Supplementary Material

Summary

Supplementary tables

Supplementary Table S1. PICO framework of the systematic review.

PICO	Domain	Definition
P	Participants	Patients with advanced pancreatic adenocarcinoma treated with FOLFIRINOX in the first-line setting[$]
I	Intervention	Gemcitabine-based chemotherapy as second-line or further line of treatment
C	Comparison	-
O	Outcomes	Objective response rate, Disease control rate, Biochemical response rate, Progression-free survival, Overall survival, Toxicity

[$] Advanced pancreatic adenocarcinoma defined as locally advanced/unresectable or metastatic pancreatic adenocarcinoma.

Supplementary Table S2. Search strategy.

Database	Data of search	Date limits	Query	Search strategy	Number or items
PubMed	11 JUN 2018	01 JAN 2011 to 11 JUN 2018	# 1	(("fluorouracil"[MeSH Terms] OR "fluorouracil"[All Fields]) AND ("irinotecan"[Supplementary Concept] OR "irinotecan"[All Fields]) AND ("oxaliplatin"[Supplementary Concept] OR "oxaliplatin"[All Fields])) OR " FOLFIRINOX" [All Fields]	291
			#2	((("pancreatic neoplasm"[MeSH Terms] OR "pancreatic neoplasms"[MeSH Terms]) OR "pancreatic cancer"[MeSH Terms]) OR "pancreatic cancers"[MeSH Terms]) OR ((" pancreatic" [All Fields] OR " pancreas" [All Fields]) AND (" cancer" [All Fields] OR " carcinoma" [All Fields] OR " adenocarcinoma" [All Fields]))	
			#3	("gemcitabine"[Supplementary Concept] OR " gemcitabine" [All Fields])	
			#4	#1 AND #2 AND #3	
Embase	11 JUN 2018	2011 to 2018	#1	(' folfirinox' /exp OR ' folfirinox')	825
			#2	(' pancreas tumor' /exp OR ' pancreas tumor')	
			#3	(' gemcitabine' /exp OR ' gemcitabine')	
			#4	#1 AND #2 AND #3	
Scopus	11 JUN 2018	2011 to 2018	#1	(folfirinox OR (fluorouracil AND irinotecan AND oxaliplatin))	340
			#2	(pancreatic OR pancreas)	
			#3	(cancer OR carcinoma OR adenocarcinoma)	
			#4	(gemcitabine)	
			#5	#1 AND #2 AND #3 AND #4	
Web of Science	12 JUN 2018	2011 to 2018	#1	(folfirinox OR (fluorouracil AND irinotecan AND oxaliplatin))	473
			#2	(pancreatic OR pancreas)	
			#3	(cancer OR carcinoma OR adenocarcinoma)	
			#4	(gemcitabine)	
			#5	#1 AND #2 AND #3 AND #4	

Supplementary Table S3. Collected variables among the selected studies.

Domain	Data
Bibliography	- Study name - Journal name - First author's name - Authors' affiliation - Corresponding address - Study DOI - Year of publication - Type of publication (full-text vs. meeting abstract)
Substantive / Risk of bias	- Country of study - Type of study (prospective vs. retrospective) - Uni-institutional or multi-institutional study - Funding source - Risk of bias evaluation
Population details	- Sample size - Diagnostic criteria (biopsy) - Number of male patients - Age (median and range) - ECOG performance status (0 vs. 1 vs. 2 vs. 3) - ECOG performance status (0-1 vs. ≥2) - Number of head/neck tumors - Primary tumor surgery (Yes vs. No) - Adjuvant chemotherapy (Yes vs. No) - Clinical stage at start of FOLFIRINOX (III vs. IV) - Clinical stage at start of Gemcitabine-based chemotherapy (III vs. IV)

	- Number of metastatic sites at start of Gemcitabine-based chemotherapy (median and range; 0 vs. 1 vs. 2 vs. 3 or more) - CA 19-9 at start of Gemcitabine-based chemotherapy (median and range) - Median (and 95%CI) progression-free survival with FOLFIRINOX (in months) - Number of cycles of FOLFIRINOX (median and range) - Reason for discontinuation of FOLFIRINOX (Progression vs. Toxicity vs. Other reasons) - Number of patients with response to FOLFIRINOX
Intervention	- Type of Gemcitabine-based chemotherapy - Dosing of Gemcitabine-based chemotherapy - Number of cycles of Gemcitabine-based chemotherapy (median and range)
Miscellaneous	- Factors associated with overall survival (prognosis) - Factors associated with progression-free survival (prognosis)
Outcomes	- Method used for response evaluation (RECIST vs. non-RECIST) - Independent imaging review (Yes vs. No) - Imaging interval (in weeks) - Biochemical response - CA 19-9 (Yes vs. No) - Definition of biochemical response - CA 19-9

	- Objective response with Gemcitabine-based chemotherapy - Disease control with Gemcitabine-based chemotherapy - Number of patients at risk (Yes vs. No) - Definition of progression-free survival - Number of progression-free survival events - Median progression-free survival – PFS (in months) - Confidence interval of PFS (95%) - Progression-free survival rate at 3 months (in %) - Progression-free survival rate at 6 months (in %) - Number of overall survival events - Median overall survival from start of Gemcitabine-based chemotherapy – OS-GEM (in months) - Confidence interval of OS (95%) - Overall survival rate at 6 months (in %) - Overall survival rate at 12 months (in %) - Median overall survival from start of FOLFIRINOX – OS-FFX (in months) - Confidence interval of OS – FFX (95%) - Overall survival rate at 12 months from start of FFX (in %) - Overall survival rate at 18 months from start of FOLFIRINOX (in %) - Method used to gauge toxicity (e.g.: CTC AE 3.0 or 4.0)

	- Rate G3/4 toxicity – overall (in %) - Rate G3/4 nausea (in %) - Rate G3/4 vomiting (in %) - Rate G3/4 diarrhea (in %) - Rate G3/4 mucositis (in %) - Rate G3/4 peripheral neuropathy (in %) - Rate G3/4 fatigue (in %) - Rate G3/4 anemia (in %) - Rate G3/4 neutropenia (in %) - Rate G3/4 febrile neutropenia (in %) - Rate G3/4 thrombocytopenia (in %) - Rate of treatment-related deaths (in %)

Supplementary Table S4. Reasons for study exclusion in the second screening round.

