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REVIEW ARTICLE

Efficacy and safety of gemcitabine-based combination therapy for the treatment of advanced pancreatic cancer: A Systematic Review and Meta-analysis

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Abstract

Introduction: Pancreatic ductal adenocarcinoma is a cause of cancer mortality, and patients present with unresectable locally advanced or metastatic disease, for which gemcitabine-based chemotherapy has been central despite modest survival gains. **Objective:** This systematic review and meta-analysis assessed whether adding a cytotoxic agent to gemcitabine improves outcomes in pancreatic cancer. **Methods:** Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 and Cochrane methods, phase III trials comparing gemcitabine plus a cytotoxic agent versus gemcitabine alone were identified (PubMed/MEDLINE 2002–2026). **Results:** Thirteen trials (14 publications; 5,090 patients; 2002–2017) were synthesized using random-effects DerSimonian–Laird models with Hartung–Knapp–Sidik–Jonkman adjustments. Adding a cytotoxic partner reduced mortality (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.82–0.95; $I^2 = 33\%$), an 0.9-month median survival increase from a 6.7-month control, with partner-dependent effects (subgroup $P = 0.013$): nab-paclitaxel showed benefit (HR: 0.72), fluoropyrimidines were beneficial (HR: 0.86; $I^2 = 0\%$), whereas platinum analogues were non-significant (HR: 0.91) and irinotecan/exatecan/pemetrexed showed no survival benefit (HR: 0.98). Progression-free survival (3 trials) improved (HR 0.80), but heterogeneity limited precision. Objective response nearly doubled (17.7% vs. 8.8%; risk ratio 1.91 random-effects), yet gains did not reliably translate into survival improvements. Toxicity increased, with neutropenia, fatigue, and neuropathy with nab-paclitaxel. **Conclusion:** Overall, gemcitabine doublets confer a survival benefit not generalizable across agents; meaningful advantage is concentrated in nab-paclitaxel and, to a lesser extent, fluoropyrimidines, supporting selection based on pharmacologic rationale and patient fitness rather than response alone.

Key words: Cytotoxic agent, gemcitabine, overall survival, pancreatic ductal adenocarcinoma

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INTRODUCTION

Pancreatic ductal adenocarcinoma remains among the deadliest solid tumors. According to GLOBOCAN 2022, an estimated 510,992 new cases and 467,409 deaths occurred globally, making pancreatic cancer the sixth leading cause of cancer-related mortality.[1] Most patients present with locally advanced, unresectable, or metastatic disease, for which systemic chemotherapy is the main treatment, intended to extend survival and relieve symptoms.[2]

In 1997, gemcitabine became the standard first-line therapy after a randomized trial showed a clinical benefit response of 23.8% versus 4.8% and median survival of 5.65 months versus 4.41 months compared with fluorouracil.[3] Gemcitabine is a prodrug analogue of deoxycytidine. It enters cells mainly via the human equilibrative nucleoside transporter 1 (hENT1) and is converted by deoxycytidine kinase into its active triphosphate form, which integrates into DNA, while its diphosphate form inhibits ribonucleotide reductase, enhancing activation.[4,5] Activation is saturable, the drug is rapidly deactivated by cytidine deaminase, and low hENT1 expression is linked to poorer outcomes with gemcitabine.[6] These limitations, together with desmoplastic stroma hindering drug delivery, supported combining gemcitabine with agents with different mechanisms and non-overlapping toxicities.

Over the next two decades, gemcitabine was tested with fluoropyrimidines, platinum analogs, topoisomerase-I inhibitors, an antifolate, and other cytotoxic agents in many phase III trials, most of which did not show a significant survival benefit individually. However, two combinations changed practice: gemcitabine plus albumin-bound (nab) paclitaxel, which reduced death risk by 28% in the MPACT trial,[7] and gemcitabine plus the epidermal growth factor receptor inhibitor erlotinib, which produced a but significant improvement in the NCIC PA.3 trial.[8] FOLFIRINOX also outperformed gemcitabine (hazard ratio [HR] for death 0.57) but is limited to patients with performance status.[9]

Several meta-analyses synthesized these findings. Heinemann *et al*. analyzed 15 trials (4,465 patients) and reported a pooled HR of 0.91 (95% confidence interval [CI] 0.85–0.97), with benefits mainly in platinum and fluoropyrimidine combinations.[10] Later analyses were similar,[11-13] while other reviews found no survival advantage from adding targeted agents to gemcitabine.[14,15] Specific partners may drive benefit, not any second cytotoxic drug.

Consequently, we conducted a systematic review and meta-analysis of randomized phase III trials to assess the effectiveness and safety of adding a cytotoxic agent to gemcitabine for advanced pancreatic cancer, focusing on overall survival. Secondary aims included progression-free survival, objective response, toxicity, and, through a pre-specified subgroup analysis, whether survival impact varies by partner drug class (platinum analogues, fluoropyrimidines, other cytotoxic agents, and albumin-bound taxane).

