

REVIEW

## Therapeutic Approach to Advanced Pancreatic Carcinoma

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undernutrition*

### ABBREVIATIONS

EGFR = epidermal growth factor  
receptor  
FDR = fixed dose rate  
5-FU = 5-fluorouracil  
Gem = gemcitabine  
LV = leucovorin  
PFS = progression-free survival  
QOL = quality of life  
RR = response rate  
TTP = time to progression  
VEGF = vascular endothelial growth  
factor

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### ABSTRACT

Pancreatic carcinoma, a chemoresistant disease, still remains a therapeutic challenge in oncology. A variety of cytotoxic agents have been tried with promising or disappointing results. Gemcitabine as a single agent or combined chemotherapy is the mainstay therapeutic approach in locally advanced or metastatic disease. Newer agents, such as tyrosine kinase inhibitors and monoclonal antibodies (bevacizumab, erbitux) are widely used nowadays in modern therapeutic algorithms with promising results.

### INTRODUCTION

Pancreatic cancer, an extremely lethal malignant disease, constitutes the fourth most common cause of cancer death. The annual diagnosis of this disease has steadily increased worldwide. During 2009 in the United States of America, 42470 new pancreatic cancer cases and 35240 related deaths were documented.<sup>1</sup> Due to lack of specific symptoms at the onset of the disease, the majority of patients present with locally advanced or metastatic inoperable disease. Thus, the overall survival rate for all stages combined is extremely poor, less than 1% at 5 years. Median survival time is about 8-12 months for locally advanced inoperable disease and 3-6 months for extensive metastatic disease.<sup>2,3</sup> Over the past decades, the cytotoxic drug gemcitabine (Gem) has proven its efficacy in improving the quality of life (QOL) in patients with pancreatic cancer, thus becoming the mainstay therapy, albeit its moderate antineoplastic effect.<sup>4</sup> All chemotherapeutic options for advanced pancreatic malignant disease cover an extended era of two periods, preceding and following Gem. Many phase II trials tested Gem combinations with various chemotherapeutic agents as front-line therapy for advanced disease; however, none of them proved superior to single Gem except erlotinib.<sup>5,6</sup> The addition of capecitabine, a platinum salt compound, and targeted monoclonal antibodies, including bevacizumab and cetuximab which were extensively investigated, provided modest interesting advances but failed to offer a clear survival benefit. Erlotinib, a new tyrosine kinase inhibitor, gained FDA approval for the small overall survival benefit recorded when combined with Gem.<sup>3,7,8</sup>

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**CHEMOTHERAPEUTIC TREATMENT FOR  
ADVANCED PANCREATIC CANCER**


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Advanced pancreatic cancer is defined as tumour encasing the superior mesenteric artery, celiac artery, aorta or inferior vena cava which represents the unresectable status of the disease. The role of radiotherapy, however, remains controversial and is under investigation in a variety of trials studying the appropriate chemotherapy combination with radiation, demonstrated by the gastrointestinal tumour study group, the European organization for research and treatment of cancer, the European study group for pancreatic cancer and the American College of Surgeons oncology group).<sup>9</sup> This review will not address all the trials highlighting the concurrent use of chemoradiation therapy for the advanced pancreatic malignant disease.<sup>10</sup> We will focus on the chemotherapeutic agents used as single agent or combination therapy in first-line therapeutic setting for locally advanced disease.

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**SINGLE AGENT CHEMOTHERAPY**


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Chemotherapeutic treatment for advanced pancreatic cancer with single agent cytotoxic drugs has been thoroughly studied, but none has provided overall response greater than 10%. Capecitabine, 5-fluorouracil (FU), anthracyclines, docetaxel, camptothecins ifosfamide, streptozocin and Gem have been tried as single agent and in variable combination settings. These therapies are detailed below.

**5-FLUOROURACIL (5-FU)**

5-Fluorouracil has been used as monotherapy since 1950 providing overall response rates (RR) even up to 67% in patients with advanced pancreatic cancer.<sup>11</sup> The biological modulation of 5-FU with concomitant use of leucovorin (LV) did not manage to demonstrate higher overall RR (RR reported: 0-9%). Bolus intravenous infusion used in earlier studies did not extend the overall survival more than 24 weeks<sup>12-14</sup>.