Study	Reference	Category	Observation
Excellent overall survival with FOLFIRINOX followed by Gemcitabine/nab-Paclitaxel or vice versa in metastatic pancreatic cancer-a single center experience	Andalibi H, Vormittag L, Winkler T, Kafka A, Weiser-Jasch O, Schima,W et al. Memo 2016;9(1):S31(abstr P39).	Inability to access full poster.	We tried to get in touch with one of the authors (UMV) through e-mail on July 15th 2018 with no success.
Cost-effectiveness of FOLFIRINOX for first-line treatment of metastatic pancreatic cancer	Attard CL, Brown S, Alloul K, Moore MJ. J Clin Oncol 2012;30(4):(suppl; abstr 199).	No adequate separate data on second-line treatment.	There was no specific data regarding either efficacy or toxicity of second-line (gemcitabine-based) chemotherapy.
Cost-effectiveness of folfirinox for first-line treatment of metastatic pancreatic cancer	Attard CL, Brown S, Alloul K, Moore MJ. Current Oncol 2014;21(1):e41-51.	No adequate separate data on second-line treatment.	There was no specific data regarding either efficacy or toxicity of second-line (Gemcitabine-based) chemotherapy.
The impact of second-line chemotherapy on advanced pancreatic cancer: A retrospective study in Reggio Emilia Clinical Cancer Centre	Baldi L, Panebianco M, Rossi PG, Mancuso P, Cassetti T, Sassatelli R, Pinto C. J Clin Oncol 2017;35(15):(suppl;abstr: e15732).	No adequate separate data on first- or second-line treatment.	Patients were treated with multiple regimens in first-line and in second-line. So separate data for patients treated with first-line FOLFIRINOX and second-line Gemcitabine-based chemotherapy are lacking.
Comparative effectiveness and resource utilization of nab-paclitaxel plus gemcitabine vs FOLFIRINOX or gemcitabine for the first-line treatment of metastatic pancreatic adenocarcinoma in a US community setting	Braiteh F, Patel MB, Parisi M, Ni QH, Park S, Faria C. Cancer Manag Res 2017;9:141-148.	No adequate separate data on second-line treatment.	There was no description of the outcomes of patients treated in first-line with FOLFIRINOX that subsequently underwent Gemcitabine-based chemotherapy.
Real-world analysis of treatment patterns examining nab-Paclitaxel plus Gemcitabine (nab-P plus G) versus FOLFIRINOX (FFX) in first-line (10 treatment (tx) of metastatic pancreatic	Braiteh F, Patel MB, Parisi M, Ni QH, Park S, Faria C. J Clin Oncol 2016;34(15):(suppl;abstr e18130).	No adequate separate data on second-line treatment.	There was no description of the outcomes of patients treated in first-line with FOLFIRINOX that subsequently underwent Gemcitabine-based chemotherapy.

adenocarcinoma (MPAC) in a US community oncology setting.			
Second-line therapy for advanced pancreatic cancer: Evaluation of prognostic factors and review of current literature	Caparello C, Vivaldi C, Fornaro L, Musettini G, Pasquini G, Catanese S, et al. Future Oncol 2016;12(7):901-908.	No adequate separate data on second-line treatment.	Patients were treated with a multitude of regimens in the second-line setting. There was no specific description of the outcomes of patients treated with Gemcitabine-based chemotherapy after FOLFIRINOX.
Impact of Nab-Paclitaxel-based Second-line Chemotherapy in Metastatic Pancreatic Cancer	Dadi N, Stanley M, Shahda S, O'Neil BH, Sehdev A. AntiCancer Res 2017;37(10):5533-39.	No adequate separate data on first- or second-line treatment.	Not all patients treated in the Nab-Paclitaxel group in the second-line received FOLFIRINOX in the first-line. Also, not all patients in the Nab-Paclitaxel group received Gemcitabine (some received Nab-Paclitaxel alone). So, there was no separate data on patients treated with FOLFIRINOX in the first-line setting and subsequently with Gemcitabine-based chemotherapy.
Growth modulation index (GMI) to assess salvage chemotherapy benefit after FOLFIRINOX progression in metastatic pancreatic adenocarcinoma	Ducoulombier A, Quintin J, Desjardin M, Hautefeuille V, Desauw C, Parzy A, et al. Eur J Cancer 2015;51(suppl 3):S430 (abstr 2294).	No adequate separate data on second-line treatment.	Not all patients were treated with Gemcitabine-based chemotherapy in the second-line setting. Moreover, the outcomes for different gemcitabine-based regimens are not declared.
Optimal therapeutic sequences in the treatment of metastatic pancreatic cancer-a retrospective analysis from two Canadian and French tertiary cancer centres	Gilabert M, Rho YS, Kavan T, Chanez B, Mamo A, Barrera I, et al. Eur J Cancer 2015;51(suppl 3):S455(abstr 2359).	Repeated study.	Full-text article already selected .
Role of second-line gemcitabine after FOLFIRINOX failure in advanced pancreatic	Lino ADR, Martins Jr RM, Abrahao CM, Moreira RB, De Sousa TTS, Gomes JR, et al.	Repeated study.	Full-text article already selected .

