Antitumour treatment
Systemic treatment of advanced pancreatic cancer

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A B S T R A C T

Pancreatic cancer belongs to the most malignant gastrointestinal cancers and, in its advanced stage, remains a deadly disease for nearly all affected patients. Treatment of metastatic adenocarcinoma of the pancreas not only involves chemotherapy and targeted therapy, but also requires attention to accompanying comorbidities as well as frequently intensive supportive treatment and psychosocial support. Gemcitabine-based combinations with fluoropyrimidines and platinum analogs have essentially failed to provide a substantial prolongation of survival and may constitute a treatment option only in patients with a good performance status. Among targeted therapies, only the EGFR tyrosine kinase inhibitor erlotinib has shown activity which is marginal in the overall population, but clinically relevant in patients developing skin rash. New avenues of polychemotherapy are presently explored since the gemcitabine-free FOLFIRINOX-regimen (infusional 5-fluorouracil/folinic acid plus irinotecan and oxaliplatin) was shown to be markedly superior to gemcitabine in selected good-performance patients. Pancreatic cancer is notably characterized as a hypovascular tumor rich in desmoplastic stromal tissue. An innovative approach to treatment therefore focuses on peritumoral fibroblasts and aims to induce a depletion of the stroma either by inhibition of the hedgehog pathway or by targeting SPARC (secreted protein acidic and rich in cysteine) via application of albumin-bound paclitaxel.

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Introduction

Only a minority of pancreatic cancer (PC) patients (15–20%) present with resectable disease at first diagnosis. Patients with locally advanced, non-metastatic PC (LAPC) represent 15–20% of patients and have a median survival of 9–11 months. Metastatic disease, by comparison, is documented in 60–70% of patients and is associated with a much shorter survival of only 6–8 months in most studies. This observation has meanwhile led to a broad consensus that LAPC and metastatic PC should be viewed as prognostically (and possibly also biologically) different disease entities which require different treatment algorithms and accordingly should be investigated in separate clinical studies.1

The present review evaluates the available armamentarium of antitumour agents and aims to clarify the present treatment options. In view of the dismal prognosis of advanced disease, it also emphasizes the importance of adequate supportive therapy and early provision of psychosocial help.

Diagnosis

Once standard imaging procedures (CT or MRT) led to the classification of the tumor as non-resectable, the patho-histological or -cytological verification of neoplastic disease needs to be performed before oncological treatment can start. The clinical constellation of a typical mass in the pancreas combined with an elevated tumor marker (CA 19-9 or CEA) alone is not sufficient. Specifically, the interpretation of elevated CA 19-9 can be confounded by any affection of the biliary system frequently accompanying pancreatic disease. Accordingly, a biopsy of the pancreatic mass or associated metastatic lesions is strongly recommended in all patients with advanced disease.
Psychosocial support

The sudden confrontation with a limitation of life expectancy to several months may cause substantial distress and poses problems most patients have not learned to cope with. Clearly, reliable information on prognosis can only be provided to patients once the diagnostic work-up has been completed and once a final report on the stage of disease has been obtained. Only then, the oncologist may provide a realistic prognosis and may propose an adequate concept of cancer treatment. Importantly, this information is intended to guide patient decisions in view of a shortened life span, it is not meant to take away all elements of hope. The oncologist therefore not only needs to clarify the technical aspects of treatment in a timely manner, he also has the task to understand the expectations and psychosocial needs of the patient. To improve patient care, a first step may be to implement routine

Table 1
Gemcitabine-based polychemotherapy regimens.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Study design</th>
<th>No of pts</th>
<th>LAPC (%)</th>
<th>ORR (%)</th>
<th>PFS/TTP (mo)</th>
<th>OS (mo)</th>
<th>1-Year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reni et al.</td>
<td>PEFG</td>
<td>Phase III</td>
<td>52</td>
<td>29</td>
<td>38.5</td>
<td>5.4</td>
<td>na</td>
<td>38.5</td>
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<tr>
<td></td>
<td>GEM</td>
<td></td>
<td>47</td>
<td>30</td>
<td>8.5</td>
<td>3.3</td>
<td>na</td>
<td>21.3</td>
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<tr>
<td>Wagner et al</td>
<td>GEM/oxiplatin/infusional 5-FU</td>
<td>Phase II</td>
<td>43</td>
<td>26</td>
<td>19</td>
<td>5.7</td>
<td>7.5</td>
<td>33</td>
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<tr>
<td>Endlicher et al</td>
<td>GEM/irinotecan/5-FU</td>
<td>Phase II</td>
<td>28</td>
<td>17</td>
<td>7.1</td>
<td>3.4</td>
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<td>25</td>
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<tr>
<td>Hess et al.</td>
<td>GEMOXEL phase II/III</td>
<td>Phase II/III</td>
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<td>24</td>
<td>41</td>
<td>4.3</td>
<td>7.8</td>
<td>na</td>
</tr>
</tbody>
</table>

GEM, gemcitabine; PEFG, cisplatin, epirubicin, gemcitabine, 5-FU; GEMOXEL, gemcitabine, oxaliplatin, capecitabine; LAPC, locally advanced pancreatic cancer; na, data not available.