MATERIALS AND METHODS

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement,[16] and the methodologies in the Cochrane Handbook.[17]

We considered randomized phase III trials involving adults with histologically or cytologically confirmed, untreated, locally advanced (unresectable), or metastatic pancreatic ductal adenocarcinoma. Trials compared gemcitabine plus additional cytotoxic agents, including albumin-bound formulations and oral fluoropyrimidine prodrugs, versus gemcitabine alone. Trials had to report overall survival as an HR with CI, or provide survival data enabling calculation. We excluded adjuvant, neoadjuvant, second-line, randomized phase II, and conference-abstract-only studies, as well as trials using non-cytotoxic agents, more than one additional drug, or two gemcitabine control arms with different infusion schedules. Combinations with targeted agents were excluded because they were synthesized separately.

Searches covered PubMed/MEDLINE from January 01, 2002 to July 31, 2026 for English reports. The PubMed strategy used terms for pancreatic neoplasms, gemcitabine, combination or comparison terms, and a randomized trial filter; equivalent strategies were adapted for other databases. Oncology proceedings were used to locate reports, and reference lists of included trials and meta-analyses were screened.

Two reviewers independently screened titles, abstracts, and texts; disagreements were resolved by a third reviewer. Two reviewers independently extracted data using a piloted form. For trials with multiple reports, the most mature overall survival analysis was selected.

A hierarchy was applied to each trial. HR and CI from the publication or update were used. If survival data were reported, we used HR and CI derived from survival curves and summary statistics by Heinemann *et al*., following Parmar *et al*.[10,18,19] Otherwise, HR was estimated from the ratio of median survivals and error from the log-rank *P*-value.[20] These trials were flagged for sensitivity analyses. For the 97.5% CI, the error used the normal quantile (2.241). Response counts were reconstructed from percentages and arm sizes, accepted if within 0.1% points.

Overall survival was assessed from randomization to death from any cause. Progression-free survival and time to progression were combined only when an HR with a CI was available, and the objective response followed each trial's

criteria. The intention-to-treat population was used whenever applicable. In the three-arm GEST trial, only gemcitabine plus S-1 versus gemcitabine alone was included, excluding S-1 monotherapy to avoid duplication of the control group. Clinical heterogeneity was documented before pooling and addressed through prespecified subgroup and sensitivity analyses.

The risk of bias (RoB) for overall survival was evaluated using the Cochrane RoB 2 tool,[21] and certainty of evidence using the GRADE approach.[22] The effect measure was the natural logarithm of the HR, with HR below 1 favoring the combination. Because the regimens, schedules, and eras differed, the primary analysis used a random-effects DerSimonian-Laird model.[23] CIs used the Hartung–Knapp–Sidik–Jonkman adjustment.[24] Statistical heterogeneity was measured using the Chi-Square Test (Cochran's Q), Tau-Squared (τ^2, between-study variance), inconsistency percentage (I^2),[25] and a 95% prediction interval was computed.[26]

The pre-specified subgroup analysis grouped trials by partner class, with a between-subgroup Q test. Sensitivity analyses included leave-one-out and cumulative meta-analyses; exclusion of the trial with an estimated HR; restriction to trials with directly reported HRs; exclusion of trials with fewer than 200 patients; restriction to trials published from 2005; and exclusion of the trial using fixed-dose-rate gemcitabine only in the experimental arm. Small-study effects were investigated using a funnel plot, Egger's regression test,[27] and Begg's rank correlation test,[28] interpreted cautiously with 13 trials. Objective response was analyzed as a risk ratio using Mantel–Haenszel fixed-effect,[29] and DerSimonian–Laird random-effects estimates. Toxicity was summarized narratively due to inconsistent event definitions and grading scales. All tests were two-sided with $\alpha = 0.05$. Analyses were conducted in Python 3.12 (NumPy, SciPy, Matplotlib); the primary DerSimonian–Laird results were verified against statsmodels (version 0.15), which exactly reproduced the pooled estimate, Q, and τ^2.

RESULTS

Through structured searches, the authors identified 110 studies from PubMed. The initial screening process involved application of predetermined eligibility criteria. After excluding 46 studies owing to unavailable full-text data, 64 were screened. Of these, 45 studies were excluded. The remaining 19 studies underwent an eligibility assessment, resulting in five studies being excluded due to inadequate data and conclusions. In this review, representative trials are excluded.[8,9,30-37] Ultimately, 14 papers satisfied the inclusion criteria and were included in this systematic review.[7,38-50] Figure 1 illustrates the selection process. Thirteen randomized phase III trials, reported in 14 publications (the GEST trial contributed a primary report and a long-term update), met the eligibility criteria.

From 2002 to 2017, 13 trials were conducted, involving 5,090 patients [Table 1]. Among 12 trials reporting arm sizes, 2,440 patients received combination therapy and 2,436 gemcitabine alone. The sample sizes ranged from 107 to 861 participants. Four trials incorporated platinum analogues, using cisplatin in three and oxaliplatin in one.[39-42] Five employed fluoropyrimidines: Bolus fluorouracil and capecitabine in three, and S-1 in one.[38,43-47] Three utilized irinotecan, pemetrexed, or exatecan,[48-50] and one involved nab-paclitaxel.[7] The HR was stated in four trials, derived from survival data in eight, and estimated by us in one [Table 1].

