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HIGHLIGHT ARTICLE

Is There a Standard of Care for the Management of Advanced Pancreatic Cancer?. Highlights from the Gastrointestinal Cancers Symposium. Orlando, FL, USA. January 25-27, 2008

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SUMMARY

Despite advances in our understanding of the molecular and genetic basis of pancreatic cancer, the outcome for this disease remains dismal. Gemcitabine, the standard chemotherapy for pancreatic cancer, offers modest improvement of tumor-related symptoms and marginal advantage of survival. Many chemotherapeutic and targeted agents have been pitted against or combined with gemcitabine in randomized phase III trials and no drug was shown to be superior to single-agent gemcitabine except two gemcitabine-containing combinations: capecitabine plus gemcitabine *vs*. gemcitabine and erlotinib. In this article, the author debates: "Is there a standard of care for the treatment of advanced pancreatic cancer?". In addition, he summarizes the key studies presented at the "Gastrointestinal Cancers Symposium" held in Orlando, FL, USA on January 25-27, 2008. The studies discussed here include the following: i) a phase I study of a chemotherapy doublet gemcitabine plus capecitabine, combined with a biologic doublet (bevacizumab plus erlotinib) in patients with advanced pancreatic adenocarcinoma (abstract #141); ii) a phase II study of gemcitabine, bevacizumab, and erlotinib in locally advanced and metastatic adenocarcinoma of the pancreas (abstract #151); iii) final results of the multicenter phase II study on gemcitabine, capecitabine, and bevacizumab in patients with advanced pancreatic cancer (abstract #198); iv) interim results from a phase II study of volociximab in combination with gemcitabine in patients with metastatic pancreatic cancer (abstract #142); v) a pilot study of combination chemotherapy with S-1 and irinotecan for advanced pancreatic cancer (abstract #155); vi) a multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer (abstract #212); vii) a phase I/II study of PHY906 plus capecitabine in patients with advanced pancreatic carcinoma (abstract #260); and viii) the final results of a phase II trial of Genexol-PM®, a novel cremophor-free, polymeric micelle formulation of paclitaxel in patients with advanced pancreatic cancer (abstract #269). Based on the results presented at the meeting, it comes to us that patients with locally advanced *vs*. metastatic pancreatic cancer should be studied separately, better understanding of the biology of pancreatic cancer is mandatory and evaluation of novel agents is crucial. We, as oncologist, have to change our attitudes towards clinical trials and need to think beyond a trial design such as gemcitabine *vs*. drug of our choice.

INTRODUCTION

What defines a standard of care is evidence of benefit to a patient, consisting of increased survival, shrinkage of tumor mass, tolerability

of the therapy, and palliation of the tumor-related symptoms. This benefit is based on comparison to current/prior standard therapy or best supportive care. In addition, the determination of a standard is typically performed through a phase III clinical trial that demonstrates statistical improvement. However, statistical improvement does not always transform into clinical improvement.

Before gemcitabine's approval, 5-fluorouracil (5-FU) was presumably a treatment for pancreatic cancer. Rubin *et al*. performed a phase II study of 5-FU plus leucovorin in thirty-one patients with pancreatic cancer. No objective response was observed with a median overall survival of 5.7 months [1]. To improve the response, three 5-FU-based regimens were evaluated including doxorubicin and mitomycin. An increased toxicity with no significant increase in response or survival benefit was observed [2].