Table 2
Fluoropyrimidine-/oxaliplatin-based chemotherapy (selected studies).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Study design</th>
<th>No of pts</th>
<th>LAPC (%)</th>
<th>ORR (%)</th>
<th>PFS/TTP (mo)</th>
<th>OS (mo)</th>
<th>1-Year survival (%)</th>
</tr>
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<tr>
<td>First-line therapy</td>
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<td></td>
<td></td>
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<tr>
<td>Ducreux et al.</td>
<td>CI 5-FU</td>
<td>Randomized Phase II</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>2.4</td>
<td>–</td>
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<tr>
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<td>Oxaliplatin</td>
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<td>17</td>
<td>6</td>
<td>0</td>
<td>2.0</td>
<td>3.4</td>
<td>–</td>
</tr>
<tr>
<td>Ghosn et al.</td>
<td>CI 5-FU + oxaliplatin</td>
<td>Phase II</td>
<td>15</td>
<td>16</td>
<td>10</td>
<td>4.2</td>
<td>9.0</td>
<td>&gt;20</td>
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<tr>
<td>Boeck et al.</td>
<td>Cepacetabine + oxaliplatin</td>
<td>Phase II</td>
<td>62</td>
<td>18</td>
<td>13</td>
<td>4.2</td>
<td>8.1</td>
<td>29</td>
</tr>
<tr>
<td>Second-line therapy</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Gebbia et al.</td>
<td>FOLFIRI4</td>
<td>Retrospective survey</td>
<td>42</td>
<td>17</td>
<td>14</td>
<td>4</td>
<td>6.7</td>
<td>na</td>
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<tr>
<td>Pelzer et al.</td>
<td>5-FU/FA + oxaliplatin</td>
<td>Randomised phase II</td>
<td>76</td>
<td>14</td>
<td>na</td>
<td>3.3*</td>
<td>6.5**</td>
<td>na</td>
</tr>
<tr>
<td>Xiong et al.</td>
<td>Cepacetabine + oxaliplatin</td>
<td>Phase II</td>
<td>39</td>
<td>5</td>
<td>3</td>
<td>2.3</td>
<td>5.4</td>
<td>21</td>
</tr>
</tbody>
</table>

LAPC, locally advanced pancreatic cancer; CI, continuous infusion; FOLFIRI4, combination of infusional 5-fluorouracil, folinic acid, and oxaliplatin; CAPOX, combination of capecitabine and oxaliplatin; 5-FU/FA, combination of 5-fluorouracil and folinic acid; na, data not available.

Table 3
Irinotecan-based chemotherapy (selected studies).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Study design</th>
<th>No of pts</th>
<th>LAPC (%)</th>
<th>ORR (%)</th>
<th>PFS/TTP (mo)</th>
<th>OS (mo)</th>
<th>1-Year survival (%)</th>
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<tbody>
<tr>
<td>First-line therapy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rocha-Lima et al.</td>
<td>GEM/irinotecan</td>
<td>Randomised phase III</td>
<td>180</td>
<td>15</td>
<td>16.1</td>
<td>3.5</td>
<td>6.3</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>GEM</td>
<td></td>
<td>180</td>
<td>13.3</td>
<td>14.4</td>
<td>3.0</td>
<td>6.6</td>
<td>20</td>
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<tr>
<td>Stathopoulos et al.</td>
<td>GEM/irinotecan</td>
<td>Randomised phase III</td>
<td>60</td>
<td>22</td>
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<td>2.8</td>
<td>6.4</td>
<td>24.3</td>
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<tr>
<td></td>
<td>GEM</td>
<td></td>
<td>70</td>
<td>14</td>
<td>10</td>
<td>2.9</td>
<td>6.5</td>
<td>21.8</td>
</tr>
<tr>
<td>Taieb et al.</td>
<td>FOLFIRI3</td>
<td>Phase II</td>
<td>40</td>
<td>27</td>
<td>37.5</td>
<td>5.6</td>
<td>12.1</td>
<td>51%</td>
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<tr>
<td>Second-line therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yi et al.</td>
<td>Irinotecan</td>
<td>Phase II</td>
<td>33</td>
<td>0</td>
<td>9</td>
<td>2</td>
<td>6.6</td>
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<tr>
<td>Gebbia et al.</td>
<td>FOLFIRI</td>
<td>Retrospective survey</td>
<td>40</td>
<td>17.5</td>
<td>15</td>
<td>3.7</td>
<td>6</td>
<td>na</td>
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<tr>
<td>Cereda et al.</td>
<td>CAPIRI/FOLFIRI</td>
<td>Observational study</td>
<td>34</td>
<td>na</td>
<td>0</td>
<td>2</td>
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<td>na</td>
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<tr>
<td>Yoo et al.</td>
<td>FOLFIRI3</td>
<td>Randomised phase II</td>
<td>31</td>
<td>na</td>
<td>0</td>
<td>2.1</td>
<td>4.2</td>
<td>na</td>
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<tr>
<td></td>
<td>FOLFIRI</td>
<td></td>
<td>30</td>
<td>na</td>
<td>2</td>
<td>1.5</td>
<td>3.7</td>
<td>na</td>
</tr>
</tbody>
</table>

GEM, gemcitabine; FOLFIRI, combination of infusional 5-fluorouracil, folinic acid, and irinotecan; CAPOX, combination of capecitabine and irinotecan; FOLFIRI3, combination of infusional 5-fluorouracil, folinic acid, and oxaliplatin; na, data not available.

Table 4
Chemotherapy with the FOLFIRINOX regimen.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Study design</th>
<th>No of pts</th>
<th>LAPC (%)</th>
<th>ORR (%)</th>
<th>PFS/TTP (mo)</th>
<th>OS (mo)</th>
<th>1-Year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conroy et al.</td>
<td>FOLFIRINOX</td>
<td>Phase II</td>
<td>46</td>
<td>24</td>
<td>26</td>
<td>8.2</td>
<td>10.2</td>
<td>43</td>
</tr>
<tr>
<td>Conroy et al.</td>
<td>FOLFIRINOX</td>
<td>Phase III</td>
<td>171</td>
<td>0</td>
<td>31.6*</td>
<td>6.4*</td>
<td>11.1*</td>
<td>48.4</td>
</tr>
<tr>
<td></td>
<td>GEM</td>
<td></td>
<td>171</td>
<td>0</td>
<td>9.4</td>
<td>3.3</td>
<td>6.8</td>
<td>20.6</td>
</tr>
</tbody>
</table>

LAPC, locally advanced pancreatic cancer; FOLFIRINOX, infusional 5-FU/folinic acid plus irinotecan and oxaliplatin; na, data not available.

