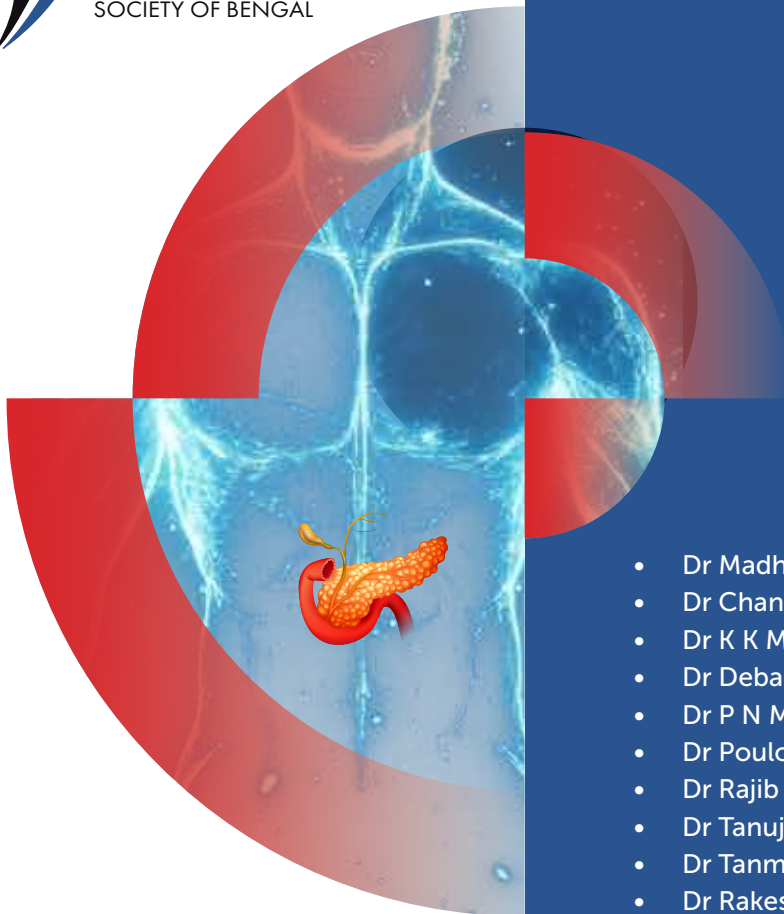


Nano-Liposomal Pegylated Irinotecan or NAL-IRI in 1st and 2nd Line Systemic Chemotherapy for metastatic Pancreatic Cancer:

**An Expert Consensus from
Oncology Society of Bengal**



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Executive Summary

Statement 1: NAL-IRI (Liposomal Pegylated Irinotecan) is different from Conventional Irinotecan in terms of pharmacokinetic profile, providing a prolonged exposure in plasma and tumours to Irinotecan & SN-38, lower dose needed to achieve similar SN-38 exposure in plasma & tumors and enhanced tumour growth inhibition in animal models which may be reflected in its safety and efficacy in Phase 3 clinical trials in mPDAC. All 9 respondents accept this statement (6 Accept Completely/3 Accept with minor reservations)

Statement 2: Based on conflicting results of the CONKO 003 and the PANCREOX studies evaluating Oxaliplatin based regimens in 2L mPDAC, and on the results of the NAPOLI 1 study (Significantly better mOS, mPFS and ORR vs 5FU/LV), **NAL-IRI + 5FU/LV may be considered best among all the 2L systemic chemotherapy.** All 9 respondents accept this statement (4 Accept Completely/4 Accept with minor reservations/1 Accept with major reservations)

Statement 3: NAL-IRI could be considered as a treatment option for patients who have been previously treated with conventional irinotecan especially for those who did not progress on prior conventional irinotecan and in those in whom the treatment interval was ≥ 5.5 months. 8 of 9 respondents accept this statement (1 Accept Completely/4 Accept with minor reservations/3 Accept with major reservations/4 Reject with reservations)

Statement 4: Based on the NAPOLI-1 trial, **the mean dose of NAL-IRI can be as low as 55.8mg/m² per dose, which is 80% of the recommended dose in the label without impact on efficacy.** All 9 respondents accept this statement (7 Accept Completely/2 Accept with major reservations)

Statement 5: The diarrhea incidence (13 % G3/4) of NAL-IRI+5FU/LV can be managed by recommended dose adjustment (as per protocol) and using loperamide (as SOS) and atropine. 7 of 8 respondents accept this statement (7 Accept Completely/1 Reject with reservations)

