Irinotecan hydrochloride trihydrate (Onivyde® pegylated liposomal) in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas

General information

Drug description [1]

Irinotecan is a topoisomerase I inhibitor acting mainly via its active metabolite, SN-38. Liposomal irinotecan (Onivyde®, Onivyde® pegylated liposomal; historical names include nal-IRI, MM 398, or PEP02) is a liposomal formulation that encapsulates irinotecan in a lipid bilayer vesicle. Encapsulation allows irinotecan to remain in circulation for longer than unencapsulated (free) irinotecan before conversion to SN-38. Thus, at equivalent doses, liposomal irinotecan demonstrates higher and sustained intratumoural levels of irinotecan and SN-38 relative to free irinotecan.

Indication [2]

Irinotecan hydrochloride trihydrate (Onivyde® pegylated liposomal) in combination with oxaliplatin, 5-FU and LV is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

Incidence [3]

In Austria, in 2022, 1,970 patients were newly diagnosed with pancreatic cancer. The age-standardised incidence rate[1] was 24.7/100,000 in men and 17.7/100,000 in women.

Current treatment[2] [4]

The ESMO treatment recommendation for the systemic treatment of advanced pancreatic cancer is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]	FDA [5, 6]
Approval status for this indication: On 21 March 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Onivyde® pegylated liposomal. <u>The CHMP adopted a new indication as follows:</u> ❖ Onivyde® pegylated liposomal is indicated in combination with oxaliplatin, 5-FU and LV for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, **Other indications**: Onivyde® pegylated liposomal is indicated in combination with 5-FU and LV for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine-based therapy. ✓ **Orphan status**	**Approval status for this indication**: On 13 February 2024, the FDA approved irinotecan liposome (Onivyde®) with oxaliplatin, fluorouracil, and leucovorin, for the first-line treatment of metastatic pancreatic adenocarcinoma. ✓ Orphan drug designation **Other indications**: ❖ Onivyde® is indicated in combination with fluorouracil and leucovorin, for the treatment of adult patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy. **Limitation of Use**: Onivyde® is not indicated as a single agent for the treatment of patients with metastatic pancreatic adenocarcinoma.

Manufacturer

Onivyde® pegylated liposomal is manufactured by Les Laboratoires Servier.

Costs [7]

Onivyde® pegylated liposomal concentrate for dispersion for infusion 4.3 mg/ml = **€ 825.00** (ex-factory price)

Posology [5]

<u>Preparation and administration</u>

[1] European Standard Population 2013.
[2] To date, there is no Onkopedia Guideline available for the treatment of adenocarcinoma of the pancreas.

- Onivyde® is a cytotoxic drug. Follow applicable special handling and disposal procedures.
- Withdraw the calculated volume of Onivyde® from the vial. Dilute Onivyde® in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted solution by gentle inversion.
- Protect diluted solution from light.
- Administer diluted solution within 4 hours of preparation when stored at room temperature or within 24 hours of preparation when stored under refrigerated conditions (2°C to 8°C). Allow diluted solution to come to room temperature prior to administration.
- Do NOT freeze.
- Infuse diluted solution intravenously over 90 minutes. Do not use in-line filters. Discard unused portion.

Premedication

- Administer a corticosteroid and an anti-emetic 30 minutes prior to Onivyde® infusion.

Warnings and precautions [5]

- **Neutropenia**
  - Severe or life-threatening neutropenia , including fatal neutropenic sepsis and fatal neutropenic fever, has occurred in patients receiving Onivyde® in combination with oxaliplatin, fluorouracil and LV and in combination with fluorouracil and LV.
  - Withhold Onivyde® for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment.
- **Diarrhoea**
  - Severe and life-threatening diarrhoea has occurred in patients receiving Onivyde® in combination with oxaliplatin, fluorouracil and leucovorin and in combination with fluorouracil and leucovorin.
  - Do not administer Onivyde® to patients with bowel obstruction.
  - Withhold Onivyde® for diarrhoea of Grade 2-4 severity. Administer loperamide for late diarrhoea of any severity.
  - Administer atropine, if not contraindicated, for early diarrhoea of any severity.
- **Interstitial lung disease (ILD)**
  - Fatal ILD has occurred in patients receiving irinotecan HCl. Discontinue Onivyde® if ILD is diagnosed.
- **Severe hypersensitivity reaction**
  - Permanently discontinue Onivyde® for severe hypersensitivity reactions.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception.

