

SPECIAL ARTICLE

ESMO Clinical Practice Guideline Express Update on the management of metastatic pancreatic cancer

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INTRODUCTION

This Express Update provides new recommendations for the following ESMO Clinical Practice Guideline (CPG): Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up.¹

View the original CPG here: <https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/cancer-of-the-pancreas-esmo-clinical-practice-guidelines>.

MANAGEMENT OF METASTATIC DISEASE

First-line treatment

In the phase III NAPOLI 3 trial, 770 patients were randomly assigned to receive 5-fluorouracil (5-FU)—folinic acid (FA)—nanoliposomal irinotecan—oxaliplatin (NALIRIFOX; 383 patients) or gemcitabine—nab-paclitaxel (GN; 387 patients).² With a median follow-up of 16.1 months, the median overall survival (OS) was 11.1 months [95% confidence interval (CI) 10.0–12.1 months] with NALIRIFOX versus 9.2 months (95% CI 8.3–10.6 months) with GN [hazard ratio (HR) 0.83, 95% CI 0.70–0.99, $P = 0.036$]. Median progression-free survival (PFS) was 7.4 months (95% CI 6.0–7.7 months) with NALIRIFOX and 5.6 months (95% CI 5.3–5.8 months) with GN (HR 0.69, 95% CI 0.58–0.83, $P < 0.0001$). PFS rates at 12 months were 27.4% (95% CI 22.3% to 32.7%) with NALIRIFOX and 13.9% (95% CI 9.7% to 18.9%) with GN. Objective responses were reported in 160 (42%) of NALIRIFOX-treated patients and 140 (36%) of GN-treated patients ($P = 0.11$). Grade ≥ 3 treatment-emergent adverse events (AEs) occurred in 322 (87%) and 326 (86%) of patients

in the NALIRIFOX and GN treatment groups, respectively; treatment-related deaths occurred in six (2%) patients in the NALIRIFOX group and eight (2%) patients in the GN group. The most common grade 3–4 AEs reported with NALIRIFOX and GN were neutropenia (14% versus 25%, respectively) and diarrhoea (20% versus 5%, respectively).

Quality of life (QoL) data from this study have not yet been published but were presented as a poster at the ESMO Congress 2023. Changes in the various European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30 QoL indices showed no significant difference between the two treatment groups.³

5-FU—FA—irinotecan—oxaliplatin (FOLFIRINOX) and NALIRIFOX have not been directly compared in a prospective clinical trial and there are no data evaluating the respective cost-effectiveness of these two regimens.

A recently published systematic review and Bayesian network meta-analysis compared the efficacy and toxicity of first-line treatment options for locally advanced and metastatic pancreatic cancer.⁴ The reported conclusion from this study was that FOLFIRINOX and NALIRIFOX might be considered the preferred options for patients who can tolerate these regimens; the final treatment choice should depend on the anticipated OS benefit, patient-tailored toxicity profile and the cost–benefit ratio. Nevertheless, GN remains an option, particularly in patients unfit for triplet therapy. Given the differences in toxicity profiles for triplet versus doublet therapy, GN may also be preferred in cases where gastrointestinal toxicity is a concern.

Second-line treatment

In the phase III GEMPAX trial, 211 patients with metastatic pancreatic cancer and a World Health Organization performance status (PS) of 0–2 were randomised to receive either gemcitabine—paclitaxel (GP) or gemcitabine alone as second-line treatment after failure of FOLFIRINOX.⁵ After a median

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follow-up of 13.6 months, the median OS was 6.4 months (95% CI 5.2-7.4 months) with GP versus 5.9 months (95% CI 4.6-6.9 months) with gemcitabine alone (HR 0.87, 95% CI 0.63-1.20, $P = 0.4095$). Median PFS was 3.1 months (95% CI 2.2-4.3 months) with GP versus 2.0 months (95% CI 1.9-2.3 months) with gemcitabine alone (HR 0.64, 95% CI 0.47-0.89, $P = 0.0067$), and the objective response rate was 17.1% (95% CI 11.3% to 24.4%) with GP versus 4.2% (95% CI 0.9% to 11.9%) with gemcitabine alone ($P = 0.008$). Overall, 16.7% of patients in the GP group and 2.9% in the gemcitabine alone group discontinued treatment due to AEs. Grade ≥ 3 treatment-related AEs were reported in 58.0% and 27.1% of patients in the GP and gemcitabine alone groups, respectively, and one grade 5 AE (acute respiratory distress) associated with both gemcitabine and paclitaxel was reported. Deterioration in QoL was higher in the gemcitabine alone group, although a difference in favour of the GP group was only statistically significant for insomnia ($P = 0.049$).

