Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer

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Neoadjuvant therapy is increasingly becoming a valid treatment option for patients with locally advanced pancreatic cancer (LAPC). In borderline resectable disease, neoadjuvant therapy is employed to improve the probability of margin-clear resections. In non-metastatic, non-resectable pancreatic cancer, treatment primarily aims to induce disease control, but may achieve conversion to surgical resectability in some patients. Several treatment modalities including chemotherapy, chemoradiotherapy (CRT) or the sequential use of both have been investigated in numerous, mostly small and non-randomized studies. Nevertheless, there is a consistent finding that neoadjuvant therapy can induce resectability in up to 30%–40% of LAPC patients. Once resection has been achieved, overall survival appears to be comparable to that observed for primarily resectable patients. Thus, patient selection evolves as an important aspect of neoadjuvant therapy; retrospective analyses identified induction chemotherapy as an appropriate tool to define LAPC patients who may benefit most from subsequent treatment with CRT. The clinical importance of induction chemotherapy may further increase once highly active protocols such as the FOLFRINOX or the gemcitabine plus nab-paclitaxel regimen are introduced into novel multimodality treatment concepts.

Key words: chemoradiotherapy, chemotherapy, neoadjuvant, pancreatic cancer

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introduction

At first diagnosis, only 10%–20% of pancreatic cancer (PC) patients present with primarily resectable disease, and locally advanced, non-metastatic PC (LAPC) is observed in up to 30% of patients [1]. Median overall survival (OS) of primarily resectable patients currently is in the order of 20–24 months, while survival is only 9–13 months in LAPC. Several autopsy studies suggest that 8%–15% of PC patients die with locally advanced disease and without metastatic spread [2]. LAPC was previously defined as non-metastatic, but surgically unresectable disease. More recently, this entity was further subdivided into borderline resectable and non-resectable disease. Compared with primarily resectable PC, borderline resectable disease is characterized by a higher risk of margin-positive resection and accordingly is associated with a higher risk of recurrence. As a result, the prognosis of borderline resectable patients is expected to be significantly better than that of non-resectable patients, but is significantly worse than that of resectable patients [3]. The present review therefore asks the clinically relevant question if the prognosis of borderline resectable and also non-resectable PC patients can be improved with the use of novel neoadjuvant treatment approaches.

diagnostic workup of LAPC patients

The diagnosis of LAPC requires dedicated, high-quality imaging implemented by pancreatic protocol computerized tomography (CT) [4]. A recent consensus statement proposed 3D imaging of the pancreas and the associated mesenteric vessels by multidetector CT as state of the art modality [5]. In selected cases, additional information may be required from endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography. Tumour resectability should be determined by multidisciplinary tumour boards. They will also estimate the probability to achieve tumour-free resection margins and can accordingly decide on the necessity to perform neoadjuvant therapy. Decision-making must also account for patient-related parameters such as performance status, comorbidity and compliance [6]. Before the start of therapeutic interventions, a histological confirmation of pancreatic adenocarcinoma is mandatory [4, 5]. This is preferably done by EUS-guided fine-needle aspiration (FNA) biopsy, but can also be achieved by CT-guided core needle biopsy. The additional use of staging laparoscopy to exclude peritoneal metastasis in LAPC patients has been suggested by some authors, but is not generally accepted [5].

definition of borderline resectable and non-resectable PC

Katz et al. assessed 2454 PC patients and classified 160 patients (7%) as borderline resectable [6]. The difficulty to provide a clear definition of borderline resectable PC is characterized by its denomination as ‘the imprecise continuum between radiologically and technically resectable and unresectable disease’ [6]. While different terminologies have been used to describe this entity, the underlying premise is that tumour down-staging is needed to achieve R0 resection in borderline resectable PC [7].

definition according to the NCCN guidelines (version 2.2012)