Psychosocial support

The sudden confrontation with a limitation of life expectancy to several months may cause substantial distress and poses problems most patients have not learned to cope with. Clearly, reliable information on prognosis can only be provided to patients once the diagnostic work-up has been completed and once a final report on the stage of disease has been obtained. Only then, the oncologist may provide a realistic prognosis and may propose an adequate concept of cancer treatment. Importantly, this information is intended to guide patient decisions in view of a shortened life span, it is not meant to take away all elements of hope. The oncologist therefore not only needs to clarify the technical aspects of treatment in a timely manner, he also has the task to understand the expectations and psychosocial needs of the patient. To improve patient care, a first step may be to implement routine
screening for distress. Psychosocial interventions may then be offered to selected patients requiring and requesting help. Another option may be to offer psychosocial support as a routine measure accompanying anticancer therapy. Expectedly this offer will be accepted only by a fraction of patients.

**Early access to palliative treatment**

Patients are usually referred to palliative care in a late stage of their disease. Improved results with regard to quality and delivery may, however, be obtained when palliative care is offered early on and is further applied during the continuum of treatment. In this context, palliative care means control of symptoms, psychological support and assistance in decision making. That approach was previously shown to be beneficial in lung cancer, a comparably malignant and incurable illness. In a randomized trial, early palliative care contributed to a better quality of life, fewer depressive symptoms (16% vs. 38%, \( P = 0.01 \)), and a longer median survival (11.6 vs. 8.9 months, \( P = 0.02 \)). Most importantly, survival was prolonged in patients receiving early palliative care despite the fact that aggressive end-of-life care was applied less frequently (33% vs. 54%, \( P = 0.05 \)). This can either be explained by the positive effects of an intensive supportive and psychosocial care on symptoms control and psychosocial well being or as the benefit from earlier referral to a hospice program. In addition, it cannot be excluded that less intravenous chemotherapy near the end of life may also have an effect on survival. These data clearly need to be confirmed prospectively in PC patients. Nevertheless, also at this stage of knowledge it may be concluded that efforts to maintain physical and psychosocial well being should be given a high priority and should be integrated into a comprehensive treatment concept.

**Management of comorbidity**

Pancreatic cancer is characterized by a number of comorbidities which often require increased attention and a close follow-up by the treating physician. Many patients suffer from pain as a primary disease-related symptom which requires appropriate medication or application of a celiac blockade. Before antitumor treatment can be started in advanced disease, it is necessary to ensure optimal bile drainage and to apply biliary stents when hyperbilirubinemia due to bile duct obstruction is present. Patients with biliary stents in place have a significant risk of recurring stent occlusion and cholangitis. They need to be well informed about their risk situation and need to have rapid access to diagnostic facilities, medical treatment and antibiotic therapy if necessary.

Patients frequently present with a marked loss of body weight and even cachexia at first diagnosis. Optimal nutritional support is necessary to stabilize body weight. In case of bowel obstruction, therapeutic measures such as parenteral feeding, surgical bypass or duodenal stenting need to be considered. When exocrine insufficiency of the pancreas is apparent accompanied by malabsorption, diarrhea, and fatty stools, oral enzyme replacement (lipase, amylase, proteases) may help to stabilize body weight. Many PC patients suffer from diabetes mellitus and its sequelae. This comorbidity may specifically gain importance when steroids are applied in the context of antiemetic medication during chemotherapy. Pre-existing sensory neuropathy may limit the application of platinum compounds in these patients.

The risk of thromboembolic complications is markedly elevated in PC patients. In most reports, the incidence ranges between 20% and 30% and has been associated with advanced disease and poor prognosis. The unfavorable outcome may be a direct result of thromboembolic complications (e.g. pulmonary embolism) or may reflect a more aggressive biology of the disease. The use of prophylactic anticoagulation remains controversial. A recent randomized study demonstrated that the prophylactic use of low-molecular weight heparin (LMWH) significantly decreased the incidence of symptomatic venous thromboembolism. This, however, had no impact on overall survival. Another randomized study investigating the prophylactic use of nadroparin did also not show a survival benefit in pancreatic-, prostate- and lung-cancer patients. Accordingly, LMWH are not recommended as prophylactic agents, but are applied as standard of care once venous thromboembolism has occurred. With regard to long-term use, there is evidence to support the application of LMWH over warfarin in cancer patients because of improved efficacy and outcome.

**Patient selection**

Clearly, it needs to be addressed to which extent clinical trials reflect patient reality since clinical trials tend to include younger patients and patients with a better socio-economic background. In a retrospective analysis, El-Rayes et al. demonstrated that patients treated within clinical trials at the Karmanos Cancer Institute had a median survival of 8.5 months as compared to patients treated at that institution outside clinical trials (5.0 months) or at non-institutional community centers (2.8 months). Performance status belongs to the most relevant prognostic factors in PC. Other parameters recommended to characterize patient subgroups are weight loss and nutritional status. While these factors appear to be reasonable in view of the disease, it needs to be taken into account that specifically weight loss is not an objective parameter since documented analyses of normal weight do not exist in most patients. Weight loss before treatment start is therefore frequently documented only as an estimate based on assumptions of the patient.

**Chemotherapy is a standard of care in advanced pancreatic cancer**

In a meta-analytical evaluation of 7 randomized controlled trials involving 432 patients with advanced PC, Sultana and coworkers...
demonstrated that chemotherapy improved survival compared to best supportive care with a hazard ratio (HR) of 0.64 (95% CI, 0.42–0.98). However, it was pointed out that there was a significant heterogeneity between studies (P = 0.0005) and that the upper limit of the confidence interval (CI) was quite close to 1.0.13

Activity of gemcitabine in 1st-line therapy

Since more than a decade, the antimitabolite gemcitabine (GEM) has been established as a chemotherapeutic standard in the treatment of advanced PC. Registration of GEM was based on a randomized trial which demonstrated the superiority of GEM over bolus 5-fluorouracil (5-FU) with regard to clinical benefit response (23.8% vs. 4.8%, P = 0.0022), and median overall survival (5.65 vs. 4.41 months, P = 0.0025).14 In addition, this study also indicated that GEM induced a marked improvement of 1-year survival (18% vs. 2%). A 1-year survival rate in the range of 18–28% was later confirmed by numerous trials testing single-agent GEM as a comparator treatment and thus established a clinically relevant milestone in the treatment of PC.

