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ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with pancreatic cancer

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The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with pancreatic cancer, published in November 2023, were adapted in December 2024, according to previously established standard methodology, to produce the Pan-Asian adapted (PAGA) ESMO consensus guidelines for the management of Asian patients with pancreatic cancer. The adapted guidelines presented in this manuscript represent the consensus opinions reached by a panel of Asian experts in the treatment of patients with pancreatic cancer representing the oncological societies of China (CSCO), Indonesia (ISHMO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), the Philippines (PSMO), Singapore (SSO), Taiwan (TOS) and Thailand (TSCO), co-ordinated by ESMO and the Singapore Society of Oncology (SSO). The voting was based on scientific evidence and was independent of the current treatment practices, drug access restrictions and reimbursement decisions in the different regions of Asia. The latter are discussed separately in the manuscript. The aim is to provide guidance for the optimisation and harmonisation of the management of patients with pancreatic cancer across the different countries of Asia, drawing on the evidence provided by both Western and Asian trials. Attention is drawn to the disparity in drug approvals and reimbursement strategies between the different countries.

Key words: ESMO, guidelines, Pan-Asian, pancreatic cancer, treatment

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INTRODUCTION

The cumulative global 5-year survival rate for pancreatic cancer is estimated to be ∼10% and, in many countries, including China, Japan and South Korea (with respective 5-year survival rates of 7.2%, 12.7% and 15.9%), it is the most deadly common malignancy in terms of survival rate.[1-5] Pancreatic cancer is frequently diagnosed late in the disease course.[6] For example, in South Korea in 2020, ∼50% of cases were diagnosed at the metastatic stage and were associated with a 5-year survival rate of just 5% compared with respective 5-year survival rates of 48.0% and 19.6% for patients with localised and regional disease.[7] Similar findings were observed in a 2012 survey by the Japanese Pancreas Society where the overall 5-year survival rate for all patients with pancreatic cancer was 13.0% compared with 85.8% in patients with Union for International Cancer Control (UICC) stage 0 disease[6] In the 2022 GLOBOCAN analysis, pancreatic cancer was identified as the fifteenth most common cancer across Asia with an age-standardised incidence rate per 100 000 (ASIR) of 3.64, but with an age-standardised mortality rate per 100 000 (ASMR) of 3.27, it was the tenth highest cause of cancer death.[8,9] There were, however, regional differences; for example, in Western Asia, pancreatic cancer had the twelfth highest incidence of all cancers (ASIR 5.46) and the sixth highest mortality rate (ASMR 5.26), while in South-Central Asia, pancreatic cancer was the twenty-second most common cancer (ASIR 1.19) and sixteenth most common cause of cancer death (ASMR 1.12).[8,9]

Pancreatic cancer is more common in males than females and across Asia in 2022 the ASIR was 4.3 per 100 000 for males and 3.0 per 100 000 for females.[8,9] In an analysis of the burden of pancreatic cancer across 52 countries in Asia between 1990 and 2019, the disease burden increased in all age groups, particularly in those aged ≥55 years, who represented 84.41% of all cases in 2019.[8,10] The highest incidence was seen in those aged 70-74 years, although there were differences between the genders with peak incidence observed at 65-69 years for males and 70-74 for females.[10]

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer, accounting for 85%-90% of all pancreatic lesions.[11-13] The greatest modifiable risk factor for developing PDAC is smoking (cigarettes), with an odds ratio (OR) of 1.74 for current smokers compared with never smokers.[6] The risk was found to increase for those who smoked more per day, with an OR for developing pancreatic cancer of 3.0 for those who smoked >35 cigarettes per day compared with never smokers.[6] Similar findings were found in a meta-analysis of 10 population-based cohort studies in Japan where the hazard ratio (HR) for the increased risk of developing pancreatic cancer for current smokers compared with never smokers was 1.81 for males and 1.59 for females.[14] Other established risk factors for developing PDAC include diabetes mellitus, heavy daily alcohol consumption, pancreatitis, diets of processed meat, high fructose drink consumption, as well as obesity and high body mass index (BMI).[6,10,15] In the aforementioned analysis of pancreatic cancer in Asian countries, a high fasting blood glucose level was also identified as a risk factor for the development of pancreatic cancer.[10]

Several nonmodifiable risk factors have also been identified for the development of pancreatic cancer. In a Korean study of 1159 patients with pancreatic cancer, individuals with familial pancreatic cancer (i.e. those with at least two affected first-degree relatives) contributed to 3.1% of all cases of pancreatic cancer.[16] An association has also been reported between other cancers and the risk of developing pancreatic cancer, with an increased risk of developing pancreatic cancer reported for individuals who are relatives of breast, ovarian, prostate, colon, bile duct and liver cancer patients.[6] In addition, several cancer predisposition syndromes have been associated with an increased risk of developing PDAC, including familial mole melanoma syndrome, Peutz–Jeghers syndrome, hereditary pancreatitis, hereditary breast–ovarian cancer syndrome, familial adenomatous polyposis and Lynch syndrome (Table 1).[6,17] Moreover, pathogenic variants of many of the genes associated with these syndromes and other cancer predisposition genes, including the DNA damage response

Table 1. Recurrent germline mutations in Asian patients with pancreatic cancer[a]

Gene symbol	Cancer predisposition syndrome	Incidence in Asian patients (%)
CDKN2A	Familial mole melanoma syndrome	0.4
CFTR	Hereditary pancreatitis	0.1-0.8
SPINK1	Hereditary pancreatitis	0.7-2.1
BRCA1	Hereditary breast–ovarian cancer syndrome	0.1-0.9
BRCA2	Hereditary breast–ovarian cancer syndrome	0.3-3.6
MLH1	Lynch syndrome	0.1-0.4
MSH2	Lynch syndrome	0.6
MSH6	Lynch syndrome	0.3-0.6
EPCAM	Lynch syndrome	0.1
ATM		0.4-1.9
BRP1		0.1-1.1
PALB2		0.1-1.0
FANCE		0.8
FANCA		0.2-0.6
BARD1		0.4
CHEK2		0.1-0.4
TP53	Li–Fraumeni syndrome	0.03-0.4
RAD51D		0.3
FANCC		0.2

ATM, *ATM* serine/threonine kinase; *BARD1*, *BRCA1* associated RING domain 1; *BRCA1*, *BRCA1* DNA repair associated; *BRCA2*, *BRCA2* DNA repair associated; *BRP1*, *BRCA1* interacting DNA helicase 1; *CDK2NA*, cyclin-dependent kinase inhibitor 2A; *CFTR*, CF transmembrane conductance regulator; *CHEK2*, checkpoint kinase 2; *EPCAM*, epithelial cell adhesion molecule; *FANCA*, Fanconi anaemia, complementation group A; *FANCC*, Fanconi anaemia, complementation group C; *FANCE*, Fanconi anaemia, complementation group E; *MLH1*, mutL homolog 1; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; *PALB2*, partner and localiser of *BRCA2*; *TP53*, tumour protein P53; *RAD51D*, RAD51 paralog D; *SPINK1*, serine peptidase inhibitor kazal type 1.

[a]Known genes associated with pancreatic cancer seen in at least one or identified in two or more studies investigating germline mutations in Asian patients with pancreatic ductal adenocarcinoma.[18-20]

genes ATM serine/threonine kinase (*ATM)* and, partner and localiser of BRCA2 (*PALB2*) have been identified in Asian patients with PDAC (Table 1).[18-20] For instance, in a Taiwanese study, 19.7% of 527 nonselected patients with pancreatic cancer carried pathogenic/likely pathogenic germline variants in homologous recombination genes.[18] Aberrations (mutations, deletions, fusions) in cyclin-dependent kinase inhibitor 2A (*CDKN2A*), as well in the KRAS proto-oncogene, GTPase (*KRAS*), GNAS complex locus (*GNAS*) and B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) genes, have been identified in precancerous lesions of PDAC and are believed to drive disease progression.[21,22] Of these, mutations in *KRAS* are the most common in PDAC and are seen in 90%-95% of cases.[2]

The most recent European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with pancreatic cancer were published in November 2023[23] with an express update on the management of metastatic pancreatic cancer published in April 2025.[24] Before the submission of the publication of the express update, a decision was taken by the ESMO and the Singapore Society of Oncology (SSO) that these latest ESMO guidelines should be adapted to provide updated Pan-Asian guidelines for the management and treatment of pancreatic cancer in patients of Asian ethnicity. This manuscript summarises the Pan-Asian adapted guidelines developed and agreed at a face-to-face working meeting that took place in Singapore on 5 December 2024, hosted by the SSO. Each recommendation is accompanied by the level of evidence (LoE), grade of recommendation (GoR) and, where applicable, ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) and ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) scores (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105826).[25,26]

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guideline[23] was prepared in accordance with the principles of ESMO standard operating procedures (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was an SSO—ESMO initiative endorsed by the Chinese Society of Clinical Oncology (CSCO), the Indonesian Society of Hematology and Medical Oncology (ISHMO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Japanese Society of Medical Oncology (JSMO), the Malaysian Oncological Society (MOS), the Philippine Society of Medical Oncology (PSMO), Taiwan Oncology (TOS) and the Thai Society of Clinical Oncology (TSCO). An international panel of experts was selected from the SSO ($n = 6$), the ESMO ($n = 6$ including the co-ordinator of the Pan-Asian Guideline adaptations, TY), and two experts from each of the nine other oncological societies. Only two of the six expert members from the SSO (JJXL and CEC) were allowed to vote on the recommendations together with the experts from each of the nine other Asian oncology societies ($n = 20$). All 20 Asian experts provided comments on the premeeting survey and one consensus response per society (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105826). Only one voting member per Asian society was present at the face-to-face meeting. The additional members including the ESMO experts were present in an advisory role only (see Supplementary Material: Methodology, available at https://doi.org/10.1016/j.esmoop.2025.105826). All the Asian experts ($n = 20$) approved the revised recommendations.

RESULTS

A. Scientific adaptations of the ESMO recommendations

In the initial premeeting survey, the 20 voting Asian experts reported on the 'acceptability' of the 66 recommendations for the diagnosis, treatment and follow-up of patients with pancreatic cancer from the most recent ESMO Clinical Practice Guideline[23] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105826), in the six categories outlined in the text below and in Table 2. A lack of agreement in the premeeting survey was established for 25 recommendations, 19 of which were discussed at the face-to-face working meeting in Singapore to adapt the recently published ESMO Clinical Practice Guideline. 'Recommendation 5e' was also discussed. For each of 'recommendations 1d, 2g and 2m' there were discrepancies relating to their applicability in certain regions of Asia and not their 'scientific acceptability'. As a result, these were not discussed at the face-to-face meeting. No new recommendations were added (see Supplementary Material: Results, available at https://doi.org/10.1016/j.esmoop.2025.105826).

The guideline recommendations below and in Table 2 for the diagnosis, treatment and follow-up of Asian patients with pancreatic cancer have been agreed by the Pan-Asian panel of experts based exclusively on the available scientific evidence and their professional opinions. It is acknowledged that regional differences in the availability of drugs, equipment and testing facilities, as well as reimbursement and access to treatment, may affect the implementation of certain of these recommendations. Where possible, the recommendations have been amended to take into account these regional differences.

1. Incidence and epidemiology—recommendations 1a-d

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 1a-d'.

2. Diagnosis pathology and molecular biology—recommendations 2a-o

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 2a-j and l-o' (Table 2),

Table 2. Summary of Asian consensus recommendations for the treatment of patients with pancreatic cancer

	Acceptability consensus
1. INCIDENCE AND EPIDEMIOLOGY	
1a. Not smoking, limiting alcohol intake and reaching and maintaining a healthy weight are highly recommended to reduce the risk of pancreatic cancer [III, A]	100%
1b. Individuals from families at risk should receive genetic counselling and be considered for enrolment in investigational screening registries [III, A]	100%
1c. Surveillance in expert centres, usually beginning at age 50 years (or 10 years earlier than the age of the youngest affected relative), is recommended in high-risk individuals to detect early pancreatic cancer [III, A]	100%
1d. Annual EUS and/or pancreatic MRI are preferred for surveillance [IV, B]	100%
2. DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY	
Imaging	
2a. Multiphasic contrast-enhanced thoracic-abdominal and pelvic CT, including late arterial phase and portal venous phase, should be used as the first-line imaging modality for suspected pancreatic cancer [III, A]	100%
2b. It is recommended that, in case of jaundice due to an obstructive head pancreatic cancer, imaging should be carried out before biliary drainage or stenting [IV, A]	100%
2c. Imaging should be carried out in the 4 weeks before starting treatment [III, A]	100%
2d. Abdominal MRI may be used when CT cannot be carried out, is inconclusive or for pancreatic cystic lesions [IV, C]; in this case chest CT is mandatory [III, A]	100%
2e. Dedicated imaging protocols are suggested [IV, B]. Comprehensive analysis of imaging findings should be incorporated in standardised reporting templates [IV, A]	100%
2f. PET-CT is not recommended for diagnosis of primary tumours [III, D] but may be useful for staging localised tumours and in cases where the presence of distant metastases is uncertain (doubtful imaging or high CA 19-9) [III, B]	100%
2g. Hepatic MRI is recommended before surgery to confirm the absence of small liver metastases [III, B]	100%
2h. Cytology or biopsy proof of pancreatic cancer should be obtained before initiation of ChT in localised disease, preferably by EUS guidance [III, A]	100%
2i. All patients with localised disease should have imaging reviewed at an MDTB with experts in pancreas imaging, pancreas surgery and oncology [III, A]	100%
Molecular biology	
2j. Patients with family history and high-risk individuals should undergo genetic counselling [III, A]	100%
2k. **Somatic** *KRAS* **testing in unresectable PDAC patients** and **germline** *BRCA* testing in PDAC patients are generally recommended [IV, B]**. Somatic *BRCA* testing in unresectable PDAC can be considered [IV, C]**	100%
2l. If a KRAS-wt tumour is identified with next-generation sequencing, additional profiling can be carried out to evaluate for rare, potentially actionable findings [IV, B]	100%
2m. For patients with metastatic pancreatic cancer and KRAS-wt tumours, MSI status, NTRK fusion status and other rare fusions should be assessed [III, B]	100%
2n. If multigene sequencing is not carried out, MSI and NTRK fusions can be detected using standard methods [IV, B]	100%
2o. CA 19-9 can be used as a serum marker to measure disease burden and potentially guide treatment decisions [III, B]	100%
3. STAGING AND RISK ASSESSMENT	100%
3a. Tumours should be staged according to the UICC TNM 8th edition staging system [III, A]	100%
3b. Resectability can be assessed using both anatomical NCCN criteria and biological and conditional features following the IAP consensus [III, B]	100%
3c. MDTB discussion in expert centres is required to define a recommended treatment strategy for patients with pancreatic cancer [III, A]	100%
4. MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE	
Treatment of resectable pancreatic cancer	
4a. Frozen section analysis of pancreatic neck transection and of common bile duct transection margins is suggested [IV, B]	100%
4b. Tumour clearance should be defined for all margins identified by the surgeon [III, B]	100%
4c. For patients with tumours in the body or tail, radical anterograde modular pancreatosplenectomy with dissection of the left hemi-circumference of the SMA to the left of the coeliac trunk is recommended [IV, A]	100%
4d. The UICC TNM eighth edition staging system should be used to classify the anatomical spread of the tumour [III, A]	100%
4e. Standard lymphadenectomy is recommended and should involve the removal **and pathological examination** of $\geq$16 lymph nodes to allow adequate pathological staging of the disease [IV, A]	100%
4f. The total number of lymph nodes examined and lymph node ratio (number of involved lymph nodes as a proportion of the number of lymph nodes examined) should be reported in the pathological analysis [IV, A]	100%
4g. Patients undergoing surgery should receive perioperative thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin, unless contraindicated [I, A]	100%
4h. **In resectable disease,** if the bilirubin level is $>$250 µmol/l, endoscopic drainage is recommended in patients with cholangitis or those in whom surgery will be delayed for longer than 2 weeks [I, B]	100%
4i. Neoadjuvant therapy is **generally** not recommended for resectable pancreatic cancer due to limited **published** phase III evidence, except in the context of clinical trials [II, **D**]	100%
4j. Following resection of pancreatic cancer, completion of 6 months of adjuvant ChT is strongly recommended [I, A]	100%
4k. Adjuvant mFOLFIRINOX **or S-1 are** recommended for patients with resected pancreatic cancer and ECOG PS 0-1 [I, A; ESMO-MCBS v1.1 score **for mFOLFIRINOX**: A**; *ESMO-MCBS v1.1 score for S-1: A***]	100%
4l. In patients who are not candidates for mFOLFIRINOX, gemcitabine–capecitabine **or S-1 are** alternative **options** [**II**, B; ESMO-MCBS v1.1 score **for gemcitabine–capecitabine**: A]	100%

