Original Article

Landscape targeted of therapy in advanced pancreatic adenocarcinoma: a network meta-analysis of randomized controlled trials [2010–2024]

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Background: Advanced pancreatic adenocarcinoma (PA) remains a formidable challenge with limited therapeutic options. Gemcitabine-based regimens, often combined with novel targeted therapies, are widely employed, yet their comparative efficacy is poorly understood. This network meta-analysis (NMA) aimed to systematically evaluate the efficacy of various targeted drug combinations in previously treated patients with advanced or metastatic PA.

Methods: A systematic search of PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov was conducted to retrieve relevant randomized controlled trials (RCTs) published between 2010 and 2024. Studies comparing targeted drug combinations with chemotherapy or chemotherapy alone in advanced/metastatic PA were included in the NMA. The primary outcomes of the study were overall survival (OS) and progression-free survival (PFS), which were assessed using hazard ratios (HRs) with 95% confidence intervals (CIs) and presented in a Forest plot. Surface under the cumulative ranking (SUCRA) scores were calculated to rank treatment efficacy.

Results: In total, 13 RCTs, comprising 4,665 patients and evaluating 13 targeted drug combinations, were included in the NMA. While no statistically significant improvements in OS or PFS were observed for most targeted drug combinations compared with gemcitabine monotherapy, epidermal growth factor receptor (EGFR)-targeted agents, particularly nimotuzumab, demonstrated a significant survival benefit in specific subgroups. Similarly, indirect comparisons among targeted therapies revealed no significant differences. The SUCRA rankings identified gemcitabine plus nimotuzumab (Gem-Nimot; 98%) as having the highest probability of ranking first for OS, followed by gemcitabine plus masitinib (Gem-Masit; 80%), gemcitabine plus erlotinib (Gem-Erlot; 70%), and gemcitabine plus sorafenib (Gem-Soraf; 23%). For PFS, Gem-Nimot (98%) ranked highest, followed by Gem-Erlot (73%), gemcitabine plus rigosertib (Gem-Rigos; 57%), and gemcitabine plus sunitinib (Gem-Sunit; 8%).

Conclusions: This NMA combining network and forest plot results showed that Gem-Nimot provided significant survival benefits in advanced PA. EGFR-targeted combinations demonstrated a significant advantage in both OS and PFS compared with gemcitabine alone, indicating that EGFR inhibition may provide real clinical benefits.

Keywords: Chemotherapy; advanced pancreatic adenocarcinoma (advanced PA); targeted drugs combinations; network meta-analysis (NMA); randomized controlled trial (RCT)

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Introduction

Pancreatic adenocarcinoma (PA) is a highly lethal malignancy (1,2). It is the seventh leading cause of cancer-related mortality worldwide, and has a dismal 5-year survival rate of approximately 8% (1,2). The aggressive nature of PA is compounded by late-stage diagnosis; 80–85% of patients present with locally advanced or metastatic disease, rendering only 15–20% eligible for surgical resection (3). Recurrence rates are high, even in patients who undergo surgery, with approximately 75% relapsing within 2 years, resulting in a 5-year survival rate of ~11% (4,5). Currently, systemic chemotherapy is the cornerstone of treatment for advanced PA.

Since its approval in 1997, gemcitabine has been the standard chemotherapeutic agent for advanced PA, offering modest survival benefits compared to fluorouracil (6). In recent years, combination regimens such as gemcitabine plus nab-paclitaxel and FOLFIRINOX (a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) have demonstrated superior efficacy over gemcitabine monotherapy, establishing them as first-line therapies for locally advanced or metastatic PA (7,8). Research has shown that FOLFIRINOX extends median overall survival (OS) to 24.2 months, compared to 6–13 months with gemcitabine, but its use is limited by significant grade 3/4 toxicities, including thrombocytopenia, neuropathy, and neutropenia (6). Due to these toxicities, FOLFIRINOX is unsuitable for many patients, particularly those with poor performance status or comorbidities (9).

To address these challenges, researchers have explored novel targeted therapies combined with gemcitabine to improve efficacy while minimizing toxicity. Targeted therapies aim to inhibit specific molecular pathways critical to tumor growth and progression. For example, olaparib, a poly(ADP-ribose) polymerase inhibitor, was shown to significantly improve the progression-free survival (PFS) of patients with germline breast cancer susceptibility gene 1/2 (BRCA1/2)-mutated metastatic PA, leading to its approval by the United States Food and Drug Administration in 2019 as a first-line maintenance therapy (10,11) Similarly, gemcitabine plus erlotinib (Gem-Erlot), an epidermal growth factor receptor (EGFR) inhibitor, has shown a modest OS benefit in advanced PA (12). Other gemcitabine-based combinations, such as those with cisplatin or tegafur (S-1), have been investigated in clinical trials, but their survival benefits remain uncertain (13,14).

Despite these advances, direct head-to-head comparisons between different targeted therapy regimens are rare, creating uncertainty in clinical decision-making. A network meta-analysis (NMA) is a robust statistical approach that allows indirect comparisons. In this study, a NMA was conducted by synthesizing data from 13 randomized controlled trials (RCTs), providing insights into the relative efficacy of multiple treatments. Specifically, this study

Highlight box

Key findings

- Using data from 13 randomized controlled trials, comprising 4,665 patients, this network meta-analysis (NMA) evaluated targeted therapy combinations for advanced pancreatic adenocarcinoma (PA).
- Most targeted combinations did not significantly improve overall survival (OS) or progression-free survival (PFS) compared with gemcitabine alone.
- Epidermal growth factor receptor (EGFR)-targeted therapy, particularly gemcitabine plus nimotuzumab (Gem-Nimot), showed consistent survival benefits. The surface under the cumulative ranking results identified this combination as the highest-ranking regimen for both OS and PFS.

