Smarter drugs emerging in pancreatic cancer therapy

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Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death in the Western world. Owing to a lack of specific symptoms and no accessible precursor lesions, primary diagnosis is commonly delayed, resulting in only 15%–20% of patients with potentially curable disease. The standard of care in advanced pancreatic cancer has improved. Apart from gemcitabine (plus erlotinib), FOLFIRINOX and the combination of gemcitabine plus nab-paclitaxel are novel and promising therapeutic options for patients with metastatic PDAC. A better molecular understanding of pancreatic cancer has led to the identification of a variety of potential molecular therapeutic targets. Many targeted therapies are currently under clinical evaluation in combination with standard therapies for PDAC. This review highlights the current status of targeted therapies and their potential benefit for the treatment of advanced PDAC.

Key words: cancer, pancreatic ductal adenocarcinoma, advanced disease, treatment, targeted therapies

introduction

Death due to pancreatic ductal adenocarcinoma (PDAC) ranks fourth among cancer-related deaths in the Western world. The only potentially curative treatment of this malignancy is surgery, but only 15%–20% are eligible. Major limiting factors are the patients’ general condition and an already locally advanced or metastatic disease. Five-year overall survival (OS) rates vary between 1% and 4%. Even after surgical resection plus adjuvant chemotherapy, OS rates do not exceed 25%–30% [1, 2]. Various treatment regimens failed to improve survival of patients. Gemcitabine was established as first-line standard chemotherapy in the late 1990s of the last century and remained the standard until recently [1, 3]. In 2011, FOLFIRINOX, a combination of 5-fluorouracil, irinotecan and oxaliplatin that has first been examined in colorectal cancer, significantly improved OS compared with gemcitabine in patients with metastatic PDAC with a good performance status, low bilirubin levels and age ≤75 years [4–6]. Recently, the combination of gemcitabine plus nanoparticle albumin-bound nab-paclitaxel has also shown to be superior to gemcitabine with respect to OS in a recent phase III trial [7].

Besides conventional chemotherapy, a variety of targeted approaches have proved benefits in different solid malignancies, such as colorectal or gastric cancer. Nevertheless, apart from erlotinib, no targeted therapy has as yet demonstrated clinical benefit in PDAC [8–11]. Meanwhile, our understanding of PDAC biology increases steadily and a variety of new drugs emerge for targeted PDAC treatment. This review aims at providing a detailed analysis on current and emerging drugs and their respective targeted pathways in PDAC.

inhibition of the epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is highly expressed in 30%–50% of PDACs [12–14]. Interestingly, EGFR-signaling input is required for pancreatic carcinogenesis even in the presence of an oncogenic K-ras mutation [15, 16]. The small molecule erlotinib is a selective inhibitor of the EGFR tyrosine kinase and was the first approved targeted therapy in PDAC (Figure 1). In a phase III trial focusing on metastatic PDACs, the combination of gemcitabine plus erlotinib improved median OS (mOS) significantly by 0.33 months (~10 days) in the whole study population [8]. However, an unplanned subgroup analysis revealed that patients developing a skin rash on erlotinib treatment benefit more with a mOS of up to 10.5 months, whereas those without did not benefit from additional erlotinib. Consequently, it is recommended to discontinue erlotinib if no rash develops within 8 weeks after start of treatment [8, 17] (Figure 1). The recently reported LAP07 trial [18] investigated the same regimen as a 4-month induction therapy before chemoradiotherapy (CRT) in patients with unresectable, locally advanced PDAC (LAPC). In contrast to metastatic disease and in agreement with the findings by Moore et al. [8], the combination of gemcitabine (Gem) plus erlotinib (E) did not add benefit compared with gemcitabine alone [mOS 13.6 months (Gem) versus 11.9 months (Gem + E), hazard ratio (HR) 1.19; $P = 0.0930$], but resulted in increased grade 3/4 toxicity [18]. Thus, further studies are warranted to precisely define the patient population displaying optimal benefit from a...
A phase II trial compared the combination of gemcitabine, erlotinib and cixutumumab, a monoclonal anti-insulin-like growth factor receptor (IGFR) antibody, with gemcitabine plus erlotinib. There were no significant differences in OS and progression-free survival (PFS), but clearly increased grade 3/4 toxicities in the experimental arm [41]. The combination of gemcitabine with another anti-IGFR mab, ganitumab (G) or conatumumab (C), a mab against TRAIL2 with gemcitabine, is currently evaluated. An interim analysis indicated a positive trend for the 6-month OS and PFS in particular for the combination of gemcitabine plus ganitumab (OS 7.3/7.5/6.2 months; PFS 5.9/3.9/2.1 months; objective therapeutic response 20%/17%/12% for G + Gem versus C + Gem versus placebo + Gem) [42]. However, a preplanned interim analysis stopped the subsequent phase III trial comparing ganitumab plus gemcitabine versus gemcitabine alone due to a lack of benefit [43].

