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Diagnosis and treatment of pancreatic cancer: an expert opinion from the 9th CECOG Pancreas Cancer Academy

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Summary Pancreatic ductal adenocarcinoma (PDAC) remains one of the most challenging malignancies, with a dismal prognosis and limited therapeutic options. The 9th CECOG Pancreas Cancer Academy brought together leading international experts to review recent advances and establish a consolidated expert opinion on the biology, diagnosis, and treatment of pancreatic cancer. Pancreatic ductal adenocarcinoma is characterized by extensive molecular heterogeneity, with *KRAS* mutations being the primary driver of most cases. Diagnosis relies on a multimodal imaging approach, while molecular diagnostics

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are increasingly essential for identifying actionable biomarkers and understanding resistance mechanisms. Multidisciplinary tumor boards are crucial for addressing all aspects of diagnosis and treatment. Treatment strategies are tailored to disease stage and patient performance status. For resectable disease, upfront surgery followed by adjuvant chemotherapy (preferably mFOLFIRINOX) remains the standard, although neoadjuvant therapy is gaining importance for borderline resectable tumors. In metastatic disease, FOLFIRINOX, NALIRIFOX, and gemcitabine–nab-paclitaxel are first-line options. Second-line therapies focus on switching drug classes and tailoring therapies according to patient fitness. Novel therapies, including targeted agents, immunotherapies, and antibody–drug conjugates, are currently being assessed in clinical trials. Despite progress, the complexity of pancreatic cancer demands continued research into biologically driven treatments and early detection strategies to improve patient survival and quality of life.

Keywords Multidisciplinary tumor board · Adjuvant · Neoadjuvant · Surgery · Metastatic · Radiotherapy

Abbreviations

BRCA	Breast cancer gene
CA	Cancer antigen
CECOG	Central European Cooperative Oncology Group
CLDN18.2	Claudin 18.2
CT	Computed tomography
CtDNA	Circulating tumor DNA
dMMR	Deficient mismatch repair
ECOG	European Cooperative Oncology Group
ENETS	European Neuroendocrine Tumor Society
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasound
EUS-FNA	Endoscopic ultrasound-guided fine-needle aspiration
FOLFORINOX	Folinic acid (leucovorin), fluorouracil (5-FU), irinotecan, oxaliplatin
FOLFOX	Folinic acid (leucovorin), fluorouracil (5-FU), oxaliplatin
gBRCA	Germline BRCA
IAP	International Association of Pancreatology
KPS	Karnofsky performance status
MCBS	Magnitude of Clinical Benefit Scale
mFOLFIRINOX	modified FOLFORINOX
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability high
NALIRIFOX	Nanoliposomal irinotecan, folinic acid (leucovorin), 5-fluorouracil (5-FU), oxaliplatin
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
OS	Overall survival
PDAC	Pancreatic ductal adenocarcinoma
PET	Positron emission tomography
PET-CT	Positron emission tomography combined with computed tomography
PRRT	Peptide receptor radionuclide therapy
RF	Radiofrequency
SSTR	Somatostatin receptor
TACE	Transarterial embolization
TNM	Tumor–node–metastasis classification of malignant tumors
UICC	Union for International Cancer Control
ULN	Upper limit of normal

Introduction

Pancreatic cancer is one of the most difficult-to-treat and deadliest cancers, with pancreatic ductal adenocarcinoma (PDAC) being the most prevalent subtype (~85%; [1]). It is predicted to become the second leading cause of cancer death worldwide, with a rise in incidence and mortality by approximately 80% between 2018 and 2040 [2]. As patients mostly do not experience any symptoms, and due to the underlying aggressive biology, metastatic disease at diagnosis is common. The 5-year survival rate across all cancer stages is estimated to be 13% in the United States, while the 5-year survival rate in advanced pancreatic cancer drops to as low as 3% [3, 4].

There are several inherent obstacles to treatment success: Surgery is rarely curative, as the pancreas is nestled among several critical vessels, which complicates both the staging and surgical removal of pancreatic tumors. More importantly, even after resection, pancreatic cancer is a rapidly spreading disease with the likely presence of micrometastases in most patients. Pancreatic cancer also tends to be resistant to many systemic cancer therapies for a variety of reasons. Therefore, real breakthroughs have been rare. However, a steady flow of research has yielded important insights into the pathological mechanisms of the disease. Research conducted over the past decade has slowly but steadily improved patient outcomes in randomized clinical trials testing various drug combinations.