Statement 6: The neutropenia associated with NAL-IRI can be managed by recommended dose adjustment (as per protocol) and using G-CSF (granulocyte-colony stimulating factor therapy. All 9 respondents accept this statement (4 Accept Completely/5 Accept with minor reservations)

Statement 7: NAL-IRI + 5FU/LV in 2L mPDAC Post Gemcitabine, provides long term survival benefits in certain group of patients, i.e. those with Age ≤ 65 years, KPS ≥ 90 , Neutrophil-to-lymphocyte ratio ≤ 5 , CA19-9 level $< 59 \times$ upper limit of normal, less likely liver metastasis. All 9 respondents accept this statement (3 Accept Completely/2 Accept with minor reservations/3 Accept with major reservations)

Statement 8: NAL-IRI FOX and FOLFIRINOX may provide equal efficacy as first-line treatment of metastatic mPDAC but have different toxicity profiles in term of diarrhea, and neutropenia. Careful patient selection should be based on the toxicity profile to observe optimum efficacy. All 9 respondents accept this statement (8 Accept Completely/1 Accept with major reservations)

Introduction and background

Pancreatic cancer is not a conventional disease, with a challenging tumor biology characterized by an abundant desmoplastic stroma. This acts a physical barrier that prevents adequate delivery of chemotherapy to tumour site, impairing its therapeutic potential and thus is considered a major contributor to chemoresistance in metastatic pancreatic ductal adenocarcinoma (mPDAC).¹ (The advent of liposomal agents such as nano-liposomal irinotecan (nal-IRI) has led to improvements in drug formulations with altered PK profiles compared with the parent compounds, which translate into improved efficacy and safety profiles in clinical practice. Compared with non-liposomal irinotecan, nal-IRI generally shows prolonged exposure in plasma (>50h) and prolonged exposure in tumors (>168 hrs.) to both Irinotecan and SN-38 and has been shown to have increased plasma half-life among other desirable PK properties.² Based on the 2 pivotal phase 3 clinical trials (NAPOLI 1 & NAPOLI 3) in mPDAC, the recent NCCN, ESMO guidelines now recommended the uses of nal-IRI in combination with 5FU/LV in 2L mPDAC in patients with who have progressed on a gemcitabine-based regimens, Further the use of nal-IRI in combination with oxaliplatin and 5 FU/LV (NALIRIFOX) has emerged as a 1st line treatment option in metastatic treatment naïve patients.^{3,4}

The objective of this expert consensus is to develop a shared understanding of the differentiated PK profile of nal-IRI vs Conventional Irinotecan, to identify the place in therapy of NAL-IRI + 5FU/LV in metastatic Pancreas Cancer in 2nd Line (post gemcitabine) and of NAL-IRI FOX (nal-IRI in combination with Oxaliplatin and 5FU/LV in 1st line mPDAC treatment from the perspective of Oncological Society of Bengal. This document will help oncologists in making major clinical decisions encountered while managing their patients with mPDAC in routine clinical practice.

Methodology

Based on a literature search in MEDLINE articles published in the past 10 years were identified and consensus statements relevant to the differentiated PK profile of nal-IRI, the place in therapy of nal-IRI & 5FU/LV in mPDAC management in 2L Post Gemcitabine and the place in therapy of NAL-IRI-FOX (nal-IRI + Oxaliplatin + 5FU/LV) were drafted. Subsequently, a 10-member consensus expert panel comprising of medical oncologists from Oncological Society of Bengal (OSB) were invited to participate in the review and agreement was sought with the statements in the context of current local practice and available evidence, The consensus statements were developed through the Delphi process: after discussion, the members independently voted on each statement using a 5-point Likert scale (A: accept completely; B: accept with minor reservations; C: accept with major reservations; D: reject with reservations; E: reject completely). A consensus was reached if at least 80% of the panel members agreed with the statement (i.e. selected either 'accept completely' or 'accept with minor reservations').⁵

Results

Consensus statements

Statement 1: NAL-IRI (Liposomal Pegylated Irinotecan) is different from Conventional Irinotecan in terms of its pharmacokinetic profile providing a prolonged exposure in plasma and tumours to Irinotecan & SN-38, lower dose needed to achieve similar SN-38 exposure in plasma & tumors and enhanced tumour growth inhibition in animal models which may be reflected in its safety and efficacy in Phase 3 clinical trials in mPDAC. All 9 respondents accept this statement (6 Accept Completely/3 Accept with minor reservations)

