Use of systematic literature reviews (SLRs) and meta-analyses (MAs) to support HTA submissions: an application in pancreatic cancer

Aksomaityte A[1]; Amonkar MM[2]; Frederickson AM[3]; Lang BM[4]; Dheban S[4]; Malbecq W[5]; Mojebi A[6]; Wu P[6];xHale B[6]; Kalyvas C[5]; Abderhalden LA[4]

[1]MSD (UK) Limited, London, UK; [2]Merck & Co., Inc., Rahway, NJ, USA; [3]PRECISIONheor, New York, NY, USA; [4]MSD, Zurich, Switzerland; [5]MSD (Europe) Inc, Brussels, Belgium; [6]PRECISIONheor, Vancouver, BC, Canada

Background

- Health Technology Assessment (HTA) aims to compare the effectiveness of a new therapy with relevant interventions. While a well-designed randomized clinical trial (RCT) remains a gold standard for such comparisons[1-3], it can be challenging to achieve for various reasons. For example, the amount of relevant therapies needed for the comparison is immense, the disease is too rare, or the therapy is aimed at a specific patient population, making it difficult to recruit a sufficient number of patients. All of which can introduce ethical issues. In these instances, systematic literature review (SLR) and meta-analysis (MA) are vital tools for the efficacy and safety assessment of of a new therapy and HTA agencies are increasingly reliant upon various MA techniques[4-5]
- We provide an example of the application of SLR/MA which quantifies the efficacy of the relevant historical chemotherapies for pancreatic cancer patients. Results from such MA applied in pancreatic cancer could be used to contextualize the comparative effectiveness of novel therapies evaluated in single-arm trials to support the clinical assessment of HTA submissions. Furthermore, results obtained from such SLR can be used as inputs in indirect treatment comparison analyses

Methods

Systematic literature review

- A systematic literature review was conducted to identify relevant studies using Embase, MEDLINE, and CENTRAL (January 1, 2000 – October 19, 2021) with additional searches of recent annual ASCO and ESMO conferences. Study eligibility criteria were pre-defined based on population, interventions, comparators, outcomes, time restrictions, and study designs (PICOTS) of interest (**Table 1**)
- Eligible studies included randomized controlled trials (RCTs), controlled clinical trials, and nonrandomized clinical trials of any pharmacologic treatments licensed by the FDA or EMA among patients (≥18 years of age, Eastern Cooperative Oncology Group performance status 0 or 1) with previously treated pancreatic cancer and who had progressed on ≥1 prior treatment
- Relevant therapies included: Gemcitabine ± Cisplatin, FOLFIRINOX (Folinic acid + 5-FU + Irinotecan + Oxaliplatin), Gemcitabine + Capecitabine, 5-FU + Leucovorin, Gemcitabine + Paclitaxel, OFF (Oxaliplatin + Fluorouracil + Folinic acid), Nanoliposomal-Irinotecan ± (Fluorouracil + Folinic acid), FOLFOX (Folinic acid + 5-FU + Oxaliplatin), and FOLFIRI (Folinic acid + 5-FU + Irinotecan)

Table 1. PICOTS criteria for the identification of the trials for the systematic literature review

Criteria	Inclusion criteria	Exclusion criteria
Population	**Interventional studies:** • Patients with advanced (unresectable and/or metastatic) pancreatic adenocarcinoma • Previously treated for advanced disease • Adult (≥18 years) • ECOG 0 or 1 • Recurrent disease when stage not specified • Irrespective of MSI-high or dMMR status **Observational studies:** • Patients with advanced (unresectable and/or metastatic) pancreatic adenocarcinoma • Previously treated for advanced disease • Adult (≥18 years) • Recurrent disease when stage not specified • MSI-H/dMMR	**Interventional studies:** Populations ECOG 2 or higher Populations with stage I or II disease Studies with patients who have CNS metastasis Studies in patients previously treated with anti-PD1/PD-L1 **Observational studies:** Populations with stage I or II disease Studies with patients who have CNS metastasis Studies in patients previously treated with anti-PD1/PD-L1
Interventions	• Gemcitabine ± cisplatin • FOLFIRINOX (folinic acid+5-FU+irinotecan+oxaliplatin) • Gemcitabine + capecitabine • 5-FU+folinic acid • Gemcitabine + paclitaxel • OFF (oxaliplatin+5-FU+folinic acid) • Nanoliposomal-irinotecan ± (5-FU+folinic acid) • FOLFOX (folinic acid+5-FU+oxaliplatin) • FOLFIRI (folinic acid+5-FU+irinotecan)	Radiation without chemotherapy Surgical intervention without systemic treatment Other nonpharmacologic treatments (eg, hyperthermia)
Comparators	Unrestricted	—
Outcomes	**At least 1 of the following outcomes[a]:** • Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP) • Duration of response (DOR) • Objective response rate (ORR) and number of patients with CR, PR, SD, PD, when available • Drug-related adverse events (AEs) • Grades 3-5 AEs (any-cause, treatment-related) • Discontinuation due to AE (DAEs) • Serious AEs (SAEs) • Patient-reported outcomes (PROs) (eg, EQ-5D, EORTC QLQ-C30)	—
Study design	• Randomized controlled trials (RCTs) • Controlled clinical trials • Nonrandomized clinical trials, including single-arm interventional studies • Observational studies involving MSI-H/dMMR patients	Case reports Case series
Time	From 2000 onwards	—
Language	English language	—