What is known, and what is new?

- Gemcitabine-based chemotherapy is the standard treatment for advanced PA. Many targeted agents have been tested with mixed or limited success.
- This NMA integrated direct and indirect evidence to provide the most updated comparison of targeted combinations from 2010 to 2024.
- The novel finding is that EGFR inhibition, especially with Gem-Nimot, results in a more robust and more consistent survival advantage than other targeted agents.

What is the implication, and what should change now?

- These results support prioritizing EGFR-targeted therapy as a potentially effective option for the treatment of advanced PA.
- Clinicians may use these findings to refine regimen selection for previously treated patients or those with metastatic disease.
- Future research should focus on confirming the benefit of EGFR-targeted strategies and identifying biomarkers to guide patient selection

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aimed to systematically review and compare the efficacy of gemcitabine-based targeted therapies and gemcitabine monotherapy in advanced PA, using data from phase III RCTs conducted between 2010 and 2024. By examining the comparative effectiveness of these regimens, our findings may inform clinical practice and guide future research on this challenging disease. We present this article in accordance with the PRISMA NMA reporting checklist (15) (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-452/rc).

Methods

This Bayesian NMA was prospectively registered with PROSPERO (No. CRD42023417204).

Search strategy

A comprehensive literature search was performed across PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov to retrieve relevant studies published between January 2010 and June 2024. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text terms, including: "pancreatic", "pancreas", "advanced pancreatic cancer", "randomized controlled trials", "chemotherapy", "gemcitabine", "epidermal growth factor receptor", "targeted therapy", "tyrosine kinase inhibitors", "erlotinib", "bevacizumab", and "sorafenib". To ensure completeness, the reference lists of identified studies and relevant review articles were manually reviewed to identify any additional eligible studies.

Selection criteria

Studies were included in the NMA if they met the following criteria: (I) phase III RCTs of patients with histologically or cytologically confirmed advanced or metastatic PA; (II) reporting at least one primary outcome of OS (defined as the time from randomization to death from any cause) or PFS (defined as the time from randomization to disease progression or death); (III) comparing targeted drug combinations with standard chemotherapy (e.g., gemcitabine) or chemotherapy alone; and (IV) published in English. The exclusion criteria included: (I) RCTs with overlapping patient populations; (II) studies with unclear or ambiguous clinical outcomes; and (III) trials with fewer than 40 participants to ensure sufficient statistical power. The selection process involved the initial screening of titles and abstracts, followed by full-text review to confirm eligibility. All the included studies were cross-verified for the most up-to-date available data.

Data extraction and quality assessment

Data extraction was performed independently by three investigators (H.M., S.W.) following the PRISMA guidelines, and any issues were resolved through discussion. The following data were extracted: trial name, first author, publication year, trial phase, study design, treatment regimen, follow-up duration, National Clinical Trial identifier, sample size, and clinical outcomes [hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and PFS].

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias Tool (version 5.4) (16), which evaluates five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each domain was rated as "low risk", "high risk", or "unclear risk", and the studies were categorized accordingly. The quality assessments were conducted independently by two reviewers, and any disagreements were resolved by consensus.

Statistical analysis

The primary study outcomes (OS and PFS) were analyzed using HRs with 95% CIs as the effect measures. Pairwise meta-analyses and corresponding forest plots were generated using the Meta-Analysis Online platform (https://metaanalysisonline.com/), which provides an interactive web-based environment for visualizing pooled HRs and CIs across included studies. A Bayesian NMA was performed using a fixed-effects consistency model, implemented in R (version 4.3.3) with the gemtc package (version 0.8-8) and Just Another Gibbs Sampler (version 4.3.1). Three independent Markov chains were run, each with 10,000 burn-in iterations and 50,000 sampling iterations, with a thinning interval of 10. Three independent Markov chains were run, each with 10,000 burn-in iterations and 15,000 sampling iterations, using a single-step iteration size to estimate the posterior distribution. Model convergence was assessed using trace plots and the Brooks-Gelman-Rubin diagnostic.

The treatment rankings were derived by calculating the surface under the cumulative ranking (SUCRA) scores,

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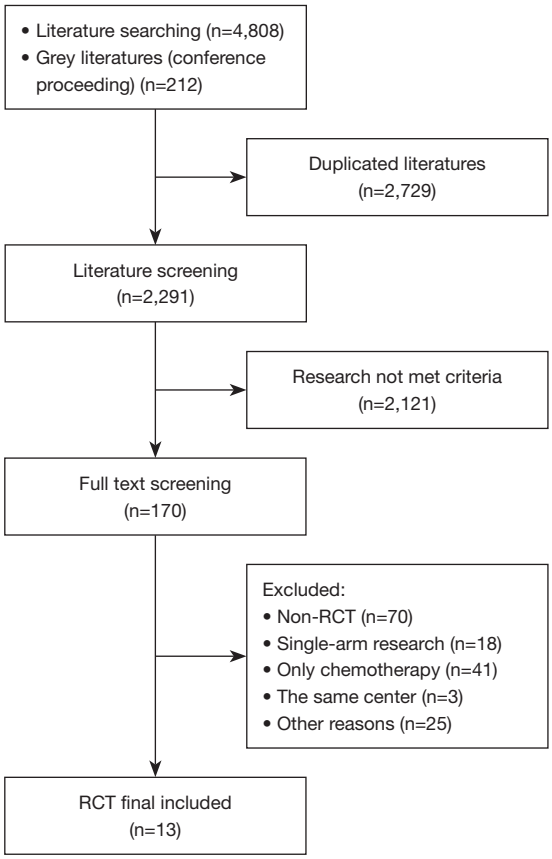


