symposium article

Annals of Oncology 24 (Supplement 4): iv5–iv10, 2013
doi:10.1093/annonc/mdt200

The management of metastatic pancreatic cancer: expert discussion and recommendations from the 14th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2012

C. Verslype[1], E. Van Cutsem[1*], M. Dicato[2], N. Arber[3], J. D. Berlin[4], M. W. Büchler[5], A. Cervantes[6], F. Ciardiello[7], M. Ducreux[8], J. Y. Douillard[9], A. Grothey[10], D. Haller[11], K. Haustermans[12,13], V. Heinemann[14], M. Hidalgo[15], R. Labianca[16], J. Li[17], J. L. Marshall[18], B. Nordlinger[19], E. M. O'Reilly[20], A. Roth[21], P. Rougier[22], D. Ryan[23], W. Schmiegel[24], T. Seufferlein[25], H. J. Schmoll[26], A. Sobrero[27], J. Tabernero[28], M. Tempero[29], J. L. Van Laethem[30], M. Ychou[31] & J. Zalcberg[32]

[1]Digestive Oncology, University Hospitals Leuven and KU Leuven, Belgium; [2]Luxembourg Medical Center, Luxembourg, Luxembourg; [3]Tel Aviv Medical Center, Tel-Aviv University, Tel Aviv, Israel; [4]Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, USA; [5]University of Heidelberg, Heidelberg, Germany; [6]Institute of Health Research INCLIVIA, University of Valencia, Valencia, Spain; [7]Second University of Naples, Naples, Italy; [8]Institut Gustave Roussy, Villejuif; [9]Centre René Gauducheau, Nantes, France; [10]Mayo Clinic, Rochester; [11]Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [12]Radiation Oncology, University Hospitals Leuven, Leuven; [13]Department of Oncology, KU Leuven, Belgium; [14]Ludwig-Maximilian-University of Munich, Munich, Germany; [15]Centro Nacional de Investigaciones Oncologicas, Madrid, Spain; [16]Giovanni XXIII Hospital, Bergamo, Italy; [17]Fudan University Cancer Center, Shanghai, China; [18]Georgetown University, Washington, USA; [19]Ambroise Paré Hospital, Boulogne, France; [20]Memorial Sloan-Kettering Cancer Center, New York, USA; [21]Geneva University Hospital, Geneva, Switzerland; [22]Hôpital Européen Georges Pompidou, Paris, France; [23]Harvard Medical School, Massachusetts General Hospital, Boston, USA; [24]University Hospital Bochum, Bochum; [25]Department of Internal Medicine I, University of Ulm, Ulm; [26]Martin Luther University, Halle, Germany; [27]San Martino Hospital, Genoa, Italy; [28]Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [29]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, USA; [30]Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium; [31]CRLC Val d'Aurelle, Montpellier, France; [32]Division of Cancer Medicine, Peter MacCallum Cancer Center, Melbourne, Australia

Key words: pancreatic cancer, gemcitabine, nab-paclitaxel, FOLFIRINOX

introduction

Pancreatic ductal adenocarcinoma (PDAC) represents a significant cause of morbidity and mortality worldwide. In the Western world, the incidence continues to increase and it ranks fourth as causes of cancer death [1]. About 60% of patients with pancreatic cancer have metastatic disease at the time of diagnosis, and of the 20% of patients who undergo a curative resection, the majority will ultimately relapse. For all stages, survival at 5 years is <5%, and for those with metastases the median survival was around 6 months until recently [2]. The metastatic setting is heterogeneous from a clinical point of view pertaining to the number and location of metastases, performance status and comorbidities. Moreover, PDAC has been shown to be genetically complex: a study of xenografts and cell lines showed that the genetic changes of resected pancreatic cancers clustered into 12 core signalling pathways, with each individual showing a unique profile of genetic changes [3].