Continued

Table 2. Continued

	Acceptability consensus
4m. Adjuvant gemcitabine or 5-FU—LV **can be considered for patients with resected** pancreatic cancer **who are not candidates for S-1 or combination ChT** [**IV**, B]	100%
4n. Adjuvant CRT is not recommended and should not be given to patients following surgery outside the setting of a clinical trial [I, E]	100%
Treatment of borderline resectable pancreatic cancer	
4o. Patients with borderline resectable pancreatic cancer have a high probability of an R1 resection and should be considered for induction treatment [III, A]	100%
4p. Patients should be included in clinical trials whenever possible [III, A]	100%
4q. If inclusion in a clinical trial is not feasible, induction therapy is recommended over initial surgery [II, A]	100%
4r. A period of induction ChT (FOLFIRINOX**/mFOLFIRINOX** or GN) and subsequent surgery, is **recommended** [**II**, B]**. CRT with S-1 can be considered as an option [II, C]**	100%
4s. Gemcitabine combined with **either S-1 [II, C]** oxaliplatin **[IV, C]** or capecitabine **[IV, C]** may be considered, when FOLFIRINOX**/mFOLFIRINOX** or GN are not feasible	100%
4t. Following induction therapy, medically fit patients without disease progression and with a decrease in CA 19-9 should undergo surgical exploration, unless contraindicated [III, A]	100%
Treatment of locally advanced pancreatic cancer	
4u. All patients must be evaluated by the local MDTB for resectability every 2-3 months [III, A]	100%
4v. Patients with locally advanced pancreatic cancer should be included in clinical trials whenever possible [III, A]	100%
4w. A conversion surgery strategy utilising the standard of care of (up to) 6 months of combination ChT (FOLFIRINOX**/mFOLFIRINOX** or GN) can be chosen [**IV**, B]	100%
4x. Exploration for resection could be discussed if there is a significant decrease in CA 19-9 level, clinical improvement and tumour downstaging [IV, B]	100%
4y. Arterial resection after induction therapy is not recommended but can be considered as a possibility in experienced centres on a case-by-case basis in selected patients [IV, D]	100%
5. MANAGEMENT OF ADVANCED DISEASE	
First-line treatment	
5a. Options to treat patients with metastatic pancreatic cancer are dependent on PS:	100%
5a-i. In patients with ECOG PS 0-1 and bilirubin level $<$1.5 times the ULN, **the following** regimens **are recommended**: FOLFIRINOX [I, A; ESMO-MCBS v1.1 score: 5]**,** NALIRIFOX [**I, A;** MCBS SCORE v1.1 score: 2]**,** GN [I, A; ESMO-MCBS v1.1 score: 3]**, or mFOLFIRINOX [III, B]**	100%
5a-ii. For patients with ECOG PS 2, KPS $\geq$70 and bilirubin level $\leq$1.5 times the ULN, GN can be considered [II, A; ESMO-MCBS v1.1 score: 3]	100%
5a-iii. For patients with ECOG PS 2, KPS $<$70 and/or bilirubin level $>$1.5 times the ULN, gemcitabine **or S-1** monotherapy **can** be considered [**IV, B**]	100%
5a-iv. For patients with ECOG PS 3-4, symptom-directed care should be considered, as the risks of any ChT likely outweigh any benefit in this setting [IV, A]	100%
5b. The efficacy of treatment should be typically evaluated every 8-12 weeks and should be based on clinical status, CA 19-9 trajectory and imaging [III, A]	100%
5c. Patients with *BRCA* mutations should receive platinum-based ChT [III, A].	100%
Second-line treatment	
5d. After FOLFIRINOX **or mFOLFIRINOX** treatment, **gemcitabine alone [III, B] or in combination with paclitaxel [III, B] or nab-paclitaxel [III, B]** may be offered to patients with ECOG PS **0-2**	100%
5e. In patients with, or who have recovered to, ECOG PS 0-1 and who have been pretreated with a gemcitabine-based regimen, liposomal irinotecan—5-FU—LV [I, B; ESMO-MCBS v1.1 score: 3] **or mFOLFIRINOX [II, B] can be considered**	100%
5f. Oxaliplatin-based second-line treatment (mFOLFOX6 or OFF) remains controversial but may be considered as an alternative in patients with ECOG PS 0-2 if not given previously [II, C]	100%
5g. For patients with ECOG PS 3-4, symptom-directed care is recommended as the risks of any ChT likely outweigh any benefit [IV, A]	100%
Third-line treatment	
5h. Most patients are considered unsuitable for third-line treatment due to poor nutritional status and/or PS In such cases, no standard regimen can be recommended and best supportive care is the appropriate treatment choice In patients with a good PS, inclusion in a clinical trial is the first option when available	100%
Precision medicine in metastatic pancreatic cancer	
5i. BRCA genetic testing should be offered to all patients with metastatic pancreatic cancer to determine eligibility for selection of platinum-based ChT, followed by maintenance with olaparib [I, B; olaparib ESMO-MCBS v1.1 score: 2] Olaparib maintenance treatment is an option for patients with a *gBRCA1/2* variant whose disease is stable or responsive to platinum-based ChT [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A]	100%
5j. In patients with MSI-H/dMMR pancreatic tumours, pembrolizumab can be proposed as second- or later-line treatment [II, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C; FDA approved; not EMA approved as a dMMR/MSI-H tumour-agnostic indication but for specific tumour types (excludes pancreatic cancer)].	100%
5k. In patients with an *NTRK* fusion, larotrectinib**,** entrectinib**, or repotrectinib are** recommended [III, A; ESMO-MCBS v1.1 score **for larotrectinib and entrectinib**: 3; ESCAT score: I-C]	100%

Continued

Table 2. Continued	
	Acceptability consensus
6. FOLLOW-UP, SUPPORTIVE CARE, LONG-TERM IMPLICATIONS AND SURVIVORSHIP	
Follow-up	
6a. For patients with resected pancreatic cancer, regular follow-up is suggested [**III**, B]	100%
Supportive and palliative care	
6b. Primary thromboprophylaxis **can** be considered in advanced pancreatic cancer patients receiving ChT **in the absence of contraindications** [I, **C**]	100%
6c. In the event of biliary obstruction, endoscopic placement of a fully covered, self-expandable metallic biliary stent is suggested [II, B]	100%
6d. Duodenal obstruction can be managed by endoscopic placement of an expandable metal stent [IV, B] **or EUS-GE (where expertise is available) [II, B] instead of surgery**	100%
6e. Effective pain control is strongly recommended and should involve a pain control specialist when required [III, A]	100%

5-FU—LV, 5-fluorouracil—leucovorin; *BRCA*, *BRCA* 1/2 [*BRCA*1/2 DNA repair associated]; CA 19-9, carbohydrate antigen 19-9; ChT, chemotherapy; CT, computed tomography; CRT, chemoradiotherapy; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale version 1.1; EUS, endoscopic ultrasound; EUS-GE, endoscopic ultrasonography-guided gastroenterostomy; FDA, United States Food and Drug Administration; FOLFIRINOX, leucovorin—5-fluorouracil—irinotecan—oxaliplatin; GN, gemcitabine—nab-paclitaxel; IAP, International Association of Pancreatology; KPS, Karnofsky Performance Scale; *KRAS*, *KRAS* proto-oncogene, GTPase; MDTB, multidisciplinary tumour board; mFOLFIRINOX, modified leucovorin—5-fluorouracil—irinotecan—oxaliplatin; mFOLFOX6, modified 5-fluorouracil—leucovorin—oxaliplatin; MRI, magnetic resonance imaging; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NALIRIFOX; liposomal irinotecan—fluorouracil—leucovorin—oxaliplatin; NCCN, National Comprehensive Cancer Network; *NTRK*, neurotrophic tyrosine receptor kinase; OFF, oxaliplatin—5-fluorouracil—leucovorin; PDAC, pancreatic ductal adenocarcinoma; PET-CT, positron emission tomography—computed tomography; PS, performance status; R1, microscopic residual tumour; S-1, tegafur—gimeracil—oteracil; SMA, superior mesenteric artery; TNM, tumour—node—metastasis; UICC, Union for International Cancer Control; ULN, upper limit of normal; wt, wild-type.

without change, and, following discussion at the face-to face meeting, the revised 'recommendation 2k'.

Although the Pan-Asian panel of experts agreed with the need for genetic testing for *BRCA1* and *BRCA2* mutations as discussed in ESMO 'recommendation 2k', they felt that it was important to clarify that this should refer to germline genetic testing because patients with these mutations have been shown to have improved outcomes to initial platinum-based chemotherapy (ChT)[27] and pathogenic variants may also be targets for poly (ADP-ribose) polymerase (PARP) inhibitors.[28-30] However, although testing for somatic *BRCA1/2* mutations may also be informative, the clinical benefit and prognostic significance is not well defined. Moreover, in many regions of Asia, testing for somatic *BRCA* mutations is not reimbursed (the applicability of these guidelines and availability of drugs and diagnostic tests are discussed in part B). The recommendation was, however, amended to include the consideration for somatic testing for *BRCA1/2* mutations although this was given a lower GOR ('*C*' compared with '*B*' for germline testing). Discussion of 'recommendation 2k' moved on to testing for somatic *KRAS* mutations, which occur in >90% of cases of PDAC with the G12D variant being the most common variant and seen in ∼40% of cases.[31] Although agents targeting *KRAS*-mutant variants are in clinical development (see discussion of the recommendations below), none have been approved for the treatment of pancreatic cancer. Screening for *KRAS* mutants may have a prognostic benefit because patients with *KRAS* wild-type tumours tend to have higher survival rates. They may also harbour other actionable molecular alterations in genes such as *NTRK*, *ROS1*, *ALK* and *RET.* While there are many regions in Asia where inhibitors targeting these alterations are not available, it was agreed that identifying *KRAS* wild-type tumours could be useful for identifying patients who may benefit from further somatic genetic testing where next-generation sequencing (NGS) may not be available or affordable for patients, thus potentially reducing costs. The discussion also turned to the timing of somatic genetic testing with several of the experts suggesting that they do not provide somatic genetic tests as standard until after progression on the first line of treatment, but it was decided not to include this in the recommendation and to only suggest which genetic tests were recommended with the text modified to read as follows and in Table 2 (**100% consensus**):

2k. ***Somatic KRAS testing in unresectable PDAC patients and germline BRCA testing in PDAC patients are generally recommended [IV, B]. Somatic BRCA testing in unresectable PDAC can be considered [IV, C; consensus = 100%].***

Figure 1 shows the algorithm for the diagnostic work-up for patients with suspected pancreatic cancer.

3. Staging and risk assessment—recommendations 3a-c

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 3a-c'.

4. Management of local and locoregional disease —recommendations 4a-z

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 4a-d, f-g, j, n-q, t-v and x-z (Table 2), without change. Following discussion at the face-to face meeting, 'recommendation 4t' was deleted

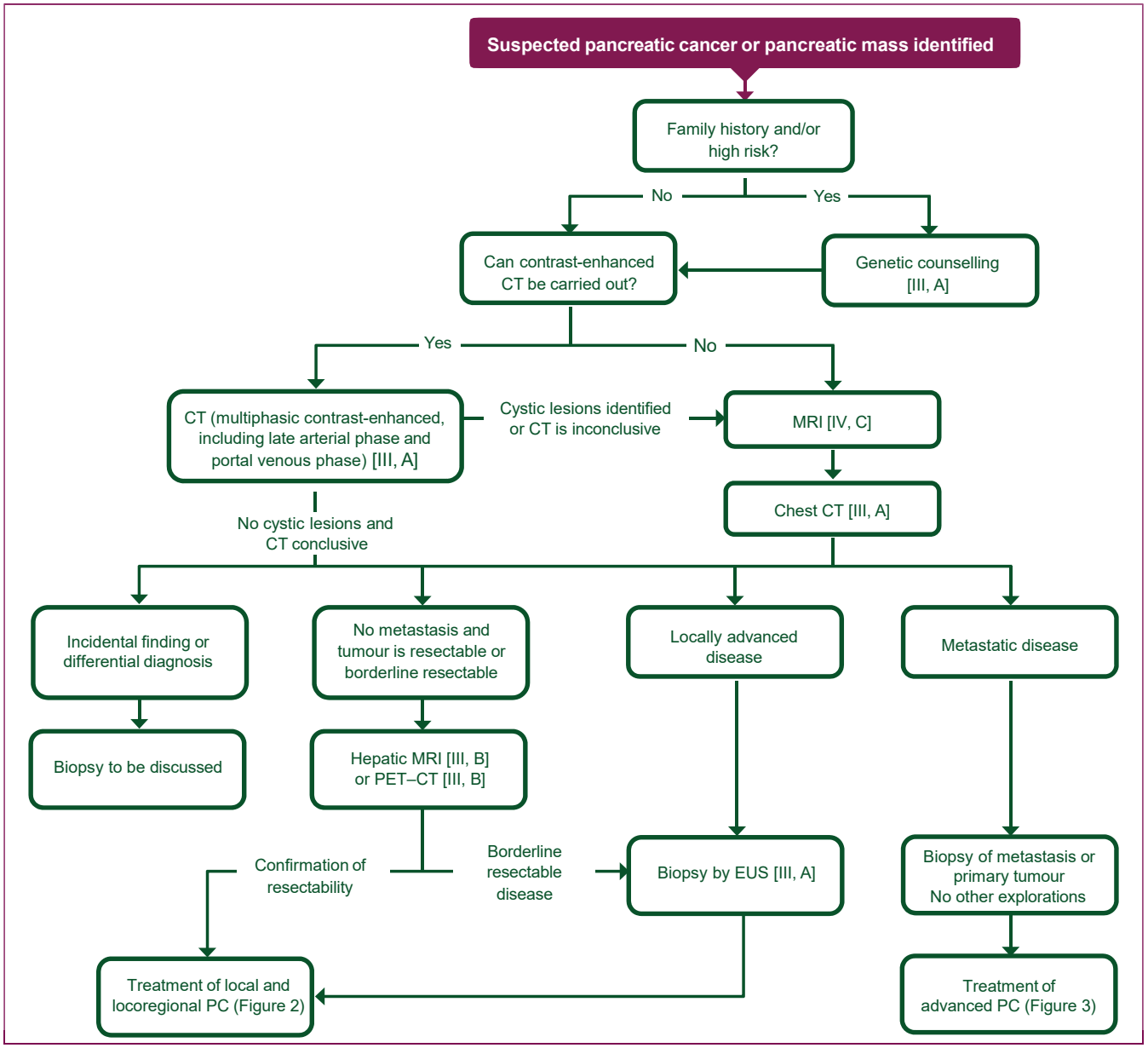

Figure 1. Diagnostic work-up of suspected pancreatic cancer.
Purple: general categories or stratification; white: management.
CT, computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; PC, pancreatic cancer; PET, positron emission tomography.

(100% consensus) and ESMO 'recommendations 4s-z' were renumbered accordingly. Following discussion at the face-to-face meeting, the original ESMO recommendations, 'recommendations 4e, h-i, k-m, r-s, and w' were revised and accepted completely (100% consensus).

Treatment of resectable pancreas cancer

For ESMO 'recommendation 4e', and the involvement of standard lymphadenectomy to ensure accurate pathological staging, there was some discussion regarding the number of lymph node stations that should be resected. While the International Study Group on Pancreatic Surgery (ISGPS) suggested a minimum of 12-15 lymph nodes (including lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a and 17b, and, for cancers of the body and tail of the pancreas, also stations 10, 11 and 18),[32] several large retrospective studies have suggested that a minimum of 11-19 lymph nodes are required for improved staging and prognostication.[33-35] Thus, it was agreed as per the original ESMO recommendation that $\geq$16 lymph nodes should be resected. It was agreed that the wording of the recommended be modified to underline the importance that all resected nodes be examined to allow for adequate pathological staging, as shown in bold below and in Table 2 (**100% consensus**) to read:

4e. *Standard lymphadenectomy is recommended and should involve the removal and pathological examination of $\geq$16 lymph nodes to allow adequate pathological staging of the disease [IV, A*; consensus = 100%*].*

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The discussion around ESMO 'recommendation 4g' centred around the need for perioperative thromboprophylaxis with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) and whether this should be assessed on a case-by-case basis. The incidence of post-operative venous thromboembolism (VTE) in Asian patients following curative surgery for hepatobiliary-pancreatic cancer was reported to be 3.4% in the control group of a Japanese randomised phase III study of 262 patients investigating whether post-operative enoxaparin prophylaxis could reduce the relative risk of VTE.[36] A systematic review investigated the relative efficacy and safety of anticoagulants for perioperative thromboprophylaxis in people with cancer, including 20 randomised controlled trials with a total of 9771 randomly assigned people with cancer who received pre-operative prophylactic anticoagulation. It found no difference between perioperative thromboprophylaxis with LMWH versus UFH and LMWH compared with fondaparinux with respect to their effects on mortality, thromboembolic outcomes, major bleeding or minor bleeding, although there was a lower incidence of wound haematoma with LMWH compared with UFH.[37] It was thus agreed that unless contraindicated, patients undergoing surgery should receive perioperative UFH or LMWH as a prophylactic anticoagulant, and the text for 'recommendation 4g' was agreed without change (**100% consensus**) to read (Table 2):

4g. *Patients undergoing surgery should receive perioperative thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin, unless contraindicated [I, A;* ***consensus = 100%****].*

Although there may be an increased risk of serious complications with preoperative endoscopic drainage for patients with early pancreatic cancer, its use was not found to increase the rate of mortality in either a multicentre randomised trial of 202 patients with cancer of the head of the pancreas[38] or in a systematic review comparing preoperative endoscopic retrograde cholangiopancreaticography with or without stenting in patients with pancreaticobiliary malignancy.[39] The Pan-Asian panel of experts agreed with the ESMO 'recommendation 4h' and the need for the use of endoscopic drainage in patients with a bilirubin level >250 µmol/l or for those for whom surgery will be delayed for >2 weeks. However, it was pointed out that neoadjuvant ChT is not a standard of care in this setting and as a result, reference to planned neoadjuvant treatment was removed from the recommendation. It was also felt that the text should emphasise that this recommendation is for patients with resectable disease and, as such, the recommendation was amended, with changes shown in bold below and in Table 2 (**100%, consensus**) to read:

4h. ***In resectable disease,*** *if the bilirubin level is >250 µmol/l, endoscopic drainage is recommended in patients with cholangitis or those in whom surgery will be delayed for longer than 2 weeks [I, B;* ***consensus = 100%****].*