Figure 1 Flowchart of study inclusion. RCT, randomized controlled trial.

which represent the probability of a treatment being the most effective or the safest. SUCRA values range from 0% to 100%, with higher values indicating better performance. Statistical heterogeneity was evaluated using Cochran's *Q* test and the I-squared (I^2) statistic, with an I^2>50% indicating substantial heterogeneity, prompting sensitivity analyses to explore potential sources. Publication bias was assessed using Egger's regression test and funnel plots, with a P value <0.10 suggesting significant asymmetry. All the statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

Study selection and characteristics

The database search retrieved 4,808 records and 212 additional records from conference proceedings. After removing duplicates and screening the abstracts, 170 studies underwent full-text review, and 13 RCTs, comprising 4,665 patients, met the inclusion criteria (*Figure 1*). The included studies evaluated the following treatments: gemcitabine monotherapy, Gem-Erlot, gemcitabine plus bevacizumab, gemcitabine plus cetuximab, gemcitabine plus axitinib, gemcitabine plus sorafenib (Gem-Soraf), gemcitabine plus masitinib (Gem-Masit), gemcitabine plus rigosertib (Gem-Rigos), gemcitabine plus sunitinib (Gem-Sunit), and gemcitabine plus nimotuzumab (Gem-Nimot). The study characteristics are summarized in *Tables 1,2* (7,16-27).

Quality assessment

The quality of the included RCTs was assessed using the Cochrane Risk of Bias Tool. Of the studies, 12 demonstrated a low risk of bias across all domains, including randomization, allocation concealment, blinding of participants and personnel, and outcome assessment (7,16-20,22-27). One study raised "some concerns" due to the incomplete reporting of blinding procedures (*Figures 2,3*). Egger's regression test yielded a P value of 0.59, indicating no evidence of publication bias.

Efficacy outcomes

OS

In total, 13 studies were included in the OS analysis, with the network geometry depicted in *Figure 4A*. Compared to gemcitabine monotherapy, while most targeted combinations failed to improve OS, Gem-Nimot demonstrated a statistically significant advantage. A subgroup meta-analysis of phase III RCTs comparing gemcitabine-based targeted therapies with gemcitabine monotherapy for OS was performed. As shown in the forest plot (*Figure 4B*), the pooled HR for all targeted combinations was 1.03 (95% CI: 0.94–1.13, P=0.55), indicating no significant OS benefit over gemcitabine alone. Among the subgroups, EGFR-targeted therapies (including erlotinib and nimotuzumab) had a pooled HR of 0.85 (95% CI: 0.65–1.11, I^2=74.9%), suggesting a trend toward improved survival, with nimotuzumab showing a statistically significant benefit in individual trials. The multi-target subgroup (HR =1.12, 95% CI: 0.98–1.29, I^2=18.7%) and vascular endothelial growth factor (VEGF)-targeted subgroup (HR =1.17, 95% CI: 0.94–1.47, I^2=0%) did not demonstrate significant advantages. No significant subgroup differences were observed (χ^2=3.27, df=2, P=0.20).

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Table 1 Summary of included randomized controlled trials evaluating gemcitabine-based treatment strategies in pancreatic cancer