adenocarcinoma: A retrospective analysis	J Clin Oncol 2015;33(3):(suppl; abstr 473).		
The nab-paclitaxel/gemcitabine regimen for patients with refractory advanced pancreatic adenocarcinoma	Palacio S, Hosein PJ, Reis I, Akunyili II, Ernani V, Pollack T, et al. Gastrointest Oncol 2018;9(1):135-9.	No adequate separate data on first-line treatment.	There were no specific outcomes for patients treated with first-line FOLFIRINOX. The most common first-line regimens were either Gemcitabine plus Cisplatin or Gemcitabine.
Second-line treatment in patients with FOLFIRINOX-refractory pancreatic adenocarcinoma (PDAC): Doublets or single-agent chemotherapy?	Pellei C, Lanese A, Bittoni A, Andrikou K, Santoni M, Conti A, et al. J Clin Oncol 2014;32(15):(suppl;abstr e15186)	No adequate separate data on second-line treatment.	There were no specific data on the outcomes of Gemcitabine-based chemotherapy (main analysis is about doublet vs single-agent).
Nab paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after failure of folfirinox: Results of an AGEO multicenter prospective cohort	Portal A, Pernot S, Arbaud C, Tougeron D, Thirot-Bidault A, De La Fouchardiere C, et al. J Clin 2015;33(15):(suppl; abstr 4123).	Repeated study.	Full-text article already selected.
Can the sequence of chemotherapy regimens influence outcome in patients with metastatic pancreatic adenocarcinoma (MPAC)?	Schmidt SL, Durkal V, Jayavalsan SP, Ritch PS, Thomas JP, Erickson B, et al. J Clin Oncol 2016;34(4):(suppl; abstr 428).	No adequate separate data on second-line treatment.	No adequate data regarding response rate, disease control rate, progression-free survival or toxicity. Overall survival data for the sequence FOLFIRINOX -> Gemcitabine plus Nab-Paclitaxel only from the beginning of first-line treatment.
Outcomes in metastatic pancreatic adenocarcinoma (MPAC) patients treated with FOLFIRINOX (FFX)/FOLFOX(FX) and gemcitabine + nab-paclitaxel (NabG)	Schmidt SL, Durkal V, Jayavalsan SP, Ritch PS, Thomas JP, Erickson B, et al. J Clin Oncol 2016;34(4):(suppl; abstr 397).	No adequate separate data on second-line treatment.	Patients treated with second-line Gemcitabine plus Nab-Paclitaxel were treated with FOLFOX or FOLFIRINOX in the first-line setting; there are no separate data for the second-line treatment according to the first-line treatment (FOLFOX vs FOLFIRINOX).
The retrospective analysis of gemcitabine + nab-paclitaxel for the	Ueno M, Kobayashi S, Ohkawa S, Tezuka S, Moriya S, Morimoto M. Pancreatology	Inability to access full poster.	We tried to get in touch with one of the authors (MU) through

treatment of advanced pancreatic cancer	2016;16(4):S31(abstr S8-5).		e-mail on July 15th 2018 with no success.
Second-line chemotherapy after disease progression following first-line FOLFOXIRI in advanced pancreatic cancer patients	Vasile E, Vivaldi C, Fornaro L, Caparello C, Musettini G, Pasquini G, et al. Ann Oncol 2015;26(suppl 6):vi90-vi105(abstr L26).	No adequate separate data on second-line treatment.	Regimens other than the ones based on Gemcitabine have been used. Also, there are no separate data for each chemotherapy regimen in the second-line setting.
Second-line treatment after disease progression following first-line chemotherapy with modified FOLFIRINOX in advanced pancreatic cancer patients: A single institution retrospective cohort study	Vivaldi C, Caparello C, Pasquini G, Musettini G, Catanese S, Lencioni M, A, et al. Ann Oncol 2015;26(suppl 4);iv1-iv100(abstr P180).	No adequate separate data on second-line treatment.	Patients were treated with a multitude of regimens in the second-line setting. There was no specific description of the outcomes of patients treated with Gemcitabine-based chemotherapy after FOLFIRINOX.
Second-line treatment after disease progression following first-line chemotherapy with modified FOLFIRINOX in advanced pancreatic cancer patients	Vivaldi C, Vasile E, Fornaro L, Caparello C, Musettini G, Pasquini G, et al. Eur J Cancer 2015;51(suppl 3):S456-457(abstr 2362).	No adequate separate data on second-line treatment.	Patients were treated with a multitude of regimens in the second-line setting. There was no specific description of the outcomes of patients treated with Gemcitabine-based chemotherapy after FOLFIRINOX.
Gemcitabine plus nab-paclitaxel in metastatic or locally inoperable pancreatic cancer-a single center experience	Vogl U, Vormittag L, Winkler T, Kafka A, Henry M, Schima W, et al. Ann Oncol 2015;26(suppl 4):iv1-iv100 (abstr P179).	Inability to access full poster.	We tried to get in touch with one of the authors (UMV) through e-mail on July 15th 2018 with no success.
Efficacy and tolerability of second-line nab-paclitaxel and gemcitabine (NG) after failing first-line FOLFIRINOX in patients (pts) with advanced pancreatic cancer (APC): A single-institution experience	Zhang H, Kellett C, Lambert PJ, Kim C. J Clin Oncol 2017;35(15):(abstr e15723).	Repeated study.	Full-text article already selected.
Second-line gemcitabine plus nab-paclitaxel (G+A) for advanced pancreatic cancer (APC) after first-line FOLFIRINOX: Single institution	Zhang Y, Hochster HS, Stein S, Lacy J. J Clin Oncol 2014;32(3):(abstr 344).	Repeated study.	Full-text article already selected.

retrospective review of efficacy and toxicity			

Supplementary Table S5. Bibliographic characteristics of the selected studies.