Earlier studies of gemcitabine showed modest activity with a response rate of 6.3% and 11% and median overall survival of 6.3 months and 5.6 months, respectively [3, 4]. The median survival reported in gemcitabine trials was akin to that of the 5-FU. However, the Carmichael *et al*. study did show clinical benefit in terms of improved performance status (17.2%), decreased pain score (28.6%), and decreased nausea (27.3%) and this study might have led to the randomized phase III study [3]. Burris *et al*. performed a multi-centered randomized, phase III clinical trial that compared 5-FU to gemcitabine [5]. Treatment with gemcitabine resulted in a relative improvement of 36% in median

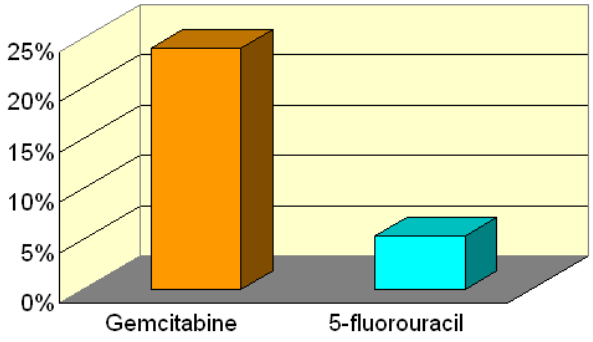

Figure 1. Clinical benefit response with gemcitabine (Burris *et al*., 1997 [5]).

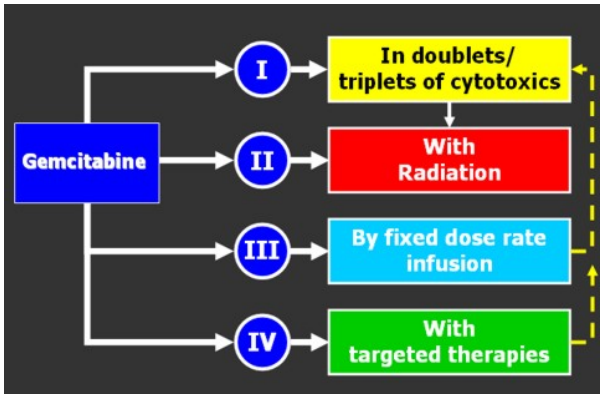

Figure 2. Study designs to improve outcome with gemcitabine.

overall survival compared to 5-FU (5.7 months *vs*. 4.2 months) and 1-year survival rates (18% *vs*. 2%). In addition to the survival benefit, gemcitabine was also superior to 5-FU in producing clinical benefit response (24% *vs*. 5%) (Figure 1). This study led to the approval of gemcitabine for 1st line chemotherapy agent.

Using gemcitabine as the control, several investigational drugs (BAY 12-9566, exatecan, SCH 66336) were compared against gemcitabine and no such agent demonstrated superiority over gemcitabine (Figure 2) [6, 7, 8].

Therefore, the study design for clinical trials for pancreatic cancer was directed towards comparing gemcitabine monotherapy or gemcitabine plus the investigational drug. This trial design allows new drugs to be tested in the first-line setting. Over the last decade, multiple cytotoxic (5-FU, capecitabine, irinotecan, cisplatin, oxaliplatin, etc) [9, 10, 11, 12, 13, 14] and targeted agents (bevacizumab, cetuximab) [15, 16] have been combined with gemcitabine in randomized phase III trials and none of such combinations showed superiority over single-agent gemcitabine.

Two large randomized phase III studies in pancreatic cancer have demonstrated the superiority of a gemcitabine-containing combination over single-agent gemcitabine: capecitabine plus gemcitabine *vs*. gemcitabine and erlotinib plus gemcitabine vs. gemcitabine [17, 18]. Preliminary data from a study by Cunningham *et al*. [17] showed a 7.4

month median survival (95% confidence interval (95% CI): 6.5-8.5 months) for subjects who received gemcitabine plus capecitabine combination therapy (n=267), significantly higher (P=0.026) when compared to 6.0 months (95% CI: 5.4-7.1 months) for those who received gemcitabine alone (n=266) (hazard ratio (HR): 0.80; 95% CI: 0.65-0.98). Moreover, 1-year survival was 19% for subjects on gemcitabine mono-therapy and 26% for those receiving the combination. However, the comparison is not equal. The HR compares the entire survival curve and favors the tail-end of the curve, where there were virtually no subjects. Thus, the HR in this trial is based heavily on these preliminary data without many subjects. However, in comparison, Herrmann *et al*. [11] reported data from a completed phase III trial; results showed that the combination of gemcitabine plus capecitabine did not significantly (P=0.314) improve overall survival compared with gemcitabine mono-therapy (8.0 *vs*. 7.3 months, respectively). This discrepancy in outcomes from two trials evaluating the gemcitabine and capecitabine combination indicates that more data are needed before determining the real value of that regimen.