Excellent clinical guidelines for diagnosis and treatment of PDAC are available [4]. However, in this rapidly evolving field, recent improvements in systemic chemotherapy have expanded the therapeutic armamentarium and increased the complexity of the decision process. This article on the management of metastatic pancreatic cancer summarizes the expert discussion, which was organized during the 14th European Society Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer (WCGIC) in June 2012 in Barcelona, Spain. Opinion leaders and experts from different nationalities, selected on scientific merit, participated in the discussion. In preparation for this expert discussion, a questionnaire was sent to all participants and the questions, answers and conclusions were rediscussed at the meeting. The final manuscript was reviewed by all experts in April 2013. Expert committee reports reflect clinical experience in addition to evidence-based medicine. As such, consensus was not always reached. The main strength, however, of this approach is that more than minimal guidelines are offered, to assist clinicians in the process of making treatment choices in daily clinical practice.

clinical assessment and staging of metastatic pancreatic cancer

The assessment of patients with metastatic disease includes history-taking, clinical examination and evaluation of performance status. Recording the presence of comorbidities is

Correspondence to: Professor Eric Van Cutsem, Digestive Oncology, University Hospital Gasthuisberg, Leuven, Belgium. Tel: +32-16-344218; E-mail: eric.vancutsem@uzleuven.be

important and carrying out a formal geriatric assessment is useful. Biochemical tests include tumor markers, full blood count, kidney and liver function tests. A contrast enhanced computed tomography (CT)-scan of chest, abdomen and pelvis represents the primary assessment modality for patients with suspicion of metastatic disease. Magnetic resonance imaging is advocated in selected cases, such as iodine contrast allergy or characterization of ill-defined/subcentimeter liver lesions, in the context of a fatty liver or to detect small peritoneal metastases. There is no defined role for FDG-PET scintigraphy at the moment.

In contrast to the patient population in clinical studies, the expert panel acknowledges the different profile of patients in daily clinical practice. Many patients are older than 75 years, at least half of them have biliary stents and are at risk for cholangitis, 20% have co-existing heart disease and up to 30% are not able to receive any systemic chemotherapy. The proportion of frail patients [defined as an Eastern Cooperative Oncology Group (ECOG) performance status of ≥2] is not exactly known.

obtaining a pathological proof

Many of the metastases are synchronous with the primary tumour and obtaining a pathological proof is necessary to confirm the diagnosis of PDAC. There is some uncertainty about the need for a biopsy of metastases when they are metachronous to the primary tumour. The panel recommends a biopsy from a metastatic lesion in case of a long (>13–14 month) interval between the resection of the primary tumour and the appearance of a new lesion, a single lesion, absence of a rise in CA19.9, and/or when the lesion arises in an uncommon area. In other instances, the contribution of obtaining a biopsy to the therapeutic decision is rather limited by the lack of biomarkers to guide treatment selection. Nevertheless, the panel emphasized the need for prospective collection of well-annotated tumour material and blood from patients, preferably within the context of clinical trials.

supportive care for patients with metastatic pancreatic cancer

Before even considering systemic chemotherapy, patients with metastatic pancreatic cancer may need interventions to guarantee relief of biliary and/or duodenal obstruction, malnutrition and pain.

In case of a biliary obstruction due to a pancreatic tumour, the endoscopic placement of a metallic biliary stent is strongly recommended. The endoscopic method is safer than the percutaneous insertion and as successful as a surgical hepatojejunostomy [5].

Duodenal obstruction is preferentially managed by endoscopic placement of an expandable metal stent, which is favoured over surgery [6,7].

Formal nutritional advice is mandatory in all patients and supplementation of pancreatic enzymes may be necessary. There are no data on the impact of additional parenteral nutrition on survival of patients with metastatic pancreatic cancer [8,9].

For pain not responsive to opioid analgesics or in case of poor tolerance, a percutaneous or EUS-guided coeliac nerve block should be considered [10]. Analgesic response rates and duration of the analgesic effect are variable [11]. Pain and tumour cachexia may be better controlled after starting systemic chemotherapy, which is a typical phenomenon that has been termed 'clinical benefit response' in gemcitabine studies, but even stronger positive effects on the quality of life have been described for FOLFIRINOX [12, 13].