Targeting downstream ‘signaling hubs’ of the IGFR using the dual PI3-kinase/mTOR inhibitor NVP-BEZ235 and a pan-histone deacetylase inhibitor, in a mouse model of PDAC, revealed promising data [44]. Accordingly, a new therapeutic approach with this dual PI3-kinase/mTOR inhibitor in combination with a MEK1/2 inhibitor is currently tested (phase Ib) [45]. In addition, an Akt-anti-sense molecule, RX-0201, is currently evaluated in combination with gemcitabine in PDAC (phase I) [43].

The mTOR inhibitor everolimus improved PFS in advanced pancreatic neuroendocrine tumors as a monotherapy [46], but failed in PDAC [47, 48]. Despite, mTOR inhibition remains interesting as the mTOR pathway is highly active in the so-
called cancer-initiating cells (GICs) [49]. GICs could play an important role in development, maintenance and metastasis of PDACs [50] and appear to be refractory to standard chemotherapy [51, 52]. In a mouse model, a relevant depletion of the CIC pool was only achieved by dual inhibition of the mTOR-signaling cascade together with the sonic hedgehog (SHH) pathway and gemcitabine [51]. Thus, mTOR inhibition remains promising to target specific tumor cell subsets (Figure 1).

c-MET is a surface marker for pancreatic GICs [53] and plays an essential role in cell survival, growth and metastasis [54]. For PDAC, a recent phase II trial investigating the c-MET inhibitor cабозантиб will give us further insights [55]. Promising preclinical data have also been published using RAF and MEK inhibitors in PDAC [56]. Interim data from a phase I trial in PDAC showed a favorable toxicity profile of a MEK inhibitor in combination with gemcitabine. The efficacy data revealed a partial response in 1 of 28 treated patients and in 3 a stable disease [57]. In contrast, the selective MEK inhibitor selumetinib failed to induce significant differences in OS and PFS. Ongoing phase I/II trials using combinations of MEK inhibitors plus gemcitabine [58, 59], as well as the Akt plus MEK inhibitors [45], will give us further clues on the relevance of these pathways in human tumors.

Recent preclinical data using a humanized xenograft approach suggested that co-activation of the MEK- and EGFR/HER2-signaling pathway is important to promote the development of PDAC [60, 61]. In line with this observation, multitargeting with trametinib and lapatinib lead to a more substantial inhibition of PDAC growth in a xenograft model [61]. Thus, clinical trials are required in the future.

Preclinical models suggest a synergistic anticancer activity of EGFR and mTOR inhibitors in different cancers [62], but toxicity limits dose-escalation in men [63]. A phase II trial using a dual targeting of MEK (selumetinib) and EGFR (erlotinib) after progress to first-line chemotherapy is still ongoing. The underlying idea for this approach is to overcome EGFR hyperactivation induced by pharmacological MEK inhibition (Figure 1). An interim analysis revealed an estimated mPFS of 2.6 months, a mOS of 7.5 months and an acceptable toxicity profile [64].

angiogenesis inhibition

In PDAC, high levels of vascular endothelial growth factor (VEGF) and its receptors are major promoters of angiogenesis and metastasis [65, 66]. Interestingly, the combination of gemcitabine plus bevacizumab failed to improve PFS and OS [67]. A dual approach targeting fibroblast growth factor (FGF) and VEGF signaling also failed [68] (see Table 1 and Figure 1).

