Editorial Commentary

ESMO 2023 pancreatic cancer guidelines signal stepwise progress

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Pancreatic ductal adenocarcinoma (PDAC) is still a devastating disease, and for those who treat PDAC patients it sometimes seems that there is little to no relevant progress. The excellent new ESMO clinical practice guideline by Conroy *et al.* (1) points to important advances in pancreatic cancer therapy that were made since the previous edition from 2015 (2).

According to the American Cancer Society the overall five-year survival for all stages of PDAC has improved from 5% some 30 years ago to 13% in the present day. The major thrust lies in greatly improved outcomes for resectable pancreatic cancer with 5-year survival increasing from 5–10% at the beginning of this period to 30–50% due to technical improvements in surgery along with combination adjuvant chemotherapy. The latest European Society of Medical Oncology (ESMO) guidelines endorse this position for resectable pancreatic cancer, recommending primary resection followed by adjuvant chemotherapy, and with greatly improved choices for adjuvant chemotherapy. The 2015 standard, 5-fluorouracil (5-FU)/folinic acid or gemcitabine monotherapy, is now only indicated for frail patients, other patients should receive mFOLFIRINOX based on the PRODIGE 24 study, or, if not eligible for this treatment, gemcitabine/capecitabine according to the ESPAC-4 study. The guideline still clearly advises against adjuvant radiochemotherapy.

Contrast enhance computed tomography (CT) scanning is recommended as the main modality for diagnosing PDAC. Abdominal magnetic resonance imaging (MRI) is used when CT is inconclusive, such as for iso-attenuating tumors or when a contrast-enhanced CT is contraindicated, and liver MRI is mentioned as being more sensitive than CT for depicting small liver metastases. Positron emission tomography-CT is not routinely recommended for the diagnosis of pancreatic cancer due to overlapping diagnostic features with autoimmune and chronic pancreatitis, and no superiority over CT in identifying distant metastasis, with false-positive and false-negative rates of 7.8% and 9.8% respectively.

For patients with borderline resectable disease, there is now a stronger recommendation for neoadjuvant therapy before surgery. Still, there is no agreement on the best induction therapy, especially regarding the inclusion of radiotherapy. The guideline remains somewhat vague with a recommendation for FOLFIRINOX or gemcitabine/nab-paclitaxel followed by chemoradiotherapy "on a case-by-case basis" without defining the criteria for the radiochemotherapy. Whilst the PREOPANC-1 trial (3) used neoadjuvant chemoradiation, the ESPAC-5 trial (4) with short course neoadjuvant regimens found effective 1-year

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overall survival rates of 78% [95% confidence interval (CI): 60–100%] for gemcitabine plus capecitabine and 84% (95% CI: 70–100%) for FOLFIRINOX, compared to 60% (95% CI: 37–97%) for capecitabine-based chemoradiotherapy and 39% (95% CI: 24–61%) for immediate surgery (P=0.0028) (4). Moreover the 1-year disease-free survival from surgery was 33% (95% CI: 19–58%) for immediate surgery and 59% (95% CI: 46–74%) for the combined neoadjuvant therapies (P=0.016) (4). It is also noteworthy that in the phase II Alliance A021501 study, neoadjuvant radiotherapy after seven cycles of mFOLFIRINOX resulted in inferior 18-month overall survival of 47.3% compared with 66.7% using eight cycles of chemotherapy with mFOLFIRINOX without radiotherapy.

The ESMO 2023 guidelines endorse the new definition for borderline resectable disease by the International Association of Pancreatology (IAP) that also includes biological criteria based on serum CA19-9 levels, and the patient's performance status, thereby broadening the patient population with indication for neoadjuvant therapy. Although intuitively this might seem reasonable, it is not evidence-based since the randomized studies that established neoadjuvant therapy for borderline-resectable patients, including PREOPANC-1 (3) and ESPAC-5 (4), used empirical anatomical staging criteria only.

For patients with locally advanced disease, a paradigm change is noticeable as in the ESMO 2015 guidelines it was only stated that "the standard of care is 6 months of gemcitabine". The new ESMO 2023 guidelines mention a "conversion surgery strategy" with intensive induction chemotherapy as an option. These ESMO 2023 guidelines call for all patients to be evaluated for resectability every 2–3 months by the local multidisciplinary tumor board. In addition arterial resection after induction therapy is listed as a possible option in experienced centers after induction therapy.