**CAPECITABINE**

Capecitabine, an oral fluoropyrimidine prodrug, which is absorbed in the intestinal tract and converted to 5-FU through three step enzyme-mediated reactions, has been examined alone in front-line therapy. Critical role to the metabolism of capecitabine has the last enzymic product of the conversion, thymidine phosphorylase, which is present at higher concentrations in the neoplasm than in normal cells, providing basis for better clinical action with fewer side-effects. Capecitabine, as first-line monotherapy, was evaluated in a study of 42 patients enrolled with advanced pancreatic malignancy. Objective partial response was documented in 3 patients (7%), and 24% showed clinical benefit. The main toxicity reported were

hand-foot syndrome (grade III), nausea and diarrhea in 17%, 10% and 12% respectively.<sup>15</sup>

**ANTHRACYCLINES**

Anthracyclines, although widely known for their anticancer potential, have been of limited efficacy in monotherapy for advanced pancreatic cancer. The novel Gastrointestinal Tumour Study Group, 30 years ago, considered adriamycin in first- and second-line treatment. A minimal therapeutic response has been recorded in 2 out of 15 previously untreated patients compared with 0 out of 10 patients with previously treated disease.<sup>16</sup> Later, the European Organization for Research and Treatment of Cancer study enrolled 41 patients to receive epirubicin as a single therapeutic agent. The overall response rate reported was 24% and the median overall survival was only three months.<sup>17</sup>

**STREPTOZOCIN AND IFOSFAMIDE**

Streptozocin and Ifosfamide have proved limited antitumor efficacy in terms of single agent first-line treatment for advanced pancreatic cancer. Studies conducted over the past decades with streptozocin and ifosfamide monotherapy have reported an overall response of 11% (3 of 27 patients included) with streptozocin and 7% - 10% with ifosfamide respectively.<sup>18</sup> Years later two phase II trials again did not manage to present median survival time greater than 12 weeks.<sup>19,20</sup>

**TAXANES**

Taxanes, especially docetaxel, have also proved limited efficacy in first-line chemotherapeutic single-agent approach in advanced disease. A phase II study by Androulakis et al, conducted with docetaxel offered as single agent treatment in 33 patients, reported only 6% RR, and one year documented survival benefit of 36% was attributed to disease stabilization.<sup>21</sup> Rougier et al, one year later, enrolled 40 patients with advanced pancreatic cancer, and tried docetaxel (100 mg/m<sup>2</sup> every 3 weeks) as a single agent. An overall RR of 15% - 38% was observed.<sup>22</sup> Many other relevant studies have also confirmed the minimal benefit associated with docetaxel monotherapy.<sup>23-25</sup>

**CAMPTOTHECINS**

Camptothecins including topotecan, irinotecan and 9-nitro-camptothecin (rubitecan), have shown limited efficacy in advanced pancreatic cancer as single agent treatment; RR of 0-29% and a median survival of 4-6.5 months have been reported in the literature. Hence, camptothecins in combination with other drugs are thoroughly studied in ongoing clinical trials aiming for better overall responses and clinical benefit.<sup>26</sup>

**GEMCITABINE**

Gemcitabine monotherapy in advanced pancreatic cancer is the only approved cytotoxic treatment providing noticeable

improvement of survival and enhancing quality of life (QOL). A trial by Burris et al has established Gem as the standard of care for the first-line setting of advanced disease considering the survival benefit of Gem monotherapy over 5FU-based palliative therapy.<sup>4,27</sup> The trial enrolled 126 patients with advanced disease, randomizing them either to a Gem infusion arm or to a 5-FU arm. The Gem arm showed better survival rates (18% vs. 2%), higher median survival (5.7 vs. 4.4 months,  $p=0.0025$ ) and a satisfactory clinical benefit (24% vs. 5%,  $p=0.0022$ ). The clinical benefit, representing QOL, related to weight gain, pain relief, and improvement in patients' activity. Later phase III studies presented a median survival of 5-6 months and an annual survival rate up to 20 %, revealing again the promising activity of Gem and its superiority to best supportive care.<sup>5</sup> A vast majority of studies have been employed to determine the best administrative way of gemcitabine (bolus infusion, prolonged administration or fixed dose rate) aiming to exceed the survival advantage. The administration of Gem in a fixed dose rate (FDR) of 10 mg/m<sup>2</sup> per minute, maximizes the intracellular concentrations of the active phosphorylated Gem metabolite, thus achieving a pharmacokinetic advantage of the maximum tolerated dose increase.<sup>28-30</sup> Based on the above data, a phase II trial randomly distributed 92 enrolled patients either to FDR Gem (1500 mg/m<sup>2</sup> with infusion rate of 10 mg/m<sup>2</sup>/min on the days 1, 8, 15 every 4 weeks) or high dose Gem (2200 mg/m<sup>2</sup>, administered over 30 minutes IV on the days 1, 8, 15 every 4 weeks). The primary trial endpoint, time to the treatment failure, was similar for both arms, but the median survival reported was 8 months in the FDR arm vs 5 months in the compared arm.<sup>31</sup> The stable infusion rate resulted in significant increase of the intracellular Gem form, thus accounting for the difference. Thus, significantly higher intracellular levels were achieved and a better overall median survival was demonstrated in patients with advanced disease who received FDR-Gem.<sup>32</sup>

