

**5.11 IRINOTECAN (NANOLIPOSOMAL),  
Solution for I.V. infusion containing nanoliposomal  
irinotecan (as sucrosofate) 43 mg in 10 mL,  
Onivyde<sup>®</sup>,  
SERVIER LABORATORIES (AUST.) PTY. LTD.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for nanoliposomal irinotecan (nal-IRI) as a first-line chemotherapy for the treatment of metastatic pancreatic adenocarcinoma (mPAC), used in combination with oxaliplatin, 5-fluorouracil (5-FU) and folinic acid/leucovorin (LV). The four-drug chemotherapy regimen is known as NALIRIFOX.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus gemcitabine plus nanoparticle albumin-bound paclitaxel (Gem+NabP). The submission considered FOLFIRINOX (non-liposomal irinotecan used in combination with oxaliplatin, 5-FU and LV) a minor comparator. The key components of the clinical issue addressed by the submission are presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Previously untreated patients diagnosed with metastatic pancreatic cancer
Intervention	NALIRIFOX regimen administered intravenously on days 1 and 15 of each 28-day cycle: <ul style="list-style-type: none"> <li>• nal-IRI 50 mg/m<sup>2</sup></li> <li>• 5-fluorouracil 2,400 mg/m<sup>2</sup></li> <li>• leucovorin/folinic acid 400 mg/m<sup>2</sup> and</li> <li>• oxaliplatin 60 mg/m<sup>2</sup></li> </ul>
Comparator	<p><u>Main comparator:</u> Gem+NabP regimen administered intravenously on days 1, 8 and 15 of each 28-day cycle:</p> <ul style="list-style-type: none"> <li>• gemcitabine 1,000 mg/m<sup>2</sup> and</li> <li>• nanoparticle albumin-bound (nab-) paclitaxel 125 mg/m<sup>2</sup></li> </ul> <p><u>Secondary (Minor) comparator:</u> FOLFIRINOX regimen administered intravenously on days 1 and 15 of each 28-day cycle:</p> <ul style="list-style-type: none"> <li>• irinotecan 180 mg/m<sup>2</sup></li> <li>• 5-fluorouracil 400 mg/m<sup>2</sup> and 5-fluorouracil 2,400 mg/m<sup>2</sup>- over 46 hours</li> <li>• leucovorin/folinic acid 50 mg and</li> <li>• oxaliplatin 85 mg/m<sup>2</sup></li> </ul>
Outcomes	<p>Primary endpoint: overall survival (OS) Secondary endpoints: progression-free survival (PFS); objective response rate (ORR) Patient reported endpoints (exploratory endpoints) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 quality of life core 30 Questionnaire (EORTC QLQ 30). EuroQol 5-dimension health status questionnaire (5 level) (EQ-5D-5L)</p> <p>Safety</p>
Clinical claim	<p><u>Main comparator:</u> NALIRIFOX is superior in terms of effectiveness compared to Gem+NabP NALIRIFOX is non-inferior in terms of overall safety compared to Gem+NabP, noting these treatments have differing adverse event profiles</p> <p><u>Secondary (Minor) comparator:</u> NALIRIFOX is superior to FOLFIRINOX because NALIRIFOX has a proven survival benefit over Gem+NabP, whereas FOLFIRINOX does not NALIRIFOX is superior to FOLFIRINOX because NALIRIFOX has proven to be of similar levels of toxicity to Gem+NabP, whereas FOLFIRINOX has historically been reserved for fitter and younger patients due to its unfavourable safety profile</p>

Source: Table 1, p10 of the submission and Appendix A of the submission.

Abbreviations: EORTC QLQ 30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 quality of life core 30 Questionnaire; EQ-5D-5L, EuroQol 5-dimension health status questionnaire (5 level); FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; nal-IRI, nanoliposomal irinotecan; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

## 2 Background

### Registration status

- 2.1 The TGA approved the registration of nal-IRI on 5 March 2024 for the indication: “in combination with oxaliplatin and 5-fluorouracil (5-FU) and leucovorin (LV) for the first-line treatment of metastatic pancreatic adenocarcinoma.”
- 2.2 Nal-IRI is also TGA-registered for the indication: “in combination with 5-FU and LV for the treatment of metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.”

### Previous PBAC consideration

- 2.3 The PBAC has not previously considered nal-IRI for the proposed indication.
- 2.4 Nal-IRI has previously been considered by the PBAC on two occasions:
- November 2016: Submission requested use in combination with 5-FU and folinic acid for the treatment of mPAC in adult patients with disease progression who have previously received gemcitabine-based therapy. The PBAC did not recommend listing on the basis of unacceptably high incremental cost for a modest and uncertain incremental clinical benefit (para 7.1, irinotecan (nanoliposomal), Public Summary Document (PSD), November 2016 PBAC meeting).
  - March 2018: Resubmission requested use in combination with 5-FU and folinic acid for the treatment of patients with mPAC who have previously failed gemcitabine-based therapy. The PBAC did not recommend listing on the basis of unacceptably high incremental cost for a modest and uncertain incremental clinical benefit (para 6.1, irinotecan (nanoliposomal), PSD, March 2018 PBAC meeting).

### 3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
<del>IRINOTECAN LIPOSOME</del> <del>NANOLIPOSOMAL IRINOTECAN</del> Injection <del>Irinotecan nanoliposomal 43mg/10mL injection, 10mL vial</del>	Published price: Public: \$3,988.62 Private: \$4,086.51  Effective price: <sup>a</sup> Public: \$ Private: \$	110mg	9
<b>Available brands</b>			
ONIVYDE®, Servier Laboratories (Aust.) Pty. Ltd Irinotecan nanoliposomal 43mg/10mL injection, 10mL vial			

Source: Table 14, p37 of the submission

<sup>a</sup> The proposed effective price was based on the published price of NabP, which is subject to a special pricing arrangement.

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private Hospitals
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> Authority Required (STREAMLINED)
<b>Severity:</b> Stage IV (metastatic)
<b>Condition:</b> <i>Adenocarcinoma of the pancreas</i> <del>Pancreatic cancer</del>
<b>Indication:</b> Stage IV (metastatic) adenocarcinoma of the pancreas
<b>Treatment Phase:</b> N/A
<b>Clinical criteria:</b>
The treatment must be in combination with oxaliplatin, 5-fluorouracil and folinic acid (leucovorin)
<b>AND</b>

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The condition must not have been treated previously with PBS-subsidised therapy
<b>AND</b>
<del>Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status score of two or less</del> Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less
<b>Prescribing Instructions:</b> A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug
<i>Caution: nanoliposomal irinotecan is not equivalent to non-liposomal irinotecan formulations and should not be interchanged.</i>
<b>Administrative Advice:</b> Not for use as neoadjuvant or adjuvant therapy
<b>Administrative Advice:</b> Special Pricing Arrangements apply

Source: Table 15, p38 of the submission.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PBS, Pharmaceutical Benefits Scheme.

- 3.2 The proposed PBS restriction for nal-IRI was modelled on the PBS restriction for NabP, which states that ‘the condition must not have been treated previously with PBS-subsidised therapy.’ If recommended, this would mean that patients would be unable to receive the alternative treatment (either nal-IRI or NabP) as second-line therapy in the case of disease progression or in the event of toxicity. The submission proposed that given there are few treatment options for mPAC, the PBAC may wish to consider allowing sequential use by removing the criterion that limits use of these treatments (nal-IRI and NabP) to the first line setting. Previously, the PBAC did not recommend nal-IRI for the treatment of patients with mPAC who have failed gemcitabine-based therapy (see paragraph 2.4).
- 3.3 The submission proposed that a patient must have an Eastern Cooperative Oncology Group (ECOG) performance score (PS) score of  $\leq 2$  to be eligible for nal-IRI, which aligned with the PBS restriction for NabP. This was not aligned with the trial evidence, in that almost all participants in the NAPOLI-3 trial had an ECOG performance status of 0 or 1. Only one patient with ECOG 2 was included in the NALIRIFOX arm and none in the Gem+NabP arm. The ESC considered it would be appropriate to limit the PBS population to ECOG PS of 0 or 1, consistent with the NAPOLI-3 trial. The ESC noted that the NCCN Guidelines do not routinely recommend treatment with NALIRIFOX for patients with an ECOG performance score of 2 (see paragraph 5.5). The Pre-PBAC response stated that clinical trials supporting the use of Gem+NabP, FOLFIRINOX and NALIRIFOX in 1L mPAC were conducted in patients with performance status of 0 or 1 (or Karnofsky performance score equivalent), and maintained that allowing nal-IRI to be used in patients with ECOG PS 2 would make it consistent with Gem+NabP and allow more treatment options for clinicians. The PBAC considered that the proposed listing should be limited to patients with ECOG PS 0 or 1 (see paragraph 7.4).
- 3.4 The proposed maximum amount for nal-IRI is 110 mg, based on the recommended dose of 50 mg/m<sup>2</sup> and a maximum body surface area of 2.2 m<sup>2</sup>.
- 3.5 The proposed number of repeats (nine) would provide patients with a total of five cycles of treatment, which is consistent with the median number of cycles of nal-IRI (five) in the NAPOLI-3 trial.

- 3.6 The proposed effective ex-manufacturer price for nal-IRI was \$ [REDACTED] per 43 mg vial, with corresponding effective DPMA of \$ [REDACTED] and \$ [REDACTED] for public and private hospitals, respectively (corresponding to a maximum amount of 110 mg). The current DPMA for non-liposomal irinotecan on the PBS is \$158.62 to \$202.91 (corresponding to a maximum amount of 800 mg).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Pancreatic adenocarcinoma (PAC) is a cancer of the exocrine pancreas. It is the most common form, accounting for 85-95% of pancreatic cancers. Pancreatic cancer is a disease with high morbidity and mortality, and is the eighth most commonly diagnosed cancer in Australia. Increasing age is the major determinant of risk for PAC.
- 4.2 Pancreatic cancer is difficult to detect in its early stages, and patients may remain asymptomatic until the advanced stages of disease. Approximately 20% of patients diagnosed with PAC present with disease that is limited to the pancreas and potentially resectable (Stage I-II), while approximately 50% present with metastatic disease (Stage IV). The remaining 30% present with disease that interfaces with major vascular structures, making it either borderline resectable or locally advanced/unresectable (stage III). Due to the typically late diagnosis, pancreatic cancer is overrepresented in mortality and is estimated to be the fourth leading cause of cancer related death in Australia. The three-year survival for patients with metastatic pancreatic cancer at diagnosis is 4%, and overall PAC three-year survival is 11%.
- 4.3 Surgery and chemotherapy (sometimes combined with radiotherapy) are the mainstays of treatment for PAC. The treatment approach is dependent on the stage of the cancer and the treatment goals of the patient and their family. Surgical resection remains the only possibility of cure. However, most patients (80% or more) are not suitable for surgery at the time of diagnosis. The treatment of mPAC is with chemotherapy or best supportive care. Chemotherapy in this context is not intended to be curative, but aims to control cancer growth, relieve symptoms, maintain or improve quality of life, and prolong survival.
- 4.4 There are multiple chemotherapy regimens that are used in clinical practice for the first-line treatment of mPAC. Australian registry data suggest that the most frequently used regimens for first line mPAC are Gem+NabP (66.5% of patients), FOLFIRINOX (10.9%) and gemcitabine monotherapy (10.3%).
- 4.5 Nal-IRI injection is a liposomal formulation that encapsulates irinotecan, a topoisomerase I inhibitor, inside a lipid bilayer vesicle. The encapsulation allows irinotecan to remain in circulation for longer than unencapsulated (free) irinotecan before conversion to its active metabolite, SN-38. The nanoliposomal formulation of

irinotecan demonstrates higher intra-tumoural concentrations,<sup>1,2</sup> thus in theory minimising systemic toxicity as compared with standard formulation irinotecan. The TGA Delegate's Overview stated there was no direct clinical evidence demonstrating that liposomal encapsulation changes the clinical efficacy or safety of irinotecan for the general population of patients with pancreatic cancer.

- 4.6 Nal-IRI (as part of NALIRIFOX regimen) is proposed as a first-line chemotherapy for the treatment of mPAC. The submission stated that NALIRIFOX has a safety profile which, while different, is sufficiently similar to Gem+NabP to allow for its use in a first-line setting in most patients, whereas FOLFIRINOX has, historically, been reserved for fitter and younger patients due to its unfavourable safety profile. The ESC did not agree with the submission's description of the place in therapy for NALIRIFOX. The ESC considered that the patient populations for Gem+NabP and NALIRIFOX would differ in clinical practice in that the NALIRIFOX patients would be relatively younger/fitter compared with Gem+NabP patients. As discussed in paragraph 3.3, the ESC considered it would be appropriate to limit the PBS population to ECOG performance status of 0 or 1 for NALIRIFOX, whereas Gem+NabP could be used in a broader group of patients, i.e. with ECOG PS of 2 or less. The PBAC considered that clinicians would be unlikely to offer NALIRIFOX to patients with ECOG status of 2, due to its toxicity profile, however the proposed restriction should be limited to patients with ECOG PS 0 or 1 (see paragraph 3.3).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 5 Comparator

- 5.1 The submission nominated Gem+NabP as the main comparator. The submission stated that Gem+NabP was the most widely used first-line therapy for the treatment of patients with mPAC (based on Australasian registry data) and would most be the regimen most replaced by NALIRIFOX. The ESC considered that a high proportion of the Gem+NabP population would not be suitable for treatment with NALIRIFOX due to its toxicity profile.
- 5.2 FOLFIRINOX and NALIRIFOX are both fluoropyrimidine-based regimens and likely to be used for treatment of similar types of patients (younger, better ECOG performance status, less comorbid). While NALIRIFOX contains the same set of active components as FOLFIRINOX, they are at different doses, and in a different dose presentation in the case of the irinotecan component. Specifically: in addition to the replacement of non-liposomal irinotecan at 180 mg/m<sup>2</sup> in the FOLFIRINOX regimen by nal-IRI at 50 mg/m<sup>2</sup>, the NALIRIFOX regimen also omits the 5-FU bolus and (unlike most other modified FOLFIRINOX regimens) uses a substantially reduced dose of oxaliplatin (60 mg/m<sup>2</sup>

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<sup>1</sup> Barbier et al., (2020), 'Differentiation of liposomal irinotecan from dose-dense non-liposomal irinotecan in patient-derived pancreatic cancer xenograft tumor models', J Clin Oncol, 38:e16724

<sup>2</sup> Kalra et al., (2014), 'Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor pro-drug conversion', Cancer Res, 74(23):7003-13

versus 85 mg/m<sup>2</sup>). The PBAC noted that the reduced dose of oxaliplatin may reduce efficacy of the combination regimen.

- 5.3 The submission acknowledged that FOLFIRINOX is an alternative treatment option recommended in international guidelines as first-line treatment of mPAC. However, it stated that the use of Gem+NabP is more than six times greater than the use of FOLFIRINOX in Australia, and as such, the therapy prescribers would most replace in clinical practice is Gem+NabP. The submission presented FOLFIRINOX as a minor comparator in an appendix to the submission. The Pre-Sub-Committee Response (PSCR) stated there are important differences in the dose intensity of the individual drugs in FOLFIRINOX compared with NALIRIFOX, and that the potential for haematological toxicity with FOLFIRINOX is the key reason it is usually reserved for use in younger patients (compared with Gem+NabP). The PSCR considered that the NAPOLI-3 trial results supported the use of NALIRIFOX in a broader patient population than the population currently treated with FOLFIRINOX, which is usually used in younger patients. The ESC considered that NALIRIFOX may be used in a proportion of patients currently treated with Gem+NabP but that FOLFIRINOX should be regarded as an additional main comparator.
- 5.4 The ESC considered that a mixed comparator approach including both Gem+NabP and FOLFIRINOX would be appropriate. The PBAC noted that Gem+NabP is currently the most frequently used treatment in the first-line setting, however considered that the main comparator for NALIRIFOX should be FOLFIRINOX, and not Gem+NabP as proposed by the submission (see paragraph 7.1).
- 5.5 The NCCN Guidelines state that “While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound paclitaxel, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX and adds considerably more expense compared to FOLFIRINOX.” (Pancreatic Adenocarcinoma, *Version 1.2024 PANC-F*, 5 of 12).

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The input described pancreatic cancer as a devastating diagnosis for patients and their families, with poor survival and limited treatment options. The input from organisations, including Pankind (the Australian Pancreatic Cancer Foundation), Pancare and Rare Cancers Australia, described the experiences of Australian patients

and emphasised an urgent need for new effective therapies. A number of comments supported the proposed PBS listing, as it would provide an alternative treatment option. It was noted that access to the therapy would be limited without PBS listing, due to cost. One health professional noted that the use of nal-IRI as part of the NALIRIFOX regimen does not appear to have any effectiveness advantage over FOLFIRINOX, while having a comparable toxicity profile and additional cost. One individual who received treatment with nal-IRI noted that the side effects associated with nal-IRI resulted in a decision to cease treatment.

### **Clinical trials**

6.3 The submission presented a direct comparison of NALIRIFOX and Gem+NabP based on one randomised controlled trial (RCT):

- NAPOLI-3 (N=770): An ongoing<sup>3</sup> Phase III, open-label, multinational, head-to-head RCT, comparing NALIRIFOX with Gem+NabP in patients with mPAC who had not previously received chemotherapy for their disease in the metastatic treatment setting. Blinding was not feasible due to the difference in treatment regimens (four components in the NALIRIFOX arm versus two in the Gem+NabP arm, and dosing on different days). The results of the data cut in July 2022 were presented. The median follow-up was 16 months for NALIRIFOX and 16.3 months for Gem+NabP.

6.4 The submission also presented a 'side by side' comparison of NALIRIFOX and FOLFIRINOX using three RCTs. The submission stated that due to poor exchangeability of the trials, neither a naïve comparison of single arms, nor a multistep indirect treatment comparison (ITC), was considered appropriate.

- NAPOLI-3 (N=770): Compared NALIRIFOX with Gem+NabP as described above.
- ACCORD11/PRODIGE4 (N=342): A French multicentre (48 sites), open label, phase II/III RCT that directly compared FOLFIRINOX and gemcitabine in patients with mPAC who had not previously been treated with chemotherapy. The data cut off for final analysis was in April 2010.
- MPACT (N=861): A multinational, open label, phase III RCT that directly compared Gem+NabP and gemcitabine in patients with mPAC who had not previously received chemotherapy for metastatic disease. The data cut off for final analysis was in September 2012. This study was previously considered by the PBAC for NabP at the March 2014 meeting.

6.5 Details of the trials presented in the submission are provided in Table 2.

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<sup>3</sup> The estimated study completion date reported by ClinicalTrials.gov is 31 December 2024 (<https://classic.clinicaltrials.gov/ct2/show/NCT04083235>; date accessed 11 March 2024)

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**Table 2: Trials and associated reports presented in the submission**

Trial ID	Report	Publication citation
<b>Indirect randomised trials</b>		
NAPOLI-3 NCT04083235	An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.	CSR March 2023
	Wainberg 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 Oct 7; 402(10409):1272-1281.
MPACT NCT00844649	Von Hoff et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.	N Engl J Med. 2013 Oct 31;369(18):1691-703.
ACCORD11/PRODIGE4 NCT00112658	Conroy et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.	Engl J Med. 2011 May 12;364(19):1817-25.
JCOG1611- GENERATE RCTs031190009	Obha et al. Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE): a multicenter, randomized, open-label, three-arm, phase 2/3 trial.	ESMO Congress 2023. Abstract 16160

Source: Table 20, p48-49 of the submission and p4 of Appendix A of submission.

Abbreviations: FOLFIRINOX, 5-fluorouracil, Leucovorin/folinic acid, standard irinotecan, and oxaliplatin; Gem, gemcitabine; mPDAC, metastatic pancreatic ductal adenocarcinoma; NabP, nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin.

Note: Only full publications are presented for NAPOLI-3, ACCORD11/PRODIGE4 and MPACT trials.

6.6 The submission described another RCT, JCOG1611-GENERATE (herein referred to as GENERATE), which was presented at the ESMO Congress on 20-24 October 2023. GENERATE (N=476) was a Japanese multicentre (45 sites), open label, Phase II/III three-armed (1:1:1) RCT that compared a modified regimen of FOLFIRINOX (mFOLFIRINOX; n=175)<sup>4</sup> and a regimen containing S-1 (a prodrug of fluorouracil), irinotecan and oxaliplatin (S-IROX; n=176) to Gem+NabP (n=176), as first-line chemotherapy for patients with pathologically confirmed metastatic or recurrent pancreatic cancer. Given this study was presented as an abstract, and a full peer review publication was not available, the submission did not include this trial in the indirect comparison. The interim results (March 2023) indicated a higher median overall survival (OS) for Gem+NabP (17.1 months; 95%CI: 14.5, 18.9) compared to mFOLFIRINOX (14 months; 95%CI: 11.4, 16.3). The updated OS results (May 2023) provided with the pre-PBAC response were similar to the interim results: Gem+NabP (17.0 months; 95%CI: 14.5, 18.9) compared to mFOLFIRINOX (14.0 months; 95%CI:

<sup>4</sup> The mFOLFIRINOX regimen used in the GENERATE trial differs from the FOLFIRINOX and mFOLFIRINOX regimens used in the ACCORD11/PRODIGE4 trial and in Australian clinical practice, respectively. The main differences relate to the dose of irinotecan (150 mg/m<sup>2</sup> in GENERATE, 180 mg/m<sup>2</sup> in ACCORD11 and Australian practice, respectively), the dose of leucovorin/folinic acid (200 mg/m<sup>2</sup> in GENERATE, 400 mg/m<sup>2</sup> in ACCORD11 and 50 mg in Australian practice) and the lack of a bolus dose of 5-FU in GENERATE compared with ACCORD11 and Australian practice (2400 mg/m<sup>2</sup>).