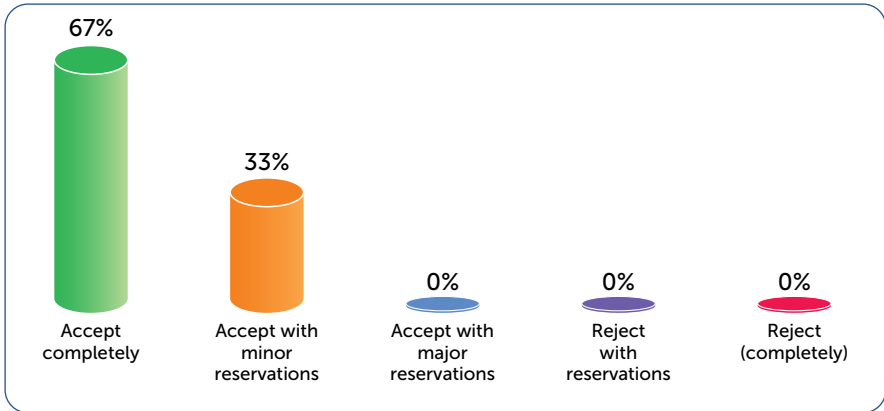
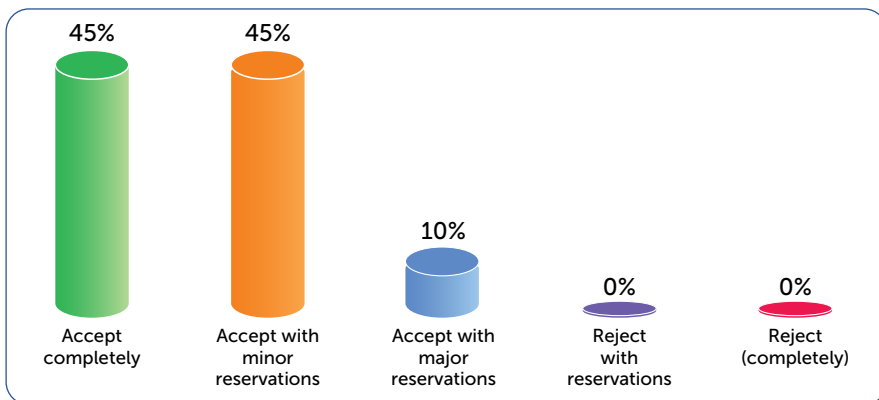


Table 1

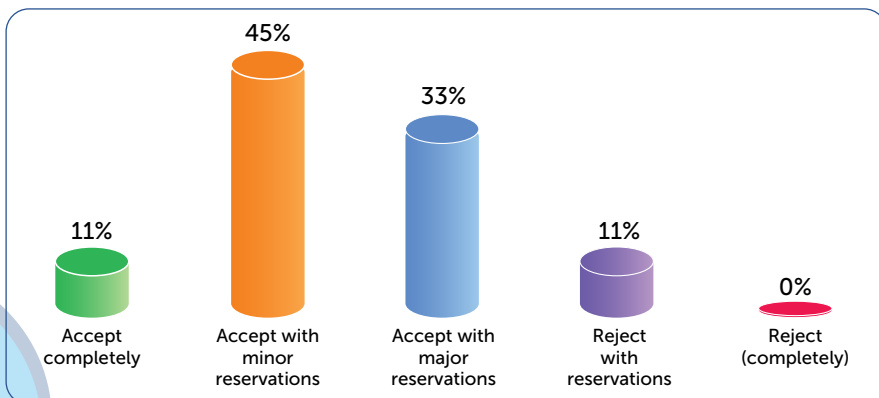
Advantage of nal-IRI encapsulation	Onivyde® or nal-IRI	Non-liposomal irinotecan
Prolonged exposure in plasma	Irinotecan and SN-38 remained in circulation for >50 h	Irinotecan and SN-38 plasma levels cleared from circulation within 8 h
Prolonged exposure in tumour growth models	Irinotecan levels persisted above 10,000 nmol/L for 168 h in tumours Prolonged SN-38 exposure above activity threshold for up to 168 h	>90% irinotecan was cleared from tumours within 24 h SN-38 exposure in tumours <48 h
Dose needed to achieve similar SN-38 exposure in plasma and tumors in tumor xenograft models	10 mg/kg	50 mg/kg
Enhanced tumour growth inhibition in animal models	~110%	~40%

