ASCO GUIDELINES

Data Supplement

Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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Table 1: Patient and Disease Characteristics

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
Oettle et al., 2014 CONKO-003	OFF	76	62	40	36	Karnofsky 70-80: 35 90-100: 41	NR	NR	NR
	FF	84	61	48	36	Karnofsky 70-80: 44 90-100: 40			
Von Hoff et al., 2013	nab-Paclitaxel plus Gemcitabine	431	62	245	186	Karnofsky 100: 69 (16%) 90: 179 (42%) 80: 149 (35%) 70: 30 (7%) 60: 2 (<1%)	Head: 191 (44%) Body: 132 (31%) Tail: 105 (24%) Unknown: 3 (1%)	Level of CA 19-9 Normal: 60 (16%) ULN to <59x ULN: 122 (32%) >/= 59x ULN: 197 (52%) CA 19-9 U/ml: 2293.7 range 1.9-6159	Chemo: 23 (5%) Radiation: 19 (4%) Whipple: 32 (7%) Stent: 80 (19%)

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine alone	430	63	257	173	Karnofsky 100: 69 (16%) 90: 199 (46%) 80: 128 (30%) 70: 33 (8%) 60: 0 (0%)	Head: 180 (42%) Body: 136 (32%) Tail: 110 (26%) Unknown: 4 (1%)	Level of CA 19-9 Normal: 56 (15%); ULN to <59x ULN 120 (32%); >/= 59x ULN 195 (53%) CA 19-9 U/ml: 2759 range 0.3-12,207	Chemo: 12 (3%) Radiation: 11 (3%) Whipple: 30 (7%) Stent: 68 (16%)
Rougier et al., 2013	Gemcitabine plus placebo	275	61	157	118	WHO 0: 102 1: 154 2: 19	Head: 117 Body: 41 Tail: 45 Entire pancreas: 72 Other: 0	NR	NR
	Gemcitabine plus aflibercept	271	62	160	111	WHO 0: 102 1: 152 2: 17	Head: 132 Body: 41 Tail: 46 Entire Pancreas: 50 Other: 2		

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
Goncalves et al., 2012 BAYPAN	Gemcitabine plus placebo	52	64	32	20	WHO 0: 18 1: 30 2: 3 NA: 1	NR	CA 19-9 Median 424 (1.3-3300)	NR
	Gemcitabine plus sorafenib	52	61	30	22	WHO 0: 16 1: 26 2: 5 NA: 5		CA 19-9 Median 471 (1.2-21500)	
Conroy et al., 2011	FOLFIRINOX	171	61	106	65	NR	Head: 67 Body: 53 Tail: 45 Multicentric: 6	NR	Stent: 27
	Gemcitabine	171	61	105	66		Head: 64 Body: 58 Tail: 45 Multicentric: 5/171		Stent: 22
Kindler et al., 2011	axitinib plus gemcitabine	314	61	191	123	WHO 0: 147 1: 162 Missing: 11	NR	NR	NR
	placebo plus gemcitabine	316	62	188	128	WHO 0: 158 1: 154 Missing: 4			

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
da Cunha Santos et al., 2010 NCIC CTG PA.3	Gemcitabine vs gemcitabine plus erlotinib in KRAS mutant patients	92	62.2	47	45	WHO 0:16 1:57 2:19 Unknown: 0	NR	NR	NR
	Gemcitabine vs gemcitabine plus erlotinib in KRAS wild type patients	25	65.6	17	8	WHO 0: 7 1: 14 2: 3 Unknown:1			
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH+ patients	50	61.0	32	18	WHO 0:11 1:24 2:14 Unknown:1			
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH- patients	57	64.7	30	27	WHO 0:12 1:35 2:10 Unknown:0			
Moinpour et al., 2010	Gemcitabine	359	65	197	162	WHO 0-1:312 2:47	NR	NR	Chemo: 14 Pancreatectomy: 36

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine plus cetuximab	361	64	188	173	WHO 0-1: 314 2: 47			Chemo: 21 Pancreatectomy: 32
Colucci et at., 2010 GIP-1	Gemcitabine	199	63	113	86	Karnofsky </=70:33 >/=80: 166	Head: 91 Body: 52 Tail: 26 Head + Body:10 Body + Tail:18 Head + Body + Tail:1 Unknown:1	NR	Surgery: 47
	Gemcitabine plus Cisplatin	201	63	125	73	Karnofsky </=70:36 >/=80: 165	Head: 101 Body: 34 Tail: 20 Head + Body: 6 Body + Tail: 39 Head + Body + Tail:1 Unknown:0		Surgery: 56
Dahan et al., 2010 FFCD 0301	LV5FU2-CDDP	102	62	65	37	WHO 0: 28 1: 51 2: 22 Not Determined: 1	Head: 57 Other: 44 Unknown: 1	CEA Median: 9 (0-2224) CA 19-9 Median: 565 (0-862200)	Chemo: 0 Radiation: 1 Resection: 13 Drainage: 4 Other Surgery: 6 Deudenal Stent: 10 Radiological/endoscopic drainage: 22
	Gemcitabine	100	65	65	35	WHO 0: 30 1: 53	Head: 49 Other: 50 Unknown: 1	CEA Median: 7 (1-3604)	Chemo: 3 Radiation: 2 Resection: 14

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
						2: 14 Not Determined: 3		CA 19-9 Median: 560 (1-156649)	Drainage: 8 Other Surgery: 6 Deudenal Stent: 5 Radiological/endoscopic drainage: 11
Cunningham et al., 2009	Gemcitabine	266	62	153	113	WHO 0: 56 1: 161 2: 49	Head: 185 Body: 36 Tail: 30 Head + Body: 7 Body + Tail: 7 Unknown: 5	NR	NR
	Gemcitabine plus Capecitabine	267	62	160	107	WHO 0: 66 1: 149 2: 52	Head: 190 Body: 29 Tail: 25 Head + Body: 10 Body + Tail: 10 Unknown: 4		
Van Cutsem et al., 2009	Gemcitabine-erlotinib plus placebo	301	61	188	113	NR	Head: 165 Body: 65 Tail: 67	NR	Radiation: 5 Antimetobolites: 14
	Gemcitabine-erlotinib plus Bevacizumab	306	62	174	132		Head: 157 Body: 79 Tail: 68		Radiation: 12 Antimetobolites: 12
Poplin et al., 2009 E6201	Gemcitabine	275	64	155	120	NR	NR	CA 19-9 Median 1961 (167-12024) CEA Median: 5.7 (2.3-30.9)	Chemo: 15 Radiation: 21 Surgery: 43