On the other hand, 569 patients were randomly assigned to receive either gemcitabine with or without erlotinib. Patients treated with the combination of gemcitabine and erlotinib had an improved overall survival with a statistically significant HR of 0.82 [18]. The median and 1-year survival rates were better for the combination treatment: 6.24 *vs*. 5.91 months and 23 *vs*. 17%, respectively. In the Moore *et al*. study, the difference, although significant, shows about 12 to 14 days of gain with erlotinib therapy. Is this clinically meaningful? Do we want to add a drug that adds toxicity with only 2 weeks of gain? In most cancers, this difference would be considered as not clinically relevant, but in pancreatic cancer, this difference becomes more meaningful because of the poor outcome of advanced pancreatic cancer, the absence of impact of most other treatment options, the relatively limited impact of the reference treatment of gemcitabine monotherapy, and the acceptable toxicity profile.

HIGHLIGHTS FROM THE GI CANCERS SYMPOSIUM 2008

Many abstracts pertaining to pancreatic cancer were presented at this meeting.. The main highlights include the following studies pertaining to the advanced pancreatic cancer.

A. Two Drug Combination

Volociximab + Gemcitabine

Interim results from a phase II study of volociximab in combination with gemcitabine in patients with advanced pancreatic cancer were also presented [19]. Volociximab is a chimeric monoclonal antibody that inhibits the functional activity of alpha5-beta1 integrin, a protein found on activated endothelial cells that are involved in the formation of blood vessels. Preclinical data suggest a direct antitumor effect. The study was a multicenter open-label, 2-cohort, single arm, phase II study. Twenty patients in cohort 1 received volociximab 10 mg/kg i.v. every 2 weeks with gemcitabine 1,000 mg/m^2 on days 1, 8, 15 of a 28 day cycle. An additional twenty patients in cohort 2 received volociximab 15 mg/kg every week on days 1, 8, 15, and 22 with gemcitabine on days 1, 8, and 15. In cohort 1, one patient had partial response (5%) and 10 had stable disease (50%) with an overall survival at 1 year of 34%. In cohort 2, two patients had partial response (10%) and 7 (35%) patients had stable disease with an overall survival of 4.8 months. Most frequent toxicities included nausea (75%), constipation (60%), diarrhea (55%), abdominal pain (50%) and pulmonary embolism (20%).

S-1 plus Gemcitabine and S-1 plus Irinotecan

Two studies of combination of S-1, a novel oral fluoropyrimidine pro-drug combined with dihydropyrimidine dehydrogenase (DPD) inhibitor, with gemcitabine and irinotecan were presented with summary results shown in Table 1 [20, 21].

B. Three Drug Combination

Gemcitabine + Bevacizumab + Erlotinib

A phase II study of gemcitabine, bevacizumab, and erlotinib in locally advanced and metastatic adenocarcinoma of the pancreas who received gemcitabine 1,000 mg/m^2 on days 1, 8, and 15, erlotinib 100 mg orally days 1-28, and bevacizumab 10 mg/kg i.v. days 1 and 15, every 28 days [22]. Twenty-eight patients with no prior therapies were enrolled and the response was evaluable in 23. Five patients achieved a confirmed partial response (22%) and 13 patients had stable disease (57%). The median time to progression was 3.4 months while median overall survival was 6.8 months. Initial report in the abstract indicated that the grade 3/4 toxicities were neutropenia 38%, thrombocytopenia 16%, thromboembolic events 14%, nausea 14%, hypertension 8%, and GI bleeding 8%. One treatment-related death occurred (hemorrhage).