[a]Only efficacy outcomes and PRO were used for study selection, although all outcomes listed were extracted.

AE, adverse events; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; MMR, mismatch repair; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PRO, patient reported outcomes; TTP, time to progression; RCT, randomized controlled trial.

Meta-analysis

- Meta-analyses of **objective response rate (ORR), progression-free survival (PFS), and overall survival (OS)** were conducted among interventional studies of relevant (licensed and/or guideline recommended) chemotherapies for pancreatic cancer patients receiving second-or-later line (≥2L) of treatment
- The primary outcome of interest was ORR. When not directly reported, ORR was derived by adding complete response and partial response events then dividing by the total number of patients. The ORR meta-analysis was performed using the Freeman-Tukey double arcsine transformation to normalize and stabilize proportion estimates. Clopper-Pearson 95% confidence interval (CI) was reported for proportions in individual studies. Fixed and random effects pooled estimate of ORR with 95% CI, I^2 and T^2 statistics, and p-value for the Cochran's Q test for heterogeneity were reported. As five or more studies were included in each meta-analysis, pooled estimates based on a random-effects model were deemed most appropriate as it naturally encompasses the statistical heterogeneity that is expected in the included studies
- Additional efficacy outcomes of interest for statistical analysis included **OS** and **PFS**. For time-to-event outcomes, meta-analyses were conducted by pooling survival Kaplan-Meier (KM) curves via methods described by Combescure et al.[6] Summary survival probabilities were obtained from the product of the pooled conditional survival probabilities. The mean and median survival times were derived from the summary survival curve assuming a linear interpolation of the survival between points. A random effects model for meta-analysis is reported as this reflects the more plausible assumption of heterogeneity in study and patient characteristics across included trials
- Survival curves were manually digitized using DigitizeIt (http://www.digitizeit.de/), and pseudo individual patient data of trial sources were estimated by applying Guyot's algorithm.[7] Meta-analyses were performed to combine results from multiple studies to obtain a precise estimate of overall treatment effect or resolve uncertainty around the efficacy of therapies.[8] SAS version 9.4 was used for conducting the meta-analyses of proportion outcomes and generation of supporting forest plots. Pooling of survival curves was estimated using the MetaSurv package with R version 4.0.1

Results

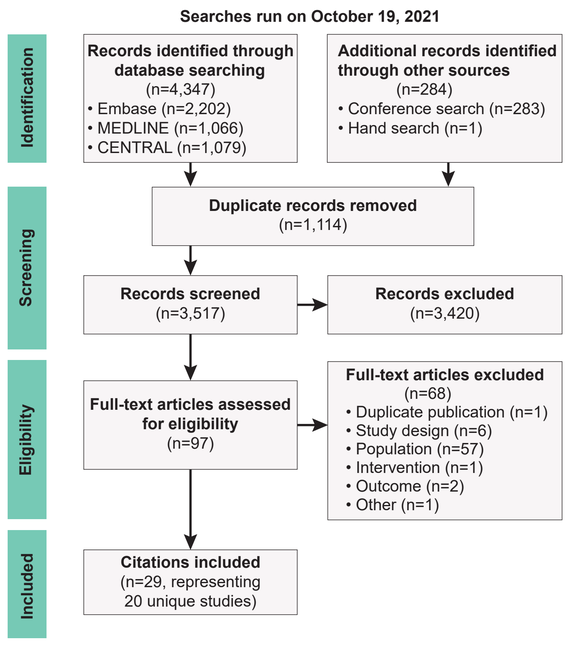
Systematic literature review

- There were 4,633 relevant records identified during the database search, resulting in 20 unique studies (10 RCTs and 10 single-arm trials) matching inclusion criteria (**Figure 1**) with reported ORR range of 0% to 22.2% (**Figure 2**), median OS range of 3.3 to 9.8 months and median PFS range of 1.38 to 5.8 months (**Table 2**)