11.4, 16.3). The PFS results were: Gem+NabP (6.7 months; 95%CI: 5.7, 7.4) compared to mFOLFIRINOX (5.8 months; 95%CI: 5.1, 6.9)<sup>5</sup>.

- 6.7 The submission noted that a full peer reviewed publication would be required in order to make a full assessment, including consideration of details such as baseline characteristics, analysis methods and patient disposition. The ESC noted that a set of slides was provided with the PSCR (which had been presented at the ESMO Congress on 22 October 2023), however the information had not been peer reviewed, and concerns remained regarding insufficient information about baseline characteristics, analysis methods and patient disposition. The ESC noted that the trial was terminated early and hence there was a risk of bias due to incomplete outcome data. The pre-PBAC response disagreed with the ESC's concerns regarding the GENERATE trial, and maintained that it was appropriate to use GENERATE trial data within an indirect comparison of NALIRIFOX and FOLFIRINOX. The pre-PBAC response noted that evidence from unpublished randomised trials is relevant for PBAC consideration, and inclusion of the GENERATE results would allow a simpler indirect comparison, with fewer steps, which is typically preferred by the PBAC. The PBAC noted that these factors did not override the concerns raised by the ESC in regard to the GENERATE trial specifically as described above, and discussed further in paragraph 7.12.
- 6.8 The key features of the trials are summarised in Table 3.

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<sup>5</sup> Obha et al (2023), ESMO presentation slides: Nab paclitaxel plus gemcitabine versus modified FOLFIRINOX or S IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE). Madrid, Spain, 22 October 2023. Provided by the sponsor with the PSCR.

**Table 3: Key features of the included evidence**

Trial	N	Design/ Median duration of follow up	Risk of bias <sup>a</sup>	Patient population	Outcomes	Use in modelled evaluation
<b>NALIRIFOX vs Gem+NabP</b>						
NAPOLI-3	770	R, OL, MC, MN, Phase III NALIRIFOX: 16 months Gem+NabP: 16.3 months	Some concerns	mPAC not previously treated with chemotherapy for metastatic disease	OS, PFS, ORR, HRQoL, Safety	OS, PFS, HRQoL
<b>FOLFIRINOX vs Gemcitabine</b>						
ACCORD11/ PRODIGE4	342	R, OL, MC (France), Phase II/ III 26.6 months	Some concerns	mPAC not previously treated with chemotherapy for metastatic disease	OS, PFS, ORR, Safety	OS, PFS
<b>Gem+NabP vs Gemcitabine</b>						
MPACT	861	R, OL, MC, MN, Phase III Gem+NabP: 9.1 months Gem: 7.4 months	Some concerns	mPAC not previously treated with chemotherapy for metastatic disease	OS, PFS, ORR, Safety	NA
<b>Gem+NabP vs FOLFIRINOX (vs S-IROX)</b>						
GENERATE	527	R, OL, MC (Japan), Phase II/III Gem+NabP: NR FOLFIRINOX: NR	Unknown	Metastatic or recurrent PAC not previously treated	OS, PFS, ORR, Safety	NA

Source: Compiled during the evaluation from Section 2 of the submission and Appendix A. Risk of bias amended during the evaluation. Abbreviations: HRQoL, health-related quality of life; MC, multi-centre; MN, multi-national; mPAC, metastatic pancreatic adenocarcinoma; NA, not applicable; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NR, not reported; OL, open label; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomised; S-IROX, S-1, irinotecan, and oxaliplatin.

<sup>a</sup> The submission stated that the overall risk of bias was low for all three trials. The evaluation considers the overall risk of bias as 'with some concerns'.

6.9 Across the three main trials (NAPOLI-3, ACCORD11/PRODIGE4 and MPACT), the overall risk of bias was rated as 'some concerns' because:

- The submission noted the open label nature of the studies, but considered it unlikely that the primary and secondary efficacy outcomes would be affected by knowledge of treatment allocation (because determination of death and progression includes well defined and objective criteria). However, the use of investigator rather than independent assessment could lead to a potential for detection bias. The lack of blinding of participants and investigators may have introduced a risk of bias, particularly for the patient-reported outcomes (PROs) in the NAPOLI-3 trial, and safety outcomes in all trials. The submission noted that the knowledge of the treatment allocation by investigators may have influenced the classification of adverse events in terms of their relatedness to the study intervention received.
- In the NAPOLI-3 trial, 134 participants (35%) in the NALIRIFOX arm and 128 participants (33.1%) in the Gem+NabP arm were censored from the progression free survival (PFS) analysis (Table 14 of the NAPOLI-3 CSR). The main reason for censoring was use of subsequent anticancer treatment without disease

progression (14.6% for NALIRIFOX and 22.5% for Gem+NabP). Patients in both arms were also censored for the following reasons: Censored on Day 1 (7.6% vs 4.9%); over 2 consecutive missing tumour assessments (1.3% vs 0.5%); withdrawal of study consent and lost to follow up (0% vs 2.1%); and censored on last tumour assessments (11.5% vs 3.1%). The submission did not provide characteristics of those who were censored, which raises some concerns about the risk of attrition bias. The censoring rule for subsequent anticancer treatment was not applied in the OS analysis (see paragraph 6.25).

- Similarly, there was a high proportion of patients censored from the OS analysis (23% for Gem+NabP and 17% for gemcitabine) and from the PFS analysis (36% in Gem+NabP and 38% in gemcitabine) in the MPACT trial (Von Hoff et al. 2013), and a high proportion of discontinuations (76.6% for FOLFIRINOX and 93% for gemcitabine) in the ACCORD11/PRODIGE4 trial (Conroy et al. 2011). The characteristics of the patients who were censored/discontinued were not provided in the publications, and this raises some concerns about the risk of attrition bias in these trials also.
- 6.10 Due to the lack of a peer-reviewed publication, it was not possible to determine the risk of bias in the GENERATE trial (see paragraph 6.7).
- 6.11 The ESC noted the recent publication of a systematic review/meta-analysis comparing NALIRIFOX, FOLFIRINOX and Gem+NabP as first-line chemotherapy for mPAC (Nichetti et al. 2024).<sup>6</sup> This meta-analysis included data from relevant arms of the NAPOLI-3, ACCORD11/PRODIGE4 and MPACT trials, as well as the following trials that were not included in the submission: HALO (Gem+NabP), RESOLVE (Gem+NabP), AVENGER500 (FOLFIRINOX) and CanStem111P (Gem+NabP). The meta-analysis of OS and PFS was based on pooled individual patient data extracted from Kaplan-Meier (KM) plots of original trials via a graphic reconstructive algorithm, while the meta-analysis of objective response rate (ORR) and Grade  $\geq 3$  adverse events was based on pooled data from each treatment arm/trial.

### **NALIRIFOX versus Gem+NabP (NAPOLI-3)**

- 6.12 A claim of superior effectiveness and non-inferior safety of NALIRIFOX to Gem+NabP was made on the outcomes of OS, PFS, ORR and adverse events (AEs).
- 6.13 The duration of treatment and number of cycles varied between treatment arms in the NAPOLI-3 trial. There was a higher median treatment duration in the NALIRIFOX arm compared to the Gem+NabP arm (24.29 weeks vs 17.57 weeks, respectively). Patients in the NALIRIFOX arm on average received approximately one more cycle of treatment compared to patients in the Gem+NabP arm (mean number of cycles 6.5 vs 5.1, respectively). While discontinuation due to disease progression was similar across

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<sup>6</sup> Nichetti F et al. (2024) 'NALIRIFOX, FOLFIRINOX, and Gemcitabine With Nab-Paclitaxel as First-Line Chemotherapy for Metastatic Pancreatic Cancer: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7(1):e2350756. doi: [10.1001/jamanetworkopen.2023.50756](https://doi.org/10.1001/jamanetworkopen.2023.50756)

both arms (48% in NALIRIFOX and 45.7% in Gem+NabP), discontinuation due to adverse events was higher in the Gem+NabP arm (23.8%) compared to the NALIRIFOX arm (14.1%). In the NALIRIFOX arm, patients who were unable to tolerate oxaliplatin (and discontinued this medication) could still continue to receive the rest of the NALIRIFOX components at the discretion of the investigator and continue in the study. This may contribute to the lower discontinuation rate due to adverse events observed in the NALIRIFOX arm compared with the Gem+NabP arm.

- 6.14 Subsequent anticancer therapies were permitted in the NAPOLI-3 trial. Over half of participants in both arms (50.5% in NALIRIFOX and 54.4% in Gem+NabP) received subsequent anticancer therapy. Subsequent fluoropyrimidine-based therapy (5-FU with or without irinotecan) was more frequent in the Gem+NabP arm, and gemcitabine-based therapy and Nab-P were more frequent in the NALIRIFOX arm. Around 20% of patients in the Gem+NabP arm and 4% of patients in the NALIRIFOX arm of the trial received nal-IRI or nal-IRI + 5-FU as a second line therapy, which would not be permitted under the proposed PBS restriction.
- 6.15 There were key differences in patient and disease characteristics identified between the NAPOLI-3 trial and the Australian setting (based on data from the PURPLE registry):
- The median age of those receiving 5FU-based regimens appears to be lower in the Australian setting (59 years among those receiving FOLFIRINOX) compared to the trial setting (65 years).
  - There is a higher proportion of patients with liver metastasis and with two or more metastatic sites in the trial setting compared to the Australian setting.
  - There is a lower proportion of patients with head of pancreas as primary tumour location in the trial setting compared to the Australian setting.
  - There is a higher proportion of patients with ECOG PS 2 in the Australian setting compared to the trial setting. The proposed PBS restriction includes ECOG PS 2 or less (although this was not supported by the PBAC, see paragraph 3.3). ECOG PS  $\geq 2$  is associated with a higher mortality risk in advanced cancer (HR 4.06; 95% CI 2.36, 6.98).<sup>7</sup>
- 6.16 A higher proportion of subsequent anticancer therapies was observed in the NAPOLI-3 trial and these therapies appear to differ between the Australian and trial settings:
- In the PURPLE registry, the most frequently received second line regimens following treatment with FOLFIRINOX were Gem+NabP (25%) and gemcitabine monotherapy (7%). Of those who received Gem+NabP as first-line therapy, 5-FU+LV+IRI (FOLFIRI) and 5-FU+LV+OX (FOLFOX) were the most widely used second line regimens (13% and 9%, respectively). Only 3% of patients received FOLFIRINOX as second line treatment following Gem+NabP. Patients in the

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<sup>7</sup> Owusuaa et al., (2022). 'Predictors of Mortality in Patients with Advanced Cancer-A Systematic Review and Meta-Analysis'. *Cancers (Basel)*, 14(2), 328, DOI: [10.3390/cancers14020328](https://doi.org/10.3390/cancers14020328).

Australian setting used Gem+NabP as a second line treatment even though the current PBS restriction for NabP restricts use to first-line treatment only.

- In the NAPOLI-3 trial, the most frequently used second line therapies following NALIRIFOX were gemcitabine monotherapy (24.3%), NabP monotherapy (17.6%) and Gem+NabP (15.4%). Among those patients who received Gem+NabP as first line therapy, gemcitabine monotherapy, FOLFIRINOX and FOLFOX were the most frequently used subsequent therapies (15.6%, 11.1% and 9.2%, respectively).
- 6.17 It is unclear how the differences in subsequent anticancer therapy between the trial and Australian settings may impact the applicability of treatment effects. The effect of subsequent anticancer therapies was captured in the OS results (paragraph 6.25).
- 6.18 The submission indicated that no statistical tests were reported on the safety endpoints for NAPOLI-3 trial, and that statistical comparisons, based on the odds ratios (OR), risk ratios (RR) and risk differences (RD) for selected AEs, were performed post hoc.

#### **NALIRIFOX versus FOLFIRINOX (NAPOLI-3, ACCORD11/PRODIGE4, MPACT trials)**

- 6.19 The submission claimed that NALIRIFOX is superior in effectiveness and safety over FOLFIRINOX because NALIRIFOX has a proven survival benefit over Gem+NabP, whereas FOLFIRINOX does not. The submission also stated that NALIRIFOX has proven to have similar levels of toxicity to Gem+NabP, whereas FOLFIRINOX has historically been reserved for fitter and younger patients due to its unfavourable safety profile. The therapeutic claim between NALIRIFOX and FOLFIRINOX made by the submission was based on inferences drawn from the results of the individual clinical trials (NAPOLI-3, ACCORD11/PRODIGE4, MPACT) relative to Gem+NabP. This is inappropriate as more robust methodologies should be applied to support the claims.
- 6.20 The following differences in the inclusion criteria, baseline characteristics, study design, setting and duration of follow-up between these trials were identified, which raises concerns regarding the validity of the indirect comparison performed.
- Patients in the ACCORD11/PRODIGE4 trial tended to be younger (around 71% under 65 years) than those in the other two trials (around 50% in NAPOLI-3 trial and 58% in MPACT were under 65 years).
  - Patients in the MPACT trial had a better performance status (equivalent to ECOG PS 0 and KPS 90-100) than patients in the other two trials (60% vs 42% vs 38% in the MPACT, NAPOLI-3 and ACCORD11/PRODIGE4 trials, respectively).
  - The trials differed in terms of metastatic disease burden. The proportion of patients who had  $\geq 2$  metastatic sites at baseline was higher in the MPACT trial (around 93%) compared to the NAPOLI-3 (around 67%) and ACCORD11/PRODIGE4 (50%) trials.

- The proportion of patients with liver metastases was slightly higher in ACCORD11/PRODIGE4 (88%) compared with the NAPOLI-3 and MPACT trials (80% and 84%, respectively).
  - The median duration of follow up was longer in the ACCORD11/PRODIGE4 trial (26.6 months) compared to the NAPOLI-3 (16-16.3 months) and MPACT trials (7.4-9.1 months).
- 6.21 The submission noted that age >65 years, high performance status and the presence of liver metastases have been shown to be independent prognostic factors of poor outcomes in mPAC (Uson Junior 2020; Decoster 2016; Conroy 2011; Yu 2021; Tereao 2021; Oweira 2017; Zhang 2023); however, the direction and magnitude of impact of the identified factors on observed outcomes is uncertain.
- 6.22 Overall, the definitions of the outcomes included in the three trials were broadly aligned. However, the NAPOLI-3 trial used a different version (1.1) of the Response Evaluation Criteria in Solid Tumours (RECIST) to measure disease, compared to the MPACT and ACCORD11/PRODIGE4 trials (version 1.0). A study comparing the use of RECIST 1.1 and RECIST 1.0 in patients treated with targeted agents for metastatic cancer showed a decrease in the number of target lesions when RECIST 1.1 was used.<sup>8</sup>

### ***Comparative effectiveness***

#### **NALIRIFOX versus Gem+NabP**

- 6.23 A summary of the efficacy results for OS, PFS and ORR from the ITT population in NAPOLI-3 trial is presented in Table 4, with the corresponding KM curves of OS and PFS presented in Figure 1 and Figure 2.

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<sup>8</sup> Kim JH, (2016), 'Comparison of the RECIST 1.0 and RECIST 1.1 in patients treated with targeted agents: a pooled analysis and review', *Oncotarget*, 7(12):13680-7, Doi: [10.18632/oncotarget.7322](https://doi.org/10.18632/oncotarget.7322).

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Table 4: Results of OS, PFS and ORR in the ITT population in NAPOLI-3 trial.

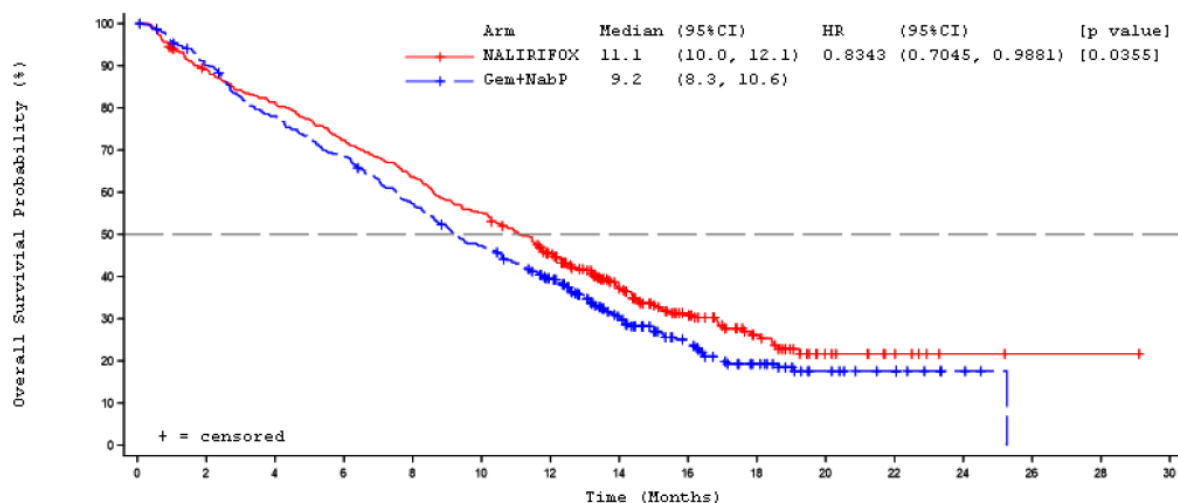
	NALIRIFOX N=383	Gem+NabP N=387
Median (95% CI) follow-up, months	16.0 (15.0, 16.8)	16.3 (15.0, 17.5)
<b>OS</b>		
Death, n (%)	259 (67.6)	285 (73.6)
Censored, n (%)	124 (32.4)	102 (26.4)
Event free probability, n, % (95% CI)		
3 months	319, 84.2 (80.2, 87.5)	315, 82.5 (78.3, 86.0)
6 months	274, 72.4 (67.6, 76.6)	261, 68.4 (63.5, 72.8)
9 months	220, 58.1 (53.0, 62.9)	196, 51.8 (46.7, 56.7)
12 months	162, 45.6 (40.5, 50.5)	140, 39.5 (34.6, 44.4)
18 months	32, 26.2 (20.9, 31.7)	28, 19.3 (14.8, 24.2)
Median (95% CI), months	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI; p-value)	<b>0.83 (0.70, 0.99; p=0.04)</b>	
Unstratified HR (95% CI; p-value)	<b>0.84 (0.71, 0.99; p=0.04)</b>	
<b>PFS</b>		
Patients with PFS Event, n (%)	249 (65.0)	259 (66.9)
PD	183 (47.8)	176 (45.5)
Death	66 (17.2)	83 (21.4)
Censored, n (%)	134 (35.0)	128 (33.1)
Event free probability, n, % (95% CI)		
3 months	248, 76.9 (72.1, 81.1)	240, 71.5 (66.5, 75.9)
6 months	164, 56.4 (50.7, 61.6)	112, 43.2 (37.6, 48.6)
9 months	113, 40.9 (35.3, 46.4)	55, 24.9 (19.8, 30.2)
12 months	61, 27.4 (22.3, 32.7)	19, 13.9 (9.7, 18.9)
18 months	9, 11.4 (7.1, 16.9)	1, 3.6 (0.5, 12.3)
Median (95% CI), months	7.4 (6.0, 7.7)	5.6 (5.3, 5.8)
Stratified HR (95% CI; p-value)	<b>0.69 (0.58, 0.83; p&lt;0.0001)</b>	
Unstratified HR (95% CI; p-value)	<b>0.69 (0.58, 0.83; p&lt;0.0001)</b>	
<b>ORR</b>		
BOR, n (%)		
CR	1 (0.3)	1 (0.3)
PR	159 (41.5)	139 (35.9)
SD	99 (25.8)	101 (26.1)
PD	38 (9.9)	56 (14.5)
NE	86 (22.5)	90 (23.3)
ORR (CR or PR), n (%)	160 (41.8)	140 (36.2)
95% CI	(36.8, 46.9)	(31.4, 41.2)
OR (95% CI; p-value)	1.26 (0.95, 1.69; p = 0.11)	

Source: Table 30, Table 31 and Table 32, p66-69 of submission.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention to treat; NabP, nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NE, not evaluable; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, Progression free survival; PR, partial response; SD, stable disease.