In the randomised phase II NEPAFOX trial in patients with resectable or borderline resectable pancreatic cancer without metastases, 21 patients were enrolled into arm A to receive up front surgery plus adjuvant gemcitabine compared with 19 patients who were enrolled into arm B to receive perioperative leucovorin—fluorouracil (5-FU)—irinotecan—oxaliplatin (FOLFIRINOX).[40] This was below the planned accrual of 126 patients and, of those enrolled, 17 patients in arm A and 7 patients in arm B underwent curative surgery with R0-resection achieved in 77% and 71% of patients, respectively. Although the median recurrence/progression-free survival (PFS) was greater in patients treated with neoadjuvant FOLFIRINOX (14.1 months) compared with those treated with adjuvant gemcitabine (8.4 months), the primary endpoint was comparable between both arms, with median overall survivals (OSs) of 22.6 months and 25.7 months, respectively.[40] In the randomised phase II NORPACT-1 trial in patients with a resectable tumour of the pancreatic head with strongly radiologically suspected PDAC, 63 patients received neoadjuvant FOLFIRINOX followed by surgery and 56 patients underwent upfront surgery followed by adjuvant ChT. With a median OS of 25.1 months for patients in the neoadjuvant FOLFIRINOX group, no survival benefit was observed compared with the upfront surgery group [median OS 38.5 months; HR 1.52, 95% confidence interval (CI) 1.00-2.33, log-rank $P = 0.050$).[41] However, in the Japanese randomised phase II/III Prep-02/JSAP05 trial, neoadjuvant or induction gemcitabine plus tegafur, gimeracil and oteracil (S-1) was compared with upfront surgery in patients with resectable or borderline resectable pancreatic cancer (BRPC). There were 182 patients in the gemcitabine—S-1 group compared with 180 in the upfront surgery group and the median OSs were 36.7 months and 26.6 months, respectively (HR 0.72, 95% CI 0.55-0.94, stratified log-rank test $P = 0.015$). The resection rate, R0-resection rate and level of morbidity was equivalent between the two groups, and there was no perioperative mortality in either group.[42] Based on this evidence, the Japanese guidelines for the treatment of pancreatic cancer recommend the use of neoadjuvant gemcitabine plus S-1.[43] While the Pan-Asian panel of experts agreed that although this evidence for the use of neoadjuvant gemcitabine plus S-1 in resectable pancreatic cancer was compelling, it was felt that, despite being obtained in a phase II/III study, the robustness of the data had not been adequately assessed because it had not been through the peer-review process but instead presented at a congress 6 years previously. As such, the results could not be given the same LoE weighting as a similar study that had been through the rigours of the peer-review process. The Pan-Asian panel of experts also felt that for ESMO 'recommendation 4i' and the use of neoadjuvant therapy, the GoR should be upgraded from '*E*': *strong evidence against efficacy or for adverse outcome, never recommended*, to '*D*': *moderate evidence against efficacy or for*

adverse outcome, generally not recommended. The text for the recommendation was modified to take this into account, with changes shown in bold below and in Table 2, (**100% consensus**) to read:

*4i. Neoadjuvant therapy is **generally** not recommended for resectable pancreatic cancer due to limited **published** phase III evidence, except in the context of clinical trials [II, **D; consensus = 100%**].*

In the PRODIGE 24-ACCORD randomised phase III trial in patients with resected pancreatic cancer who had an Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) of 0-1, adjuvant modified FOLFIRINOX (mFOLFIRINOX) was compared with adjuvant gemcitabine. A total of 247 patients were treated with mFOLFIRINOX and 246 patients were treated with gemcitabine, and the respective disease-free survivals (DFSs) were 21.6 months and 12.8 months (stratified HR for cancer-related event, second cancer or death 0.58, 95% CI 0.46-0.73, $P < 0.001$), with DFS rates at 3 years of 39.7% and 21.4%. The median OS was 54.4 months for the mFOLFIRINOX group and 35.0 months for the gemcitabine group (stratified HR for death 0.64, 95% CI 0.48-0.86, $P = 0.003$) with OS rates at 3 years of 63.4% and 48.6%, respectively.[44] Because of these findings, the Pan-Asian panel of experts agreed with the use of adjuvant mFOLFIRINOX for the treatment of patients with resected pancreatic cancer who had an ECOG PS of 0-1 as described in ESMO 'recommendation 4k'. However, in some regions in Asia, S-1 is the preferred treatment in this setting. Evidence for the efficacy of adjuvant S-1 for the treatment of patients with resected pancreatic cancer was seen in the Japanese randomised phase III JASPAC-01 trial where 192 patients were assigned to receive adjuvant S-1 and 193 patients assigned to receive adjuvant gemcitabine. Of these, 187 and 190, respectively, received the relevant ChT. The median OS was 46.5 months for patients in the S-1 group and 25.5 months in the gemcitabine group (HR for mortality of S-1 compared with gemcitabine 0.57, 95% CI 0.44-0.72, P noninferiority < 0.0001, $P < 0.0001$ for superiority). The 5-year OS rates were 44.1% and 24.4%, respectively.[45] The percentage of lymph-node-negative patients was higher in the JASPAC-01 study (36%) compared with the PRODIGE 24-ACCORD study (22%).[44,45] While S-1 and mFOLFIRINOX have not been compared in the adjuvant setting, they have been assessed in the Korean randomised phase III MPACA-3 trial in the second line setting for patients with metastatic pancreatic cancer who had progressed on gemcitabine where mFOLFIRINOX treatment resulted in superior survival rates than S-1 alone (median OS 9.2 months versus 4.9 months, respectively; adjusted HR 0.4, 95% CI 0.2-0.7, $P = 0.002$). However, in this Asian cohort of patients, mFOLFIRINOX had a significantly higher rate of grade 3-4 events (56%) compared with S-1 (17%, $P < 0.001$).[46] In a systematic review and network meta-analysis assessing adjuvant chemotherapies for resected pancreatic adenocarcinoma, both mFOLFIRINOX and S-1 demonstrated a DFS benefit versus gemcitabine—capecitabine, gemcitabine—erlotinib, gemcitabine—nab-paclitaxel (GN). OS benefits were reported for S-1 versus gemcitabine in combination with erlotinib, capecitabine and nab-paclitaxel, and for mFOLFIRINOX versus gemcitabine—erlotinib.[47] While this study concluded that mFOLFIRINOX is the preferred adjuvant ChT, it suggested that S-1 should be considered in Asian populations.[47] The decision on the choice of adjuvant therapy should be individualised to patients based on their wishes, comorbidities and disease factors. The Pan-Asian panel of experts agreed that S-1 should be included in the recommendation but there was a great deal of discussion about whether to give it the same GoR as mFOLFIRINOX. In the end, it was agreed, based on the safety and currently available evidence, that S-1 be given the same GoR as mFOLFIRINOX, namely *'A': strong evidence for efficacy with a substantial clinical benefit, strongly recommended*. Thus, ESMO 'recommendation 4k' was amended to include S-1, as shown in bold in the text below and in Table 2, to read (**100% consensus**):

*4k. Adjuvant mFOLFIRINOX **or S-1 are** recommended for patients with resected pancreatic cancer and ECOG PS 0-1 [I, A; ESMO-MCBS v1.1 score **for mFOLFIRINOX**: A; **ESMO-MCBS v1.1 score for S-1: A; consensus = 100%**].*

Although the JASPAC-01 study only included patients with ECOG PS 0-1, in Japan, S-1 is routinely used for older patients and those with an ECOG PS of 2 and in the aforementioned systematic review and meta-analysis, S-1 was found to have both a DFS and OS benefit over gemcitabine—capecitabine, which is the suggested alternative adjuvant ChT for the treatment of patients with ECOG PS 2 or who are not candidates for mFOLFIRINOX. This recommendation was based on the randomised phase III ESPAC-4 trial, which compared adjuvant gemcitabine alone or in combination with capecitabine. In this study, patients were included with a World Health Organization (WHO) performance status of 2 (which is approximately equivalent to ECOG PS 2) although the numbers were small (9 in the monotherapy group and 12 in the combination group). Any survival benefit for the combination seen in the overall population (HR 0.82, 95% CI 0.68-0.98, $P = 0.032$) was not seen for patients with a WHO status of 2 (HR for death 0.56, 95% CI 0.18-1.78), although PS was not found to be associated with survival in a univariate analysis.[48] In a 2017 meta-analysis comparing adjuvant ChT for resected pancreatic cancer, both S-1 and gemcitabine—capecitabine were found to be the most effective adjuvant therapies available at that time, although comparison of overall grade 3-4 adverse events found gemcitabine—capecitabine to have greater toxicity than S-1 (HR 0.07, 95% CI 0.00-38.28).[49] It was thus agreed to include S-1 in the recommendation but, although both the ESPAC-4 and JASPAC-01 trials were phase III, they had either low or no patients with ECOG PS 2, so the LoE was reduced from *'I': evidence*

from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity, to '*II*': *small, randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity.* ESMO 'recommendation 4l' was amended, as shown in bold below and in Table 2, to read (**100% consensus**):

4l. *In patients who are not candidates for mFOLFIRINOX, gemcitabine—capecitabine* ***or S-1 are*** *alternative* ***options*** *[**II**, B; ESMO-MCBS v1.1 score* ***for gemcitabine—capecitabine****: A****; consensus = 100%****].*

For ESMO 'recommendation 4m', which suggests that for frail patients adjuvant treatment should be either gemcitabine or 5-FU/leucovorin (5-FU—LV), the discussion turned to the definition of frail patients. The randomised controlled phase III ESPAC-3 trial compared adjuvant gemcitabine with 5-FU—LV following pancreatic cancer resection and included 64 patients (12%) in each arm who had an ECOG PS of 2. In the overall population, the median survival was 23.6 months for patients treated with gemcitabine compared with 23.0 months for patients treated with 5-FU—LV (log-rank χ^2 0.74, HR 0.94, 95% CI 0.81-1.08, $P = 0.39$), and in a univariate survival analysis, the respective 12- and 24-month survival rates for patients with ECOG PS 2 were 72.1% and 38.2%.[50] In a retrospective cohort study investigating the use and association with survival of adjuvant ChT in patients with PDAC who were ≥80 years of age, receipt of adjuvant ChT was associated with a longer median survival (17.2 months) compared with those who did not receive adjuvant ChT (12.7 months; HR 0.72, 95% CI 0.65-0.79, $P < 0.001$).[51] These data demonstrate that the use of adjuvant ChT is beneficial following resection, but it was decided to simplify the wording of ESMO 'recommendation 4m' and remove mention of frailty, and instead to discuss its application to those patients who may not be candidates for the combination ChT regimens mentioned in 'recommendations 4k and 4l'. However, it was felt that the LoE for this cohort of patients should be downgraded to 'IV': retrospective cohort studies or case-control studies for this use. Thus, ESMO 'recommendation 4m' was modified, with changes shown in bold below and in Table 2 to read (**100% consensus**):

4m. *Adjuvant gemcitabine or 5-FU—LV* ***can be considered for patients with resected pancreatic cancer who are not candidates for S-1 or combination ChT [IV, B; consensus = 100%]****.*

Treatment of borderline resectable pancreatic cancer

BRPC should be defined by both anatomical and biological criteria (see discussion).[52] The relevance of chemoradiotherapy (CRT) in BRPC, which is mentioned in ESMO 'recommendation 4r', was questioned. In the randomised phase II PANDAS/PRODIGE 44 trial which investigated the use and safety of CRT, patients with BRPC were treated with four cycles of mFOLFIRINOX and then randomly assigned before surgery to receive either two further cycles of mFOLFIRINOX alone or two further cycles of mFOLFIRINOX followed by capecitabine-based CRT.[53] Of the enrolled patients, 37 (69%) in the FOLFIRINOX-alone group and 31 (55%) in the CRT group had tumour resections, with R0, the primary endpoint, achieved in 20 (54.1%) and 18 (58.1%) of patients, respectively. The median OS was 32.8 months for the FOLFIRINOX-alone group compared with 30 months for the CRT group.[53] In the randomised phase II A021501 study, which compared mFOLFIRINOX with mFOLFIRINOX plus hypofractionated radiotherapy (RT), patients without disease progression underwent pancreatectomy followed by post-operative treatment with 5-FU, leucovorin plus oxaliplatin (FOLFOX6). Interim data for the first 30 assessable patients enrolled in to each arm, revealed 17 patients (57%) in the mFOLFIRINOX alone group underwent R0-resection compared with 10 (33%) patients in the mFOLFIRINOX plus RT group and the respective median OSs of assessable patients were 29.8 months versus 17.1 months.[54] These findings demonstrate that, while induction mFOLFIRINOX has a favourable OS, preoperative CRT did not improve R0-resection rates or OS. In a meta-analysis and systematic review assessing the use of FOLFIRINOX or gemcitabine-based ChT for BRPC and locally advanced pancreatic cancer (LAPC), which encompassed 23 studies comprising 2930 patients, the overall resection rates for patients with BRPC were 53% for FOLFIRINOX and 55% for gemcitabine-based ChT, and the respective R0-resection rates were 75% and 81%. The OS was not significantly different for patients with BRPC treated with FOLFIRINOX (32.9 months) compared with those treated with GN (28.6 months, $P = 0.285$).[55] The Pan-Asian panel of experts agreed that there was no evidence for the benefit of RT alongside induction FOLFIRINOX or GN for patients with BRPC and, because there were two randomised controlled trials supporting this, the LoE was upgraded from '*III*' to '*II*'. Discussion then moved on to the use of concurrent CRT with S-1, and the Japanese randomised phase II/III GABARNANCE study compared GN with concurrent S-1 plus RT as an induction treatment of BRPC in 112 patients.[56] The R0-resection rates were similar between the two groups (60.7% and 57.1%, respectively). The median OS was not significantly different between the two groups (23.1 months for the GN group and 31.5 months for the CRT group; HR 0.758, 95% CI 0.472-1.219, $P = 0.2518$) and the 2-year OS rates were 48.2% and 62.8%, respectively.[56] In this study, S-1 was given at a systemic dose (80 mg/m^2); thus it was felt that CRT may benefit certain groups of patients. Indeed, it was revealed that some of the experts treated pancreatic cancer as a systemic disease, therefore, the addition of a systemic dose of ChT to RT may be a good option. Thus, based on these data and the discussion around it, the Pan-Asian panel of experts agreed

that concurrent CRT with S-1 should be included as an option, although the GoR was '*C*', which was lower than for induction ChT, and the text for 'recommendation 4r' was modified, as shown in bold below and in Table 2, to read (**100% consensus**):

4r. *A period of induction ChT (FOLFIRINOX**/mFOLFIRINOX** or GN) and subsequent surgery, is **recommended** [II, B]. **CRT with S-1 can be considered as an option [II, C; consensus = 100%].***

Although the evidence for options beyond FOLFIRINOX and GN for the induction treatment of BRPC is limited, the Pan-Asian panel of experts agreed that the use of gemcitabine combined with either oxaliplatin or capecitabine are options. This was based on a phase III study that compared gemcitabine-oxaliplatin with gemcitabine alone in advanced and metastatic disease,[57] and a phase III study in patients with advanced pancreatic cancer that compared gemcitabine—capecitabine with gemcitabine alone.[58] However, it was felt that there might be other options available, in particular the combination of gemcitabine—S-1. In the joint Japanese and Taiwanese randomised phase III GEST study, which compared gemcitabine alone, S-1 alone and gemcitabine—S-1 in 834 patients with LAPC and metastatic pancreatic cancer, the overall response rate (ORR) was 13% in the gemcitabine-alone group compared with 21% in the S-1 group (compared with gemcitabine alone, $P = 0.02$) and 29% in the gemcitabine—S-1 group (compared with gemcitabine alone, $P < 0.001$).[59] The respective median PFS was 4.1 months, 3.8 months and 5.7 months, with the combination demonstrating superiority over gemcitabine alone (HR 0.66, 97.5% CI 0.54-0.81, $P < 0.001$). The median OS was 8.8 months for gemcitabine alone compared with 9.7 months for S-1 alone and 10.1 months for the combination although the combination was not found to demonstrate superiority for survival over gemcitabine (HR 0.88, 97.5% CI 0.71-1.08, $P = 0.15$).[59] In the Japanese phase II/III PREP-02/JSAP-05 trial comparing neoadjuvant or induction gemcitabine—S-1 followed by surgery with upfront surgery in patients with resectable pancreatic cancer or BRPC, the resection rate, R0-resection rate and morbidity of the operation were equivalent between the two groups; however, the median OS was significantly longer in patients receiving neoadjuvant gemcitabine—S-1 (36.7 months) compared with upfront surgery (26.6 months; HR 0.72, 95% CI 0.55-0.94, $P = 0.015$).[42] The Pan-Asian panel of experts agreed that in cases of BRPC where neoadjuvant treatment with FOLFIRINOX or GN may not be feasible, S-1 combined with gemcitabine should be an option and included in ESMO 'recommendation 4s'. As mentioned above, the LoE for gemcitabine combined with oxaliplatin and capecitabine is extrapolated from data for the advanced setting and was downgraded from '*II*' to '*IV*', whereas it was felt that the LoE was greater for gemcitabine—S-1, which was given a score of '*II*'. Thus, the text of ESMO 'recommendation 4s' was modified to incorporate gemcitabine—S-1 and the new LoEs, with changes shown in bold below and in Table 2 to read (**100% consensus**):

4s. *Gemcitabine combined with **either S-1 [II, C]** oxaliplatin **[IV, C]** or capecitabine **[IV, C]** may be considered, when FOLFIRINOX**/mFOLFIRINOX** or GN are not feasible **[consensus = 100%].***

Following the discussion for ESMO 'recommendation 4r' in which concurrent RT with S-1 was suggested as an option for patients with BRPC but CRT based on other ChT regimens was not recommended, it was felt that ESMO 'recommendation 4t', which considered the use of CRT with capecitabine, contradicted this. Thus, the Pan-Asian panel of experts agreed (**100% consensus**) to delete ESMO 'recommendation 4t'. As a result of this, ESMO 'recommendations 4u to z' were renumbered accordingly (Table 2).