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### COMBINATION THERAPY

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Many combinations of chemotherapeutic agents have been tried in patients with advanced pancreatic cancer providing higher overall response rate without a clear clinical benefit over single agent Gem.<sup>5,33-40</sup> Literature review indicates that all possible chemotherapeutic combinations have been tested without dampening the antitumor activity of the single agents (5F-U, Gem, oxaliplatin, docetaxel, platinum, irinotecan). In this review, we present an overview of the data published concerning the combination treatments. It is noteworthy that only two phase III studies, comparing Gem monotherapy to combined erlotinib or capecitabine, respectively, have confirmed a considerable overall survival benefit.<sup>41,42</sup>

### COMBINATIONS BASED ON 5-FU

Randomized well-designed trials have failed to demonstrate survival benefit with 5-FU based chemotherapy. Only higher response rates have been reported with combined therapy in advanced pancreatic cancer governing the necessity of other treatment options.<sup>4,43-52</sup> All the relevant studies have been reported by Cullinan et al who have compared three chemotherapeutic regimens in advanced disease. A phase II randomized trial analyzed data in 385 patients assigned to receive either 5-FU alone or 5-FU plus doxorubicin, or 5-FU plus doxorubicin and mitomycin (FAM). The objective response rate and the median survival recorded did not differ in the three arms. Median survival reported was 5.5 months for all therapies.<sup>47</sup> Another trial, published by Cullinan et al, assigned 187 patients to three therapeutic arms; the arm of 5-FU alone, the arm of 5-FU plus doxorubicin plus cisplatin and the third arm of 5-FU plus cyclophosphamide, methotrexate, vincristine and mitomycin. None of the combinations presented better overall survival compared to 5-FU monotherapy.<sup>50</sup> More recently the Eastern Cooperative Oncology Group E2297 trial compared the IV administration of Gem (1000 mg/m<sup>2</sup>) and 5-FU (600 mg/m<sup>2</sup>, days 1,8,15 every 4 weeks) vs only Gem (1000 mg/m<sup>2</sup>) in 322 patients.<sup>33</sup> The study showed a trend of better survival in the combination group (6.7 vs 5.4 months,  $p=0.09$ ), but not at a statistically significant level. Additionally, 5-FU was given in bolus infusion, which has proven to be of lower efficacy than the infusion administration and this must be taken into consideration in results analysis. In the CONCO-002 study, 466 patients were randomized to receive either 5-FU/LV and Gem or Gem alone. There were no differences noted in the two arms, but the median survival was better in the combination group (6.2 vs 5.85 months,  $p=0.68$ ), though not statistically significant.<sup>35</sup>

### 5-FU COMBINATIONS VERSUS BEST SUPPORTIVE CARE

Two large meta-analyses have compared 5-FU based combinations to best supportive care.<sup>53,54</sup> In the Cochrane meta-analysis, 5 studies with 7043 patients enrolled were included. Chemotherapy treatment reduced annual mortality quite significantly ( $p= 0.00001$ , odds ratio 0.37). Concurrent chemoradiation induced annual survival rates of 58% compared to 0% ( $p=0.001$ ) of the best supportive care group.<sup>53</sup> No differences in the annual mortality were found in the arm with single agent 5-FU compared to the combination arm (odds ratio 0.90). Trials comparing single-agent therapies to single Gem (odds ratio 1.34,  $p=0.17$ ) and Gem monotherapy to combined (odds ratio 0.88) have also been analysed.

### COMBINATIONS OF 5FU WITH IRINOTECAN AND OXALIPLATIN

The combination of 5-FU with LV and irinotecan with or without oxaliplatin has been investigated in a trial including 47