Note: Results in **bold** indicate statistically significant difference (p < 0.05).

Figure 1: Kaplan-Meier Curves of Overall Survival (ITT) in NAPOLI-3 trial.



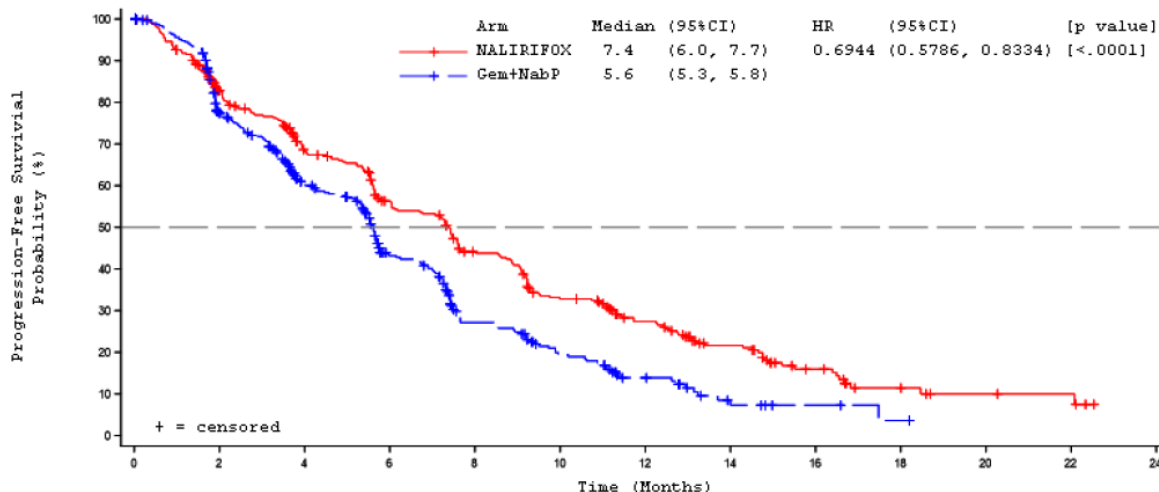
No. at Risk:

NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
Gem+NabP	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0

Source: Figure 11, p67 of submission.

Abbreviations: CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; ITT, intention to treat; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival (ITT) in NAPOLI-3 trial.



No. at Risk:

NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
Gem+NabP	387	267	182	112	60	38	19	6	3	1	0	0	0

Source: Figure 12, p68 of submission.

Abbreviations: CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; ITT, intention to treat; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin.

6.24 NALIRIFOX showed a statistically significant improvement in OS compared with Gem+NabP (HR 0.83; 95% CI: 0.70, 0.99; p-value = 0.04). The median OS was 11.1 months (95% CI: 10.0, 12.1) for the NALIRIFOX arm and 9.2 months (95% CI: 8.3, 10.6) for the Gem+NabP arm, with a magnitude of 1.9 months improvement in median OS. Although the trial results indicate a statistically significantly improved survival with

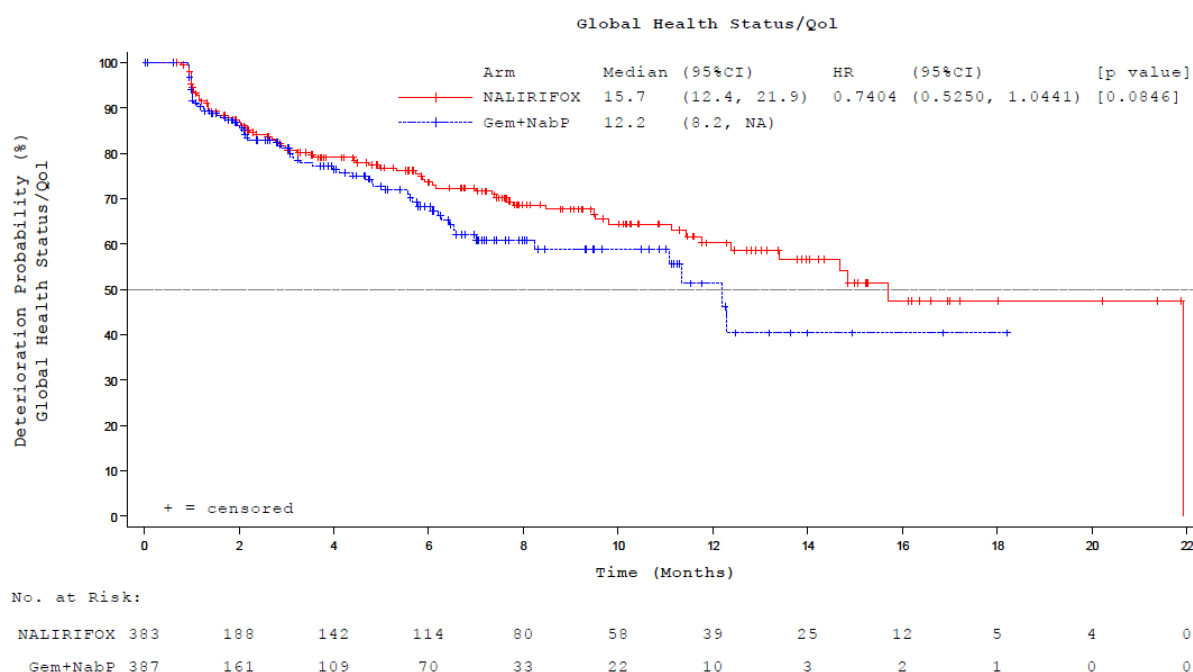
NALIRIFOX compared to Gem+NabP, the 95% CI had an upper limit that was very close to 1.

- 6.25 Patients who started subsequent anticancer therapies without disease progression or death were censored for PFS outcomes; however, these censoring rules were not applied to OS. Thus, the OS outcome would likely also capture the treatment effect of subsequent anticancer therapies that over half of the patients in the NAPOLI-3 trial received. Sensitivity analysis for OS in the ITT population, censored at the date of initiation of any subsequent anticancer therapy showed that there was a significantly longer survival for NALIRIFOX compared with Gem+NabP (median survival, 15.1 months vs. 9.2 months; HR 0.71; 95% CI: 0.56, 0.90;  $p < 0.01$ ).
- 6.26 NALIRIFOX showed a statistically significant improvement in PFS compared with Gem+NabP (HR 0.69; 95% CI: 0.58, 0.83;  $p$ -value  $< 0.0001$ ). The median PFS was 7.4 months (95% CI: 6.0, 7.7) for the NALIRIFOX arm and 5.6 months (95% CI: 5.3, 5.8) for the Gem+NabP arm, with a magnitude of 1.8 months improvement in median PFS.
- 6.27 In reviewing the KM curves for PFS (Figure 2), a high level of censoring (and/or discontinuation) prior to Month 6 of treatment is observed, with 182 patients (47%) remaining in the Gem+NabP arm and 210 patients (54.8%) remaining in the NALIRIFOX arm by Month 4. It is also observed that by Month 8, many patients in the Gem+NabP arm were censored, with only 60 patients (15.5%) continuing the study. While the proportions of censoring were similar across arms at the time of the data cut (35% in NALIRIFOX and 33.1% in Gem+NabP), a higher proportion of patients in the Gem+NabP arm compared to the NALIRIFOX arm were censored due to starting subsequent anticancer therapy without disease progression (22.5% vs 14.6%, respectively; Table 14, p77 of the NAPOLI-3 CSR). This may bias the results in favour of NALIRIFOX. Patients in the NALIRIFOX and Gem+NabP arms were also censored for the following reasons: Censored on Day 1 (7.6% vs 4.9%, respectively); over 2 consecutive missing tumour assessments (1.3% vs 0.5%, respectively); withdrawal of study consent and lost to follow up (0% vs 2.1%, respectively); and censored on last tumour assessments (11.5% vs 3.1%, respectively).
- 6.28 The submission stated that the improvements in median OS (1.9 months) and median PFS (1.8 months) were clinically meaningful for mPAC. The median OS gain accepted for Gem+NabP in the PBAC's consideration of NabP in March 2014 was similar to the OS gain presented in this submission (1.9 months). However, the PBAC considered that the most reliable estimate of the OS gain was the uncensored increment of 2.1 months, observed in more than 50% of the participants in the trial (Paclitaxel-nanoparticle albumin bound, PSD, March 2014 PBAC meeting). A consensus of clinical experts of the American Society of Clinical Oncology (ASCO) have proposed a meaningful benefit in terms of OS and PFS to patients with metastatic pancreatic cancer receiving first line systemic treatment. The ASCO group identified an HR range of 0.6 to 0.75 corresponding to an improvement in median OS within a range of 3 to 5 months as the minimal clinically important difference (MCID) in OS over standard therapy. In terms of PFS, an incremental gain ranging from 3 to 5 months was

proposed to be clinically meaningful. Neither the OS nor PFS outcome results from the NAPOLI-3 trial met these criteria. The ESC noted the modest magnitude of improvement seen in the trial, and agreed with the commentary that consideration should be given to whether it is clinically meaningful. The pre-PBAC response stated that any statistically significant improvement in mPAC survival is meaningful.

- 6.29 No statistically significant difference was observed between the treatments in terms of ORR, although the OR numerically favoured NALIRIFOX (OR 1.26; 95% CI: 0.95, 1.69; p=0.11).
- 6.30 The KM curves for the time to deterioration (TTD) based on the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC-QLQ-C30) Global Health Status/Quality of Life (QoL) in the ITT population are presented in Figure 3. The TTD results of the EORTC QLQ-C30 numerically favoured NALIRIFOX compared to Gem+NabP (HR 0.74; 95% CI: 0.53, 1.04; p=0.085), although this was not statistically significant. The median TTD was 15.7 months in the NALIRIFOX arm and 12.2 months in the Gem+NabP arm.

Figure 3: Kaplan-Meier curve for time to deterioration based on EORTC-QLQ-C30 (ITT) in NAPOLI-3 trial.



Source: Figure 15, p71 of submission.

Abbreviations: CI, confidence interval; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life core questionnaire; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; NabP, nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; QoL, quality of life.

### NALIRIFOX versus FOLFIRINOX

- 6.31 The submission presented a ‘side by side’ comparison of the key efficacy and safety outcomes of the NAPOLI-3, ACCORD11/PRODIGE4 and MPACT trials. The submission stated that due to poor exchangeability of the trials, neither a naïve comparison of single arms, nor a multistep ITC, was considered appropriate.

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- 6.32 A multistep ITC comparing the ITT population of NAPOLI-3, MPACT and ACCORD11/PRODIGE4 trials was conducted during the evaluation to compare NALIRIFOX vs FOLFIRINOX using two common reference groups: gemcitabine and Gem+NabP. Results should be interpreted with caution noting the potential transitivity issues across these trials (see paragraphs 6.20 to 6.21).
- 6.33 Table 5 presents the results of OS, PFS and ORR reported across all trials.

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Table 5: Results of OS, PFS and ORR across the trials

	ACCORD11/PRODIGE4 N=342		MPACT N=861		NAPOLI-3 N=770	
Treatment arm	FOLFIRINOX	Gem	Gem+NabP	Gem	NALIRIFOX	Gem+NabP
n	171	171	431	430	383	387
Median follow up, months (95% CI)	26.6 (20.5, 44.9)		9.1 (0.1, 36.9)	7.4 (0.0, 31.3)	16.0 (15.0, 16.8)	16.3 (15.0, 17.5)
<b>Overall Survival</b>						
Death, n (%)	273 (79.8)		333 (77.3)	359 (83.5)	259 (67.6)	285 (73.6)
Event free probability, % (95% CI)						
6 months	75.9 (NR)	57.6 (NR)	67 (62, 71)	55 (50, 60)	72.4 (67.6, 76.6)	68.4 (63.5, 72.8)
12 months	48.4 (NR)	20.6 (NR)	35 (30, 39)	22 (18, 27)	45.6 (40.5, 50.5)	39.5 (34.6, 44.4)
18 months	18.6 (NR)	6.0 (NR)	16 (12, 20)	9 (6, 12)	26.2 (20.9, 31.7)	19.3 (14.8, 24.2)
Median (95% CI), months	11.1 (9.0, 13.1)	6.8 (5.5, 7.6)	8.5 (7.9, 9.5)	6.7 (6.0, 7.2)	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI; p-value)	<b>0.57 (0.45, 0.73); p &lt; 0.001</b>		<b>0.72 (0.62, 0.83); p &lt; 0.001</b>		<b>0.83 (0.70, 0.99); p = 0.04</b>	
<b>Progression-Free Survival</b>						
PFS Event, n (%)	317 (92.7)		276 (64.0)	266 (61.8)	249 (65.0)	259 (66.9)
Event free probability, % (95% CI)						
6 months	52.8	17.2	44 (39, 50)	25 (20, 30)	56.4 (50.7, 61.6)	43.2 (37.6, 48.6)
12 months	12.1	3.5	16 (12, 21)	9 (5, 14)	27.4 (22.3, 32.7)	13.9 (9.7, 18.9)
18 months	3.3	0	NR	NR	11.4 (7.1, 16.9)	3.6 (0.5, 12.3)
Median (95% CI), months	6.4 (5.5, 7.2)	3.3 (2.2, 3.6)	5.5 (4.5, 5.9)	3.7 (3.6, 4.0)	7.4 (6.0, 7.7)	5.6 (5.3, 5.8)
Stratified HR (95% CI; p-value)	<b>0.47 (0.37, 0.59); p &lt; 0.001</b>		<b>0.69 (0.58, 0.82); p &lt; 0.0001</b>		<b>0.69 (0.58, 0.83); p &lt; 0.0001</b>	
<b>Objective Response rate</b>						
BOR, n (%)						
CR	1 (0.6)	0 (0.0)	1 (0.002)	0 (0.0)	1 (0.3)	1 (0.3)
PR	53 (31.0)	16 (9.4)	98 (22.7)	31 (7.2)	159 (41.5)	139 (35.9)
SD	66 (38.6)	71 (41.5)	118 (27.4)	122 (28.4)	99 (25.8)	101 (26.1)
PD	26 (15.2)	59 (34.5)	86 (20.0)	110 (25.6)	38 (9.9)	56 (14.5)
NE	25 (14.6)	25 (14.6)	128 (29.7)	167 (38.8)	86 (22.5)	90 (23.3)
ORR (CR or PR), n (%)	54 (31.6)	16 (9.4)	99 (23.0)	31 (7.2)	160 (41.8)	140 (36.2)
95% CI	(24.7, 39.1)	(5.4, 14.7)	(19, 27)	(5, 10)	(36.8, 46.9)	(31.4, 41.2)
RR/OR (95% CI; p-value)	NR; p < 0.001		<b>RR = 3.19 (2.18, 4.66); p &lt; 0.001</b>		OR = 1.26 (0.95, 1.69); p = 0.11	

Source: Table 4, Table 5 and Table 6, p15-17 of Appendix A.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; FOLFIRINOX, 5-fluorouracil, Leucovorin/folinic acid; irinotecan and oxaliplatin; Gem, gemcitabine; HR, hazard ratio; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NE, not evaluable; NR, not reported; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RR, response-rate ratio; SD, stable disease.

Note: Results in bold indicate statistically significant difference (p < 0.05).

6.34 Based on a naïve comparison, the data in Table 5 suggest a slightly longer median PFS for NALIRIFOX (7.4 months; 95% CI: 6.0, 7.7) compared to FOLFIRINOX (6.4 months; 95% CI: 5.5, 7.2) noting there was substantial overlap of the 95% CIs. The median OS showed no difference between NALIRIFOX (11.1 months; 95% CI: 10.0, 12.1) and FOLFIRINOX (11.1 months; 95% CI: 9.0, 13.1). ORR was also higher for NALIRIFOX (41.8%; 95% CI: 36.8, 46.9) compared with FOLFIRINOX (31.6%; 95% CI: 24.7, 39.1), and in this case there was only a slight overlap in the 95% CIs.

6.35 Table 6 presents the results of the multistep ITC conducted during the evaluation.

**Table 6: Multistep indirect treatment comparison of NALIRIFOX vs FOLFIRINOX using NAPOLI-3, MPACT and ACCORD11/PRODIGE4 trials**

Step	Population	Comparison	OS-HR (95% CI) P-value	PFS-HR (95% CI) P-value	ORR-OR (95% CI) P-value
1	FOLFIRINOX vs Gem+NabP <sup>a</sup>	ITC (via Gem)	0.79 (0.60, 1.05) p=0.102	<b>0.68 (0.51, 0.92)</b> p=0.011	1.17 (0.55, 2.45) p=0.687
2	NALIRIFOX vs Gem+NabP <sup>b</sup>	H2H	<b>0.83 (0.70, 0.98)</b> p=0.032	<b>0.69 (0.58, 0.82)</b> p<0.0001	1.27 (0.95, 1.69) p=0.111
3	NALIRIFOX vs FOLFIRINOX <sup>c</sup>	ITC (via Gem+NabP)	1.05 (0.76, 1.46) p=0.777	1.01 (0.72, 1.43) p=0.941	1.09 (0.49, 2.41) p=0.838

Source: Produced during the evaluation using Table 4, Table 5 and Table 6, p15-17 of Appendix A

Abbreviations: FOLFIRINOX, 5-fluorouracil, Leucovorin/folinic acid; irinotecan and oxaliplatin; Gem, gemcitabine; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; H2H, head-to-head; HR, hazard ratio; ITC, indirect treatment comparison; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Statistically significant differences shown in bold (p<0.05).

<sup>a</sup> 1 = ACCORD11/PRODIGE4 trial versus MPACT trial

<sup>b</sup> 2 = NAPOLI-3 trial

<sup>c</sup> 3 = 2 versus 1

6.36 As shown in Table 5, treatment with FOLFIRINOX resulted in a statistically significant improvement in OS compared with gemcitabine (HR 0.57; 95% CI: 0.45, 0.73; p < 0.001). Similarly, a significant improvement was observed for Gem+NabP compared to gemcitabine (HR 0.72; 95% CI: 0.62, 0.83; p < 0.001). These data may suggest a larger effect in OS for FOLFIRINOX than Gem+NabP when these are compared against gemcitabine; however, there was substantial overlap of the 95% CIs. The multistep ITC (Table 6) showed no statistically significant difference between FOLFIRINOX and Gem+NabP for OS (HR 0.79; 95% CI: 0.60, 1.05; p=0.102). FOLFIRINOX appears to have a larger effect in PFS than Gem+NabP when these are compared against gemcitabine (HR 0.47; 95% CI: 0.37, 0.59 vs HR 0.69; 95% CI: 0.58, 0.82, respectively), as shown in Table 5. The results of the multistep ITC showed a significant improvement in PFS for FOLFIRINOX compared to Gem+NabP (HR 0.68 ; 95% CI: 0.51, 0.92; p=0.011).

6.37 The results of the multistep ITC of NALIRIFOX vs FOLFIRINOX (via common reference groups) presented in Table 6 showed no statistically significant difference for PFS or OS (HR 1.01; 95% CI: 0.72, 1.43; p=0.941 and HR 1.05; 95% CI: 0.76, 1.46; p=0.777, respectively). The results of the multistep ITC of NALIRIFOX vs FOLFIRINOX also indicated no statistically significant difference for ORR (OR 1.09; 95% CI: 0.49, 2.41; p=0.838; Table 6).

- 6.38 The ESC noted that the recently published meta-analysis of seven phase 3 trials including treatment with NALIRIFOX, FOLFIRINOX and Gem+NabP (Nichetti et al., 2024) found similar results to the naïve and multistep ITCs described above, with no statistically significant difference seen for FOLFIRINOX vs NALIRIFOX in PFS (HR 1.21; 95% CI: 0.86-1.70; p=0.28) or OS (HR 1.06; 95% CI: 0.81-1.39; p=0.65).
- 6.39 The PSCR provided additional information relating to the GENERATE trial (conference presentation slides), which included limited patient demographic and baseline disease characteristics data. Compared with the population included in the NAPOLI-3 trial, more patients in the GENERATE trial were ECOG PS 0 (67.2% versus 42.6%), fewer patients had metastatic disease (94.6% versus 100%), fewer had two or more metastatic sites (37.6% versus 67.3%), and fewer had liver metastasis (68.7% versus 79.9%). As well as these differences, the ESC also noted that a modified FOLFIRINOX regimen was used in the GENERATE trial that differed from the regimens used in (i) the ACCORD11/PRODIGE4 trial – including a lower LV dose (200 mg/m<sup>2</sup> versus 400 mg/m<sup>2</sup>, respectively), and a lower 5-FU dose (no bolus dose versus 400 mg/m<sup>2</sup>, respectively), and (ii) the regimen currently used in Australian practice – including a lower 5-FU dose (no bolus dose versus 400 mg/m<sup>2</sup>, respectively). This difference has the potential to bias the results of the analysis in GENERATE against FOLFIRINOX.
- 6.40 Despite differences between the trials, the PSCR provided the results of a one-step Bucher ITC in the PSCR (Table 7). The PSCR reported that the one-step ITC of OS supported the submission’s claim of superior efficacy of NALIRIFOX compared with FOLFIRINOX (HR 0.64; 95% CI: 0.46-0.89; p=0.008). The pre-PBAC response maintained that NALIRIFOX was superior to FOLFIRINOX on the basis of the one-step ITC (Table 7).