Meta-analysis

- Of the 20 unique studies identified, 19 of them (including 29 unique treatment arms) evaluated relevant chemotherapies among 1,792 patients who had progressed on prior treatment reported ORR (**Figure 2**). The random effects pooled estimate of ORR was 6.8% (95% CI: 4.5 – 9.4%)
- Median **PFS** (15 studies; 24 survival curves) was 2.8 months (95% CI: 2.4-3.3) with PFS rates at 6, 12, and 24 months of 23.3% (95% CI: 18.2%-29.6%), 6.8% (95% CI: 4.6%-10.1%), and 0.5% (95% CI: 0.2%-1.2%), respectively (**Figure 3**)
- Median **OS** (18 studies; 28 survival curves) was 6.2 months (95% CI: 5.3-7.1) with OS rates at 6, 12, and 24 months of 51.9% (95% CI: 45.8%-58.9%), 20.7% (95% CI: 17.3%-24.7%), and 3.1% (95% CI: 1.9%-4.9%), respectively (**Figure 4**)

Figure 1. PRISMA flow diagram for interventional studies



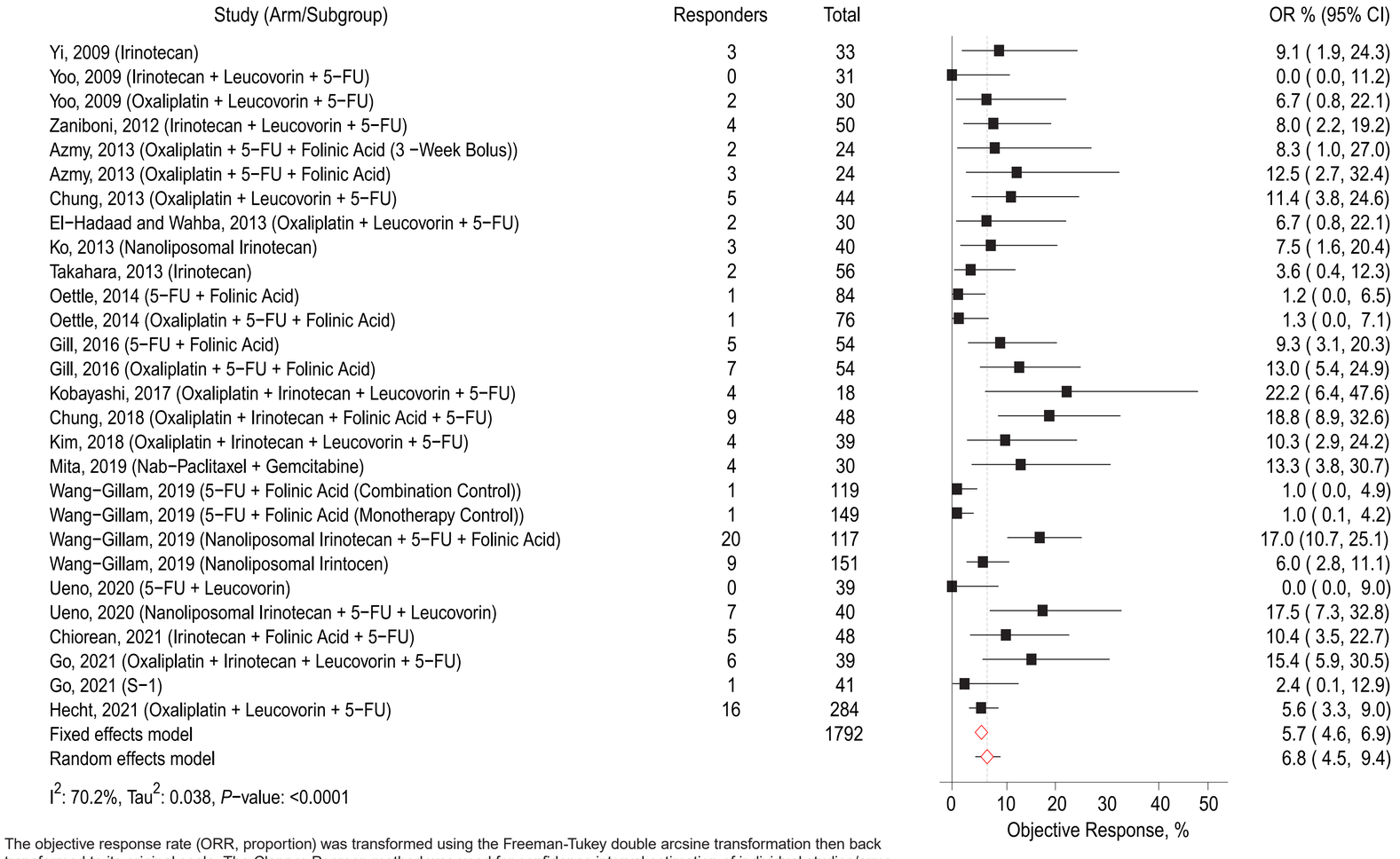
Note: The search for observational studies was conducted on 7 July 2021. There were no observational studies identified matching the SLR criteria.

