

Supplementary Data

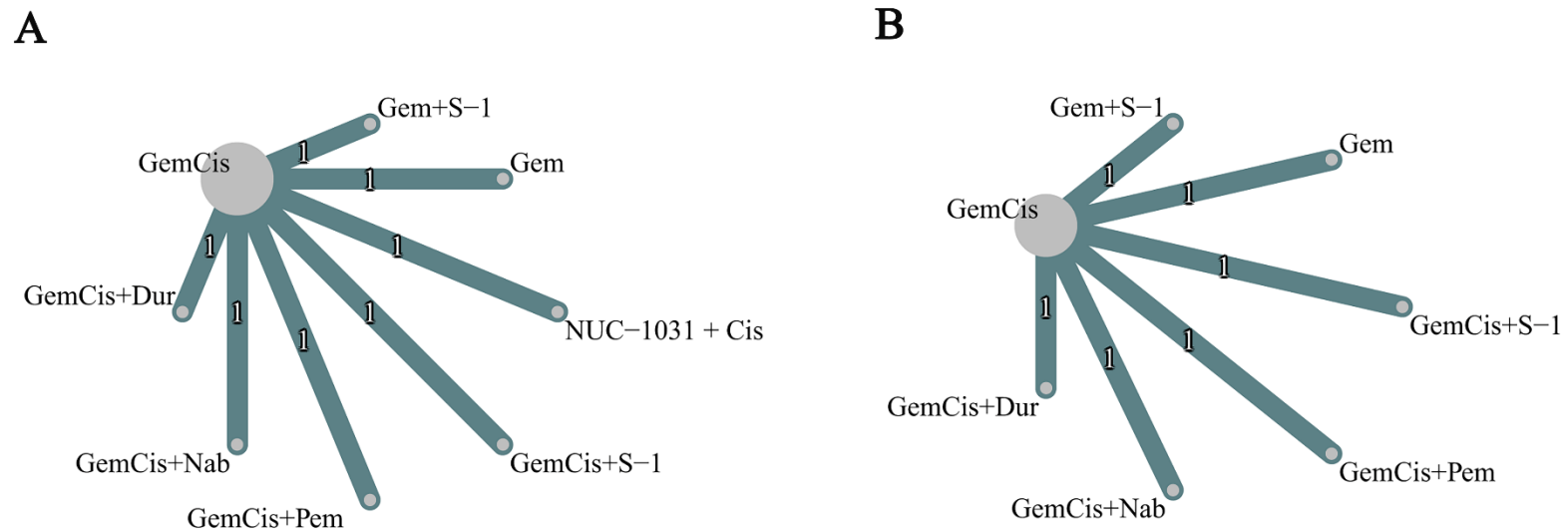


Figure S1. Network plot for progression-free survival (A) and overall-survival (B) for first-line trials. The thickness of the connecting line corresponds to the number of trials between comparators. Abbreviation: Gem, Gemcitabine; Cis, Cisplatin; GemCis, Gemcitabine and Cisplatin; Dur, Durvalumab; Pem, Pembrolizumab; Nab, Nab-paclitaxel.

Table S1. League Table Showing Indirect Comparisons Among First-Line Treatments for progression-free survival (PFS)^a

Gem	.	1.58 (1.28; 1.97)	.	.	.	.	.
1.84 (1.36; 2.50)	Gem+S-1	0.86 (0.69; 1.07)	.	.	.	.	.
1.58 (1.28; 1.97)	0.86 (0.69; 1.07)	GemCis	1.34 (1.12; 1.59)	1.08 (0.86; 1.37)	1.16 (1.01; 1.33)	1.34 (1.04; 1.72)	0.69 (0.58; 0.82)
2.12 (1.60; 2.80)	1.15 (0.87; 1.52)	1.34 (1.12; 1.59)	GemCis+Dur	.	.	.	.
1.72 (1.25; 2.36)	0.93 (0.68; 1.28)	1.08 (0.86; 1.37)	0.81 (0.60; 1.09)	GemCis+Nab	.	.	.
1.84 (1.43; 2.38)	1.00 (0.77; 1.29)	1.16 (1.01; 1.33)	0.87 (0.70; 1.09)	1.07 (0.82; 1.41)	GemCis+Pem	.	.
2.12 (1.52; 2.96)	1.15 (0.82; 1.61)	1.34 (1.04; 1.72)	1.00 (0.73; 1.36)	1.23 (0.87; 1.74)	1.15 (0.86; 1.54)	GemCis+S-1	.
1.09 (0.83; 1.45)	0.59 (0.45; 0.79)	0.69 (0.58; 0.82)	0.52 (0.40; 0.66)	0.64 (0.48; 0.86)	0.59 (0.48; 0.74)	0.52 (0.38; 0.70)	NUC-1031 + Cis

Abbreviation: Gem, Gemcitabine; Cis, Cisplatin; GemCis, Gemcitabine and Cisplatin; Dur, Durvalumab; Pem, Pembrolizumab; Nab, Nab-paclitaxel; NUC-1031 is a phosphoramidate modification of gemcitabine. ^aHazard ratios (HRs) and 95% CIs for the pairwise comparisons of the network meta-analysis from indirect comparisons. Comparisons should be read from left to right. The HRs for comparisons are in the cell in common between the column-defining and row-defining treatment. For progression-free survival (PFS), an HR of less than 1 favors row-defining treatment.