Treatment of locally advanced pancreatic cancer

While the Pan-Asian panel of experts agreed that standard of care combination ChT could be used in a conversion strategy for patients with LAPC, as was suggested in the original ESMO 'recommendation 4x' (now renumbered as 'recommendation 4w'), it was queried whether such a conversion strategy actually has a survival benefit for these patients. This question is difficult to resolve because it is unlikely that there would be a study that compares surgery following induction treatment with no surgery. Thus, while the wording for this recommendation and the GoR, which was '*B*': *strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended*, should remain the same, it was felt that the LoE was not strong enough for a level '*I*' and was downgraded to '*IV*'. This change was agreed by all the Pan-Asian panel of experts (**100% consensus**) to read, with the change shown in bold (Table 2):

4w. *A conversion surgery strategy utilising the standard of care of (up to) 6 months of combination ChT (FOLFIRINOX**/mFOLFIRINOX** or GN) can be chosen [**IV, B; consensus = 100%**].*

For original ESMO 'recommendation 4y' (now renumbered 'recommendation 4x'), it was discussed whether high-risk patients with LAPC would benefit from radical surgery and whether the use of diagnostic laparoscopy to assess the operability should be included in the text for those patients for whom there has been a significant decrease in carbohydrate antigen 19-9 (CA 19-9), a clinical improvement, or tumour downstaging. Although not in any guidelines, diagnostic laparoscopy is common practice in certain institutes across Asia; however, it was felt that this

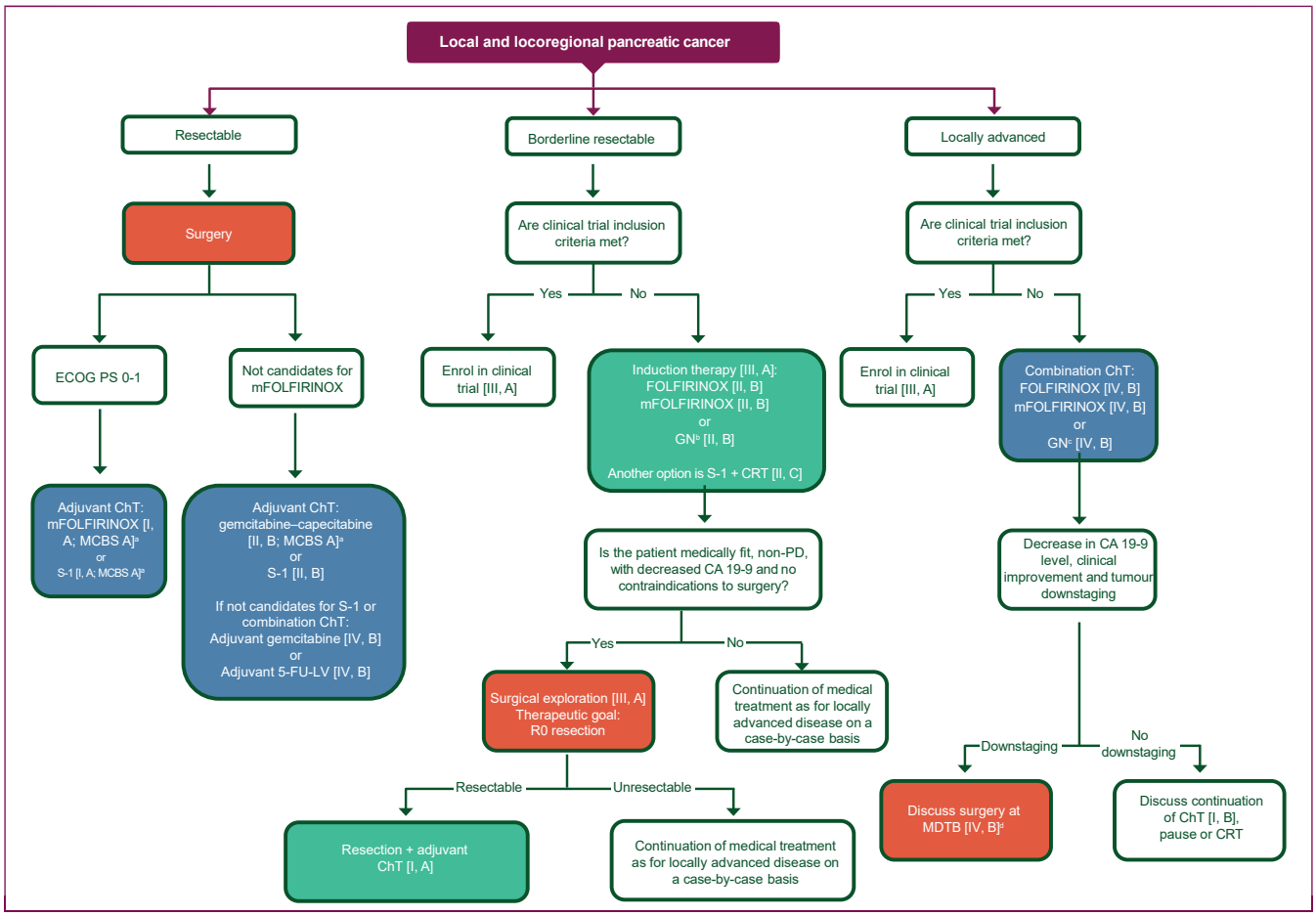

Figure 2. Treatment algorithm for local and locoregional pancreatic cancer.
Purple: general categories or stratification; orange: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments; white: other aspects of management.
5-FU, 5-fluorouracil; CA 19-9, carbohydrate antigen 19-9; ChT, chemotherapy; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin—5-fluorouracil—irinotecan—oxaliplatin; GN, gemcitabine—nab-paclitaxel; LV, leucovorin; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MDTB, multidisciplinary tumour board; mFOLFIRINOX, modified leucovorin—5-fluorouracil—irinotecan—oxaliplatin; PD, progressive disease; PS, performance status; R0, no tumour at the margin (defined as no cancer cells within 1 mm of all resection margins); S-1, tegafur—gimeracil—oteracil.
[a]ESMO-MCBS v1.1was used to calculate scores for new therapies/indications approved by the EMA or FDA.[25] The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]Not EMA or FDA approved as induction therapy.
[c]Not EMA or FDA approved for locally advanced disease.
[d]To be discussed if significant decrease in CA 19-9 level, clinical improvement and tumour downstaging.

procedure was covered by the wording '*exploration for resection*' in the recommendation and should thus remain unchanged (**100% consensus**) to read as below and in Table 2:

4x. *Exploration for resection could be discussed if there is a significant decrease in CA 19-9 level, clinical improvement and tumour downstaging [IV, B].*

Figure 2 shows the diagnostic work-up and treatment algorithm for patients with local and locoregional pancreatic cancer.

5. Management of advanced disease—recommendations 5a-k

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 5a-ii, a-iv, b, c, g-j' (Table 2), without change, and, following discussion at the face-to face meeting, the revised 'recommendations 5a-i, a-iii and d-f'. Although not discussed at the face-to-face meeting, 'recommendation 5k' was also revised as discussed below.

First-line treatment

There are several randomised trials and meta-analyses that have investigated the best first-line treatment options for fitter patients with advanced disease. Some of the key studies are discussed below. FOLFIRINOX showed significantly greater response rates and survival when compared with gemcitabine as first-line therapy in the phase III PRODIGE 4/ACCORD 11 trial.[60] In this trial of 342 patients with metastatic disease and an ECOG PS of 0-1, the ORR was 31.6% for FOLFIRINOX and 9.4% for gemcitabine ($P <$

0.001) and the respective median PFS was 6.4 months compared with 3.3 months (HR 0.47, 95% CI 0.37-0.59, $P < 0.001$). With a median follow-up of 26.6 months, the median OS for FOLFIRINOX was 11.1 months compared with 6.8 months for gemcitabine (HR 0.57, 95% CI 0.45-0.73, $P < 0.001$) and the OS rates at 6, 12 and 18 months for FOLFIRINOX were 75.9%, 48.4% and 18.6% compared with 57.6%, 20.6% and 6.0% for gemcitabine. With a median follow-up of 26.6 months, a greater improvement in global health status was observed for patients treated with FOLFIRINOX compared with patients treated with gemcitabine ($P < 0.001$). Responses to the Quality of Life Questionnaire C30 revealed that the time until definitive deterioration (≥20 point clinically important large difference) was significantly longer for FOLFIRINOX compared with gemcitabine, including for global health status ($P < 0.001$), physical ($P = 0.001$), role ($P < 0.001$), cognitive ($P = 0.015$) and social functioning ($P < 0.001$), as well as across the following five symptom domains: fatigue, nausea/vomiting, pain, dyspnoea (each $P < 0.001$) and constipation ($P = 0.033$).[61] In the phase III MPACT trial, in metastatic pancreatic cancer, GN showed a significantly greater response rate and survival over gemcitabine.[62] A total of 861 patients with metastatic disease and a Karnofsky Performance Status (KPS) score of ≥70 were enrolled and the ORR by independent review for GN was 23% compared with 7% for gemcitabine (response rate ratio 3.19, 95% CI 2.18-4.66, $P < 0.001$) and the median PFS was 5.5 months versus 3.7 months (HR 0.69, 95% CI 0.58-0.82, $P < 0.001$).[62] With a median follow-up of 13.9 months, the median OS for patients treated with GN was 8.7 months compared with 6.6 months for patients treated with gemcitabine alone (HR 0.72, 95% CI 0.62-0.83, $P < 0.001$). The OS rates at 6, 12 and 24 months for patients treated with GN were 66%, 35% and 10% compared with 55%, 22% and 5% for patients treated with gemcitabine alone.[63] Patients' quality of life was not evaluated. These data support the inclusion of GN as a first-line treatment for advanced pancreatic cancer and are further supported by results from a systematic review and meta-analysis comparing data for the first-line treatment of metastatic pancreatic cancer with either GN or FOLFIRINOX, where the respective ORRs were 24% and 25% and no significant difference was found between the PFS for the two treatments (HR 0.88, 95% CI 0.71-1.1, $P = 0.26$).[64] Although in this analysis there was a median weighted OS difference of 1.15 months in favour of FOLFIRINOX ($P = 0.03$), the whole population OS was similar for FOLFIRINOX and GN (HR 0.99, 95% CI 0.84-1.16, $P = 0.9$).[64] The addition of mFOLFIRINOX in the first-line setting for advanced disease was also proposed during the face-to-face meeting. It has been assessed in several late-stage clinical trials in comparison with GN and other agents. In the Japanese phase II/III JCOG1611/GENERATE trial, GN was compared with both mFOLFIRINOX and S-1—irinotecan—oxaliplatin (S-IROX) in 527 patients with metastatic or recurrent pancreatic cancer who had an ECOG PS of 0-1.[65] Interim analysis of this trial included data from 426 patients and the median PFS was 6.7 months for GN, 5.8 months for mFOLFIRINOX (HR compared with GN 1.15, 95% CI 0.91-1.45) and 6.7 months for S-IROX (HR compared with GN 1.07, 95% CI 0.84-1.35). The OS was 17.1 months for GN, 14.0 months for mFOLFIRINOX (HR compared with GN 1.31, 95% CI 0.97-1.77, one-sided log-rank test $P = 0.9622$) and 13.6 months for S-IRINOX (HR compared with GN 1.35, 95% CI 1.00-1.82, one-sided log-rank test $P = 0.9769$). The predictive probability for achieving superiority over GN at the final analysis was determined to be 0.73% in the mFOLFIRINOX arm and 0.48% in the S-IRINOX arm and, as a result of futility, the trial was terminated.[65] Also, no significant difference in survival between mFOLFIRINOX and GN was reported for the phase II PASS-01 trial.[66] In this trial in 160 patients with *de novo* metastatic PDAC who had an ECOG PS of 0-1 and did not have a germline *BRCA1/2* or *PALB2* mutation, 24% of patients treated with mFOLFIRINOX had a best response of partial response compared with 29% for those treated with GN, and the respective median PFSs were 4.0 months compared with 5.1 months ($P = 0.14$). The median OS was 8.4 months for mFOLFIRINOX and 9.7 months for GN.[66] The use of mFOLFIRINOX in the first line is further supported by data from a systematic review and meta-analysis for patients with advanced pancreatic cancer who were initially treated with mFOLFIRINOX.[67] The ORR was 34.6% and the 6- and 12-month PFS rates were 56.3% and 20.6%, respectively. In this study, the 6- and 12-month OS rates were calculated to be 79.7% and 47.6%, respectively.[67] GN has also been used as a comparator against a number of other ChT regimens, including liposomal irinotecan (nal-IRI), oxaliplatin, leucovorin and 5-FU (NALIRIFOX) and 5-FU—LV—nal-IRI. While no significant difference was seen in the response rate between NALIRIFOX and GN in the phase III NAPOLI 3 trial, a significant survival advantage was observed.[68] In this trial, of 770 treatment-naïve patients with metastatic PDAC and an ECOG PS of 0-1, the per investigator ORR for patients treated with NALIRIFOX was 41.8% compared with 36.2% for patients treated with GN (OR 1.26, 95% CI 0.95-1.69, $P = 0.11$) and the respective median PFSs were 7.4 months and 5.6 months (HR 0.69, 95% CI 0.58-0.83, $P < 0.0001$). The median OS was 11.1 months for patients treated with NALIRIFOX and 9.2 months for patients treated with GN (HR 0.83, 95% CI 0.70-0.99, $P = 0.036$) and the 6-, 12- and 18-month survival rate for NALIRIFOX was 72.4%, 45.6% and 26.2% compared with 68.4%, 39.5% and 19.3% for GN.[68] No significant survival difference was seen between GN and 5-FU—LV—nal-IRI in the phase II GIANT trial.[69] In this trial of 176 patients ≥70 years of age with an ECOG PS of 0-2, the median OS for GN was 4.7 months, compared with 4.4 months for 5-FU—LV—nal-IRI ($P = 0.72$).[69] Although the above data provide compelling evidence for the inclusion of GN and mFOLFIRINOX, a systematic review and Bayesian network analysis comparing data from 79 randomised controlled trials, which included 22 168 patients with LAPC or metastatic pancreatic cancer, found that NALIRIFOX or FOLFIRINOX should be the preferred treatment if tolerable, with GN a viable alternative.[70] However, to keep all options available to treating

physicians, the Pan-Asian panel of experts agreed that GN and mFOLFIRINOX should be included as options, alongside FOLFIRINOX and NALIRIFOX, for the first-line treatment of patients with advanced pancreatic cancer who have an ECOG PS of 0-1 and a bilirubin level <1.5 times the upper limit of normal (ULN) and the text of 'recommendation 5a-i' was modified, as shown in bold below and in Table 2 to read (**100% consensus**):

5a-i. *In patients with ECOG PS 0-1 and bilirubin level <1.5 times the ULN,* ***the following*** *regimens* ***are recommended****: FOLFIRINOX [I, A; ESMO-MCBS v1.1 score: 5],* ***NALIRIFOX [I, A; MCBS SCORE v1.1 score: 2],*** *GN [I, A; ESMO-MCBS v1.1 score: 3]* ***or mFOLFIRINOX [III, B] consensus = 100%.***

As has been discussed above for 'recommendation 4s', two of the treatment arms of the phase III GEST study were S-1 and gemcitabine. The noninferiority of S-1 over gemcitabine was reported for both the median PFS (HR 1.09, 95% CI 0.90-1.33, $P = 0.02$ for noninferiority) and median OS (HR 0.96, 97.5% CI 0.78-1.18, $P < 0.001$ for noninferiority).[59] Based on these findings, it was agreed to include S-1 in 'recommendation 5a-iii'. The Pan-Asian panel of experts were unaware of any large prospective studies that had investigated either S-1 or gemcitabine in patients with an ECOG PS of 2, KPS ≥70 and bilirubin levels >1.5 ULN and felt that the LoE for this recommendation should be downgraded from '*I*' to '*IV*' and, because of this, the GoR should also be downgraded from '*A*' to '*B*'. Thus, recommendation 5a-iii was modified, with changes shown in bold in the text below and in Table 2, to read (**100% consensus**):

5a-iii. *For patients with ECOG PS 2, KPS <70 and/or bilirubin level >1.5 times the ULN, gemcitabine* ***or S-1*** *monotherapy* ***can*** *be considered [****IV, B; consensus = 100%****].*

Second-line treatment

The Pan-Asian panel of experts agreed with the use of gemcitabine alone for treatment in the second-line setting following either FOLFIRINOX or mFOLFIRINOX, as suggested in ESMO 'recommendation 5e', but questioned whether GN and gemcitabine in combination with paclitaxel should also be included. In the randomised phase III PRODIGE 65-UGCI 36-GEMPAX UNICANCER study, 211 patients with PDAC who had previously received FOLFIRINOX were randomly assigned 2 : 1 to receive gemcitabine–paclitaxel or gemcitabine alone.[71] The ORR was 17.1% for gemcitabine–paclitaxel compared with 4.2% for gemcitabine alone ($P = 0.008$) and, with respective median durations of follow-up of 13.4 months and 13.8 months, the median PFS was significantly longer for patients treated with gemcitabine–paclitaxel (3.1 months) compared with those treated with gemcitabine alone (2.0 months; HR 0.64, 95% CI 0.47-0.89, $P = 0.0067$). There was, however, no significant difference observed in the median OS between gemcitabine–paclitaxel (6.4 months) and gemcitabine alone (5.9 months; HR 0.87, 95% CI 0.63-1.20, $P = 0.4095$), although in subgroup analyses defined by patient age, tumour location and other stratification factors, gemcitabine–paclitaxel showed better OS outcomes in patients ≤64 years of age and with a baseline CA 19-9 level ≥59 times ULN.[71] Although it has been suggested that gemcitabine alone or GN are the best options for patients following FOLFIRINOX treatment,[72] there are no randomised trial data for GN in the second-line setting for patients with pancreatic cancer; however, in a Korean phase II trial, GN was assessed in 40 patients with advanced pancreatic cancer following FOLFIRINOX failure and the 6-month survival rate (72.5%) achieved superiority over the prespecified assumed OS rate of 20% for best supportive care ($P < 0.001$).[73] In this study, the ORR was 15.0% and the median PFS and median OS were 5.8 months and 9.9 months, respectively. Thus, the Pan-Asian panel of experts agreed that gemcitabine alone or in combination with either paclitaxel or nab-paclitaxel should be included in 'recommendation 5d' and that the GoR should be upgraded from *'C': insufficient evidence for efficacy or benefit does not outweigh the risk of the disadvantages (adverse events, costs, …) optional* to '*B*': *strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended*. They felt that, because gemcitabine alone or in combination with either paclitaxel or nab-paclitaxel had no demonstrated survival advantage in a randomised trial in the second-line setting following FOLFIRINOX or mFOLFIRINOX, the LoE for each should be '*III*'. The original ESMO recommendation suggested this should be an option for '*patients with ECOG PS 0-1 and a favourable comorbidity*' but it was felt that this wording could be simplified and that these treatments would be suitable for patients with ECOG PS 0-2. Thus 'recommendation 5d' was modified, as shown in the text below and in Table 2, to read (**100% consensus**):