To explore these recent advances in the diagnosis and treatment of pancreatic cancer, the Central European Cooperative Oncology Group (CECOG) hosted its 9th edition of the “Pancreas and Cholangiocellular Cancers Academy” in June 2025 in Vienna, Austria. Experts from Austria, France, Germany, Italy, Spain, the United Kingdom, and Canada discussed the biology, diagnosis, and treatment of pancreatic cancer, including its management in local/locoregional and metastatic settings.

This report summarizes the most current expert opinion on the diagnosis and treatment of pancreatic cancer, as presented at the 9th CECOG Pancreas Cancer Academy.

Biology

Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer [1] and originates in the exocrine cells of the pancreatic ducts. There is extensive ongoing research about the signatures of different subtypes of PDAC [5]. Since 2015, when Moffitt et al. identified the classic and basal-like subtypes [6], several strides have been made toward a more granular understanding of PDAC. In a comprehensive genetic analysis of bulk tumor samples, Bailey et al. [7] identified 32 mutated genes and four pancreatic cancer subgroups. These subgroups include the squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated subtypes. Inter- and intratumor heterogeneity, however, is high.

RAS mutations are the most important driver of PDAC [8], with 85% of patients carrying a *KRAS* mutation [9]. An increasing number of other biomarkers are becoming available, offering prognostic tools and directed treatment opportunities [9]. These include mutational activation of oncogenes (predominantly *KRAS*), inactivation of tumor suppressor genes (*TP53, p16/CDKN2A, SMAD4*), inactivation of genome maintenance genes (mostly somatic, e.g., *hMLH1, MSH2*), and alterations in genes specifically involved in the homologous recombination repair (mostly germline, e.g., *BRCA 1/2*). *KRAS* wild-type metastatic PDAC is considered a unique molecular entity [9].

The tumor microenvironment also plays a crucial role in regulating surrounding tumor vascularization, the extracellular matrix, cancer-associated fibroblasts, and metabolic pathways in PDAC progression, as well as treatment resistance mechanisms for which targeted drugs are being developed [10, 11]. Finally, the microbiome is increasingly understood to play an important role, especially in early-onset PDAC in very young patients [12].

Diagnosis

Imaging

The primary goal of staging is to determine whether a tumor is resectable, borderline resectable, or locally advanced. A multi-modality approach, including computed tomography (CT), endoscopic ultrasound (EUS), and positron emission tomography (PET) in combination with CT (PET-CT), is essential in the assessment of tumor location and size and of peripancreatic venous, arterial vascular, locoregional, and metastatic involvement. Computed tomography provides superior spatial resolution, which is essential for evaluating the precise degree of contact between the tumor and major peripancreatic arteries and veins. International standards, such as the National Comprehensive Cancer Network (NCCN) Guidelines [13], emphasize that the definition of "borderline" relies heavily on the degree of vascular encasement, which is most reliably measured and standardized on CT scans. In addition, staging for PDAC requires an assessment of the chest, abdomen, and pelvis to rule out distant metastases. Furthermore, CT allows for a rapid, "one-stop" comprehensive scan of the lungs and abdomen in a single session. Magnetic resonance imaging (MRI) is significantly more time-consuming and is not the standard for evaluating lung parenchyma, often requiring a separate CT of the chest regardless. An MRI examination is recommended only when CT findings are equivocal or before surgery in borderline or locally advanced disease. While MRI is a valuable adjunct for clarifying indeterminate liver lesions or pancreatic findings, CT remains the preferred primary staging tool. This preference is consistent with international clinical standards, which recommend high-quality, multiphasic CT as the initial diagnostic and staging modality to determine resectability [9, 13].