Study characteristics [1, 8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
NAPOLI-3 NCT04083235	770 (1:1)	**NALIRIFOX** (liposomal irinotecan 50 mg/m², oxaliplatin 60 mg/m², leucovorin 400 mg/m², and fluorouracil 2400 mg/m², administered sequentially as a continuous IV infusion over 46 h) on days 1 and 15 of a 28-day cycle	**nab-paclitaxel** 125 mg/m² + **gemcitabine** 1000 mg/m², administered IV, on days 1, 8, and 15 of a 28-day cycle	OS in the ITT population	16.1 months	**ongoing**[3], randomised, open-label, multicentre, phase 3 study	CA 19-9	Ipsen	NAPOLI-3 trial [1]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=383 vs. 387)
❖ Histological or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting. ❖ Initial diagnosis of metastatic disease must have occurred ≤6 weeks prior to screening.	❖ Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy. ❖ Prior treatment of pancreatic adenocarcinoma with chemotherapy in the adjuvant setting, except those	❖ Median age (range; IQR): 64.0 (20–85; 57–70) vs. 65.0 (36–82; 59–70) years ❖ Male sex: 53% vs. 59% ❖ Race: • White: 82% vs. 84% • Asian: 5% vs. 5% • Black or African American: 3% vs. 2% • Other: 2% vs. 2%

[3] The NAPOLI-3 trial is currently ongoing; the estimated study completion date is 12/2024.

- One or more metastatic lesions measurable by CT scan (or MRI), according to RECIST Version 1.1 criteria.
- ECOG PS of 0 or 1.
- Adequate biological parameters as demonstrated by the following blood counts:
  - ANC ≥2000/mm^3 without the use of haemopoietic growth factors within the last 7 days prior to randomisation.
  - Platelet count ≥100,000/mm^3 .
  - Haemoglobin ≥9 g/dL obtained ≤14 days prior to randomisation.
- Adequate hepatic function as evidenced by:
  - Serum total bilirubin ≤1.5x ULN (biliary drainage is allowed for biliary obstruction), and
  - AST and ALT ≤2.5x ULN (≤5x ULN is acceptable if liver metastases are present).
- Adequate renal function as evidenced by creatinine clearance ≥30 mL/min.
- Adequate coagulation studies (obtained ≤14 days prior to randomisation) as demonstrated by prothrombin time and partial thromboplastin time within normal limits (≤1.5xULN).

where at least 12 months have elapsed since completion of the last dose and no persistent treatment-related toxicities are present.

- Patient has only localised advanced disease.
- Documented serum albumin <3 g/dL.
- Known history of CNS metastases.
- Clinically significant gastrointestinal disorder.
- History of any second malignancy in the last 2 years.
- Concurrent illnesses that would be a relative contraindication to trial participation.
- Use of strong inhibitors or inducers of CYP3A, CYP2C8 and UGT1A1.
- Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma.
- Known low or absent dihydropyrimidine dehydrogenase activity.

  - Multiple: 1% vs. 0
  - American Indian or Alaska Native: 0 vs. 1%
  - Native Hawaiian or other Pacific Islander: 0 vs. <1%
  - Not reported: 7% vs. 7%
- ECOG performance status score
  - 0: 42% vs. 43%
  - 1: 58% vs. 57%
  - 2: <1% vs. 0
- Metastatic sites
  - 1: 30% vs. 36%
  - 2: 31% vs. 28%
  - ≥3: 39% vs. 36%
- Liver metastases: 80% vs. 80%
- Geographical region:
  - North America: 31% vs. 32%
  - East Asia: 3% vs. 3%
  - Rest of the world: 66% vs. 66%
- Main pancreatic tumour location
  - Head: 38% vs. 40%
  - Other: 62% vs. 60%
- Baseline CA 19–9:
  - <37 U/mL: 16% vs. 18%
  - ≥37 U/mL: 84% vs. 82%
  - Median: 1856.0 vs. 1544.0
- Any previous anti-cancer therapy: 6% vs. 7%
  - Chemotherapy: 4% vs. 4%
  - Radiotherapy: 3% vs. 2%
  - Surgical procedure: 5% vs. 7%
- Time from diagnosis of metastatic disease at study entry to randomisation, weeks:
  - Mean: 2% vs. 2%
  - Median: 3.0 vs. 3.6

Efficacy (I vs. C)