Trial/first author, year (journal)	Randomization	Treatment arm	Follow-up (months)	n	OS		PFS	
					Median (months)	HR (95% CI)	Median (months)	HR (95% CI)
Qin 2023 (*J Clin Oncol*)	1:1	Gemcitabine + nimotuzumab; gemcitabine + placebo	NA	41	10.9	0.66 (0.42–1.05)	4.2	0.60 (0.37–0.99)
			NA	41	8.5		3.6	
Schultheis 2017 (*Annals of Oncology*)	1:1	Gemcitabine + nimotuzumab; gemcitabine + placebo	NA	96	8.6	0.69 (0.49–0.98)	5.3	0.71 (0.52–1.02)
			NA	96	6		3.6	
Hammel 2016 (*JAMA*)	1:1	Gemcitabine + erlotinib; gemcitabine + placebo	34.3	219	11.9	1.19 (0.97–1.45)	6.5	1.12 (0.92–1.36)
			35.9	223	13.6		7.8	
Moore 2023 (*J Clin Oncol*)	1:1	Gemcitabine + erlotinib; gemcitabine + placebo	NA	285	6.24	0.82 (0.69–0.99)	3.75	0.77 (0.64–0.92)
			NA	284	5.91		3.55	
Kindler 2010 (*J Clin Oncol*)	1:1	Gemcitabine + bevacizumab; gemcitabine + placebo	NA	302	5.8	1.04 (0.88–1.24)	3.8	NA
			NA	300	5.9		2.9	
Kindler 2011 (*J Clin Oncol*)	1:1	Gemcitabine + axitinib; gemcitabine + placebo	6.2	314	8.5	1.01 (0.79–1.31)	4.4	1.01 (0.78–1.30)
			6.1	316	8.3		4.4	
Rougier 2013 (*European Journal of Cancer*)	1:1	Gemcitabine + aflibercept; gemcitabine + placebo	NA	271	6.5	1.165 (0.921–1.473)	3.7	1.018 (0.828–1.253)
			NA	275	7.8		3.7	
Philip 2010 (*J Clin Oncol*)	1:1	Gemcitabine + cetuximab; gemcitabine	NA	372	5.9	1.06 (0.91–1.23)	3.4	1.07 (0.93–1.24)
			NA	371	6.3		3	
Deplanque 2015 (*Annals of Oncology*)	1:1	Gemcitabine + masitinib; gemcitabine	NA	173	7.7	0.89 (0.70–1.13)	NA	NA
			NA	176	7.1		NA	
Middleton 2017 (*Lancet Oncol*)	1:1	Gemcitabine + vandetanib; gemcitabine + placebo	NA	72	8.83	1.21 (0.95–1.53)	8.04	1.11 (0.88–1.41)
			NA	70	8.95		6.09	
Bergmann 2015 (*European Journal of Cancer*)	1:1	Gemcitabine + sunitinib; gemcitabine + placebo	NA	52	7.09	1.21 (0.95–1.52)	2.7	1.15 (0.89–1.48)
			NA	54	8.56		3.1	
O'Neil 2015 (*Annals of Oncology*)	2:1	Gemcitabine + rigosertib; gemcitabine	NA	106	6.1	1.24 (0.85–1.81)	3.4	0.96 (0.68–1.36)
			NA	54	6.4		3.4	
Gonçalves A 2012 (*Annals of Oncology*)	1:1	Gemcitabine + sorafenib; gemcitabine + placebo	27.7	50	8	1.27 (0.84–1.93)	3.8	1.04 (0.70–1.54)
			27.7	52	9.2		5.7	

CI, confidence interval; HR, hazard ratio; NA, not applicable; OS, overall survival; PFS, progression-fee-survival.

The SUCRA rankings identified Gem-Nimot (98%), Gem-Masit (80%), Gem-Erlot (70%), and Gem-Soraf (23%) as the top and bottom performers for OS (*Figure 4C*).

PFS

In total, 11 studies were included in the PFS analysis (*Figure 5A*). Similar to OS, the Gem-Nimot regimen showed a statistically significant benefit in individual trials. A subgroup meta-analysis was conducted to compare the PFS of gemcitabine-based targeted therapies with gemcitabine monotherapy. As shown in the forest plot (*Figure 5B*), the pooled HR for all targeted combinations was 0.98 (95% CI: 0.88–1.08, P=0.66), indicating no significant overall improvement in PFS compared with gemcitabine alone. Among the subgroups, the EGFR-targeted agents (erlotinib and nimotuzumab) had a pooled HR of 0.82 (95% CI: 0.63–1.06, I^2=73.6%), suggesting a trend toward improved PFS. Notably, Gem-Nimot demonstrated a statistically significant benefit (HR =0.61, 95% CI: 0.37–0.99), indicating superior disease control

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Table 2 Baseline characteristics of the included randomized controlled trials

Trial/first author, year (journal)	n	Treatment arm	Age (years) (median)	Male (%)	Disease status	ECOG (%)		
						0	1	2
Qin 2023 (*J Clin Oncol*)	41	Gemcitabine + nimotuzumab	53	66	Locally advanced 22%; metastatic 78%	NA	NA	NA
	41	Gemcitabine + placebo	57	59	Locally advanced 20%; metastatic 80%	NA	NA	NA
Schultheis 2017 (*Annals of Oncology*)	96	Gemcitabine + nimotuzumab	64	65.6	Locally advanced 25.8%; metastatic 74.2%	NA	NA	NA
	96	Gemcitabine + placebo	63.2	59.1	Locally advanced 17.2%; metastatic 83.9%	NA	NA	NA
Hammel 2016 (*JAMA*)	219	Gemcitabine + erlotinib	63	50.7	NA	NA	NA	NA
	223	Gemcitabine + placebo	64	52.5	NA	NA	NA	NA
Moore 2023 (*J Clin Oncol*)	285	Gemcitabine + erlotinib	63.7	47.7	Locally advanced 23.5%; metastatic 76.5%	29.8	50.9	18.9
	284	Gemcitabine + placebo	64	57.0	Locally advanced 25%; metastatic 75%	29.9	51.8	18.3
Kindler 2010 (J Clin Oncol)	302	Gemcitabine + bevacizumab	63.7	58	Locally advanced 16%; metastatic 84%	37	51	12
	300	Gemcitabine + placebo	65	61	Locally advanced 15%; metastatic 85%	38	52	10
Kindler 2011 (J Clin Oncol)	314	Gemcitabine + axitinib	61	61	Locally advanced 25%; metastatic 72%	47	52	NA
	316	Gemcitabine + placebo	62	59	Locally advanced 23%; metastatic 72%	50	49	NA
Rougier 2013 (*European Journal of Cancer*)	271	Gemcitabine + aflibercept	62	59	NA	38	56	6
	275	Gemcitabine + placebo	61	57	NA	37	56	7
Philip 2010 (*J Clin Oncol*)	372	Gemcitabine + cetuximab	63.7	51	Locally advanced 21%; metastatic 79%	NA	NA	NA
	371	Gemcitabine	64.3	54	Locally advanced 22%; metastatic 78%	NA	NA	NA
Deplanque 2015 (*Annals of Oncology*)	173	Gemcitabine + masitinib	NA	NA	NA	NA	NA	NA
	176	Gemcitabine	NA	NA	NA	NA	NA	NA
Middleton 2017 (*Lancet Oncol*)	72	Gemcitabine + vandetanib	66.5	40	Locally advanced 29%; metastatic 71%	21	43	8
	70	Gemcitabine + placebo	67.5	43	Locally advanced 29%; metastatic 71%	19	43	8
Bergmann 2015 (*European Journal of Cancer*)	52	Gemcitabine + sunitinib	66.5	55.8	Locally advanced 21.4%; metastatic 68.5%	46.2	53.8	0
	54	Gemcitabine + placebo	61.2	51.9	Locally advanced 19.2%; metastatic 75%	42.6	57.4	0
O'Neil 2015 (*Annals of Oncology*)	106	Gemcitabine + rigosertib	63.2	65	Metastatic 97%	26	67	7
	54	Gemcitabine	61.8	57	Metastatic 98%	24	74	2
Gonçalves A 2012 (*Annals of Oncology*)	50	Gemcitabine + sorafenib	61	58	Locally advanced 17%; metastatic 83%	34	55	11
	52	Gemcitabine + placebo	64	62	Locally advanced 23%; metastatic 77%	35	59	6

ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

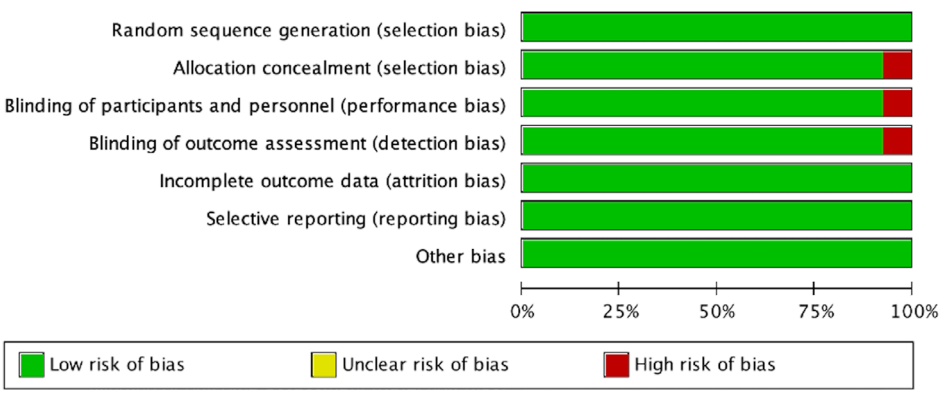


Figure 2 The risk of bias summary showing the reviewers' assessment of the risk of bias for each included study.

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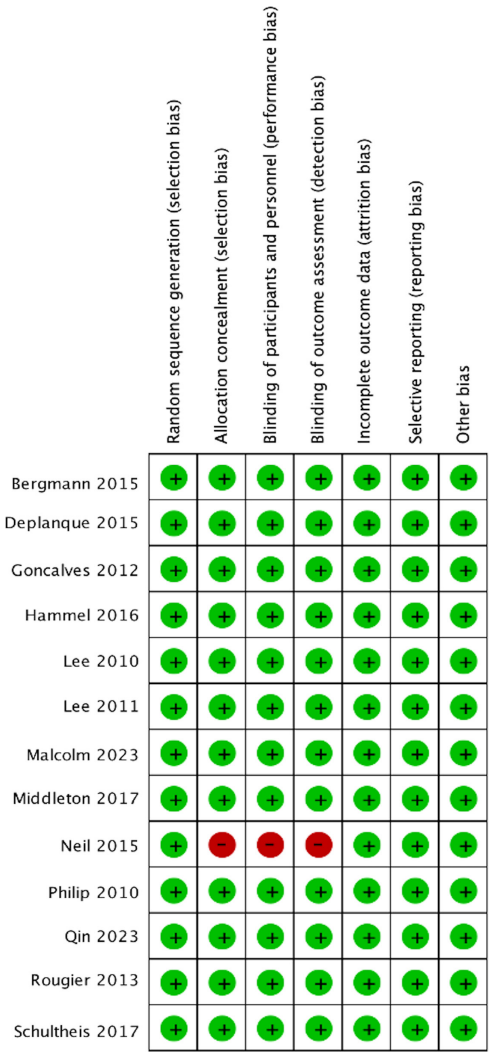


Figure 3 The risk of bias graph showing the reviewers' assessment of the risk of bias (presented as percentages for all the included studies). +, indicates low risk of bias; –, indicates high risk of bias.

compared with monotherapy. The multi-target subgroup (HR =1.09, 95% CI: 0.94–1.25, I^2=0%) and VEGF-targeted subgroup (HR =1.05, 95% CI: 0.94–1.16, I^2=0%) did not show any significant advantages. There was no significant difference among the subgroups (χ^2=3.58, df=2, P=0.17). The SUCRA rankings favored Gem-Nimot (98%), Gem-Rigos (57%), and Gem-Sunit (8%) for PFS (*Figure 5C*).

Discussion

Advanced PA poses a significant therapeutic challenge due to its aggressive biology, late diagnosis, and limited treatment options. With the emergence of targeted therapies, researchers have explored various combinations of gemcitabine and targeted agents to assess their therapeutic potential (28). This NMA comprehensively evaluated the efficacy of gemcitabine-based targeted regimens compared with gemcitabine monotherapy in patients with advanced PA, synthesizing data from 13 phase III RCTs conducted over the past 15 years.