To ensure consistent results, imaging protocols should be set up, as suboptimal imaging compromises detection and staging. The CT protocol should include specifications on scan type, oral/IV contrast, phases, slice thickness, and reconstructions. Advanced software supports the planning of surgery by creating three-dimensional images of the tumor location in relation to essential structures, such as large vessels. In the future, AI-assisted radiologic diagnostics may help detect cancers at an earlier, possibly curable stage. The recently published PANORAMA trial demonstrated that, on average, the use of AI substantially improved PDAC detection on routine CT scans compared to expert radiology readers with a median experience of 9.0 years (interquartile range: 6.0–14.5), potentially enabling earlier detection of PDAC and thereby improving patient outcomes [14]. It is also crucial to monitor early and indirect signs of cancer and cancer progression, especially ductal changes or focal atrophy in high-risk patients. For atypical presentations or mimics, including inflammatory conditions or other neoplasms, EUS-FNA (endoscopic ultrasound-guided fine needle aspiration) or percutaneous biopsy is critical to guide therapy.

Molecular diagnostics

Clinicians need to understand which alterations are prognostic, pathogenetic, and druggable. Therefore, broad molecular sequencing, ideally using next-generation sequencing (NGS) methodology, should be conducted before or at the time of first-line systemic therapy [9]. A significant challenge in molecular testing is selecting the appropriate panel. Tumor tissue remains the current standard for NGS-based molecular diagnostics, as it allows for robust detection of

complex genomic alterations, including gene fusions, copy-number amplifications, and large genomic deletions [13]. This is particularly critical in pancreatic cancer, where such alterations may have direct therapeutic or prognostic relevance but can be challenging to identify using alternative approaches [9, 13]. However, adequate tumor tissue is frequently difficult to obtain due to anatomical constraints, limited biopsy material, or poor sample quality. In these situations, liquid biopsy approaches based on circulating tumor DNA (ctDNA) represent a promising complementary strategy. An increasing body of evidence demonstrates that key driver alterations—most notably *KRAS* mutations—can be detected in blood with high reliability, supporting the clinical utility of plasma-based NGS for molecular profiling when tissue is insufficient or unavailable [13].

Regarding the interpretation of NGS outcomes and their potential clinical translation, the establishment of molecular tumor boards is strongly recommended.

The current European Society for Medical Oncology (ESMO) guidelines list *BRCA* mutations, microsatellite instability high (MSI-H)/deficient mismatch repair (dMMR), and *NTRK* fusion as potential targets for precision medicine in metastatic PDAC [9, 15]. Regarding *BRCA*, there is increasing evidence to focus not only on germline *BRCA* (*gBRCA*), but "beyond" homologous recombination deficiency (HRD) and non-core alterations ("BRCAness"). In the context of *KRAS*, druggable *KRAS* alterations such as *G12C* and, more frequently in PDAC, *G12D* have been identified, although panRAS drugs are also changing the druggable landscape for PDAC patients. In patients with *KRAS* wild-type tumors, multigene sequencing (with both DNA and RNA) must be performed, as other actionable mutations such as MSI, *NTRK*, *BRAF*, or *FGFR* can frequently be found in these patients [9].

Sequential biopsy and liquid biopsy/ctDNA testing may help to understand resistance mechanisms. Additionally, ctDNA is a promising tool for monitoring the development of polyclonal resistance during treatment, guiding treatment decisions. The ctDNA fraction will also help to identify false-negative ctDNA test results [16].

Surgical or laparoscopic exploration may be considered in selected, exceptional cases—for example, when less invasive diagnostic approaches have failed and the results would directly impact clinical management—but such strategies are not routinely recommended [9]. While endoscopic retrograde cholangiopancreatography (ERCP)-based sampling and bile cytology have been explored as diagnostic tools in cholangiocarcinoma [17], the evidence supporting their utility in PDAC is more limited and currently not recommended [9].

Initial considerations in the treatment of local or locoregional disease

Local or locoregional disease is anatomically categorized as resectable, borderline resectable with venous involvement, or advanced with arterial involvement [13]. However, as surgical and imaging techniques, along with molecular diagnostics, have evolved over time, it has become increasingly clear that a definition based on anatomical considerations alone is insufficient. Therefore, the definition of resectable status is increasingly influenced by aspects of tumor biology, disease burden, and the patient's performance status [9, 18, 19]. Candidate markers under consideration for determining cellular spread include positive cytology from washings obtained at laparoscopy or ctDNA [20].