Patients with metastatic pancreatic cancer are at risk for potentially lethal thromboembolic complications. A retrospective cohort study showed that venous thromboembolism occurs in over one-third of pancreatic cancer patients and, whether symptomatic or incidental, is strongly associated with worsened mortality [14]. Although the evidence is growing that prophylactic anticoagulation with low molecular weight heparins reduces the incidence of thrombosis in pancreatic cancer [15], its routine general use is not yet recommended. Further investigation is warranted, particularly in the era of new oral non-coumarin anticoagulants.

systemic therapy for patients with advanced pancreatic cancer: overview of the available options

Until 2010, gemcitabine remained the sole agent with demonstrated benefit for patients with advanced pancreatic cancer [12]. The drug was the comparator arm in many studies (summarized in Tables 1 and 2), and the clinical value of gemcitabine in this patient population includes a good tolerability and safety profile, a limited response rate (around 5%–10%) and 1-year overall survival (OS) of around 20% [16]. Consistently, gemcitabine arms in clinical studies demonstrated a median survival of around 6 months. Combinations of gemcitabine with a platinum derivative or fluoropyrimidines have only been associated with a significant improvement in OS in pooled and meta-analyses [17, 18].

A Canadian phase III trial showed that the addition of the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib modestly prolonged OS when combined with gemcitabine alone (HR, 0.81, $P = 0.038$) [19]. The corresponding median and 1-year OS rates for patients who received gemcitabine plus erlotinib versus (versus) gemcitabine were 6.2 and 5.9 months, and 23% versus 17%, respectively. Patients who developed a grade ≥2 skin rash had a median survival of 10.5 months and a remarkable 1-year OS of 43%. Despite this finding, there is no predictive marker, and it remains unclear how to select patients for the treatment with erlotinib. No other biologicals have so far demonstrated efficacy in phase III trials (summarized in Table 3).

A major breakthrough was reported in 2010 by a French multicenter group who randomly assigned 342 patients with metastatic pancreatic adenocarcinoma with a good performance status (ECOG 0 or 1), <75 years old and nearly normal bilirubin (≤1.5 times the upper limit of the normal range) to FOLFIRINOX [fluorouracil (400 mg/m2) given as a bolus

Table 1. Combination of gemcitabine with cytotoxic chemotherapy

Author	*N*	Treatment	Stage IV (%)	RR (%)	PFS/TTP (months)	OS (months)
Roche Lima [27]	360	GEM versus	82	4	3	6.6
		GEM + irinotecan		16[a]	3.4	6.3
Oettle [28]	565	GEM versus	91	9	3.6	6.3
		GEM + pemetrexed		18	5.2	6.2
Abou-Alfa [29]	349	GEM versus	NA	6	3.8	6.2
		GEM + exatecan		8	3.7	6.7
Heinemann [30]	195	GEM versus	73	8	3.1	6
		GEM + cisplatin		10	5.3	7.5
Louvet [31]	313	GEM versus.	70	17.3	3.7	7.1
		GEM + oxaliplatin		26.8[a]	5.8[a]	9.0
Poplin [32]	832	GEM versus	88	6	2.6	4.9
		GEM FDR versus		10	3.5	6.2
		GEM + oxaliplatin		9	2.7	5.7
Van Hoff [21]	861	GEM versus	100	7	3.7	6.7
		GEM + nab-paclitaxel		23[a]	5.5[a]	8.5[a]

[a]statistically significant finding; GEM, gemcitabine; 5FU/FA, 5-fluoruracil/folinic acid; PFS/TTP, progression-free survival/time to tumour progression; OS, overall survival.