Currently, no clinical trial data are available to guide second-line treatment after failure of NALIRIFOX. However,

second-line treatment with a gemcitabine-based regimen would be a rational approach for those patients who are well enough to receive further anticancer treatment.

An updated algorithm for the management of metastatic pancreatic cancer is shown in Figure 1.

Recommendations

First-line treatment

- Options to treat patients with metastatic pancreatic cancer are dependent on PS:
 - In patients with an Eastern Cooperative Oncology Group (ECOG) PS of 0-1, a bilirubin level of <1.5 times the upper limit of normal and no major comorbidities, two regimens should be recommended as first-line chemotherapy: FOLFIRINOX [I, A; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 score: 5 (versus gemcitabine)] or NALIRIFOX [I, A; ESMO-MCBS v1.1 score: 2 (versus GN)].
 - GN can also be used in these patients [I, B; ESMO-MCBS v1.1 score: 3 (versus gemcitabine)].

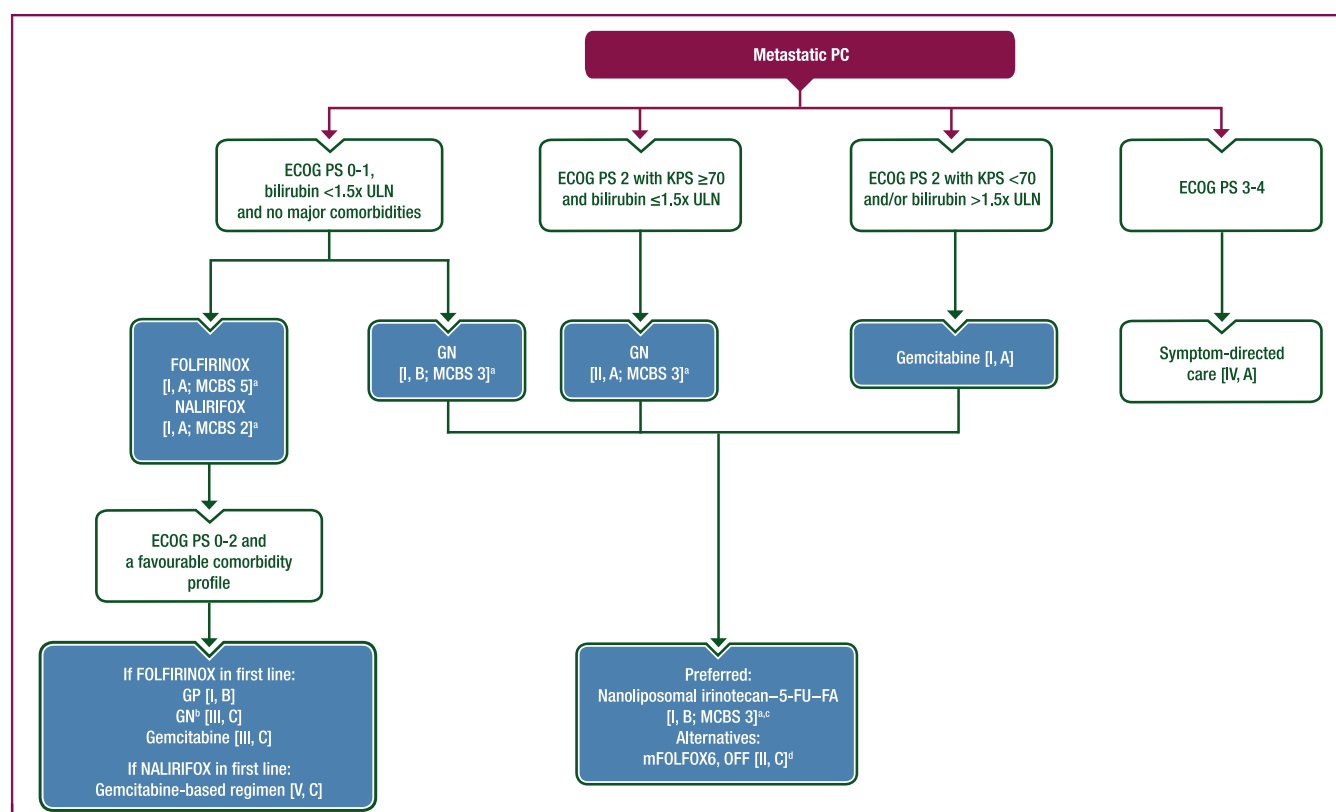


Figure 1. Systemic treatment of metastatic PC.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FA, folinic acid; FDA, Food and Drug Administration; FOLFIRINOX, 5-FU-FA-irinotecan-oxaliplatin; GN, gemcitabine-nab-paclitaxel; GP, gemcitabine-paclitaxel; KPS, Karnofsky performance status; MCBS, Magnitude of Clinical Benefit Scale; mFOLFIOX6, modified leucovorin-5-fluorouracil-oxaliplatin; NALIRIFOX, 5-FU-FA-nanopiposomal irinotecan-oxaliplatin; OFF, oxaliplatin-5-FU-FA; PC, pancreatic cancer; PS, performance status; ULN, upper limit of normal.

^aESMO-MCBS v1.1⁶ was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^bNot EMA or FDA approved as second-line therapy.

^cOnly in patients with, or who have recovered to, ECOG PS 0-1.

^dIf not given previously.

Table 1. ESMO-MCBS table for first-line therapies/indications in metastatic pancreatic cancer

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score ^a
Erlotinib—gemcitabine	Metastatic pancreatic cancer	PA.3 ⁸ Phase III NCT00026338	Placebo—gemcitabine Median OS: 5.9 months	OS gain: 0.3 months	OS: 0.82 (0.69-0.99)	No QoL benefit	1 (Form 2a)
FOLFIRINOX ^b	Metastatic pancreatic cancer in patients with good PS	PRODIGE 4/ ACCORD 11 ^{9,10} Phase II/III NCT00112658	Gemcitabine Median OS: 6.8 months	OS gain: 4.3 months	OS: 0.57 (0.45-0.73)	Delayed deterioration in QoL	5 (Form 2a)
Gemcitabine—nab-paclitaxel	First-line treatment of adult patients with metastatic adenocarcinoma of the pancreas	MPACT ¹¹ Phase III NCT00844649	Gemcitabine Median OS: 6.6 months	OS gain: 2.1 months	OS: 0.72 (0.62-0.83)	QoL evaluation was not planned	3 (Form 2a)