The definition of borderline resectable tumours includes the following characteristics: (i) no distant metastases; (ii) venous involvement of the superior mesenteric vein (SMV) or portal vein demonstrating tumour abutment with impingement and narrowing of the lumen, encasement of the SMV/portal vein, but without encasement of the nearby arteries, or short-segment venous occlusion resulting from either tumour thrombus or encasement, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction; (iii) gastroduodenal artery encasement up to the hepatic artery with either short-segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; (iv) tumour abutment of the superior mesenteric artery (SMA) not to exceed >180° of the circumference of the vessel wall [4]. By contrast, non-metastatic pancreatic tumours are considered non-resectable if the following characteristics are fulfilled: (i) >180° SMA- or celiac artery encasement; (ii) unreconstructable SMV/portal vein occlusion; (iii) aortic invasion or encasement; (iv) metastases to lymph nodes beyond the field of resection [4].

MD Anderson classifications of borderline resectable PC

In addition to the purely radiological criteria of the NCCN guidelines, Katz et al. [6] initially included more patient-related factors and proposed a subgrouping of borderline resectable patients into three distinct subtypes: Group A was defined by radiological criteria including tumour abutment of the visceral arteries or short-segment occlusion of the SMV. In group B, patients had findings suggestive, but not diagnostic of metastasis, and group C was characterised by medical comorbidities and marginal performance status (supplementary Table S1, available at Annals of Oncology online). The attribution of patients to the MD Anderson subsets was specifically important with regard to the duration of neoadjuvant treatment, which was markedly shorter in group C compared with groups A or B (4 versus 16 versus 15 weeks, \( P = 0.002 \)). More recently, also the MD Anderson group has focused on a primarily radiographic-based definition of borderline resectable PC; however, a uniformly accepted set of criteria that define patients with borderline resectable disease still does not exist [8].

outcome of borderline resectable patients

Evidence regarding outcome of borderline resectable PC patients is limited. Katz reported on 160 patients that had a median OS of 18 months and a 5-year survival rate of 18%. Among this patient group, 41% underwent surgical tumour resection and had an OS of 40 months. In non-resected patients, median OS was much shorter and reached only 13 months [6]. Survival data with regard to the MD Anderson groups A, B and C are also summarized in supplementary Table S1, available at Annals of Oncology online.
strategies to apply neoadjuvant therapy

Due to the lack of randomized studies, the optimal performance of neoadjuvant therapy remains a matter of debate. Patients with borderline resectable tumours principally have the choice of upfront surgery. However, the risk of margin-positive resection is substantial in this group of patients and is related to an unfavourable outcome. Accordingly, there is a general assumption that neoadjuvant therapy is specifically beneficial in borderline resectable tumours and improves the fraction of resectable tumours. In their evaluation of 160 patients with borderline resectable PC, Katz et al. [6] reported that 78% completed preoperative therapy and restaging, and 41% underwent pancreatectomy. In initially non-resectable disease, treatment primarily aims to achieve tumour control and may become eligible for surgery. Regular evaluation of secondary resectability therefore remains an important task specifically in responding patients. At present time, there is hardly any evidence to demonstrate the differential benefit from neoadjuvant therapy in borderline resectable versus non-resectable PC since most studies evaluated LAPC as one group. As local tumour reduction together with systemic tumour control remain primary goals in borderline resectable and unresectable patients, common treatment strategies may be employed initially in both entities.

The parameter of choice to judge the efficacy of conversion therapy is its ability to induce tumour response and to prevent tumour progression. Most studies investigating neoadjuvant therapy in PC have used chemoradiotherapy (CRT) as a concurrent application of systemic chemotherapy and radiation [9]. Owing to the development of more active regimens, also induction treatment with chemotherapy alone is in a process of evaluation.

chemotherapy alone in LAPC

Most of the randomized trials investigating gemcitabine-based combination chemotherapy in advanced PC not only included patients with metastatic disease, but also evaluated 20%–30% of LAPC patients. In four randomized trials, median survival of LAPC patients treated with chemotherapy alone was in the range of 9–12 months [10–13]. Gemcitabine-based combination chemotherapy induced higher response rates (26% and 27%) than single-agent gemcitabine (4% and 15%). In addition, response rates obtained in LAPC were at least as high as those observed in metastatic disease when identical regimens were applied (Table 1). This observation is in accordance with results of a meta-analysis obtained by Gillen et al. [9] in non-resectable LAPC patients: they reported that neoadjuvant treatment with combination chemotherapy resulted in a higher resection rate compared with single-agent chemotherapy (33% versus 27%).

chemoradiation in LAPC

The use of CRT alone in LAPC is based on limited evidence. One randomized study demonstrated the superiority of 5-fluorouracil (5-FU)-based CRT compared with best supportive care [14]. A meta-analysis of two randomized studies using outdated radiation regimens indicated that CRT prolonged survival compared with radiation alone [15–17].