Tumors should be staged according to the 8th edition staging system of the Union for International Cancer Control (UICC) tumor–node–metastasis (TNM) classification [21]. Resectability should be assessed according to NCCN criteria under additional consideration of the International Association of Pancreatology (IAP) consensus [9, 13, 19]. Joint decision-making within the framework of a multidisciplinary tumor board is necessary to develop an adequate treatment strategy for each patient [9].

Surgery

The current best evidence suggests that upfront surgery remains the gold standard for anatomically resectable pancreatic cancer with fewer complications and similar survival to neoadjuvant therapy followed by surgery [22]. The median survival after immediate resection followed by adjuvant chemotherapy ranges between 30 and 54 months [23–25]. A potential limitation of a surgery-first approach is the fact that approximately 35% of patients do not undergo adjuvant therapy after surgery [26], which impairs systemic disease control. After surgery with a curative intent, systemic spread is frequent, with 70–85% of patients dying from systemic rather than local recurrence [27–29].

To properly select patients for upfront surgery, high-risk features should be considered, including indeterminate imaging findings, markedly elevated cancer antigen (CA) 19-9, large primary tumors, regional lymph nodes, excessive weight loss, and extreme pain [13]. Especially for biologically borderline resectable disease (CA 19-9 > 500 U/mL, positive lymph nodes [16]), neoadjuvant chemotherapy should be considered in a similar fashion as for locally advanced tumors. The addition of radiation is not recommended in this setting [9].

Neoadjuvant therapy additionally offers the chance to evaluate tumor biology in the aforementioned situations, as very aggressive forms of pancreatic cancer can progress extremely rapidly, carrying a high risk of both local tumor growth and the appearance of metas-

tases [30, 31]. In these situations, upfront surgery would not provide any benefit to patients. Furthermore, chronological age per se is not a contraindication for resection, in contrast to the patient's general condition and physiological reserve [9, 32].

Neoadjuvant/induction treatment

The aim of preoperative systemic therapy is to improve survival outcomes in upfront resectable disease and, additionally, to shrink borderline resectable local or locoregional tumors to a resectable stage. However, it has been postulated that "localized" pancreatic cancer does not really exist, since metastatic seeding of cells and subclones can start well before the primary malignancy has been detected [33, 34]. This hypothesis is also supported by the fact that most studies comparing surgery versus neoadjuvant treatment, using the purely anatomical definition of resectability, have found conflicting results on the R0 resection rate and a potential survival benefit [24, 35, 36].

The ESMO guidelines refer to preoperative systemic therapy as "neoadjuvant" in the case of upfront resectable disease and as "induction" in borderline resectable disease [9]. In resectable disease, ESMO guidelines recommend immediate surgery followed by adjuvant chemotherapy. In patients with borderline resectable tumors, induction therapy should only be considered in those with a high probability of a resulting R1 resection [9]. All other patients should be considered for clinical trial participation, whenever possible, because induction therapies established in the resectable setting or chemo-radiotherapy combinations only reach category II or III evidence levels in borderline resectable disease [9]. The ESMO-recommended induction protocols are FOLFIRINOX± chemoradiotherapy or gemcitabine–nab-paclitaxel± chemoradiotherapy [9]. However, the results of the PANDAS trial—presented after the publication of the ESMO guidelines—did not show any advantage in adding chemoradiotherapy (50.4 Gy in 28 fractions with capecitabine 825 mg/m^2 twice daily, 5 days a week) to induction chemotherapy with mFOLFIRINOX in borderline resectable patients [37]. If restaging after neoadjuvant/induction therapy shows a stable local finding or remission, surgical explorations should be offered in borderline as well as in locally advanced PDAC, as surgery can often be performed, including vascular resections when required, in experienced centers [38, 39].

In patients with locally advanced disease, enrollment in a clinical trial is preferred. If the inclusion criteria are not met, FOLFIRINOX or gemcitabine–nab-paclitaxel are ESMO-recommended strategies to attempt tumor downstaging, a decrease in CA 19–9 levels, and general clinical improvement [9]. Achieving a CA 19-9 decrease of >50% or a normalization of CA 19-9 after neoadjuvant treatment was found to be significantly associated with better overall survival (OS) in a pooled analysis of 17 trials [40]. If successful, potential surgery should be discussed in a multidisciplinary tumor board [9]. Importantly, ESMO guidelines note that changes in the residual tumor through neoadjuvant therapy may complicate the determination of tumor size and extent of vascularization by imaging. For instance, persistent perivascular soft tissue may strongly resemble residual tumor in EUS, MRI, or CT [9]. Therefore, after completion of neoadjuvant therapy, multidisciplinary tumor boards should base their decisions on tumor resectability on the totality of evidence from imaging findings, serum CA 19-9, performance status, and clinical response to neoadjuvant/induction therapy [9].