Statement 2: Based on conflicting results of the CONKO 003 and the PANCREOX studies evaluating Oxaliplatin based regimens in 2L mPDAC, and on the results of the NAPOLI 1 study (Significantly better mOS, mPFS and ORR vs 5FU/LV), **nal-IRI + 5FU/LV may be considered best among all the 2L systemic chemotherapy.** All 9 respondents accept this statement (4 Accept Completely/4 Accept with minor reservations/1 Accept with major reservations)

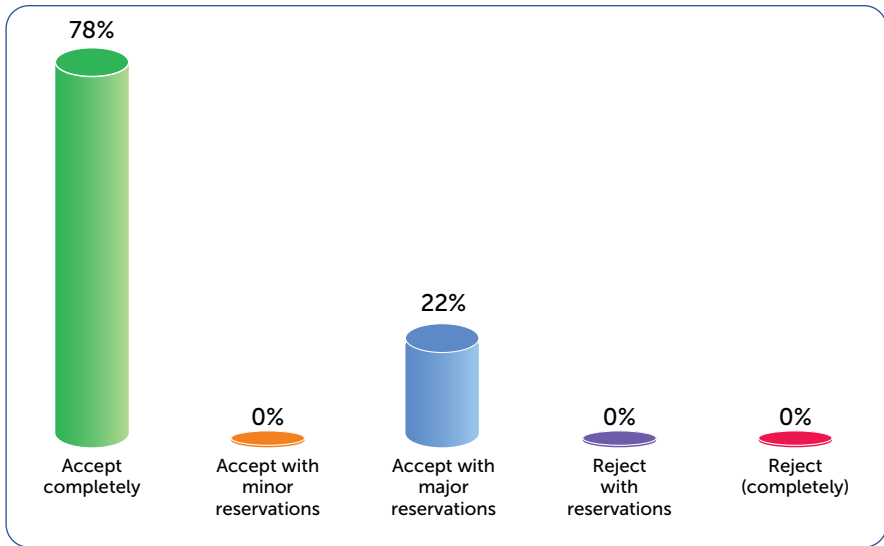


NAPOLI-1 is the only randomized phase 3 trial in 2L mPDAC, it demonstrates 6.2 months mOS with NAL-IRI & 5-FU/LV vs 4.2 months with 5FU/LV with a HR ratio of 0.67 (33% reduction in risk of death). A statistically significant increase in mPFS was observed with nal-IRI + 5-FU/LV (3.1 months) vs 5-FU/LV (1.5 months). A significantly better ORR was observed with NAL-IRI +5-FU/LV at 16% in comparison to 5-FU/LV at 0.8%.³

Statement 3: NAL-IRI could be considered as a treatment option for patients who have been previously treated with conventional irinotecan especially for those who did not progress on prior conventional irinotecan and in those in whom the treatment interval was ≥ 5.5 months. Patients without prior Irinotecan (IRI) exposure and patients who received prior IRI without disease progression experienced significantly longer OS (7.7 months, $p=0.002$ and OS, 9.0 months, $p=0.04$).⁶ An interval between conventional IRI and nal-IRI ≥ 5.5 months was significantly associated with prolonged OS of 10.2 m (3.3 – 12.1) versus 4.3 m (95% CI 2.1 – 5.9; $p=0.003$).⁷ 8 of 9 respondents accept this statement (1 Accept Completely/4 Accept with minor reservations/3 Accept with major reservations/4 Reject with reservations)