Most studies used 5-FU as reference chemotherapy in combination with radiation doses of 50–60 Gy. Also the combination of gemcitabine with radiation has been investigated in multiple studies. Owing to the increased toxic effect of this regimen, a reduction of either chemotherapy- or radiation dose became necessary and so far prevented the definition of one standard regimen. A recent meta-analysis (three randomized studies and one retrospective comparative study) suggested that the combination of radiation with gemcitabine might be more effective than the combination with 5-FU [18].

Gillen recently evaluated 111 trials including 4394 PC patients [9]. Neoadjuvant therapy involved chemotherapy in 96% and radiation therapy in 94% of studies. For non-resectable patients, the estimated overall response rate was 35%. Given a stable disease rate of 42%, disease control was obtained in 77% of patients. Among patients with initially non-resectable tumours, surgical exploration was carried out in 47%. The overall resection rate after neoadjuvant therapy was 33%, of which 79% were carried out as R0 resections. By contrast, primarily unresectable patients, who were not resected, had a median OS of 10.2 months, while the 33% resected patients survived for a median of 20.5 months [9]. In summary, this analysis demonstrates that neoadjuvant therapy predominantly

<table>
<thead>
<tr>
<th>References</th>
<th>Regimen</th>
<th>LAPC</th>
<th>Metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR (%)</td>
<td>PFS/TTP (months)</td>
</tr>
<tr>
<td>Louvet [10]</td>
<td>Gem + Oxaliplatin 51</td>
<td>27.4</td>
<td>7.4</td>
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<tr>
<td></td>
<td>Gem 47</td>
<td>14.9</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Gem 24</td>
<td>4.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Poplin [12]</td>
<td>Gem 86</td>
<td>na</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>Gem + Oxaliplatin</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

LAPC, locally advanced pancreatic cancer; ORR, objective response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival; Gem, gemcitabine; FDR, fixed-dose rate.
applied as CRT can induce remissions in about one-third of LAPC patients. Tumour resection was achieved in one-third of LAPC patients and was associated with markedly prolonged survival which was comparable to that reported for initially resectable PC patients. Comparable data were also described by other systematic reviews and meta-analyses [19, 20]. Using more restrictive study selection criteria, Laurence et al. [20] determined an overall resectability rate of 40% after application of neoadjuvant CRT to patients with initially non-resectable PC. However, these authors also state that the quality of the currently available data is poor and that it is presently not possible to draw firm conclusions with regard to the benefit from neoadjuvant CRT.

upfront chemoradiation followed by gemcitabine versus gemcitabine alone in LAPC

The concept of upfront CRT is based on (i) improvement of tumour control, (ii) reduction of metastatic potential of the primary tumour and (iii) achievement of resectability. In their systematic review on the treatment of LAPC, Huguet et al. [21] concluded that upfront application of CRT was not superior to exclusive chemotherapy in terms of OS, but increased treatment-related toxic effects. Further data provided by two randomized studies comparing upfront CRT followed by gemcitabine to gemcitabine alone are inconclusive (Table 2): The FFCD/SFRO study randomly assigned patients either to 5-FU/cisplatin-based CRT followed by gemcitabine or to gemcitabine alone [22]. Owing to low recruitment, this study was stopped prematurely with 119 patients included. OS was markedly shorter in the CRT arm compared with the gemcitabine arm (8.6 versus 13 months, \(P = 0.03\)). The rather poor result obtained in the CRT arm was explained by its significantly greater treatment-related toxic effect resulting in a reduction of gemcitabine application compared with the chemotherapy-alone arm. In the maintenance phase, the median total dose of gemcitabine was only 46% (6,845 mg) in the CRT arm compared with the control arm (15,000 mg). The results of this study may be interpreted to the extent that upfront application of intensive CRT is counterproductive when it results in a major attenuation of subsequent systemic therapy.