In metastatic disease, the standard options for first-line chemotherapy (FOLFIRINOX, gemcitabine/nab-paclitaxel, gemcitabine monotherapy) and second-line chemotherapy have remained unchanged. Recently, the randomized NAPOLI-3 phase III study found that NALIRIFOX (liposomal irinotecan–5-FU–LV–oxaliplatin) significantly improved median overall survival (11.1 months) compared to gemcitabine-nab-paclitaxel (9.2 months; P=0.04). The place of NALIRIFOX in standard treatment algorithms however, including the difficult question whether it should replace classical FOLFIRINOX was not discussed. The ESMO 2015 guidelines simply stated that there is "no role for personalized therapy in this cancer". Fortunately, this has changed, albeit so far only for small patient subgroups. Genetic testing for germline BRCA mutations (5–7% of Caucasian patients) should now be performed in all patients with stage IV PDAC to select patients for platinum-based chemotherapy, and for maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors notably olaparib. Somatic testing of tumors may also identify additional BRCA mutations. It should be noted however that a randomised phase II trial in patients with gBRCA mutations although demonstrating a high response rate for gemcitabine-cisplatin failed to demonstrate a survival benefit for the addition of veliparib. Moreover whilst the POLO trial in metastatic PDAC patients with gBRCA variants that had not progressed following a 16-week platinum-containing regimen showed improved median progression free survival with maintenance olaparib compared with placebo there was no improvement in overall survival.

KRAS testing with additional genetic profiling for KRAS wildtype tumors should also be considered to identify NTRK fusions (1–2%) targetable with specific inhibitors, larotrectinib or entrectinib, as well as other rare druggable alterations. For the first time, immunotherapy with checkpoint inhibitors is listed as a therapy option, unfortunately only for the tiny subgroup of patients with microsatellite-unstable-high (MSI-H)/mismatch repair deficient tumors (dMMR) that constitute less than one percent of PDAC patients. In a study of 22 PDAC patients with MSI-H/dMMR treated with pembrolizumab there was one complete responder and three partial responders a median progression free survival of 2.1 months and a median overall survival of 3.7 months. The new ESMO guidelines suggest MSI-testing for KRAS wildtype tumors only since recent studies show that MSI prevalence is higher in these tumors (5), in our opinion KRAS-mutated tumors should also be tested.

The comparison of the two guidelines shows that some progress has been made during the last ten years. Current developments give some hope that the future may even be brighter. Several ongoing phase III studies will shed light on the optimal multimodal perioperative treatment (6). After years of failure to inhibit KRAS, the dominant genetic driver in PDAC, KRAS G12C inhibitors have now been licensed (although not yet for PDAC), and inhibitors specific for the KRAS G12D mutation that is present in about 40% of PDAC patients as well as pan-RAS inhibitors are being tested in phase I clinical trials (7). Although the first

monotherapy results in PDAC are not overwhelming (8), combinations with chemotherapy, with other targeted therapies like EGFR antibodies or with immunotherapy may have a relevant benefit for PDAC patients (7), not only in stage IV disease but also as induction therapy in locally advanced tumors or in the perioperative management. For KRAS wildtype patients, successful therapies for rare genetic alterations, e.g., NRG-1 fusions, are being developed (9). Transcriptomic signatures that guide systemic therapy are on the horizon (10) and are being tested in clinical studies, e.g., for the selection of the best adjuvant therapy in the randomized phase III ESPAC-6 study (NCT05314998).

Resistance mechanisms against chemotherapy are increasingly better understood which will also pave the way to more effective treatment strategies (10,11). Plasticity of PDAC tumors takes place over time through clonal evolution, and has recently been shown to occur with chemotherapy. Transcriptome analysis combined with high-resolution mapping of whole-tissue sections identified the development of hybrid molecular subtypes in pancreatic cancer cells coexpressing both classical-like (GATA6) and basal-like (KRT17) subtype markers in conjunction cytochrome P4503A responsible for detoxification pathways metabolizing the prodrug irinotecan (11). The persistence of GATA6^{hi} and KRT17^{hi} cells post-chemotherapy was significantly associated with poor survival after mFOLFIRINOX but not gemcitabine treatment (11).

Antibody-drug conjugates that are having a great impact in other cancer types are now also in clinical trials for PDAC, with targets including Claudin 18.2, Trop-2 and human epidermal growth factor receptor 2 (HER2) (12). Although results for immunotherapy have so far been disappointing in microsatellite-stable PDAC, there has been progress in understanding the obstacles to successful therapy, and different avenues are being pursued to establish this modality also for PDAC (13). This includes, among others, novel antibodies, oncolytic viruses, cellular therapies, and vaccines. The future role of cellular therapies in solid tumors is hard to predict, but chimeric antigen receptor (CAR) T cell cells against mesothelin, claudin 18.2 and carcinoembryonic antigen (CEA) and others as well as T cell receptor (TCR)-engineered T cells are currently being tested in PDAC (14). The first results for individualized neoepitope vaccines are promising, and larger studies are under way (15). We are cautiously optimistic that the next 10 years will bring more relevant progress for our patients and make the diagnosis "pancreatic cancer" a little bit less fearsome.

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