Axitinib is a small molecule that inhibits VEGFR-1–3, platelet-derived growth factor receptor (PDGFR) and c-kit (CD117). Following promising phase I/II results, a phase III trial revealed no benefit of adding axitinib to gemcitabine [69]. Similarly, afibreccept, an engineered fusion protein that traps VEGF-A/B and placental growth factor, did also not improve OS in combination with gemcitabine [70].

Sorafenib is a multitargeted inhibitor addressing Ras/Raf/MEK/ERK, VEGFR-2/-3 and the PDGFR (Figure 1) [71, 72]. In preclinical xenograft models, a relevant tumor growth inhibition was demonstrated [72]. In a phase I trial, more than half of the patients experienced stabilization of their disease [73]. However, a subsequent phase II study failed to demonstrate a significant benefit for sorafenib plus gemcitabine with respect to PFS, OS or response rate [74]. Sunitinib is another multitargeted inhibitor targeting VEGFR-1–3, PDGFR, c-kit, fms-related tyrosine kinase 3 and rearranged during transfection proto-oncogene 75–80]. In line with disappointing preclinical data [80, 81], several phase II trials failed to show activity in advanced PDAC in combination with gemcitabine or as a single agent [82, 83]. However, a small randomized phase II trial comparing sunitinib maintenance therapy with observation in patients with metastatic PDAC who exhibited no progression after 6 months of chemotherapy showed interesting results. The primary outcome measure, probability of being progression-free at 6 months (PFS-6) from randomization, was significantly improved in the sunitinib arm compared with observation (22.9% versus 7.1%; P < 0.01). Disease stabilization (51.9% versus 21.4%; P = 0.02) and 2-year OS (22.9% versus 7.1%; P = 0.11) were also superior to the observational arm [84]. These data point to a potential effect of antiangiogenic drugs in PDAC, at least in the maintenance setting. However, the role of an antiangiogenic therapy in PDAC remains still unclear. One reason for the therapeutic failure of angiogenesis inhibitors in PDAC may be the specific desmoplastic reaction of these tumors that prevents sufficient perfusion and induces tumor hypoxia (see below) [64, 85–87].

Table 1. Survival data for erlotinib, gemcitabine and bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine + erlotinib</th>
<th>Gemcitabine + erlotinib + bevacizumab</th>
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<tbody>
<tr>
<td>PFS</td>
<td>3.6</td>
<td>4.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.61–0.86), P = 0.0002*</td>
<td></td>
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<tr>
<td>OS</td>
<td>7.1</td>
<td>6.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.89 (0.74–1.07), P = 0.2087*</td>
<td></td>
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*The difference was statistically significant at the P-value <0.05.

CI, confidence interval; PFS, progression-free survival; OS, overall survival; HR, hazard ratio.

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their diffusion into the cytoplasm [92]. PDEδ activity has a direct impact on K-ras signaling by increasing the amount of Ras at the plasma membrane [92]. Using a small molecule interfering with the mammalian binding site of PDEδ, proliferation of K-ras-dependent human PDAC cells was inhibited in vivo and in vitro [93]. This may provide a new strategy to target K-ras-dependent malignancies.

**the tumor stroma as a new target in pancreatic cancer**

Desmoplasia means an excessive proliferation of fibrotic tissue with a modified extracellular matrix providing a protumorigenic environment [94–96]. Pancreatic stellate cells (PSCs) predominantly drive the stroma reaction [97, 98]. There is an intimate crosstalk between PSCs and pancreatic cancer cells. This crosstalk involves a set of distinct signaling cascades, which act in feedback and forward loops to control matrix synthesis, cell growth, migration and invasion. (for more details, see Figure 2). PSCs may also play a role in metastasis as they were found to accompany pancreatic cancer cells to metastatic sites and to stimulate angiogenesis [99]. The massive stroma reaction causes hypovascularization of PDACs resulting in hypoxia and epithelial–mesenchymal transition. This, in turn, selects for more aggressive tumor subclones [100], lowers the concentration of chemotherapeutic agents in the tumor center and changes tumor metabolism to increased glycolysis [101]. Thus, it is conceivable to develop potential therapeutic strategies to target also the stroma as outlined in Figure 1.