The ECOG E4201 study compared gemcitabine-based CRT followed by gemcitabine to treatment with gemcitabine alone [23]. After enrolment of 74 patients, also this study was terminated early due to low accrual. No differences were obtained with regard to response rate (6% versus 5%) and median progression-free survival (PFS, 6.0 versus 6.7 months). However, the rate of stable disease at 3 months was greater (68% versus 35%) as was OS (11.1 versus 9.2 months, \(P = 0.017\)). Owing to the limited patient number, there was a wide overlapping of confidence intervals around the median OS; the results should therefore be interpreted with some caution [24]. Nevertheless, this small study might indicate that the addition of CRT to systemic therapy may have improved survival through an improvement of local control, while distant metastasis and with it PFS were not affected. On the other hand, the survival benefit induced by the addition of CRT to gemcitabine treatment was small (1.9 months) and points to the

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**Table 2. Randomized comparison of upfront CRT followed by chemotherapy versus chemotherapy alone in LAPC**

<table>
<thead>
<tr>
<th>References</th>
<th>Regimen</th>
<th>n</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
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<tbody>
<tr>
<td>Chauffert [22]</td>
<td>CRT(^a) → Gem</td>
<td>59</td>
<td>na</td>
<td>na</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Gem</td>
<td>60</td>
<td></td>
<td></td>
<td>13.0*</td>
</tr>
<tr>
<td>Loehrer [23]</td>
<td>CRT(^b) → Gem</td>
<td>34</td>
<td>6</td>
<td>6.0</td>
<td>11.1**</td>
</tr>
<tr>
<td></td>
<td>Gem</td>
<td>37</td>
<td>5</td>
<td>6.7</td>
<td>9.2</td>
</tr>
</tbody>
</table>

LAPC, locally advanced pancreatic cancer; Gem, gemcitabine; CRT, chemoradiation; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

\(^a\)CRT: 60 Gy plus concurrent chemotherapy with 5-fluorouracil/cisplatin.

\(^b\)CRT: 50.4 Gy plus concurrent chemotherapy with gemcitabine.

\(*P = 0.03; ** P = 0.017."

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The notion that locoregional tumour control expectedly has a small impact on outcome.

**sequence of chemotherapy followed by chemoradiation in LAPC**

About one-third of LAPC patients develop overt metastasis during the initial phase of treatment [25]. These patients are unlikely to benefit from locoregional treatment such as upfront CRT and rather require systemic chemotherapy. This is specifically true for CRT regimens where chemotherapy is mainly used as a radiosensitizing component and has low systemic anticancer therapy. Primary application of systemic chemotherapy therefore aims at tumour reduction and selection of patients without rapid development of distant metastasis.

Two retrospective studies suggested that induction chemotherapy followed by CRT in selected patients may be an optimal neoadjuvant approach for LAPC (Table 3). Huguet et al. [25] evaluated LAPC patients and investigated whether initial chemotherapy could be used to select patients who would benefit from subsequent CRT. LAPC patients were analysed after an initial chemotherapy of at least 3 months; 29% of patients developed metastasis after three months of chemotherapy and therefore were not eligible for CRT. Among the remaining patients with non-metastatic disease, those who received subsequent CRT had a markedly better outcome than those who continued on chemotherapy alone (OS: 15.0 versus 11.7 months, \(P = 0.0009\)). These data are in line with another retrospective analysis by Krishnan et al. [26]. The authors analysed 323 consecutive LAPC patients that were either treated with CRT as initial therapy (\(n = 247\)) or had received induction chemotherapy with gemcitabine for a median duration of 2.5 months before CRT (\(n = 76\)). Induction chemotherapy was associated with a significant improvement of PFS (6.4 versus 4.2 months, \(P < 0.001\)) and OS (11.9 versus 8.5 months, \(P < 0.001\)). Interestingly, the use of induction chemotherapy did not lead to a significant difference in the pattern of recurrence [26]. In support of this rationale, Katz et al. [6] proposed a treatment algorithm including the sequential use of induction chemotherapy followed by CRT in non-progressing patients.