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine fixed-dose rate infusion	277	61	160	117			CA 19-9 Median: 1148 (136-9651) CEA Median: 5.9 (2.4-30.1)	Chemo: 17 Radiation: 23 Surgery: 42
	Gemcitabine plus oxaliplatin	272	63	124	148			CA 19-9 Median: 1077 (90-9301) CEA Median: 6.3 (2.4 -35.5)	Chemo: 10 Radiation: 21 Surgery: 32
Bernhard et al., 2008 SAKK 44/00-CECO/PAN.1.3.001	Capecitabine plus Gemcitabine	160	62	86	74	Karnofsky 90-100: 84 60-80: 76	NR	NR	NR
	Gemcitabine	159	62	85	74	Karnofsky 90-100: 84 60-80: 75			
Herrmann et al., 2007	Capecitabine plus Gemcitabine	160	NR	86	74	Karnofsky 90-100: 84 60-80: 76	NR	NR	NR
	Gemcitabine	159		85	74	Karnofsky 90-100: 84 60-80: 75			
Moore et al., 2007	Erlotinib plus Gemcitabine	285	63.7	136	149	WHO 0: 85 1: 145 2: 54	NR	NR	FU or Gem given concurrently as a radiosensatizer only: 20 Radiation: 22 Resection: 19

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Placebo plus Gemcitabine	284	64.0	162	122	WHO 0: 85 1: 174 2: 52			FU or Gem given concurrently as a radiosensatizer only: 25 Radiation: 25 Resection: 29
Abou-Alfa et al., 2006	Exatecan plus Gemcitabine	174	63.0	92	83	Karnofsky 90-100: 90 70-80: 81 60: 4	NR	CA 19-9 Median: 1053 (0.8-1237761)	NR
	Gemcitabine	174	62.3	99	99	Karnofsky 90-100: 90 70-80: 82 60: 2		CA 19-9 Median: 597 (1.3-304332)	
Stathopoulos et al., 2006	irinotecan plus gemcitabine	60	64	39	21	WHO 0-1: 52 2: 8	NR	NR	Surgery: 11 No Prior Treatment: 49
	gemcitabine	70	64	42	28	WHO 0-1: 8 2: 10			Surgery: 16 No Prior Treatment: 54
Heinemann et al., 2006	gemcitabine plus cisplatin	98	64	64	34	Karnofsky 100: 20 90: 24 80: 27 70: 8	Head: 55 Body: 19 Tail: 24	NR	NR
	gemcitabine	97	66	60	37	Karnofsky 100: 19 90: 21 80: 29 70: 13	Head: 55 Body: 24 Tail: 18		
Reni et al., 2005	PEFG	52	62	24	28	Karnofsky >70: 37 </= 70: 15	NR	NR	NR

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine	47	59	24	23	Karnofsky >70: 35 </= 70: 12			
Louvet et al., 2005	Gemcitabine	156	60.1	53	47	WHO 0: 28 1: 54 2: 18	Head: 50 Body: 37 Tail: 13	Median: 1424	NR
	Gemcitibine plus oxaliplatin	157	61.3	60	40	WHO 0: 31 1: 52 2: 17	Head: 54 Body: 27 Tail: 19	Median: 965	
Rocha Lima et al., 2004	Gemcitabine plus Irinotecan	180	63.2	103	73	WHO 0:51 1:90 2:34 3:1 missing:4	NR	NR	Radiation: 11
	Gemcitabine	180	60.2	96	73	WHO 0:42 1:91 2:36 3:0 missing:11			Radiation: 14
Berlin et al., 2002 E2297	Gemcitabine	162	64.3	87	75	WHO 0:56 1:84 2:22	Head:81 Body: 19 Tail: 27 Unknown: 35	NR	NR
	Gemcitabine plus 5-FU	160	65.8	83	77	WHO 0:36 1:102 2:22	Head: 87 Body: 36 Tail: 21 Unknown: 17		
Maisey et al., 2002	PVI 5-FU	107	62	68	39	WHO 0:18 1:59	NR	NR	NR

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
						2:28 3: 1			
	PVI 5-FU plus mitomycin	102	61	62	40	WHO 0:20 1:54 2:24 3:1			

Abbreviations: CONKO, Charité Onkologie; OFF, Oxaliplatin, fluoruracil, plus folinic acid; FF, fluoruracil, plus folinic acid; NR, not reported; CA, cancer antigen; ULN, upper limit of normal; Chemo, chemotherapy; WHO, World Health Organization; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; EGFR, Epidermal growth factor receptor; FISH, fluorescence in situ hybridization; GIP, Gruppo Italiano Pancreas; FFCD, Fédération Francophone de Cancérologie Digestive; LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination ; CEA, Carcinoembryonic antigen; SAKK, Swiss Group for Clinical Cancer Research; CECOG, Central European Cooperative Oncology Group; FU, fluorouracil; Gem, Gemcitabine; PEFG, cisplatin, epirubicin, 5-fluorouracil, gemcitabine; PVI, protracted venous infusion

Table 2: OUTCOMES: Survival (OS), progression free survival (PFS) and disease free survival (DFS) and adverse events (AEs)