Gemcitabine is a cornerstone of PA treatment, with FOLFIRINOX and gemcitabine plus nab-paclitaxel established as first-line options for patients with good performance status (29). However, the toxicity of FOLFIRINOX limits its applicability, necessitating alternative strategies. Targeted therapies, such as olaparib for BRCA1/2-mutated PA, have shown promise in specific subsets of patients, significantly improving PFS (12). Similarly, Gem-Erlot has been shown to modestly enhance OS and PFS (16), and nimotuzumab has been shown to benefit patients with K-Ras wild-type PA (24). Although most targeted combinations did not show a statistically significant improvement in OS or PFS compared with gemcitabine monotherapy, EGFR-targeted therapies, especially Gem-Nimot, demonstrated a significant benefit. As shown in the forest plot (*Figure 5B*), the EGFR subgroup showed a trend toward improved OS (pooled HR =0.82, 95% CI: 0.63–1.06), and Gem-Nimot achieved a significant improvement in PFS (HR =0.61, 95% CI: 0.37–0.99) (30,31).

Targeted therapies in PA aim to disrupt key oncogenic pathways. Erlotinib, cetuximab, and nimotuzumab target EGFRs, which drive tumor growth via the Ras/Raf/MEK/ERK and PI3K/AKT pathways (32). Bevacizumab, axitinib, and elpamotide inhibit VEGF receptors, critical for tumor angiogenesis (33). Tipifarnib, a farnesyltransferase inhibitor, disrupts HRAS signaling (34), while masitinib targets KIT receptors to inhibit cell survival and proliferation (35). Rigosertib, a Ras mimetic, inhibits PLK1 and PI3K pathways, inducing cell-cycle arrest (36). Ganitumab, an IGF1R antagonist, blocks mitogenic signaling (37). However, only EGFR- and BRCA-targeted agents have achieved trial endpoints, suggesting that pathway-specific efficacy may depend on tumor molecular profiles.

The genomic landscape of PA is dominated by mutations in KRAS, CDKN2A, TP53, and SMAD4 (38). While KRAS-targeted therapies, such as adagrasib and sotorasib, have shown efficacy in non-small cell lung cancer, their role in PA remains investigational (39,40). The heterogeneity of PA subtypes, driven by distinct combinations of somatic mutations, underscores the need for personalized

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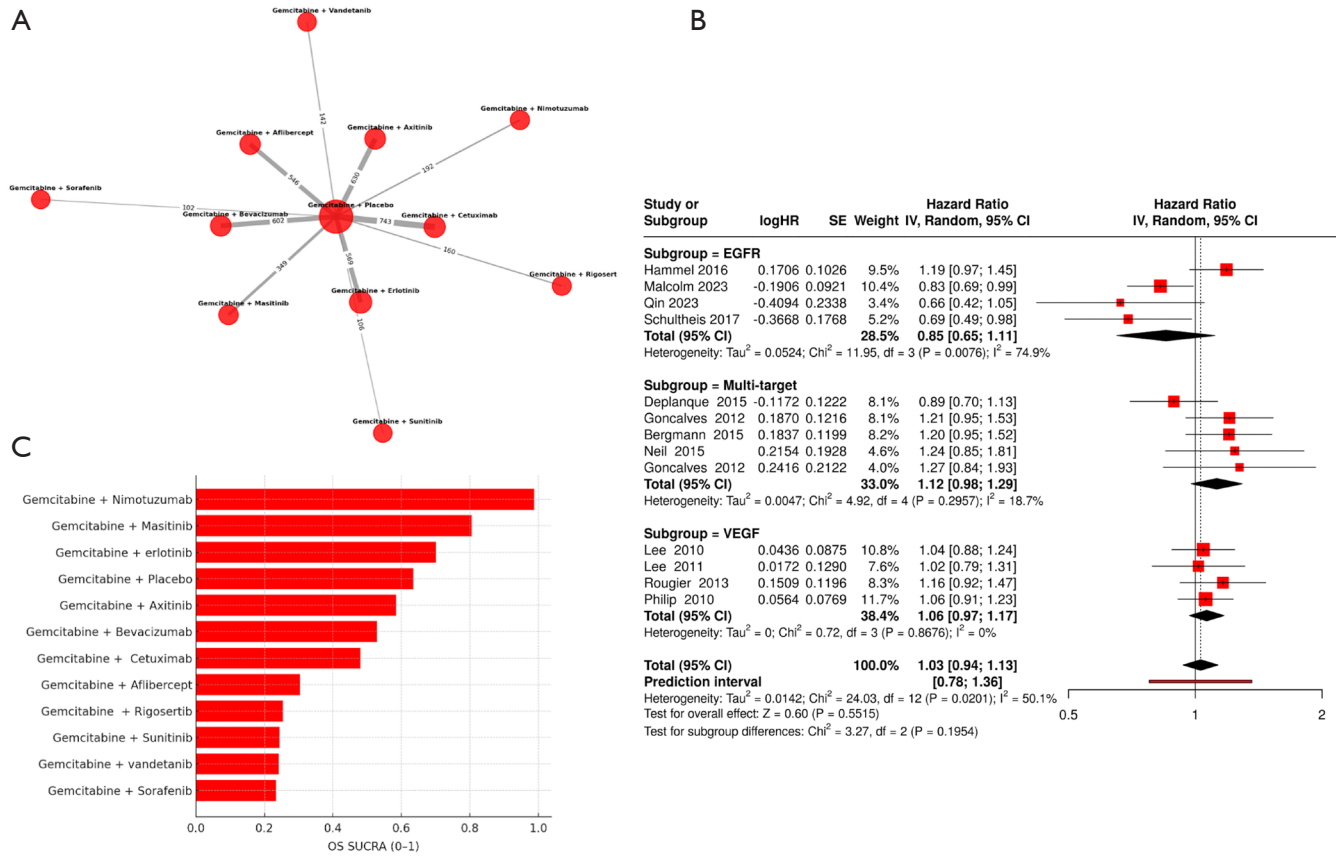