Recently, data from the first randomized phase II trial investigating a sequential approach of induction chemotherapy

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**References**


investigating 122 borderline resectable patients that received different preoperative treatment protocols 84 patients had a stable disease, 15 patients a partial response and 23 progressive disease by RECIST. Although only one patient had his disease down-staged to resectable status by imaging criteria, 85 patients were able to undergo pancreatectomy after surgical exploration (with 81 patients achieving a R0 resection) [28]. The authors therefore concluded that each patient with borderline resectable disease should undergo surgical exploration after neoadjuvant treatment in the absence of metastases.

surgery in initially non-resectable disease

The evaluation of surgical resectability after induction chemotherapy and/or CRT in patients with non-resectable disease may be a different one compared with the more aggressive approach for borderline resectable patients discussed above. An evaluation of surgical resectability (based on imaging modalities) should be carried out e.g. after induction chemotherapy and also after the completion of an eventual subsequent CRT (ideally within the setting of a multidisciplinary tumour board and with the goal of a R0 resection). There is currently no evidence available to support a ‘routine’ surgical exploration for the assessment of resectability in this patient population [21, 24].

innovative strategies to improve outcome in LAPC

Given the genetic complexity of PC, it is difficult to assume that improvement of locoregional treatment alone will make a major contribution to prolong survival [24]. Therefore, several new avenues are investigated to improve treatment efficacy in LAPC. One of them is the exploration of new and active chemotherapy regimens such as the FOLFIRINOX multidrug combination or the use of nab-paclitaxel combined with gemcitabine. Another option is to move into the direction of personalized medicine and to improve molecular patient selection.

FOLFIRINOX: a new strategy to improve treatment efficacy in LAPC

Conroy and et al. recently reported the high efficacy of the FOLFIRINOX regimen [29]. In a randomized phase III trial, exclusively carried out in metastatic PC, FOLFIRINOX was compared with single-agent gemcitabine and demonstrated its superiority with regard to objective response rate (32% versus 9%, P < 0.001), PFS (HR 0.47, P < 0.001) and OS (HR 0.57, P < 0.001). This phase III study essentially confirmed the data of a previous phase II study which had included both, LAPC and metastatic PC (Table 4). Interestingly, the response rate among 11 LAPC patients was nearly identical to that observed in 35 metastatic patients (27% versus 26%) [30].

Preliminary data on the efficacy of (neoadjuvant) FOLFIRINOX in LAPC are presently available from several retrospective and registry analyses (summarized in Table 4). Hosein et al. [31] reported a retrospective analysis of 18 patients with unresectable or borderline resectable LAPC. R0 resection after neoadjuvant FOLFIRINOX was achieved in 5

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**Table 3.** Sequential application of chemotherapy followed by CRT in three LAPC studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Type of study</th>
<th>n</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tbody>
<tr>
<td></td>
<td>→ CRT</td>
<td>analysis*</td>
<td>72</td>
<td>10.8</td>
<td>15.0</td>
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<td>Krishnan [26]</td>
<td>CRT</td>
<td>Retrospective</td>
<td>247</td>
<td>4.2</td>
<td>8.5</td>
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<tr>
<td></td>
<td>→ CRT</td>
<td>Gem-based CT</td>
<td>76</td>
<td>6.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Mukherjee [27]</td>
<td>Gem/Cap → CRT</td>
<td>Randomized</td>
<td>38</td>
<td>10.4</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>→ Cap-based CRT</td>
<td>phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LAPC, locally advanced pancreatic cancer; Gem, gemcitabine; PFS, progression-free survival; OS, overall survival; CT, chemotherapy; CRT, chemoradiation; Cap, capecitabine.