Study	Intervention	# of patients	Outcome
Oettle et al., 2014 CONKO-003	OFF	76	The median overall survival 5.9 months; 95% CI, 4.1 to 7.4) (hazard ratio [HR], 0.66; 95% CI, 0.48 to 0.91; log-rank P .010). Time to progression (2.9 months; 95% CI, 2.4 to 3.2) was significantly extended also (HR, 0.68; 95% CI, 0.50 to 0.94; log-rank P .019). Rates of adverse events were similar between treatment arms, with the exception of grades 1 to 2 neurotoxicity, which were reported in 29 patients (38.2%) in the [(P .001).
	FF	84	The median overall survival (3.3 months; 95% CI, 2.7 to 4.0) was significantly improved (hazard ratio [HR], 0.66; 95% CI, 0.48 to 0.91; log-rank P .010). Time to progression (2.0 months; 95% CI, 1.6 to 2.3) was significantly extended also (HR, 0.68; 95% CI, 0.50 to 0.94; log-rank P .019). Rates of adverse events were similar between treatment arms, with the exception of grades 1 to 2 neurotoxicity, which were reported in and six patients (7.1%) in the OFF and FF groups, (P .001).
Von Hoff et al., 2013	nab-Paclitaxel plus Gemcitabine	431	The median overall survival was 8.5 months (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The survival rate was 35% at 1 year, and 9% at 2 years. The median progression-free survival was 5.5 months. (hazard ratio, 0.69; 95%

Study	Intervention	# of patients	Outcome
			CI, 0.58 to 0.82; P<0.001); the response rate according to independent review was 23% versus 7% in the two groups (P<0.001). The most common adverse events of grade 3 or higher were neutropenia (38%), fatigue (17%); and neuropathy (17% Febrile neutropenia occurred in 3% neuropathy of grade 3 or >r higher improved to grade 1 or lower in a median of 29 days
	Gemcitabine alone	430	The median overall survival was 6.7 months (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The survival rate was 22% at 1 year and 4% at 2 years. The median progression-free survival was 3.7 months in the gemcitabine group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001); The response rate according to independent review was 23% versus 7% in the two groups (P<0.001). The most common adverse events of grade 3 or higher were 27%; fatigue .7%, and neuropathy 1%). Febrile neutropenia occurred in 1% of the patients; neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 day
Rougier et al., 2013	Gemcitabine plus placebo	275	The study was stopped for futility following a planned interim analysis of OS in 427 randomized patients. With a median follow-up of 7.9 months, based on the 546 patients at study termination.

Study	Intervention	# of patients	Outcome
	Gemcitabine plus aflibercept	271	Median OS was 7.8 months in the gemcitabine plus placebo arm (n=275) versus 6.5 months in the gemcitabine plus aflibercept arm (n=271), which was not significant (hazard ratio 1.165, 95% confidence interval (CI) 0.921-1.473, p=0.2034). Median progression-free survival was 3.7 months in both arms. Treatment discontinuations due to adverse events were more frequent in the aflibercept than in the placebo-containing arm (23% versus 12%).
Goncalves et al., 2012 BAYPAN	Gemcitabine plus placebo	52	Median and the 6-month PFS were 5.7 months and 48%. (P = 0.902, stratified log-rank test) Median overall survivals was 9.2 (P = 0.231, log-rank test). Overall response rates were similar (19%).
	Gemcitabine plus sorafenib	52	The median and the 6 month PFS were 3.8 months and 33% (P = 0.902, stratified log-rank test), respectively The median overall survivals was 8 months (P = 0.231, log-rank test). The overall response rates were similar 23%.
Conroy et al., 2011	FOLFIRINOX	171	The median overall survival was 11.1 months, (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 6.4 months , (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001) The objective response rate was 31.6%, (P<0.001).

Study	Intervention	# of patients	Outcome
			More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabinee group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001
	Gemcitabine	171	The median overall survival was 6.8 months, (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 3.3 months , (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate was 9.4, (P<0.001)
Kindler et al., 2011	Axitinib plus gemcitabine	314	At an interim analysis in January, 2009, the independent data monitoring committee concluded that the futility boundary had been crossed. Median overall survival was 8.5 months (95% CI 6.9-9.5) for gemcitabine plus axitinib (n=314, data missing for two patients; hazard ratio 1.014, 95% CI 0.786-1.309; one-sided p=0.5436).
	Placebo plus Gemcitabine	316	The most common grade 3 or higher adverse events for gemcitabine plus axitinib were hypertension (20 [7%] events, abdominal pain (20 [7%] ,fatigue (27 [9%] , and anorexia (19 [6%]/ Median overall survival was 8.3 months (6.9-10.3) (n=316; hazard ratio 1.014, 95% CI 0.786-1.309; one-sided p=0.5436). The most common grade 3 or higher adverse events for gemcitabine plus placebo were hypertension 5 [2%] events, abdominal pain (17 [6%]), fatigue and 21

Study	Intervention	# of patients	Outcome
			[7%]), and anorexia and 11 [4%]).
da Cunha Santos et al., 2010 NCIC CTG PA.3	Gemcitabine vs gemcitabine plus erlotinib in KRAS mutant patients	92	KRAS analysis was successful in 117 patients, and EGFR FISH analysis was successful in 107 patients. KRAS mutations were identified in 92 patients (78.6%), and EGFR amplification or high polysomy (FISH-positive results) was identified in 50 patients (46.7%). The hazard ratio of death between gemcitabine /erlotinib and gemcitabine /placebo was 0.66 (95% confidence interval [CI], 0.28-1.57) for patients with wild-type KRAS and 1.07 (95% CI, 0.68-1.66) for patients with mutant KRAS (P value for interaction = .38), and the hazard ratio was 0.6 (95% CI, 0.34-1.07) for FISH-negative patients and 0.90 (95% CI, 0.49-1.65) for FISH-positive patients (P value for interaction = .32).
	Gemcitabine vs gemcitabine plus erlotinib in KRAS wild type patients	25	
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH+ patients	50	
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH- patients	57	