Study	Type of study	Multicentric study	Country of origin	Year of publication	Type of publication	Funding source
Aung et al	Retrospective	No	Canada	2017	Meeting abstract	Not stated
Chan et al	Retrospective	No	USA	2016	Meeting abstract	Not stated
El Rassy et al	Retrospective	No	Lebanon	2017	Full-text article	Not stated
Fernandes et al	Retrospective	No	Brazil	2017	Meeting abstract	Not stated
Gilabert et al	Retrospective	Yes	France and Canada	2017	Full-text article	Not stated
Lino et al	Retrospective	No	Brazil	2015	Full-text article	Not stated
Nguyen et al	Retrospective	No	USA	2017	Full-text article	UCI biostatistics facility
Okano et al	Retrospective	No	Japan	2016	Meeting abstract	Not stated
Ozaka et al	Retrospective	No	Japan	2018	Meeting abstract	Not stated
Portal et al	Prospective observational	Yes	France	2015	Full-text article	Not stated
Salem et al	Retrospective	Yes	USA	2014	Meeting abstract	Not stated
Sarabi et al	Retrospective	No	France	2017	Full-text article	Not stated
Vendrell et al	Retrospective	Yes	Portugal	2017	Meeting abstract	Not stated
Viaud et al	Retrospective	Yes	France	2017	Full-text article	Not stated
Zhang H et al	Retrospective	Yes	Canada	2018	Full-text article	Not stated
Zhang Y et al	Retrospective	No	USA	2015	Full-text article	None

Supplementary Table S6. Characteristics of the populations from the selected studies.

Study	Sample size	Male (%)	Age – median (range)	ECOG 0/1 (%)	Stage IV at start of Gemcitabine (%)	Progression on FOLFIRINOX (%)	Objective response to FOLFIRINOX (%)
Gemcitabine monotherapy							
Aung et al (1)	50	27 (54.0)	62 (28-74)	-	37 (74.0)	-	-
Chan et al (1)	36	22 (61.1)	58.5 (41-77)	30 (83.3)	36 (100.0)	-	-
Fernandes et al	28	19 (67.9)	55 (38-75)	-	-	28 (100.0)	39.0
Gilabert et al	72	45 (62.5)	63.5 (32-75)	-	64 (88.9)	61 (84.7)	40.0
Lino et al	20	16 (80.0)	57 (43-74)	13 (65.0)	20 (100.0)	20 (100.0)	-
Sarabi et al	42	22 (52.4)	63.5 (47-76)	38 (90.5)	41 (97.6)	35 (83.3)	-
Viaud et al	96	49 (51.0)	62 (38-80)	45 (46.9)	87 (90.6)	81 (84.4)	40.0
Zhang H et al (1)	8	6 (75.0)	68	6 (75.0)	6 (75.0)	-	-

Study	Sample size	Male (%)	Age – median (range)	ECOG 0/1 (%)	Stage IV at start of Gemcitabine (%)	Progression on FOLFIRINOX (%)	Objective response to FOLFIRINOX (%)
Gemcitabine plus Nab-Paclitaxel							
Aung et al (2)	17	11 (64.7)	58 (35-71)	-	12 (70.6)	-	-
Chan et al (2)	33	24 (72.7)	60 (44-77)	31 (93.9)	33 (100.0)	-	-
El Rassy et al	12	10 (83.3)	61 (52-74)	-	12 (100.0)	12 (100.0)	-
Nguyen et al	30	16 (53.3)	63 (46-78)	-	26 (86.7)	22 (73.3)	3.3
Okano et al	10	-	-	-	-	-	-
Ozaka et al	25	16 (64.0)	66 (40-73)	25 (100.0)	25 (100.0)	-	-
Portal et al	57	27 (47.4)	59.9 (35-92)	45 (78.9)	57 (100.0)	54 (94.7)	39.0
Salem et al	12	-	-	-	-	-	-
Vendrell, et al	30	-	64 (45-78)	-	27 (90.0)	-	-
Zhang H et al (2)	30	15 (50.0)	62	26 (86.7)	22 (73.3)	-	-
Zhang Y et al	28	11 (39.3)	61 (50-74)	27 (96.4)	23 (82.1)	27 (96.4)	28.6

Supplementary Table S7. Treatment characteristics.