Thirteen trial reports were evaluated across the five RoB 2 domains concerning overall survival, focusing on the impact of treatment assignment. There were some concerns regarding the 13 trials.

Since overall survival is objective, the lack of blinding likely did not affect the primary outcome, although it may have influenced the response and toxicity assessment. Adding a second cytotoxic drug to gemcitabine reduced the mortality risk (random-effects HR: 0.88, 95% CI: 0.82–0.95, $P = 0.0008$; [Figure 2]). Heterogeneity was low to moderate ($Q = 18.02$, 12 degrees of freedom, $P = 0.12$, $I^2 = 33\%$, $\tau^2 = 0.006$). Under an exponential survival model, this HR corresponds to approximately 0.9 months longer median survival from a 6.7-month control.

Survival effects varied by drug (test for subgroup differences $Q = 10.86$, 3 degrees of freedom, $P = 0.013$; [Table 3]). Nab-paclitaxel had the largest effect (HR 0.72, 0.62–0.83; one trial with 861 patients). Fluoropyrimidines were beneficial (five trials, 1,940 patients; HR: 0.86, 0.78–0.95, $P = 0.002$; $I^2 = 0\%$; Hartung–Knapp interval, 0.75–0.98). Platinum analogs had an uncertain, non-significant effect (four trials, 1,015 patients; HR: 0.91, 0.77–1.08; $I^2 = 34\%$), with the GIP-1 trial differing from the others. Irinotecan, exatecan, and pemetrexed had none (three trials, 1,274 patients; HR: 0.98, 0.87–1.11; $I^2 = 0\%$). Excluding nab-paclitaxel, subgroup differences disappeared ($Q = 2.95$, 2 degrees of freedom, $P = 0.23$). Across 12 cytotoxic doublets, excluding nab-paclitaxel (4,229 patients), the combined HR was 0.91 (0.85–0.97; $P = 0.005$) with no heterogeneity ($I^2 = 0\%$; $\tau^2 = 0$) and a 95% prediction interval of 0.85–0.98.

Among platinum trials, oxaliplatin plus fixed-dose-rate gemcitabine improved progression-free survival and response rates (26.8% versus 17.3%), with median survival of 9.0 versus 7.1 months,[40] whereas cisplatin improved progression-free survival (HR: 0.75, $P = 0.053$) and stable disease without a significant survival benefit.[41] The largest platinum trial, GIP-1, found no survival, progression-free survival, or response advantage, and less clinical benefit with the combination therapy.[42]

Among fluoropyrimidines, bolus fluorouracil improved progression-free survival but not overall

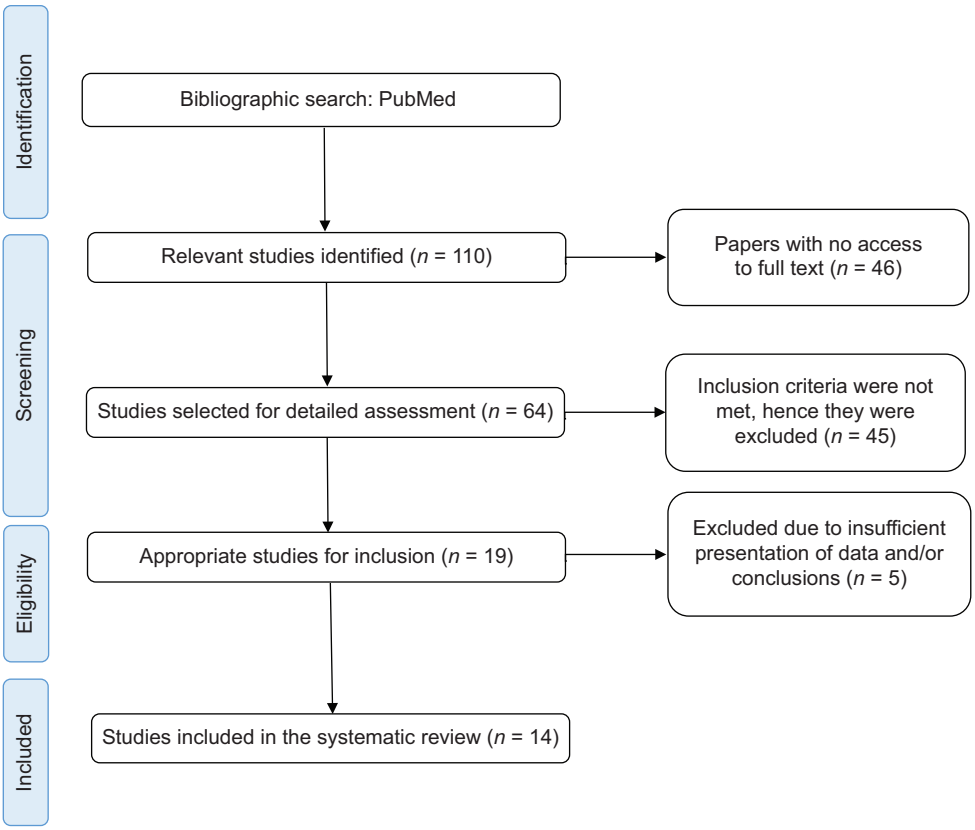


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart depicting the literature search and study selection process for the systematic review.