Gemcitabine-based chemotherapy doublets

While the introduction of GEM clearly improved therapeutic efficacy and 1-year survival, its impact on median overall survival remained modest. More intensive combination chemotherapies involving fluoropyrimidines, platinum analogs and other cytotoxic agents have been investigated in numerous phase II and III trials. Most of these failed, however, to show a statistically significant survival benefit compared to GEM alone.15 The true benefit gained from GEM-based combination chemotherapy therefore still remains a matter of debate. The problem can best be described based on a recent trial comparing GEM plus capecitabine (GEM + CAP) to GEM alone.16 GEM-CAP significantly improved response rate (19.1% vs. 12.4%, P = 0.034) and progression-free survival (HR = 0.78, P = 0.004), however, only a strong trend toward improvement was reached with regard to overall survival (7.1 vs. 6.2 months; HR = 0.86, P = 0.08). The level of statistical significance could only be achieved by pooling the results of this trial with other two randomised trials reaching a total of 935 patients (HR, 0.86; 95% CI, 0.75–0.98, P = 0.02).18 While the authors proclaimed GEM + CAP as one of the standard first-line options, this statement appears not sufficiently supported by the hazard ratio.

Meta-analytical evaluation of gemcitabine-based doublets

Since single studies were frequently criticized because of their underpowered statistical design, several meta-analyses were performed to allow more reliable conclusions based on larger patient numbers.13 Heinemann and coworkers reported a meta-analysis of fifteen trials comparing GEM versus GEM plus cytotoxic agent (GEM + X) which revealed a significant survival benefit for GEM + X with a pooled hazard ratio (HR) of 0.91, P = 0.004.15 An identical HR (0.91; 95% CI, 0.85–0.97) was also published by Sultana and coworkers.13

When different combination partners were evaluated separately, the analysis of platinum-based combinations indicated a HR of 0.85 (95% CI:0.76–0.96, P = 0.010), while for fluoropyrimidine-based combinations a HR of 0.90 (95% CI: 0.81–0.99, P = 0.030) was reported. No risk reduction was observed in the group of trials combining GEM with irinotecan, exatecan or pemetrexed (HR = 0.99).15

In a more recent evaluation, Vaccaro et al. analyzed seven randomised trials including 2422 patients in which single-agent GEM was compared to combinations of GEM with cisplatin, oxaliplatin or capecitabine.17 This analysis included the more recent trial by Colucci and coworkers published in 2010.18 and showed a HR of 0.94 (P = 0.61) for GEM plus cisplatin. For the combination of GEM plus oxaliplatin a HR of 0.86 (P = 0.04), and for GEM plus capecitabine a HR of 0.86 (P = 0.04) were reported.17 In addition, the authors stated that power calculations reliably (80% power, two-tailed alpha of 0.05) rule out the possibility that GEM-based doublets could improve 1-year survival by more than 5%. As a consequence and in view of the promising FOLFIRINOX data, they concluded that clinical research should move away from the investigation of GEM-based combinations and should seek for more effective strategies.17

Gemcitabine-based polychemotherapy regimens

Several studies investigated GEM-based polychemotherapy regimens involving 3–4 cytotoxic agents (Table 1). Reni and coworkers performed a small randomised trial (n = 99) testing the PEFG-regimen (cisplatin, epirubicin, fluorouracil, and GEM) versus GEM alone.19 Progression-free survival at 4 months was evaluated as a primary endpoint and was superior in the PEFG-arm (60% vs. 28%, HR = 0.46). While median overall survival was nearly identical in both treatment arms, the proportion of patients surviving at 1 year was greater in the PEFG-group (38.5% vs. 21.3%). Further three trials were performed to evaluate the efficacy of GEM combined with a fluoropyrimidine plus oxaliplatin or irinotecan.20–22 They induced median overall survival times in the range of 7.5 to 8.3 months and reported 1-year survival rates of 25% and 33%. The efficacy parameters favor polychemotherapy compared to GEM alone. However, with regard to survival, the benefit appears to be less clear as observed in the FOLFIRINOX regimen. None of the indicated studies reported inclusion criteria as rigorous as reported for the Conroy study.23

5-Fluorouracil-based regimen

Since Burris and coworkers had demonstrated that 5-fluorouracil (5-FU) was significantly inferior to GEM, this agent appeared to have lost clinical relevance in the treatment of PC.14 It needs, however, to be mentioned that application of 5-FU as a bolus-regimen most probably represents the least effective way, this agent can be applied. Subsequently performed studies provide more insight into the topic of infusional 5-FU regimens. Ducreux and coworkers performed a randomized trial comparing bolus 5-FU (500 mg/m²/day for 5 days) to an infusional 5-FU regimen (1000 mg/m²/day for 5 days) plus cisplatin 100 mg/m² on day 1 or day 2) in 207 patients with advanced PC. Median overall survival was short and comparable in both treatment arms (102 vs. 112 days).24 The combination of 5-FU plus mitomycin was investigated by Maisey and coworkers in a randomized phase III study using 5-FU in the control arm. In both treatment arms, 5-FU was applied as a protracted venous infusion (300 mg/m²/day for a maximum of 24 weeks). Also in this trial, the combination arm failed to induce a significant survival benefit compared to 5-FU alone (5.1 months vs. 6.5 months, P = 0.34).25 These studies lead to the conclusion that neither infusional 5-FU alone nor its combination with cisplatin or mitomycin C induced a major improvement of survival in PC.