*Retrospective evaluation of 181 LAPC patients. After 3 months of chemotherapy, 53 patients (29%) developed metastatic disease and were excluded from the analysis.

followed by CRT became available: within the SCALOP study, 114 LAPC patients received a gemcitabine/capecitabine regimen as induction treatment, and subsequently 74 non-progressing patients were randomly allocated to a gemcitabine- versus a capecitabine-based CRT (50.4 Gy) approach [27]. Although this was a small phase II study, the obtained data suggested that a capecitabine-based CRT regimen might be preferable to a gemcitabine-based regimen in the context of consolidation chemoradiotherapy after a course of induction chemotherapy: patients in the capecitabine-based CRT arm not only had a longer PFS and OS (Table 3), but also a trend for a better quality of life and a lower rate of adverse events [27]. The efficacy data from SCALOP are in concordance with the results from the two previous retrospective LAPC analyses (Table 3); however, they stand in contrast to a meta-analysis which suggested that the combination of radiation with gemcitabine might be more effective than the combination with 5-FU [18].

**the role of surgery after neoadjuvant treatment in LAPC**

**surgery in initially borderline resectable disease**

In PC patients who receive neoadjuvant treatment for a tumour that initially was classified as borderline resectable the role of subsequent surgery is essential to achieve a long-lasting disease-free interval or even cure. In this context, the role of imaging as a basis for the decision to proceed to surgery after neoadjuvant treatment has to be discussed critically. There is increasing evidence that response of borderline resectable PC to neoadjuvant therapy is not necessarily reflected by standard radiographic indicators. In a recent single-centre study investigating 122 borderline resectable patients that received different preoperative treatment protocols 84 patients had a stable disease, 15 patients a partial response and 23 progressive disease by RECIST. Although only one patient had his disease down-staged to resectable status by imaging criteria, 85 patients were able to undergo pancreatectomy after surgical exploration (with 81 patients achieving a R0 resection) [28]. The authors therefore concluded that each patient with borderline resectable disease should undergo surgical exploration after neoadjuvant treatment in the absence of metastases.
of 18 (28%) of patients. Gunturu [32] reported on 16 LAPC patients that achieved an overall response rate of 50% and a disease control rate of 94%. This group modified the FOLFIRINOX regimen so that only 17% (6 of 35) of patients received full dose FOLFIRINOX at the first cycle. The authors concluded that despite routine dose modifications, the response to treatment was not significantly different from the historical control group previously reported by Conroy. Faris et al. evaluated 12 LAPC patients and observed a response rate of 42% [33]. Peddi and et al. [34] evaluated 23 borderline and non-resectable PC patients from a FOLFIRINOX registry (n = 61). The regimen was modified in about half of the patients beginning with the first cycle. Deletion of the 5-FU bolus and dose reduction of irinotecan were the two most common modifications applied. In spite of the dose reductions, FOLFIRINOX remained effective inducing either a partial remission or stable disease in the majority of patients (Table 4). Prophylactic growth factor support was given in 67% of patients beginning with the first cycle. Another 10% of patients received G-CSF in subsequent cycles. Given this support, grade 3–4 neutropenia was limited to 20% and only 3 of 61 patients (5%) developed neutropenic fever [34]. The latest report on the role of conventional FOLFIRINOX in LAPC was a prospective database analysis by Marthey et al.: preliminary data from the first 53 enrolled patients showed a response rate of 30% with a corresponding disease control rate of 83%. Sequential CRT was applied in 62% of patients and 32% underwent subsequent tumour resection [35]. It is of interest to note that throughout the various studies comparable response rates were obtained in LAPC and metastatic disease. These preliminary analyses, therefore, support the substantial activity of FOLFIRINOX also in LAPC and give rise to the expectation that response rates in the range of 25%–40% can be achieved by intensive chemotherapy alone [36]. Prospective studies are required to test the efficacy and tolerability of FOLFIRINOX in LAPC patients, also with regard to the use of more liberal inclusion criteria and with an optimal use of supportive therapy.