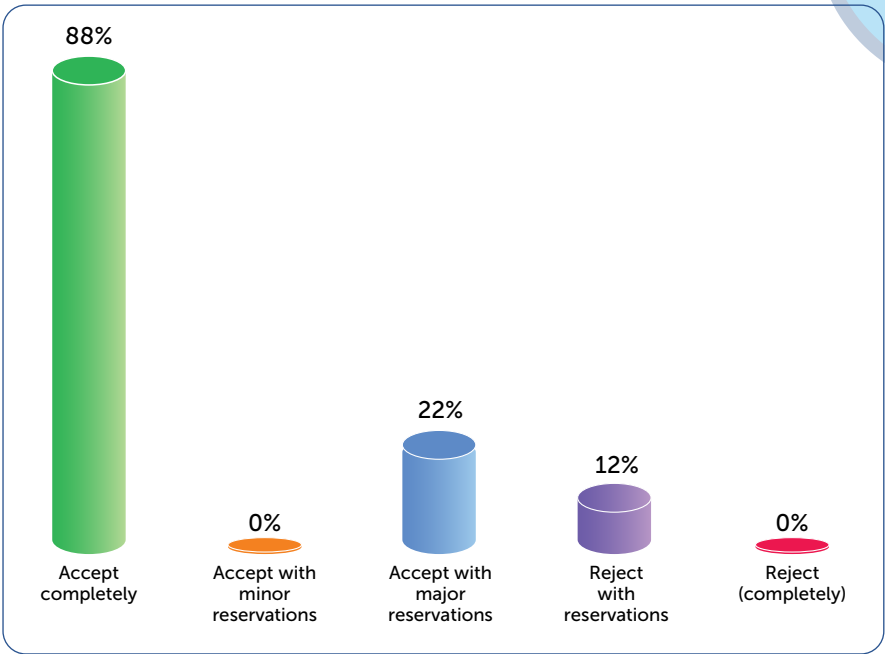


Statement 4: Based on the NAPOLI-1 trial, the mean dose of NAL-IRI can be as low as 55.8mg/m² per dose, which is 80% of the recommended dose in the label without impact on efficacy. All 9 respondents accept this statement (7 Accept Completely/2 Accept with major reservations)



Overall, patients allocated to nal-IRI + 5-FU/LV in the NAPOLI-1 trial were exposed to mean dose intensities of 167.5mg/m² over 6 weeks. This amounts to a mean of 55.8mg/m² per dose, which is 80% of the recommended dose in the label. There is no impact on efficacy compared with patients without any modification or dose reduction.³

Statement 5: The diarrhea incidence (13 % G3/4) of NAL-IRI+5FU/LV can be managed by recommended dose adjustment (as per protocol) and using loperamide (as SOS) and atropine. 7 of 8 respondents accept this statement (7 Accept Completely/1 Reject with reservations)



Diarrhoea is a very common adverse reaction: in the clinical study (NAPOLI-1) Grade 3/4 diarrhoea occurred in 12.8% of patients. Early onset diarrhoea (≤ 24 hours after administration) occurred in 29.9% of patients. For 3.4% of patients, it is accompanied by cholinergic symptoms (rhinitis, increased salivation, flushing, diaphoresis, miosis, bradycardia, hyperperistalsis). Late diarrhoea: the median time onset is 8 days.⁸

Table 2

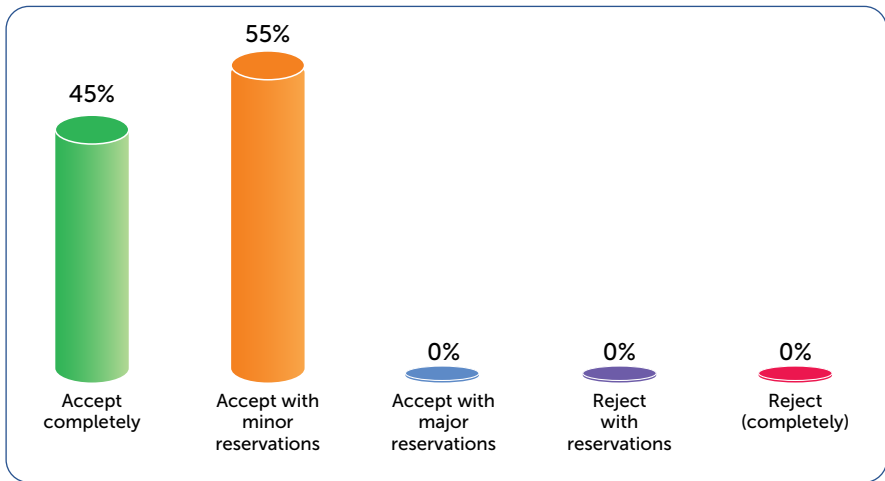
Diarrhoea	A new cycle of therapy should not begin until diarrhoea resolves to \leq grade 1 (2-3 stools/day more than pre-treatment frequency)		
Grade 2	A new cycle of therapy should not begin until diarrhoea resolves to \leq grade 1 (2-3 stools/day more than pre-treatment frequency)		
Grade 3 or grade 4	First occurrence Reduce NAL-IRI dose to 50 mg/m ² Reduce 5-FU dose by 25% (1800 mg/m ²)	Second occurrence Reduce NAL-IRI dose to 43 mg/m ² Reduce 5-FU dose by 25% (1350 mg/m ²)	Third occurrence Discontinue treatment

In First line: Intravenous rehydration (Isotonic or saline balanced), Loperamide (Opioids): 4mg + 2mg every unformed stool (max 16mg/day)