Table 2. Combination of gemcitabine with fluoropyrimidines

Author	*N*	Treatment	Stage IV (%)	RR (%)	PFS / TTP (months)	OS (months)
Berlin [33]	327	GEM versus	90	6	3.2	5.4
		GEM + bolus 5FU/FA		7	3.4	6.7
Riess [34]	466	GEM versus	77	NA	3.5	5.9
		GEM + 5FU/FA			3.5	6.2
Herrmann [35]	319	GEM versus	80	7.8	3.9	7.2
		GEM + capecitabine		10	4.3	8.4
Cunningham [36]	533	GEM versus	71	12.1	3.8	6.2
		GEM + capecitabine		19.4	5.3[a]	7.1

[a]Statistically significant finding; GEM, gemcitabine; 5FU/FA, 5-fluorouracil/folinic acid; PFS/TTP progression-free survival/time to tumour progression; OS, overall survival.

followed by 2400 mg/m^2 given as a 46-h continuous infusion, leucovorin (400 mg/m^2), irinotecan (180 mg/m^2), oxaliplatin (85 mg/m^2) every 2 weeks) or gemcitabine (1000 mg/m^2 weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks) [13]. Sixty percent of patients had cancers of the body and tail of pancreas; only 15.8% in the FOLFIRINOX arm and 12.9% in the GEM arm had biliary stents. The trial was terminated early upon recommendation of the DSMB since the primary end point was met at an interim analysis on 192 events with 342 patients accrued of 360 planned. The median OS was 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group (HR 0.57; 95% CI, 0.45–0.73; $P < 0.001$). The median progression-free survival (PFS) was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR 0.47; 95% CI, 0.37–0.59; $P < 0.001$). The objective response rate (ORR) was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group ($P < 0.001$). FOLFIRINOX was more toxic than gemcitabine: 5.4% of patients in this group had febrile neutropenia. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of their quality of life versus 66% in the gemcitabine group (HR, 0.47; 95% CI, 0.30–0.70; $P < 0$ 0.001) [20]. Based on this study, FOLFIRINOX is considered a standard treatment option for patients with advanced pancreatic cancer with good performance status. There are, however, major concerns about the toxicity of the original FOLFIRINOX schedule and therefore, modifications of FOLFIRINOX (e.g. omitting bolus 5-FU, lower starting dose of irinotecan, dose reduction of all agents by 20%, use of growth factors upfront) are often implemented, although the impact of these changes on efficacy remains unclear.

More recently, results have been presented for the nanoparticle albumin-bound form of paclitaxel (Taxol, nab-paclitaxel) in first-line treatment of patients with metastatic pancreatic cancer [21]. The Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) study randomly assigned 861 metastatic pancreatic cancer patients (with normal bilirubin values) to nab-paclitaxel (125 mg/m^2) followed by gemcitabine (1000 mg/m^2) on days 1, 8 and 15 every 4 weeks, or gemcitabine (1000 mg/m^2 weekly for 7 weeks in cycle 1, then on days 1, 8 and 15 every 4 weeks). The study showed a statistically significant improvement in OS compared with patients

Table 3. Combination of gemcitabine with biologicals

Author	*N*	Treatment	Stage IV (%)	RR (%)	PFS/TTP (months)	OS (months)
Bramhall [37]	239	GEM versusversus	90	11	3.1	5.5
		GEM + marimastat		16	2.2	5.5
Van Cutsem [38]	688	GEM versus	82	16	3.4	6.3
		GEM + zarnestra		4	3.0	6.6
Moore [19]	569	GEM versus	76	9	3.6	5.9
		GEM + erlotinib		8	3.8	6.2[a]
Van Cutsem [39]	607	GEM + erlotinib versus.	100	8.6	3.6	6.0
		GEM + erlotinib + bevazicumab		13.5	4.6 [a]	7.1
Kindler [40]	602	GEM versus	100	13	2.9	5.9
		GEM + bevacizumab		10	3.9	5.8
Philip [41]	745	GEM versus.	78	14	3.0	5.9
		GEM + cetuximab		12	3.4	6.3
Kindler [42]	632	GEM versus	72	2	4.4	8.3
		GEM + axitinib		5	4.4	8.5

[a]Statistically significant finding; GEM, gemcitabine; 5FU/FA, 5-fluorouracil/folinic acid; PFS/TTP survival/time to tumour progression; OS, overall survival.