5d. *After FOLFIRINOX* ***or mFOLFIRINOX*** *treatment,* ***gemcitabine alone [III, B] or in combination with paclitaxel [III, B] or nab-paclitaxel [III, B]*** *may be offered to patients with ECOG PS* ***0-2*** *[****consensus = 100%****].*

The phase III NAPOLI-1 study compared 5-FU–LV alone, nal-IRI alone or nal-IRI plus 5-FU (nal-IRI–5-FU–LV) or 5-FU–LV in patients with metastatic PDAC who had previously been treated with gemcitabine-based therapy.[74] In the extended follow-up there was no improvement in the median OS for patients treated with nal-IRI monotherapy (4.9 months) compared with those treated with 5-FU–LV (4.2 months; HR 1.07, $P = 0.568$), but a significant survival benefit was seen with nal-IRI–5-FU–LV (median OS 6.2 months) compared with 5-FU–LV (unstratified HR 0.75, 95% CI 0.57-0.99, $P = 0.039$).[74] In the randomised phase III CONKO-003 trial, which compared 5-FU–LV with and without oxaliplatin in 160 patients with gemcitabine-refractory pancreatic cancer, the median OS for patients

treated with 5-FU—LV—oxaliplatin (OFF) was 5.9 months, which was significantly longer than the 3.3 months reported for patients treated with 5-FU—LV (HR 0.66, 95% CI, 0.48-0.91, log-rank $P = 0.010$).[75] Time to progression was also significantly longer for patients treated with OFF (2.9 months) compared with those treated with 5-FU—LV (2.0 months; HR 0.68, 95% CI 0.50-0.94, log-rank $P = 0.019$).[75] Furthermore, in a subanalysis of the randomised phase III MPACT study comparing gemcitabine alone with GN in metastatic pancreatic cancer, the median OS for patients treated with subsequent FOLFOX or OFF was 9.5 months for patients who were originally treated with gemcitabine alone compared with 13.5 months for patients originally treated with GN (HR 0.58, 95% CI 0.34-0.98, $P = 0.038$).[76] These data support the use of oxaliplatin-based therapies in the second line for patients with ECOG PS 0-2 that was the focus of ESMO 'recommendation 5f'. The discussion then turned to the addition of mFOLFIRINOX, which may also be beneficial in the second-line setting. This was shown in the Korean phase III MPACA-3 study that compared mFOLFIRINOX with S-1 in the second-line setting in 80 patients with gemcitabine-refractory metastatic pancreatic cancer.[46] The ORR for mFOLFIRINOX (15%) was higher than for S-1 (2%; $P = 0.04$). The median PFS was longer for mFOLFIRINOX (5.2 months) compared with S-1 (2.2 months; HR 0.4, 95% CI 0.2-0.6, $P < 0.001$) as was the median OS (9.2 months for mFOLFIRINOX compared with 4.9 months for S-1; HR 0.4, 95% CI 0.2-0.7, $P = 0.002$).[46] Although these data support the use of mFOLFIRINOX in the second-line setting for the treatment of patients with advanced pancreatic cancer, it was noted that patients with a ECOG PS of 2 should not be treated with mFOLFIRINOX and that it may be more suited to ESMO 'recommendation 5e', which discussed the second-line treatment of patients with advanced disease who have previously been treated with a gemcitabine-based regimen. Thus, it was agreed that ESMO 'recommendation 5e' should be modified to include mFOLFIRINOX, as shown in bold below and in Table 2, but 'recommendation 5f' should remain unchanged to read (**100% consensus**):

5e. *In patients with, or who have recovered to, ECOG PS 0-1 and who have been pretreated with a gemcitabine-based regimen, liposomal irinotecan—5-FU—LV [I, B; ESMO-MCBS v1.1 score: 3**] or mFOLFIRINOX [II, B] can be considered [consensus = 100%***]

5f. *Oxaliplatin-based second-line treatment (mFOLFOX6 or OFF) remains controversial but may be considered as an alternative in patients with ECOG PS 0-2 if not given previously [II, C**; consensus = 100%***].

Although not discussed at the face-to-face meeting, it was suggested that repotrectinib should be added as an option for the treatment of tumours harbouring an *NTRK* fusion alongside larotrectinib and entrectinib. All three agents have been approved by the United States Food and Drug Administration (FDA) as tumour-agnostic treatments for solid tumours harbouring *NTRK* gene fusions, with repotrectinib being granted accelerated approval in June 2024.[77-79] This approval was based on the phase I/II TRIDENT-1 trial of 88 patients with locally advanced or metastatic *NTRK* fusion-positive tumours, including 48 patients who had received prior tyrosine kinase inhibitors (TKIs). The confirmed ORR was 58% for the TKI-naïve cohort and 50% for the prior TKI cohort. The 12-month duration of response was 86% and 39% and the 12-month PFS was 56% and 22%, respectively.[79-82] Based on these findings and the US FDA approval, the experts retrospectively agreed to modify 'recommendation 5k' to include repotrectinib as shown in the text below in bold and in Table 2 (**100% consensus**):

5k. *In patients with an NTRK fusion, larotrectinib, entrectinib, **or repotrectinib are** recommended [III, A; ESMO-MCBS v1.1 score **for larotrectinib and entrectinb**: 3; ESCAT score: I-C**; consensus = 100%***].

Figure 3 shows the algorithm for the diagnostic work-up and systemic treatment of patients with advanced pancreatic cancer.

6. Follow-up, supportive care, long-term implications and survivorship—recommendations 6a-e

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations c and e' (Table 2), without change, and, following discussion at the face-to face meeting, the revised 'recommendations 6b and d'. Although not discussed at the face-to-face meeting, 'recommendation 6a' was also revised as discussed below.

In the survey, all experts agreed with ESMO 'recommendation 6a' that there was insufficient evidence of an impact on OS for the regular follow-up of patients with resected pancreatic cancer (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105826). However, between the time when the results of the survey were received and the face-to-face meeting, the results of a prospective trial including 333 patients who had undergone resection for PDAC were published.[83] In this study, patients were stratified according to post-operative follow-up that was either symptomatic follow-up (with no routine imaging) or routine imaging. The respective median OSs were 23 months and 28 months ($P = 0.01$). In patients who were asymptomatic for recurrence of their pancreatic cancer, the respective median OSs were 21 months and 30 months ($P = 0.03$). Furthermore, in multivariable regression analyses, routine imaging was associated with receiving recurrence-focussed treatment (adjusted OR 2.57, 95% CI 1.22-5.41, $P = 0.01$) and prolonged OS (adjusted HR 0.75, 95% CI 0.56-0.99, $P = 0.04$).[83] As a result, the Pan-Asian panel of experts retrospectively agreed that ESMO 'recommendation 6a' should be amended to remove the text:

although there is insufficient evidence of an impact on OS and the LoE should be upgraded from 'IV' to 'III' (**100% consensus**) to read (Table 2):

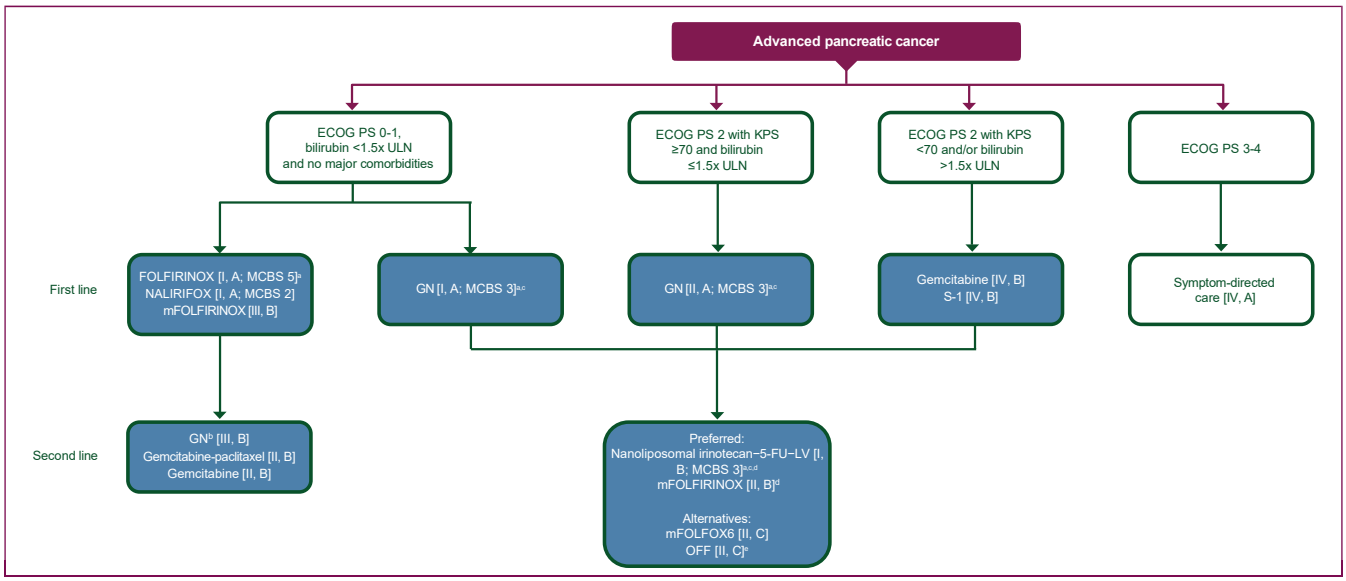

Figure 3. Systemic treatment of advanced pancreatic cancer.
Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin—5-fluorouracil—irinotecan—oxaliplatin; GN, gemcitabine—nab-paclitaxel; KPS, Karnofsky Performance Status; LV, leucovorin; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mFOLFOX6, modified leucovorin—5-fluorouracil—oxaliplatin; OFF, oxaliplatin—fluorouracil—leucovorin; PS, performance status; S-1, tegafur—gimeracil—oteracil; ULN, upper limit of normal.
[a]ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA or FDA.[25] The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]Not EMA or FDA approved as second-line therapy.
[c]EMA and FDA approved in metastatic pancreatic cancer only (not advanced pancreatic cancer).
[d]Only in patients with, or who have recovered to, ECOG PS 0-1.
[e]If not given previously.

6a. *For patients with resected pancreatic cancer, regular follow-up is suggested [**III, B; consensus = 100%**].*

VTE occurs in 20%-25% of patients with PDAC and the respective incidence for patients with localised, regional and metastatic disease during the first year after cancer diagnosis was reported to be 4.2%, 4.9% and 20.0% per 100 patient-years.[84,85] In a meta-analysis of randomised controlled trials of primary ambulatory prophylaxis in patients with advanced pancreatic cancer receiving ChT that included a total of 1013 patients, the rate of VTE was lower in patients receiving prophylaxis (5.43%) compared with 12.07% in the control group (pooled risk ratio 0.44, 95% CI 0.20-0.99, $P = 0.05$).[86] The relative risk for major bleeds between the two groups was, however, not statistically significant (4.11% in the prophylaxis group versus 3.27% in the control group; pooled relative risk 1.25, 95% CI 0.47-3.31, $P = 0.65$). In the randomised phase IIIb CASSINI trial, 834 high-risk ambulatory patients with cancer with a Khorana score of ≥ 2 (scale 0-6 with higher scores indicating higher risk of VTE) were randomly assigned to receive either rivaroxaban or placebo.[87] The VTE rate while on treatment for the rivaroxaban group was 2.6% compared with 6.4% for the placebo group (HR 0.40, 95% CI 0.20-0.80) with no significant difference in major bleeding (HR 1.96, 95% CI 0.59-6.49, $P = 0.26$).[87] In a prespecified subgroup analysis of patients with pancreatic cancer, VTE occurred in 9.6% of patients in the rivaroxaban group compared with 13.0% of patients in the placebo group (HR 0.70, 95% CI 0.34-1.43, $P = 0.328$) and the incidence of major bleeding was similar (1.5% versus 2.3%, respectively).[88] In a Taiwanese study assessing VTE in Asian patients with pancreatic cancer following ChT, and with a median follow-up of 7.7 months, VTE occurred in 8.0% (67/838) of patients.[89] Although VTE was not associated with poorer survival outcomes (non-VTE compared with VTE, log-rank $P = 0.29$), early-onset VTE that occurred within 1.5 months after ChT initiation was found to be an independent negative prognosticator of OS (non-VTE versus early-onset, log-rank $P < 0.001$). Furthermore, in a Japanese prospective cohort study based on a nationwide clinical registry that included 1006 patients, among all cancers investigated, pancreatic cancer was associated with the highest risk of bleeding events (multivariate analysis with colorectal cancer as baseline HR 3.88, 95% CI 2.11-7.14, $P < 0.0001$).[90] However, the VTE rate at baseline was 8.5% and, with a median follow-up of 362.0 days, there were 11 (1.1%) VTE events ranging from 0.5% to 1.4% across tumour stages.[90] Similar findings were also reported in a Taiwanese population-based cohort study with VTE rates reported to be between 1.8% and 3.1%.[91] It was felt that, because the VTE rate seems lower in Asian patients with pancreatic cancer than that reported for Caucasian patients and thromboprophylaxis has not been shown to have an OS benefit, the GoR for ESMO 'recommendation 6b' should be downgraded from '*B': strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended*, to '*C*': *insufficient evidence for efficacy or benefit*

does not outweigh the risk of the disadvantages (adverse events, costs, …) optional. It was agreed to include a short comment regarding the absence of contraindications and thus the text was modified, as shown in bold below and in Table 2, to read (**100% consensus**):

6b. *Primary thromboprophylaxis **can** be considered in advanced pancreatic cancer patients receiving ChT **in the absence of contraindications** [I, **C; consensus = 100%**].*

The evidence for the use of endoscopic placement of an expandable metal stent over surgery for the management of malignant duodenal obstruction is relatively weak.[92] There have been no prospective clinical studies that have directly compared the two approaches and in five systematic reviews and/or meta-analyses comparing endoscopic stenting with surgery for gastric outlet obstruction, four found that the outcomes were generally more favourable with stent placement,[93-96], particularly in the palliative setting for patients with a relatively short life expectancy.[95] However, two studies suggested surgery may be more favourable for patients with a better prognosis and good PS,[93,95] while one study suggested that surgery was associated with lower re-intervention rates than stents.[97] Moreover, in the updated European Society of Gastrointestinal Endoscopy clinical guideline, it was recommended that self-expanding metal stents be used for the treatment of malignant duodenal obstruction.[92] As a result of these findings, the Pan-Asian panel of experts agreed with ESMO 'recommendation 6d' and the use of endoscopic placement of expandable metal stents over surgery for the management of duodenal obstruction. The discussion turned to whether the use of endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) should also be included in the recommendation. In the phase III DRA-GOO study, 97 patients with malignant gastric outlet obstruction due to unresectable primary gastroduodenal or pancreatobiliary malignancies were randomised to receive either EUS-GE or duodenal stenting.[98] The primary outcome was the 6-month re-intervention rate, which was significantly lower in the EUS-GE group (4%) compared with the duodenal stent group (29%; risk ratio 0.15, 95% CI 0.04-0.61, $P = 0.0020$). Furthermore, the stent patency was longer in the EUS-GE group (median not reached in either group; HR 0.13, 95% CI 0.08-0.22, log-rank $P < 0.0001$) and the percentage of adverse events was similar between the two groups (24% for the EUS-GE group compared with 23% for the duodenal stent group).[98] Thus, based on the discussion described above, it was agreed that EUS-GE, where expertise is available, should be included in 'recommendation 6d' with a GoR of '*B*', which is the same as endoscopic placement of a metal stent. Because this was based on a relatively small phase III study, its inclusion was assigned an LoE of '*II*': *small, randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity.* The modified recommendation, with changes shown in bold in the text below and in Table 2 reads (**100% consensus**):

6d. *Duodenal obstruction can be managed by endoscopic placement of an expandable metal stent [IV, B] **or EUS-GE (where expertise is available) [II, B] instead of surgery [consensus = 100%].***

DISCUSSION OF THE RECOMMENDATIONS

Anatomically resectable and biologically resectable

It is estimated that 10%-15% of patients with pancreatic cancer are diagnosed with resectable disease while a further 30%-35% are diagnosed with BRPC.[15] In a systematic review and meta-analysis that included 111 studies and 4394 patients, preoperative/induction therapy was found to result in an estimated resection probability of 30% for patients who were initially staged to be nonresectable (BRPC or LAPC) before treatment. Furthermore, the estimated R0-resection rate was comparable between tumours deemed to be resectable before neoadjuvant treatment (82.1%) and those that were not (79.2%).[99] These findings highlight that greater consideration should be given to patients with nonresectable pancreatic cancer to receive neoadjuvant therapy with subsequent re-evaluation for resection.