**Table 7: One-step ITC of NALIRIFOX vs FOLFIRINOX OS using GENERATE and NAPOLI-3 (Gem+NabP as common comparator) – proposed by PSCR based on GENERATE results**

	GENERATE		NAPOLI-3	
	mFOLFIRINOX N=175	Gem+NabP N=176	NALIRIFOX N=383	Gem+NabP N=387
Median (95%CI)	14.0 (11.4-16.3)	17.0 (14.5-18.9)	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified OS HR (95% CI); p-value	1.29 (0.98, 1.70); NR		<b>0.83 (0.70, 0.99); p=0.04</b>	
ITC – NALIRIFOX vs FOLFIRINOX (95% CI) p-value	<b>0.64 (0.46, 0.89); p=0.008</b>			

Source: PSCR – Table 2, page 5, Ohba et al (2023) ESMO presentation slides, slide 10, Table 4. Results in bold indicate statistically significant differences (p < 0.05)

### Comparative harms

#### NALIRIFOX versus Gem+NabP

- 6.41 A summary of the key treatment emergent adverse events (TEAEs) in the NAPOLI-3 trial is presented in Table 8.

Table 8: Summary of key adverse events in the NAPOLI-3 trial.

AEs	NALIRIFOX N=370	Gem+NabP N=379	OR [95% CI]	RR [95% CI]	RD [95% CI]
	n/N (%)	n/N (%)	OR and RR < 1 favour NALIRIFOX		RD < 0 favour NALIRIFOX
<b>Any cause TEAEs</b>					
Any cause TEAEs	369/370 (99.73%)	376/379 (99.21%)	2.94 [0.30, 28.43]	1.01 [0.99, 1.02]	0.01 [-0.01, 0.02]
Grade ≥ 3 TEAEs	322/370 (87.03%)	326/379 (86.02%)	1.09 [0.72, 1.66]	1.01 [0.96, 1.07]	0.01 [-0.04, 0.06]
SAEs	201/370 (54.32%)	195/379 (51.45%)	1.12 [0.84, 1.50]	1.06 [0.92, 1.21]	0.03 [-0.04, 0.10]
TEAEs leading to treatment discontinuation	118/370 (31.89%)	112/379 (29.55%)	1.12 [0.82, 1.52]	1.08 [0.87, 1.34]	0.02 [-0.04, 0.09]
TEAEs leading to discontinuation of nal-IRI	63/370 (17.03%)	NA	NE	NE	NE
TEAEs leading to reduction of any IMP	208/370 (56.22%)	190/379 (50.13%)	1.28 [0.96, 1.70]	1.12 [0.98, 1.28]	0.06 [-0.01, 0.13]
TEAEs leading to reduction of nal-IRI	194/370 (52.43%)	NA	NE	NE	NE
TEAEs leading to interruption of any IMP	16/370 (4.32%)	4/379 (1.06%)	<b>4.24</b> <b>[1.40, 12.80]</b>	<b>4.10</b> <b>[1.38, 12.14]</b>	<b>0.03</b> <b>[0.01, 0.06]</b>
TEAEs leading to interruption of nal-IRI	7/370 (1.89%)	NA	NE	NE	NE
TEAEs leading to death	22/370 (5.95%)	23/379 (6.07%)	0.98 [0.54, 1.79]	0.98 [0.56, 1.73]	0.00 [-0.04, 0.03]
<b>Drug-related TEAEs</b>					
Any Drug-related TEAEs	352/370 (95.14%)	352/379 (92.88%)	1.50 [0.81, 2.77]	1.02 [0.99, 1.06]	0.02 [-0.01, 0.06]
Drug-related Grade ≥ 3 TEAEs	262/370 (70.81%)	258/379 (68.07%)	1.14 [0.83, 1.55]	1.04 [0.95, 1.14]	0.03 [-0.04, 0.09]
Drug-related SAEs	98/370 (26.49%)	72/379 (19.00%)	<b>1.54</b> <b>[1.09, 2.17]</b>	<b>1.39</b> <b>[1.07, 1.82]</b>	<b>0.07</b> <b>[0.01, 0.13]</b>
Drug-related TEAEs leading to treatment discontinuation	94/370 (25.41%)	88/379 (23.22%)	1.13 [0.81, 1.57]	1.09 [0.85, 1.41]	0.02 [-0.04, 0.08]
Drug-related TEAEs leading to discontinuation of nal-IRI	40/370 (10.81%)	NA	NE	NE	NE
Drug-related TEAEs leading to reduction of any IMP	198/370 (53.51%)	184/379 (48.55%)	1.22 [0.92, 1.63]	1.10 [0.96, 1.27]	0.05 [-0.02, 0.12]
Drug-related TEAEs leading to interruption of any IMP	12/370 (3.24%)	3/379 (0.79%)	<b>4.20</b> <b>[1.18, 15.01]</b>	<b>4.10</b> <b>[1.17, 14.40]</b>	<b>0.02</b> <b>[0.00, 0.04]</b>
Drug-related TEAEs leading to death	6/370 (1.62%)	8/379 (2.11%)	0.76 [0.26, 2.22]	0.77 [0.27, 2.19]	0.00 [-0.02, 0.01]

Source: Table 33 (adapted), p76 of submission.

Abbreviations: AE, adverse event; CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OR, odds ratio; RD, risk difference; RR, relative risk; SAE, serious adverse event; TEAE, treatment emergent adverse event.

Note: Results in **bold** indicate statistically significant difference ( $p < 0.05$ ) based on post hoc analyses. This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

6.42 Overall, the NALIRIFOX arm appears to have a higher incidence of drug-related TEAEs compared to the Gem+NabP arm across most categories including Grade ≥3 TEAEs (70.8% vs 68.1%), serious adverse events (SAEs; 26.5% vs 19.0%), and TEAEs leading

to discontinuation (25.4% vs 23.2%), reduction (53.5% vs 48.6%) and interruption of treatment (3.2% vs 0.8%). The Gem+NabP arm had a higher incidence of drug-related TEAEs leading to death (2.1% vs 1.6%; 8 deaths versus 6 deaths). A similar trend was observed for any cause of TEAEs with slightly higher incidences for NALIRIFOX across most categories.

- 6.43 Based on post hoc analyses, there were statistically significantly more patients in the NALIRIFOX arm who reported drug-related TEAEs leading to interruption of the treatment regimen (OR 4.20; 95% CI: 1.18, 15.01) and drug-related SAEs (OR 1.54; 95% CI: 1.09, 2.17). Similarly, any cause TEAEs leading to interruption of the treatment regimen were statistically significantly higher for NALIRIFOX compared to Gem+NabP (OR 4.24; 95% CI: 1.40, 12.80).
- 6.44 Summaries of the most frequently reported individual all-cause and drug-related Grade 3-4 TEAEs with a difference in incidence between treatment arms of  $\geq 2\%$  are presented in Table 9 and Table 10.

**Table 9: Summary of all-cause Grade 3-4 TEAEs by system organ class and preferred term with a difference in incidence between treatment arms of  $\geq 2\%$  in the NAPOLI-3 trial (Safety Population)**

AEs	NALIRIFOX	Gem+NabP	OR [95% CI]	RR [95% CI]	RD [95% CI]
	n /N (%)	n /N (%)	OR and RR < 1 favours NALIRIFOX		RD < 0 favours NALIRIFOX
Any Grade 3-4 TEAEs	322/370 (87.03%)	326/379 (86.02%)	1.09 [0.72, 1.66]	1.01 [0.96, 1.07]	0.01 [-0.04, 0.06]
<b>Gastrointestinal disorders</b>					
Diarrhoea	75/370 (20.27%)	17/379 (4.49%)	<b>5.41</b> [3.13, 9.37]	<b>4.52</b> [2.72, 7.50]	<b>0.16</b> [0.11, 0.20]
Nausea	44/370 (11.89%)	10/379 (2.64%)	<b>4.98</b> [2.47, 10.06]	<b>4.51</b> [2.30, 8.82]	<b>0.09</b> [0.06, 0.13]
Vomiting	26/370 (7.03%)	8/379 (2.11%)	<b>3.51</b> [1.57, 7.85]	<b>3.33</b> [1.53, 7.26]	<b>0.05</b> [0.02, 0.08]
Abdominal pain	16/370 (4.32%)	14/379 (3.69%)	1.18 [0.57, 2.45]	1.17 [0.58, 2.36]	0.01 [-0.02, 0.03]
<b>General disorders and administration site conditions</b>					
Fatigue	23/370 (6.22%)	20/379 (5.28%)	1.19 [0.64, 2.21]	1.18 [0.66, 2.11]	0.01 [-0.02, 0.04]
Asthenia	33/370 (8.92%)	19/379 (5.01%)	<b>1.86</b> [1.04, 3.33]	<b>1.78</b> [1.03, 3.07]	<b>0.04</b> [0.00, 0.08]
Oedema peripheral	0/370 (0.00%)	5/379 (1.32%)	NE	NE	-0.01 [-0.02, 0.00]
Pyrexia	3/370 (0.81%)	6/379 (1.58%)	0.51 [0.13, 2.05]	0.51 [0.13, 2.03]	-0.01 [-0.02, 0.01]
Mucosal inflammation	8/370 (2.16%)	1/379 (0.26%)	<b>8.35</b> [1.04, 67.13]	<b>8.19</b> [1.03, 65.20]	<b>0.02</b> [0.00, 0.03]
<b>Blood and lymphatic system disorders</b>					
Anaemia	39/370 (10.54%)	66/379 (17.41%)	<b>0.56</b> [0.37, 0.85]	<b>0.61</b> [0.42, 0.88]	<b>-0.07</b> [-0.12, -0.02]
Neutropenia	52/370 (14.05%)	93/379 (24.54%)	<b>0.50</b> [0.35, 0.73]	<b>0.57</b> [0.42, 0.78]	<b>-0.10</b> [-0.16, -0.05]
Thrombocytopenia	3/370 (0.81%)	14/379 (3.69%)	<b>0.21</b> [0.06, 0.75]	<b>0.22</b> [0.06, 0.76]	<b>-0.03</b> [-0.05, -0.01]
Leukopenia	4/370	17/379	<b>0.23</b>	<b>0.24</b>	<b>-0.03</b>

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AEs	NALIRIFOX	Gem+NabP	OR [95% CI]	RR [95% CI]	RD [95% CI]
	n /N (%)	n /N (%)	OR and RR < 1 favours NALIRIFOX		RD < 0 favours NALIRIFOX
	(1.08%)	(4.49%)	<b>[0.08, 0.70]</b>	<b>[0.08, 0.71]</b>	<b>[-0.06, -0.01]</b>
<b>Metabolism and nutrition disorders</b>					
Decreased appetite	32/370 (8.65%)	10/379 (2.64%)	<b>3.49</b> <b>[1.69, 7.21]</b>	<b>3.28</b> <b>[1.64, 6.57]</b>	<b>0.06</b> <b>[0.03, 0.09]</b>
Hypokalaemia	56/370 (15.14%)	15/379 (3.96%)	<b>4.33</b> <b>[2.40, 7.80]</b>	<b>3.82</b> <b>[2.20, 6.64]</b>	<b>0.11</b> <b>[0.07, 0.15]</b>
Dehydration	12/370 (3.24%)	4/379 (1.06%)	<b>3.14</b> <b>[1.00, 9.83]</b>	3.07 [1.00, 9.44]	<b>0.02</b> <b>[0.00, 0.04]</b>
<b>Investigations</b>					
Neutrophil count decreased	36/370 (9.73%)	51/379 (13.46%)	0.69 [0.44, 1.09]	0.72 [0.48, 1.08]	-0.04 [-0.08, 0.01]
Weight decreased	11/370 (2.97%)	1/379 (0.26%)	<b>11.58</b> <b>[1.49, 90.17]</b>	<b>11.27</b> <b>[1.46, 86.84]</b>	<b>0.03</b> <b>[0.01, 0.05]</b>
Platelet count decreased	3/370 (0.81%)	9/379 (2.37%)	0.34 [0.09, 1.25]	0.34 [0.09, 1.25]	-0.02 [-0.03, 0.00]
White blood cell count decreased	6/370 (1.62%)	18/379 (4.75%)	<b>0.33</b> <b>[0.13, 0.84]</b>	<b>0.34</b> <b>[0.14, 0.85]</b>	<b>-0.03</b> <b>[-0.06, -0.01]</b>
<b>Skin and subcutaneous tissue</b>					
Alopecia	0/370 (0.00%)	2/379 (0.53%)	NE	NE	-0.01 [-0.01, 0.00]
Rash	0/370 (0.00%)	2/379 (0.53%)	NE	NE	-0.01 [-0.01, 0.00]
Rash maculo-papular	0/370 (0.00%)	1/379 (0.26%)	NE	NE	0.00 [-0.01, 0.00]
<b>Nervous system disorders</b>					
Neuropathy peripheral	12/370 (3.24%)	22/379 (5.80%)	0.54 [0.27, 1.12]	0.56 [0.28, 1.11]	-0.03 [-0.06, 0.00]
<b>Respiratory, thoracic and mediastinal disorders</b>					
Dyspnoea	2/370 (0.54%)	8/379 (2.11%)	0.25 [0.05, 1.19]	0.26 [0.05, 1.20]	-0.02 [-0.03, 0.00]
<b>Musculoskeletal and connective tissue disorders</b>					
Pain in extremity	1/370 (0.27%)	0/379 (0.00%)	NE	NE	0.00 [0.00, 0.01]
<b>Infections and infestations</b>					
Pneumonia	5/370 (1.35%)	13/379 (3.43%)	0.39 [0.14, 1.09]	0.39 [0.14, 1.09]	-0.02 [-0.04, 0.00]

Source: Table 35, p81-82 of the submission.

Abbreviations: AE, adverse event; CI, confidence interval; Gem, gemcitabine; IMP, investigational medicinal product; NA, not applicable; NabP, nanoparticle albumin bound paclitaxel; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NE, not estimable; OR, odds ratio; RD, risk difference; RR, relative risk; TEAE, treatment emergent adverse event.

Results in **bold** indicate statistically significant difference ( $p < 0.05$ ).

Table 10: Summary of drug-related Grade 3-4 TEAEs by system organ class and preferred term in the NAPOLI-3 trial with a difference in incidence between treatment arms of  $\geq 2\%$  (Safety Population)

AEs	NALIRIFOX N=370	Gem+NabP N=379	OR [95% CI]	RR [95% CI]	RD [95% CI]
	n /N (%)	n /N (%)	OR and RR < 1 favours NALIRIFOX		RD < 0 favours NALIRIFOX
Any drug-related Grade 3-4 TEAEs	259/370 (70.00%)	255/379 (67.28%)	1.13 [0.83, 1.55]	1.04 [0.94, 1.15]	0.03 [-0.04, 0.09]
<b>Gastrointestinal disorders</b>					
Diarrhoea	72/370 (19.46%)	12/379 (3.17%)	<b>7.39</b> [3.94, 13.87]	<b>6.15</b> [3.39, 11.13]	<b>0.16</b> [0.12, 0.21]
Nausea	42/370 (11.35%)	8/379 (2.11%)	<b>5.94</b> [2.75, 12.83]	<b>5.38</b> [2.56, 11.30]	<b>0.09</b> [0.06, 0.13]
Vomiting	20/370 (5.41%)	5/379 (1.32%)	<b>4.27</b> [1.59, 11.51]	<b>4.10</b> [1.55, 10.80]	<b>0.04</b> [0.02, 0.07]
<b>General disorders and administration site conditions</b>					
Fatigue	20/370 (5.41%)	14/379 (3.69%)	1.49 [0.74, 3.00]	1.46 [0.75, 2.85]	0.02 [-0.01, 0.05]
Asthenia	27/370 (7.30%)	14/379 (3.69%)	<b>2.05</b> [1.06, 3.98]	<b>1.98</b> [1.05, 3.71]	<b>0.04</b> [0.00, 0.07]
Mucosal inflammation	7/370 (1.89%)	1/379 (0.26%)	7.29 [0.89, 59.54]	7.17 [0.89, 58.00]	0.02 [0.00, 0.03]
<b>Nervous system disorders</b>					
Neuropathy peripheral	12/370 (3.24%)	22/379 (5.80%)	0.54 [0.27, 1.12]	0.56 [0.28, 1.11]	-0.03 [-0.06, 0.00]
<b>Blood and lymphatic system disorders</b>					
Neutropenia	52/370 (14.05%)	88/379 (23.22%)	<b>0.54</b> [0.37, 0.79]	<b>0.61</b> [0.44, 0.83]	<b>-0.09</b> [-0.15, -0.04]
Anaemia	27/370 (7.30%)	55/379 (14.51%)	<b>0.46</b> [0.29, 0.75]	<b>0.50</b> [0.32, 0.78]	<b>-0.07</b> [-0.12, -0.03]
Thrombocytopenia	2/370 (0.54%)	13/379 (3.43%)	<b>0.15</b> [0.03, 0.68]	<b>0.16</b> [0.04, 0.69]	<b>-0.03</b> [-0.05, -0.01]
Leukopenia	3/370 (0.81%)	17/379 (4.49%)	<b>0.17</b> [0.05, 0.60]	<b>0.18</b> [0.05, 0.61]	<b>-0.04</b> [-0.06, -0.01]
<b>Investigations</b>					
Neutrophil count decreased	36/370 (9.73%)	50/379 (13.19%)	0.71 [0.45, 1.12]	0.74 [0.49, 1.10]	-0.03 [-0.08, 0.01]
WBC count decreased	6/370 (1.62%)	18/379 (4.75%)	<b>0.33</b> [0.13, 0.84]	<b>0.34</b> [0.14, 0.85]	<b>-0.03</b> [-0.06, -0.01]
<b>Metabolism and nutrition disorders</b>					
Decreased appetite	24/370 (6.49%)	2/379 (0.53%)	<b>13.08</b> [3.07, 55.73]	<b>12.29</b> [2.93, 51.64]	<b>0.06</b> [0.03, 0.09]
Hypokalaemia	27/370 (7.30%)	6/379 (1.58%)	<b>4.89</b> [2.00, 12.00]	<b>4.61</b> [1.93, 11.03]	<b>0.06</b> [0.03, 0.09]

Source: Table 37, p87-88 of submission.

Abbreviations: AE, adverse event; CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; IMP, investigational medicinal product; NA, not applicable; NALIRIFOX, 5-fluorouracil, leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NE, not estimable; OR, odds ratio; RD, risk difference; RR, relative risk; TEAE, treatment emergent adverse event.

Note: Results in **bold** indicate statistically significant difference ( $p < 0.05$ ) based on post hoc analyses. This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

- 6.45 Based on post-hoc analyses, statistically significantly more patients in the NALIRIFOX arm than in the Gem+NabP arm reported the following all-cause Grade 3-4 TEAEs:

gastrointestinal disorders including diarrhoea (OR=5.41; 95% CI 3.13, 9.37), nausea (OR=4.98; 95% CI 2.47, 10.06) and vomiting (OR=3.51; 95% CI 1.57, 7.85); general disorders and administration site conditions including asthenia (OR=1.86; 95% CI 1.04, 3.33) and mucosal inflammation (OR=8.35; 95% CI 1.04, 67.13), metabolism and nutrition disorders including decreased appetite (OR=3.49; 95% CI 1.69, 7.21), hypokalaemia (OR=4.33; 95% CI 2.40, 7.80) and dehydration (OR=3.14; 95% CI 1.00, 9.83); and weight decreased (OR=11.58; 95% CI 1.49, 90.17). Statistically significantly more patients in the Gem+NabP arm than in the NALIRIFOX arm reported the following all cause Grade 3-4 TEAEs: blood and lymphatic system disorders including anaemia (OR=0.56; 95% CI 0.37, 0.85), neutropenia (OR=0.50; 95% CI 0.35, 0.73), thrombocytopenia (OR=0.21; 95% CI 0.06, 0.75) and leukopenia (OR=0.23; 95% CI 0.08, 0.70); and WBC count decreased (OR=0.33; 95% CI 0.13, 0.84).