Study	N	Treatment schedule	Number of treatment cycles (median)	Number of treatment cycles (range)
Gemcitabine monotherapy				
Aung et al (1)	50	Not described	2	1 - 7
Chan et al (1)	36	Gemcitabine 1000 mg/m2 D1,8,15[#]	2	-
Fernandes et al	28	Not described	3	1 - 8
Gilabert et al	72	Gemcitabine 1000 mg/m2 D1,8,15	3	1 - 8
Lino et al	20	Gemcitabine 1000 mg/m2 D1,8,15	2	1 - 8
Sarabi et al	42	Not described	1.5	1 - 13
Viaud et al	96	Gemcitabine 1000 mg/m2 D1,8,15	2	1 - 14
Zhang H et al (1)	8	Not described	2	-
Gemcitabine plus Nab-Paclitaxel				
Aung et al (2)	17	Not described	2	1 - 9
Chan et al (2)	33	Gemcitabine 1000 mg/m2 D1,8,15 plus Nab-Paclitaxel 125 mg/m2 D1,8,15[#]	5.5	-
El Rassy et al	12	Gemcitabine 1000 mg/m2 D1,8,15 plus Nab-Paclitaxel 125 mg/m2 D1,8,15	3	1 - 16
Nguyen et al	30	Not described	4	1 - 21
Okano et al	10	Not described	-	-
Ozaka et al	25	Not described	-	-
Portal et al	57	Gemcitabine 1000 mg/m2 D1,8,15 plus Nab-Paclitaxel 125 mg/m2 D1,8,15	4	1 - 12
Salem et al	12	Not described	2	1 - 10
Vendrell, et al	30	Not described	6	1 - 13
Zhang H et al (2)	30	Not described	3	-
Zhang Y et al	28	Gemcitabine 1000 mg/m2 D1,8,15 plus Nab-Paclitaxel 100 mg/m2 D1,8,15	2	1 - 9

[#] Based on dose-intensity calculation.

Supplementary Table S8. Risk of bias assessment.

Domain	Selection	Ascertainment		Causality	Reporting		Overall Quality
Question	Does the patients represent the whole experience of the investigator (center)?[#]	Was the exposure adequately ascertained?[$]	Were the outcomes adequately ascertained?[&]	Was follow-up long enough for outcomes to occur?[‡]	Enough details to enable practitioners to make inferences about their own practice?[¶]		Sum
					Efficacy	Toxicity	
Non-comparative studies							
El Rassy, 2017	X	X	O	O	X	X	4
Fernandes, 2017	X	X	O	O	X	O	3
Gilabert, 2017	X	X	X	X	X	O	5
Lino, 2015	X	X	X	O	X	O	4
Nguyen, 2017	X	X	X	O	X	X	5
Okano, 2016	O	X	O	O	X	X	3
Ozaka, 2018	X	X	O	O	X	X	4
Portal, 2015	X	X	X	X	X	X	6
Salem, 2014	X	X	O	O	X	O	3
Sarabi, 2017	X	X	X	X	X	X	6
Vendrell, 2017	X	X	O	O	X	X	4
Viaud, 2017	X	X	X	X	X	X	6
Zhang Y, 2015	X	X	X	O	X	X	5

Domain	Selection	Ascertainment		Causality	Reporting		Overall Quality
Question	Does the patients represent the whole experience of the investigator (center)?[#]	Was the exposure adequately ascertained?[$]	Were the outcomes adequately ascertained?[&]	Was follow-up long enough for outcomes to occur?[‡]	Enough details to enable practitioners to make inferences about their own practice?[¶]		Sum
					Efficacy	Toxicity	
Comparative studies							
Aung, 2017	X	X	X	X	X	O	5
Chan, 2016	X	X	X	O	X	O	4
Zhang H, 2018	X	X	X	X	X	X	6

X = YES, O = No/Unknown

[#] Some studies did not clearly state that all consecutive patients were enrolled, but they clearly defined inclusion criteria.

[$] Some studies did not fully describe dosing and schedule, but since there is a standard regimen for both Gemcitabine monotherapy and Gemcitabine plus Nab-paclitaxel, the description of the drug used was considered acceptable.

[&] Proper definition of time-to-event outcomes (overall survival and progression-free survival) included date of treatment start, date of the event, and definition of the event. Response evaluation also had to be performed by RECIST (versions 1.0 or 1.1).

[‡] Adequate follow-up was arbitrarily defined as ≤ 20% censoring rate for progression-free survival; for the response rate and disease-free survival outcomes, > 80% of patients had to be assessable for response.

[¶] Feasibility of the studied regimen included adequate description of the toxicity profile (at least grade 3 to 4 toxicities).

Supplementary Table S9. Evaluation of response to treatment.

Study	N	Method of response evaluation	Radiological review	Objective response rate (%)	Disease control rate (%)
Gemcitabine monotherapy					
Aung et al (1)	50	Unknown	No/Unknown	-	-
Chan et al (1)	36	Unknown	No/Unknown	-	-
Fernandes et al	28	RECIST 1.1	No/Unknown	1 (3.5)	5 (17.8)
Gilabert et al	72	RECIST 1.1	No/Unknown	8 (11.1)	25 (34.7)
Lino et al	20	RECIST	No/Unknown	-	-
Sarabi et al	42	RECIST 1.0	No/Unknown	-	11 (26.1)
Viaud et al	96	RECIST 1.1	No/Unknown	8 (8.3)	32 (33.3)
Zhang H et al (1)	8	RECIST 1.0[$]	No/Unknown	-	-
Gemcitabine plus Nab-Paclitaxel					
Aung et al (2)	17	Unknown	No/Unknown	-	-
Chan et al (2)	33	Unknown	No/Unknown	-	-
El Rassy et al	12	Unknown	No/Unknown	3 (25.0)	6 (50.0)[&]
Nguyen et al	30	RECIST 1.1	Yes	5 (30.0)	17 (56.7)
Okano et al	10	Unknown	No/Unknown	0 (0.0)	5 (50.0)
Ozaka et al	25	Unknown	No/Unknown	3 (12.0)	16 (64.0)
Portal et al	57	RECIST 1.1	No/Unknown	10 (17.5)	33 (57.8)
Salem et al	12	RECIST	No/Unknown	1 (8.3)	3 (25.0)
Vendrell, et al	30	Unknown	No/Unknown	-	-
Zhang H et al (2)	30	RECIST 1.0[$]	No/Unknown	-	-
Zhang Y et al	28	RECIST 1.1[#]	Yes	5 (17.8)	13 (34.2)

[$] RECIST used only to evaluate response to first-line FOLFIRINOX.
[#] Review by the investigators with independent onsite radiologists.
[&] Conservative estimate (only 10 patients assessed for response).