In this context, a three-armed randomized phase II study is important which compared the efficacy of the single agents 5-FU (1000 mg/m²/day continuous infusions days 1–4) and oxaliplatin (130 mg/m² day 1) to the combined application of both drugs (OXFU).26 Median overall survival was markedly higher in the OXFU-combination arm (9.0 months) than with 5-FU (2.4 months) or oxaliplatin (3.4 months) alone. This trial, for the first time, demonstrated in PC that clinically relevant efficacy can be achieved by
the combination of 5-FU plus oxaliplatin, while the respective single agents were essentially ineffective. A critical view of this study is, however, recommended not only because of the very low number of patients included (n = 63), but also because of a major imbalance of tumor stage in the three treatment groups (Table 2). The clinical efficacy of infusional 5-FU/leucovorin combined with oxaliplatin (OFF-regimen) was later confirmed in the 2nd-line treatment of PC patients.\(^\text{30}\)

Capecitabine plus oxaliplatin (CapOx)

The first randomized study to evaluate the oral fluoropyrimidine capecitabine in combination with oxaliplatin (CapOx) as a palliative first-line treatment was a German AIO trial (Table 2). CapOx was compared to the combination of capecitabine plus GEM (Cap/Gem) or the combination of GEM plus oxaliplatin (mGemOx). Similar clinical efficacy was observed for the three drug combinations with regard to PFS (4.2, 5.7, 3.9 months) and overall survival (8.1, 9.0, 6.9 months). Expectedly, significant differences were observed in toxicity profiles, but side-effects were manageable.\(^\text{28}\) In the setting of second-line treatment, the clinical activity of CapOx was moderate (PFS = 2.3 months, OS = 5.4 months)\(^\text{31}\) (Table 2).

Irinotecan-based chemotherapy

The evidence on the activity of irinotecan in PC is limited (Table 3). Among others, this may be due to two randomized trials demonstrating that the addition of irinotecan to GEM did not increase treatment efficacy compared to GEM alone.\(^\text{32,33}\) Due to the remarkable clinical activity of the FOLFIRINOX regimen the question arises to which extent irinotecan is responsible for this effect. Some evidence may come from a phase II study by Taieb and coworkers\(^\text{34}\) who investigated a modified FOLFIregimen (FOLFIrI3) where irinotecan (90 mg/m\(^2\)) was applied on days 1 and 3 of a 2-week schedule. This regimen showed high efficacy (ORR 37.5%, PFS 5.6 months, OS 12.1 months) in the first-line treatment of advanced PC which needs, however, to be verified by controlled trials. In a randomized study performed in the setting of second-line treatment, a dose-reduced FOLFIRI3 regimen showed only moderate activity which was comparable to that of a modified FOLFOX regimen.\(^\text{18}\)

FOLFIRINOX a new treatment standard

It is the merit of Conroy and coworkers to have introduced the FOLFIRINOX regimen, a combination of infusional 5-FU/folinic acid, irinotecan, and oxaliplatin, into the treatment of metastatic PC.\(^\text{23}\) In a randomized phase III trial, FOLFIRINOX was compared to single-agent GEM and demonstrated the clear superiority of FOLFIRINOX with regard to objective response rate (31.6% vs. 9.4%, \(P < 0.001\)), progression-free survival (6.4 months vs. 3.3 months; HR 0.47, \(P < 0.001\)) and overall survival (11.1 months vs. 6.8 months; HR 0.57, \(P < 0.001\)). Also 1-year survival was markedly greater in the FOLFIRINOX- compared to the GEM arm (48.4% vs. 20.6%) (Table 4). While, the therapeutic activity achieved by FOLFIRINOX is unprecedented in randomized studies investigating metastatic PC, it is supported by a previous phase II study from the same group which provided nearly identical results (ORR = 26%, time to progression 8.2 months, overall survival 10.2 months).\(^\text{59}\) In addition, the results are credible because the efficacy parameters obtained in the GEM arm fit very well to previously published data\(^\text{23}\) (Table 4). Expectedly, the toxicity associated with the FOLFIRINOX regimen was greater than with GEM alone. Specifically, grade 3–4 neutropenia (45.7% vs 21%, \(P < 0.001\)) and febrile neutropenia (5.4% vs. 1.2%, \(P = 0.03\)) were more frequent in the combination arm and required the application of granulocyte colony stimulating factor (G-CSF) in 42.5% vs. 5.3% (\(P < 0.001\)). Also, the incidence of grade 3–4 thrombocytopenia, diarrhea, and sensory neuropathy was significantly greater in the FOLFIRINOX group. The treatment-associated mortality was, however, low with only one toxic death reported in each arm.

The expectedly higher toxicity of the FOLFIRINOX regimen did not appear to have a significant impact on global health status and quality of life. Only diarrhea had higher scores during the first eight cycles of combination treatment. In addition, time to definitive degradation of global health status/quality of life was significantly longer in the FOLFIRINOX-arm. Certainly, it cannot be excluded that this observation represents, at least in part, a carry-over effect of the improved progression-free survival. However, it also may support the conclusion that, specifically in a highly malignant disease like PC, treatment efficacy is a more important determinant of quality of life than treatment-associated toxicity.

Reviewing the Conroy study the question arises, how these results can be explained in view of the numerous studies on combination chemotherapy reported in the literature. The clinical relevance of the Conroy study can probably be best understood by an evaluation of the inclusion criteria. In contrast to the majority of published studies, the Conroy trial is limited to patients with metastatic PC. In fact, GEM-based combinations such as the GemOx regimen did not induce a clear benefit in locally advanced compared to metastatic PC.\(^\text{20}\)

The expected intensity of the polychemotherapy regimen required strict observation of rigorous selection criteria. Specifically, hyperbilirubinemia needed to be excluded to avoid irinotecan-associated toxicity. The results of the Conroy study are therefore valid only for previously untreated patients aged 18–75 years with a good performance status (ECOG status score of 0 or 1), nearly normal bilirubin (<1.5 upper limit of normal) and without a history of ischemic cardiac disease. The exclusion of hyperbilirubinemia caused an important shift in patient selection in that the rate of patients with tumors of the pancreatic head (38%) and those with biliary stents was relatively low (14.3%). By comparison, other studies have reported a rate of pancreatic head tumors in the range of 52% to 70% (Table 5). This stringent patient selection may also be the reason why, despite a markedly increased rate of neutropenia in the FLOFIRINOX arm, no cholangitis was observed throughout the study. In addition, education, monitoring and active management of study centers may have contributed to a remarkably low mortality rate (2/342).