In Second line (after Loperamide): Octreotide: Somatostatin analogues and Budesonide (Steroids), Antibiotics: if fever, neutropenia or other sign of infection

Specific treatments: Uridine triacetate: prodrug of the 5-FU antidote (DPD deficit), Atropine: for Irinotecan's cholinergic acute diarrhoea, in prevention or after reaction onset.⁹

Statement 6: The neutropenia associated with NAL-IRI can be managed by recommended dose adjustment (as per protocol) and using G-CSF (granulocyte-colony stimulating factor therapy. All 9 respondents accept this statement (4 Accept Completely/5 Accept with minor reservations)

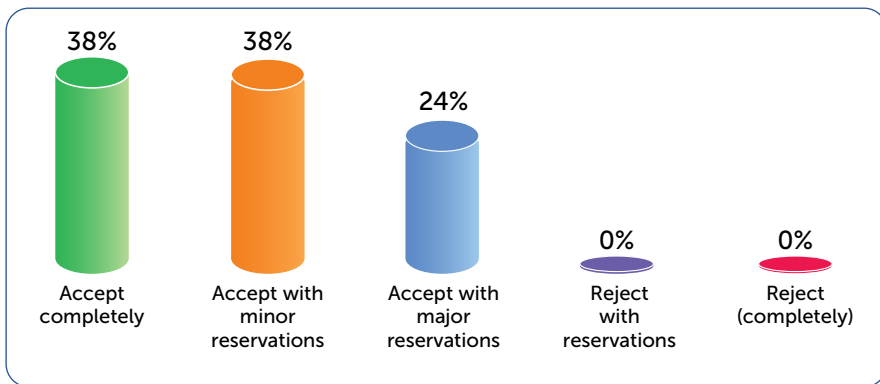


In NAPOLI 1 trial, Grade 3 or 4 neutropenia occurred in 117 patients (27%) assigned nal-IRI + 5 FU/LV Granulocyte colony stimulating factor was administered to 20 (17%) patients receiving nal-IRI + 5 FU/LV.³

Table 3

Neutropenia	A new cycle of therapy should not begin until the absolute neutrophil count is $\geq 1500/\text{mm}^3$		
Grade 3 or grade 4 ($<1000/\text{mm}^3$) or neutropenic fever	First occurrence Reduce Nal-IRI dose to 50 mg/m ² Reduce 5-FU dose by 25% (1800mg/m ²)	Second occurrence Reduce Nal-IRI dose to 43 mg/m ² Reduce 5-FU dose by 25% (1350 mg/m ²)	Third occurrence Discontinue treatment
Thrombocytopenia Leukopenia	A new cycle of therapy should not begin until the platelet count is $\geq 100,000/\text{mm}^3$ Dose modifications for Leukopenia and Thrombocytopenia are based on NCI toxicity grading and are the same as recommended for neutropenia above		

Statement 7: NAL-IRI + 5FU/LV in 2L mPDAC Post Gemcitabine, provides long term survival benefits in certain group of patients, i.e. those with Age ≤ 65 years, KPS ≥ 90 , Neutrophil-to-lymphocyte ratio ≤ 5 , CA19-9 level $< 59 \times$ upper limit of normal, less likely liver metastasis. All 9 respondents accept this statement (3 Accept Completely/2 Accept with minor reservations/3 Accept with major reservations)



A greater proportion of patients receiving nal-IRI +5-FU/LV (25%; n=29) vs 5-FU/LV (13%; n=20) survived ≥ 1 year. The nomogram revealed that there are few factors that influences OS from the NAPOLI-1 study which were KPS, presence of liver metastasis, baseline albumin (g/dL), neutrophil/lymphocyte ratio, baseline CA19-9 (U/mL), disease stage at diagnosis, and body mass index (kg/m²).¹⁰