Supplementary Table S10. Toxicity data (part 1).

Study	Treatment-related mortality (%)	Any G3/4 toxicity (%)	Nausea G3/4 (%)	Vomiting G3/4 (%)	Diarrhea G3/4 (%)	Mucositis G3/4 (%)	Neuropathy G3/4 (%)	Fatigue G3/4 (%)
Gemcitabine monotherapy								
Aung et al (1)	-	-	-	-	-	-	-	-
Chan et al (1)	-	-	-	-	-	-	-	-
Fernandes et al	0 (0.0)	5 (17.8)	-	-	-	-	-	-
Gilabert et al[&]	0 (0.0)	-	-	-	-	-	-	-
Lino et al	-	-	-	-	-	-	-	-
Sarabi et al[$]	0 (0.0)	6 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Viaud et al[$]	0 (0.0)	34 (35.4)	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (19.8)
Zhang H et al (1)	-	-	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)	3 (37.5)

Study	Treatment-related mortality (%)	Any G3/4 toxicity (%)	Nausea G3/4 (%)	Vomiting G3/4 (%)	Diarrhea G3/4 (%)	Mucositis G3/4 (%)	Neuropathy G3/4 (%)	Fatigue G3/4 (%)
Gemcitabine plus Nab-Paclitaxel								
Aung et al (2)	-	-	-	-	-	-	-	-
Chan et al (2)	-	-	-	-	-	-	-	-
El Rassy et al	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nguyen et al[$]	-	-	5 (16.7)	-	1 (3.3)	-	1 (3.3)	1 (3.3)
Okano et al	-	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (20.0)	-
Ozaka et al	0 (0.0)	-	0 (0.0)	-	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)
Portal et al[$]	0 (0.0)	21 (36.8)	2 (3.5)	2 (3.5)	1 (1.8)	1 (1.8)	7 (12.3)	5 (8.8)
Salem et al	-	-	-	-	-	-	-	-
Vendrell, et al	0 (0.0)	12 (40.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	1 (3.3)	1 (3.3)
Zhang H et al (2)	-	-	0 (0.0)	0 (0.0)	2 (6.7)	-	0 (0.0)	1 (3.3)
Zhang Y et al	0 (0.0)	-	-	-	-	-	-	

[$] Based on CTCAE 4.0.
[&] Based on CTCAE 3.0.

Supplementary Table S11. Progression-free survival after start of Gemcitabine-based chemotherapy (PFS).

Study	N	Median progression-free survival (months)	Progression-free survival 95%CI (months)	3-month progression-free survival rate (%)	6-month progression-free survival rate (%)
Gemcitabine monotherapy					
Aung et al (1)	50	-	-	-	-
Chan et al (1)	36	1.9	-	28.0[$]	19.3[$]
Fernandes et al	28	2.0	0.2 – 7.7	-	-
Gilabert et al	72	2.5	0.2 – 10.8	-	-
Lino et al	20	2.0	1.2 – 2.8	35.1[$]	20.1[$]
Sarabi et al	42	-	-	-	-
Viaud et al	96	2.1	2.0 – 2.6	30.4[$]	16.0
Zhang H et al (1)	8	2.5	-	37.5[$]	0.0
Gemcitabine plus Nab-Paclitaxel					
Aung et al (2)	17	-	-	-	-
Chan et al (2)	33	2.4	-	42.4[$]	23.6[$]
El Rassy et al	12	4.9	-	-	-
Nguyen et al	30	3.7	2.7 – 6.1	60.2[$]	29.2[$]
Okano et al	10	5.1	0.0 – 12.5	56.6[$]	22.8[$]
Ozaka et al	25	6.0	-	84.5[$]	50.0
Portal et al	57	5.1	3.2 – 6.2	64.0[$]	39.0
Salem et al	12	3.3	1.8 - NR	-	8.0[‡]
Vendrell, et al	30	6.4	3.0 – 8.5	82.9[#]	57.4[#]
Zhang H et al (2)	30	3.6	-	66.7[$]	20.0[$]
Zhang Y et al	28	2.8[‡]	0.4 – 8.4[‡,&]	-	-

[$] Based on digital extraction method.
[‡] Time to treatment failure.
[&] Range.
[#] Data obtained directly from author.
NR = not reached.

Supplementary Table S12. Overall Survival after start of Gemcitabine-based chemotherapy (OS-GEM).