Gemcitabine + Capecitabine + Bevacizumab

Final results of the phase II study of gemcitabine, capecitabine, and bevacizumab in patients with advanced pancreatic cancer were presented [23]. Patients received bevacizumab 15 mg/kg i.v. day 1, capecitabine 650 mg/m^2 bid days 1-14, and gemcitabine 1,000 mg/m^2 i.v. days 1 and 8; cycles repeated every 21 days. Among 50 patients, one patient achieved complete response (2%), 10 partial response (20%), and 30 stable disease (60%). Median progression free survival and overall survival were 5.8 and 9.8 months, respectively. Grade 3/4 toxicities included neutropenia 38%, thrombocytopenia 16%, thromboembolic events 14%, nausea 14%, hypertension 8%, and GI bleeding 8%. One treatment-related death occurred (hemorrhage).

C. Four Drug Combination

Gemcitabine + Capecitabine + Bevacizumab + Erlotinib

A phase I study of a chemotherapy doublet (gemcitabine plus capecitabine), combined with a biologic doublet (bevacizumab plus erlotinib) in patients with advanced pancreatic adenocarcinoma was presented (the TARGET trial) [24]. Patients with advanced (including locally advanced) were treated at 4 cohorts of escalating capecitabine doses (days 1-21): 910 mg/m^2, 1,160 mg/m^2, 1,400 mg/m^2, and 1,660 mg/m^2. The doses of co-administered gemcitabine (1,000 mg/m^2 days 1, 8, and 15), bevacizumab (5 mg/kg days 1 and 15), and

Table 1. Results of two studies of combination of S-1 plus gemcitabine or S-1 plus irinotecan.

	S-1 + gemcitabine [20]	S-1 + irinotecan [21]
No. of patients	38	16
Schema	Gemcitabine 1,000 mg/m^2 over 30 min on days 1 and 8; S-1 40 mg/m^2 orally twice daily from day 1 to day 14, repeated every 3 weeks	Irinotecan 100 mg/m^2 on days 1 and 15; S-1 80 mg/m^2 for 14 consecutive days, followed by a 14-day rest period
Response rate	23.5%	43.7 %
Time to progression or progression free survival	Progression free survival: 5.4 months	Time to progression: 4.9 months
Median survival	9.3 months	11.3 months
Grade 3-4 toxicities	Neutropenia: 10.0% Leucopenia: 2.8% Thrombocytopenia: 0.9% Anemia: 1.4% Anorexia: 4% Rash: 2% Fatigue: 2% Hyperglycemia: 2%	Neutropenia: 31% Diarrhea: 6%

erlotinib (100 mg/day) every 28 days were constant. dose-limiting toxicity occurred in one patient at 910 mg/m^2 (grade 3 epistaxsis) and two patients at 1,660 mg/m^2 (grade 3 diarrhea, and grade 3 skin rash for more than 7 days). No patient developed GI perforation or pneumonitis; while a GI bleed (grade 1) was seen in one patient. Among evaluable 14 patients, there were 5 confirmed partial responses (36%) and a 50% decrease in CA 19-9 by 8 weeks was seen in 9 patients (64%). The maximal tolerable dose of capecitabine in this four drug cytotoxic/biologic combination is 1,660 mg/m^2 and a follow-on phase II study is planned.

D. Newer Agents

Genexol-PM® (GPM): A Novel Cremophor-Free, Polymeric Micelle Formulation of Paclitaxel

GPM is a novel micellar formulation of paclitaxel in a low molecular weight biodegradable synthetic polymer. The maximal tolerable doses for GPM in preclinical and phase I studies are higher than that for cremophor-based paclitaxel. At maximal tolerable dose for each formulation, GPM was more effective than cremophor-based paclitaxel or gemcitabine against several tumor models including 2 pancreatic cancer xenografts. The rationale for development of GPM is synthesized in Figure 3.