Table 2. Summary of overall survival and progression-free survival in the studies identified in the SLR

Source	Treatment	N	Median OS (95% CI)	Median PFS (95% CI)
Yi et al, 2009	Irinotecan	33	6.6 (5.8 - 7.4)	2 (0.7 - 3.3)
Yoo et al, 2009	Irinotecan + Leucovorin + 5-FU	31	3.82 (2.87 - 4.74)	1.91 (1.59 - 2.21)
Yoo et al, 2009	Oxaliplatin + Leucovorin + 5-FU	30	3.43 (1.84 - 5.01)	1.38 (1.17 - 1.59)
Pelzer et al, 2011	Oxaliplatin + 5-FU + Folinic Acid	23	4.82 (4.29 - 5.35)	NR (NR - NR)
Zaniboni et al, 2012	Irinotecan + Leucovorin + 5-FU	50	5 (1 - 17)	3.27 (NR - NR)
Azmy et al, 2013	Oxaliplatin + 5-FU + Folinic Acid	24	8 (4 - 12)	NR (NR - NR)
Azmy et al, 2013	Oxaliplatin + 5-FU + Folinic Acid (3 -Week Bolus)	24	9 (3.5 - 13)	NR (NR - NR)
Chung et al, 2013	Oxaliplatin + Leucovorin + 5-FU	44	7.15 (5.61 - 8.71)	NR (NR - NR)
El-Hadaad and Wahba, 2013	Oxaliplatin + Leucovorin + 5-FU	30	5.06 (4.45 - 5.67)	NR (NR - NR)
Ko et al, 2013	Nanoliposomal Irinotecan	40	5.2 (NR - NR)	2.4 (NR - NR)
Takahara et al, 2013	Irinotecan	56	5.3 (4.5 - 6.8)	NR (NR - NR)
Oettle et al, 2014	Oxaliplatin + 5-FU + Folinic Acid	76	5.9 (4.1 - 7.4)	2.9 (2.4 - 3.2)
Oettle et al, 2014	5-FU + Folinic Acid	84	3.3 (2.7 - 4)	2 (1.6 - 2.3)
Gill et al, 2016	Oxaliplatin + 5-FU + Folinic Acid	54	6.01 (3.12 - 7.92)	3.02 (1.68 - 5.06)
Gill et al, 2016	5-FU + Folinic Acid	54	9.79 (6.57 - 16.66)	2.83 (1.84 - 7.06)
Kobayashi et al, 2017	Oxaliplatin + Irinotecan + Leucovorin + 5-FU	18	9.8 (6.4 - 13.1)	2.8 (2.3 - 3.1)
Chung et al, 2018	Oxaliplatin + Irinotecan + Folinic Acid + 5-FU	48	9 (6.4 - 11.6)	5.8 (3.7 - 7.9)
Kim et al, 2018	Oxaliplatin + Irinotecan + Leucovorin + 5-FU	39	8.5 (5.6 - 11.4)	3.8 (1.5 - 6)
Mita et al, 2019	Nab-Paclitaxel + Gemcitabine	30	7.6 (5.7 - 8.6)	3.8 (3.3 - 4.8)
Wang-Gillam et al, 2019	Nanoliposomal Irintocen	151	4.9 (4.2 - 5.6)	2.7 (2.1 - 2.9)
Wang-Gillam et al, 2019	5-FU + Folinic Acid (Combination Control)	119	4.2 (3.3 - 5.3)	1.5 (1.4 - 1.8)
Wang-Gillam et al, 2019	5-FU + Folinic Acid (Monotherapy Control)	149	4.2 (3.6 - 4.9)	1.6 (1.4 - 1.8)
Wang-Gillam et al, 2019	Nanoliposomal Irinotecan + 5-FU + Folinic Acid	117	6.2 (4.8 - 8.4)	3.1 (2.7 - 4.2)
Ueno et al, 2020	Nanoliposomal Irinotecan + 5-FU + Leucovorin	40	6.3 (5.2 - NR)	2.7 (1.5 - 5)
Ueno et al, 2020	5-FU + Leucovorin	39	NR (6.1 - NR)	1.5 (1.4 - 1.6)
Chiorean et al, 2021	Irinotecan + Folinic Acid + 5-FU	58	6.5 (5.6 - 7.8)	2.9 (2.2 - 4.2)
Go et al, 2021	Oxaliplatin + Irinotecan + Leucovorin + 5-FU	39	9.2 (7.2 - 11)	5.2 (2.5 - 6.9)
Go et al, 2021	S-1	41	4.9 (3.8 - 8.4)	2.2 (1.7 - 2.6)
Hecht et al, 2021	Oxaliplatin + Leucovorin + 5-FU	284	6.28 (NR - NR)	2.1 (NR - NR)