Study	N	Median overall survival (months)	Overall survival 95%CI (months)	6-month overall survival rate (%)	12-month overall survival rate (%)
Gemcitabine monotherapy					
Aung et al (1)	50	3.1	0.2 – 10.6	16.0	0.0
Chan et al (1)	36	4.8	-	47.0[$]	15.7[$]
Fernandes et al	28	5.6	0.4 – 11.5	-	-
Gilabert et al	72	-	-	-	-
Lino et al	20	5.7	3.9 – 7.4	44.1[$]	22.0[$]
Sarabi et al	42	3.6	2.1 – 5.1	37.7	11.5
Viaud et al	96	3.7	2.5 – 5.2	35.0	10.0
Zhang H et al (1)	8	3.8	-	0.0	0.0
Gemcitabine plus Nab-Paclitaxel					
Aung et al (2)	17	4.6	1.2 – 11.6	35.0	0.0
Chan et al (2)	33	6.1	-	53.1[$]	22.8[$]
El Rassy et al	12	NR	-	83.3	-
Nguyen et al	30	12.4	6.8 – 15.0	66.3[$]	50.3[$]
Okano et al	10	7.8	2.8 – 12.7	66.8[$]	16.5[$]
Ozaka et al	25	10.2	-	82.5[$]	38.2[$]
Portal et al	57	8.8	6.2 – 9.7	69.0	15.0
Salem et al	12	-	-	-	-
Vendrell, et al	30	11.4	8.4 – 16.5	93.0[#]	44.1[#]
Zhang H et al (2)	30	5.7	-	49.0[$]	19.7[$]
Zhang Y et al	28	5.4	0.5 – 19.9[&]	-	-

[$] Based on digital extraction method.
[&] Range.
[#] Data obtained directly from author.
NR = not reached.

Supplementary Sable S13. Overall Survival after start of FOLFIRINOX (OS-FFX).

Study	N	Median overall survival (months)	Overall survival 95%CI (months)	12-month overall survival rate (%)	18-month overall survival rate (%)
Gemcitabine monotherapy					
Aung et al (1)	50	-	-	-	-
Chan et al (1)	36	-	-	-	-
Fernandes et al	28	-	-	-	-
Gilabert et al	72	13.6	2.0 – 35.0	58.4[$]	29.4[$]
Lino et al	20	-	-	-	-
Sarabi et al	42	13.4	3.3 – 30.7[&]	-	-
Viaud et al	96	11.2	10.4 – 14.0	46.0	-
Zhang H et al (1)	8	-	-	-	-
Gemcitabine plus Nab-Paclitaxel					
Aung et al (2)	17	-	-	-	-
Chan et al (2)	33	-	-	-	-
El Rassy et al	12	-	-	-	-
Nguyen et al	30	13.7	11.0 – 17.7	60.9[$]	20.2[$]
Okano et al	10	-	-	-	-
Ozaka et al	25	17.4	-	82.6[$]	46.3[$]
Portal et al	57	18.0	16 – 21.2	82.0	50.0
Salem et al	12	16.2	14.3 – NR	-	-
Vendrell, et al	30	22.1[#]	16.9 – 29.3[#]	85.4[#]	60.5[#]
Zhang H et al (2)	30	-	-	-	-
Zhang Y et al	28	-	-	-	-

[$] Based on digital extraction method.
[&] Range.
[#] Data obtained directly from author.
NR = not reached.

Supplementary Table S14. Biochemical response rate (BRR) to Gemcitabine-based chemotherapy.

Study	N	Response criteria	Biochemical response rate (%)
Gemcitabine plus Nab-Paclitaxel			
Nguyen et al	30	≥ 50% drop in CA 19-9 levels	19 (63.3)
Zhang Y et al	28	≥ 30% drop in CA 19-9 levels	13 (46.4)

Supplementary Table S15. Toxicity data (part 2).

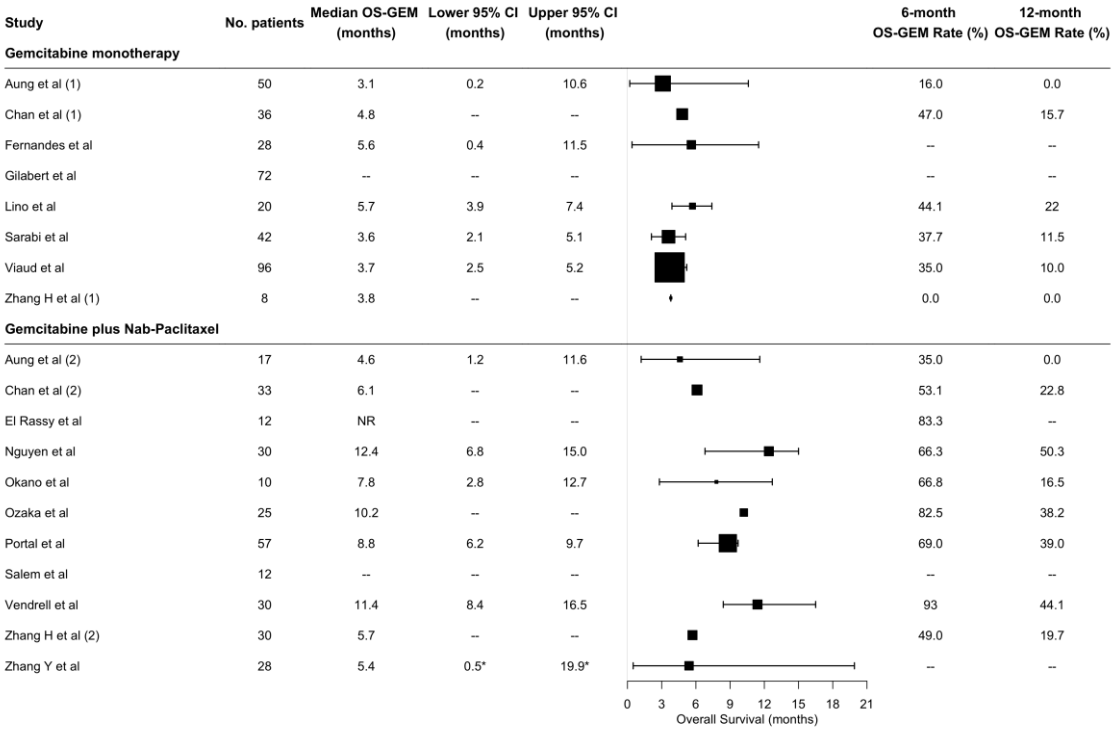
Study	Anemia G3/4 (%)	Neutropenia G3/4 (%)	Febrile neutropenia (%)	Thrombocytopenia G3/4 (%)
Gemcitabine monothetarpy				
Aung et al (1)	-	-	-	-
Chan et al (1)	-	-	-	-
Fernandes et al	-	-	-	-
Gilabert et al[&]	-	-	-	-
Lino et al	-	-	-	-
Sarabi et al[$]	0 (0.0)	4 (9.5)	0 (0.0)	1 (2.4)
Viaud et al[$]	3 (3.1)	12 (12.5)	-	6 (6.3)
Zhang H et al (1)	0 (0.0)	1 (12.5)	-	1 (12.5)