We presented the final results of a phase II study of GPM in patients with chemo-naïve pancreatic cancer who were treated with 3-h i.v. GPM every 3 weeks [25]. Among 56 evaluable patients, overall response rate was 6.7% with median time to progression of 3.0 months and median overall survival of 6.2 months. The most common grade 3 toxicities were neutropenia (17.8%), fatigue (17.8%), infection (13.3%), and peripheral sensory neuropathy (11.1%). The results of this study suggests that treatment with GPM at a dose of 300 mg/m^2 given every 3 weeks was well tolerated and resulted in progression free survival similar to that seen historically with gemcitabine. Future studies of GPM in combination with gemcitabine are being planned.

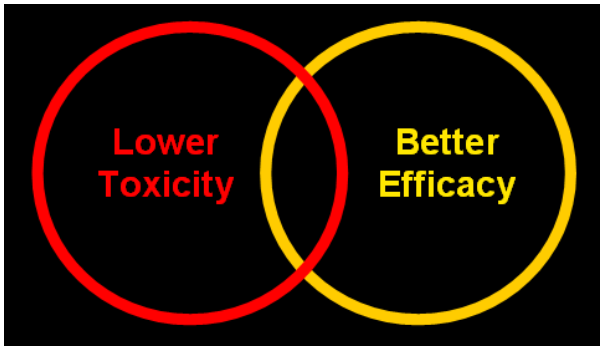

Figure 3. Rationale for development of Genexol-PM®.

PHY906: A Traditional Chinese Medicine Botanical

PHY906 is a formulation of traditional Chinese medicine botanicals which has shown synergistic antitumor activity with capecitabine in PANC-1 cell lines and is a potent inhibitor of NF-kappaB [26]. In addition, studies in other tumor types have shown that PHY906 may reduce chemotherapy-induced GI toxicities, in particular nausea, vomiting, and diarrhea. Moreover, earlier data also suggested that PHY906 does not alter pharmacokinetics of capecitabine. These data prompted us to perform a phase I/II study of a dose intense weekly (7/7) schedule for capecitabine plus PHY906 (funded by the National Comprehensive Cancer Network; NCCN). We presented results of the phase I part of the study in which we were able to escalate dose to 1,750 mg/m^2 without any dose-limiting toxicity [27]. The ongoing phase II study is assessing efficacy and quality of life in gemcitabine-refractory pancreatic cancer patients. Correlative chemokine (IL-2, IL-4, IL-5, IL-10, TNF-alpha, IFN-gamma) levels, as surrogates for NF-kappaB expression, will be quantified by cytometric bead array in order to help to elucidate PHY906 mode of action.

DISCUSSION

Although we have made incremental progress in the treatment of pancreatic cancer, the prognosis of patients with this disease remains extremely poor. Gemcitabine remains

the standard of care for treating patients with pancreatic cancer. Apparently, many oncologists are still using single-agent gemcitabine in pancreatic cancer due to lack of a shift to the gemcitabine-erlotinib or gemcitabine-capecitabine combination. On the other hand, many trials are still ongoing that were designed to evaluate gemcitabine plus an investigational drug or add another to gemcitabine-erlotinib combination. Moreover, the US Food and Drug Administration still allows trials with a gemcitabine monotherapy arm.

So, some questions arise regarding the identification of the standard therapy (Figure 4) [28]:

- Is there a standard of care for advanced pancreatic cancer?
- Is gemcitabine really a standard?
- Do we need to continue to compare everything to gemcitabine? Or, do we need to start over again and find newer, better agents? (Since gemcitabine has offered only a modest benefit to our patients, other than it arguably helps in improving symptoms, at least in terms of pain scores).