**MMP inhibition**

Stroma regulating matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that control physiological and pathological matrix turnover [102], thus controlling tumor invasion and metastasis [103, 104]. Several isoforms are overexpressed in PDAC, e.g. MMP-1, -2 and -9 [105, 106]. In turn, the inhibition of MMPs appears an appropriate therapeutic target [85]. Marimastat is a multi-MMP inhibitor and has been compared as a single agent with gemcitabine in patients with metastatic PDAC. Intriguingly, this study showed a comparable OS in both groups (HR 0.84), at least at the highest administered dose of marimastat (25 mg, b.i.d.). These promising results led to the initiation of a trial with marimastat (low-dose 10 mg bid) plus gemcitabine. No significant difference was observed in the combination group compared with gemcitabine plus placebo [107, 108]. Another trial investigating tanomastat, a specific inhibitor of MMP-1, -2, -3 and -9, had to be stopped due to a significantly shortened OS in the experimental group at the first interim analysis [109]. In conclusion, therapeutic concepts using MMP inhibition deserve to be further evaluated (Figure 1).

**hedgehog inhibitors**

Hedgehogs are signaling proteins that play a pivotal role during embryogenesis and can promote tumor development [85, 110, 111]. In PDAC, SHH signaling is restricted to the stromal compartment and enhances the desmoplastic reaction [112, 113]. A whole-genome sequencing approach first identified the hedgehog-signaling pathway as hyperactive in PDACs [88]. Hedgehog signaling modulates proliferation by activating cyclin-dependent kinases [114], as well as differentiation by stimulation of neurotrophic and angiogenic factors [115] or expression of SNAI1, a zinc finger protein involved in metastasis [116]. The signaling cascade is activated upon binding of the hedgehog ligand to the PATCHED 1 protein on target cells, removing the inhibitory effect of smoothened (SMO). This results in the translocation of GLI, a family of zinc-finger transcription...
To bypass the stroma-induced hurdles, chemotherapeutic drug conjugation factors, into the nucleus to regulate transcription of target genes [110] (Figure 1). A preclinical study revealed a transient increase of intratumoral gemcitabine concentrations and improved disease stabilization by a hedgehog inhibitor pretreatment [85]. This marked the path for phase II clinical trials currently evaluating hedgehog inhibition in PDAC with, for example, vismodegib (V) [86] or saridegib [117]. Interestingly, the published literature remains controversial despite successful preclinical studies. A phase II trial for saridegib and gemcitabine had to be stopped after an interim analysis due to a shortened PFS in the saridegib group [117]. A recent phase Ib/II trial compared the combination of gemcitabine plus vismodegib (V) or placebo. A promising trend for OS and PFS in the interim analysis could not be confirmed in the final analysis (Gem + placebo versus Gem + V; mOS 6.9 versus 6.1 months, HR 1.04; mPFS 4.0 versus 2.5 months, HR 0.81) [86, 118]. Erismodegib, a smoothened inhibitor, is currently tested in combination with FOLFIRINOX [119] or gemcitabine. Reasons for the disappointing results of hedgehog inhibition could be arising SMO mutations under therapy and compensatory feedback loops leading to a (hyper-) activation of the PI3-kinase pathway or downstream targets of the hedgehog pathway (e.g. Gli2) [85, 120]. The most common mutations cause an inactivation of the patched receptor with a ligand-independent activation of the hedgehog receptor SMO. A dual targeting of the hedgehog pathway and the PI3-kinase pathway could be a possible approach for some tumors—as shown in medulloblastoma [121], but a compensatory PI3-kinase activation is not seen in all cancers upon hedgehog inhibition (Figure 1) [122].

drug conjugation

To take advantage of tumor hypoxia in PDAC, one can also use prodrugs that are activated in this rather hypoxic environment. TH302 is a 2-nitroimidazole hypoxia-activated prodrug of dibromo-isophosphoramide mustard, a DNA-alkylating agent. Hypoxia causes the reduction of the 2-nitroimidazole and leads to a release of bromo-isophosphoramide. The analysis of a randomized phase II trial exhibited a median PFS for TH302 plus gemcitabine of 6.0 months (340 mg/m^2; P = 0.008) and 5.6 months (240 mg/m^2, P = 0.060), respectively, compared with 3.6 months with gemcitabine alone. Median survival rates were not significantly improved. The response rates were 26% or 17% (TH302 higher/lower dose), compared with 10% with gemcitabine alone. Interestingly, there was no major toxicity observed using TH302 [132–134].