- 6.46 Based on post hoc analyses, statistically significantly more patients in the NALIRIFOX arm than in the Gem+NabP arm reported drug-related Grade 3-4 TEAEs in line with those seen in the all-cause Grade 3-4 TEAEs analysis (i.e. gastrointestinal disorders and metabolism and nutrition disorders). Similarly, statistically significantly more patients in the Gem+NabP arm than in the NALIRIFOX arm reported drug-related Grade 3-4 TEAEs in line with those seen in the all-cause Grade 3-4 TEAE analysis (i.e. blood and lymphatic system disorders including neutropenia and WBC count decreased). Differences in TEAEs between treatments were generally larger for the drug-related TEAE analysis compared with the all-cause TEAE analysis.
- 6.47 There were six participants (1.6%) with any treatment-emergent TEAEs leading to death related to any study medication in the NALIRIFOX arm, each occurring in one patient: sepsis, febrile neutropenia, pancytopenia, general physical health deterioration, peritumoural oedema and ischaemic stroke. This compares to eight participants (2.1%) with TEAEs leading to death related to any study medication in the Gem+NabP arm: sepsis in five participants (1.3%) and febrile neutropenia, general physical health deterioration and pneumonitis in one participant (0.3%) each.

#### **NALIRIFOX versus FOLFIRINOX**

- 6.48 A summary of the most frequently reported drug-related Grade 3-4 AEs in the three trials is presented in Table 11. A comparison of drug-related AEs is presented, as any cause AEs were not reported in the publications for ACCORD11/PRODIGE4 and MPACT trials.

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Table 11: Summary of most frequently reported Grade 3-4 drug-related adverse events in the trials

TRAE	Intervention	Comparator	Risk estimates	
			OR (95% CI) <sup>a</sup>	RD (95% CI) <sup>a</sup>
<b>NAPOLI-3</b>	<b>NALIRIFOX n/N (%)</b>	<b>Gem+NabP n/N (%)</b>		
Grade ≥3 Neutropenia	52/370 (14.05%)	88/379 (23.22%)	<b>0.54</b> <b>(0.37, 0.79)</b>	<b>-0.09</b> <b>(-0.15, -0.04)</b>
Grade ≥3 Leukopenia	3/370 (0.81%)	17/379 (4.49%)	NS	NS
Grade ≥3 Thrombocytopenia	2/370 (0.54%)	13/379 (3.43%)	<b>0.15</b> <b>(0.03, 0.68)</b>	<b>-0.03</b> <b>(-0.05, -0.01)</b>
Grade ≥3 Anaemia	27/370 (7.30%)	55/379 (14.51%)	<b>0.46</b> <b>(0.29, 0.75)</b>	<b>-0.07</b> <b>(-0.12, -0.03)</b>
Grade ≥3 Febrile neutropenia	7/230 (1.9%)	9/379 (2.4%)	0.79 (0.29, 2.15)	0 (-0.03, 0.02)
Grade ≥3 Fatigue	20/370 (5.41%)	14/379 (3.69%)	1.49 (0.74, 3)	0.02 (-0.01, 0.05)
Grade ≥3 Diarrhoea	72/370 (19.46%)	12/379 (3.17%)	<b>7.39</b> <b>(3.94, 13.87)</b>	<b>0.16</b> <b>(0.12, 0.21)</b>
Grade ≥3 Peripheral neuropathy	12/370 (3.24%)	22/379 (5.80%)	0.54 (0.27, 1.12)	-0.03 (-0.06, 0.00)
Grade ≥3 Vomiting	20/370 (5.41%)	5/379 (1.32%)	<b>4.27</b> <b>(1.59, 11.51)</b>	<b>0.04</b> <b>(0.02, 0.07)</b>
AE leading to death	6/370 (1.62%)	8/379 (2.11%)	0.76 (0.26, 2.22)	0 (-0.02, 0.01)
<b>ACCORD11/PRODIGE4</b>	<b>FOLFIRINOX n/N (%)</b>	<b>Gem n/N (%)</b>	<b>OR (95% CI)<sup>a</sup></b>	<b>RD (95% CI)<sup>a</sup></b>
Grade ≥3 Neutropenia	75/164 (45.73%)	35/167 (20.96%)	<b>3.18</b> <b>(1.96, 5.15)</b>	<b>0.25</b> <b>(0.15, 0.35)</b>
Grade ≥3 Thrombocytopenia	15/165 (9.09%)	6/168 (3.57%)	<b>2.7</b> <b>(1.02, 7.14)</b>	<b>0.06</b> <b>(0, 0.11)</b>
Grade ≥3 Anaemia	13/166 (7.83%)	10/168 (5.95%)	1.34 (0.57, 3.15)	0.02 (-0.04, 0.07)
Grade ≥3 Febrile neutropenia	9/166 (5.42%)	2/169 (1.18%)	<b>4.79</b> <b>(1.02, 22.5)</b>	<b>0.04</b> <b>0, 0.08)</b>
Grade ≥3 Fatigue	39/165 (23.64%)	30/169 (17.75%)	1.43 (0.84, 2.45)	0.06 (-0.03, 0.15)
Grade ≥3 Diarrhoea	21/165 (12.73%)	3/169 (1.78%)	<b>8.07</b> <b>(2.36, 27.61)</b>	<b>0.11</b> <b>(0.05, 0.16)</b>
Grade ≥3 Peripheral neuropathy	15/166 (9.04%)	0.5/169 (0.30%)	<b>33.48</b> <b>(1.98, 565.14)</b>	<b>0.09</b> <b>(0.04, 0.13)</b>
Grade ≥3 Vomiting	24/166 (14.46%)	14/169 (8.28%)	1.87 (0.93, 3.76)	0.06 (-0.01, 0.13)
AE leading to death	1/167 (0.60%)	1/169 (0.59%)	1.01 (0.06, 16.32)	0 (-0.02, 0.02)
<b>MPACT</b>	<b>Gem+NabP n/N (%)</b>	<b>Gem n/N (%)</b>	<b>OR (95% CI)<sup>a</sup></b>	<b>RD (95% CI)<sup>a</sup></b>
Grade ≥3 Neutropenia	153/405 (37.78%)	103/388 (26.55%)	<b>1.68</b> <b>(1.24, 2.27)</b>	<b>0.11</b> <b>(0.05, 0.18)</b>
Grade ≥3 Leukopenia	127/405 (31.352%)	63/388 (16.24%)	NS	NS
Grade ≥3 Thrombocytopenia	52/405 (12.84%)	36/388 (9.28%)	1.44 (0.92, 2.26)	0.04 (-0.01, 0.08)
Grade ≥3 Anaemia	53/405 (13.09%)	48/388 (12.37%)	1.07 (0.7, 1.62)	0.01 (-0.04, 0.05)
Grade ≥3 Febrile neutropenia	14/421 (3.33%)	6/402 (1.49%)	2.27 (0.86, 5.97)	<b>0.02</b> <b>(0, 0.04)</b>

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TRAE	Intervention	Comparator	Risk estimates	
Grade ≥3 Fatigue	70/421 (16.63%)	27/402 (6.72%)	<b>2.77</b> <b>(1.74, 4.42)</b>	<b>0.1</b> <b>(0.06, 0.14)</b>
Grade ≥3 Diarrhoea	24/421 (5.70%)	3/402 (0.75%)	<b>8.04</b> <b>(2.4, 26.92)</b>	<b>0.05</b> <b>(0.03, 0.07)</b>
Grade ≥3 Sensory neuropathy	70/421 (16.63%)	3/402 (0.75%)	<b>26.52</b> <b>(8.28, 84.99)</b>	<b>0.16</b> <b>(0.12, 0.20)</b>
Grade ≥3 Vomiting	19/421 (4.51%)	12/402 (2.99%)	1.54 (0.74, 3.21)	0.02 (-0.01, 0.04)
AE leading to death	18/421 (4.28%)	18/402 (4.48%)	0.95 (0.49, 1.86)	0 (-0.03, 0.03)

Source: Table 1 and Table 2, p11-12 of Appendix A.

Abbreviations: AE, adverse event; CI, confidence interval; FOLFIRINOX, 5-fluorouracil, Leucovorin/folinic acid, standard irinotecan, and oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; NS, not specified; OR, odds ratio; RD, risk difference; RR, risk ratio; TRAE, treatment-related adverse event.

<sup>a</sup> Based on post hoc analyses of direct comparisons included in each trial. All safety analyses were based on safety populations.

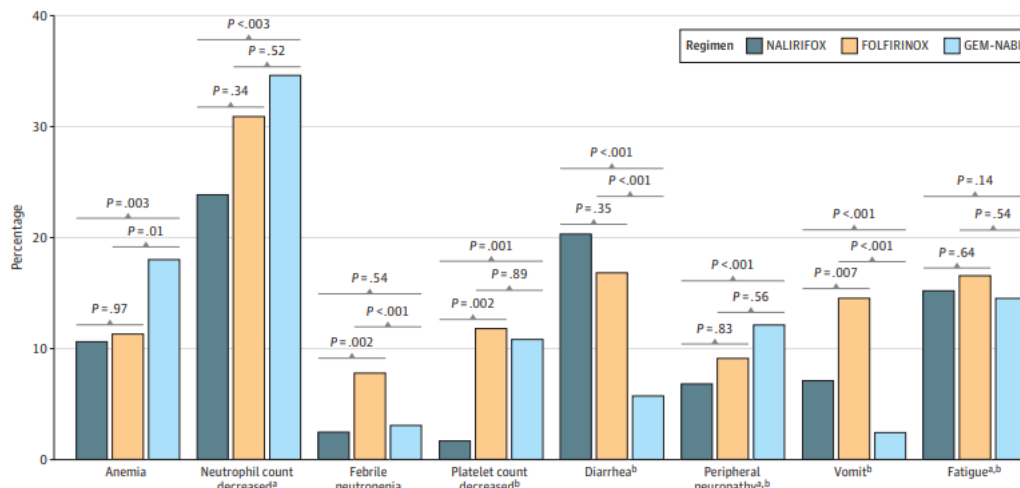
Note: In the ACCORD11/PRODIGE4 and NAPOLI-3 trials, includes Grade 3 and Grade 4 events only; In the MPACT trial, includes Grade 3, 4 and possibly Grade 5 events. This is unclear in the publication.

Results in bold indicate a statistically significant difference ( $p < 0.05$ ) based on post hoc analyses. This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

- 6.49 The most frequent Grade 3-4 drug-related AEs ( $\geq 10\%$  of patients) for FOLFIRINOX were neutropenia (45.7%), fatigue (23.6%), vomiting (14.5%) and diarrhoea (12.7%). In contrast, diarrhoea (19.5%) and neutropenia (14.1%) were the most frequent Grade  $\geq 3$  drug-related AEs ( $\geq 10\%$  of patients) for NALIRIFOX. With the exception of diarrhoea and AEs leading to death (which were reported at a higher frequency for NALIRIFOX), and anaemia (which was reported at a similar frequency to NALIRIFOX), all adverse events for which data were available were reported at a higher frequency with FOLFIRINOX compared to NALIRIFOX; however, the reported higher frequency of AEs seen with FOLFIRINOX may be overestimated due to the longer duration of treatment follow up in the FOLFIRINOX arm in the ACCORD11/PRODIGE4 trial (median 26.6 months [95%CI: 20.5, 44.9]) compared to the NALIRIFOX arm in the NAPOLI-3 trial (median 16.0 months [95%CI: 15.0, 16.8]).
- 6.50 Based on post hoc analyses, FOLFIRINOX appears to be associated with statistically significantly more adverse events than gemcitabine for neutropenia, thrombocytopenia, febrile neutropenia, diarrhoea and peripheral neuropathy, whereas Gem+NabP is found to be associated with statistically significantly more adverse events than gemcitabine for neutropenia, fatigue, diarrhoea and sensory neuropathy.
- 6.51 The ESC noted that the Nichetti et al. (2024) meta-analysis presented a comparison of the incidence of Grade  $\geq 3$  AEs across NALIRIFOX, FOLFIRINOX and Gem+NabP. As shown in Figure 4, and consistent with the results presented in the submission and described above, Gem+NabP is associated with a higher incidence of  $\geq$  Grade 3 haematological AEs than NALIRIFOX ( $p=0.003$ ,  $<0.003$  and  $0.001$  for anaemia, neutrophil count decreased and platelet count decreased, respectively), while NALIRIFOX is associated with a higher incidence of  $\geq$  grade 3 diarrhoea ( $p<0.001$ ). The incidence of Grade  $\geq 3$  diarrhoea was also numerically higher for NALIRIFOX compared

with FOLFIRINOX (20.3% versus 16.8%), although this difference was not statistically significant ( $p=0.35$ ).

Figure 4: Reporting Incidence of Grade 3 or Higher Toxic Effects According to the Pooled Treatment Regimens



Source: Nichetti et al. (2024) – Figure 3, page 8

P values of adjusted logistic regression models are plotted for each comparison.

FOLFIRINOX indicates irinotecan, oxaliplatin, folinic acid, and fluorouracil; GEM-NABP, gemcitabine and nab-paclitaxel; NALIRIFOX, liposomal irinotecan, oxaliplatin, folinic acid, and fluorouracil.

<sup>a</sup> Equivalent terms reported separately in original reports were pooled before the analysis, including neutrophil count decreased and neutropenia, peripheral neuropathy and peripheral sensory neuropathy, and fatigue and asthenia.

<sup>b</sup> The following toxic effects were not detailed in all trials: platelet count decreased and fatigue rates were not available in CanStem111P trial results; diarrhea rates were not available in HALO trial results; peripheral neuropathy rates were not available in CanStem111P, HALO, and AVENGER500 trial results; vomit rates were not available in CanStem111P, MPACT, HALO, and AVENGER500 trial results.

## Benefits/harms

### NALIRIFOX versus Gem+NabP

6.52 A summary of the comparative benefits and harms of NALIRIFOX versus Gem+NabP is presented in Table 12.

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Table 12: Summary of comparative benefits and harms for NALIRIFOX and Gem+NabP

Event	NALIRIFOX n (%)		Gem+NabP n (%)		Absolute Difference	HR (95% CI) <sup>a</sup>
<b>BENEFITS</b>	<b>N=383</b>		<b>N=387</b>			
<b>Overall survival (median duration of follow up 16.0 months in NALIRIFOX and 16.3 months in Gem+NabP)</b>						
Deaths, n/N (%)	259/383 (67.6)		285/387 (73.6)		-	<b>0.83 (0.70, 0.99) p=0.04</b>
Median OS, months (95% CI)	11.1 (10.0, 12.1)		9.2 (8.3, 10.6)		1.9	
% Alive at 3 months (95% CI)	84.2 (80.2, 87.5)		82.5 (78.3, 86.0)		1.7%	
% Alive at 6 months (95% CI)	72.4 (67.6, 76.6)		68.4 (63.5, 72.8)		4.0%	
% Alive at 9 months (95% CI)	58.1 (53.0, 62.9)		51.8 (46.7, 56.7)		6.3%	
% Alive at 12 months (95% CI)	45.6 (40.5, 50.5)		39.5 (34.6, 44.4)		6.1%	
% Alive at 18 months (95% CI)	26.2 (20.9, 31.7)		19.3 (14.8, 24.2)		6.9%	
<b>Progression free survival</b>						
Progressed, n (%)	249/383 (65.0)		259/387 (66.9)		-	<b>0.69 (0.58, 0.83) p&lt;0.0001</b>
Median PFS, months (95% CI)	7.4 (6.0, 7.7)		5.6 (5.3, 5.8)		1.8	
% not progressed at 3 months (95% CI)	76.9 (72.1, 81.1)		71.5 (66.5, 75.9)		5.4%	
% not progressed at 6 months (95% CI)	56.4 (50.7, 61.6)		43.2 (37.6, 48.6)		13.2%	
% not progressed at 9 months (95% CI)	40.9 (35.3, 46.4)		24.9 (19.8, 30.2)		16.0%	
% not progressed at 12 months (95% CI)	27.4 (22.3, 32.7)		13.9 (9.7, 18.9)		13.5%	
% not progressed at 18 months (95% CI)	11.4 (7.1, 16.9)		3.6 (0.5, 12.3)		7.8%	
<b>HARMS (Grade 3-4)</b>	<b>N=370</b>	<b>N=379</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients</b>		<b>RD (95% CI)</b>
				<b>NALIRIFOX</b>	<b>Gem+NabP</b>	
Diarrhoea	75	17	<b>4.52</b> [2.72, 7.50]	20.3	4.5	<b>0.16</b> [0.11, 0.20]
Hypokalaemia	56	15	<b>3.82</b> [2.20, 6.64]	15.1	4.0	<b>0.11</b> [0.07, 0.15]
Nausea	44	10	<b>4.51</b> [2.30, 8.82]	11.9	2.6	<b>0.09</b> [0.06, 0.13]
Decreased appetite	32	10	<b>3.28</b> [1.64, 6.57]	8.7	2.6	<b>0.06</b> [0.03, 0.09]
Vomiting	26	8	<b>3.33</b> [1.53, 7.26]	7.0	2.1	<b>0.05</b> [0.02, 0.08]
Asthenia	33	19	<b>1.78</b> [1.03, 3.07]	8.9	5.0	<b>0.04</b> [0.00, 0.08]
Weight decreased	11	1	<b>11.27</b> [1.46, 86.84]	3.0	0.3	<b>0.03</b> [0.01, 0.05]
Mucosal inflammation	8	1	<b>8.19</b> [1.03, 65.20]	2.2	0.3	<b>0.02</b> [0.00, 0.03]
Dehydration	12	4	<b>3.07</b> [1.00, 9.44]	3.2	1.1	<b>0.02</b> [0.00, 0.04]
Neutropenia	52	93	<b>0.57</b> [0.42, 0.78]	14.1	24.5	<b>-0.10</b> [-0.16, -0.05]
Anaemia	39	66	<b>0.61</b> [0.42, 0.88]	10.5	17.4	<b>-0.07</b> [-0.12, -0.02]
Thrombocytopenia	3	14	<b>0.22</b> [0.06, 0.76]	0.8	3.7	<b>-0.03</b> [-0.05, -0.01]
Leukopenia	4	17	<b>0.24</b> [0.08, 0.71]	1.1	4.5	<b>-0.03</b> [-0.06, -0.01]
White blood cell decreased	6	18	<b>0.34</b> [0.14, 0.85]	1.6	4.8	<b>-0.03</b> [-0.06, -0.01]

Source: Table 30 and Table 31, p66-68 and Table 35, p81-82 of submission.

Abbreviations: CI, confidence interval; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; HR, hazard ratio; NALIRIFOX, 5-fluorouracil, Leucovorin/folinic acid, nanoliposomal irinotecan (nal-IRI), and oxaliplatin; OS, overall survival; PFS, progression free survival; RD, risk difference; RR, risk ratio.

<sup>a</sup> Hazard ratio and 95% CI stratified by ECOG performance status (0/1), region (North America/East Asia/Rest of the world), and liver metastases (Yes/No). A hazard ratio <1 indicates an advantage for NALIRIFOX.

Note: Results in **bold** indicate statistically significant difference ( $p < 0.05$ ).

### **NALIRIFOX versus FOLFIRINOX**

6.53 The ‘side by side’ comparison between NALIRIFOX and FOLFIRINOX presented in the submission did not allow for a quantitative comparison of the benefits and harms of NALIRIFOX and FOLFIRINOX. The multistep ITC conducted during the evaluation, as well as the results of the recent Nichetti et al. (2024) meta-analysis, suggest no difference between NALIRIFOX and FOLFIRINOX in effectiveness outcomes. Accordingly, a benefits/harms table has not been presented for this indirect comparison.

### **Clinical claim**

#### **NALIRIFOX versus Gem+NabP**

6.54 The submission claimed that NALIRIFOX is superior in terms of effectiveness compared to Gem+NabP based on a direct comparison (NAPOLI-3 trial). The ESC considered this claim may not be adequately supported because:

- Although the trial results indicate an overall improved survival with NALIRIFOX compared to Gem+NabP (HR 0.83 [95% CI: 0.70, 0.99] p-value = 0.04), the 95% CI had an upper limit that is very close to 1.
- The submission claimed that the improvements in the median OS (1.9 months) and median PFS (1.8 months) were clinically meaningful for pancreatic cancer and were similar to the magnitude of OS benefit accepted for Gem+NabP (1.8 months) when the PBAC recommended its inclusion on the PBS in March 2014. However, the ASCO group considered an incremental gain ranging from 3 to 5 months in the median OS and PFS to be clinically meaningful (paragraph 6.28). Neither the primary OS nor PFS outcomes from the NAPOLI-3 trial meet these criteria. The pivotal evidence to support the claim was an open label trial (NAPOLI-3). There were some concerns of attrition bias given the high proportion of patients who were censored mainly due to receiving subsequent anticancer therapy without disease progression (22.5% vs 14.6%), which may bias PFS results in favour of NALIRIFOX.
- A higher proportion of subsequent anticancer therapies was observed in the trial compared with the Australian setting, and these therapies appear to differ across treatment interventions compared to the Australian setting (paragraph 6.16). Patients in the Australian setting used Gem+NabP as second line treatment even though the current PBS restriction for NabP restricts use to first-line treatment only. It is unclear how these differences may impact the applicability of treatment effects.

