Robustness of Outcomes in Indirect Comparison Methods of Pegylated Liposomal Irinotecan for the Treatment of Metastatic Pancreatic Cancer in Patients who Have Progressed Following Gemcitabine-Based Therapy

HTA36

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OBJECTIVES

Management of metastatic pancreatic ductal adenocarcinoma (mPDAC) is very challenging resulting in modest outcomes compared to other common cancers in Europe. For many years, gemcitabine was the standard systemic therapy available to patients with mPDAC. This research aimed to indirectly compare pegylated liposomal irinotecan, 5-fluorouracil (5-FU), leucovorin (LV) (nal-IRI/5-FU/LV) and oxaliplatin regimen (mFOLFOX6) for second-line mPDAC in patients who have received gemcitabine-based chemotherapy, standard of care selected by INFARMED for the reimbursement assessment.

METHODS

A systematic literature review (SLR) identified all relevant randomized controlled trials of nal-IRI/5-FU/LV and FOLFOX. The electronic search was performed using defined keywords in the databases PubMed®, Web of Science™ and CENTRAL (Cochrane). Inclusion criteria are presented in Table 1. The screening procedure resulted in a final evidence base for the SLR of 7 publications (Figure 1). Feasibility assessment revealed that five of this seven studies did not contribute to the network of evidence.

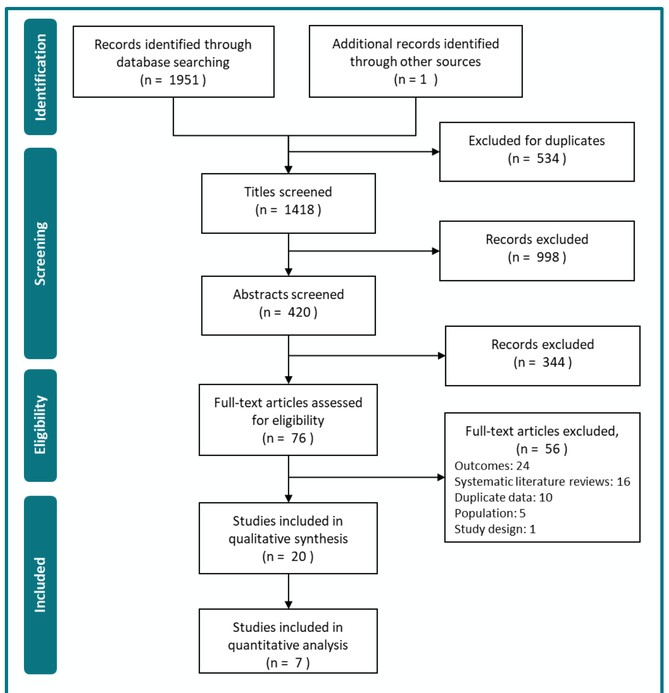

Figure 1. PRISMA diagram for mPancreatic Cancer SLR

Table 1. Inclusion criteria for the SLR

Population	Metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine-based therapy.
Interventions	All chemotherapy regimens based on oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV)
Outcomes	Efficacy: Overall survival Progression-free survival Quality of life Response rate Safety: All-grade treatment related AEs Treatment related grade ≥3 AEs Discontinuation due to AEs AEs related mortality
Study design	Prospective randomized control trials (Phase 2–3)

Indirect comparisons of overall survival (OS), progression-free survival (PFS), time to quality-of-life deterioration (EORTC-QLQ-C30), grade 3-4 treatment related adverse events (TRAE) and treatment discontinuation due to AEs were performed based on unadjusted anchored Bucher method, matching-adjusted indirect treatment comparison (MAIC), and simulated treatment comparison (STC). Matching was based on known prognostic and predictive factors: age, sex, body mass index, line of treatment, ECOG performance status, liver metastases and prior gemcitabine combination therapy. Hazard ratios (HRs) and Odds Ratios (OR) comparing nal-IRI/5-FU/LV and mFOLFOX6 were estimated. Weighted Cox models, quasi-binomial model, and 95% confidence intervals (CI) estimated by robust sandwich estimators were adopted in the MAIC analysis.

Table 2. Baseline characteristics of patients with mPDAC in relevant randomised controlled trials

Treatment	nal-IRI/5-FU/LV[1]	5-FU/LV[1]	mFOLFOX6[2]	5-FU/LV[2]
N	117	119	54	54
Age, years, mean	63.2	61.0	65.0	67.0
Female, %	41.0	43.7	42.6	44.4
BMI (Kg/m^2), mean	23.3	23.6	23.7	24.3
ECOG status 0-1, %	91.5	90.8	88.9	94.5
Prior Gem comb therapy, %	54.7	53.8	25.9	22.2
Liver metastases, %	64.1	70.6	57.4	68.5

Source: 1) **nal-IRI/5-FU/LV** versus **5-FU/LV**. Wang-Gillam A et all (https://pubmed.ncbi.nlm.nih.gov/26615328/)
2) **mFOLFOX6** versus **5-FU/LV**. Sharlene Gill et all (https://pubmed.ncbi.nlm.nih.gov/27621395/)

RESULTS

Baseline characteristics of patients with mPDAC in the two trials included in the comparison were presented in Table 2. Liver metastasis were more prevalent and prior gemcitabine combination therapy was more frequent in patients include in the NAPOLI-1[1] than those in the PANCREOX[2] trial (Table 2).