patients with locally advanced pancreatic cancer. The regimen, named “Folfirinox,” was given every 2 weeks (oxaliplatin 85 mg/m<sup>2</sup> day 1 for 2 hours; irinotecan 180 mg/m<sup>2</sup> day 1 for 90 min; LV 400 mg/m<sup>2</sup> for 2 hours and then; 5-FU 400 mg/m<sup>2</sup> bolus and then, 2400 mg/m<sup>2</sup> in continual 46-hour infusion). An overall good response was recorded in 12 (26%) patients, and complete response in 2 patients (4%). The median time to progression (TTP) and the median overall survival reported was respectively 8.2 and 10.2 months. Grade 3 or 4 neutropenia was noted in 52% (febrile neutropenia in 2 patients), whereas nausea, vomiting, diarrhea and neuropathy were observed in 20%, 17%, 17% and 15% respectively.<sup>55</sup> Ghosn M et al investigated the role of FOLFOX (5-FU with LV and oxaliplatin combination) in 30 patients with advanced cancer. Overall response in 8 (27%) patients, a median TTP of 4 months and median survival 7.5 months was reported. Grade 3 or 4 toxicity including neutropenia, thrombocytopenia and anemia occurred in 27%, 10% and 10% of patients respectively.<sup>56</sup> In another trial, 40 patients were treated with the FOLFIRI combination (5-FU with LV and irinotecan). The overall response rate and the stable disease rate achieved was 37.5% and 27.5%, respectively. The median TTP and overall survival reported were respectively 4 and 7.5 months. Grade 3 or 4 toxicity included neutropenia, nausea, vomiting and diarrhea in 35%, 27% and 15% respectively.<sup>57</sup> To clarify the possible benefit of the above chemotherapeutic combinations, phase III studies should be designed and comparisons with Gem monotherapy should be done.

**THERAPIES WITH OTHER COMBINED AGENTS**

The combination of cisplatin and cytarabine has been investigated in an early study. Partial response in 7 out of 18 patients with measurable disease and median response duration up to 6.2 months has been reported.<sup>58</sup> A more recent study combined cisplatin (100 mg/m<sup>2</sup>, on day 1), cytarabine

(2 mg/m<sup>2</sup> x 2 IV, day 1) and 5-FU (250 mg/m<sup>2</sup> in continuous intravenous administration daily) with caffeine (400 mg/m<sup>2</sup>, subcutaneously post cytarabine administration) and enrolled 30 patients with advanced pancreatic cancer. The cycle was repeated every 28 days and the median number of cycles given was 3 per patient. Complete and partial response was noted in 2 and 3 patients with overall response of 16.7% noted (95% confidence interval 6.8-32.4%). A median survival of 5 (0.3-32.4) months was reported. It is worth mentioning that 16.7% and 10% of patients were alive after one and two years respectively. However, the observed hematological toxicity of the combination limited its use.<sup>59</sup>

**COMBINATIONS BASED ON GEMCITABINE**

Gemcitabine (Gem) has been the cornerstone agent in all combinations designed to treat advanced pancreatic cancer. Four metaanalyses have investigated the potential therapeutic advantage of gemcitabine-based combinations over monotherapy.<sup>53,54,60-62</sup> Two of them did not prove survival superiority of the combined Gem over Gem alone while the other two insisted on significant survival benefit for the groups of combined therapy.<sup>53,54,60-62</sup> It is of interest that the latest analyses were conducted by two irrelevant scientific groups, and showed an ideal rate of hazard ratio for the deaths in the combined arm (HR 0.91, 95% confidence interval 0.85-0.97). The diversity of the final results of the four metaanalyses is attributed to European study results which were incorporated in the final analysis. This European study randomized patients to single gemcitabine and to gemcitabine plus/minus capecitabine arm. Results were announced at the 13<sup>th</sup> European Cancer Conference Meeting in 2005, and were published individually in 2007 favouring the combined treatment arm.<sup>63</sup> This European study has not been included in the analyses of the two previous metaanalyses. All treatment combinations based on gemcitabine are described in **Table 1**.

**TABLE 1. Treatment Combinations Based on Gemcitabine (Gem)**

Study	Patients (No.)	Chemo-drugs	Overall Survival (mos)	p value	PFS (mos)	p value
Berlin et al <sup>33</sup>	322	Gem+FU	6.7	0.09	3.4	0.022
		Gem	5.4		2.2	
Herrmann et al <sup>36</sup>	319	Gem+Cap	8.4	0.2	4.8	0.02
		Gem	7.4		4	
Heinemann et al <sup>39</sup>	219	Gem +cisplatin	7.6	0.12	5.3	0.053
		Gem	6		3.1	
Louvet et al <sup>38</sup>	326	Gem+oxaliplatin	9	0.13	5.8	0.04
		Gem	7.1		3.7	
Rocha et al <sup>34</sup>	342	Irinotecan+ Gem	6.3	0.78	3.5	0.35
		Gem	6.6		3	

Cap = capecitabine; FU = 5-fluorouracil; Gem = gemcitabine; PFS = progression-free survival

**GEMCITABINE COMBINED TO 5-FU**

The combination of gemcitabine with 5-FU, administered as a bolus or in infusion settings, has been attempted. The three phase III studies conducted to confirm the optimal results of the previous phase II failed to prove any benefit from the combined administration of Gem with 5-FU ( $\pm$  biological moderation with LV) over the single Gem therapy.<sup>33,35,64</sup>