Adjuvant treatment

The aim of adjuvant therapy is to eradicate residual tumor cells and distant micrometastases, which cannot be surgically removed. In patients with resectable tumors, ESMO guidelines therefore recommend tumor resection followed by 6 months of adjuvant chemotherapy [9]. The choice of adjuvant chemotherapy is primarily guided by the patient's fitness. In patients with European Cooperative Oncology Group (ECOG) performance status 0–1, mFOLFIRINOX [41] is considered the gold standard and was determined by ESMO to have the highest clinical benefit (Magnitude of Clinical Benefit Scale [MCBS] score A) [9]. In older patients (>75 years) and those with an ECOG performance status of 2 or any other contraindications to mFOLFIRINOX, gemcitabine-capecitabine is recommended, with an MCBS score of A [9]. In very frail patients, adjuvant gemcitabine or 5-fluorouracil-leucovorin (5-FU-LV) can be attempted [9].

Perioperative treatment

Offering a category-I-recommended regimen for adjuvant chemotherapy as pre- or perioperative treatment ensures that all patients receive the same systemic therapy while they are still in a reasonably good clinical condition before surgery. This approach has the advantage of generating a treatment effect that increases R0 resection rates and provides a time interval to identify aggressive tumor biology and identify frail patients in whom unnecessary resections should be avoided.

For patients at high risk of futile upfront resection—such as those with large tumor size, elevated CA 19-9, and borderline disease—perioperative or total neoadjuvant chemotherapy using a category-I-recommended adjuvant regimen (e.g., mFOLFIRINOX) may be considered, especially when biliary drainage is stable. Critical data are awaited from ongoing randomized controlled trials, including PREOPANC-3 [42] and ALLIANCE A021806 [43], which may redefine perioperative strategies in resectable pancreatic cancer. Lacking confirmatory evidence, perioperative strate-

gies are currently not included in ESMO guidelines [9].

Radiotherapy

Given the aggressive nature of pancreatic cancer, radiotherapy can be a further pillar in a multidisciplinary approach. Initially, radiotherapy was mostly used for pain management and symptom control, but there is ongoing debate on its potential role in locally advanced PDAC. The rationale for using radiotherapy is to downsize tumors, enhance the likelihood of R0 resection, and assess tumor biology, as the procedure allows for the observation of treatment response before surgery. Currently, the role of radiotherapy is that of a complementary tool in the treatment armamentarium for PDAC, especially when used in combination with standard and novel chemotherapies, stromal modulators, and immunotherapy. Therefore, current ESMO guidelines do not recommend a role for radiotherapy. Previous limitations of the development of radiotherapy in pancreatic cancer included suboptimally designed trials, which had no adequate quality control. Therefore, to better understand the role of radiotherapy in the treatment of pancreatic cancer, more and better-designed trials regarding the use of various modalities of radiotherapy, be it as monotherapy or in combination with chemotherapy or with immune checkpoint inhibitors, are needed.

Treatment of metastatic disease

Treatment options for metastatic disease are dependent on the patient's performance status, bilirubin levels, and the molecular profile of the tumor.

First-line treatment of metastatic disease

According to an express update of current ESMO guidelines [15], FOLFIRINOX is recommended as the first-line option in fit patients with bilirubin $<1.5\times$ the upper limit of normal (ULN) with an evidence level of I, a grade of recommendation of A, and an MCBS of 5, followed by NALIRIFOX (IA and MCBS 2) and gemcitabine–nab-paclitaxel (IB, MCBS 3). However, clinical trials such as PASS-01 [44] suggest that FOLFIRINOX may have limited benefit in basal-like PDAC compared to the classic subgroup.