tumor-associated inflammation

Even at the early stages of tumor development leukocytes, leading to a local immunosuppression, infiltrate the stroma [135, 136]. CD40, a member of the tumor necrosis factor family, plays a central role for the T-cell-dependent antitumor priming

Table 2. Nab-paclitaxel/gemcitabine compared with gemcitabine monotherapy [1]

<table>
<thead>
<tr>
<th></th>
<th>Nab-paclitaxel + gemcitabine (n = 431)</th>
<th>Gemcitabine (n = 430)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>8.5</td>
<td>6.7</td>
<td>0.72</td>
<td>0.000015</td>
</tr>
<tr>
<td>1-year OS (%)</td>
<td>35</td>
<td>22</td>
<td>0.000200</td>
<td></td>
</tr>
<tr>
<td>2-year OS (%)</td>
<td>9</td>
<td>4</td>
<td>0.021234</td>
<td></td>
</tr>
<tr>
<td>mPFS</td>
<td>5.5</td>
<td>3.7</td>
<td>0.69</td>
<td>0.000024</td>
</tr>
</tbody>
</table>

*The difference was statistically significant at the P-value <0.05.
HR, hazard ratio; CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival.
and activity, which relies on a CD40-mediated 'licensing' of antigen-presenting cells [136–138]. Based on this concept, a phase I trial was drafted testing the combination of the CD40-mab CP-870.893 and gemcitabine for patients with not resectable PDAC [136]. Twenty-one patients received the combination therapy with a median PFS of 5.6 months and an OS of 7.4 months [136]. A few patients had a clear tumor response, which even allowed secondary surgical resection. Intriguingly, the subsequent histopathological analysis of the resected tumor sample revealed an absence of the typical leukocyte infiltration and dramatically diminished stromal reaction. These ‘first in men’ data got further support from a mouse model also showing reduced inflammation as well as a reduced tumor- and stroma-load. Pathophysiologically, the driving force of this effect seems to be a CD40-dependent activation of macrophages rather than an activation of cytotoxic T-cells [136]. A still recruiting phase I trial evaluates the role of CP-870.893 plus gemcitabine in the neoadjuvant and adjuvant setting [139].

**Autophagy as a new therapeutic concept**

Autophagy describes a cellular recycling process, which mainly involves degradation of damaged organelles or proteins [140]. Autophagy plays an essential role for cellular homeostasis, energy balance as well as for the defense from potential toxins [141, 142], all fundamental processes for the development and maintenance of a malignant tumor [49]. Of note, different autophagy-associated genes increases with the progression of pancreatic precursor lesions (PanIN 1–3) toward the invasive carcinoma stage [145, 146]. Several preclinical studies reveal a significantly better efficacy of gemcitabine when combined with genetic or pharmaceutical inhibition of autophagy [146, 147]. Chloroquine, a drug used for malaria, is an inhibitor of autophagy and exhibited a relevant antitumor activity in PDAC in a preclinical model [146]. A recent phase I/II trial in patients with PDAC examines its effects in combination with gemcitabine plus nab-paclitaxel [148].

**Targeted therapies and chemoradiation**

The role of CRT in PDAC is still unclear. There are some promising data in LAPC. However, increased survival rates come at the expense of substantially increased toxicity as shown in a trial comparing gemcitabine + radiation [149]. There are other trials that failed to show a benefit of CRT in LAPC. In the LAP07 trial, a LAPC patient cohort with stable disease upon induction chemotherapy was exposed either to capectabine or capectabine plus radiation, revealing no clinical benefit for the patients in the CRT arm [18].

Data on combinations of CRT with targeted agents are still preliminary. A recent phase II trial reported no benefit for the addition of bevacizumab to a regimen of capectabine-based chemoradiation followed by gemcitabine [150]. Promising survival rates (1-year OS 66%, 2-year OS 25% and 4-year OS 11%) were shown in a single-arm phase II study using cetuximab, gemcitabine and oxaliplatin followed by chemoradiation with cetuximab and capectabine in LAPC with acceptable toxicity [151].