6.55 The submission claimed that NALIRIFOX is non-inferior in terms of overall safety compared to Gem+NabP, noting that these treatments have differing adverse event

profiles. The ESC considered this claim is uncertain based on the clinical data presented in the submission for the following reasons:

- The pivotal evidence to support the safety claim was an open label trial (NAPOLI-3). The unblinded nature of the trial may have introduced detection bias in the measurement adverse events outcomes.
- Based on post hoc analyses, there were statistically significantly more patients in the NALIRIFOX arm who reported all-cause and drug-related TEAEs leading to interruption of the treatment regimen (OR 4.24; 95% CI 1.40, 12.80 and OR 4.20; 95% CI: 1.18, 15.01, respectively) and drug-related serious adverse events (OR 1.54; 95% CI: 1.09, 2.17). The safety profiles of NALIRIFOX and Gem+NabP appear to be different, with more Gastrointestinal disorder (diarrhoea, nausea and vomiting) and Metabolism and nutrition disorder (decreased appetite, and hypokalaemia) drug-related Grade 3-4 TEAEs, as well as drug-related Grade 3-4 asthenia, reported in the NALIRIFOX arm, and more Blood and lymphatic system disorder (neutropenia, anaemia, thrombocytopenia, leukopenia and WBC count decreased) Grade 3-4 TEAEs in the Gem+NabP arm.

6.56 The PSCR noted the following statement regarding comparable safety between NALIRIFOX and Gem+NabP in the TGA Delegate’s Overview): it has “a similar level of toxicity overall, and a toxicity profile that is acceptable in the context of this fatal disease and the toxicities of existing therapeutic options.” However, the ESC considered that the higher incidence of Grade  $\geq 3$  diarrhoea was clinically relevant in this population because it presents a risk to the elderly and unwell, and is a reason that the use of NALIRIFOX (like FOLFIRINOX) will likely be limited to younger, fitter patients. The PBAC considered that severe diarrhoea was a significant concern for this population (see paragraph 7.9).

6.57 The PBAC considered that the claim of superior comparative effectiveness of NALIRIFOX versus Gem+NabP was supported by the data, based on statistically significant improvements in PFS and OS for NALIRIFOX patients in NAPOLI-3, although the magnitude was small and may not be clinically meaningful (1.8 months for PFS, 1.9 months for OS; Table 4).

6.58 The PBAC considered that the claim of non-inferior comparative safety of NALIRIFOX versus Gem+NabP was not adequately supported by the data, noting increased rates of drug-related serious adverse events, as well as all-cause and drug-related TEAEs leading to interruption of treatment, for NALIRIFOX patients in NAPOLI-3 (Table 8). The PBAC also noted that the safety profiles of NALIRIFOX and Gem+NabP appear to be different as outlined in paragraph 6.55.

#### **NALIRIFOX versus FOLFIRINOX**

6.59 The submission claimed that NALIRIFOX is superior to FOLFIRINOX in terms of effectiveness because NALIRIFOX has a proven survival benefit over Gem+NabP, whereas FOLFIRINOX does not. This was based on the findings of three trials: NAPOLI-3

(NALIRIFOX versus Gem+NabP), MPACT (Gem+NabP versus gemcitabine) and ACCORD11/PRODIGE4 (FOLFIRINOX versus gemcitabine). The ESC considered this claim was not supported based on the evidence presented because:

- The submission's clinical claim was not supported by a robust clinical comparison but was 'inferred' on the basis that NALIRIFOX has a proven survival benefit over Gem+NabP, whereas FOLFIRINOX does not.
- Based on a naïve (unanchored) comparison, NALIRIFOX appears to have a longer median PFS compared to FOLFIRINOX (7.4 months [95% CI: 6.0, 7.7] vs 6.4 months [95% CI: 5.5, 7.2]), however, there was substantial overlap of the 95% CIs. There was no observed difference in the median OS between NALIRIFOX and FOLFIRINOX (11.1 months in both arms). A higher ORR was observed for NALIRIFOX (41.8%) compared to FOLFIRINOX (31.6%).
- The results of the multistep ITC of NALIRIFOX vs FOLFIRINOX (via common reference groups) conducted during the evaluation showed no statistically significant difference for PFS, OS or ORR (HR 1.01 [95% CI: 0.72, 1.43], HR 1.05 [95% CI: 0.76, 1.46] and OR 1.09 [95% CI: 0.49, 2.41], respectively). These ITC results appear to be consistent with the NCCN guidelines, which state that the NALIRIFOX regimen does not appear to have an advantage over FOLFIRINOX and adds considerably more expense.<sup>9</sup>
- The ESC noted that the results of a recent meta-analysis by Nichetti et al. (2024) also showed no statistically significant difference between FOLFIRINOX and NALIRIFOX for OS, PFS and ORR.

6.60 The submission claimed that NALIRIFOX is superior to FOLFIRINOX in terms of overall safety because NALIRIFOX has proven to be of similar levels of toxicity to Gem+NabP, whereas FOLFIRINOX has historically been reserved for fitter and younger patients due to its unfavourable safety profile. This claim was not supported based on the evidence presented because:

- The clinical claim was 'inferred' based on the results of studies that had different durations of follow-up (median 16.0 months for NAPOLI-3 versus 26.6 months for ACCORD11/PRODIGE4), which is likely to bias in favour of NALIRIFOX. In addition, as previously noted, there were some concerns in terms of risk of bias, including differences in trial design, setting and baseline characteristics such as age, performance status, metastatic disease burden and liver metastases. The direction and magnitude of the impact of these differences on outcome results is uncertain.
- the non-inferior safety claim against Gem-NabP was not accepted (paragraph 6.58, therefore the inference does not hold.
- The ESC noted that the results of a recent meta-analysis by Nichetti et al. (2024) suggested that NALIRIFOX was associated with lower incidence of some grade 3 or

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<sup>9</sup> NCCN Guidelines Version 1.2024 Pancreatic Adenocarcinoma (PANC-F, 5 of 12)

higher haematological adverse events compared with FOLFIRINOX (see Figure 4), however the incidence of Grade  $\geq 3$  diarrhoea may be higher with NALIRIFOX compared with FOLFIRINOX (20.3% versus 16.8%, respectively), although this did not reach statistical significance ( $p=0.35$ ).

- 6.61 The ESC also considered that the statement above that “NALIRIFOX has proven to be of similar levels of toxicity to Gem+NabP” does not represent clinical consensus. Due to its toxicity profile, NALIRIFOX like FOLFIRINOX, will likely be reserved for younger, fitter patients.
- 6.62 The PBAC considered that the claim of superior comparative effectiveness of NALIRIFOX over FOLFIRINOX was not supported by the data.
- 6.63 The PBAC considered that the claim of superior comparative safety of NALIRIFOX over FOLFIRINOX was not supported by the data.

### ***Economic analysis***

#### **Base case and alternative scenario**

- 6.64 The submission presented a stepped economic evaluation, including cost-effectiveness and cost-utility analyses versus Gem+NabP based on the results from the NAPOLI-3 trial as the base case.
- 6.65 The submission presented an alternative scenario using a mixed weighted comparator incorporating FOLFIRINOX and assuming superiority of NALIRIFOX over FOLFIRINOX. Two approaches were used for modelling the FOLFIRINOX arm of the model. The first analysis presented in the submission used FOLFIRINOX data from the OS and PFS curves from ACCORD11/PRODIGE4 presented in Conroy et al. (2011), with extrapolation of OS and PFS using the Weibull and Gompertz functions, respectively, based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) assessments. The effect of the application of results for FOLFIRINOX as reported by Conroy 2011 is that it indirectly assumes that FOLFIRINOX is superior to Gem+NabP (consistent with Table 5 and Table 6).
- 6.66 A second analysis proposed by the submission assumed non-inferiority of FOLFIRINOX to Gem+NabP and used the OS and PFS curves for Gem+NabP from the NAPOLI-3 trial to inform the FOLFIRINOX arm of the model. The ESC noted the limitations of the data available to assess the comparative effectiveness and safety of FOLFIRINOX and Gem+NabP, however for the purposes of economic modelling, considered it was reasonable to consider that FOLFIRINOX was more effective than Gem+NabP based on the evidence presented in the commentary (Table 5, Table 6) and consistent with the meta-analysis published by Nichetti 2024. The ESC noted that conflicting evidence was reported in the abstract and presentation slides of the GENERATE study, which appeared to favour Gem+NabP in comparison with FOLFIRINOX for OS, however there was insufficient information available to assess the study (see paragraph 6.7).

6.67 A summary of the key components of the economic evaluation is presented in Table 13.

**Table 13: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	Submission base case: NALIRIFOX vs. Gem+NabP Alternative scenario (mixed weighted comparator): NALIRIFOX vs. Gem+NabP vs. FOLFIRINOX
Time horizon	5 years in the model base case versus 16.1 months (median follow-up) in trial
Discounting	5% per annum (applied to outcomes and end-of-life costs) Drug and drug administration costs, costs of subsequent therapies and costs of treating AEs were applied as a one-off cost at the start of the model, therefore not discounted.
Outcomes	Quality-adjusted life-years gained Life-years gained
Health states	Free of progression Progressed Dead
Methods used to generate results	Partitioned survival analysis model. The model was informed by PFS and OS time-to-event data from the NAPOLI-3 trial which determined the distribution of patients across the three health states.
Extrapolation method	OS and PFS KM data from the NAPOLI-3 trial were truncated at selected time points where 10% of patients remain at risk. Parametric models were fit to the data from these time points and extrapolated over the 5-year time horizon. The selection for best fitting curve was based on AIC and BIC assessments.  The submission assumed a constant and continuous treatment effect for both endpoints (assuming proportional hazards assumptions were met).  23% of QALYs (and 13% of costs) for the NALIRIFOX arm and 30% of QALYs (11% of costs) for the Gem+NabP occur in the extrapolated period. About 45% of incremental LYs were accrued in the extrapolated period.
Cycle length	28 days
Health related quality of life	EQ-5D-5L data from the NAPOLI-3 trial were used to inform the utility values for the Free of Progression and Progressed health states. Sensitivity analyses were based on published results (SIEGE trial and Romanus 2012). Disutilities related to AEs for each of the treatment arms were based on TEAE rates from the NAPOLI-3 trial and average disutility values from literature (Takumoto et al, 2022; Attard et al, 2014; Tam et al, 2013).
Costs related to subsequent anticancer therapy	Current PBS restriction does not allow for the use of NabP second- or subsequent-line and nal-IRI is not PBS-listed; therefore, the submission applied the lower cost PBS-listed paclitaxel and irinotecan as substitutes, and actual costs of these medications were tested in sensitivity analysis.
Costs related to AE management	Clinician advice was sought to inform the management of AEs and these were costed in accordance with the recommendations of the PBAC Manual of Resource Items and their Associated Costs.

Source: Compiled during the evaluation using data from Table 46, p111 of the submission Sections 3.4, 3.5 and 3.6

Abbreviations: AEs, adverse events; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; EQ-5D-5L, EuroQol 5-dimension health status questionnaire (5 level); FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; KM, Kaplan-Meier; NabP, nanoparticle albumin-bound paclitaxel; nal-IRI, nanoliposomal irinotecan; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid; OS, overall survival; PBAC; Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PFS, progression-free survival; QALYs, quality-adjusted life years; TEAE, treatment emergent adverse event

6.68 The model relied on the PFS and OS time-to-event data from the NAPOLI-3 trial to determine the distribution of patients across the health states. Although the trial

results indicate an overall improved survival with NALIRIFOX compared to Gem+NabP (HR of 0.834; 95% CI, 0.705, 0.988), the 95% CI had an upper limit that is very close to 1. This measure of uncertainty is not reflected in the results presented, and therefore results should be interpreted with caution. The ESC acknowledged that while the approach taken was reasonable and consistent with PBAC guidelines, the use of KM data and extrapolations do not implicitly capture uncertainty with regard to the treatment effect. The ESC noted that more conservative extrapolation approaches were tested in sensitivity analyses.

- 6.69 The submission applied a time horizon of 5 years. The duration of the time horizon is long relative to the NAPOLI-3 trial duration (median follow up of 16.1 months) and for the type of cancer considered (3-year net survival for distant cancers reported to be 4%, Cabasag et al. 2022). The ESC noted that when the PBAC considered NabP in March 2014, the NabP submission used the time horizon directly from the trial data (3.6 years in the treatment arm and 2.9 years in the comparator arm). The ESC considered that a shorter time horizon of 3 to 4 years may be appropriate for the current submission, however noted that reducing the time horizon to 3 years had minimal impact on the ICER.

#### **Extrapolation time points**

- 6.70 The submission applied the KM data from the NAPOLI-3 trial for both PFS and OS up until the point where 10% of patients remained at risk (Pocock et al, 2002). Based on this, the NALIRIFOX OS and PFS KM functions were used for 19 (17.5 months) and 16 (14.7 months) cycles, respectively, and the Gem+NabP OS and PFS KM functions were used for 18 (16.6 months) and 11 (10.1 months) cycles, respectively. Parametric models were fitted to the data from these time points and extrapolated over the 5-year time horizon.
- 6.71 The submission's nominated time points resulted in the exclusion of a substantial number of patients (77 out of 770 patients in the NAPOLI-3 trial) from the base case analysis. These time points also represented those where the observed incremental difference for OS was the largest (i.e. the widest gap between the KM curves) which favoured NALIRIFOX. The ICER was sensitive to the time point selected, and the selected extrapolation point (10%) was associated with the most favourable ICER compared to the 5% and 15% timepoints tested in sensitivity analyses.
- 6.72 Using an approach from GebSKI et al, 2018<sup>10</sup>, the optimal time points for commencing extrapolation with sufficient number of patients at risk for meaningful interpretation of the KM plot would be Cycle 24 for OS and Cycle 18 for PFS. These timepoints were tested during the evaluation (Table 17) and the ICER increased to \$35,000 to < \$45,000/quality-adjusted life year (QALY) gained (+15% increase from base case). The ESC considered the GebSKI approach to be a more robust method for determining

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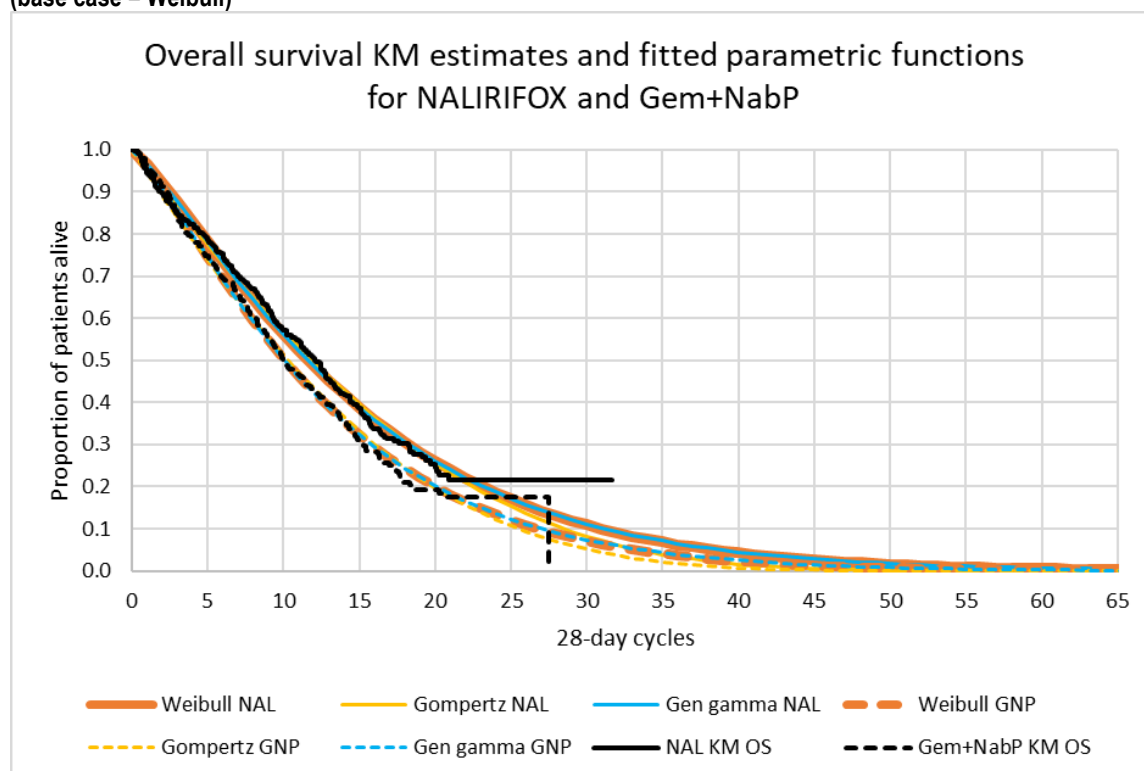
<sup>10</sup> GebSKI et al. "Data maturity and follow-up in time-to-event analyses." *International journal of epidemiology* 47.3 (2018): 850-859.

extrapolation points within the model for PFS and OS. The Pre-PBAC response noted that extending the KM data used in the model to 24 cycles, as proposed in the ESC advice, resulted in a switch from the KM data at a point where only 6 (1.6%) and 7 (1.8%) patients remain at-risk in the NALIRIFOX and Gem+NabP arms, respectively. The Pre-PBAC response noted that the result of this change is that the model assumes a plateau in the survival curve from Cycle 21 to Cycle 24, suggesting that no patients die in either arm for a period of approximately 3 months.

### **Extrapolation of OS**

- 6.73 The submission assumed a constant and continuous treatment effect for the OS end point for the full horizon of the model based on the conclusion that the proportional hazards assumption was not violated.
- 6.74 The submission applied the Weibull function to extrapolate the OS survival curve based on AIC and BIC assessments. The AIC and BIC values for the Weibull, Gompertz and Generalised gamma functions were very similar. The commentary noted that the selected Weibull function may be plausible, however it did not necessarily fit the data well. Considerations of clinical plausibility were not discussed in the submission. One of the key differences between the Weibull, Gompertz and Generalised Gamma functions was the degree of narrowing between the intervention and comparator curves (Figure 5). Gompertz produced a more conservative approach with an obvious narrowing of the curves and that reached zero by Cycle 61 (compared to Cycles 102 for Weibull and 107 for Generalised gamma) which is likely to be more clinically plausible. The choice of the parametric function used for the extrapolation of OS is an important driver of the ICER (Table 17). The PSCR stated that the application of a Gompertz function for extrapolation of OS was inappropriate as it was statistically not the best fitting model. The ESC agreed with the commentary that the Gompertz extrapolation provided more clinically plausible OS outcomes, as it reached zero by Cycle 61 compared with Cycle 102 for Weibull. The pre-PBAC response disagreed with the ESC's advice regarding extrapolation function for the OS survival curve, maintaining that the Weibull function was most appropriate based on AIC and BIC.

Figure 5: Extrapolation of OS in the NALIRIFOX and Gem+NabP treatment arms using different parametric function (base case = Weibull)



Source: Tab 'OS extrapolation 28-day' Attachment 8 of the submission

Abbreviations: Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; GNP, gemcitabine and (nab-) paclitaxel; NAL, NALIRIFOX; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; OS, overall survival; KM, Kaplan-Meier.

### Extrapolation of PFS

- 6.75 The submission assumed a constant and continuous treatment effect for the PFS end point for the full horizon of the model based on their conclusion that proportional hazards assumption was not violated.
- 6.76 The submission applied the Weibull function to extrapolate the PFS curve based on AIC and BIC assessments. The comparisons of the parametric functions and the KM data from NAPOLI-3 presented by the submission were difficult to interpret. Based on visual inspection, the best fitting curves appear to be the Weibull, Gompertz and Generalised gamma functions. The choice of parametric function for the PFS was not identified to be an important driver of the ICER (Table 17).

### Model inputs and extrapolation of OS and PFS for FOLFIRINOX

- 6.77 The submission presented two analyses based on assumptions made on the clinical claims of FOLFIRINOX against Gem+NabP, as discussed in paragraph 6.65.
- 6.78 In the analysis where the submission considered FOLFIRINOX is superior to Gem+NabP (aligned with the clinical data in Table 5 and Table 6), the submission utilised the OS and PFS curves as presented in Conroy et al, 2011 and applied the Weibull function for OS and Gompertz function for PFS based on AIC and BIC assessments (alternative

scenario 1). None of the selected and tested parametric functions fit the data well, thus the reliability of the extrapolation and impact on the results is highly uncertain.

- 6.79 The submission also presented an analysis that considered FOLFIRINOX is non-inferior to Gem+NabP, which assumed that the Gem+NabP OS and PFS curves from NAPOLI-3 are directly applicable to the FOLFIRINOX arm (alternative scenario 2), i.e. the analysis assumed that FOLFIRINOX was non-inferior to Gem+NabP. The ESC considered that alternative scenario 2 was not informative for decision making (see paragraph 6.66). It was noted that incremental QALYs calculated in alternative scenario 2 exceeded the incremental QALYs calculated in the submission's base case (Table 17), due to the use of Gem+NabP OS and PFS data from the NAPOLI-3 trial (as in submission base case), with an additional QALY gain due to reduced AEs for FOLFIRINOX patients (derived from Conroy et al, 2011).