**CISPLATIN PLUS GEMCITABINE**

All preclinical studies designed to treat advanced disease with the combination of cisplatin and Gem supported their synergetic action. It is claimed that the Gem prodrug enhances increased formation of cisplatin-DNA complexes breaking the mechanisms to cisplatin resistance. The subsequent incorporation of Gem triphosphate form in DNA complexes is platinum action related.<sup>65,66</sup> Although well established, the basis of anticancer action, three phase III studies investigating the role of the combination cisplatin /gem failed to favour better survival.<sup>39,67,68</sup>

**COMBINATION OF CISPLATIN, EPIRUBICIN, 5-FU AND GEMCITABINE (PEFG)**

Reni et al in a phase II trial studied the PEFG combination (cisplatin, epirubicin, 5-FU and gemcitabine) in 49 patients with advanced pancreatic cancer. PEGF was repeated every 28 days. Overall response rates up to 58%, clinical benefit in 78%, a median time-to-progression (TTP) up to 7.5 months and a median survival time of 11 months have been reported. Neutropenia (grade 3-4) was observed in almost half of the cycle.<sup>69</sup> Another multicenter phase III study later compared the PEFG arm to the Gem single agent. The PEFG regimen showed higher overall response rate (39% vs 9%) and a median TTP up to 4 months in 104 patients enrolled. Annual survival rates recorded did not differ in the arms (39% vs 21%) although the 2-year survival rate (12% vs 2%) was statistically significantly different. Hazard ratio for the deaths recorded was significantly lower for PEFG-treated patients (0.65; 95% confidence interval 0.43-0.99,  $p=0.047$ ). Hematological toxicity included neutropenia and thrombocytopenia with the combined treatment arm presenting higher rates (43% vs 14%) of neutropenia (grade 3 or 4) and thrombocytopenia (30% vs 1%).<sup>70</sup>

**COMBINATION OF GEMCITABINE WITH IRINOTECAN**

All phase II and III trials administering irinotecan as a single agent or combined with Gem have reported its minimal therapeutic value.<sup>71,72</sup>

**COMBINATION OF GEMCITABINE AND DOCETAXEL**

All literature reported phase II studies evaluating the anticancer efficacy of docetaxel combined to Gem provide

satisfactory response rates. Response rates up to 12-18%, median overall survival of 4.7-8.9 mo and myelotoxicity of grade 3-4 neutropenia have been reported.<sup>73-76</sup> Apart from the phase II trial of Cascinu et al with 18 patients enrolled who presented only one partial response and claimed grade 3 fatigue as major side-effect in 9 patients, the remaining trials reported encouraging results.<sup>76</sup> Phase III trials, have not yet been published.

**CAPECITABINE PLUS GEMCITABINE**

Capecitabine combined with Gem as first line therapy has been supported by the National Cancer Research Network (NCRN) of the Upper Gastrointestinal Cancer Clinical Study Group. It is based on the preliminary results of a randomized trial of 533 patients treated either with Gem monotherapy or in combination with capecitabine.<sup>7</sup> Overall response rates of 14.2% for the group of the combined therapy (GEM-CAP) vs 7.1% of monotherapy ( $p<0.008$ ), median survival 7.4 versus 6 months (hazard ratio 0.8,  $p=0.014$ ) and annual survival rates 26% and 19% respectively have been reported. Neutropenia, thrombocytopenia, diarrhea and hand – foot syndrome as the toxicity profile were more frequently encountered in the combined treated arm. Many arguments have been raised against the trial, based on the short period of final results collection and publishing. Investigators have been troubled by the negative results of prior phase III trials testing the Gem combination with fluoropyrimidines.<sup>33,35</sup> Hermann et al in another noteworthy trial including 316 patients, studied Gem monotherapy vs. combined with capecitabine. The median survival time was longer in the combination arm (8.4 vs 7.3 months), although not statistically significant ( $p=0.314$ ). A basic difference from the NCRN study was the rest period between the repeated cycles resulting in less intensive but higher tolerability of GEM-CAP.<sup>36</sup> Bernard et al supported the clinical benefit response and QOL in patients treated with GEM-CAP or Gem alone. Of 319 patients enrolled, 19 % of patients receiving the combination therapy and 20% the Gem alone group presented with better clinical response and median time duration of 9.5 and 6.5 weeks, respectively.<sup>78</sup>