**nab-paclitaxel plus gemcitabine**

Von Hoff et al. [37] reported a phase I-II study evaluating the combination of gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel). This study was limited to patients with metastatic disease. However, the response rate of 48% and the median OS of 12.2 months obtained in 44 patients at the MTD level was encouraging and points to the substantial antitumour activity of this combination. It is hypothesized that the antitumour effect of nab-paclitaxel is mediated via depletion of the peritumoural stroma and a subsequently improved transport of chemotherapeutic agents such as gemcitabine to the tumour. The first publication of the phase III MPACT trial (gemcitabine versus gemcitabine plus nab-paclitaxel in metastatic PC) at the ASCO-GI meeting 2013 recently reported not only a significant increase in median OS for the combination (6.7 versus 8.5 months, P = 0.000015), but also a significant improvement in PFS (3.7 versus 5.5 months) and in the overall response rate (7% versus 23%) [38]. Nab-Paclitaxel thus may serve as an active drug for neoadjuvant treatment options in LAPC, e.g. also within a sequential approach combining gemcitabine/nab-paclitaxel (thereby inducing a stroma depletion) followed by FOLFIRINOX [39, 40].

**Patient selection based on molecular parameters of the tumour**

In an autopsy series the loss of Smad4/DPC4 expression was observed in only 22% of LAPC patients compared with 73% of patients with metastatic disease [2]. These data may relate to previous reports stating that Samd4 inactivation was associated with poorer survival in surgical series of PC [41, 42]. Crane reported a phase II study where 69 LAPC patients received initial chemotherapy with gemcitabine/oxaliplatin plus cetuximab followed by CRT plus cetuximab. Also in this study, Smad4 expression significantly correlated with a local rather than distant dominant pattern of disease progression [43]. In contrast, a retrospective translational study from a large surgical series (n = 471) showed that Smad4 expression was

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**Table 4. Efficacy of FOLFIRINOX in LAPC based on objective response rate**

<table>
<thead>
<tr>
<th>References</th>
<th>Study design</th>
<th>Stage of disease</th>
<th>n</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
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<td>Conroy [30]</td>
<td>Phase II</td>
<td>LAPC</td>
<td>11</td>
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<td>76</td>
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<tr>
<td>Peddi [34]</td>
<td>Registry</td>
<td>LAPC</td>
<td>18</td>
<td>6</td>
<td>28</td>
<td>50</td>
<td>17</td>
<td>34</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic</td>
<td>22</td>
<td>0</td>
<td>18</td>
<td>46</td>
<td>36</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>Marthey [35]</td>
<td>Prospective database</td>
<td>LAPC</td>
<td>53</td>
<td>0</td>
<td>30</td>
<td>53</td>
<td>17</td>
<td>30</td>
<td>83</td>
</tr>
</tbody>
</table>

LAPC, locally advanced pancreatic cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.
not correlated with recurrence pattern but was predictive for benefit from adjuvant chemotherapy [44]. Interestingly, the chemokine receptor CXCR4 was a strong independent prognostic biomarker associated with distant metastatic recurrence in this investigation. As inconclusive data on Smad4 have been reported from mainly retrospective studies [45], the need for prospective translational investigations (ideally conducted within prospective clinical trials) becomes evident. This specifically holds true for subentities like LAPC, where separate biomarker studies still are very rare [46]. However, if a predictor of early metastatic spread could be identified, patients without the predictor should be those to obtain the greatest benefit from intensified locoregional treatment, while patients at a higher risk of metastasis should rather receive systemic therapy [24].