Study	Intervention	# of patients	Outcome
Moinpour et al., 2010	Gemcitabine	359	The two treatment arms did not differ statistically in the percentage of patients with successful worst pain palliation. Longitudinal analyses showed significantly improved emotional well-being for patients on both arms by weeks 13 and 17 (P < .01 and P < .001). An exploratory longitudinal analysis of worst pain showed significant decreases at all time points for both arms (P < .01 and P < .001). Significant treatment arm differences for either worst pain or emotional well-being were not observed at any of the assessment times.
	Gemcitabine plus cetuximab	361	
Colucci et at., 2010 GIP-1	Gemcitabine	199	Median overall survival was 8.3 months (HR, 1.10; 95% CI, 0.89 to 1.35; P = .38). Median progression-free survival was 3.9 months (HR, 0.97; 95% CI, 0.80 to 1.19; P = .80). The objective response rate was 10.1% in A (P = .37). Clinical benefit was experienced by 23.0% in (P = .057).
	Gemcitabine plus Cisplatin	201	Median overall survival was 7.2 months (HR, 1.10; 95% CI, 0.89 to 1.35; P = .38). Median progression-free survival was 3.8 months, (HR, 0.97; 95% CI, 0.80 to 1.19; P = .80). Clinical benefit was experienced by 15.1% in B (P = .057). The objective response rate was 12.9% (P = .37). Combination therapy produced more hematologic toxicity, without relevant differences in non-hematologic toxicity.

Study	Intervention	# of patients	Outcome
Dahan et al., 2010 FFCD 0301	LV5FU2-CDDP	102	Median OS in Arm A was 6.6 months. (p = 0.85). Median progression-free survival was similar between Arms A and B. More grade 3/4 toxicities were observed when LV5FU2-CDDP was administered as a first-line treatment at 79% (p = 0.018)
	Gemcitabine	100	Median OS in 8.0 months (p = 0.85). Median progression-free survival was similar between Arms A and B. More grade 3/4 toxicities were observed when gemcitabine was administered as a first-line treatment 64% (p = 0.018).
Cunningham et al., 2009	Gemcitabine	266	Objective response rate with GEM was 12.4%; P = .034) Objective response rate with GEM-CAP was 19.1%; P = .034) Progression-free survival (hazard ratio [HR], 0.78; 95% CI, 0.66 to 0.93; P = .004) and was associated with a trend toward improved OS (HR, 0.86; 95% CI, 0.72 to 1.02; P = .08) compared with GEM alone. This trend for OS benefit for GEM-CAP was consistent across different prognostic subgroups according to baseline stratification factors (stage and performance status) and remained after adjusting for these stratification factors (P = .077).
	Gemcitabine plus Capecitabine	267	

Study	Intervention	# of patients	Outcome
Van Cutsem et al., 2009	Gemcitabine-erlotinib plus placebo	301	Median OS was 7.1 (hazard ratio [HR], 0.89; 95% CI, 0.74 to 1.07; P = .2087); this difference was not statistically significant. Median OS was 6.0 months (hazard ratio [HR], 0.89; 95% CI, 0.74 to 1.07; P = .2087); this difference was not statistically significant. Adding bevacizumab to gemcitabine-erlotinib significantly improved PFS (HR, 0.73; 95% CI, 0.61 to 0.86; P = .0002). Treatment with bevacizumab plus gemcitabine-erlotinib was well tolerated: safety data did not differ from previously described safety profiles for individual drugs
	Gemcitabine-erlotinib plus Bevacizumab	306	
Poplin et al., 2009 E6201	Gemcitabine	275	Median survival and 1-year survival were 4.9 months (95% CI, 4.5 to 5.6) and 16%, (95% CI, 5.4 to 6.9), (HR, 0.83; stratified log-rank P = .04. The median survival and 1-year survival were 6.2 months (HR, 0.83; stratified log-rank P = .04), 21% and (95% CI, 4.9 to 6.5). Grade 3/4 neutropenia and thrombocytopenia were greatest with GEM FDR. The median survival and 1-year survival were 5.7 months (95% CI, 4.9 to 6.5) and 21% (HR, 0.88; stratified log-rank P = .22). *None of these differences met the prespecified criteria for significance. Survival was 4 months for those with metastatic disease.
	Gemcitabine fixed-dose rate infusion	277	
	Gemcitabine plus oxaliplatin	272	

Study	Intervention	# of patients	Outcome
Bernhard et al., 2008 SAKK 44/00-CECO/PAN.1.3.001	Capecitabine plus Gemcitabine	160	Clinical benefit response of 19% treated with GemCap with a median duration of 9.5 weeks, respectively (P < .02). 54% of patients treated with GemCap had no Clinical benefit response.
	Gemcitabine	159	Clinical benefit response of 19% treated with Gem with a median duration of 9.5 weeks, (P < .02) 60% treated with Gem had no clinical benefit response (remaining patients were not assessable). There was no treatment difference in QOL (n = 311). QOL indicators were improving under chemotherapy (P < .05). These changes differed by the time to failure, with a worsening 1 to 2 months before treatment failure (all P < .05).
Herrmann et al., 2007	Capecitabine plus Gemcitabine	160	Median OS was 8.4 months, (P = .234). Post hoc analysis in patients with good KPS (score of 90 to 100) showed a significant prolongation of median OS of 10.1, P = .014).
	Gemcitabine	159	Median OS time was 7.2 months (P = .234). Post hoc analysis in patients with good KPS (score of 90 to 100) showed a significant reduction of median OS time of 7.4 months, P = .014). The overall frequency of grade 3 or 4 adverse events was similar in each arm. Neutropenia was the most frequent grade 3 or 4 adverse event in both arms

Study	Intervention	# of patients	Outcome
Moore et al., 2007	Erlotinib plus Gemcitabine	285	Overall survival based on an intent-to-treat analysis was significantly prolonged on the erlotinib/ gemcitabine arm with a hazard ratio (HR) of 0.82 (95% CI, 0.69 to 0.99; P = .038, adjusted for stratification factors; median 6.24 months). One-year survival was 23% P = .023). Progression-free survival was significantly longer with erlotinib plus gemcitabine with an estimated HR of 0.77 (95% CI, 0.64 to 0.92; P = .004).
	Placebo plus Gemcitabine	284	Overall survival based on an intent-to-treat analysis was significantly prolonged on the erlotinib/ gemcitabine arm with a hazard ratio (HR) of 0.82 (95% CI, 0.69 to 0.99; P = .038, adjusted for stratification factors; 5.91 months). One-year survival was 17%; P = .023). Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization. There was a higher incidence of some adverse events with erlotinib plus gemcitabine.
Abou-Alfa et al., 2006	Exatecan plus Gemcitabine	174	Median survival time was 6.7 months.and 6.2 months for gemcitabine alone (P = .52). One complete response (CR; < 1%) and 11 partial responses (PRs; 6.3%) were observed. Grade 3 and 4 toxicities neutropenia (30%); thrombocytopenia (15%).