**OXALIPLATIN PLUS GEMCITABINE**

Oxaliplatin, a platinum compound, showed to be efficient and well tolerated in combination with Gem by patients with advanced pancreatic cancer.<sup>78</sup> In a phase III GERCOR/GISCAD Intergroup study with randomized distribution of 313 patients with advanced carcinoma, the combination FDR-Gem with oxaliplatin (GEMOX) was comparatively tested with Gem as a single agent. Although, not any significant improvement in the overall response (27% vs 17%), in the median progression free time (5.8 vs 3.7 months) and in the clinical benefit for patients offered by GEMOX, the median survival time observed was 9 vs 7.1 months in both the arms.<sup>38</sup> Two variables, the FDR-gem administration vs

the 30-minute infusion and the oxaliplatin administration vs non-oxaliplatin were considered in analysis of the trial. It is troublesome if the results are associated with different Gem administration, or with the concomitant use of oxaliplatin, or with both of them. The protocol ECOG 6201 was designed to answer questions raised from earlier studies<sup>7,32,38</sup> and all primary results were announced at the 2006 ASCO Conference. As numerous previous studies, the protocol ECOG 6201 showed very limited median survival benefit, with a second chemotherapeutic agent added to Gem and also proved that the administration of FDR-Gem was of limited extra benefit with increased toxicity.<sup>3,7,71</sup>

#### **NEWER TARGETED THERAPIES IN ADVANCED PANCREATIC CANCER**

The identification of molecular mechanisms implicated in tumour growth, invasion, metastasis, angiogenesis and resistance to apoptosis of pancreatic cancer has led to the development of targeted molecular agents, designed to disable the essential cellular pathways. Clinical trials have been conducted to investigate the therapeutic efficacy of the standard Gem treatment in combination with all the new molecular agents. Most of the published trials have failed to show better survival benefit over the gained by Gem single agent. Erlotinib, the only tyrosine kinase inhibitor, exceptionally presented a two-week better median survival.<sup>79,80</sup>

#### **GEMCITABINE-BASED CHEMOTHERAPY WITH MOLECULAR TARGETED AGENTS**

##### *Gemcitabine and Cetuximab*

The epidermal growth factor receptor (EGFR) promotes oncogenic activities in human cells like uncontrolled proliferation, angiogenesis and apoptosis inhibition, in terms of inappropriate activation or overexpression. The EGFR has been correlated with poor prognosis in case of overexpression in the tumours; thus it has been investigated as a possible target for systemic therapy. All preclinical data suggest that EGFR inhibitors may increase the antitumor activity of Gem in case they are incorporated in a therapeutic regimen. Cetuximab, a monoclonal antibody targeting the EGFR, in combination with Gem has been investigated in a phase II trial with 41 patients. The reported response rate of 12.2% and the disease stabilization achieved in 63.4% led to a phase III trial design.<sup>81,82</sup> The Southwest Oncology Group (SWOG, SO205) conducted this phase III trial attempting to show better survival benefit over the standard Gem therapy. Seven-hundred thirty-five patients enrolled were randomized to receive either Gem or Gem-cetuximab. A median survival of 6 months in the Gem arm versus 6.5 in the combination arm, and progression-free survival (PFS) of 3 and 3.5 months respectively have been reported.<sup>81,82</sup>

##### *Gemcitabine and Erlotinib*

Moore et al have investigated the role of a tyrosine kinase inhibitor, erlotinib, in advanced pancreatic cancer disease via a III phase trial including 569 patients.<sup>83</sup> The randomly assigned patients to Gem - erlotinib or standard Gem treatment were analyzed and a statistically significant improvement of overall survival (6.37 vs 5.91 months  $p=0.0038$ ) and PFS was reported. The erlotinib arm showed a median survival of 6.24 months and 1-year survival rate of 23% compared to 5.91 months and 17% of the Gem arm. Regarding QOL no significant difference was noted in both arms. Skin and gastrointestinal toxicity ranged up to 6% in the erlotinib arm versus 1% to the control. The skin rash grading was claimed to correlate positively with control disease regardless of the EGFR status expression in the tumour section.

##### *Gemcitabine and Bevacizumab*

Angiogenesis principally mediated by the vascular endothelial growth factor (VEGF) family of proteins is an appealing target of therapy. Bevacizumab, a humanized antibody against VEGF, has been incorporated in combination treatments of advanced pancreatic cancer and examined in a number of clinical trials. Kindler H et al, in a phase II study, tried the combination of bevacizumab to standard Gem and showed response rate of 19% whereas Cancer and Leukemia Group B (CALGB) in a phase III randomized trial did not show any survival improvement on bevacizumab addition to Gem.<sup>84-86</sup> The bevacizumab arm presented 5.7 month median survival vs 6.0 months in the control arm. The reported PFS was 4.8 months vs 4.3 months respectively. Although the addition of bevacizumab to Gem did not confer better overall survival, the investigators insisted on the possible effective antitumor activity of the VEGF antibody. Another trial, the AVITA, with 607 patients enrolled, tested a triple therapy with bevacizumab /gemcitabine and erlotinib aiming to demonstrate a survival benefit. Progression-free survival was significantly improved with a month prolongation but no overall survival benefit was found.<sup>84-90</sup> Bevacizumab was reported to be safe and tolerant with no major adverse events documented (thrombosis, epistaxis, bleeding, perforation, hypertension, proteinuria). Other trials have been conducted to examine the combination of bevacizumab with other agents or treatment modalities of pancreatic cancer, but have not succeeded in demonstrating any benefit. Fogelman et al studied a three-agent (gemcitabine, oxaliplatin and bevacizumab) chemotherapeutic regimen in advanced disease and reported 1-year survival rate of 40% and a response rate of 39%.<sup>87</sup> Gem and oxaliplatin with bevacizumab addition has also been examined in another phase II study by Kim et al with 82 enrolled patients.<sup>88</sup> The 6-month survival was 65%, the median overall survival was 8.1 months and the time to progression was reported at 5.7 months. The concomitant monoclonal antibody treatment