Figure 4 Summary of OS results from the network meta-analysis. (A) Network plot of all treatment comparisons included in the OS analysis. The width of each connecting line is proportional to the number of trials comparing the two treatments, while the node size reflects the number of participants randomized to each intervention. (B) Forest plot showing pooled HRs and 95% CIs for OS for each gemcitabine-based targeted therapy compared with gemcitabine monotherapy. (C) SUCRA probabilities ranking all regimens according to their likelihood of providing the best OS benefit. CI, confidence interval; HR, hazard ratio; IV, inverse variance; OS, overall survival; SE, standard error; SUCRA, surface under the cumulative ranking.

approaches (41). For example, patients with BRCA1/2 mutations or KRAS wild-type tumors may benefit from specific targeted therapies, but these subgroups represent only 10–15% of cases (3). The broader applicability of targeted therapies requires further elucidation of resistance mechanisms and the identification of predictive biomarkers.

Our findings indicate that in PA, gemcitabine combined with EGFR-targeted agents, particularly nimotuzumab, demonstrated notable therapeutic efficacy, whereas other targeted agents, including VEGF inhibitors and multi-target tyrosine kinase inhibitors, showed limited benefits. These results suggest that EGFR-targeted combinations with gemcitabine may offer superior clinical outcomes, providing a promising direction for the development of future targeted combination therapies. However, it is important to note that pancreatic ductal adenocarcinoma harbors a high frequency of KRAS mutations (approximately 90%), which are known to confer intrinsic resistance to EGFR inhibition. Consequently, the efficacy of EGFR-targeted therapies may be restricted to patients with KRAS wild-type tumors.

Future research should therefore focus on the development of precise KRAS inhibitors targeting common variants such as G12D, G12A, G12R, and G12S, which represent the dominant mutational spectrum in pancreatic cancer. Although several KRAS-directed agents have emerged, such as sotorasib, adagrasib, and RMC-9805, most remain in early clinical development, and a phase III trial has yet to be completed. Taken together, these findings emphasize that molecular stratification based on KRAS

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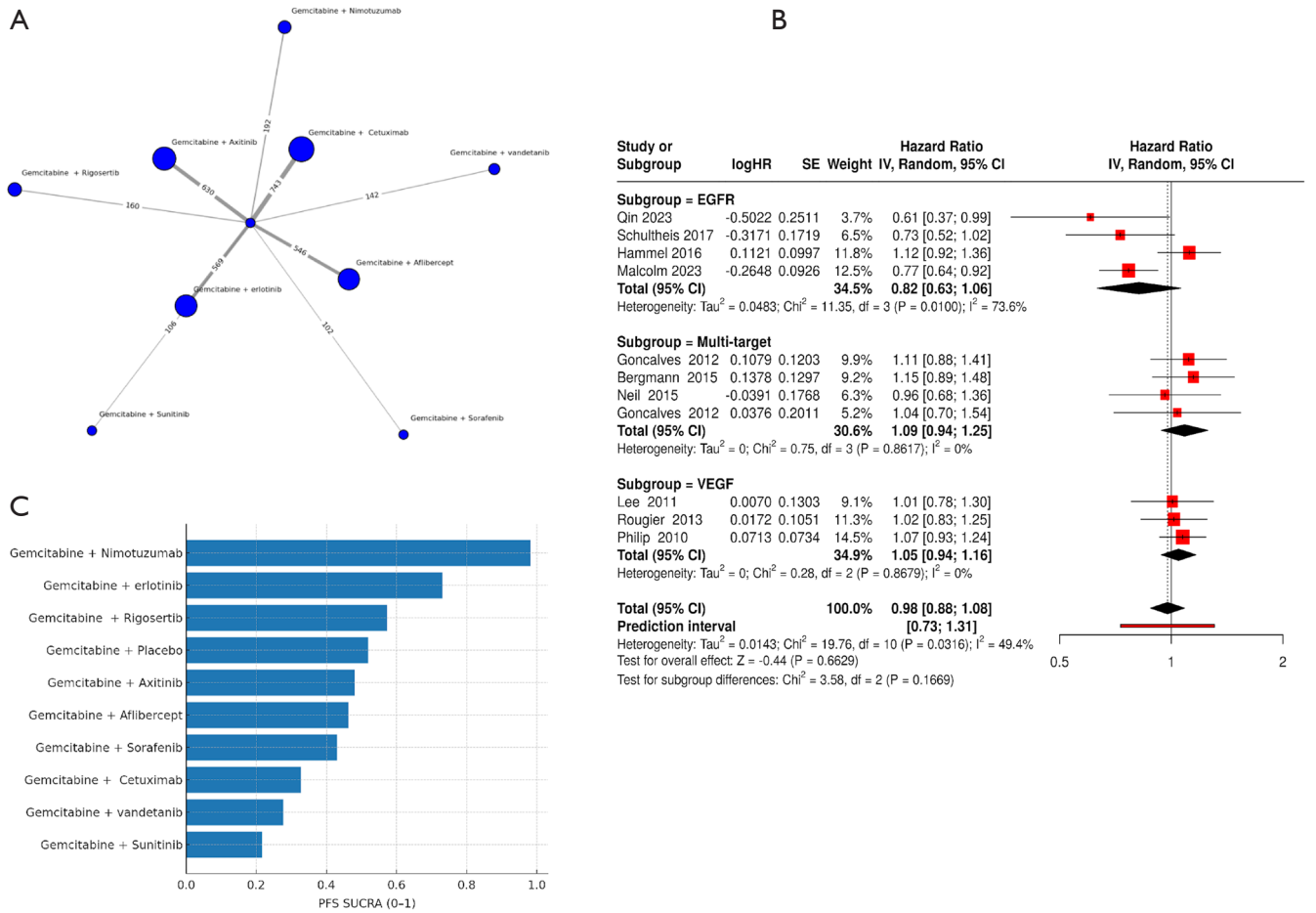