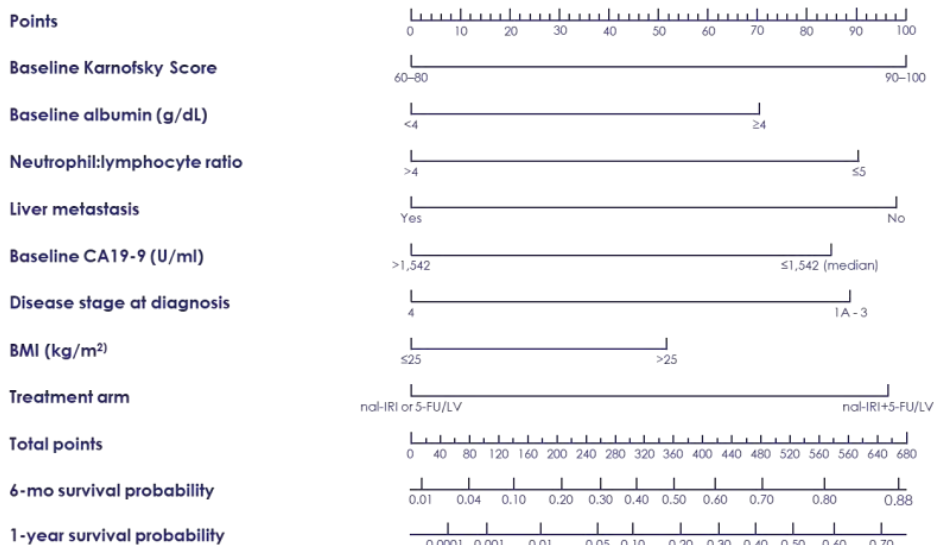


Figure 1: Nomogram to predict overall survival in patients with metastatic pancreatic cancer treated with nal-IRI +5-FU/LV in the NAPOLI-1 study

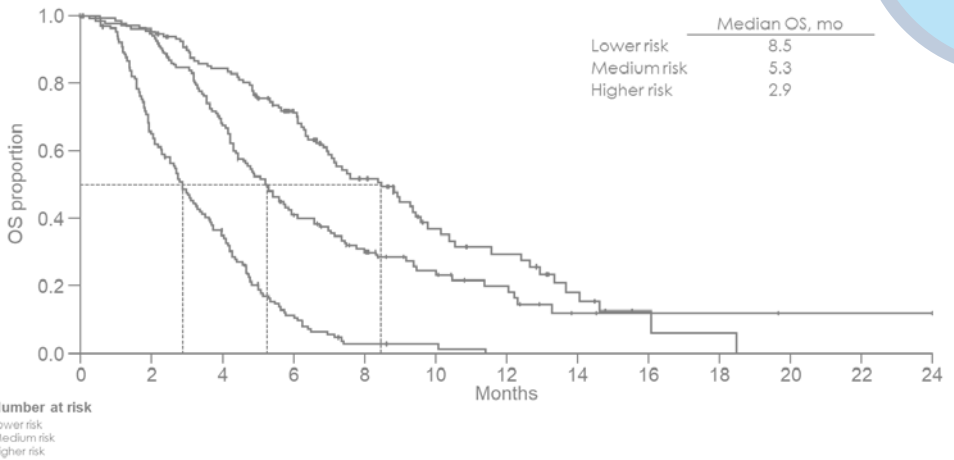
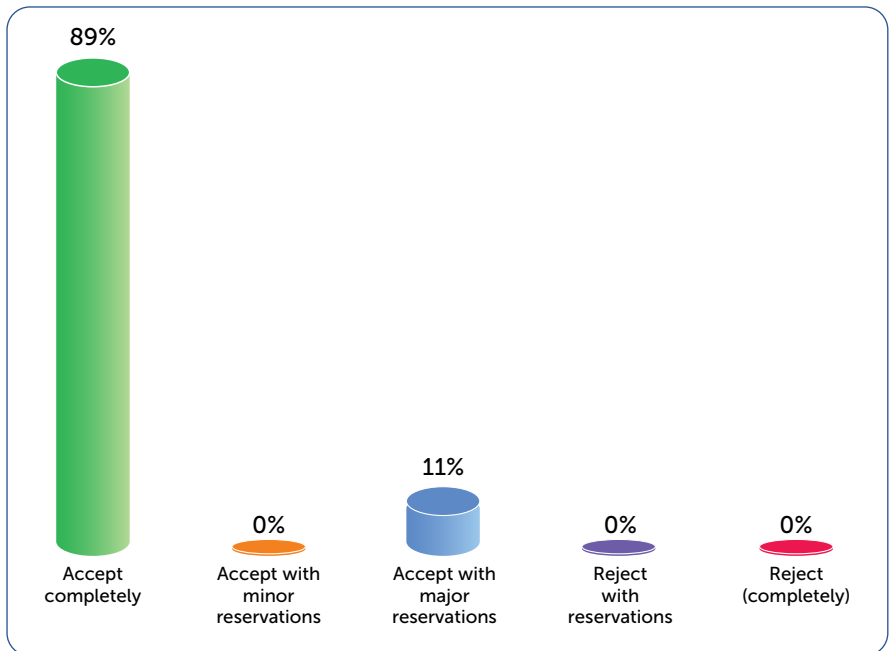