**Discussion**

**Personalized therapies for pancreatic cancer**

PDAC is a heterogeneous and genetically highly complex disease. The most commonly identified mutations are K-ras and CDKNA2, however, so far no direct targeting strategy succeeded. Upon mutation of both K-ras and CDKNA2 not just a single pathway, but a variety of pathways is activated, including feedback loops [88, 94]. Thus, targeted therapies maybe more efficient when the central hubs in a signaling network are identified that upon successful targeting predict a tumor response. In line with this notion, a recent phase II trial examined new specific PDAC targets using immunohistochemical, transcriptional and genomic analyses of metastatic biopsies [88, 152]. An interim analysis indicates that patients with high expression levels of topoisomerase could benefit more from irinotecan-based regimens than those lacking [152]. The Avatar-mouse model uses serialpassaging of human tumor specimen in mice to assess the optimal clinical response to different regimens. First effects were shown in a patient with good preclinical response to treatment with mitomycin C after developing resistance to gemcitabine [153]. Genome-wide sequencing of this tumor showed inactivation of PaIB2, an inhibitor the tumor suppressors BRCA1/2. Knowing that the preclinical response in a mouse model could correlate with molecular alterations it might be a guide for future therapeutic decisions [153].

Masitinib, an oral tyrosine kinase inhibitor for c-kit, PDGFR and FGRFR3, appears as a good example for personalized medicine in PDAC [154]. A placebo-controlled, randomized clinical trial did not show any benefit for masitinib in combination with gemcitabine (P = 0.74; HR 0.9). However, the study design included a whole blood-based transcriptome signature and the assessment of the pain level at therapy induction. A subgroup analysis exhibited a significantly improved OS at 12 and 18 months upon treatment with masitinib when this particular transcriptome signature indicative of aggressive disease was present in the tumor. Similar effects were observed in patients with increased pain levels (see Table 3; signature: combination versus Gem: 6 versus 11 months; high pain level: combination versus Gem: 5.5 versus 8.1 months) [155, 156].

**Targeting multiple cell types comprising PDAC**

Established genetic signatures in PDAC could represent an important corner stone for future targeted therapies. Besides medical benefits this also touches socioeconomic issues, for example, cost-effectiveness. Cellular heterogeneity of PDAC comprising CiCs and stromal cells poses a difficult challenge. CiCs show a high level of resistance for common therapies and play a pivotal role in tumor recurrence [157]. PSCs are likely to generate a niche for tumor stem cells [158] and to induce desmoplasia, causing reduced diagnostic sensitivity, decreased penetration of chemotherapeutic agents and an early infiltration into the surrounding tissues (Figure 2). New therapeutic approaches will have to integrate various targets in different pathways. However, the first experiences with such multitargeting strategies suggest that toxicity may be a limiting factor.
Table 3. Biomarker-based assessment of masitinib and gemcitabine therapy [155, 156]

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Gem + placebo (mOS)</th>
<th>Gem + masitinib (mOS)</th>
<th>P-value*/HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>7.0</td>
<td>7.7</td>
<td>0.74/0.90</td>
</tr>
<tr>
<td>Genetic signature</td>
<td>5.0</td>
<td>11.0</td>
<td>0.000038/0.29</td>
</tr>
<tr>
<td>Patients without genetic signature</td>
<td>14.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pain beyond defined level (VAS score &gt;20 mm)</td>
<td>5.4</td>
<td>8.1</td>
<td>0.01/0.61</td>
</tr>
<tr>
<td>Patients without pain (VAS score &lt;5 mm)</td>
<td>15.4</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*The difference was statistically significant at the P-value <0.05.

mOS, median overall survival; Gem, gemcitabine; HR, hazard ratio; VAS, visual analog scale (0–100 mm).

Conclusion

In summary, besides numerous disappointments with targeted therapies in PDAC, these compounds barely the potential for a better treatment of pancreatic cancer. Novel chemotherapeutic backbones that deplete tumor stroma such as nab-paclitaxel plus gemcitabine may turn out to be more advantageous combination partners for targeted agents compared with gemcitabine alone. It will be the crucial challenge to establish biomarkers in the tumor and/or in the blood that allow the prediction of tumor response. However, we also need biomarkers that allow a molecular monitoring of the tumor before, during and after therapy to customize the treatment according to the actual molecular profile of the tumor and its evolution under therapy. Smart drugs need smart applications.

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Disclosure

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