Table 4. Cross-trial comparison of grade 3/4 adverse events of FOLFIRINOX [13] and Nab-paclitaxel/gemcitabine combination [21]

Grade 3/4 adverse events	FOLFIRINOX (%)	Nab-paclitaxel/ gemcitabine (%)
Neutropenia	46	38
Febrile neutropenia	5	3
Thrombocytopenia	9	13
Neuropathy	9	17
Fatigue	24	17
Diarrhoea	13	6

receiving gemcitabine alone (median of 8.5 versus 6.7 months, HR 0.72, $P = 0.000015$). The 1-year OS rate increased from 22% to 35% ($P = 0.0002$). There were similar statistically significant benefits for the combination arm in terms of PFS (5.5 versus 3.7 months, HR 0.69, $P = 0.000024$) and ORR (23% versus 7%, $P = 1.1 \times 10^{-10}$). The most common grade ≥3 treatment-related adverse events in the study for nab-paclitaxel and gemcitabine versus gemcitabine alone were neutropenia (38% versus 27%), fatigue (17% versus 7%) and neuropathy (17% versus 1%) [21]. A cross-trial comparison of the side-effects seen for FOLFIRINOX and the nab-paclitaxel/gemcitabine combination is given in Table 4.

In contrast to a few years ago, we have now several treatment options for patients with metastatic pancreatic cancer. The challenge for the clinician is how to best select one of these options for the individual patient.

first-line treatment of patients with metastatic pancreatic cancer

The performance status of the patient, the serum bilirubin level, the side-effect and tolerability profile of the drug, and its availability are currently the most important selection tools for a given treatment. Patients should be offered participation in clinical trials whenever possible. Given the existence of effective therapy schedules, and taking into account their side-effects and tolerability, the following selection is suggested by the panel:

(i) FOLFIRINOX or the nab-paclitaxel/gemcitabine combination are reference treatments in fit patients (10%–35% of the population: ECOG 0/1, <75 years old, no or limited comorbidities, serum bilirubin value <1.5 ULN). The anticipated benefits may be greater with FOLFIRINOX although toxicity is considered higher for FOLFIRINOX. It has to be mentioned that these statements have been made based on cross-study comparisons, as direct comparative studies have not been conducted.
(ii) Combination of gemcitabine with erlotinib, platinum derivatives or fluoropyrimidines represents options in fit patients, who are not considered candidates for FOLFIRINOX or nab-paclitaxel (20%–30% of population).
(iii) Gemcitabine monotherapy may be reserved for patients with poor performance status, the elderly and/or significant comorbidities (20%–30% of population).

Despite some promising data, there are currently no validated predictive markers available for the most effective systemic treatments. For gemcitabine, the presence of human equilibrative nucleoside transporter 1 (hENT1) on tumour cells may be a relevant predictive marker for gemcitabine. The presence of hENT1 may allow gemcitabine to enter the tumour cells and exert its cytotoxic effects. Interesting data have been gathered in the adjuvant setting following resection of pancreatic cancer [22], but there are no published validated data for gemcitabine in the advanced setting. A phase III study with a lipid-conjugated form of gemcitabine (CO-1.01 compound) that can enter the cells by a hENT1 independent way failed to show a difference in OS compared with gemcitabine (press release Clovis Oncology, Inc.).