Figure 5 Summary of PFS results from the network meta-analysis. (A) Network plot of treatment comparisons included in the PFS analysis, with the line width proportional to the number of trials and the node size proportional to sample size. (B) Forest plot presenting pooled HRs and 95% CIs for PFS for each gemcitabine-based targeted combination versus gemcitabine monotherapy. (C) SUCRA-based ranking of all regimens according to their probability of being the most effective for improving PFS. CI, confidence interval; HR, hazard ratio; IV, inverse variance; PFS, progression-free survival; SE, standard error; SUCRA, surface under the cumulative ranking.

mutational status is essential to optimize the efficacy of targeted therapies in pancreatic cancer.

Limitations

This study had a number of limitations. First, the 15-year span of the included studies might have introduced time-related heterogeneity, as clinical practice and therapeutic standards have evolved during this period. Second, several studies included in this meta-analysis did not report data on PFS, which might have affected the completeness and robustness of the overall analysis. The absence of PFS information limited our ability to perform a comprehensive comparison of treatment efficacy across all included trials and might have introduced uncertainty in the interpretation of survival outcomes. Third, this NMA included trials with heterogeneous study populations, treatment lines, and clinical settings, which might have introduced potential bias. Differences in patient characteristics, disease stage, and prior treatments across studies could have affected treatment responses and survival outcomes. Although subgroup analyses based on molecular targets were performed to partially address this issue, the lack of uniform patient-level data limited our ability to conduct more detailed stratified analyses. Fourth, most of the included studies did not perform or report detailed molecular profiling of patients, such as KRAS or EGFR mutation status. This lack of genetic information limited our ability to conduct subgroup

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analyses based on molecular alterations. Consequently, subgroup analyses in this study were performed according to the molecular targets of the drugs rather than patient-specific genotypes. Future studies incorporating biomarker-driven stratification need to be conducted to better evaluate the efficacy of targeted therapies in defined molecular subgroups. Fifth, this study was based on aggregated data extracted from published clinical trials rather than individual patient data (IPD). As a result, adjustments for important covariates such as age, sex, disease stage, and molecular status could not be performed. This might have diluted the true treatment effects or introduced residual confounding across studies. Although this limitation is inherent to most NMAs based on trial-level data, we acknowledge that future analyses incorporating IPD would allow for more precise estimation and covariate adjustment.

Conclusions

This NMA, which included 13 RCTs comprising 4,665 patients, provides a comprehensive comparison of gemcitabine-based targeted therapies with gemcitabine monotherapy in the treatment of advanced PA. No targeted combination significantly improved OS or PFS compared to gemcitabine alone, and indirect comparisons among targeted therapies showed no significant differences. The SUCRA rankings identified Gem-Nimot (98%) as having the highest probability of ranking first for OS, followed by Gem-Masit (80%), Gem-Erlot (70%), and Gem-Soraf (23%). For PFS, Gem-Nimot (98%) ranked highest, followed by Gem-Erlot (73%), Gem-Rigos (57%), and Gem-Sunit (8%). Although the SUCRA rankings reflect the relative probability of treatment efficacy among different regimens, their clinical significance should be interpreted with caution. A higher SUCRA value does not necessarily indicate a clinically meaningful benefit. In this study, Gem-Nimot showed the highest SUCRA probabilities for both OS and PFS (98%), suggesting a potential therapeutic advantage; however, this finding mainly reflects the trend and consistency of the observed effects rather than definitive superiority. Other regimens, such as Gem-Masit, Gem-Erlot, and Gem-Soraf, ranked lower, and did not demonstrate any clear clinical benefits. Therefore, SUCRA rankings should be regarded as complementary indicators of relative efficacy trends rather than direct evidence of clinical superiority. These findings highlight the limited efficacy of current targeted therapies in PA and underscore the urgent need for personalized treatment strategies targeting specific molecular subtypes. Future research should focus on integrating genomic profiling, overcoming resistance mechanisms, and developing novel combination therapies to improve outcomes for patients with this devastating disease.

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Footnote

Reporting Checklist: The authors have completed the PRISMA NMA reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-452/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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