Study	Intervention	# of patients	Outcome
	Gemcitabine	174	Median survival time was 6.2 months (P = .52). One CR (< 1%) and eight PRs (4.6%) were observed. Grade 3 and 4 toxicities neutropenia (15%); thrombocytopenia (4%).
Stathopoulos et al., 2006	Irinotecan plus Gemcitabine	60	The overall response rate was 15% (95% CI 5.96-24.04 and 95% CI 2.97-17.03, respectively; P=0.387). The median time to tumor progression was 2.8 months and median survival time was 6. One-year survival was 24.3%.
	Gemcitabine	70	The overall response rate was 10% (95% CI 5.96-24.04 and 95% CI 2.97-17.03, respectively; P=0.387). The median time to tumor progression was 2.9 months and median survival time was 6.5 months. One-year survival was 21.8%.
Heinemann et al., 2006	Gemcitabine plus Cisplatin	98	Median progression-free survival of 5.3 months; hazard ratio [HR] = 0.75; P = .053). Median overall survival was superior at 7.5 months), an advantage which did not, however, reach statistical significance (HR = 0.80; P = .15). Tumor response rate was 10.2%. Tumor response rates were comparable between treatment arms (10.2% v 8.2%).

Study	Intervention	# of patients	Outcome
			The rate of stable disease was, however, greater in the combination arm at 60.2% P < .001). Grade 3 to 4 hematologic toxicity did not exceed 15% in both treatment arms. Median progression-free survival of 3.1 months; hazard ratio [HR] = 0.75; P = .053). Median overall survival was 6.0 months, an advantage which did not, however, reach statistical significance (HR = 0.80; P = .15). Tumor response rate was 8.2%. The rate of stable disease was, however, greater in the combination arm was 40.2%; P < .001). Grade 3 to 4 hematologic toxicity did not exceed 15% in both treatment arms.
	Gemcitabine	97	
Reni et al., 2005	PEFG	52	The largest differences between arms favored PEFG. Expressed as improvement greater than or equal to 10 points from baseline (PEFG/gemcitabine), these were: emotional function (43/18%), fatigue (41/17%), QOL (55/29%), pain (64/41%), and flatulence (50/26%). Only change in sexual function favored gemcitabine (19/42%). Physical function, fatigue, appetite, and satisfaction with healthcare improved in 40-46% of partial responders compared with 0-12% of patients with stable disease.
	Gemcitabine	47	
Louvet et al., 2005	Gemcitabine plus oxaliplatin	157	Response rate (26.8%; P = .04) Progression-free survival (5.8; P = .04),] Clinical benefit (38.2%; P = .03).

Study	Intervention	# of patients	Outcome
			Median overall survival (OS) was 9.0 (P = .13). Higher incidence of National Cancer Institute Common Toxicity Criteria grade 3 and 4 toxicity per patient was observed for platelets (14.0%), vomiting (8.9%), and neurosensory symptoms (19.1%).
	Gemcitabine	157	Response rate (17.3%, P = .04) Progression-free survival (3.7 months; P = .04). Clinical benefit (26.9%, P = .03). Median overall survival (OS) for 7.1 months, respectively (P = .13). Grade 3 and 4 toxicity per patient was observed for platelets 3.2%, vomiting (3.2%), and neurosensory symptoms (0%).
Rocha Lima et al., 2004	Gemcitabine plus Irinotecan	180	Median survival times were 6.3 months for IRINOGEM (95% CI, 4.7 to 7.5 months) and 6.6 months for GEM (95% CI, 5.2 to 7.8 months; log-rank P =.789). Tumor response rates were 16.1% (95% CI, 11.1% to 22.3%) for IRINOGEM (chi2 P <.001). Median TTP was 3.5 months for IRINOGEM (log-rank P =.352). However, subset analyses in patients with locally advanced disease suggested a TTP disadvantage with IRINOGEM (median, 7.7 v 3.9 months). CA 19-9

Study	Intervention	# of patients	Outcome
			progression was positively correlated with tumor progression. The incidence of grade 3 diarrhea was higher in the IRINOGEM group but grade 3 to 4 hematologic toxicities and quality-of-life outcomes were similar.
	Gemcitabine	180	Median survival times were 6.6 months (95% CI, 5.2 to 7.8 months; log-rank P =.789). Tumor response rates were and 4.4% (95% CI, 1.9% to 8.6%) (chi2 P <.001). Median TTP was 3.0 months (log-rank P =.352). Subset analyses in patients with locally advanced disease suggested a TTP disadvantage with GEM (median, 3.9 months). CA 19-9 progression was positively correlated with tumor progression. The incidence of grade 3 diarrheas was lower but grade 3 to 4 hematologic toxicities and quality-of-life outcomes were similar. .
Berlin et al., 2002 E2297	Gemcitabine	162	Median survival was 5.4 months (P =.09). Progression-free survival was 2.2 months, (P =.022). Objective responses were uncommon and were observed in only 5.6% of patients treated with gemcitabine. Most toxicities were hematologic or gastrointestinal; no significant differences were noted between the two treatment arms.