Table S2. League Table Showing Indirect Comparisons Among First-Line Treatments for overall-survival (OS)^a

Gem	.	1.57 (1.26; 1.95)	.	.	.	.
1.67 (1.24; 2.23)	Gem+S-1	0.94 (0.77; 1.15)	.	.	.	.
1.57 (1.26; 1.95)	0.94 (0.77; 1.15)	GemCis	1.25 (1.02; 1.52)	1.07 (0.85; 1.36)	1.21 (1.05; 1.39)	1.27 (1.00; 1.61)
1.95 (1.46; 2.62)	1.17 (0.89; 1.55)	1.25 (1.02; 1.52)	GemCis+Dur	.	.	.
1.68 (1.22; 2.31)	1.01 (0.74; 1.37)	1.07 (0.85; 1.36)	0.86 (0.63; 1.17)	GemCis+Nab	.	.
1.90 (1.47; 2.45)	1.14 (0.90; 1.45)	1.21 (1.05; 1.39)	0.97 (0.76; 1.23)	1.13 (0.86; 1.48)	GemCis+Pem	.
1.99 (1.45; 2.74)	1.20 (0.88; 1.63)	1.27 (1.00; 1.61)	1.02 (0.75; 1.39)	1.19 (0.85; 1.65)	1.05 (0.80; 1.38)	GemCis+S-1

Abbreviation: Gem, Gemcitabine; Cis, Cisplatin; GemCis, Gemcitabine and Cisplatin; Dur, Durvalumab; Pem, Pembrolizumab; Nab, Nab-paclitaxel. ^aHazard ratios (HRs) and 95% CIs for the pairwise comparisons of the network meta-analysis from indirect comparisons. Comparisons should be read from left to right. The HRs for comparisons are in the cell in common between the column-defining and row-defining treatment. For overall survival (OS), an HR of less than 1 favors column-defining treatment.

Table S3. Ranking of first-line treatments for overall progression-free survival (PFS) (left) and overall survival (OS) (right) based on P-score

Ranking - PFS		Ranking - OS	
1st line treatment	P-score	1st line treatment	P-score
GemCis + Dur	0.8781	GemCis + S-1	0.8143
GemCis + S-1	0.8561	GemCis + Dur	0.7891
GemCis + Pem	0.6369	GemCis + Pem	0.7370
Gem + S-1	0.6354	GemCis + Nab	0.4609
GemCis + Nab	0.5121	Gem + S-1	0.4328
GemCis	0.3383	GemCis	0.2657
NUC-1031 + Cis	0.1055	Gem	0.0002
Gem	0.0377		

Abbreviation: Gem, Gemcitabine; Cis, Cisplatin; GemCis, Gemcitabine and Cisplatin; Dur, Durvalumab; Pem, Pembrolizumab; Nab, nab-paclitaxel.

Table S4. Certainty of Evidence Table (GRADE). First line treatment - Overall survival (OS)

№ of studies	Study design	Risk of bias	Certainty assessment				№ of patients		Effect		Certainty
			Inconsistency	Indirectness	Imprecision	Other considerations	1 st line OS	Risk of Death In Control	Relative (95% CI)	Absolute (95% CI)	
GemCis vs Gem - Overall survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.64 (0.52 to 0.80)		⊕⊕⊕⊕ High
Gem+S-1 vs GemCis - Overall survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.94 (0.78 to 1.15)		⊕⊕⊕⊕ High
GemCis+Dur vs GemCis - Overall survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.80 (0.66 to 0.97)		⊕⊕⊕⊕ High
GemCis+S-1 vs GemCis - Overall survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.79 (0.63 to 0.99)		⊕⊕⊕⊕ High
GemCis+Pem vs GemCis - Overall survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.83 (0.72 to 0.95)		⊕⊕⊕⊕ High

№ of studies	Study design	Risk of bias	Certainty assessment				№ of patients		Effect		Certainty
			Inconsistency	Indirectness	Imprecision	Other considerations	1 st line OS	Risk of Death In Control	Relative (95% CI)	Absolute (95% CI)	
GemCis+Nab vs GemCis - Overall Survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.93 (0.74 to 1.19)		⊕⊕⊕⊕ High

Table S5. Certainty of Evidence Table (GRADE). First line treatment - Progression free survival (PFS)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 st line OS	Risk of Death In Control	Relative (95% CI)	Absolute (95% CI)	
GemCis vs Gem - Progression free survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.63 (0.51 to 0.77)		⊕⊕⊕⊕ High
Gem+S-1 vs GemCis - Progression free survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.86 (0.70 to 1.07)		⊕⊕⊕⊕ High
GemCis+Dur vs GemCis - Progression free survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.75 (0.63 to 0.89)		⊕⊕⊕⊕ High
GemCis+S-1 vs GemCis - Progression free survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.75 (0.58 to 0.97)		⊕⊕⊕⊕ High
GemCis+Pem vs GemCis - Progression free survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.86 (0.75 to 1.00)		⊕⊕⊕⊕ High
GemCis+Nab vs GemCis - Progression free survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 0.92 (0.72 to 1.16)		⊕⊕⊕⊕ High

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 st line OS	Risk of Death In Control	Relative (95% CI)	Absolute (95% CI)	
NUC-1031+Cis vs GemCis - Progression free survival											
1	randomised trials	not serious	not serious	not serious	not serious	none			HR 1.45 (1.18 to 1.70)		⊕⊕⊕⊕ High

Abbreviation: Gem, Gemcitabine; Cis, Cisplatin; GemCis, Gemcitabine and Cisplatin; Dur, Durvalumab; Pem, Pembrolizumab; Nab, Nab-paclitaxel; NUC-1031 is a phosphoramidate modification of gemcitabine. **CI**: Confidence interval; **HR**: Hazard Ratio