**Summary**

High-level evidence from sufficiently powered randomized trials carried out in neoadjuvant treatment of LAPC is largely missing. In addition, conclusions from systematic reviews and meta-analyses are limited due to the lack of consistent definitions of unresectable versus borderline resectable disease between different studies. The available data therefore need to be viewed with caution, and firm conclusions can only be drawn once more mature evidence is provided. Nevertheless, the following summary may be helpful for treatment of LAPC in daily clinical practice (Figure 1): in borderline resectable patients, neoadjuvant therapy is intended to increase the probability of tumour-free resection margins. The primary goal of treatment in non-resectable patients is achievement of tumour control, but with increasing antitumour activity also conversion to resectability will move into the focus. The efficacy of neoadjuvant treatment as a conversion therapy may be judged based on its ability to induce radiographic tumour responses (mainly for non-resectable patients) or to enable a subsequent R0 resection (for borderline resectable PC), respectively. A clear superiority of single treatment modalities such as neoadjuvant CRT or chemotherapy cannot be defined at present. If chemotherapy alone is used, combination chemotherapy appears to achieve higher response rates than single-agent chemotherapy. New options arise with the development of the FOLFIRINOX regimen, while several cohort studies support the activity of FOLFIRINOX also in LAPC, this needs to be verified in prospective clinical studies.

**Figure 1.** Proposed treatment algorithm for LAPC patients outside clinical trials. In patients with borderline resectable PC, neoadjuvant treatment of about 2 months (with either chemotherapy or CRT) could be carried out in order to improve the R0 resection rate; subsequent surgical exploration is recommended for all patients without evidence for distant metastasis. In patients with non-resectable, non-metastatic PC induction chemotherapy for about 2-3 months is recommended; in patients with disease control, subsequent CRT should be delivered in order to improve local tumour response. A regular evaluation of surgical resectability based on radiographic findings is recommended after induction chemotherapy and after CRT. PC, pancreatic cancer; CT, chemotherapy; CRT, chemoradiotherapy.

**Disclosure**

The authors have declared no conflicts of interest.
Emerging approaches for treating HER2-positive metastatic breast cancer beyond trastuzumab

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Because metastatic breast cancer (MBC) is incurable in most cases, the goals of treatment are improvement in quality of life, management of symptoms, and prolonged survival. The human epidermal growth factor receptor 2 (HER2) is overexpressed in up to 30% of breast tumors, and before the development of HER-targeted therapy, HER2 positivity was predictive of poorer clinical outcomes. Trastuzumab and pertuzumab (anti-HER2 monoclonal antibodies), lapatinib (a small molecule inhibitor of HER2 and the epidermal growth factor receptor [EGFR]) are approved for treating HER2-positive MBC in the United States. Although trastuzumab plus chemotherapy is currently regarded as the first-line standard of care for HER2-positive MBC, it is not without shortcomings; these include its association with certain adverse events (e.g. cardiotoxic effect) and development of resistance. A number of investigational agents that target HER2 and other members of that receptor family are in clinical development for patients with HER2-positive MBC whose disease has progressed on trastuzumab. In addition, in an effort to overcome treatment resistance, clinical trials are evaluating combination therapy (investigational HER-targeted agents with trastuzumab or lapatinib). This review discusses recently completed and ongoing phase II and III clinical trials of investigational HER-targeted agents in the setting of trastuzumab-pretreated/progressive, HER2-positive MBC.

Key words: HER inhibitors, HER2-positive, metastatic breast cancer, monoclonal antibodies, neoadjuvant therapy, trastuzumab

introduction

In 2013, it is estimated that there will be 39 620 breast cancer-related deaths among women in the United States [1] and 88 886 in Europe [2]. Systemic treatment modalities for breast cancer management include cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these modalities, with selection based on a number of factors (including patient and tumor characteristics, stage of disease, and patient preference) [3]. In most cases, metastatic breast cancer (MBC) is incurable, and the goals of treatment are to optimize quality of life, manage symptoms, and prolong survival.

Approximately 25%–30% of breast tumors overexpress human epidermal growth factor receptor 2 (HER2, a transmembrane tyrosine kinase [TK] receptor within the HER family), a tumor characteristic that tends to occur in younger patients and, before the advent of HER2-directed therapy, predicted a poor clinical outcome [4, 5]. This review focuses on the current status of investigational anti-HER2 agents actively being evaluated in phase II or III clinical trials, specifically in the setting of trastuzumab-pretreated/progressive MBC, and includes an overview of accumulating neoadjuvant data for earlier use of anti-HER2 combinations. Relevant clinical trials were selected for inclusion based on searches of PubMed, key oncology congresses, and the ClinicalTrials.gov registry.

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