Study	Intervention	# of patients	Outcome
	Gemcitabine plus 5-FU	160	Median survival was 6.7 months (P =.09). Progression-free survival was 3.4 months (P =.022). Objective responses were uncommon and were observed in only 6.9%.. Most toxicities were hematologic or gastrointestinal; no significant differences were noted between the two treatment arms.
Maisey et al., 2002	PVI 5-FU	107	The overall response rate was 8.4% (95% confidence interval [CI]) 3.2% to 13.7% 95% (P =.04). Median failure-free survival was 2.8 months (P =.14). Median survival was 5.1 months (P =.34). Toxicities were mild. No differences in infection were seen. No patients developed hemolytic uremic syndrome.
	PVI 5-FU plus mitomycin	102	The overall response rate was 17.6%; (95% confidence interval [CI] 10.3% to 25.1%, (P =.04). Median failure-free survival was 2 3.8 months (P =.14). Median survival was 6.5 months (P =.34). Toxicities in both arms were mild. There was an increased incidence of neutropenia in the 5-FU plus MMC arm (P <.01), although no differences in infection were seen. No patients developed hemolytic uremic syndrome. Global QOL improved significantly after 24 weeks of treatment compared with

Study	Intervention	# of patients	Outcome
			baseline for patients receiving 5-FU plus MMC, although there was no statistically significant difference in QOL between arms.

Abbreviations: CONKO, Charité Onkologie; OFF, Oxaliplatin, fluoruracil, plus folinic acid; FF, fluoruracil, plus folinic acid; OS, overall survival; PFS, progression free survival; APC, advanced pancreatic cancer; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; EGFR, Epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HRQL, health-related quality of life; GIP, Gruppo Italiano Pancreas; FFCD, Fédération Francophone de Cancérologie Digestive; LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination; GEM, Gemcitabine; CAP, Capecitabine; FDR, fixed dose rate; GEMOX, gemcitabine and oxaliplatin; SAKK, Swiss Group for Clinical Cancer Research; CECOG, Central European Cooperative Oncology Group; CBR, clinical benefit response; QOL, quality of life; PEFG, cisplatin, epirubicin, 5-fluorouracil, gemcitabine; IRINOGEM, irinotecan plus gemcitabine; FU, fluorouracil; PVI, protracted venous infusion; MMC, mitomycin

Table 3: Systematic Reviews and Meta-analyses (Metastatic)

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
Sgouros J (1), Maraveyas A Excess premature (3-month) mortality in advanced pancreatic cancer could be related to fatal vascular thromboembolic events. A hypothesis based on a systematic review of phase III chemotherapy studies in advanced pancreatic cancer.	Acta Oncol. 2008;47(3):337-46.	A Medline and EMBASE search was done for chemotherapy or chemotherapy based phase III studies in advanced pancreatic cancer published since 1997. Similar search was done at the American Society of Clinical Oncology web site for abstracts presented since 2000. Three months mortality was based on the survival curves presented.	Fourteen papers and five abstracts met our criteria and are included in our review. Six thousand two hundred and twelve patients participated in these trials and 1,447 (23.3%) died in the first 3-month period. Figures were worse in patients with metastases and poorer performance status. Assuming that most deaths during treatment happened during the first 3-months, cause of death was reported in only 40 cases (2.8%). Progressive cancer was reported as cause of death in 21 of these cases. Less frequent causes of death were reported to be infections, 'complications of cancer', thromboembolic events and renal failure.	Overall treatment-related deaths represent a very small percentage of the deaths happening during the 3-month period, and are unlikely to be under-reported given the Good Clinical Practice oversight of these trials. Progressive cancer is likely to be an important cause of early mortality but given the very select nature of the trial-related population this cannot explain the phenomenon of 3-month early death burden of 23.3%. Our hypothesis, supported by multiple autopsy series, is that early death burden in advanced pancreatic cancer trial patients is likely to be due to under-reported vascular thromboembolic events. Thromboprophylaxis needs to be addressed in future trials.
Yang ZY (1), Yuan JQ, Di MY, Zheng DY, Chen JZ, Ding H, Wu	PLoS One. 2013;8(3):e57528. doi:	PubMed, EMBASE, The Cochrane Library and abstracts of recent major conferences were systematically searched	Sixteen studies containing 1,308 advanced pancreatic cancer patients treated with gemcitabine plus erlotinib were included. The reported	Gemcitabine plus erlotinib represent a new option for the treatment of advanced pancreatic cancer, with mild but clinically meaningful additive efficacy compared with gemcitabine alone. Its safety profile