The NAPOLI-3 trial [45] found a superior response rate (41.8% vs. 36.2%) and OS (11.1 vs. 9.2 months) in patients receiving NALIRIFOX than in those receiving gemcitabine–nab-paclitaxel, respectively, with a better toxicity profile than FOLFIRINOX [46], which enables the use of NALIRIFOX also in older patients. The ESMO guidelines recommend gemcitabine–nab-paclitaxel in patients with ECOG performance status 2, Karnofsky performance status (KPS) ≥ 70, and bilirubin $\leq 1.5\times$ ULN, and gemcitabine in those with ECOG performance status 2, KPS < 70, and bilirubin $>1.5\times$ ULN. Patients with ECOG performance status 3 or 4 should receive symptom-directed care [15].

Testing patients for biomarkers is important, especially when it comes to treatment selection in the maintenance setting. In germline BRCA-mutated tumors, the POLO trial showed that progression-free survival was longer with maintenance olaparib than with placebo [47]. Based on the POLO trial [47], clinical guidelines recommend initiation of olaparib maintenance for germline *BRCA 1/2*-mutated metastatic disease after ≥ 16 weeks of platinum therapy without progression [9, 13, 48].

A DNA damage response (DDR) mutation is a predictive biomarker for a survival benefit from platinum-based chemotherapy [49], especially in the first-line treatment of metastatic PDAC. Therefore, all patients with advanced PDA should be tested for DDR to ensure that DDR-mutated patients are treated with platinum-based therapy [49]. Trials are ongoing to explore the importance of RNA signatures and GATA6 as predictive biomarkers. Apart from novel treatment strategies and targeted agents under investigation in clinical trials (e.g., mitazalimab, elraglusib, zolbetuximab), some drugs currently approved in later treatment lines, such as sotorasib, are also being explored for use in first-line therapy.

Second-line treatment of metastatic disease

The treatment of metastatic PDAC in the second line depends on the type of first-line treatment, as a switch in treatment modality, e.g., from mFOLFIRINOX or NALIRIFOX to a gemcitabine-based regimen, is important [15]. Patients with gemcitabine–nab-paclitaxel in the first line should preferably receive nanoliposomal irinotecan-5-FU-folinic acid or FOLFOX [15]. Patients in the GEMPAX trial receiving gemcitabine plus paclitaxel or gemcitabine alone as second-line treatment after a first line containing 5-fluorouracil, oxaliplatin, and irinotecan had significantly improved progression-free survival and objective response rate, although no OS benefit was found [50].

Several trials have shown that it is essential to determine the individually tolerated maximum dose and that dose reduction per se does not limit the treatment effect. The most important aspect in terms of 1-year survival rate is the number of cycles received, not the absolute dose [51]. Other prognostic factors for long-term survival included younger age (≤ 65 years), higher KPS (≥ 90), a neutrophil-to-lymphocyte ratio ≤ 5, lower CA 19-9 level ($<59\times$ ULN), and no liver metastases [52]. Results from CONKO-003 [53], PANCREAOX [54], and a study of S-1 versus SOX [55] for the second-line use of oxaliplatin in patients with gemcitabine-refractory PDAC have been conflicting and data on irinotecan in the second-line setting are limited [56]. Overall, sequential treatment strategies have led to an improved prognosis for patients with metastatic PDAC, but so far, most treatment reg-

imens are limited to chemotherapy combinations [57, 58].

Molecules targeting *RAS* and other molecular targets may further improve prognosis in the future. Various targeted therapies are available for different *KRAS* subtypes. However, resistance mechanisms linked to *KRAS G12C* inhibition are known and combination strategies to enhance inhibition efficacy are under investigation.

Experimental treatments in the metastatic setting

Disease-free survival rates remain modest for pancreatic cancer overall, underlining the need for biologically driven treatment approaches to improve long-term outcomes.

Checkpoint inhibitors have been shown to be effective in microsatellite unstable/mismatch repair-deficient advanced PDAC [59] but also in patients with *BRCA*-mutated metastatic PDAC [60]. Additionally, novel immunotherapies (anti-CD40, anti-CD73, etc.) are being explored. Quemliclustat, a potent and selective small-molecule inhibitor of soluble and cell-bound CD73, shows promise in treatment-naive metastatic PDAC when combined with gemcitabine–nab-paclitaxel with or without zimberelimab [61]. This regimen is currently under investigation in a phase 3 study. The anti-CD40 antibody sotigalimab, however, did not increase treatment benefit in patients with first-line metastatic PDAC when added to nivolumab and gemcitabine–nab–paclitaxel [62].