Figure 2: Kaplan-Meier survival curves showing overall survival probability stratified by risk group

Statement 8: NAL-IRI FOX and FOLFIRINOX may provide equal efficacy as first-line treatment of metastatic mPDAC but have different toxicity profiles in term of diarrhea, and neutropenia. Careful patient selection should be based on the toxicity profile to observe optimum efficacy. All 9 respondents accept this statement (8 Accept Completely/1 Accept with major reservations)



Based on the metaanalysis performed by Nichetti et al., no difference was observed between FOLFIRINOX and NALIRIFOX in terms of mOS and mPFS. NALIRIFOX was associated with lower incidence of grade 3 or higher haematological toxic effects with compared to FOLFIRINOX.¹¹

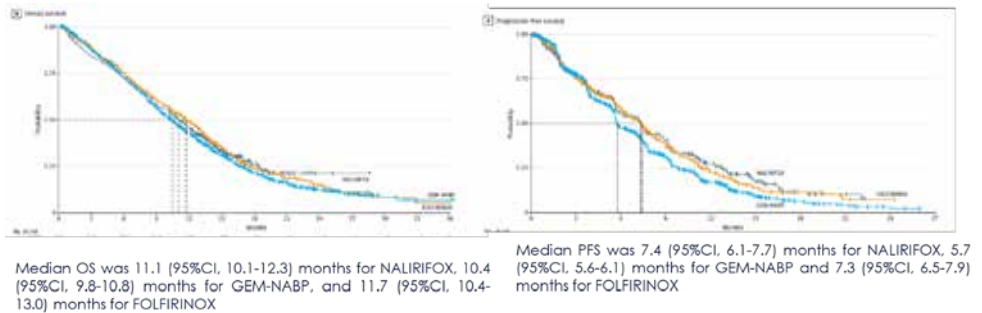


Figure 3: mOS and mPFS of the 3 regimens are comparable

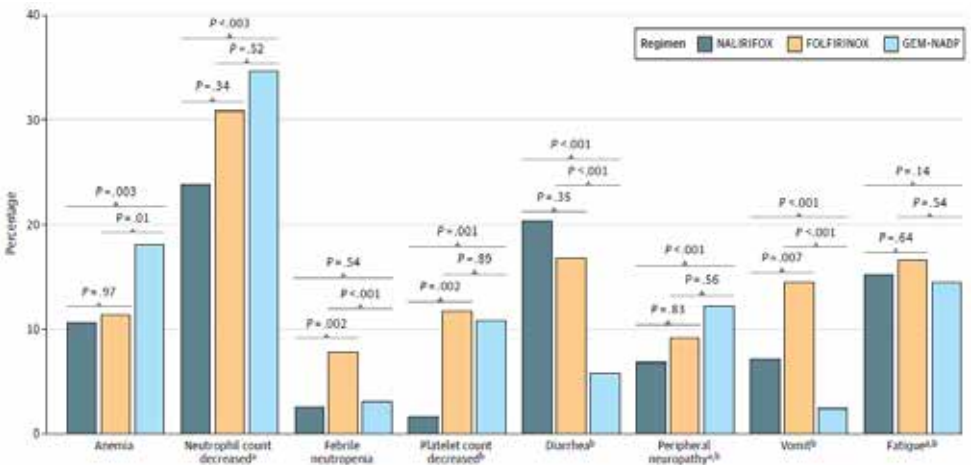


Figure 4: NAL-IRI-FOX was associated lower incidence of hematological toxic effects and peripheral neuropathy

Conclusion

mPDAC represents a major health burden because of its aggressive nature and the complexities involved in its diagnosis and management. To familiarise the clinicians with uses of NAL-IRI in mPDAC care and provide local practical guidance, our consensus group developed this initial set of recommendations for using NAL-IRI in management of mPDAC in local clinical practice. We discussed the current state of mPDAC management, reviewed the best available evidence and international guidelines, and crafted statements that address real-world situations encountered by clinicians. We recognise that many aspects of mPDAC treatment lack high-level evidence; Moreover, clinical experiences, patient preferences, and resources availability vary across West Bengal, and the therapy should be individualised in this context. In conclusion, Nal-IRI in combination with 5-FU/LV only or additionally, in combination with Oxaliplatin can be a treatment of choice for patients with mPDAC in India.

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