### Health state utility values

- 6.80 Quality-of-life data using EQ-5D-5L from the NAPOLI-3 trial were used to inform the utility values for the Free of Progression and Progressed health states for the base case analysis. The submission did not describe from which time points the utility values from the NAPOLI-3 trial were derived and how these were used to inform the utility values for the health states; however, the PSCR clarified that the Free of Progression health state utility value was the averaged utility observed at visits prior to the date of progression while Progressed health state was the averaged utility observed at visits after date of progression. The ESC noted these values were unpublished and were not able to be externally verified. The utility values applied for the base case analysis were higher than those available from the literature<sup>11,12</sup> and those reported at baseline and end of treatment in the NAPOLI-3 trial. The difference between Free of progression and Progressed values was larger (0.07) in the base case than those in literature (range from 0.04 to 0.07). These comparisons and utility values used in the economic evaluation are presented in Table 14. The ESC noted that utility values were as an important driver of the ICER, however considered that the use of trial-based utilities as described in the PSCR was appropriate.

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<sup>11</sup> NICE's HTA assessment of Gem+NabP for untreated mPAC

<sup>12</sup> Yoo et al. "Health-Related Quality of Life of Patients with Metastatic Pancreatic Cancer: A Systematic Literature Review." *Cancer Management and Research* (2022): 3383-3403.

Table 14 : Utility values used in the economic evaluation and comparisons to trial and literature

	Base case		Used in sensitivity analyses	
<b>Applied in the economic evaluation</b>				
Health state	NAPOLI-3	SEIGE trial <sup>a</sup> – Devlin value set	SEIGE trial <sup>a</sup> – crosswalk method	Romanus 2012 <sup>b</sup> – UK adjustment
Free of progression	0.85	0.79	0.70	0.74
Progressed	0.78	0.75	0.65	0.67
Differences between health states	0.07	0.04	0.05	0.07
<b>Comparison to trial and literature</b>				
As reported in NAPOLI-3 trial	NALIRIFOX		Gem+NabP	
Baseline, mean (SD)	0.803 (0.1266)		0.804 (0.1350)	
End of treatment, mean (SD)	0.747 (0.1846)		0.754 (0.2047)	
Change from baseline to end of treatment, mean (SD)	-0.063 (0.1852)		-0.080 (0.2184)	
Literature	Yoo et al, 2022		Takumoto et al, 2022	
	Newly diagnosed	0.46 to 0.75	Stable health state without AEs	0.468 to 0.634
	Previously treated	0.72	Progressive disease	-0.119 to 0.112

Source: Table 52, p135 of the submission and added to during the evaluation

Abbreviations: Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; SD, standard deviation; UK, United Kingdom.

<sup>a</sup> The SEIGE trial was a Phase II, dose-scheduling trial of Gem+NabP with EQ-5D-5L data captured over a period of 12 months.

<sup>b</sup> Romanus et al, 2012 was a health-related quality of life study of US patients with advanced pancreatic cancer deemed not appropriate for surgical resection. Utility values adjusted to the UK population were from NICE’s assessment of Gem+NabP.

6.81 Disutilities associated with AEs from each of the treatment arms were included in the economic model as a one-off QALY loss. The incremental QALY loss applied for NALIRIFOX vs Gem+NabP was -0.0006, and for NALIRIFOX vs FOLFIRINOX was 0.0074. These were estimated based on:

- Averaged reported disutility values from three publications (Takumoto et al, 2022; Attard et al, 2014; Tam et al, 2013).
- TEAE event rates from the NAPOLI-3 trial to inform the NALIRIFOX and Gem+NabP arms (and Conroy et al, 2011 to inform the FOLFIRINOX arm for the alternative scenario).
- Duration of AEs from responses to a clinician survey. No further information regarding the nature of the survey, type and number of clinicians surveyed, method of collecting and collation of data was provided, contrary to recommendations in Appendix 1 of the PBAC Guidelines.

6.82 Given that the utility values from patients in the NAPOLI-3 trial were used to inform the base case analysis, it would be inappropriate to include disutility related to AEs because these would likely have been captured within the trial and would result in double counting. This was tested during the evaluation and removal of AE-related disutility had a small impact on the ICER (< 1% change).

## **Costs**

- 6.83 The costs of first-line drug and administration costs were based on regimens administered to patients in the NAPOLI-3 trial (and Conroy et al, 2011 for FOLFIRINOX), the average number of treatment cycles reported, and relevant PBS and Medicare Benefits Schedule (MBS) listed costs. This was appropriate.
- 6.84 The submission also included costs of subsequent systemic anticancer therapies as reported in the NAPOLI-3 trial, which includes the use of Gem+NabP, NabP monotherapy and nal-IRI. Given that these medications are not PBS-listed for subsequent-line therapy, the submission applied the lower cost PBS-listed paclitaxel and irinotecan as substitutes. This adds uncertainty to the analysis because the treatment effect of the use of subsequent therapies was captured within the OS outcome, but the costs were underestimated. In the NAPOLI-3 trial, more patients in the NALIRIFOX arm (33%) received subsequent treatment with Gem+NabP and NabP monotherapy compared with patients in the Gem+NabP arm (12%).
- 6.85 Overall, the cost of subsequent therapies was not identified to be an important driver of the ICER. However, in a scenario presented in the submission where nal-IRI and NabP were available for use as subsequent therapies, the ICER increased to \$35,000 to < \$45,000 per QALY gained (+17%) from the base case. This indicates that the ICER is likely sensitive to the cost of the drugs, specifically nal-IRI and NabP, which are substantially more expensive compared to the other chemotherapy drugs.
- 6.86 The economic evaluation incorporated the costs associated with Grade 3 or 4 TEAEs as reported from the NAPOLI-3 trial. The cost per AE was multiplied by the difference in the proportion of patients experiencing each AE across treatment arms to estimate the overall cost, and applied this as a one-off cost. The submission estimated that the cost of managing AEs was \$1,651.43 for the NALIRIFOX treatment group and \$1,495.85 for the Gem+NabP treatment group.
- 6.87 The commentary considered that the estimates were mostly reasonable except for the costs of managing Grade 3 to 4 diarrhoea and mucosal inflammation which was substantially underestimated. The PSCR suggested that not all patients experiencing diarrhoea and mucosal inflammation due to treatment are hospitalised for these events, however did not acknowledge that only Grade 3 and 4 events were costed in the economic model. The ESC noted that the ICER was sensitive to this cost, and advised that the alternative AE costs provided in the evaluation should be applied. The pre-PBAC response disagreed with the proposed amendment to the AE costs for diarrhoea and mucosal inflammation. The pre-PBAC response stated that a more reasonable assumption could be that 50% of patients with Grade 3 mucosal inflammation are hospitalised (derived from is DRG G70) which would result in the application of a cost of \$1,689.32 (= \$3,378.63 x 50%) to the proportion of patients experiencing Grade 3 mucosal inflammation in the economic model.
- 6.88 A summary of the key drivers of the model is provided in the Table 15.

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Table 15: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ [redacted] <sup>1</sup> /QALY gained
Including FOLFIRINOX as secondary comparator <sup>a</sup>	About 11% of patients in Australia receive FOLFIRINOX as first-line treatment. <sup>13</sup> FOLFIRINOX and NALIRIFOX are both fluoropyrimidine-based regimens (only difference being the preparation of irinotecan) and likely to be used for treatment of similar types of patients (younger, better ECOG performance status, less comorbid). The ESC agreed with the commentary that FOLFIRINOX is a relevant comparator.	High, favours NALIRIFOX.  Incorporating 10% use of FOLFIRINOX increases the ICER to \$ [redacted] <sup>2</sup> /QALY gained (+27%) <sup>c</sup> .  Alternative assumptions are explored in sensitivity analyses, see below.
Utilities	From NAPOLI-3 trial. Free of progression: 0.85; Progressed: 0.78  The utility values applied for the base case analysis were higher than those available from the literature and those reported at baseline and end of treatment in the NAPOLI-3 trial (Table 14).	High, favours NALIRIFOX.  Use of utility values from the SEIGE trial <sup>b</sup> (crosswalk method) increased the ICER to \$ [redacted] <sup>2</sup> /QALY gained (+22%).
Extrapolation time points for OS (and PFS)	Point of extrapolation set to point where 10% of patients remained at risk (cycle 19 for NALIRIFOX and 18 for Gem+NabP). The selected truncation points were earlier than those suggested by methodological studies and excluded 77 out of 770 patients from the base case analysis. It also represented the time points where the observed incremental difference for OS was the largest; i.e. widest gap between the KM curves.  The ESC noted that using the Gebski approach, the optimal time points for commencing extrapolation with sufficient number of patients at risk for meaningful interpretation of the KM plot would be Cycle 24 for OS and Cycle 18 for PFS.	High, favours NALIRIFOX.  Use of OS: Cycle 24; PFS: Cycle 18 <sup>a</sup> increased the ICER to \$ [redacted] <sup>2</sup> /QALY gained (+15%).
OS parametric function	Weibull selected based on AIC and BIC. The Gompertz function has similar AIC and BIC values and is considered more conservative and clinically plausible.	High, favours NALIRIFOX.  Using the Gompertz function increases the ICER to \$ [redacted] <sup>2</sup> /QALY gained (+16%). The ESC considered the Gompertz extrapolation provided more clinically plausible OS outcomes compared with Weibull.

Source: Compiled during the evaluation based on Section 3.9 of the submission

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid; OS, overall survival; QALY, quality-adjusted life year; 5-FU, 5-fluorouracil.

<sup>a</sup> Using a mixed (weighted) comparator approach

<sup>b</sup> The SEIGE trial was a Phase II, dose-scheduling trial of Gem+NabP with EQ-5D-5L data captured over a period of 12 months.

<sup>c</sup> Assuming FOLFIRINOX is superior to Gem+NabP

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$35,000 to < \$45,000

6.89 A summary of the results of the stepped economic analysis is presented in Table 16.

<sup>13</sup> Lee, B, (2023), 'Use of Metastatic Pancreatic Cancer Treatment Algorithms in Routine Clinical Practice in Australia - a PURPLE Translational Registry study'

Table 16: Results of the stepped economic evaluation

Data	Costs (\$)			Health outcomes			Incremental cost-effectiveness ratio
	NALIRIFOX	Gem+NabP	Incremental	NALIRIFOX	Gem+NabP	Incremental	
Step 1: Trial based analysis	Drug and administration costs, costs of subsequent therapies and treating AEs			Life years			
	■	■	■	1.0976 LYs	0.9279 LYs	0.1697 LYs	■ <sup>1</sup> / LY gained
Step 2: Modelled analysis (LYs) <sup>a</sup>	As above plus cost of end-of-life care			Discounted life years			
	■	■	■	1.0977 LYs	0.9359 LYs	0.1618 LYs	■ <sup>1</sup> / LY gained
Step 3: Modelled analysis (QALYs) <sup>a</sup>	As above			Transformation using utility values			
	■	■	■	0.8972 QALYs	0.7584 QALYs	0.1388 QALYs	■ <sup>1</sup> / QALY gained

Source: Table 58, p151 of the submission

Abbreviations: AEs, adverse events; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; ICER, incremental cost-effectiveness ratio; LY, life-year; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; QALYs, quality-adjusted life-years.

<sup>a</sup> Time horizon of 5 years

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

6.90 The results of the economic evaluation should be interpreted with caution because:

- The NALIRIFOX and Gem+NabP OS curves from the NAPOLI-3 trial had substantial overlap in their 95% CI and this measure of uncertainty is not reflected in the results presented.
- The selective extrapolation of time points and underestimation of the cost of managing AEs favours NALIRIFOX.
- The presumed constant treatment effect over time (uncertainty in meeting proportional hazards assumption) favours NALIRIFOX.
- There was uncertainty in how utility values for the health states were derived from the NAPOLI-3 trial, and these were higher than those reported in the literature. This favours NALIRIFOX.
- There was uncertainty in the therapeutic claim of superior effectiveness of NALIRIFOX over FOLFIRINOX, which has an impact on how FOLFIRINOX is modelled.

6.91 These results were based on the published prices of the comparators. The results of key univariate and multivariate sensitivity analyses are summarised in Table 17.

6.92 The ESC advised that a multivariate sensitivity analysis would be informative, including the following changes to the economic model: 1) revising the truncation points for OS and PFS (see paragraph 6.72; 2) applying the Gompertz function for OS extrapolation (see paragraph 6.74); and 3) revising the AE costs for diarrhoea and mucosal inflammation (see paragraph 6.87); 4) applying a mixed comparator approach based on alternative scenario 1 assuming FOLFIRINOX efficacy from Conroy 2011. Results are provided in Table 17 assuming proportions of use for FOLFIRINOX, ranging from 0% to 100%.

6.93 The ESC also noted that the superiority of NALIRIFOX over FOLFIRINOX in terms of effectiveness had not been demonstrated (see paragraph 6.59). Thus, a cost-minimisation approach could be considered for the proportion of patients where FOLFIRINOX is replaced (instead of step 4 above). The ESC noted that the proposed drug cost per patient treated with NALIRIFOX was approximately four times the corresponding cost for FOLFIRINOX (\$| compared with \$|; Table 18). It was noted that the meta-analysis by Nichetti et al. (2024) had suggested some differences in AE profiles of NALIRIFOX and FOLFIRINOX, however the comparative safety claim had not been supported by the evidence presented in the submission (see paragraph 6.60). The ESC advised it may be relevant to consider differential costs for AEs if adequately supported by clinical evidence.

Table 17: Sensitivity analyses

Variables altered in the sensitivity analysis	Incremental costs (\$)	Incremental QALYs	ICER /QALY gained	Change to ICER
<b>Base case</b>		0.1388	■ <sup>1</sup>	-
<b>Discount rate (base case = 5%)</b>				
• 0%		0.1464	■ <sup>1</sup>	-■%
• 3.5%		0.1410	■ <sup>1</sup>	-■%
<b>Time horizon (base case = 5 years)</b>				
• 3 years		0.1274	■ <sup>1</sup>	-■%
• 4 years		0.1363	■ <sup>1</sup>	-■%
<b>Utility weights (base case = NAPOLI-3 EQ-5D-5L UK)</b>				
• Romanus 2012 UK		0.1210	■ <sup>2</sup>	+■%
• SEIGE trial – Devlin value set		0.1283	■ <sup>1</sup>	+■%
• SEIGE trial - crosswalk		0.1140	■ <sup>2</sup>	+■%
<b>OS extrapolation function (base case = Weibull)</b>				
• Generalised gamma		0.1399	■ <sup>1</sup>	-■%
• Gompertz		0.1221	■ <sup>2</sup>	-■%
<b>OS switch from KM to model (base case = 10% patients at-risk)</b>				
• 5% patients at-risk		0.1236	■ <sup>2</sup>	+■%
• 15% patients at-risk		0.1182	■ <sup>2</sup>	+■%
• OS: Cycle 24; PFS: Cycle: 18 <sup>a</sup>		0.1216	■ <sup>2</sup>	+■%
<b>Subsequent therapy (base case = PBS-listed regimens only)</b>				
• Subsequent therapies exactly as observed in NAPOLI-3 regardless of PBS-listings		0.1388	■ <sup>2</sup>	+■%
<b>Revised costs of AEs</b>				
• Hospitalisation costs to manage diarrhoea and mucosal inflammation <sup>b</sup>		0.1388	■ <sup>2</sup>	+■%
<b>Alternative scenario 1 with FOLFIRINOX as secondary comparator in the indicated percentage assuming FOLFIRINOX efficacy from Conroy 2011 (indirectly assumes FOLFIRINOX is superior to Gem+NabP, and that NALIRIFOX is superior to FOLFIRINOX and Gem+NabP) (base case = 0%)</b>				
• 5% of use in FOLFIRINOX		0.1357	■ <sup>2</sup>	+■%
• 10% of use in FOLFIRINOX		0.1326	■ <sup>2</sup>	+■%
• 15% of use in FOLFIRINOX		0.1295	■ <sup>2</sup>	+■%
• 25% of use in FOLFIRINOX		0.1233	■ <sup>3</sup>	+■%
• 50% of use in FOLFIRINOX		0.1077	■ <sup>4</sup>	+■%

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Variables altered in the sensitivity analysis	Incremental costs (\$)	Incremental QALYs	ICER /QALY gained	Change to ICER
• 75% of use in FOLFIRINOX		0.0921	<sup>5</sup>	+ %
• 100% of use in FOLFIRINOX		0.0765	<sup>6</sup>	+ %
<u>Alternative scenario 2 with FOLFIRINOX as secondary comparator in the indicated percentage applying FOLFIRINOX efficacy from Gem+NabP arm of NAPOLI-3 (assumes FOLFIRINOX is non-inferior to Gem+NabP, and that NALIRIFOX is superior to FOLFIRINOX and Gem+NabP) (base case = 0%)</u>				
• 5% of use in FOLFIRINOX		0.1392	<sup>1</sup>	+ %
• 10% of use in FOLFIRINOX		0.1396	<sup>2</sup>	+ %
• 100% of use in FOLFIRINOX		0.1469	<sup>4</sup>	+ %
<b>Multivariate sensitivity analysis</b>				
<b>ESC respecified base case</b>				
1) Revised truncation points at cycles 24 (OS) and 18 (PFS) per GebSKI approach;				
2) Gompertz for OS extrapolation; and				
3) Revised AE costs (Diarrhoea=(\$3,219.92; Mucosal inflammation (stomatitis)= \$13,283.46)				
4) Alternative scenario 1 with FOLFIRINOX as secondary comparator in the indicated percentage assuming FOLFIRINOX efficacy from Conroy 2011 (indirectly assumes FOLFIRINOX is superior to Gem+NabP)				
• 0% of use in FOLFIRINOX		0.1092	<sup>3</sup>	+ %
• 50% of use in FOLFIRINOX		0.0849	<sup>5</sup>	+ %
• 100% of use in FOLFIRINOX		0.0606	<sup>6</sup>	+ %

Source: Table 60, p154 of the submission, Table 13 of Appendix A and added to from results and analyses conducted during the evaluation the submission's economic model (Attachment 8)

Abbreviations: AEs, adverse events; ICER, incremental cost-effectiveness ratio; EQ-5D-5L, EuroQol 5-dimension health status questionnaire (5 level); FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; KM, Kaplan-Meier; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid; OS, overall survival; PBS, Pharmaceutical Benefits Scheme; PFS, progression-free survival; QALY, quality-adjusted life-year; UK, United Kingdom.

<sup>a</sup> Using GebSKI's approach described in paragraph 6.72.

<sup>b</sup> Based on DRG G67 and DRG G03C from NHCD Cost weights AR-DRG version 11.0 (2020-21).

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$35,000 to < \$45,000

<sup>3</sup> \$45,000 to < \$55,000

<sup>4</sup> \$75,000 to < \$95,000

<sup>5</sup> \$95,000 to < \$115,000

<sup>6</sup> \$155,000 to < \$255,000

6.94 The pre-PBAC response presented a respecified base case corresponding to an ICER of \$35,000 to < \$45,000/QALY. The pre-PBAC response applied the following: 1) Switch from KM data to parametric extrapolation for OS when 10% of patients remain at-risk (as for submission base case); 2) Weibull parametric function used for OS extrapolation (as for submission base case); 3) Revised AE costs for mucosal inflammation as discussed in paragraph 6.87; 4) FOLFIRINOX as the comparator in 10.9% of patients; 5) FOLFIRINOX has non-inferior efficacy compared to Gem+NabP (as used in Alternative scenario 1 as shown in Table 17); 6) Folinic acid (Leucovorin) applied at a flat dose of 50 mg instead of BSA-based dosing (400 mg/m<sup>2</sup>) based on EViQ advice.

6.95 The pre-PBAC response acknowledged that NALIRIFOX could substitute for FOLFIRINOX in some patients, however, the extent to which FOLFIRINOX is included in the economic analysis should be limited to the extent to which it is used in practice.

The pre-PBAC response stated that FOLFIRINOX is used in 10.9% of patients in the first-line setting based on data from the PURPLE registry (Lee 2023).

- 6.96 The pre-PBAC response claimed that NALIRIFOX can be used first-line in elderly as well as younger patients with mPAC. It was stated that NALIRIFOX is associated with a lower risk of Grade 3 or 4 neutropenia, leukopenia, anaemia and thrombocytopenia than Gem+NabP and FOLFIRINOX, and over 50% of patients recruited to the NAPOLI-3 trial were aged  $\geq 65$  years (up to 85 years). The PBAC did not agree with the claim in the pre-PBAC response that NALIRIFOX can be used first-line in a majority of elderly patients, because it considered that in many cases elderly or frail patients would not be suitable for treatment with NALIRIFOX due to its toxicity profile.

### Drug cost/patient/course

- 6.97 A summary of the drug cost per course is presented in Table 18.