Anchored Bucher method, MAIC and STC resulted in significant improvements in terms of OS and PFS with nal-IRI/5-FU/LV vs. FOLFOX (Figure 2), with the risk of death reduced by 54% (hazard ratio [HR]=0.46, 95%CI: 0.26, 0.79) to 56% (HR=0.44, 95%CI: 0.26, 0.76); PFS improved by: Bucher HR=0.57 (95%CI: 0.35, 0.95); MAIC HR=0.58 (95%CI: 0.35, 0.96); STC HR=0.60 (95%CI: 0.36, 0.99). Time to quality-of-life deterioration was numerically improved by: Bucher HR=0.61 (95%CI: 0.27, 1.35); MAIC HR=0.67 (95%CI: 0.30, 1.51). The odds of treatment discontinuation due adverse events was significantly lower (-91%) with nal-IRI/5-FU/LV (MAIC OR=0.09; 95%CI: 0.092, 0.38). Nal-IRI/5-FU/LV was associated with a 60% (Bucher OR=0.40; 95%CI: 0.13, 1.29) to 69% (MAIC OR=0.31; 95%CI: 0.09, 1.01) reduction in the odds of grade 3-4 TEAEs. Dose delays were more common with mFOLFOX6 (Figure 2).

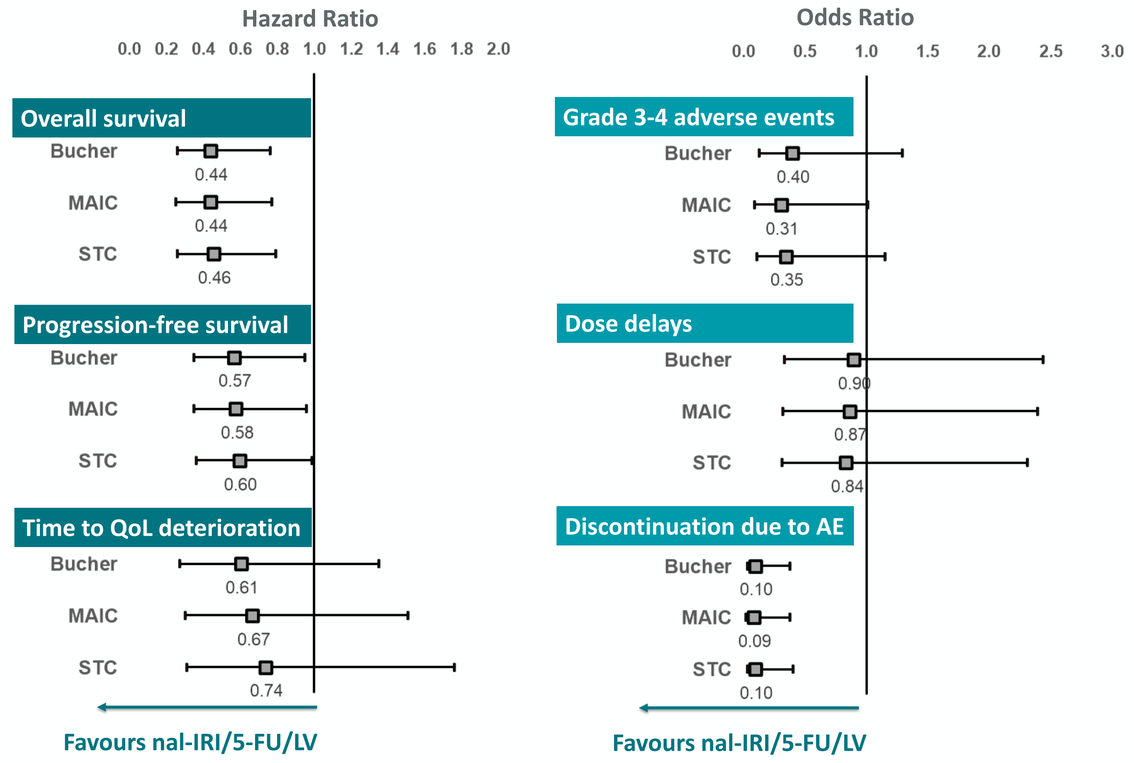

Figure 2. Relative treatment effect of nal-IRI/5-FU/LV over FOLFOX in metastatic pancreatic ductal adenocarcinoma

DISCUSSION

- A limited treatment landscape highlights the unmet need for therapeutic strategies that can extend survival while minimizing treatment-related toxicities in advanced pancreatic cancer.
- After first-line gemcitabine-based therapy the combination of nanoliposomal irinotecan with 5-FU/LV showed an improvement in OS, PFS and response rate over 5-FU/LV in the randomised phase III NAPOLI-1 trial.
- In the absence of head-to-head trials this study provides evidence of indirect superior efficacy and better tolerability of nal-IRI/5-FU/LV relative to oxaliplatin regimen mFOLFOX6.
- Analyses were limited by the small sample size of the clinical evidence available in the literature and results should be interpreted considering this constraint.

= CONCLUSION

Pegylated liposomal irinotecan combination is more efficacious and has a better safety profile than mFOLFOX6 for the treatment of metastatic pancreatic cancer in patients who have progressed following gemcitabine-based therapy.