Besides treatment with RAS inhibitors, the high prevalence of *RAS* mutations opens a window for other approaches, such as vaccines targeting mutated *KRAS* [63]. Other types of *RAS* mutations and even *RAS* wild-type are also being explored (pan-RAS inhibition). The RAS(ON) multi-selective inhibitor daraxonrasib (RMC-6236) is currently being evaluated in second-line settings in the RASolute 302 phase 3 versus standard-of-care chemotherapy [64].

Other interesting target proteins are Claudin 18.2 (CLDN18.2; [65]) and GSK-3β [66]. For Claudin 18.2-expressing tumors, the most advanced data are available for zolbetuximab in combination with gemcitabine–nab–paclitaxel. The GLEAM trial, however, showed benefit in favor of the addition of zolbetuximab [67]. There are also bispecific antibodies and antibody–drug conjugates (ADCs) being investigated for Claudin 18.2. Regarding GSK-3β, elraglusib, which inhibits this enzyme, is being investigated in combination with gemcitabine–nab-paclitaxel in previously untreated metastatic pancreatic cancer [66].

Other novel targets such as FGFR1-4 inhibitors (targeting *FGFR2* fusion) [68], an MTA-cooperative PRMT5 inhibitor (targeting *MTAP* deletion; [69, 70]), TROP2-directed ADCs (59), and an MDM2-p53 antagonist [71] are also currently under investigation.

Treatment of pancreatic neuroendocrine tumors

Pancreatic neuroendocrine tumors are rare. Both the ESMO guidelines and a European Neuroendocrine Tumor Society (ENETS) guidance paper [72] have been developed to aid in their diagnostic workup and treatment [73]. Diagnostic and therapeutic decision-making should be based on key features, including proliferative activity, somatostatin receptor (SSTR) expression, tumor growth rate, and the extent of the disease. Treatment options for advanced pancreatic neuroendocrine tumors include somatostatin analogues, chemotherapy (anthracyclines, alkylating agents, anti-metabolites, etc.), systemic treatments, targeted therapies (bevacizumab, everolimus, tyrosine kinase inhibitors such as sunitinib, cabozantinib, surufatinib), and peptide receptor radionuclide therapy (PRRT). Other loco-regional treatments are trans-arterial embolization (TACE), radioembolization, and radiofrequency (RF) ablation in liver-limited/dominant disease.

Conclusion

The 9th CECOG Pancreas Cancer Academy covered a wide range of topics, from tumor biology to standard and promising future treatment concepts. Pancreatic cancer is very complex in its biology and treatment, and progress has been slow but steadily advancing in the recent decades. The present expert opinion summarizes current knowledge on the biology, diagnosis, and treatment of pancreatic cancer. Overall, pancreatic cancer remains a complex and difficult-to-treat disease and therefore it is essential that interdisciplinary treatment strategies are being developed under the auspices of a multidisciplinary tumor board. Ongoing extensive research exploring emerging knowledge of molecular prognostic markers and potentially druggable targets will hopefully be rewarded with breakthroughs in some of the many subtypes of this enormously complex entity.

Take-home message

- Pancreatic ductal adenocarcinoma is driven by diverse genetic alterations, with *KRAS* mutations being predominant. Multimodal imaging and molecular diagnostics are essential for accurate staging and treatment selection. Liquid biopsy helps to monitor treatment outcomes and understand resistance mechanisms.
- Multidisciplinary tumor boards are crucial for accurate diagnosis and determination of personalized treatment strategies. Upfront surgery and adjuvant mFOLFIRINOX are standard for fit patients with resectable disease, while neoadjuvant therapy is increasingly considered for (borderline) resectable tumors. Perioperative therapy is also explored.

- In a metastatic setting, FOLFIRINOX, NALIRIFOX, and gemcitabine–nab-paclitaxel are first-line options. Second-line therapies rely on switching to a different drug class and are also tailored to the patient's fitness.
- Immunotherapies and novel targeted agents, specifically RAS inhibitors, show great promise; however, additional research is required to demonstrate clinically relevant improvements in clinical and patient-reported outcomes.

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