While the anatomical assessment of resectability of localised PDAC is primarily based on the extent of involvement of the surrounding tissues and major blood vessels,[100] there is a growing appreciation of the importance of both the tumour biology and patient-related conditional factors.[101] These contribute to the biological assessment of resectability, and, in 2017, the International Association of Pancreatology proposed criteria based on the anatomical assessment, tumour biology [including no proven distant metastases, serum CA 19-9 >500 IU/ml nor regional lymph node metastases diagnosed by biopsy or positron emission tomography—computed tomography (PET-CT)] and patient condition (ECOG PS ≥2) to define BRPC.[52] Additional biological and host-related factors were proposed by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. Biological factors included using the PET-CT maximum standardised uptake values of the primary tumour and the tumour response to neoadjuvant therapy. Host-related factors that might affect resectability included age and Charlson—Deyo comorbidity, as well as markers of a systemic inflammatory response (such as the modified Glasgow Prognostic Score or neutrophil/lymphocyte ratio).[102,103] It is thus important that, as well as the anatomical considerations, these biological and patient factors be taken into consideration when evaluating tumour resectability.

mFOLFIRINOX dosing regimens

The FOLFIRINOX treatment regimen is oxaliplatin (85 mg/m^2 given as a 2-h infusion), LV (400 mg/m^2 given as a 2-h

infusion immediately after oxaliplatin), irinotecan (180 mg/m^2 given during the last 90 min of LV) and 5-FU (given as a 400 mg/m^2 bolus followed by 2400 mg/m^2 given as a 46-h continuous infusion).[104,105] The main grade 3-4 adverse events seen in ≥5% of patients were neutropenia (seen in 45.7% of 171 patients with metastatic disease), febrile neutropenia (5.4%), thrombocytopenia (9.1%), anaemia (7.8%), fatigue (23.6%), vomiting (14.5%), diarrhoea (12.7%), sensory neuropathy (9.0%), elevated alanine aminotransferase (7.3%) and thromboembolism (6.6%).[60]

While there is evidence that compared with the standard FOLFIRINOX regimen, mFOLFIRINOX provides much of the benefit with fewer adverse events,[106] there is no standard for how FOLFIRINOX is modified. Modifications typically include: (i) differing doses of one or more components of the chemotherapies, (ii) omission of the 5-FU bolus, (iii) variation in duration of continuous 5-FU administration (24-48 h).

mFOLFIRINOX was first assessed in the adjuvant setting in the phase III PRODIGE 24-ACCORD trial with the following dosing regimen: oxaliplatin (85 mg/m^2 as a 2-h infusion), LV (400 mg/m^2 as a 2-h infusion), irinotecan (180 mg/m^2 infused during the last 90 min of LV) and 5-FU (2400 mg/m^2 infused over 46 h, with no bolus). During the study, the dose of irinotecan was reduced to 150 mg/m^2 in accordance with a protocol-specified safety analysis.[44] Grade 3-4 adverse events occurred in 75.9% of the 238 patients treated with mFOLFIRINOX and those occurring in ≥5% included neutropenia (28.4%), fatigue (11.0%), diarrhoea (18.6%), nausea (5.5%), vomiting (5.1%), sensory peripheral neuropathy (9.3%), paraesthesia (12.7%) and increased γ-glutamyltransferase (18.3%).[44] Many of the grade 3-4 adverse events were lower in patients treated with mFOLFIRINOX compared with FOLFIRINOX, including the level of neutropenia and febrile neutropenia (seen in 3.0% of patients treated with mFOLFIRINOX).[44,60]

The PRODIGE 24-ACCORD trial was conducted across France and Canada and the main patient population was likely to have been Caucasian. As such, the adverse events and their reported frequencies may not be applicable for Asian patients. mFOLFIRINOX has been assessed in two prospective clinical trials in Asian patients, namely the Korean phase III MPACA-3 trial in the second-line setting for patients with metastatic pancreatic cancer, and in the Japanese phase II/III JCOG1611-GENERATE trial in patients with progressive or metastatic pancreatic cancer.[46,65] In the MPACA-3 trial, 39 patients were treated with mFOLFIRINOX. The regimen comprised 65 mg/m^2 oxaliplatin (90 min infusion), followed by 135 mg/m^2 irinotecan (90 min) and 400 mg/m^2 LV (2 h) followed by a 24-h infusion of 1000 mg/m^2 5-FU. Grade 3-4 adverse events were reported for 56% of patients treated with mFOLFIRINOX with neutropenia (28%), leukopenia (23%), anaemia (15%), fatigue (8%), blood bilirubin increased (8%), nausea (5%), hypalbuminaemia (5%) and alanine aminotransferase increased (5%) grade 3-4 AEs occurring in ≥5% of patients.[46] In the JCOG1611-GENERATE trial, patients were treated with 85 mg/m^2 oxaliplatin, 150 mg/m^2 irinotecan, 200 mg/m^2 LV and 2400 mg/m^2 5-FU. Adverse events occurring in the ≥5% of 171 patients treated with mFOLFIRINOX were neutropenia (51.5%), anorexia (22.8%), white blood cell infection (16.4%), alanine transaminase increased (11.7%), anaemia (10.5%), aspartate aminotransferase increased (9.4%), febrile neutropenia (8.8%), nausea (8.8%), diarrhoea (8.8%) and neuropathy (8.2%).[65]

Table 3 provides details of other mFOLFIRINOX regimens that have been assessed in different settings for the treatment of pancreatic cancer. The optimum dosing regimen and sequencing/timing of delivery of mFOLFIRINOX treatment has yet to be determined.

Oncogene-driven pancreatic cancer and targeted therapies

Most patients are diagnosed with pancreatic cancer at an advanced stage and for these patients the outlook is poor, with the global 5-year survival rate for patients diagnosed with advanced/metastatic disease estimated to be ∼10%. Few options are available for patients beyond the second line, as is highlighted in ESMO 'recommendation 5h' which reads:

5h. Most patients are considered unsuitable for third-line treatment due to poor nutritional status and/or PS

In such cases, no standard regimen can be recommended and best supportive care is the appropriate treatment choice.

In patients with a good PS, inclusion in a clinical trial is the first option when available.

The development and assessment of targeted therapies has the potential to revolutionise the treatment and outlook for patients with pancreatic cancer. For example, the randomised phase III POLO trial demonstrated the efficacy of the PARP inhibitor olaparib in patients with germline *BRCA1/2* mutations and is recommended as an option as a maintenance treatment of these patients if their disease is stable or responsive to platinum-based ChT ('recommendation 5i'; Figure 4).[28] Although *NTRK* gene fusions are rare in pancreatic cancer (Table 1), larotrectinib, entrectinib and repotrectinib have been approved by the United States FDA for the tumour-agnostic treatment of tumours harbouring *NTRK1/2/3* fusions[77-79,107] and, although the LoE is low for pancreatic cancer, are recommended in the second-line setting ('recommendation 5k'; Figure 4).[80-82,108-110] The inclusion of these agents in these recommendations highlights the importance of somatic tumour profiling (as discussed in 'recommendations 2k, 2m and 2n'); however, many regions in Asia do not subsidise such tests (see section B on the applicability of the recommendations).

KRAS is the most frequently mutated gene seen in pancreatic cancer, specifically in patients with PDAC. There are multiple ongoing studies evaluating pan-RAS or KRAS variant-specific inhibitors with several in late-stage clinical development.[111,112] One such inhibitor is the KRAS G12C inhibitor, sotorasib, which was assessed in a single group

Table 3. mFOLFIRINOX regimens used in the treatment of pancreatic cancer

Treatment setting	Oxaliplatin (mg/m^2)	Irinotecan (mg/m^2)	Leucovorin (mg/m^2)	5-fluorouracil		
				Bolus (mg/m^2)	Infusion time (h)	(mg/m^2)
Borderline resectable/locally advanced						
Induction ChT in BRPC[54]	85	180	400	None	46-48	2400
Neoadjuvant/induction ChT followed by RT in LAPC[118]	85	180	400	None	46	2400
Induction ChT for LAPC and BRPC[119]	85	165	None	None	46	2400
Induction ChT in BRPC[120]	85	150	400	None	46	2400
Adjuvant						
Adjuvant[44]	85	180[a]	400	None	46	2400
	85	150[a]	400	None	46	2400
Advanced						
First-line						
First-line for metastatic or recurrent pancreatic cancer[65]	85	150	200	None	N/A	2400
First-line for unresectable and metastatic pancreatic cancer[121]	85	150	400	None	46	2400
First-line for locally advanced and metastatic pancreatic cancer[122]	85	135	400	300	46	2400
First-line for advanced pancreatic cancer[123]	85	150[b]	200	None	48	2800[b]
	85	165[b]	200	None	48	3200[b]
First-line for advanced pancreatic cancer[124]	63.75	135	300	300	46	1800
Second-line						
Second-line for metastatic pancreatic cancer[46]	65	135	400	None	24	1000
Second-line in unresectable pancreatic cancer[125]	85	150	200	None	46	2400
Mixed						
Metastatic pancreatic cancer[126]	68	135	400	None	46	2400
Metastatic/nonmetastatic pancreatic cancer[127]	85	180	400	None	46	2400

BRPC, borderline resectable pancreatic cancer; ChT, chemotherapy; LAPC, locally advanced pancreatic cancer; N/A, not available; RT, radiotherapy.
[a]Following a protocol-specified safety analysis, irinotecan was reduced from 180 mg/m^2 to 150 mg/m^2.
[b]Considering a manageable toxicity, irinotecan was increased from 150 mg/m^2 to 165 mg/m^2 and 5-fluorouracil was increased from 2800 mg/m^2 to 3200 mg/m^2.

analysis of the phase I/II CODEBREAK 100 trial of 38 patients with advanced *KRAS G12C*-mutated pancreatic cancer, where the confirmed ORR was 21% and the disease control rate was 84%. The median PFS was 4.0 months and the median OS was 6.9 months.[113] RMC-6236 is a RAS(ON) multiselective, tri-complex inhibitor of the active GTP-bound state and was assessed in a phase I study of 127 patients with PDAC harbouring *KRAS G12X* or other *RAS* mutations. For patients with *KRAS G12X*-mutated PDAC, the confirmed ORR in the second line was 29%, the median PFS was 8.5 months, and the median OS was 14.5 months. For patients with PDAC harbouring other *RAS* mutations, the ORR was 25% and the respective median PFS and OS were 7.6 months and 14.5 months.[114] Furthermore, tumour-agnostic approval has been given by the FDA for several targeted therapies.[115] These include pembrolizumab for unresectable or metastatic tumours with deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) ('recommendation 5j'; Figure 4). The combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib has also been given tumour-agnostic approval by the FDA for the treatment of patients with unresectable or metastatic solid tumours, pretreated or without a valid treatment option, harbouring a *BRAF V600E* mutation,[115] and, in a case report, a patient with *KRAS* wild-type PDAC harbouring a *BRAF* N486_490del deletion was treated with dabrafenib—trametinib in the third line and had a prolonged (>18 month) partial response.[116] This case report was part of a larger study that identified 14 patients with advanced/metastatic *KRAS* wild-type PDAC, five of whom had potentially actionable mutations (three *BRAF* alterations, one *RET* fusion, and one *FGFR* fusion), as well as a druggable *EGFR* variant.[116] Of these patients, five were matched with targeted therapies and three showed durable benefit, including one patient with an *EGFR* alteration (treated in the first line with erlotinib followed, when a *MET* amplification emerged, by osimertinib—campatinib; in this patient, the overall response to targeted therapy lasted >17 months) and another patient with a *RET* fusion (treated with pralsetinib in the fifth line who had a duration of response lasting 11 months).[116] These data highlight the potential for targeted therapies to alter the therapeutic landscape of pancreatic cancer outcomes but also demonstrate the need, where possible, to identify if patients are eligible and to enrol them on to clinical trials to further the clinical development of these and other agents. However, unfortunately, at present many regions of Asia do not reimburse targeted NGS panel testing, which may limit the identification of such patients.

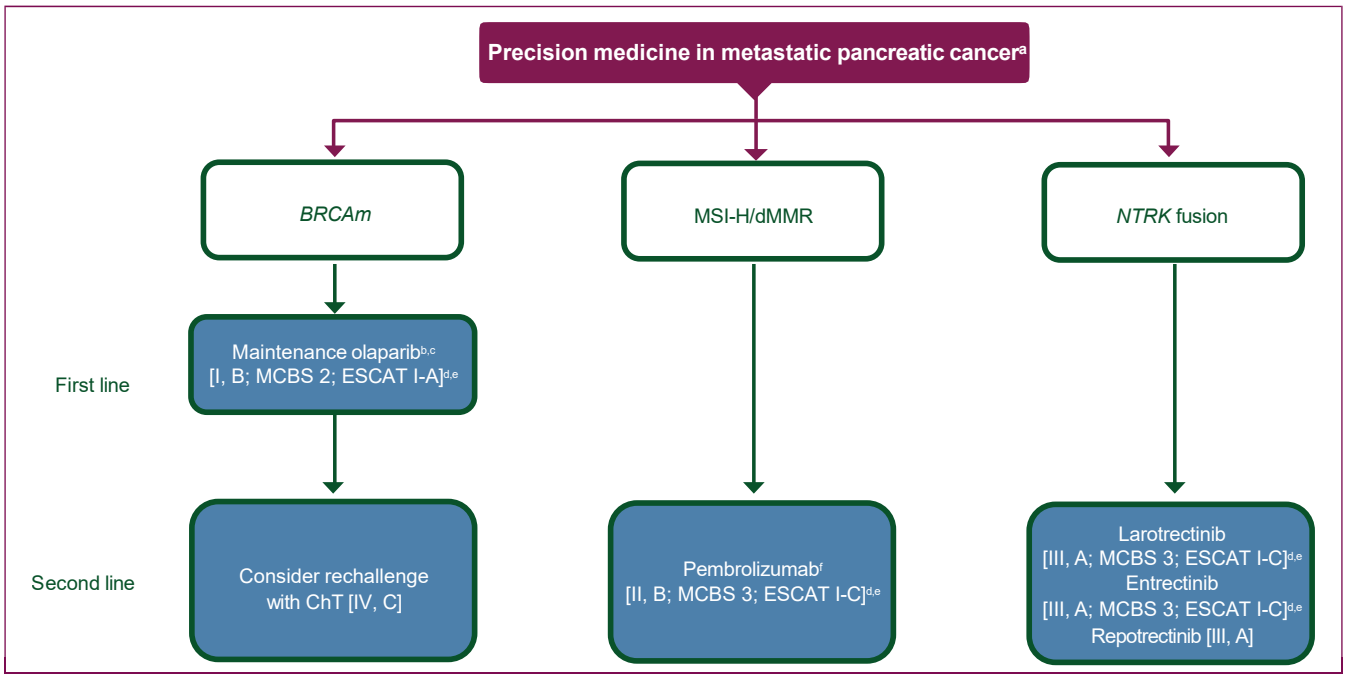

Figure 4. Precision medicine in metastatic pancreatic cancer.
Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
ChT, chemotherapy; dMMR, mismatch repair deficient; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; g, germline; m, mutated; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high.
[a]Although rare, the use of tumour-agnostic targeted therapy informed by next-generation sequencing with corresponding approvals by regulatory agencies could be considered.
[b]EMA and FDA approved in patients with metastatic pancreatic cancer and *gBRCA* mutations.
[c]For patients whose disease is stable or responsive to platinum-based ChT.
[d]ESMO-MCBS v1.1[25] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[26]
[f]FDA approved; not EMA approved as a dMMR/MSI-H tumour-agnostic indication but for specific tumour types (excludes pancreatic cancer).

There is a real need to promote and drive for the enrolment of Asian patients in clinical trials to further the clinical development of novel agents and to better inform the optimal treatment of patients with pancreatic cancer in Asia.

B. Applicability of the recommendations

Following the face-to-face meeting in Singapore, the Pan-Asian panel of experts agreed and accepted completely (**100% consensus**) the revised ESMO recommendations for the diagnosis, treatment and follow-up of pancreatic cancer in patients of Asian ethnicity (Table 2). However, the applicability of each of the guideline recommendations is impacted by the individual drug and testing approvals and reimbursement policies for each region. The drug and treatment availability for the regions represented by the 10 participating Asian oncological societies is summarised in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105826, and individually for each region in Supplementary Tables S4-S13, available at https://doi.org/10.1016/j.esmoop.2025.105826.

CSCO:

The medical system in China mainly consists of basic medical insurance, urban and rural medical assistance, and supplementary medical insurance. This covers various groups of people such as urban workers, urban residents and rural residents. For biomarker-related diagnostic tests, 40% of patients pay entirely 'out of pocket'; 60% receive partial reimbursement but are required to pay 10%-40% of the full cost for *KRAS* mutation testing (by PCR), *BRCA* mutation testing (by PCR) and MSI testing [PCR or immunohistochemistry (IHC)]. There is, however, no reimbursement for targeted NGS panel testing. For the costs of drugs, 10% of patients will pay entirely 'out of pocket', while 10% will be covered by private insurance and 70%-80% will have employer/social insurance. All drugs for treating pancreatic cancer are approved in China but only gemcitabine, entrectinib and larotrectinib are reimbursed (for 10%-40% of the cost). Unless covered by insurance, the full cost of the other drugs must be covered by the patients. In China, the anti-epidermal growth factor receptor (EGFR) antibody nimotuzumab is approved in combination with gemcitabine for the first-line treatment of wild-type pancreatic cancer and the nanoliposomal irinotecan, HR070803, is approved in the second-line setting. S-1 is also approved in the adjuvant and palliative setting (see Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105826). The average time from European Medicines Agency (EMA)/FDA approval for a drug to be

approved in China is 1-2 years and, following approval, drugs are usually accessible within 1 year. Administrative medical policy and cost are limiting factors to accessing new treatments and biomarker-related diagnostic tests/tools. The level of efficacy of drugs is another limiting factor for accessing new treatments, while diagnostic value can limit access to new biomarker-related tests and tools.