In conclusion, the Conroy study reflects only a limited spectrum of the clinical reality. Through its selection criteria the results of the study are therefore applicable only for selected patients. In addition, the clinical use of FOLFIRINOX requires specialized centers experienced in the supportive care of patients with an elevated risk of neutropenic infections. The Conroy study also entails a perspective regarding the development of PC treatment. For the first time, a GEM-free combination chemotherapy has successfully been used in a randomized phase III trial. This study therefore paved the way for future regimens not incorporating GEM. In addition, the high efficacy of FOLFIRINOX in the metastatic setting, for the first time, provides a sufficiently strong rationale to investigate intensive polychemotherapy in the context of multidisciplinary perioperative treatment.

Inhibitors of the epidermal growth factor receptor (EGFR)

Inhibition of the EGFR has become an established treatment strategy in several solid tumors such as colorectal- or lung cancer. In PC both, the anti-EGFR directed antibody cetuximab and the oral
EGFR tyrosine kinase inhibitor erlotinib were tested in several randomised trials. Only the combination of GEM with erlotinib proved to be effective and was registered for treatment of metastatic PC.

**Gemcitabine plus erlotinib**

Moore and coworkers performed a randomized trial to compare GEM plus erlotinib versus GEM alone. The addition of erlotinib to GEM induced a statistically significant improvement of progression-free (HR = 0.77, P = 0.004) and overall survival (HR = 0.82, P = 0.038), while objective response rate was not significantly different between treatment arms. Since overall survival of LAPC patients was only marginally affected (HR = 0.94), registration of GEM plus erlotinib was limited to metastatic disease in Europe. Despite the statistical superiority of the combination, its effect on median survival time was rather low (6.24 months vs. 5.91 months; Δ = 0.33 months) which remains the source of controversial debates. In this context, it was of interest to note that patients with a rash grade ≥2 derived the greatest benefit from the addition of erlotinib, while survival remained short if no rash was evident (10.5 vs. 5.3 months). Rash of all grades was observed in 70% of patients and usually developed during the first 2–4 weeks of treatment. In the PA3 study the dose of erlotinib was limited to 100 mg/day since at the dose of 150 mg/day 11 of 23 patients required dose reductions because of toxicity. A later study by Boeck et al.51 GEM + axitinib Phase III 316 25 5 4.4 8.5 na

The German AIO PK0104 trial compared first-line treatment with GEM plus erlotinib to capetitabine plus erlotinib. At disease progression, patients were scheduled to cross over to the respectively other chemotherapy, while treatment with erlotinib was stopped. This study indicated that both treatment strategies induced nearly identical survival times (6.6 months vs. 6.9 months). First-line treatment with GEM/erlotinib was, however, more effective than erlotinib/placebo regimen. This indicates that the addition of erlotinib to GEM induces a statistically significant improvement of progression-free and overall survival, while its effect on median survival time is rather low.

**Inhibition of angiogenesis**

The combination of angiogenesis inhibitors such as bevacizumab or axitinib with GEM-based regimens has essentially failed to improve survival in advanced PC patients. Again, it became clear that promising data obtained at the phase II level did not necessarily translate into a statistically and clinically relevant survival benefit when tested in phase III studies. It has been argued that PC in most cases represents a hypovascularized tumor where inhibition of angiogenesis as a modulator of tumor growth is a priori ineffective. On the other hand, it cannot be excluded that GEM is an inappropriate combination partner for angiogenesis inhibitors and that a fluoropyrimidine-based chemotherapy backbone may lead to a different outcome. Last but not least, it may be hypothesized that the lack of predictive factors did not allow a proper selection of those patients who would have responded to angiogenesis inhibitors. This topic was addressed in a randomized study comparing GEM/erlotinib plus bevacizumab to GEM/erlotinib plus placebo. The addition of bevacizumab had no significant effect on overall survival when the whole study population was analyzed (HR 0.89, P = 0.21). However, bevacizumab significantly prolonged survival in patients whose tumors were located in the tail of the pancreas (HR 0.54, P = 0.0025) or those who presented with elevated levels of baseline CRP (HR 0.65, P = 0.0009) or lactate dehydrogenase (HR 0.59, P = 0.0013). From this observation the authors concluded that perhaps patients with more aggressive disease, as indicated by elevated CRP or LDH, might benefit to a greater extent from bevacizumab than others.

**Targeting the stroma**

Pancreatic cancer is characterized by hypovascularity and desmoplastic stroma which both may contribute to impaired drug delivery and subsequent resistance to chemotherapy. An innova-

**Table 6**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Study design</th>
<th>No of pts</th>
<th>LAPC (%)</th>
<th>ORR (%)</th>
<th>PFS/TTP (mo)</th>
<th>OS (mo)</th>
<th>1-Year survival (%)</th>
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<td>3.4</td>
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</table>

GEM, gemcitabine; Bev, bevacizumab; LAPC, locally advanced pancreatic cancer.

tive approach to deplete stromal tissue has been introduced by clinical application of nab-paclitaxel. Preclinical evidence supports the assumption that intratumoral uptake of nab-paclitaxel is facilitated through binding of albumin to SPARC (secreted protein acidic and rich in cysteine). This extra-cellular matrix glycoprotein is expressed in the peritumoral stroma and at the invasion front of tumors and is involved in cell migration, proliferation, angiogenesis and tissue remodeling. The rationale to use nab-paclitaxel in PC is based on molecular analyses demonstrating overexpression of SPARC in pancreatic tumors. Previous work by Infante and coworkers had shown that the expression of SPARC in peritumoral fibroblasts was a negative prognostic factor in patients with resected PC, while SPARC expression in tumor cells did not appear to correlate with survival.

The clinical efficacy of nab-paclitaxel in metastatic PC was recently investigated by von Hoff and coworkers in a phase I/II trial. At the maximal tolerated dose (MTD) (GEM 1000 mg/m² plus nab-paclitaxel 125 mg/m² once a week for three weeks every 28 days) a response rate of 48% was achieved which was accompanied by a PFS of 7.9 months, an OS of 12.2 months and a 1-year survival rate of 48%. A phase III trial is presently ongoing to confirm these promising results. In human PC xenograft models treated with GEM plus nab-paclitaxel, depletion of desmoplastic stroma was associated by increased drug delivery leading to a 2.8-fold increase of intratumoral GEM concentrations.