with bevacizumab, cetuximab with or without Gem has been studied by Ko et al.<sup>89</sup> Fifty-seven patients were given both the antibodies and the rate response was 10.7% in the Gem arm, while no survival data have been published yet. Kindler et al in another phase II trial reconfirmed the results of Ko et al. The 139 patients studied were offered either Gem, erlotinib and bevacizumab or bevacizumab /cetuximab or Gem. No significant difference for overall survival or progression-free survival was reported.<sup>90</sup>

Bevacizumab failure in therapeutic trials addressed the need for other angiogenic inhibitors targeting the non VEGF pathways. Sorafenib, a multitargeted kinase inhibitor of VEGFR, platelet derived growth factor (PDGFR), c-kit, Raf1 and Ftl3 was tested in a phase II trial but it was inactive.<sup>91</sup> Axitinib, another multitargeted inhibitor of VEGFR and other kinase receptors, has been evaluated for its antitumor action with Gem in a phase II trial and a median survival of 6.9 months vs 5.6 months of the single agent Gem has been reported although the finding was not statistically significant.<sup>92</sup> Phase III trials of axitinib combinations are ongoing. Aflibercept, a recombinant infusion protein inhibiting VEGF, another angiogenic inhibitor, is being examined in a phase III trial with Gem. Cilengitide inhibiting integrins is being investigated in a phase II trial in patients with advanced pancreatic cancer with Gem co- administration but no significant results have been shown.<sup>93</sup> Other agents, against principal integrin receptors  $\alpha$ ,  $\beta$ , like volociximab, are also in early phase trials with no published data so far.

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#### OTHER POTENTIAL THERAPEUTIC TARGETS

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##### THE PI3K AND AKT PATHWAY

The PI3K-AKT pathway is an important regulator of cell growth and survival. Increased dysregulation of many components of the pathway contributes to tumorigenesis. It is known that PI3K activates AKT, which has been implied in a multiple group of targets, including the transcription factor (NFKB) and the mammalian target of rapamycin (mTOR). The mTOR and NFKB are ideal targets of anticancer novel agents based on the fact that AKT is amplified and the PI3K AKT pathway is found activated in 20% and 59% of pancreatic cancer. Temsirolimus, an mTOR inhibitor, and curcumin, an NFKB inhibitor, have been evaluated in anticancer pancreatic treatments with the front line therapy containing Gem. Temsirolimus has been of limited efficacy when used in patients with advanced disease. Other antineoplastic agents, like everolimus and sirolimus, are currently tried in phase II trials.<sup>94-96</sup> Curcumin, the NFKB inhibitor, is involved in the expression of regulated gene products such as Bcl2, BclXL, COX2, CyclineD1 and Survivin (all defined as anti-apoptotic proteins). Unfortunately combination with Gem did not man-

age to show some biological activity.<sup>94-97</sup> Bortezomib, a proteasome inhibitor of NFKB, failed to show any benefit when tried in a phase II trial as well.<sup>98</sup>

##### THE CYCLO-OXYGENASE PATHWAY (COX)

The cyclo-oxygenase receptor (Cox2) inducible by growth factors, cytokines, and other tumour promoters is overexpressed in 90% of pancreatic cancer cells. The Cox-mediated mechanisms in pancreatic cancer proliferation are too complex, implying various mitogenic signalling pathways and molecules mediating resistance to apoptosis. Chuang et al reported in 2008 the antitumor action of celecoxib (COX2 inhibitor) but all phase II trials of its combination with Gem did not finally give promising results.<sup>99</sup> Also, no significant benefit has been reported by Dragovich et al in another phase II trial.<sup>100</sup> A phase III trial of Gem, celecoxib and curcumin is in progress.