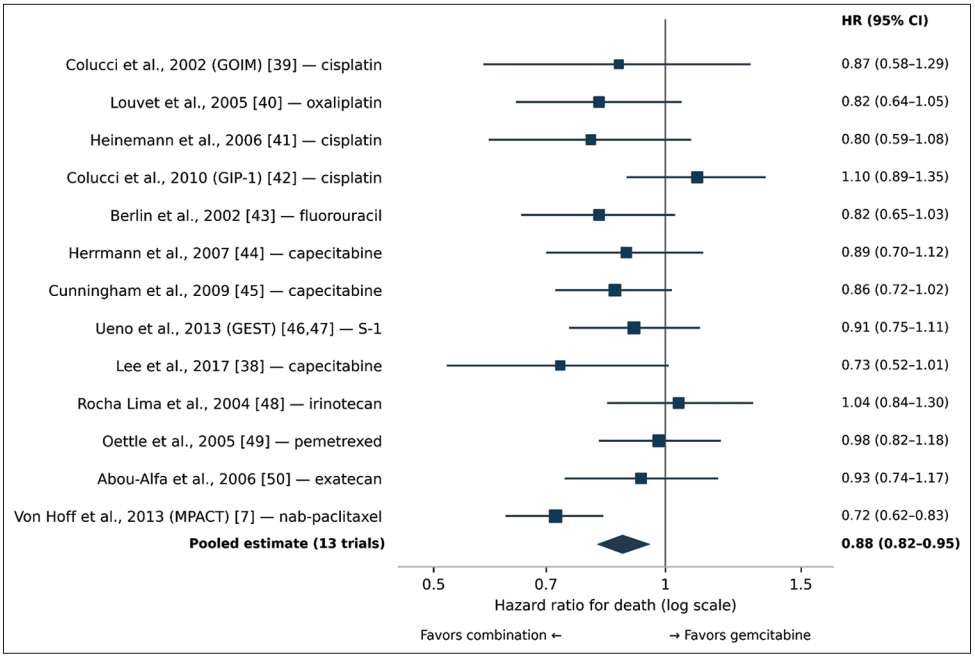


Figure 2: Forest plot illustrating the hazard ratio for mortality using gemcitabine-based combinations compared to gemcitabine alone, categorized by partner drug class

survival.[43] Capecitabine increased response and progression-free survival in the largest trial,[45] and improved response in the Korean trial.[38] In the GEST trial, the median survival was 9.9 versus 8.8 months and 1-year survival was 40.4% versus 35.0%.[47] Pemetrexed and irinotecan increased response but not survival, and exatecan did not change either.[50] In the MPACT, 1-year and 2-year survival rates were 35% versus 22% and 9% versus 4%,

Table 1: Characteristics of the included randomized phase III trials

Trial	Setting	No. of patients	Combination regimen	Met., %	Median OS, mo	OS HR (95% CI)
Von Hoff *et al.*, 2013 (MPACT)[7]	North America, Europe, Australia	431/430	Nab-Paclitaxel 125 mg/m^2+gem d1,8,15, q4w	100	8.5 versus 6.7	0.72 (0.62–0.83)
Lee *et al.*, 2017[38]	South Korea	214	Gem d1,8,15+capecitabine 1660 mg/m^2, q4w	—	10.3 versus 7.5	0.73 (0.52–1.01)†
Colucci *et al.*, 2002 (GOIM)[39]	Italy	53/54	Gem+cisplatin 25 mg/m^2 weekly (6 of 7 wk)	62/54	—	0.87 (0.58–1.29)*
Louvet *et al.*, 2005[40]	France, Italy	157/156	FDR gem (10 mg/m^2/min) d1+oxaliplatin 100 mg/m^2 d2, q2w	68/70	9.0 versus 7.1	0.82 (0.64–1.05)*
Heinemann *et al.*, 2006[41]	Germany	98/97	Gem d1,8,15+cisplatin 50 mg/m^2 d1,15, q4w	80/79	7.5 versus 6.0	0.80 (0.59–1.08)*
Colucci *et al.*, 2010 (GIP-1)[42]	Italy	201/199	Gem+cisplatin 25 mg/m^2 weekly	84 (overall)	7.2 versus 8.3	1.10 (0.89–1.35)
Berlin *et al.*, 2002[43]	USA (ECOG)	160/162	Gem+bolus 5-FU 600 mg/m^2 weekly, 3 of 4 wk	89/90	6.7 versus 5.4	0.82 (0.65–1.03)*
Herrmann *et al.*, 2007[44]	Multicenter, Europe	160/159	Gem d1,8+capecitabine 650 mg/m^2 twice daily d1–14, q3w	80/79	8.4 versus 7.2	0.89 (0.70–1.12)*
Cunningham *et al.*, 2009[45]	Multicenter, Europe	267/266	Gem d1,8,15+capecitabine 830 mg/m^2 twice daily d1–21, q4w	70/71	—	0.86 (0.72–1.02)
Ueno *et al.*, 2013 (GEST)[46,47]	Japan, Taiwan	275/277	Gem d1,8+S-1 60–100 mg/day (by BSA) d1–14, q3w	76 (overall)	9.9 versus 8.8	0.91 (0.75–1.11)‡
Rocha Lima *et al.*, 2004[48]	Multicenter	180/180	Gem d1,8+irinotecan 100 mg/m^2 d1,8, q3w	82/81	6.3 versus 6.6	1.04 (0.84–1.30)*
Oettle *et al.*, 2005[49]	Multicenter	283/282	Gem 1250 mg/m^2 d1,8+pemetrexed 500 mg/m^2 d8, q3w	90/92	6.2 versus 6.3	0.98 (0.82–1.18)*
Abou-Alfa *et al.*, 2006[50]	Multicenter	175/174	Gem d1,8+exatecan 2 mg/m^2 d1,8, q3w	79/78	6.7 versus 6.2	0.93 (0.74–1.17)*