Table 18: Drug cost per patient for proposed and comparator drugs<sup>a</sup>

	NALIRIFOX			Gem+NabP			FOLFIRINOX		
	Trial [NAPOLI]	Model	Financial estimates	Trial [NAPOLI]	Model	Financial estimates	Trial [Conroy]	Model	Financial estimates
Mean dose/vials (per cycle)	nal-IRI: 78 mg <sup>b</sup>	nal-IRI: 2.1 vials <sup>c</sup>	nal-IRI: 2.1 vials	Gem: 1611 mg NabP: 192 mg <sup>b</sup>	Gem: 0.1 vial (1000 mg); 0.9 vial (2000 mg) NabP: 2.2 vial <sup>c</sup>	Gem: 0.1 vial (1000 mg); 0.9 vial (2000 mg) NabP: 2.2 vial	NR <sup>f</sup>	IRI: 0.4 vial (40 mg); 2.7 vials (100 mg) <sup>g</sup>	IRI: 0.4 vial (40 mg); 2.7 vials (100 mg) <sup>g</sup>
Mean number of cycles	6.5	6.5	6.5	5.1	5.1	5.1	5 <sup>e</sup>	5 <sup>e</sup>	5 <sup>e</sup>
Cost/patient/cycle <sup>d</sup> (\$)	■	■	■	■	■	■	■ <sup>h</sup>	■	■
Cost/patient/course <sup>d</sup> (\$)	■	■	■	■	■	■	■	■	■

Source: Table 26, pp 156-157 of the trial report, Section 3 workbook, sheet 3a of the utilisation-and-cost-model.

Abbreviations: Gem, gemcitabine; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; IRI, irinotecan; NabP, nanoparticle albumin-bound paclitaxel; nal-IRI, nanoliposomal irinotecan; NR, not reported.

<sup>a</sup> As calculated in the submission

<sup>b</sup> Mean dose intensity of 88% for nal-IRI, 90% for Gemcitabine and 85% for NabP provided in 'Exposure data' in Attachment 8 of the submission

<sup>c</sup> As presented in 'Vial calculation' in Attachment 8 of the submission.

<sup>d</sup> Cost for the treatment regimen

<sup>e</sup> Adjusted to 28-day cycles

<sup>f</sup> Reports a relative dose intensity of fluorouracil, irinotecan, oxaliplatin to be 82%, 81% and 78% respectively

<sup>g</sup> Based on dose intensity as per NAPOLI-3 trial

<sup>h</sup> Calculated based dosing regimen, relative dose intensity as reported in Conroy et al, 2011 and BSA, AEMP, markup and public/private weighting as presented in the submission

### Estimated PBS usage & financial implications

- 6.98 This submission was not considered by DUSC.
- 6.99 The submission used an epidemiological approach to estimate the financial implications associated with the proposed listing of nal-IRI.

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6.100 A summary of the key inputs in the financial analysis are summarised in Table 19.

Table 19: Key inputs for financial estimates

Parameter	Value applied and source	Comment
<b>Eligible population</b>		
Incident patients – pancreatic cancer	█ <sup>1</sup> in Year 1, increasing to █ <sup>2</sup> in Year 6 AIHW Cancer incidence data 2023	Annual growth rate assumed to be 4% beyond 2023.
Incident patients – metastatic pancreatic cancer	80% applied annually Santucci 2022, PURPLE Registry, Cancer Council 2022, Loveday 2019, Malik 2012, Puckett 2022	The evaluation considered this may be overestimated as the submission used the term 'metastatic' in the financial impact estimates to include those with Stage III (locally advanced/unresectable) and Stage IV (metastatic) pancreatic cancer. Not all patients with Stage III disease would progress to Stage IV disease. The ESC considered that most patients with Stage III disease would progress to Stage IV disease and that the estimated see value was reasonable.
Treatment rate – metastatic pancreatic cancer	57.3% applied annually Santucci 2022, PURPLE Registry	The commentary considered this was reasonable. The PSCR emphasised that the estimates include a variable which separately calculates the proportion of patients who opt for chemotherapy treatment based on data from the PURPLE registry, and that the population was not overestimated.
<b>Treatment utilisation</b>		
Uptake rate (world without 1L NALIRIFOX)	Gem+NabP - █%; Gemcitabine (mono) - █%; FOLFIRINOX - █%; Other 1L tx - █%. Santucci 2022, PURPLE Registry	The commentary considered this was reasonable.
NALIRIFOX uptake/substitution rates	Gem+NabP - █% in Year 1, █% in Year 2 and █% in Years 3-6; Gemcitabine (mono) - █%; FOLFIRINOX - █%; Other 1L tx - █%. Assumption	The submission estimates of substitution from Gem+NabP to NALIRIFOX are uncertain and likely to be high given the toxicity profile of NALIRIFOX. The submission assumed the substitution rates from other first-line treatments such as FOLFIRINOX to be █% which is unlikely. FOLFIRINOX is considered a relevant secondary comparator as data from the PURPLE registry data suggests that about 11% of patients receive FOLFIRINOX as first line treatment for mPAC in Australia.
Number treated (NALIRIFOX)	█ <sup>1</sup> in Year 1, increasing to █ <sup>1</sup> in Year 6.	Likely overestimated due to the proposed uptake rate of NALIRIFOX from Gem+NabP and the assumption relating to no FOLFIRINOX substitution.
Average duration of treatment per patient	6.5 cycles NAPOLI-3 trial	The commentary considered this was reasonable
Scripts dispensed	█ <sup>3</sup> in Year 1, increasing to █ <sup>3</sup> in Year 6. Product of NALIRIFOX treatment population by 13 (2 administrations per cycle x 6.5 cycles)	Calculation of scripts dispensed has been verified.
<b>PBS/RPBS costs</b>		
Nal-IRI	\$1,300 - Published AEMP	
	\$█ - Effective AEMP	
Average vials of nal-IRI per administration	2.13 NAPOLI-3 trial	Average number of vials per administration were based on actual doses administered in the NAPOLI-3 trial. This is appropriate.
MBS costs	\$118.30 MBS item number 13950	The commentary considered this was reasonable.

Source: Table 61, p156 of the submission; Table 62, p161 of the submission; Table 63, p162 of the submission; Section 4.5.2, p172 of the

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submission

Abbreviations: AEMP, Approved ex-manufacturer price; AIHW, Australian Institute of Health and Welfare; FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; IRI, irinotecan; MBS, Medicare Benefits Schedule; mPAC, metastatic pancreatic adenocarcinoma; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin; nal-IRI, nanoliposomal irinotecan; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; tx, treatment; 1l, first line.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 10,000 to < 20,000

6.101 The estimated use and financial implications for the PBS listing of nal-IRI are summarised in Table 20.

6.102 The submission incorrectly applied co-payments to all scripts. EFC medications should only attract a co-payment for each initial script but not repeats. Therefore, co-payment costs were overestimated. This was corrected during the evaluation. The discrepancies were small (about 1% difference).

**Table 20: Estimated use and financial implications (effective price of nal-IRI)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed <sup>a</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of nal-IRI</b>						
Cost to PBS/RPBS less co-payments	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Estimated financial implications for other medications in NALIRIFOX regimen</b>						
Cost to PBS/RPBS less co-payments	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>
<b>Estimated financial implications for substituted Gem+NabP</b>						
Cost to PBS/RPBS less co-payments	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Net cost to MBS (80%)	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Net cost to Australian Government health budget	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>

Source: Table 71, p168 of the submission; Table 74, pp170-171 of the submission; Table 76, p172 of the submission; Table 77, p174 of the submission and corrected during the evaluation to reflect the correct co-payment calculation

Abbreviations: Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; MBS, Medicare Benefits Schedule; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

<sup>a</sup> Assuming 13 scripts per year as estimated by the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 10,000 to < 20,000

<sup>3</sup> \$10 million to < \$20 million

<sup>4</sup> \$20 million to < \$30 million

<sup>5</sup> net cost saving

6.103 The submission assumed that substitution rates from Gem+NabP to NALIRIFOX would be █% in the first year, █% in the second year, and █% from Year 3 onwards. The commentary suggested that these substitution rates were overestimated. The pre-PBAC response maintained that a mature uptake/substitution rate of █% by Year 4 was reasonable and proposed that NALIRIFOX will be preferred over Gem+NabP due to

superior overall survival, progression-free survival, and associated improved quality-of-life. The PBAC considered that a substitution rate of 10% was not realistic given the toxicity profile of NALIRIFOX. NALIRIFOX is likely to be used in younger, fitter and patients with less comorbidities, as is the case with FOLFIRINOX, while Gem+NabP tends to be used in older, less fit patients. The submission assumed a substitution rate of 10% from other first-line treatments such as FOLFIRINOX (see Table 19). The ESC considered this was not appropriate as NALIRIFOX will substitute for FOLFIRINOX, and it was noted that this approach underestimated the cost of the listing, because alternative therapies such as FOLFIRINOX are less costly than Gem+NabP.

- 6.104 Table 21 presents the sensitivity analyses included in the submission and conducted during the evaluation. These include an alternative scenario using a mixed comparator approach incorporating FOLFIRINOX.

Table 21: Results of sensitivity analyses

Year	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Year 6 (2029)	Total (% change over 6 years)
<b>Net financial impact (base case)<sup>a</sup></b>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	-
<b>Uptake among Gem+NabP (base case: █% in Year 1, █% in Year 2 and █% in Years 3-6, substituted to NALIRIFOX)</b>							
30% in the first year, increasing by 20% each year until 4 years, stabilising at 90% in year 4	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	+12%
Assume constant at 50% across all years	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	-39%
<b>Proportion of pancreatic cancer patients with metastatic disease (base case: 80%)</b>							
Excluding those with Stage III disease (50%)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	-38%
Assuming half of those with Stage III disease will progress to Stage IV (65%)	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	-19%
<b>Alternative scenario with FOLFIRINOX as a secondary comparator (█% of treated population FOLFIRINOX) (base case = █%)</b>							
Uptake rate among FOLFIRINOX, █% in Year 1, █% in Year 2 and █% in Years 3-6, substituted to NALIRIFOX	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	23%
Assume constant at 50% across all years	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>3</sup>	15%

Source: Compiled during the evaluation using Attachment 11 of the submission and corrected to reflect the correct co-payment calculation  
Abbreviations: Gem+NabP, gemcitabine plus nanoparticle albumin-bound paclitaxel; FOLFIRINOX, Fluorouracil, Folinic Acid, Irinotecan, Oxaliplatin; NALIRIFOX, nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil, leucovorin/folinic acid, and oxaliplatin.

<sup>a</sup> Values presented in this table differs from that in the submission because these numbers represent the net impact on the health budget. The submission presented net impact on PBS/RPBS (including co-pay).

The redacted values correspond to the following ranges:

<sup>1</sup> \$10 million to < \$20 million

<sup>2</sup> \$0 to < \$10 million

<sup>3</sup> \$20 million to < \$30 million

## Financial Management – Risk Sharing Arrangements

6.105 No risk sharing arrangement (RSAs) was proposed in the submission. The submission stated that the estimated extent of use of nal-IRI was expected to be stable and predictable.

For more detail on PBAC’s view, see section 7 PBAC outcome.

## 7 PBAC Outcome

7.1 The PBAC did not recommend nanoliposomal irinotecan (nal-IRI) in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) for use as a four-drug chemotherapy regimen known as NALIRIFOX, for the first-line treatment of metastatic

pancreatic adenocarcinoma (mPAC). The PBAC considered that the combination regimen known as FOLFIRINOX (containing irinotecan, 5-FU, LV and oxaliplatin) was the relevant main comparator in the proposed population, rather than gemcitabine with nanoparticle albumin-bound paclitaxel (Gem+NabP) as nominated by the submission. The PBAC considered that the submission had not established superiority of NALIRIFOX to FOLFIRINOX. The PBAC considered there is a high clinical need for new effective treatments for pancreatic cancer, however the submission's clinical claims were not supported by the clinical evidence.

- 7.2 The primary reason for this outcome was due to the comparative clinical evidence presented.
- 7.3 The PBAC considered there was a high clinical need for effective therapies for patients with pancreatic cancer, and noted this was described in the consumer comments. The PBAC also noted that while the consumer comments expressed a strong desire for new treatment options, there were mixed views regarding the potential clinical benefits and risks of the proposed PBS listing of nal-IRI as part of the NALIRIFOX regimen, in comparison with treatments that are currently available (paragraph 6.2).
- 7.4 In regard to the restriction, the submission proposed that a patient must have an ECOG PS score of  $\leq 2$  to be eligible for nal-IRI, which aligned with the PBS restriction for NabP. However, the PBAC considered that access should be limited to patients with ECOG PS 0 to 1, consistent with the clinical evidence supporting its use (the NAPOLI-3 trial), and consistent with clinical practice guidelines such as the NCCN guidelines (paragraph 3.3). The PBAC considered it was unlikely that NALIRIFOX would be offered to ECOG 2 patients as the risk of severe diarrhoea with NALIRIFOX made it a relatively toxic combination compared with Gem+NabP.
- 7.5 The PBAC did not accept the clinical place in therapy proposed by the submission. The submission noted that Gem+NabP is the treatment most widely used in the first line setting currently. The submission proposed that NALIRIFOX would substitute for Gem+NabP for the majority of patients currently treated with Gem+NabP in this setting. While the submission proposed that NALIRIFOX would become the preferred first line treatment option for patients that are currently treated with Gem+NabP for mPAC (with use in up to  $\frac{1}{2}$  of these patients), the PBAC considered that many of these patients would not be suitable for treatment with NALIRIFOX, due to its toxicity profile, which is more similar to that of FOLFIRINOX than Gem+NabP. The submission acknowledged that the PBS listing of NALIRIFOX could substitute for FOLFIRINOX, but considered this would only occur in a minority of patients currently treated with this regimen, and assumed no substitution of FOLFIRINOX in the base case economic evaluation and financial estimates.
- 7.6 The PBAC noted that Gem+NabP is currently the most frequently used treatment in the first-line setting, however considered that the submission's nomination of Gem+NabP as main comparator was inappropriate, because the population in which NALIRIFOX will be used is closer to the population treated with FOLFIRINOX. The PBAC

considered that FOLFIRINOX was the appropriate main comparator for NALIRIFOX for the proposed listing. The PBAC noted that characteristics of this population may include younger age and good performance status (ECOG PS 0 to 1), as discussed in paragraph 5.2.

- 7.7 The PBAC noted that the evidence for the comparison between NALIRIFOX and Gem+NabP was based on a head-to-head, RCT – known as NAPOLI-3, while the evidence for the comparison between NALIRIFOX and FOLFIRINOX was based on an indirect comparison across three RCTs – NAPOLI-3, ACCORD11/PRODIGE4 (FOLFIRINOX versus gemcitabine) and MPACT (Gem+NabP versus gemcitabine).
- 7.8 On the basis of direct evidence presented by the submission, the comparison of NALIRIFOX and Gem+NabP resulted in improvements of approximately 1.9 months in median OS and 1.8 months in median PFS over a median duration of follow-up of approximately 16 months. The PBAC noted that the median OS was 11.1 months for NALIRIFOX and 9.2 months for Gem+NabP, resulting in a statistically significant improvement in OS for NALIRIFOX (HR 0.83; 95% CI: 0.70, 0.99). The PBAC considered the clinical claim of superior effectiveness of NALIRIFOX over Gem+NabP was supported by the data, although the magnitude was small and may not be clinically meaningful.
- 7.9 While overall rates of adverse events were similar across both arms in NAPOLI-3, the PBAC considered that the claim of non-inferior comparative safety of NALIRIFOX versus Gem+NabP was not adequately supported by the data, due to increased rates of drug-related serious adverse events, as well as all-cause and drug-related TEAEs leading to interruption of treatment, for NALIRIFOX patients in NAPOLI-3 compared with Gem+NabP. The PBAC also noted that the safety profiles of NALIRIFOX and Gem+NabP were different as shown in Table 9, for example higher rates of Grade 3-4 diarrhoea (20.3% versus 4.5%) and nausea (11.9% versus 2.6%) occurred in patients receiving NALIRIFOX, and higher rates of Grade 3-4 neutropenia (14.1% versus 24.5%) occurred in patients receiving Gem+NabP. The PBAC considered that higher rates of gastrointestinal toxicities such as diarrhoea and nausea with NALIRIFOX would be significant for patients and impact quality of life.
- 7.10 The PBAC noted that the submission did not present a formal statistical comparison between NALIRIFOX and FOLFIRINOX. During the evaluation, an unanchored indirect comparison of OS based on the NALIRIFOX arm of the NAPOLI-3 trial, and the FOLFIRINOX arm of the ACCORD11/PRODIGE4 trial suggested no difference in efficacy between the treatments (median OS of 11.1 months for both treatments). The PBAC also noted that a multistep indirect treatment comparison (ITC) (with both gemcitabine and Gem+NabP as common comparators) suggested no difference between NALIRIFOX and FOLFIRINOX for OS (HR 1.05; 95% CI 0.76, 1.46). The PBAC noted a similar result in a recently published meta-analysis by Nichetti et al (2024) of 7 phase 3 trials (HR 1.06; 95% CI 0.81, 1.39). Based on these analyses, the PBAC considered that the submission's clinical claim of superior effectiveness of NALIRIFOX over FOLFIRINOX was not supported.

- 7.11 The PBAC noted that the submission did not present conclusive evidence to suggest that NALIRIFOX has improved safety over FOLFIRINOX as the ‘side by side’ comparison between NALIRIFOX and FOLFIRINOX presented in the submission did not allow for a quantitative comparison (see paragraph 6.53). The PBAC considered that the claim of superior comparative safety of NALIRIFOX over FOLFIRINOX was not supported by the data. It was noted that the published meta-analysis (Nichetti et al 2024), reported that FOLFIRINOX and NALIRIFOX have similar toxicities.
- 7.12 The PBAC noted that both the PSCR and Pre-PBAC response presented a single-step ITC using data from the recently presented GENERATE trial, which directly compared FOLFIRINOX with Gem+NabP. The pre-PBAC response claimed that Gem+NabP was non-inferior to FOLFIRINOX based on the results from the GENERATE trial, and that NALIRIFOX was superior to FOLFIRINOX on the basis of the one-step ITC (Table 7). The PBAC noted the ESC’s concerns around the GENERATE trial (such as differences between treatment arms in patient and disease characteristics, the use of a modified FOLFIRINOX regimen that may bias against FOLFIRINOX, and inadequate reporting of analysis methodology). The PBAC noted further concerns including the higher proportion of patients discontinuing due to AEs with FOLFIRINOX (34.3% versus 23.9% for Gem+NabP). The PBAC noted the substantially longer median OS for Gem+NabP in the GENERATE trial versus the NAPOLI-3 trial (17.0 versus 9.2 months), raising concerns as to whether the assumption of transitivity was met in the one-step ITC. The PBAC also noted that the reported median OS achieved with Gem+NabP in the GENERATE trial of 17 months was longer than has been reported in other trials. The PBAC further noted that the improvement in median OS of approximately 3 months for Gem+NabP compared with FOLFIRINOX that was reported for the GENERATE trial, was longer than the improvement in median PFS of approximately one month, and that this may reflect the OS results being impacted by subsequent treatments (paragraph 6.6). The PBAC noted the ITC based on the GENERATE trial had not been evaluated, however due to multiple concerns, considered that it was unreliable.
- 7.13 The PBAC noted that the submission presented a cost-utility analysis, comparing NALIRIFOX with Gem+NabP. The PBAC did not consider this analysis using Gem+NabP as the comparator to be informative because it considered that FOLFIRINOX was the appropriate main comparator (paragraph 7.1). The PBAC noted the submission also presented alternative modelled scenarios to incorporate FOLFIRINOX as a comparator in a proportion of patients, which assumed that NALIRIFOX was superior to FOLFIRINOX. The PBAC considered these scenarios were not informative as they relied on the clinical claim of superior efficacy of NALIRIFOX over FOLFIRINOX, a claim which it considered was not supported (paragraph 7.10).
- 7.14 The PBAC noted the estimated use and financial implications presented by the submission (Table 20). The PBAC considered that the submission’s assumption that NALIRIFOX would replace Gem+NabP in up to 1% of patients was not reasonable, and that replacement of FOLFIRINOX should have been modelled. The PBAC noted that the estimates were highly sensitive to the medicines replaced, and the additional cost

was not justified as the submission had not demonstrated clinical superiority over the most relevant comparator, which was FOLFIRINOX.

- 7.15 The PBAC considered that a resubmission would need to nominate FOLFIRINOX as the main comparator, and if there was insufficient evidence to support a claim of superiority of NALIRIFOX over FOLFIRINOX in terms of efficacy or safety, the appropriate form of economic evaluation would be a cost-minimisation approach.
- 7.16 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Servier is disappointed by this decision but welcomes the PBAC's recognition of the need for new effective treatment options for patients living with metastatic pancreatic cancer in the first-line setting. Servier will consider options to resolve the issues PBAC have identified, in the hope that Australian patients can access nanoliposomal irinotecan through the PBS for the treatment of pancreatic cancer in a timely way.