ISHMO:

In Indonesia, almost 80% of the population is covered by government health insurance, although the coverage for cancer treatment is principally limited to standard ChT drugs including gemcitabine, oxaliplatin, 5-FU and irinotecan. This means that the costs of new drugs are not covered by government health insurance although most patients have other insurance [either private (20%-30% of patients) or through employer/social schemes (30%-40% of patients)], meaning 10% of patients will pay for their drug costs entirely 'out of pocket' with the average patient covering an estimated 20%-30% of the cost of their cancer drug treatment. Although approved, olaparib is still very expensive and patients are required to cover 10% of the full cost. In Indonesia, adjuvant S-1 is approved for gastric cancer indications and adjuvant nimotuzumab is approved for pancreatic cancer although neither is covered by national insurance. Nab-paclitaxel, nanoliposomal irinotecan, entrectinib and larotrectinib are not approved or available in Indonesia (see Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105826). Government health insurance does not cover molecular biomarker tests and 10%-15% of patients pay entirely 'out of pocket' for these tests. Patients are required to cover 10%-20% of the full cost of diagnostic tests. Access to certain diagnostic tests can be limited because not all oncology centres are capable of providing them. These include testing for *KRAS* mutations, *BRCA* mutations and MSI. Furthermore, the cost of targeted NGS panel testing is still very expensive in Indonesia. The fact that biomarker testing is not available in all cancer treatment service centres is one of the biggest limiting factors to accessing new biomarker-related diagnostic tests and tools, although access is often constrained by the capacity to carry them out, including the ability of the pathologist and the availability of necessary reagents. For accessing new treatments, the biggest limiting factor is entry into the country due to the high cost of drug excise duty, although there is also a delay in approval by the national drug agency and, depending on the drugs, it can take an average of between 5 and 10 years for approval to be granted in Indonesia from the date of EMA/FDA approval. Once approval is given in Indonesia, drugs can become available within 6 months.

ISMPO:

In India, the health insurance provided by the government is limited to the cover of basic oncology treatment and does not cover treatment options such as targeted therapies. Moreover, biomarker-related diagnostic tests are not covered by government insurance, meaning that all patients are expected to cover the full cost (see Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105826). In India, 50% of patients have no insurance, meaning that they will have to pay entirely 'out of pocket' for any treatment not covered by the government, whereas 25% of patients have private insurance and the remaining 25% are covered by employer/social insurance. With the exception of irinotecan and nal-IRI, most ChT options for the treatment of pancreatic cancer are approved and, with the exception of oxaliplatin, are covered by the Indian health care system. Olaparib is also approved but not covered by the health care system. Once a drug has been approved by the EMA/FDA, the average time to approval in India is ∼1 year and, when approved, drugs can become accessible within 2 months. Costs are the biggest limiting factors to accessing new treatments. As well as availability and awareness, cost is also a major factor in accessing new biomarker-related diagnostic tests and tools.

JSMO:

Universal health care in Japan is staggered depending on age, with adults aged $<$70 years required to pay for 30% of their treatment costs, those aged 70-74 years required to pay 20%, and those $\geq$75 years required to pay 10%. Nearly all ($>$99%) patients' treatments are covered by Japanese insurance. Furthermore, any expenses over ∼¥80 000 (∼€500) per month are reimbursed depending on patients' income. Only drugs approved by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) are available and these are reimbursed accordingly. With the exception of capecitabine, all common drugs for the treatment of pancreatic cancer are approved in Japan (see Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105826). In Japan, S-1 is approved for perioperative and advanced-stage pancreatic cancer. For drugs to be approved in Japan, their safety and efficacy must have been assessed in a clinical trial involving Japanese patients. This can delay drug approval in Japan but for any drugs developed simultaneously as a part of a global clinical trial, including Japan, approval will typically be given within 1 year from approval in the EMA/FDA. If a drug has already been approved for other cancers it will be made available following approval for a new indication. However, if it has not been approved in Japan previously, it can take between 2 and 3 months for reimbursement. The biggest limiting factors to assessing new treatments and new diagnostic tests and tools in Japan are that only those approved by the PMDA are available and these have to have been assessed in Japanese patients. Also, in Japan, NGS testing is not permitted before first-line treatment.

KSMO:

The health security system in Korea has two components: mandatory social health insurance and medical aid. All citizens are covered by the National Health Insurance (NHI) system. Its main sources of funding include contributions from those who are insured and government

subsidies. The medical aid programme is a form of public assistance that uses government subsidies to provide low-income groups with health care services. Since 2009, the Korean government has provided support via a copayment system for patients with rare incurable diseases, which includes cancer patients. These patients are entitled to reduced rates of medical expenses although the NHI takes a conservative stance on genetic testing and does not cover diagnostic PCR testing for *KRAS* mutations or *BRCA* mutations. It also does not reimburse MSI testing by either PCR or IHC, meaning that patients need to cover the full cost. Patients also need to cover 80% of targeted NGS panel testing costs, which is estimated to cost 1.2 million won (∼$860). All drugs for the treatment of pancreatic cancer are approved in Korea and most of the cost is covered by the NHI; as a result, 'out of pocket' contributions for drug costs are usually 5% (see Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2025.105826). In 2020, the average review time for new drug approval by the Korean regulatory authority was 353 days based on a study assessing 225 new drug applications between 2011 and 2020. However, due to late submission of drug applications in Korea (the median difference was ∼493 days), approval was given a median 551 days after EMA/FDA approval.[117] The biggest limitations to accessing new treatments include the lack of professional personnel in the review department, the lack of coordination with international standards of related regulations and the lack of linkage with foreign regulatory agencies and a mutual certification system. The biggest limiting factors for accessing new biomarker-related diagnostic tests and tools are limitations on research and development costs, a lack of proper management for the collection, storage and distribution of clinical samples entering the development stage, and no systematic establishment of sample information.

MOS:

Malaysia uses a two-tiered health care system in which the government-run health care sector (serving 80% of cancer patients) co-exists with a private health care system (serving 20% of cancer patients) to provide universal health care access. However, for a population of 35 million, there are 175 oncologists, of whom over half (95 oncologists) work in the private sector. In oncology services there is a tendency towards a partnership and collaboration of services of the private—public health care sectors where the best of each system can be harnessed towards a more cost-effective and improved health care system. For biomarker-related diagnostic tests, 80% of patients will have to cover the full costs. For example, *KRAS* mutation testing by PCR is covered by insurance in the private setting but in the government setting patients will have to pay the full cost, and the cost of MSI testing is only reimbursed in private and tertiary health care centres. *BRCA* mutation analysis is generally not subsidised or covered by insurance. Although all drugs for the treatment of pancreatic cancer are approved in Malaysia, only the standard chemotherapeutics are reimbursed, meaning for all other drugs patients need to cover the full cost (see Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2025.105826). Regarding drug costs, 15% of patients have private insurance and 15% are covered by employer/social insurance, meaning 70% will have to pay entirely 'out of pocket'. In Malaysia it can take between 1 and 2 years for a drug to be approved after EMA/FDA approval. In the private health care system, once approval has been given, a drug can be made available immediately, whereas in the government system it can take between 2 and 5 years. The biggest limiting factors to accessing new treatments and new biomarker-related diagnostic tests and tools are financial.

PSMO:

The Philippine government is in the process of developing a universal health care law to increase financial support to patients' needs for treatment such as ChT, surgery and RT. However, at present in the Philippines, the health care system is mostly nonreimbursable because the government only provides ∼US$100 for a patient's treatment. Biomarker-related diagnostic tests are not covered by the health care system and, although readily available, there is no reimbursement from the government (see Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2025.105826). However, *BRCA* and MSI testing is partially covered by pharmaceutical companies. Targeted NGS panel testing is not available in the Philippines but is sent out to private companies. Patient 'out of pocket' contributions towards drug costs are usually ≥95%. It is estimated that ∼65% of patients do not have insurance and have to pay 'entirely out of pocket' for drug costs, whereas 30% have private insurance and 5% have employer/social insurance. Most ChT reagents are readily available, although nab-paclitaxel and nanoliposomal irinotecan are not locally available but can be sought from neighbouring countries such as Singapore. The average time for drugs to be approved after they have received EMA/FDA approval is ∼6 months, although they are not reimbursed. The biggest limiting factors to accessing new drugs are cost and the fact that they have to be procured from outside of the Philippines. Cost and turn-around time are the biggest limiting factors for accessing new diagnostic-related tests and tools.

SSO:

The health care system of Singapore uses a mixed financing system that includes nationalised insurance schemes (MEDISHIELD LIFE) and compulsory savings (MEDISAVE). Government subsidies (Medication Assistance Fund) are available for a proportion of drug costs, but this is dependent on monthly per capita household income and only covers the costs of those approved drugs on Singapore's cancer drug list (CDL). It is estimated that ∼70% of patients have supplementary private insurance while 10% have employer/social insurance, which helps towards the costs of those drugs not on Singapore's CDL. It will also help towards diagnostic tests such as NGS, which patients need to cover 100% of the cost of in Singapore. Singapore's CDL covers all drugs currently used for the treatment of pancreatic cancer, including S-1, with variable reimbursement based on governmental subsidies depending on per capita household income (see Supplementary Table S11,

available at https://doi.org/10.1016/j.esmoop.2025.105826), deductions from MEDISAVE ($3600 Singapore dollars per year for cancer-related services) and the use of MEDISHIELD LIFE ($600 per year for cancer-related services). It can take between 3 and 12 months for a drug to be given in Singapore from the time it is approved by the EMA/FDA. Once approved, drugs can be made available shortly after with 'out of pocket' payment but it can take between 3 and 12 months for the drug to appear on the CDL and be covered for reimbursement. Aside from approval time for reimbursement for new drugs, cost is the biggest limiting factor for accessing new drugs and new biomarker-related diagnostic tests and tools.

TOS:

In Taiwan, the NHI gives nearly 100% coverage for reimbursed drugs meaning that patients usually have no 'out of pocket' expenses for drug costs. However, for those drugs not covered by the NHI, patients will be expected to cover the full cost. Although IHC testing for MSI is reimbursed, patients have to cover the full cost of *KRAS* PCR tests. Patients also have to cover the full cost of PCR tests for *BRCA* mutations, although NGS-based germline *BRCA* testing from blood is partially reimbursed (60%-70% of the cost) (see Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2025.105826). Oxaliplatin and irinotecan are only approved in the first-line setting for the treatment of pancreatic cancer in Taiwan and only as part of FOLFIRINOX. Similarly, approval for nab-paclitaxel is limited to first-line therapy for metastatic disease in combination with gemcitabine. All available regimens are not approved or reimbursed for before adjuvant setting. nal-IRI is approved in the second-line setting in combination with 5-FU. With respect to targeted therapies for the treatment of pancreatic cancer, olaparib and larotrectinib are approved in Taiwan but entrectinib is not. Also approved in Taiwan is S-1, for the treatment of advanced disease. The average time from EMA/FDA approval to approval in Taiwan is 1-2 years and drugs can be made available almost immediately for 'out of pocket' or private insurance payment. Otherwise, it can take a further 1-2 years for a drug to be reimbursed by the NHI. Cost is the biggest limiting factor for accessing new drugs and new biomarker-related diagnostic tests and tools. Another limiting factor for accessing new drugs is the survival gain.

TSCO:

In Thailand, the health care system has three different medical schemes: civil servants (∼20% of the population), social security (∼10% of the population) and universal coverage (∼70% of the population). Access to medications is restricted to those listed in the national essential drugs list, which is chosen based on economic considerations relative to the country's gross domestic product. For diagnostic biomarker-related tests, MMR IHC tests are fully reimbursed. *BRCA* mutation PCR-based testing, *KRAS* mutation testing, MSI PCR-based testing and targeted NGS panel testing are not reimbursed. As a result, 95% of patients pay entirely 'out of pocket' for biomarker-related tests, with 5% receiving some form of reimbursement. Regarding drug costs, two-thirds of patients are covered by universal coverage while ∼23% are covered by employment insurance (8% government, 15% private sector). A further 5% are covered by private insurance, meaning ∼5% of patients are not covered by insurance and have to cover their drug costs entirely 'out of pocket' (see Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2025.105826). All drugs for the treatment of pancreatic cancer are approved in Thailand but only the costs for gemcitabine and 5-FU, as well as adjuvant FOLFIRINOX, are fully covered by the health care system, with patients having to cover 70% of the cost for capecitabine, oxaliplatin and irinotecan. For nab-paclitaxel, nanoliposomal irinotecan, olaparib, entrectinib and larotrectinib, patients need to cover the full cost either through insurance or through 'out of pocket' payment. It can take 2 years from a drug being approved by the EMA/FDA for approval in Thailand, but newly approved drugs can be made available to patients immediately when approved. Costs, including the lack of reimbursement, are the biggest limiting factors to accessing new drugs and new biomarker-related tests and tools in Thailand.

CONCLUSIONS

The results of the voting by the Asian experts both before and after the face-to-face meeting in Singapore showed 65.2% concordance with the ESMO recommendations for the treatment of patients with pancreatic cancer (Supplementary Table S2 and Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105826). These recommendations therefore constitute the consensus clinical practice guidelines for the treatment of patients with pancreatic cancer in Asia. The variations in the availability for the patients of diagnostic testing, drugs and, therefore, treatment possibilities between the different regions represented reflect the differences in the organisation of their health care systems and their reimbursement strategies, and will have a significant impact on the implementation of the scientific recommendations in certain regions. Thus, policy initiatives are advised, based on this guideline document, in order to improve the access of all pancreatic cancer patients across all the Asian regions.

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33.
2. Wood LD, Canto MI, Jaffee EM, et al. Pancreatic cancer: pathogenesis, screening, diagnosis, and treatment. *Gastroenterology*. 2022;163(2):386-402.e381.
3. Zhao C, Gao F, Li Q, et al. The distributional characteristic and growing trend of pancreatic cancer in China. *Pancreas*. 2019;48(3):309-314.
4. nippon.com. Early detection crucial: Japan's 10-year cancer survival rate stands at 53.3. 2023. Available at https://www.nippon.com/en/japan-data/h01626/. Accessed October 4, 2024.
5. Statista Research Department. Five-year relative survival rate of leading types of cancer in South Korea in 2022. 2024. Available at https://www.statista.com/statistics/1440857/south-korea-five-year-relative-survival-rate-of-main-cancers. Accessed October 4, 2024.
6. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. *Nat Rev Gastroenterol Hepatol*. 2021;18(7):493-502.
7. Kang MJ, Jung KW, Bang SH, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2020. *Cancer Res Treat*. 2023;55(2):385-399.
8. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263.
9. Ferlay JEM, Lam F, et al. *Global Cancer Observatory: Cancer Today*. International Agency for Research on Cancer. Available at https://gco.iarc.fr/. Accessed July 25, 2023.
10. Xiang X, Chen X, He Y, et al. Pancreatic cancer challenge in 52 Asian countries: age-centric insights and the role of modifiable risk factors (1990-2019). *Front Oncol*. 2023;13:1271370.
11. Mormul A, Wloszek E, Nowoszewska J, et al. Rare non-neuroendocrine pancreatic tumours. *Cancers (Basel)*. 2023;15(8):2216.
12. McGuigan A, Kelly P, Turkington RC, et al. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol*. 2018;24(43):4846-4861.
13. Niksic M, Matz M, Valkov M, et al. World-wide trends in net survival from pancreatic cancer by morphological sub-type: an analysis of 1,258,329 adults diagnosed in 58 countries during 2000-2014 (CONCORD-3). *Cancer Epidemiol*. 2022;80:102196.
14. Koyanagi YN, Ito H, Matsuo K, et al. Smoking and pancreatic cancer incidence: a pooled analysis of 10 population-based cohort studies in Japan. *Cancer Epidemiol Biomarkers Prev*. 2019;28(8):1370-1378.
15. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. *J Am Med Assoc*. 2021;326(9):851-862.
16. Kim M, Kim H, Han Y, et al. The incidence and clinical features of familial pancreatic cancer in Korea. *J Hepatobiliary Pancreat Sci*. 2022;29(6):659-669.
17. Matsubayashi H, Takaori K, Morizane C, et al. Familial pancreatic cancer: concept, management and issues. *World J Gastroenterol*. 2017;23(6):935-948.
18. Cheng SM, Su YY, Chiang NJ, et al. Germline mutations of homologous recombination genes and clinical outcomes in pancreatic cancer: a multicenter study in Taiwan. *J Biomed Sci*. 2024;31(1):21.
19. Mizukami K, Iwasaki Y, Kawakami E, et al. Genetic characterization of pancreatic cancer patients and prediction of carrier status of germline pathogenic variants in cancer-predisposing genes. *EBioMedicine*. 2020;60:103033.
20. Yin L, Wei J, Lu Z, et al. Prevalence of germline sequence variations among patients with pancreatic cancer in China. *JAMA Netw Open*. 2022;5(2):e2148721.
21. Kanda M, Matthaei H, Wu J, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. *Gastroenterology*. 2012;142(4):730-733.e739.
22. Wu J, Matthaei H, Maitra A, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. *Sci Transl Med*. 2011;3(92):92ra66.
23. Conroy T, Pfeiffer P, Vilgrain V, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(11):987-1002.
24. Conroy T, Ducreux M, ESMO Guidelines Committee. ESMO Clinical Practice Guideline Express Update on the management of metastatic pancreatic cancer. *ESMO Open*. 2025;10(4):104528.
25. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
26. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular targets (ESCAT). *Ann Oncol*. 2018;29(9):1895-1902.
27. Wattenberg MM, Asch D, Yu S, et al. Platinum response characteristics of patients with pancreatic ductal adenocarcinoma and a germline BRCA1, BRCA2 or PALB2 mutation. *Br J Cancer*. 2020;122(3):333-339.
28. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381(4):317-327.
29. Reiss KA, Mick R, O'Hara MH, et al. Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2, or PALB2. *J Clin Oncol*. 2021;39(22):2497-2505.
30. Shroff RT, Hendifar A, McWilliams RR, et al. Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious BRCA mutation. *JCO Precis Oncol*. 2018;2:1-15.
31. Nusrat F, Khanna A, Jain A, et al. The clinical implications of KRAS mutations and variant allele frequencies in pancreatic ductal adenocarcinoma. *J Clin Med*. 2024;13(7):2103.
32. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). *Surgery*. 2014;156(3):591-600.
33. Huang L, Jansen L, Balavarca Y, et al. Significance of examined lymph node number in accurate staging and long-term survival in resected stage I-II pancreatic cancer-more is better? A large international population-based cohort study. *Ann Surg*. 2021;274(6):e554-e563.
34. Li YF, Xiang YC, Zhang QQ, et al. Impact of examined lymph node count on prognosis in patients with lymph node-negative pancreatic body/tail ductal adenocarcinoma. *J Gastrointest Oncol*. 2020;11(4):644-653.