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
XY, Huang YF, Mao C, Tang JL. Gemcitabine plus erlotinib for advanced pancreatic cancer: a systematic review with meta-analysis.	10.1371/journal.pone.0057528. Epub 2013 Mar 5.	to identify relevant publications. Studies that were conducted in advanced pancreatic cancer patients treated with gemcitabine plus erlotinib (with or without comparison with gemcitabine alone) and reporting objective response rate, disease control rate, progression-free survival, time-to-progression, overall survival, 1-year survival rate and/or adverse events were included. Data on objective response rate, disease control rate, 1-year survival rate and adverse events rate, respectively, were combined mainly by using Meta-Analyst software with a random-effects model. Data on progression-free survival, time-to-progression and overall	median progression-free survival (or time-to-progression), median overall survival, 1-year survival rates, objective response rates and disease control rates were 2-9.6 months, 5-12.5 months, 20%-51%, 0%-28.6% and 25.0%-83.3%, respectively. The weighted 1-year survival rate, objective response rate and disease control rate based on studies reporting robust results were 27.9%, 9.1% and 57.0%, respectively. According to the studies with relevant data, the incidences of total and severe adverse events were 96.3% and 62.9%, respectively. The most frequently reported adverse events were leucopenia, rash, diarrhea, vomiting, neutropenia, thrombocytopenia, anaemia, stomatitis, drug-induced liver injury, fatigue and fever. Compared with gemcitabine alone, the progression-free survival and overall survival with gemcitabine plus	is generally acceptable, although careful management is needed for some specific adverse events.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
		survival were summarized descriptively.	erlotinib were significantly longer, but there were also more deaths and interstitial lung disease-like syndrome related to this treatment.	
Li Y (1), Sun J, Jiang Z, Zhang L, Liu G. Gemcitabine and S-1 combination (GS) chemotherapy versus gemcitabine (GEM) alone for locally advanced and metastatic pancreatic cancer: a meta-analysis of randomized controlled trials in Asia.	J Chemother. 2015 Aug;27(4):227-34.	Relevant trials were identified by searching databases. Five trials were selected in this article. The indicators we used were overall response rate, disease control rate, 1-year survival rate and haematological toxicities.	Meta-analysis of the pooled data demonstrated that the overall response rate (risk ratio, RR = 2.52, 95% confidence interval, CI: 1.85-3.42, P < 0.00001) and disease control rate (RR = 1.24, 95% CI: 1.12-1.37, P < 0.0001) were significantly different for the GS and GEM alone chemotherapies. Among the group of patients, 43.4% in the GS group and 31.4% in the GEM group survived more than a year. According to this, patients who use the GS regiment may have a better prognosis than the GEM regiment (RR = 1.62, 95% CI: 1.12-2.33, P = 0.04). The combination chemotherapy with GEM and S-1 group had higher haematological toxicities including neutropaenia (RR = 1.58, 95% CI: 1.17-	Overall response rate and disease control rate as well as 1-year survival rate in patients who received GS were superior to those treated with GEM alone. Combination chemotherapy with GEM and S-1 may offer greater benefits in the treatment of pancreatic cancer than GEM alone, although the GS group had higher haematological toxicities. Combination chemotherapy with GEM and S-1 might be an option of first-line chemotherapy for pancreatic cancer patients, at least in Asia. Mini Abstract: This systematic review analysing randomized controlled trials (RCTs) comparing S-1 combination chemotherapy versus GEM alone for locally advanced and metastatic pancreatic cancer demonstrated greater efficacy for S-1 combination in term of response, disease control and 1-year survival proportion.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
			2.14, P = 0.003) and thrombocytopaenia (RR = 1.85, 95% CI: 1.28-2.67, P = 0.001). The incidence of anaemia was much the same in the two groups (RR = 1.22, 95% CI: 0.87-1.70, P = 0.24).	
Sultana A(1), Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer.	J Clin Oncol. 2007 Jun 20;25(18) :2607-15.	There are a large number of randomized controlled trials involving chemotherapy in the management of advanced pancreatic cancer. Several chemotherapeutic agents, either alone or in combination with other chemotherapy or novel agents, have been used. The aim of these meta-analyses was to examine the different therapeutic approaches, and the comparisons examined were as follows: chemotherapy versus best supportive care; fluorouracil (FU) versus FU combination	One hundred thirteen randomized controlled trials were identified, of which 51 trials involving 9,970 patients met the inclusion criteria. Chemotherapy improved survival compared with best supportive care (hazard ratio [HR] = 0.64; 95% CI, 0.42 to 0.98). FU-based combination chemotherapy did not result in better overall survival compared with FU alone (HR = 0.94; 95% CI, 0.82 to 1.08). There was insufficient evidence of a survival difference between gemcitabine and FU, but the wide CI includes clinically important differences in both directions, making a clear conclusion difficult (HR = 0.75; 95% CI, 0.42 to 1.31).	There was a significant survival benefit for chemotherapy over best supportive care and gemcitabine combinations over gemcitabine alone. This supports the use of gemcitabine-based combination chemotherapy in the treatment of advanced pancreatic cancer.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
		chemotherapy; gemcitabine versus FU; and gemcitabine versus gemcitabine combination chemotherapy. Relevant trials were identified by searching databases, trial registers, and conference proceedings. The primary end point was overall survival.	Survival was improved after gemcitabine combination chemotherapy compared with gemcitabine alone (HR = 0.91; 95% CI, 0.85 to 0.97).	
Ying JE(1), Zhu LM, Liu BX. Developments in metastatic pancreatic cancer: is gemcitabine still the standard?	World J Gastroenterol. 2012 Feb 28;18(8): 736-45.	In the past 15 years, we have seen few therapeutic advances for patients with pancreatic cancer, which is the fourth leading cause of cancer-related death in the United States.	Currently, only about 6% of patients with advanced disease respond to standard gemcitabine therapy, and median survival is only about 6 months. Moreover, phase III trials have shown that adding various cytotoxic and targeted chemotherapeutic agents to gemcitabine has failed to improve overall survival, except in cases in which gemcitabine combined with erlotinib show minimal survival benefit. Several meta-analyses have shown that the combination of	Strikingly, a phase III trial in 2010 showed that, in comparison to gemcitabine alone, the FOLFIRINOX regimen in patients with advanced disease and good performance status, produced better median overall survival, median progression-free survival, and objective response rates. This regimen also resulted in greater, albeit manageable toxicity.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
			gemcitabine with either a platinum analog or capecitabine may lead to clinically relevant survival prolongation, especially for patients with good performance status. Meanwhile, many studies have focused on the pharmacokinetic modulation of gemcitabine by fixed-dose administration, and metabolic or transport enzymes related to the response and toxicity of gemcitabine.	
Banu E(1), Banu A, Fodor A, Landi B, Rougier P, Chatellier G, Andrieu JM, Oudard S. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients	Drugs Aging. 2007;24(10):865-79.	We conducted a systematic review and meta-analysis of published data on the use of gemcitabine-based doublets compared with gemcitabine alone in chemotherapy-naive patients with advanced and metastatic pancreatic cancer treated in randomised controlled phase II-III trials with overall survival as the principal	Gemcitabine-based doublets were associated with small but significant reductions in the risk of death at 6, 12 and 18 months of 8% (95% CI 3, 13), 4% (95% CI 2, 7) and 3% (95% CI 1, 5), respectively ($p<0.005$ for all timepoints). No heterogeneity between studies was observed. Subgroup analyses showed an overall survival benefit for gemcitabine-based doublets in clinical trials testing the same planned dose intensity of gemcitabine in comparative	This meta-analysis of data obtained from randomised controlled phase II-III trials of patients with advanced pancreatic cancer showed a small but significant improvement in overall survival for patients receiving gemcitabine-based doublets compared with gemcitabine alone.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
with advanced and metastatic pancreatic cancer.		or secondary endpoint. To this end, a literature search was performed using Cochrane methodology. The relative risks with 95% confidence intervals were estimated based on adjusted number of deaths and patients at risk according to the extent of follow-up and censoring. Twenty-three randomised clinical trials including 5886 patients met the inclusion criteria. In these trials, 2932 patients were randomly assigned to receive gemcitabine-based doublets and 2954 patients to receive gemcitabine alone.	arms, using platinum salt-based protocols and with survival as the primary endpoint.	
Zagouri F(1), Sergentanis TN, Chrysikos D, Zografos CG, Papadimitriou CA, Dimopoulos	Pancreas. 2013 Jul;42(5): 760-73.	This is the first systematic review of the literature to synthesize all available data coming from trials and evaluate the efficacy and safety of	The search strategy retrieved 439 articles. Of these articles, 237 were irrelevant, 113 were reviews, and 21 were case reports. After searching the references of all reviews and remaining articles, 29	Regarding the evaluation of molecular targeted therapies in pancreatic cancer, it should be stressed that although multiple agents have been tested, only 9 phase 3 trials have been conducted and one agent (erlotinib) has been approved by FDA for use in clinical practice. Nevertheless,