Data cutoff: 23 July 2022; median follow-up: 16.1 months

Median OS: 11.1 months (95% CI, 10.0–12.1) vs. 9.2 months (8.3–10.6); HR 0.83 (95% CI, 0.70–0.99); p=0.036
OS at 12 months: 45.6% (40.5–50.5) vs. 39.5% (34.6–44.4)
OS at 18 months: 26.2% (20.9–31.7) vs. 19.3% (14.8–24.2)
Median PFS: 7.4 (95% CI, 6.0–7.7) vs. 5.6 (5.3–5.8) months; HR 0.69 (0.58–0.83); p<0.0001
PFS rates at 12 months: 27.4% (22.3–32.7) vs. 13.9% (9.7–18.9)
PFS rates at 18 months: 11.4% vs. 3.6%
Objective response: 42% vs. 36%; p=0.11
Median duration of response: 7.3 months (95% CI, 5.8–7.6) vs. 5.0 months (3.8–5.6); HR 0.67 (95% CI, 0.48–0.93)
Subsequent systemic anticancer therapy: 51% vs. 54%

Safety (I vs. C, n=370 vs. n=379)

Any TEAE: >99% vs. 99%
Any treatment-related TEAE: 95% vs. 93%
Grade ≥3 TEAE: 87% vs. 86%
Grade ≥3 treatment-related TEAE: 71% vs. 68%
Any TEAE leading to discontinuation: 32% vs. 30%
Any treatment-related TEAE leading to discontinuation: 25% vs. 23%
Any TEAE leading to dose reduction: 56% vs. 50%
Any treatment-related TEAE leading to dose reduction: 54% vs. 49%
Any serious TEAEs: 54% vs. 52%
Any treatment-related serious TEAEs: 27% vs. 19%
TEAEs leading to death: 6% vs. 6%

	Treatment-related TEAEs leading to death: 2% vs. 2%

Patient-reported outcomes [11]

- The EORTC QLQ-C30 was completed at baseline, day 1 of each 28-day cycle and at the end of treatment.
- A mixed model repeated measures model was used to describe the global health status (GHS) evolution over time between treatment arms.
- Time until definitive deterioration (TUDD) was defined as the time between randomization and first occurrence of a decrease ≥ 10 points in QLQ-C30 score without further improvement of ≥ 10 points or further data due to discontinuation.
- Mean GHS scores at baseline were similar between treatment arms (62.1 vs. 61.2); from week 16, there was a trend towards improvement in GHS scores in the NALIRIFOX arm relative to the gemcitabine+nab-paclitaxcel arm.
- Median TUDD of GHS: 15.7 months vs. 12.2 months with; stratified Cox HR 0.74 (95% CI, 0.53–1.04); nominal p=0.08.
- Definitive deterioration in GHS at 6 months: 26.4% vs. 31.7%.
- The TUDD of physical, role and emotional functioning, pain, dyspnoea and constipation were longer, with nominal p ≤ 0.05, in patients who received NALIRIFOX versus gemcitabine+nab-paclitaxel.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +1.9 months	0.83 (0.70–0.99)	HR>-0.65-0.70 AND gain 1.5 months	2	>20% increase in grade 3-4 toxicities impacting daily life	not significant	-1[4]	1
Adapted	NC	2A	≤12 months	OS: +1.9 months	0.83 (0.70–0.99)	HR>0.70	1	-	not significant	-	1

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	unclear[5] unclear risk	yes[6] high risk	unclear

Ongoing trials [14]

NCT number/trial name	Description	Estimated study completion date
NCT04083235/ NAPOLI-3	Please see above.	12/2024
NCT03861702	A phase II study to evaluate the efficacy of liposomal irinotecan in combination with oxaliplatin,LV, and 5-FU for patients with locally advanced pancreatic carcinoma.	08/2024
NCT05047991	A multicenter, randomized, open-label, parallel-controlled, phase II study to evaluate the differences of safety and efficacy of irinotecan liposome injection-containing regimens vs. nab-paclitaxel plus gemcitabine in patients with previously untreated, metastatic pancreatic adenocarcinoma.	11/2024
NCT03693677	Randomized phase II study comparing 5FU/LV+Nal-IRI, gemcitabine+nab-paclitaxel or a sequential regimen of 2 months 5FU/LV+Nal-IRI followed by two months of gemcitabine+nab-paclitaxel, in metastatic pancreatic cancer.	12/2024
NCT04662112	Multicenter phase I/IIa study of NASOX (Nal-IRI + S-1 + oxaliplatin) as first-line treatment for patients with locally advanced or metastatic pancreatic adenocarcinoma.	12/2024
NCT04617457	Open-label, single arm phase II trial investigating the efficacy, safety and QoL of neoadjuvant chemotherapy with liposomal irinotecan combined with oxaliplatin and 5-FU/folinic acid followed by curative surgical resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas.	09/2025
NCT04539808/ NeoOPTIMIZE	An open-label, phase II trial to assess the efficacy of adaptive switching of FOLFIRINOX or gemcitabine/nab-paclitaxel as a neoadjuvant strategy for patients with resectable and borderline resectable/locally advanced unresectable pancreatic cancer.	10/2025