Values are shown as gemcitabine combination/gemcitabine alone. Patient numbers are randomized totals; Lee *et al.* provided only the total randomized (214). Median OS in months. A dash (—) signifies that the value was not extracted or tabulated; it does not imply zero. Met.: Metastatic disease patients, OS: Overall survival, HR: Hazard ratio for death (combination compared to gemcitabine alone), CI: Confidence interval, gem: Gemcitabine, 5-FU: Fluorouracil, FDR: Fixed-dose-rate infusion, BSA: Body surface area, d: Treatment day, wk: Week, q2w: Every 2 weeks, q3w: Every 3 weeks, q4w: Every 4 weeks. Unless otherwise specified, gemcitabine doses are 1000 mg/m^2. *HR and 95% CI derive from survival data outlined in the manuscript (reference 10); these were not directly reported by each trial. †Lee *et al.*: HR and 95% CI are estimated from median survival and log-rank P=0.06; confirm this approximation with the source before combining data. ‡GEST: the interval shown is a 97.5% CI from a longer-term report, not a 95% CI. Both GEST reports pertain to a single trial

respectively, with a median progression-free survival of 5.5 versus 3.7 months.[7]

The pooled estimates remained consistent across the sensitivity analyses, with values between 0.87 and 0.89. The leave-one-out estimates ranged from 0.86 (0.80–0.92) excluding GIP-1 to 0.91 (0.85–0.97) excluding the MPACT trial [Figure 3b]. Excluding MPACT reduced I^2 from 33% to 0%. In the cumulative analysis, the upper confidence limit first fell below 1 in 2006 (seven trials; HR: 0.91, 0.83–0.997) and remained below 1 thereafter, reaching 0.88 (0.82–0.95) with all 13 trials included. Limiting the analysis to four trials with directly reported HRs yielded 0.88 (0.74–1.04; $P = 0.13$), matching the overall point estimate but with a broader interval and higher heterogeneity ($I^2 = 74\%$), as MPACT and GIP-1 were at opposite ends of the spectrum. The funnel plot was symmetric [Figure 3a]. Both Egger's (intercept 0.36, standard error 1.42, P = 0.80) and Begg's tests (Kendall's $\tau = -0.23$, P = 0.31) indicated no small-study effects; Egger's test remained non-significant after excluding MPACT (P = 0.18). Sensitivity analyses showed consistent pooled estimates (0.87–0.89). The leave-one-out estimates varied from 0.86 (0.80–0.92) without GIP-1 to 0.91 (0.85–0.97) without the MPACT trial [Figure 3b]. Removing MPACT decreased I^2 from 33% to 0%. In the cumulative analysis, the upper confidence limit dropped below 1 in 2006 (seven trials; HR: 0.91, 0.83–0.997) and remained below 1, reaching 0.88 (0.82–0.95) with all 13 trials included. Restricting the analysis to four trials with directly reported HRs yielded 0.88 (0.74–1.04; P = 0.13), which aligned with the overall estimate but with a wider interval and greater heterogeneity ($I^2 = 74\%$), as MPACT and GIP-1 were at opposite ends.

Nine trials (3,656 patients) allowed for the reconstruction of objective response counts. An objective response occurred in 324 of 1,830 patients (17.7%) who received the combination and 161 of 1,826 patients (8.8%) who received gemcitabine alone. The Mantel–Haenszel risk ratio was 2.01 (1.68–2.39), and the random-effects risk ratio was 1.91 (1.45–2.51; P < 0.0001; $I^2 = 51\%$; Q P = 0.04; 95% prediction interval: 0.90–4.07) [Figure 4a]. Excluding nab-paclitaxel, the risk ratio was 1.70 (1.36–2.13; $I^2 = 13\%$). Higher response rates did not translate into survival improvements: irinotecan and pemetrexed increased response (risk ratios 3.62 and 2.09, respectively) without affecting survival.