NALIRIFOX	First-line treatment of adult patients with metastatic adenocarcinoma of the pancreas	NAPOLI 3 ^{2,12} Phase III NCT04083235	Gemcitabine—nab-paclitaxel Median OS: 9.2 months Median PFS: 5.6 months	OS gain: 1.9 months PFS gain: 1.8 months	OS: 0.83 (0.70-0.99) PFS: 0.69 (0.58-0.83)	Not qualified for an ESMO-MCBS credit >20% increase in grade 3-4 toxicities impacting daily life	2 (Form 2a)

5-FU, 5-fluorouracil; CI, confidence interval; EMA, European Medicines Agency; FA, folinic acid; FDA, Food and Drug Administration; FOLFIRINOX, 5-FU—FA—irinotecan—oxaliplatin; HR, hazard ratio; MCBS, Magnitude of Clinical Benefit Scale; NALIRIFOX, 5-FU—FA—nanoliposomal irinotecan—oxaliplatin; OS, overall survival; PFS, progression-free survival; PS, performance status; QoL, quality of life.

^aESMO-MCBS v1.1⁶ was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^bRegimen without a specific licensed indication in pancreatic cancer.

Second-line treatment

- After FOLFIRINOX treatment, GP can be offered to patients with an ECOG PS of 0-2 and a favourable comorbidity profile [I, B]. Other options are GN [III, C; not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved as second-line therapy] or gemcitabine alone [III, C].
- After NALIRIFOX treatment, a gemcitabine-based regimen may be offered to patients with an ECOG PS of 0-2 and a favourable comorbidity profile [V, C].

METHODOLOGY

This Express Update was developed in accordance with the ESMO standard operating procedures for CPG eUpdate development (<http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). All recommendations provided

are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated in algorithms by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. A table of ESMO-MCBS scores for first-line treatment options in metastatic pancreatic cancer is included in Table 1. ESMO-MCBS v1.1⁶ was used to calculate scores for new therapies/indications approved by the EMA or FDA (<https://www.esmo.org/Guidelines/ESMO-MCBS>). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this eUpdate. LoEs and GoRs have been applied

Table 2. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

Levels of evidence	
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
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aReprinted by permission of Oxford University Press on behalf of the Infectious Diseases Society of America.⁷

using the system shown in Table 2.⁷ Statements without grading were considered justified standard clinical practice by the authors. For future updates to the pancreatic cancer CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/cancer-of-the-pancreas-esmo-clinical-practice-guidelines>.

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