[4] Toxicity adjustment.
[5] The NAPOLI-3 trial is currently ongoing.
[6] The funder of the study participated in study design, data collection, data analysis, data interpretation, and review and approval of the manuscript.

NCT06345300	Liposomal irinotecan, oxaliplatin, 5-FU/calcium folinate in combination with camrelizumab for borderline resectable pancreatic cancer: a prospective, exploratory study.	12/2025
NCT04233866/ GIANT	A randomized phase II study of gemcitabine and nab-paclitaxel compared with 5-FU, LV, and liposomal irinotecan in older patients with treatment naïve metastatic pancreatic cancer.	12/2025
NCT06210360	NALIRIFOX as perioperative treatment in patients with high-risk resectable pancreatic cancer : a multicentre, randomized, open-label trial.	04/2027
NCT06259058	Evaluate the efficacy and safety of stereotactic body radiation therapy followed by NALIRIFOX vs. NALIRIFOX for borderline resectable pancreatic cancer: a phase Ib/II, multicentre, open-label trial.	12/2027

Available assessments

- No assessments were identified via NICE, CADTH, ICER, G-BA or NIHR.

Other aspects and conclusions

- In March 2024, the **CHMP adopted a new indication** for Onivyde® pegylated liposomal is indicated in combination with oxaliplatin, 5-FU and LV for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. In February 2024, the **FDA approved** Onivyde® with oxaliplatin, 5-FU, and LV for the first-line treatment of metastatic pancreatic adenocarcinoma.
- **NAPOLI-3** (NCT04083235) is an **ongoing**, randomised, open-label, phase 3 study aiming to compare the efficacy and safety of NALIRIFOX vs. nab-paclitaxel and gemcitabine as first-line therapy for metastatic pancreatic ductal adenocarcinoma. Eligible participants were ≥18 years with histologically or cytologically confirmed pancreatic ductal adenocarcinoma previously untreated in the metastatic setting. Patients who received previous treatment for pancreatic ductal adenocarcinoma with chemotherapy in the adjuvant setting were excluded. Patients had to have one or more metastatic tumours measurable with CT or MRI and an ECOG PS of 0 or 1.
- The **primary endpoint was OS in the ITT population**. Median OS was 11.1 months (95% CI, 10.0–12.1) with NALIRIFOX vs. 9.2 months (8.3–10.6) with nab-paclitaxel–gemcitabine; **HR 0.83** (95% CI, 0.70–0.99; p=0.036).
- For **patients-reported outcomes**, currently, only **abstract data** is available. However, GHS scores showed a trend towards improvement in GHS scores in the NALIRIFOX arm relative to the gemcitabine+nab-paclitaxcel arm.
- The **original and adapted ESMO-MCBS** was applied, resulting in a **final adjusted magnitude of clinical benefit of 1 with both scales**.
- The **risk of bias** of NAPOLI-3 trial was considered **unclear,** referring to its ongoing status. However, the risk is **increased** by the open-label trial design and the involvement of the sponsor in study design, data collection, data analysis and data interpretation.
- Currently, NAPOLI-3 is the only ongoing phase 3 trial evaluating the assessed indication. Several phase 2 trials, assessing irinotecan hydrochloride trihydrate in different trial settings, are listed above.
- **Final analysis data of NAPOLI-3, including patient-reported outcomes** – supported by further phase 3 data – is required to determine the role of irinotecan hydrochloride trihydrate for the first-line treatment in patients with metastatic adenocarcinoma of the pancreas.