Three trials (1,794 patients) provided a progression-free survival HR with CI. The combined HR was 0.80 (0.66–0.97; P = 0.02), with significant heterogeneity ($I^2 = 69\%$; Q P = 0.04; individual HRs: 0.69 for MPACT, 0.78 for capecitabine, and 0.97 for GIP-1) [Figure 4b]. With only three trials, the Hartung–Knapp interval was broad (0.52–1.22), making this estimate exploratory.

Quantitative pooling of toxicity data was not feasible. Nab-paclitaxel increased grade 3 or higher neutropenia (38% compared to 27%), fatigue (17% compared to 7%), and peripheral neuropathy (17% compared to 1%).[7] In European and Korean capecitabine trials, overall grade 3–4 toxicity was comparable between groups, with neutropenia most common.[38,44] Cisplatin trials indicated higher hematological toxicity in the combination arm, without significant non-hematological increase.[41,42] Combined single-arm gemcitabine–capecitabine data showed 19.7% grade 3 or higher neutropenia (95% CI 12.8–26.7).[51]

We did not combine subgroup data because definitions and reporting varied, but three sources provide insights. In extended GEST analysis, the HR for gemcitabine combined with S-1 was 0.74 (95% CI 0.56–0.98) for patients with a performance status of 1, 1.01 (97.5% CI 0.79–1.30) for those with a performance status of 0, and 0.73 (0.51–1.04) for patients with locally advanced disease.[47] In the Swiss–Central European capecitabine study, post hoc analysis of patients with a Karnofsky score of 90–100 showed a survival of 10.1 versus 7.4 months ($P = 0.014$), although the difference was not statistically significant.[44] A meta-analysis found similar HRs by performance status.[10]

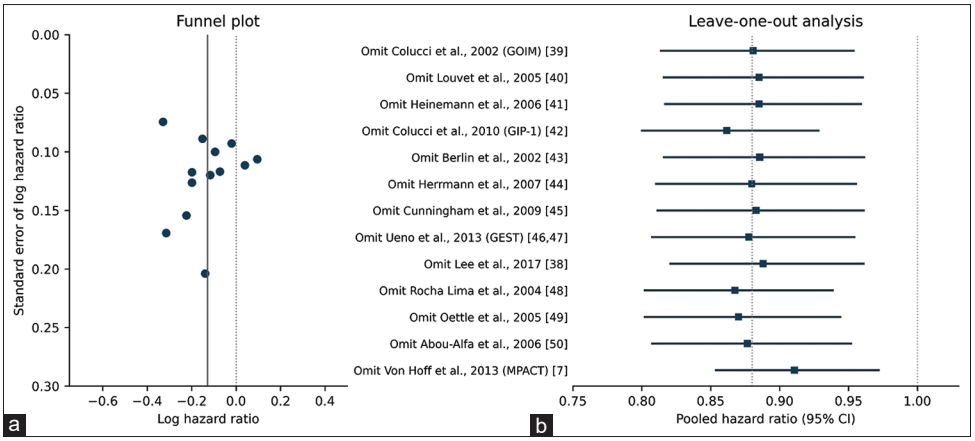


Figure 3: (a) Funnel plot depicting log hazard ratio against standard error; the shaded region represents the pseudo 95% confidence interval surrounding the random-effects estimate (Egger $P = 0.80$). (b) Leave-one-out analysis showing pooled hazard ratio (95% confidence interval) after excluding each trial; the dashed line indicates the primary estimate