Study	Anemia G3/4 (%)	Neutropenia G3/4 (%)	Febrile neutropenia (%)	Thrombocytopenia G3/4 (%)
Gemcitabine plus Nab-Paclitaxel				
Aung et al (2)	-	-	-	-
Chan et al (2)	-	-	-	-
El Rassy et al	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nguyen et al[$]	7 (23.3)	0 (0.0)	0 (0.0)	10 (33.3)
Okano et al	0 (0.0)	5 (50.0)	0 (0.0)	5 (50.0)
Ozaka et al	3 (12.0)	10 (40.0)	1 (4.0)	1 (4.0)
Portal et al[$]	2 (3.5)	7 (12.3)	-	4 (7.0)
Salem et al	-	-	-	-
Vendrell, et al	1 (3.3)	3 (10.0)	0 (0.0)	5 (16.7)
Zhang H et al (2)	1 (3.3)	7 (23.3)	-	4 (13.3)
Zhang Y et al	7 (25.0)	5 (17.9)	0 (0.0)	7 (25.0)

[$] Based on CTCAE 4.0.
[&] Based on CTCAE 3.0.

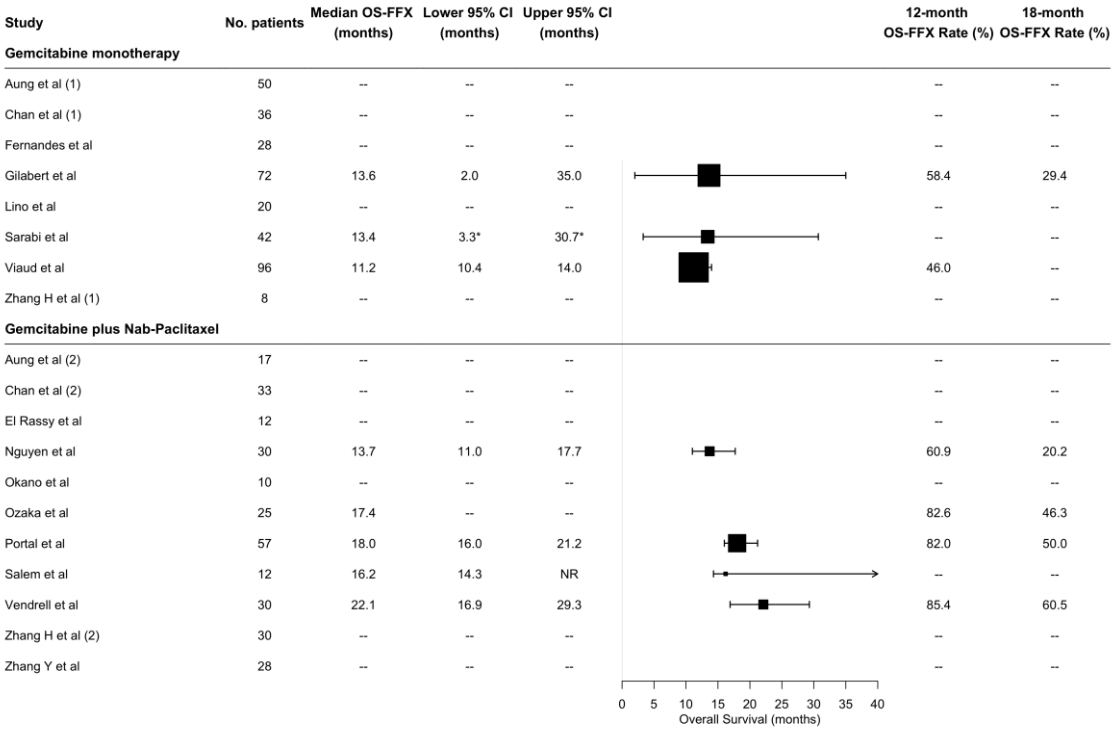
Supplementary figures

Supplementary Figure S1. Overall survival from the start of Gemcitabine-based chemotherapy (OS-GEM) across different studies using Gemcitabine-based chemotherapy (median, 6-month OS-GEM rate, and 12-month OS-GEM rate).



Supplementary Figure S1 legend. (*) Interval refers to range and not 95% confidence interval.

Supplementary Figure S2. Overall survival from the start of FOLFIRINOX (OS-FFX) across different studies using Gemcitabine-based chemotherapy (median, 12-month OS-FFX rate, and 18-month OS-FFX rate).



Supplementary Figure S2 legend. (*) Interval refers to range and not 95% confidence interval.

Supplementary Figure S3. Funnel plot of ln Odds (Response) vs. study sample size.