This treatment approach is in line with another stroma-directed strategy that aims to facilitate drug delivery by improved tumor perfusion. Paracrine hedgehog signaling from pancreatic tumor cells notably induces stromal cells to form desmoplastic tissue. Preclinical data suggest that inhibition of hedgehog signaling causes stromal depletion and subsequent stimulation of angiogenesis. As a result, increased vascular density and improved tumor perfusion may augment delivery and efficacy of chemotherapeutic agents.

Several clinical studies are presently ongoing to test this hypothesis in PC patients (Table 7).

Second-line treatment

An evaluation of 2nd-line therapy in randomised trials indicates that 16–57% of PC patients did receive salvage chemotherapy after failure of 1st-line GEM. Median survival in GEM-resistant patients receiving best supportive care was 2.3 months in a small randomised trial. Meanwhile, several clinical studies (mainly phase II) support the clinical efficacy of 2nd-line treatment with overall survival times of 3–9 months (calculated from the start of second-line therapy) and PFS/TTP durations of 2–5 months. Gem-resistant patients in good performance status and with high motivation should therefore be offered 2nd-line regimens preferably consisting of fluoropyrimidines plus oxaliplatin. Patients not tolerating 2nd-line combination therapy may receive fluoropyrimidines alone.

Only limited data are available on how to treat patients after progression on FOLFIRINOX therapy. The rate of 2nd-line treatment in the phase-III trial by Conroy and coworkers was 47% in the FOLFIRINOX-arm and 50% in the GEM arm. The most common 2nd-line regimens after FOLFIRINOX were GEM (82.5%) or GEM-based combinations (12.5%).

Based on this observation it may be speculated that neither intensity nor efficacy of first-line therapy are critically important for the implementation and outcome of second-line therapy.

Prognostic and predictive factors

Prognostic factors are patient- and tumor related factors that predict patient outcome (mostly survival) independent of treatment. By contrast, predictive factors predict response of the tumor to treatment (measured in terms of tumor size or survival).

Optimal management of metastatic PC includes the evaluation of these parameters for optimal guidance of therapy. The following analyses differentiate parameters determined before the start of treatment (baseline parameters) from those obtained during treatment (dynamic parameters).

Baseline parameters of the patient

Among baseline parameters, specifically performance status has gained some attention and has been discussed as one of the most prominent prognostic factors in advanced PC. In fact, there is some evidence indicating that only patients with a good performance status (ECOG 0–1) derive a significant benefit from combination chemotherapy (HR = 0.76, p < 0.0001), while patients with a poor performance status do not (HR = 1.08, p = 0.40). This conclusion is supported by most studies performing a separate analysis of good- and bad performance patients. It was, however, contradicted by a recent Italian study where the combination of GEM plus cisplatin was not superior to GEM alone independent of the performance status.

Further baseline parameters such as CA 19-9, LDH and CRP have been identified to correlate with survival, but are not ready to determine the choice of treatment. In the FOLFIRINOX-trial

Table 7

<table>
<thead>
<tr>
<th>Studies</th>
<th>Design of study</th>
<th>Regimen</th>
<th>No of pts</th>
<th>Overall survival (months)</th>
<th>Level of significance</th>
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<td>PA3 study</td>
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<td>6.6 vs. 6.9</td>
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<td>Intergroup trial</td>
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<td>372</td>
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<td>5.0 (grade 0–1)</td>
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<td>GEMOXCE trial</td>
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<td>64</td>
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GEM, gemcitabine; PA3 study, gemcitabine/erlotinib vs. gemcitabine; AVITA study, gemcitabine/erlotinib ± bevacizumab; Cross-over AIO study, gemcitabine/erlotinib vs. capcitabine/erlotinib; Intergroup trial S0205, gemcitabine plus cetuximab vs. gemcitabine.

Molecular parameters of the tumor

Specifically, when targeted therapies are employed, the question arises to which extent the expression or amplification of tumor-related targets can be used to predict outcome. So far, only few reports are available focussing on this topic. A first data set has been generated from the PA.3 study which compared GEM plus erlotinib to GEM plus placebo. This analysis was compromised by a low retrieval rate of tumor probes allowing molecular analyses only in small subsets of patients. Among evaluable patients, EGFR amplification or high polysomy were observed in 47%, and KRAS mutations in 79% of tumors. Neither EGFR-IHC, nor EGFR-FISH or KRAS mutation status were significantly related to outcome. The retrospective nature of this investigation, the low percentage of KRAS wild-type tumors combined with the low availability of tumor probes are relevant limitations to these analyses.

Molecular parameters of the EGFR pathway were also analyzed in the AIO cross-over trial which compared GEM/erlotinib to capcitabine/erlotinib. Again, this study did not show a significant correlation between EGFR-IHC or EGFR-FISH and survival. KRAS mutations (all in codon 12) were observed in 70% of tumors. In univariate biomarker analyses, KRAS mutation status was significantly associated with overall survival favoring KRAS wild-type patients (HR 0.60 P = 0.005). This observation supports the role of KRAS as a predictor of response to erlotinib, but needs to be verified in a controlled prospective study.

An important step into the molecular classification of PC has recently been described by Collisson and coworkers. This group performed a molecular analysis of pancreatic tumors and identified three subgroups characterized by distinct gene signatures: (1) the classical type with a high expression of adhesion-associated and epithelial genes, (2) the quasi-mesenchymal type showing high expression of mesenchyme-associated genes, and (3) the exocrine-like subtype expressing tumor cell-derived digestive enzyme genes. These subgroups were not only different with regard to clinical outcome; first analyses performed in cell lines also suggest different response to treatment. Given that these data are verified, a new door is opened for stratified treatment of PC patients according to the molecular signature of their tumors.

Pharmacodynamic parameters

GEM is a nucleoside analog which requires specific membrane transporter proteins for active uptake into the tumor cell. Among these, the human equilibrative nucleoside transporter 1 (hENT1) and, to a lesser degree, the human concentrative nucleoside transporter 3 (hCNT3) have been identified as important determinants of sensitivity to GEM. Accordingly, data obtained in vitro showed resistance to GEM in tumor cells lacking hENT1 expression. These results were supported by clinical analyses indicating a significantly less favorable outcome in tumors without hENT1 expression.