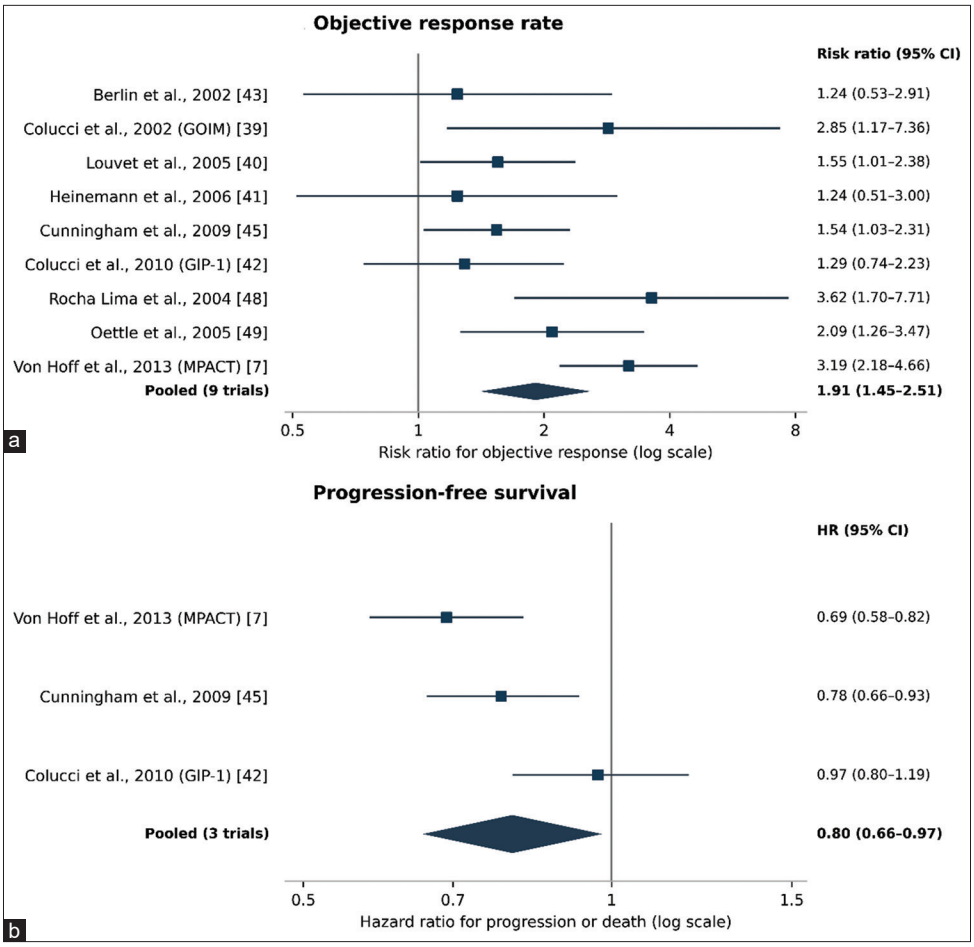


Figure 4: (a) Objective response (risk ratio; counts from published percentages). (b) Progression-free survival (hazard ratio). Random-effects models; squares proportional to weight; diamonds show pooled estimates

DISCUSSION

In this meta-analysis of 13 randomized phase III trials and 5,090 patients, adding a second cytotoxic agent to gemcitabine produced a 12% reduction in the risk of death (HR: 0.88, 95% CI: 0.82–0.95) and nearly doubled the response rate. Two observations are noteworthy. First, the effect depended on the partner drug: It was greatest with nab-paclitaxel (HR: 0.72) and fluoropyrimidines (HR: 0.86), whereas platinum analogues (HR: 0.91) and topoisomerase-I inhibitors or antifolates (HR: 0.98) contributed little. Second, the prediction interval (0.73–1.07) indicates that, despite the effect, a gemcitabine combination cannot be presumed to outperform gemcitabine alone. For a control median survival of 6.7 months, the pooled average equates to an increase of approximately 1 month, and for doublets other than nab-paclitaxel (HR: 0.91), about two-thirds of a month, suggesting a limited impact for most combinations.

Our estimate for the 12 non-taxane doublets (HR: 0.91, 0.85–0.97) matches that of Heinemann *et al*. for 15 cytotoxic doublet trials,[10] despite the datasets' differences. The fluoropyrimidine outcome (HR 0.86) is consistent with gemcitabine plus capecitabine (HR: 0.85, 0.75–0.95),[51] and an earlier meta-analysis.[11] Conversely, the platinum estimate was weaker than the previously reported 0.85.[10,11] This reflects the GIP-1 trial (HR 1.10 (0.89–1.35))[42] and a letter pooling cisplatin trials to HR 0.94 (0.76–1.17).[52] Findings on targeted agents also showed no survival benefit with gemcitabine administration.[14,15] Thus, nab-paclitaxel and erlotinib are notable amid the negative phase III results.

Nab-paclitaxel's albumin-bound formulation improves drug delivery rather than being a novel cytotoxic agent. Preclinical studies indicate that it lowers cytidine deaminase and enhances gemcitabine exposure in tumors,[53] and reducing desmoplastic stroma may improve delivery,[54] although its relevance in patients remains unverified. The regimen showed activity in phase I/II before phase III confirmation.[55] For capecitabine, mouse studies indicate effects in pancreatic cancer and a potential effect on cytidine deaminase;[56] distinct toxicities permit near-complete dosing of both. Conversely, irinotecan, exatecan, and pemetrexed increased response rates but not survival, possibly from myelosuppression and dose reduction. The gemcitabine infusion schedule is pharmacologically significant: Fixed-dose-rate infusion boosts intracellular triphosphate accumulation,[57] and Louvet *et al*.'s oxaliplatin trial used it only in the experimental

group,[40] prompting exclusion in sensitivity analysis (HR 0.89).

FOLFIRINOX demonstrated an HR of 0.57 compared to gemcitabine, with median survival times of 11.1 versus 6.8 months.[9] NALIRIFOX also enhances survival compared with gemcitabine plus nab-paclitaxel.[58] Consequently, guidelines advocate multi-agent regimens for fit patients.[59] Our results support this, suggesting that among gemcitabine-based regimens, nab-paclitaxel offers the most significant survival benefit, whereas fluoropyrimidine provides a smaller advantage. The addition of other cytotoxic agents to gemcitabine is unlikely to improve survival. However, gemcitabine-based doublets, particularly with capecitabine or S-1, remain viable for patients unsuitable for triplet or quadruplet regimens, although they have not been tested in dedicated trials.