For nab-paclitaxel, phase I/II studies suggested that a high expression of secreted protein acidic and rich in cysteine (SPARC) was associated with increased median OS [23]. The data on SPARC expression of the MPACT-trial may shed light on the role of SPARC as a prognostic and/or predictive marker in metastatic pancreatic cancer.

duration and evaluation of treatment

Patients are generally treated until progression or treatment-limiting toxicity. Treatment breaks may be offered to some patients with limited disease burden. Treatment evaluation should be done by a contrast-enhanced CT of chest/abdomen and determination of serum CA19.9. The appropriate interval between evaluations is 8 weeks, which may be shortened to 6 weeks in the early phase of treatment to identify non-responding patients and may be prolonged to 12 weeks after achieving disease control.

second-line treatment of patients with metastatic pancreatic cancer

While there are established standard treatments in the first-line setting, there are only limited data to support a standard second-line chemotherapy regimen. At least 30% of patients are candidates for a second-line treatment, provided they have a good performance status (ECOG 0/1). The choice of a regimen depends on the performance status and the first-line treatment. For patients who have received prior gemcitabine-based therapy, the only established therapy is the combination of 5-fluorouracil, leucovorin and oxaliplatin (OFF), according to the results from the phase III Charité Onkologie Clinical (CONKO)-003 trial [24]. The study evaluated the OFF regimen (folinic acid 200 mg/m^2 followed by 5-fluorouracil 2 g/m^2/4 h on d1, d8, d15, d22 and oxaliplatin 85 mg/m^2 on days 8 and 22; after a rest of 3 weeks the next cycle was started on d43) versus best supportive care (BSC). The study was prematurely closed because of poor accrual (inclusion of 46 patients), but the presented results showed significant improvements for OFF regimen when compared with BSC, in median OS (4.8 months versus 2.3, HR 0.45). The median OS for the sequence GEM-OFF was 9.1 versus 7.9 months for GEM-BSC (HR 0.50, $P = 0.031$) respectively.

Following FOLFIRINOX, the expert panel considers gemcitabine to be appropriate.

A phase II study with FOLFIRINOX in 27 patients in second line following gemcitabine showed interesting efficacy, but raised safety concerns (55% grade 3/4 neutropenia, 1 toxic death) [25].

surgical resection or ablation of metastases

Surgical resection or ablation of metastases is not recommended. However, patients with a favourable tumour biology, albeit very rare, may be offered surgery [26]. The criteria to consider surgery include: good tumour control (>12 months) and very limited disease (single liver/lung metastasis).

conclusions and clinical research agenda

Over the past 15 years, 1-year survival of patients with metastatic pancreatic cancer has improved from 2% to approaching 50% in selected patients with combination chemotherapy. The choice for FOLFIRINOX, nab-paclitaxel/gemcitabine or gemcitabine monotherapy is mainly driven by age, performance status, comorbidities and therapy availability. Candidate predictive makers (e.g. hENT1, SPARC) need to be validated to increase the benefit–risk ratio of the current treatment regimens.

Unfortunately, many of the patients with advanced pancreatic cancer have a poor performance status and may not tolerate the newer more intensive cytotoxic regimens. Therefore, modification of the current regimens and combination with newer targeted agents represent an unmet need. Patients should be preferably treated within the framework of prospective clinical studies. Those studies should contain as many translational components as possible, as more insights will only come from a better understanding of pancreatic tumour biology.

disclosure

The authors have declared no conflicts of interest.

references

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11–30.
2. Coleman MP, Gatta G, Verdecchia A et al. EUROCARE Working Group. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol 2003; 14(Suppl 5): V128–V149.
3. Jones S, Zhang X, Parsons DW et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 2008; 321: 1801–1806.
4. Seufferlein T, Bachet JB, Van Cutsem E et al. ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23(Suppl 7): vii33–40.
5. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev 2006; 19: CD004200.
6. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Engl J Med 2001; 344: 1681–1687.
7. Jeurnink SM, van Eijck CH, Steyerberg EW et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 2007; 7: 18.
8. Bozzetti F, Arends J, Lundholm K et al. ESPEN guidelines on parenteral nutrition: non-surgical oncology. Clin Nutr 2009; 28: 445–454.
9. Pelzer U, Arnold D, Govercin M et al. Parenteral nutrition support for patients with pancreatic cancer. Results of a phase II study. BMC Cancer 2010; 10: 86.
10. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007; 102: 430–438.
11. Wyse JM, Carone M, Paquin SC et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol 2011; 29: 3541–3546.
12. Burris HA, 3rd, Moore MJ, Andersen J et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15: 2403–2413.
13. Conroy T, Desseigne F, Ychou M et al. Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817–1825.
14. Menapace LA, Peterson DR, Berry A et al. Symptomatic and incidental thromboembolism are both associated with mortality in pancreatic cancer. Thromb Haemost 2011; 106: 371–378.
15. Maraveyas A, Waters J, Roy R et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012; 48: 1283–1292.