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#### OTHER TARGETED AGENTS

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Farsenyle transferase inhibitor, tipifarnib, and matrix metalloproteinase inhibitor, marimastat, have been tested in pancreatic cancer treatment but with no survival benefit.<sup>101-103</sup> The agent AMG655,<sup>104</sup> a humanized antibody targeting human death receptor 5 (DR5) activating caspases, leading to apoptosis in tumor cells, has been intensively studied for its antitumor activity in a phase I trial. Four of the seven enrolled patients have reduced CA19-9 levels >70%, a median progression-free survival of 5.3 months and a 6-month survival rate up to 76% have been reported. The phase II randomized trial testing the AMG655 in addition to Gem although completed has not yet reported the results.<sup>104</sup>

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#### TREATMENT OPTIONS FOR GEMCITABINE-RESISTANT PANCREATIC CANCER

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While a standard of care for front-line treatment of advanced pancreatic cancer is established with gemcitabine monotherapy, all data to guide treatment options for patients progressed post Gem acquired resistance is limited. There is no standard therapeutic option for post Gem failure. The CONKO-3 study examined oxaliplatin, 5FU, LV combination (OFF) and 5FU, LV (FF) in 168 patients refractory to Gem.<sup>105</sup> An overall survival improvement of two months in the OFF combination has been reported. A significant prolongation of PFS in the OFF schedule has been published (13 weeks versus 9 weeks). Another phase III study randomized Gem refractory patients either to rubitecan or physicians individual choice.<sup>105,106</sup> The study failed to show a statistically significant improvement in overall survival (3.7 months versus

3.1 months). Cartwright et al examined in a phase II trial the capecitabine administration in 41 patients with measurable disease post Gem single agent prior treatment.<sup>107</sup> Three of the 41 patients presented an objective partial response and the overall survival rate was 9.5%. Another phase II trial examined capecitabine administration but in combination with oxaliplatin in a second line setting. Of the 39 enrolled patients, one presented a minimal partial response and ten patients had stable disease. The median overall survival was 23 weeks and PFS was 9.9 weeks. Second-line treatment options used in trials conducted are fraught with problems such as small number of patients enrolled and a major difficulty of the ability to compare the trials. Problems regarding status adequate information about performance, disease and other factors with known impact on survival are difficult to be resolved. It is suggested that all patients with disease progression on first-line therapy should be enrolled to participate in clinical trials. Further randomized trials are needed in the future to investigate further therapeutic options for this dreadful disease.

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#### OTHER RELEVANT THERAPEUTIC OPTIONS

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Based on the observation that normal and malignant pancreatic tissues express estrogen and somatostatin receptors, hormone manipulation in advanced disease has been suggested. Tamoxifen, as a single agent anti-estrogen blockage compound, has minimum efficacy with induced rates of overall response <10%. Three randomized placebo-controlled trials of tamoxifen versus placebo in advanced pancreatic cancer have not managed to demonstrate any survival benefit.<sup>108-111</sup> Octreotide has been studied in 2 randomized phase II trials as somatostatin receptor inhibitor but neither the standard dose of octreotide nor its combination with 5FU when compared to placebo demonstrated any survival benefit.<sup>112-114</sup>

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#### PRACTICE GUIDELINE FOR LOCALLY ADVANCED PANCREATIC CANCER

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Patients with locally advanced pancreatic cancer and adequate performance status should be considered to undergo gemcitabine-based chemotherapy either with concomitant use of oxaliplatin or with capecitabine, based on the aggressive therapeutic value of the combination schedule. Gemcitabine with the tyrosine kinase inhibitor erlotinib is a reasonable therapeutic combined option with no extremely adverse toxicity profile in patients of good performance status and hereditary risk factors (BRCA, PALB2 mutations). On the basis of refractory to gemcitabine or recurrent disease, fluoropyrimidines analogues with platinum-based combination or 5FU/LV regimens should be tried with the view of palliation

care in case of prior treatment failure or poor performance status. The possibility of induction in clinical trials may be considered for patients with high risk factors or poor correspondence to first line treatment setting.

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#### CONCLUSION

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Pancreatic cancer remains a surprisingly chemoresistant disease. Therapeutic options are still limited. Gemcitabine, the only FDA approved chemotherapeutic agent, has been thoroughly tried alone or in combination with other drugs but no further clinical benefit has been measured and a very modest survival benefit has been achieved. A large variety of novel agents targeting molecular signalling pathways combined with one another or with cytotoxic drugs may offer a great promise in the future. Among the key molecular pathways involved, only the EGFR tyrosine kinase inhibitor, erlotinib, has been demonstrated with a significant survival benefit. Further investigation of signal transduction and embryonic pathways and clarification of the implicated role of cancer stem cells, should be done. Future development of targeted therapeutic options should focus on blockade of multiple signalling pathways at different levels to maximize the achieved benefit of the novel therapeutic agents.

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