N, number of patients in a trial population; NR, not reported; OS, overall survival; PFS, progression-free survival.

Figure 2. Meta-analysis of objective response in chemotherapies assessed in interventional studies including ≥2L pancreatic cancer patients



The objective response rate (ORR, proportion) was transformed using the Freeman-Tukey double arcsine transformation then back transformed to its original scale. The Clopper-Pearson method was used for confidence interval estimation of individual studies/arms. Responders denotes the number of participants who observed an objective response (complete response + partial response).
CI, confidence interval; OR, objective response.

Figure 3. Meta-analysis of progression-free survival in chemotherapies assessed in interventional studies including ≥2L pancreatic cancer patients

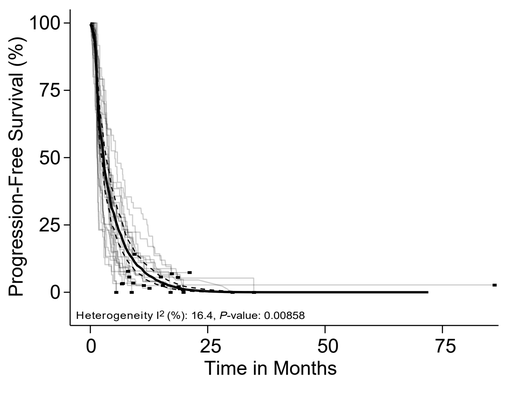
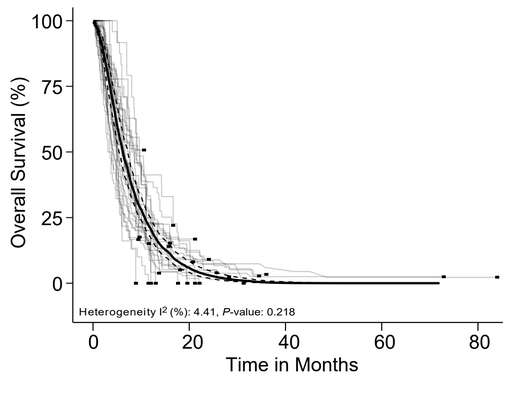


Figure 4. Meta-analysis of overall survival in chemotherapies assessed in interventional studies including ≥2L pancreatic cancer patients



Kaplan-Meier estimates of PFS among 24 study arms and for OS among 28 study arms.

Progression-free survival is defined as time from date of first dose to disease progression or death by any cause, whichever occurs first. Overall survival is defined as time from date of first dose to death by any cause. The grey lines represent the Kaplan-Meier estimates for progression-free survival events in each study. The black square represents the end of follow-up for each corresponding study. The thick black line represents the random effects pooled survival curve estimate for progression-free survival with 95% confidence bands (dashed lines). *P*-value refers to Cochran's Q test for heterogeneity.

Conclusions

- HTA agencies rely on an array of tools to evaluate a new therapy including SLR/MA, indirect treatment comparisons, network meta-analysis, and others. For example, results from such MA applied in pancreatic cancer can be used to contextualize the comparative effectiveness of novel therapies evaluated in single-arm trials to support HTA submissions
- With the vast number of therapies being developed/approved compounded with the expanding body of literature, HTA agencies increasingly rely upon synthesized evidence to inform decision making

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