on the frequency of dose-limiting toxicities (DLT) of S-1 with concurrent radiotherapy in patients with locally advanced pancreatic cancer [15]. Twenty-one patients (50 mg/m^2: 3 patients, 60 mg/m^2: 5 patients, 70 mg/m^2: 6 patients, 80 mg/m^2: 7 patients) were enrolled in this trial. The recommended dose of S-1 therapy with concurrent radiotherapy was 80 mg/m^2. A multi-institutional phase II trial of this regimen in patients with locally advanced pancreatic cancer is now underway.





Keywords bevacizumab; cetuximab; Chemotherapy, Adjuvant; Epidermal Growth Factor; erlotinib; Fluorouracil; gemcitabine; oxaliplatin; Pancreatic Neoplasms; Paclitaxel; Radiation; Radiotherapy, Adjuvant; S 1 (combination); sorafenib; Vascular Endothelial Growth Factor A

Abbreviations ASCO: American Society of Clinical Oncology; CALGB: Cancer and Leukemia Group B; CONKO: Charité Onkologie - clinical studies in GI cancers; ECOG: Eastern Cooperative Oncology Group; ESPAC: European Study Group of GITSG: Gastrointestinal Tumor Study Group; Pancreatic Cancer; LN: lymph nodes; LNR: ratio of metastatic to examined lymph nodes; RECIST: Response Evaluation Criteria in Solid Tumors

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