Gemcitabine was approved based on symptom improvement, and there has been no rigorous assessment of survival with gemcitabine therapy. I think that gemcitabine is not a meaningful backbone for the addition of other anticancer therapies for pancreas cancer and that we need to explore newer agents. We definitely need to identify surrogates for survival. We need to learn from our mistakes and patients with locally advanced pancreatic cancer should be studied separately from metastatic pancreatic cancer in future studies. In addition, the oncologists need to change their attitudes towards clinical trials. Development of novel agents and approaches are urgently needed in conjunction with improvement in access to clinical trials for patients. In short, there is no current clear standard of care for the treatment of advanced pancreatic cancer.

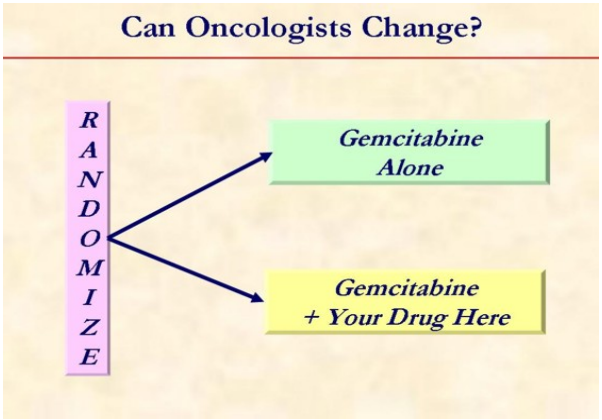

Figure 4. We, as oncologist, have to change our attitudes towards clinical trials and need to think beyond a trial design such as gemcitabine *vs*. drug of our choice.

Keywords Antibodies, Monoclonal; bevacizumab; capecitabine; cetuximab; erlotinib; Fluorouracil; gemcitabine; irinotecan; Pancreatic Neoplasms; Protein Kinase Inhibitors; Protein-Tyrosine Kinase; Receptor, Epidermal Growth Factor; S 1 (combination)

Abbreviations DPD: dihydropyrimidine dehydrogenase; GPM: Genexol-PM®; HR: hazard ratio

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References

1. Rubin J, Gallagher JG, Schroeder G, Schutt AJ, Dalton RJ, Kugler JW, et al. Phase II trials of 5-

fluorouracil and leucovorin in patients with metastatic gastric or pancreatic carcinoma. Cancer 1996; 78:1888-91. [PMID 8909307]

2. Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. JAMA 1985; 253:2061-7. [PMID 2579257]

3. Carmichael J, Fink U, Russell RC, Spittle MF, Harris AL, Spiessi G, Blatter J. Phase II study of gemcitabine in patients with advanced pancreatic cancer. Br J Cancer 1996; 73:101-5. [PMID 8554969]

4. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, et al. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 1994; 12:29-34. [PMID 7960602]

5. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, 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; 15:2403-13. [PMID 9196156]

6. Moore MJ, Hamm J, Dancey J, Eisenberg PD, Dagenais M, Fields A, 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; 21:3296-302. [PMID 12947065]

7. Cheverton P, Friess H, Andras C, Salek T, Geddes C, Bodoky G, et al. Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy-naïve patients with advanced pancreatic cancer (APC). J Clin Oncol 2004; ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Suppl):4005.

8. Lersch C, van Cutsem E, Amado R, Ehninger G, Heike M, Kerr D, 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 20: 2001. Abstract No: 608.

9. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Bowen Benson A 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; 20:3270-5. [PMID 12149301]

10. Reiss H, Helm A, Niedergethmann M, Schmidt-Wolf I, Moik M, Hammer C, 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 2005; ASCO Annual Meeting Proceedings. Vol 23, No 16S (June 1 Suppl):LBA4009.

11. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schüller J, 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; 25:2212-7. [PMID 17538165]

12. Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, 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; 22:3776-83. [PMID 15365074]

13. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, 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; 23:3509-16. [PMID 15908661]

14. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schönekäs H, Rost A, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 2006; 24:3946-52. [PMID 16921047]

15. Kindler HL, Niedzwiecki D, Hollis D, Oraefo E, Schrag D, Hurwitz H, et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis od Cancer and Leukemia Group B (CALGB) 80303. ASCO Gastrointestinal Cancers Symposium 2007. Abstract No: 108.

16. Philip PA, Benedetti J, Fenoglio-Preiser C, Zalupski M, Lenz H, O'Reilly E, et al. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. J Clin Oncol 2007; ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Suppl): LBA4509.

17. Cunningham D, Chau I, Stocken C, Davies C, Dunn J, Valle J, et al. Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer Suppl 2005; 3:12. Abstract PS11.

18. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht J, Gallinger S, et al. Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). J Clin Oncol 2005; 23(16S part I). Abstract No: 1.

19. Evans T, Valle J, Berlin J, Glynne-Jones R, Anthoney D, Huang R, et al. Interim results from a phase II study of volociximab in combination with gemcitabine (GEM) in patients (pts) with metastatic pancreatic cancer (MPC). 2008 Gastrointestinal Cancers Symposium. Abstract No: 142.

20. Oh D, Choi I, Yoon S, Choi I, Kim J, Oh S, et al. A multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer. 2008 Gastrointestinal Cancers Symposium. Abstract No: 212.

21. Shitara K, Komatsu Y, Yuki S, Munakata M, Muto O, Shimaya S, Sakata Y. Pilot study of combination chemotherapy with S-1 and irinotecan (IRIS) for advanced pancreatic cancer. 2008 Gastrointestinal Cancers Symposium. Abstract No: 155.

22. Blaszkowsky LS, Zhu AX, Abrams T, Clark JW, Earle C, Kwak E, et al. A phase II study of gemcitabine (GEM), bevacizumab (BEV), and erlotinib (E) in locally advanced and metastatic adenocarcinoma of the pancreas. 2008 Gastrointestinal Cancers Symposium. Abstract No: 151.

23. Iyer RV, Yu J, Garrett CR, Litwin AM, Kuvshinoff B, Tarquini M, et al. Gemcitabine, capecitabine, and bevacizumab in patients with advanced pancreatic cancer (APC): Final results of the multicenter phase II study. 2008 Gastrointestinal Cancers Symposium. Abstract No: 198.

24. Starling N, Watkins D, Chau I, Norman A, Fairhead E, Thomas J, et al. A phase I study of a chemotherapy doublet (gemcitabine plus capecitabine [GemCap]), combined with a biologic doublet (bevacizumab plus erlotinib) in patients with advanced pancreatic adenocarcinoma (PC): The TARGET Trial. 2008 Gastrointestinal Cancers Symposium. Abstract No: 141.

25. Saif MW, Rubin MS, Figueroa JA, Kerr RO. Multicenter phase II trial of Genexol-PM (GPM), a novel Cremophor-free, polymeric micelle formulation of paclitaxel in patients with advanced pancreatic cancer (APC): Final results. 2008 Gastrointestinal Cancers Symposium. Abstract No: 269.

26. Saif MW, Liu S, Elfiky A, Jiang Z, Cheng Y. Synergistic activity of PHY906 with capecitabine in pancreatic carcinoma. J Clin Oncol 2007; ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 15116.

27. Hoimes CJ, Lamb L, Elligers K, Mezes M, Grant N, Ruta S, et al. A phase I/II study of PHY906 plus capecitabine (CAP) in patients (pts) with advanced pancreatic carcinoma (PC). 2008 Gastrointestinal Cancers Symposium. Abstract No: 260.

28. Saif MW. Pancreatic cancer: highlights from the 42nd annual meeting of the American Society of Clinical Oncology, 2006. JOP. J Pancreas (Online) 2006; 7:337-48. [PMID 16832131]