A key insight from this dataset is the disconnection between response and survival. Irinotecan increased response rates by nearly fourfold, and pemetrexed doubled them; however, neither extended survival. Because assessing objective response via imaging in pancreatic cancer is challenging, response rates alone should not be used to determine phase III evaluation. Patient-centered outcomes are crucial in palliative contexts. The Swiss-Central European trial showed no difference in clinical benefit and quality of life between gemcitabine–capecitabine and gemcitabine alone,[60] whereas GIP-1 reported numerically less clinical benefit with cisplatin.[42] Combinations that increase toxicity without improving survival or symptoms provide no patient benefit.

Survival differences depend heavily on post-progression treatments. In the GEST trial, only 44.8% of patients assigned to gemcitabine and 55.9% assigned to S-1 received both drugs across first- and second-line therapy, explaining why the combination benefited this subgroup of patients.[47] Thus, combination therapy can be used as an initial sequential treatment. Older trials were conducted when second-line options were restricted, and modern trials with comprehensive post-progression treatments may show smaller survival differences between arms.

Two of the 13 trials (766 patients) were conducted in Japan, Taiwan, and Korea. The GEST trial comparing gemcitabine plus S-1 to gemcitabine alone showed no overall superiority (updated HR 0.91, 97.5% CI 0.75–1.11),[47] but demonstrated a survival benefit in patients with performance status 1 (HR 0.74, 95% CI 0.56–0.98), aligning with findings that combinations benefit fit patients.[10] The Korean gemcitabine–capecitabine trial reported a median survival of 10.3 versus 7.5 months (P = 0.06).[38] These results resemble those of Western trials (I^2 = 0%), supporting the global applicability of the fluoropyrimidine effect, although few East Asian trials prevented formal regional testing.

In targeted combinations, two yielded notably different outcomes. Erlotinib achieved an HR of 0.82 (0.69–0.99) and a progression-free survival HR of 0.77 (0.64–0.92),[8] while cetuximab had an HR of 1.06 (0.91–1.23),[36] and bevacizumab showed a survival of 5.8 months versus 5.9 months (P = 0.95).[37] A meta-analysis of 23 trials assessing targeted agents with gemcitabine reported no survival advantage (HR: 0.97, 0.92–1.02).[14] As trials were not evaluated here, no comparisons are provided.

For patients eligible for gemcitabine-based therapy but not an intensive triplet regimen, evidence supports gemcitabine with nab-paclitaxel if performance status and neuropathy risk are manageable. This combination showed a survival benefit (HR: 0.72; 1-year survival of 35% versus 22%) but increased neutropenia, fatigue, and neuropathy (17% versus 1% for grade 3 or higher neuropathy).[7] If unavailable or inappropriate, a fluoropyrimidine partner (capecitabine or S-1) offers smaller benefit (HR: 0.86), with grade 3–4 toxicity comparable to gemcitabine alone.[38,44] Irinotecan, exatecan, or pemetrexed is not recommended, and platinum analogues provide uncertain benefit. These conclusions should be considered alongside the prediction interval, preferences, comorbidities, and availability.

The strengths of this analysis include its focus on randomized phase III trials, a predefined subgroup structure, prediction intervals to quantify heterogeneity, sensitivity analyses, and identification of each HR's source. However, several limitations exist. First, aggregate data were used; individual patient data would permit adjustment for performance status, disease extent, and CA19-9 levels. Second, eight of 13 HRs were derived from published survival data, and one from median survival and a P-value. These standard derivations are less precise than reported HRs, and an analysis restricted to directly reported HRs did not exclude a null effect (HR: 0.88, 0.74–1.04). Third, the analysis was influenced by MPACT (12.5% of the random-effects weight and the largest single effect), and heterogeneity vanished when it was excluded, suggesting that two distinct effects were combined. Fourth, the subgroup analysis was observational, with few trials per class and only one taxane trial, so its conclusions are hypothesis-generating. Fifth, all trials were open-label, and post-progression therapies evolved, potentially reducing survival differences in older trials. Sixth, progression-free survival, response, safety, and small-study effect analyses were limited by few trials, reconstruction conventions, inability to pool adverse events, and unpublished trials.

The findings highlight three priorities. First, new gemcitabine combinations should not be assessed by response rate alone, because agents that doubled this rate did not improve survival. Second, formulation-level innovations that modify pharmacokinetics or tumor delivery, such as nab-paclitaxel, have shown promise compared with traditional cytotoxic additions. These innovations warrant exploration with

nanocarriers, prodrugs, and stroma-targeted delivery. Third, trials should stratify or predefine analyses by performance status and prospectively collect standardized toxicity data, enabling consistent benefit-harm analyses.

CONCLUSION

Adding a second cytotoxic agent to gemcitabine improves survival in advanced pancreatic cancer (HR 0.88), with increased response rates and toxicity. However, the benefit is mainly seen with nab-paclitaxel (HR 0.72) and fluoropyrimidines (HR 0.86), not irinotecan, exatecan, or pemetrexed. Platinum-based combinations lack dependable benefit. The prediction interval cautions against generalizing the average, and evidence certainty is moderate for survival and low for other outcomes. Future evaluations should prioritize survival and delivery-based pharmacological rationale over response rates.

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