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Abbreviations: 5_FU=5-fluorouracil, AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CT=computed tomography, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GHS=global health score, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, ILD=interstital lung disease, Int.=intention, LV=leucovorin, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NALIRIFOX= liposomal irinotecan+oxaliplatin+leucovorin+fluorouracil, NICE=National Institute for Health Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse events, TUDD=time until definitive deterioration, ULN=upper limit of normal

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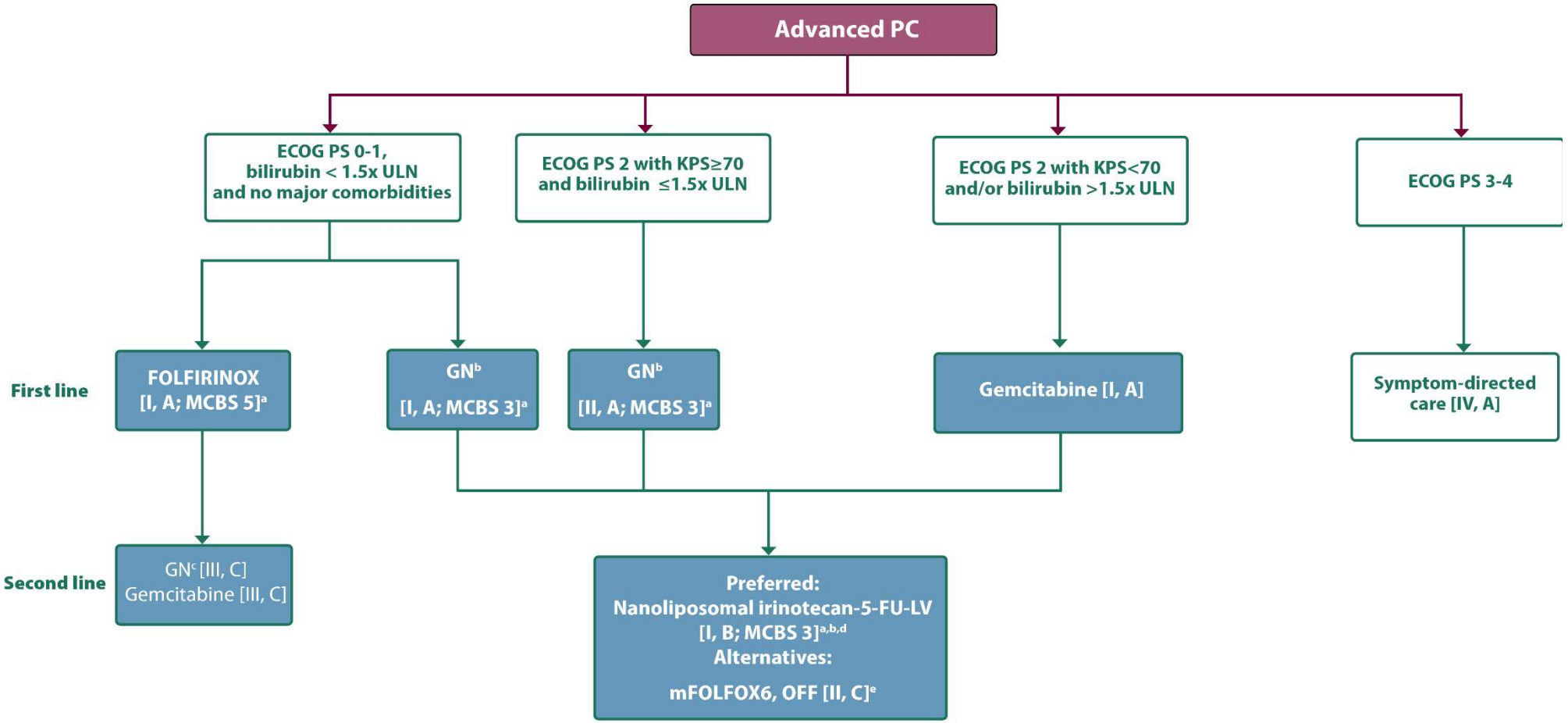
Appendix – Figure 1: Therapy algorithm for the treatment of advanced pancreatic cancer



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; MCBS, ESMO-Magnitude of Clinical Benefit Scale; LV, leucovorin; mFOLFOX6, modified leucovorin–5-fluorouracil–oxaliplatin; OFF, oxaliplatin–fluorouracil–leucovorin; PC, pancreatic cancer; PS, performance status; 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. 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 EMA and FDA approved in metastatic PC only (not advanced PC).

c Not EMA or FDA approved as second-line therapy.

d Only in patients with, or who have recovered to, ECOG PS 0-1.

e If not given previously.