16. Storniolo AM, Enas NH, Brown CA et al. An investigational new drug treatment program for patients with gemcitabine: results for over 3000 patients with pancreatic carcinoma. Cancer 1999; 85: 1261–1268.
17. Sultana A, Smith CT, Cunningham D et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007; 25: 2607–2615.
18. Heinemann V, Boeck S, Hinke A et al. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer 2008; 8: 82.
19. Moore MJ, Goldstein D, Hamm J et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007; 25: 1960–1966.
20. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol 2013; 31: 23–29.
21. Von Hoff DD, Ervin TJ, Arena FP et al. Final results of a randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). J Clin Oncol 2012; suppl 34: abstr LBA148.
22. Maréchal R, Bachet JB, Mackey JR et al. Levels of gemcitabine transport and metabolism proteins predict survival times of patients treated with gemcitabine for pancreatic adenocarcinoma. Gastroenterology 2012; 143: 664–674.
23. Von Hoff DD, Ramanathan RK, Borad MJ et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol 2011; 29: 4548–4554.
24. Pelzer U, Schwaner I, Stieler J et al. Best supportive care (BSC. versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer 2011; 47: 1676–1681.
25. Assaf E, Verlinde-Carvalho M, Delbaldo C et al. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma. Oncology 2011; 80: 301–306.
26. Müller SA, Tarantino I, Martin DJ et al. Pancreatic surgery: beyond the traditional limits. Recent Results Cancer Res 2012; 196: 53–64.
27. Rocha Lima CM, Green MR, Rotche R et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004; 22: 3776–3783.
28. Oettle H, Richards D, Ramanathan RK et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. Ann Oncol 2005; 16: 1639–1645.
29. Abou-Alfa GK, Letourneau R, Harker G et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. J Clin Oncol 2006; 24: 4441–4447.
30. Heinemann V, Quietzsch D, Gieseler F et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 2006; 24: 3946–3952.
31. Louvet C, Labianca R, Hammel P et al. GERCOR; GISCAD. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005; 23: 3509–3516.
32. Poplin E, Feng Y, Berlin J et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009; 27: 3778–3785.
33. Berlin JD, Catalano P, Thomas JP et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 2002; 20: 3270–3275.
34. Riess H, Helm A, Niedergethmann I et al. A randomised, prospective, multicentre, phase III trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs gemcitabine alone in patients with advanced pancreatic cancer. J Clin Oncol 2005; suppl 16: abstr 4009.
35. Herrmann R, Bodoky G, Ruhstaller T et al. Swiss Group for Clinical Cancer Research; Central European Cooperative Oncology Group. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 2007; 25: 2212–2217.
36. Cunningham D, Chau I, Stocken DD et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009; 27: 5513–5518.
37. Bramhall SR, Rosemurgy A, Brown PD et al. Marimastat Pancreatic Cancer Study Group. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. J Clin Oncol 2001; 19: 3447–3455.
38. Van Cutsem E, van de Velde H, Karasek P et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol 2004; 22: 1430–1438.
39. Van Cutsem E, Vervenne WL, Bennouna J et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009; 27: 2231–2237.
40. Kindler HL, Niedzwiecki D, Hollis D et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol 2010; 28: 3617–3622.
41. Philip PA, Benedetti J, Corless CL et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol 2010; 28: 3605–3610.
42. Kindler HL, Ioka T, Richel DJ et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. Lancet Oncol 2011; 12: 256–262.