Evaluation of dynamic parameters during therapy

Several parameters may help to guide treatment decisions during therapy. Among others, CA 19-9 kinetics, performance status, body weight and pain have been reported as useful markers to define treatment efficacy in combination with imaging. While an elevated pretreatment level of CA 19-9 has been identified as an independent negative prognostic factor in several studies, the clinical relevance of CA 19-9 kinetics during therapy is more controversial. Several authors reported prolonged survival in CA 19-9 responders defined e.g. by a >20% reduction of CA 19-9 baseline levels within the first 8 weeks of treatment. This was, however, not confirmed by others.

Erlotinib-induced skin toxicity

An important dynamic parameter evolving during therapy is erlotinib-induced skin toxicity. It typically develops during the initial 4 to 8 weeks of anti-EGFR directed treatment (Table 8). In the PA.3 study, 36% of patients developed skin toxicity grade ≥2. These patients had a median survival which was 5 months longer than that of patients without skin toxicity (10.5 months vs. 5.3 months, P < 0.001). Also the rate of 1-year survival was nearly 3-fold greater in patients with skin toxicity grade ≥2 (43% vs. 16%, P < 0.001). Patients with a good performance status (P = 0.03) and those younger than 65 years (P = 0.01) were more likely to develop skin rash in the PA.3 trial.

A Spanish single-arm phase II study (n = 156) indicated that patients with skin toxicity grade 1 lived markedly longer than patients without any skin toxicity (6.8 months vs. 3.8 months, P < 0.001). Also this study could show that skin toxicity ≥2 was associated with prolonged survival when compared to skin toxicity grade <2 (10.2 months vs. 5.0 months, P = 0.001). Since grading of skin toxicity is, to some extent, subjective and may also depend on

### Table 8

<table>
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<th>Clinical trial identifier</th>
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<th>Regimen</th>
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<td>PFS</td>
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<td>Preoperative setting</td>
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<td>Effect of treatment on stromal cell and tumor cell hedgehog signaling</td>
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<td>NCT01064622</td>
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<td>Recurrent or metastatic disease</td>
<td>GEM ± GDC-0449</td>
<td>118</td>
<td>PFS</td>
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Nab-paclitaxel, nano-particle albumin-bound paclitaxel; GDC-0049, oral small-molecule inhibitor of the hedgehog pathway; OS, overall survival; PFS, progression-free survival.

Treatments of Metastatic Pancreatic Cancer

![Fig. 1. Treatment of metastatic pancreatic cancer. GEM, gemcitabine; 5-FU/FA, 5-fluorouracil + folinic acid; Cape, capecitabine; OFF, oxaliplatin + 5-fluorouracil + folinic acid; FOLFOX, 5-fluorouracil, folinic acid, oxaliplatin; FOLFIRINOX, 5-fluorouracil + folinic acid + oxaliplatin + irinotecan. “Only in patients who meet the inclusion criteria of the Conroy study: metastatic disease, age <75 years, ECOG 0–1, bilirubin <1.5 UNL.

The available data also demonstrate that the survival times (4–5 months) of non-rash patients are lower than expected for an unselected patient population treated with single-agent GEM. This observation entails several considerations: first, non-rash patients represent a poor-prognosis subgroup; second, a negative interaction of GEM and erlotinib cannot be excluded and requires alternative regimens to be explored; third, due to the short survival of this poor prognosis subgroup, treatment decisions should be made early to allow an appropriate benefit.80

Perspective for the design of future clinical trials

According to a consensus report of the National Cancer Institute of the United States, harmonization of clinical trials with respect to patient populations is sought to reduce heterogeneity between studies.81 Comparability between studies may markedly be improved given that the following recommendations are realized: 1) Patients with locally advanced and metastatic disease should be investigated in separate trials. 2) Patients with unfavorable ECOG performance status (ECOG PS ≥ 2) should be studied in separate and appropriately designed clinical trials. 3) Additional patient characteristics such as weight loss or nutritional status should be given more consideration in the selection strategy; 4) Early withdrawal from the study without receiving meaningful treatment should be considered in separately performed subgroup analyses. 5) Harmonization of eligibility criteria should be performed across trials.82 6) With the availability of 2nd- and 3rd-line treatment options post-study treatment should be documented and reported in studies investigating overall survival as a primary endpoint. 7) Future trials need to incorporate translational research as a major driving force of clinical research.83 This requires not only the prospective collection of tumor- and blood samples, but also upfront introduction of translational endpoints into the trial design. A major task of the future consists in the identification and validation of prognostic and predictive biomarkers which may help to define clinically relevant subgroups of PC.

How to treat advanced pancreatic cancer in daily clinical practice (Fig. 1)?

At present time, only GEM and erlotinib are registered for treatment of advanced pancreatic cancer. According to the European registration, the use of erlotinib is limited to patients with metastatic PC. Given that erlotinib is not available in all European countries, single-agent GEM remains the standard reference treatment of advanced PC.

A treatment algorithm may be based on a primary evaluation of the performance status: (1) We recommend not to apply chemotherapy or at least to question its use in patients with a Karnofsky performance status (KPS) < 60%. (2) In patients with a KPS 70%-80%, GEM can be applied as a single agent or in combination with erlotinib. Treatment with erlotinib should be re-evaluated according to the development of rash after 4–8 weeks and should be stopped if no rash occurred. (3) Patients with a very good KPS of 90–100% and high motivation may be offered intensive polychemotherapy with the FOLFIRINOX regimen if the inclusion criteria defined in the Conroy study are met, otherwise they should receive treatment with GEM (plus erlotinib).

At disease progression, all patients should be offered second-line therapy which can be performed with single agents or combination chemotherapy according to performance status, overlapping side effects from previous therapy and patient wish (Fig. 1). As a general measure we recommend early use of supportive and psycho-social care to control pain, to stabilize body weight and to improve the psycho-social condition of the patient.

References