35. Wang W, Shen Z, Zhang J, et al. A novel criterion for lymph nodes dissection in distal pancreatectomy for ductal adenocarcinoma: a population study of the US SEER database. *Ann Surg Oncol*. 2022;29(3):1533-1539.
36. Shinke G, Takeda Y, Ohmura Y, et al. Randomized, controlled, multicenter phase II study of postoperative enoxaparin treatment for venous thromboembolism prophylaxis in patients undergoing surgery for hepatobiliary-pancreatic malignancies. *Ann Gastroenterol Surg*. 2024;8(5):868-876.
37. Matar CF, Kahale LA, Hakoum MB, et al. Anticoagulation for perioperative thromboprophylaxis in people with cancer. *Cochrane Database Syst Rev.* 2018;7(7):CD009447.
38. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med*. 2010;362(2):129-137.
39. Mumtaz K, Hamid S, Jafri W. Endoscopic retrograde cholangiopancreaticography with or without stenting in patients with pancreaticobiliary malignancy, prior to surgery. *Cochrane Database Syst Rev.* 2007;2007(3):CD006001.
40. Goetze TO, Reichart A, Bankstahl US, et al. Adjuvant gemcitabine versus neoadjuvant/adjuvant FOLFIRINOX in resectable pancreatic cancer: the randomized multicenter phase II NEPAFOX trial. *Ann Surg Oncol*. 2024;31(6):4073-4083.
41. Labori KJ, Bratlie SO, Andersson B, et al. Neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer (NORPACT-1): a multicentre, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2024;9(3):205-217.
42. Unno M, Motoi F, Matsuyama Y, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05). *J Clin Oncol*. 2019;37(suppl 4):189. 189.
43. Okusaka T, Nakamura M, Yoshida M, et al. Clinical Practice Guidelines for Pancreatic Cancer 2022 from the Japan Pancreas Society: a synopsis. *Int J Clin Oncol*. 2023;28(4):493-511.
44. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018;379(25):2395-2406.
45. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016;388(10041):248-257.
46. Go SI, Lee SC, Bae WK, et al. Modified FOLFIRINOX versus S-1 as second-line chemotherapy in gemcitabine-failed metastatic pancreatic cancer patients: a randomised controlled trial (MPACA-3). *Eur J Cancer.* 2021;157:21-30.
47. Parmar A, Chaves-Porras J, Saluja R, et al. Adjuvant treatment for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Crit Rev Oncol Hematol*. 2020;145:102817.
48. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389(10073):1011-1024.
49. Xu JB, Jiang B, Chen Y, et al. Optimal adjuvant chemotherapy for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Oncotarget*. 2017;8(46):81419-81429.
50. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *J Am Med Assoc*. 2010;304(10):1073-1081.
51. Mehtsun WT, McCleary NJ, Maduekwe UN, et al. Patterns of adjuvant chemotherapy use and association with survival in adults 80 years and older with pancreatic adenocarcinoma. *JAMA Oncol*. 2022;8(1):88-95.
52. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology*. 2018;18(1):2-11.
53. Lambert A, Bouche O, Ayav A, et al. LBA62 Preoperative modified FOLFIRINOX (mFOLFIRINOX) with or without chemoradiation (CRT) in borderline resectable pancreatic cancer (BRPC): results from the randomized phase II trial PANDAS/PRODIGE 44. *Ann Oncol*. 2024;35:S1252.
54. Katz MHG, Shi Q, Meyers J, et al. Efficacy of preoperative mFOLFIRINOX vs mFOLFIRINOX plus hypofractionated radiotherapy for borderline resectable adenocarcinoma of the pancreas: the A021501 phase 2 randomized clinical trial. *JAMA Oncol*. 2022;8(9):1263-1270.
55. Eshmuminov D, Aminjonov B, Palm RF, et al. FOLFIRINOX or gemcitabine-based chemotherapy for borderline resectable and locally advanced pancreatic cancer: a multi-institutional, patient-level, meta-analysis and systematic review. *Ann Surg Oncol*. 2023;30(7):4417-4428.
56. Ikeda M, Nomura S, Kobayashi T, et al. Randomized phase II/III trial of gemcitabine plus nab-paclitaxel versus concurrent chemoradiotherapy with S-1 as neoadjuvant treatment for borderline resectable pancreatic cancer: GABARNANCE study. *J Clin Oncol*. 2024;42(suppl 17):LBA4014.
57. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol*. 2005;23(15):3509-3516.
58. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009;27(33):5513-5518.
59. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol*. 2013;31(13):1640-1648.
60. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.
61. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol*. 2013;31(1):23-29.
62. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703.
63. Goldstein D, El-Maraghi RH, Hammel P, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst*. 2015;107(2):dju413.
64. Pusceddu S, Ghidini M, Torchio M, et al. Comparative effectiveness of gemcitabine plus nab-paclitaxel and FOLFIRINOX in the first-line setting of metastatic pancreatic cancer: a systematic review and meta-analysis. *Cancers (Basel)*. 2019;11(4):484.
65. Ohba A, Ozaka M, Ogawa G, et al. 1616O Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE): a multicentred, randomized, open-label, three-arm, phase II/III trial. *Ann Oncol*. 2023;34:S894.
66. Knox JJ, Jaffee EM, O'Kane GM, et al. Early results of the PASS-01 trial: pancreatic adenocarcinoma signature stratification for treatment-01. *J Clin Oncol*. 2024;42(suppl 17):LBA4004.
67. Tong H, Fan Z, Liu B, et al. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. *Sci Rep*. 2018;8(1):8666.
68. Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. *Lancet*. 2023;402(10409):1272-1281.
69. Dotan E, Catalano PJ, Lenchik L, et al. A randomized phase II study of gemcitabine and nab-paclitaxel compared with 5-fluorouracil, leucovorin, and liposomal irinotecan in older patients with treatment-naïve metastatic pancreatic cancer (GIANT): ECOG-ACRIN EA2186. *J Clin Oncol*. 2024;42(suppl 16):4003.

70. Mastrantoni L, Chiaravalli M, Spring A, et al. Comparison of first-line chemotherapy regimens in unresectable locally advanced or metastatic pancreatic cancer: a systematic review and Bayesian network meta-analysis. *Lancet Oncol*. 2024;25(12):1655-1665.
71. De La Fouchardiere C, Malka D, Cropet C, et al. Gemcitabine and paclitaxel versus gemcitabine alone after 5-fluorouracil, oxaliplatin, and irinotecan in metastatic pancreatic adenocarcinoma: a randomized phase III PRODIGE 65-UCGI 36-GEMPAX UNICANCER Study. *J Clin Oncol*. 2024;42(9):1055-1066.
72. Taieb J, Abdallah R. How I treat pancreatic cancer. *ESMO Open*. 2020;4(suppl 2):e000818.
73. Huh G, Lee HS, Choi JH, et al. Gemcitabine plus nab-paclitaxel as a second-line treatment following FOLFIRINOX failure in advanced pancreatic cancer: a multicenter, single-arm, open-label, phase 2 trial. *Ther Adv Med Oncol*. 2021;13:17588359211056179.
74. Wang-Gillam A, Hubner RA, Siveke JT, et al. NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: final overall survival analysis and characteristics of long-term survivors. *Eur J Cancer*. 2019;108:78-87.
75. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol*. 2014;32(23):2423-2429.
76. Vogel A, Rommler-Zehrer J, Li JS, et al. Efficacy and safety profile of nab-paclitaxel plus gemcitabine in patients with metastatic pancreatic cancer treated to disease progression: a subanalysis from a phase 3 trial (MPACT). *BMC Cancer*. 2016;16(1):817.
77. United States Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions. 2018. Available at https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions. Accessed March 24, 2025.
78. United States Food and Drug Administration. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. 2019. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc. Accessed March 24, 2025.
79. United States Food and Drug Administration. FDA grants accelerated approval to repotrectinib for adult and pediatric patients with NTRK gene fusion-positive solid tumors. 2024. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-repotrectinib-adult-and-pediatric-patients-ntrk-gene-fusion-positive. Accessed March 24, 2025.
80. Besse B, Springfeld C, Baik C, et al. Update from the ongoing phase 1/2 registrational trial of repotrectinib: results in TKI-naïve and TKI-pretreated patients with NTRK fusion-positive advanced solid tumors (TRIDENT-1). *Eur J Cancer*. 2022;174:S75-S76.
81. Chen MF, Yang S-R, Shia J, et al. Response to repotrectinib after development of NTRK resistance mutations on first- and second-generation TRK inhibitors. *JCO Precis Oncol*. 2023;7:e2200697.
82. Solomon BJ, Drilon A, Lin JJ, et al. 1372P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: update from the phase I/II TRIDENT-1 trial. *Ann Oncol*. 2023;34:S787-S788.
83. Andel PCM, van Goor I, Augustinus S, et al. Routine imaging or symptomatic follow-up after resection of pancreatic adenocarcinoma. *JAMA Surg*. 2025;160(1):74-84.
84. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006;166(4):458-464.
85. Farge D, Bournet B, Conroy T, et al. Primary thromboprophylaxis in pancreatic cancer patients: why clinical practice guidelines should be implemented. *Cancers (Basel)*. 2020;12(3):618.
86. Thein KZ, Quick DP, Oo TH. Updated meta-analysis of randomized controlled trials on primary ambulatory thromboprophylaxis (PATP) in patients with advanced pancreatic cancer (APC) receiving chemotherapy. *Blood*. 2019;134(suppl 1):3469.
87. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med*. 2019;380(8):720-728.
88. Vadhan-Raj S, McNamara MG, Venerito M, et al. Rivaroxaban thromboprophylaxis in ambulatory patients with pancreatic cancer: results from a pre-specified subgroup analysis of the randomized CASSINI study. *Cancer Med*. 2020;9(17):6196-6204.
89. Chen JS, Hung CY, Chang H, et al. Venous thromboembolism in Asian patients with pancreatic cancer following palliative chemotherapy: low incidence but a negative prognosticator for those with early onset. *Cancers (Basel)*. 2018;10(12):501.
90. Ohashi Y, Ikeda M, Kunitoh H, et al. One-year incidence of venous thromboembolism, bleeding, and death in patients with solid tumors newly initiating cancer treatment: results from the cancer-VTE registry. *Thromb Res*. 2022;213:203-213.
91. Chew TW, Gau CS, Wen YW, et al. Epidemiology, clinical profile and treatment patterns of venous thromboembolism in cancer patients in Taiwan: a population-based study. *BMC Cancer*. 2015;15:298.
92. Dumonceau JM, Tringali A, Papanikolaou IS, et al. Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated October 2017. *Endoscopy*. 2018;50(9):910-930.
93. Bian SB, Shen WS, Xi HQ, et al. Palliative therapy for gastric outlet obstruction caused by unresectable gastric cancer: a meta-analysis comparison of gastrojejunostomy with endoscopic stenting. *Chin Med J (Engl)*. 2016;129(9):1113-1121.
94. Hosono S, Ohtani H, Arimoto Y, et al. Endoscopic stenting versus surgical gastroenterostomy for palliation of malignant gastroduodenal obstruction: a meta-analysis. *J Gastroenterol*. 2007;42(4):283-290.
95. Jeurnink SM, van Eijck CH, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol*. 2007;7:18.
96. Zheng B, Wang X, Ma B, et al. Endoscopic stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction. *Dig Endosc*. 2012;24(2):71-78.
97. Minata MK, Bernardo WM, Rocha RS, et al. Stents and surgical interventions in the palliation of gastric outlet obstruction: a systematic review. *Endosc Int Open*. 2016;4(11):E1158-E1170.
98. Teoh AYB, Lakhtakia S, Tarantino I, et al. Endoscopic ultrasonography-guided gastroenterostomy versus uncovered duodenal metal stenting for unresectable malignant gastric outlet obstruction (DRA-GOO): a multicentre randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2024;9(2):124-132.
99. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med*. 2010;7(4):e1000267.
100. Chiorean EG, Chiaro MD, Tempero MA, et al. Ampullary adenocarcinoma, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2023;21(7):753-782.
101. Rompen IF, Habib JR, Wolfgang CL, et al. Anatomical and biological considerations to determine resectability in pancreatic cancer. *Cancers (Basel)*. 2024;16(3):489.
102. Oba A, Del Chiaro M, Satoi S, et al. New criteria of resectability for pancreatic cancer: a position paper by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS). *J Hepatobiliary Pancreat Sci*. 2022;29(7):725-731.
103. Wu HY, Li JW, Li JZ, et al. Comprehensive multimodal management of borderline resectable pancreatic cancer: current status and progress. *World J Gastrointest Surg*. 2023;15(2):142-162.
104. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer–a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol*. 2005;23(6):1228-1236.
105. Ychou M, Conroy T, Seitz JF, et al. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors. *Ann Oncol*. 2003;14(3):481-489.
106. Kang H, Jo JH, Lee HS, et al. Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer. *World J Gastrointest Oncol*. 2018;10(11):421-430.

107. Gouda MA, Thein KZ, Hong DS. Tissue-agnostic targeting of neurotrophic tyrosine receptor kinase fusions: current approvals and future directions. *Cancers (Basel)*. 2024;16(19):3395.
108. Demetri GD, De Braud F, Drilon A, et al. Updated integrated analysis of the efficacy and safety of entrectinib in patients with NTRK fusion-positive solid tumors. *Clin Cancer Res*. 2022;28(7):1302-1312.
109. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271-282.
110. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol*. 2020;21(4):531-540.
111. Bannoura SF, Khan HY, Azmi AS. KRAS G12D targeted therapies for pancreatic cancer: has the fortress been conquered? *Front Oncol*. 2022;12:1013902.
112. Zhou X, Ji Y, Zhou J. Multiple strategies to develop small molecular KRAS directly bound inhibitors. *Molecules*. 2023;28(8):3615.
113. Strickler JH, Satake H, George TJ, et al. Sotorasib in KRAS p.G12C-mutated advanced pancreatic cancer. *N Engl J Med*. 2023;388(1):33-43.
114. Garrido-Laguna I, Wolpin BM, Park W, et al. Safety, efficacy, and on-treatment circulating tumor DNA (ctDNA) changes from a phase 1 study of RMC-6236, a RAS(ON) multi-selective, tri-complex inhibitor, in patients with RAS mutant pancreatic ductal adenocarcinoma (PDAC). *J Clin Oncol*. 2025;43(suppl 4):722.
115. Tateo V, Marchese PV, Mollica V, et al. Agnostic approvals in oncology: getting the right drug to the right patient with the right genomics. *Pharmaceuticals (Basel)*. 2023;16(4):614.
116. Mehdi M, Szabo A, Shreenivas A, et al. Chemotherapy-free treatment targeting fusions and driver mutations in KRAS wild-type pancreatic ductal adenocarcinoma, a case series. *Ther Adv Med Oncol*. 2024;16:17588359241253113.
117. Choi H, Lee H, Park B, et al. Changes in the review period of drug application and a drug lag from the FDA and the EMA: an Industry survey in South Korea between 2011 and 2020. *Ther Innov Regul Sci*. 2023;57(3):552-560.
118. Nanda RH, El-Rayes B, Maithel SK, et al. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. *J Surg Oncol*. 2015;111(8):1028-1034.
119. Blazer M, Wu C, Goldberg RM, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. *Ann Surg Oncol*. 2015;22(4):1153-1159.
120. Yoo C, Lee SS, Song KB, et al. Neoadjuvant modified FOLFIRINOX followed by postoperative gemcitabine in borderline resectable pancreatic adenocarcinoma: a phase 2 study for clinical and biomarker analysis. *Br J Cancer*. 2020;123(3):362-368.
121. Soni S, Jain A, Goyal V, et al. Modified FOLFIRINOX as the first-line chemotherapy in unresectable and metastatic pancreatic adenocarcinoma—a single-center experience in India. *Ann Pancreat Cancer*. 2023;6:9.
122. Stein SM, James ES, Deng Y, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer*. 2016;114(7):737-743.
123. Vivaldi C, Caparello C, Musettini G, et al. First-line treatment with FOLFOXIRI for advanced pancreatic cancer in clinical practice: patients' outcome and analysis of prognostic factors. *Int J Cancer*. 2016;139(4):938-945.
124. Vocka M, Petruzelka L. Modified FOLFIRINOX in the treatment of pancreatic cancer — efficiency and toxicity. *Gastroenterol Hepatol*. 2016;70:413-417.
125. Tezuka S, Ueno M, Oishi R, et al. Modified FOLFIRINOX versus sequential chemotherapy (FOLFIRI/FOLFOX) as a second-line treatment regimen for unresectable pancreatic cancer: a real-world analysis. *Cancer Med*. 2022;11(4):1088-1098.
126. Li X, Ma T, Zhang Q, et al. Modified-FOLFIRINOX in metastatic pancreatic cancer: a prospective study in Chinese population. *Cancer Lett*. 2017;406:22-26.
127. Mahaseth H, Brutcher E, Kauh J, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas*. 2013;42(8):1311-1315.