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
MA, Filipits M, Bartsch R. Molecularly targeted therapies in metastatic pancreatic cancer: a systematic review.		molecular targeted drugs in unresectable and metastatic pancreatic cancer.	conference abstracts and 15 PubMed articles were also included. Overall, 112 studies were eligible for the systematic review.	erlotinib has exhibited modest results, as the gain in survival was only 0.4 months. However, molecularly targeted agents seem to mark the beginning of a new era in the context of unresectable and metastatic pancreatic cancer. It would be tempting to hypothesize an analogy in developments after the introduction of imatinib for the treatment of gastrointestinal stromal tumors. In any event, as molecular profiling surpasses the borders of morphological classifications, direct consequent molecularly targeted therapy may well contribute to the individualization of treatment in the challenging group of patients with metastatic/unresectable pancreatic cancer. It is thus anticipated that better selection of patients at the individual level will contribute to sizably better performance of the newly developed and explored molecularly targeted agents. Of great importance seems to be IGF1R monoclonal antibody inhibitors, which have entered phase 3 trials.

Data Supplement 3: Literature Search Strategy for Pancreatic Cancer (Potentially Curable, Locally Advanced, Unresectable and Metastatic) and Health Disparities for Pancreatic Cancer

Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. The searches of the English-language literature published from January 2000 to June 2015 combined pancreatic neoplasm terms and follow-up-related terms and MeSH headings. Results of the databases searches were supplemented with hand searching of the bibliographies of systematic reviews and selected seminal articles, and contributions from Expert Panel members' personal files.

Disease and Treatments

Search: ("carcinoma, pancreas"[MeSH Terms] OR ((cancer[TIAB] OR neoplasm[TIAB] OR neoplasms[TIAB] OR tumor[TIAB] OR tumors[TIAB] OR tumour[TIAB] OR tumours[TIAB] OR malignant[TIAB] OR malignancy[TIAB] OR malignancies[TIAB] OR carcinoma[TIAB] OR carcinomas[TIAB] OR carcinomatosis[TIAB] OR carcinomatoses[TIAB] OR adenocarcinoma[TIAB] OR adenocarcinomas[TIAB] OR oncology[TIAB] AND ("pancreas"[MeSH Terms] OR "pancreatic"[TIAB])) AND "palliative care"[MeSH Terms] AND ("critical illness"[MeSH Terms] OR "home care services"[MeSH Terms] OR "hospitalization"[MeSH Terms] OR "hospices"[MeSH Terms] OR "terminal care"[MeSH Terms] OR "advance care planning"[MeSH Terms] OR "terminally ill"[MeSH Terms] OR "patient care team"[MeSH Terms] OR "quality of life"[MeSH Terms] OR ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms])) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR "randomized controlled trials as topic"[MeSH Terms] OR clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "clinical trials as topic"[MeSH Terms] OR "controlled clinical trials as topic"[MeSH Terms] OR "randomized controlled trials as topic"[MeSH Terms] OR "clinical trials, phase ii as topic"[MeSH Terms] OR "clinical trials, phase iii as topic"[MeSH Terms] OR "clinical trials, phase iv as topic"[MeSH Terms] OR clinical trial, phase II[pt] OR clinical trial, phase III[pt] OR clinical trial, phase IV[pt] OR "random allocation"[MeSH Terms] OR "random allocation"[tiab] OR "randomly allocated"[tiab] OR "double-blind method"[MeSH Terms] OR "single-blind method"[MeSH Terms]) OR ((random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab]) AND (clinical[tiab] OR control[tiab] OR controlled[tiab] OR "control groups"[MeSH Terms])) OR ((single[tiab] OR single-[tiab] OR double[tiab] OR double-[tiab] OR triple[tiab] OR triple-[tiab] OR multi[tiab] OR multi-[tiab] OR evaluator[tiab] OR assessor[tiab] OR interviewer[tiab]) AND (mask[tiab] OR masked[tiab] OR masking[tiab] OR blind[tiab] OR blinded[tiab] OR blinding[tiab])) OR (("placebos"[MeSH Terms] OR placebo[tiab] OR placebos[tiab] OR random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomization[tiab]) AND ("research design"[MeSH Terms] OR "comparative study"[tiab] OR comparative study[pt] OR "evaluation studies as topic"[MeSH Terms:noexp] OR evaluation studies[pt] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "validation studies as topic"[MeSH Terms] OR "follow-up studies"[MeSH Terms] OR "follow-up study"[tiab] OR "follow up study"[tiab] OR "follow-up studies"[tiab] OR "follow up studies"[tiab] OR "prospective studies"[MeSH Terms] OR prospective[tiab] OR "epidemiologic research design"[MeSH Terms] OR "epidemiologic

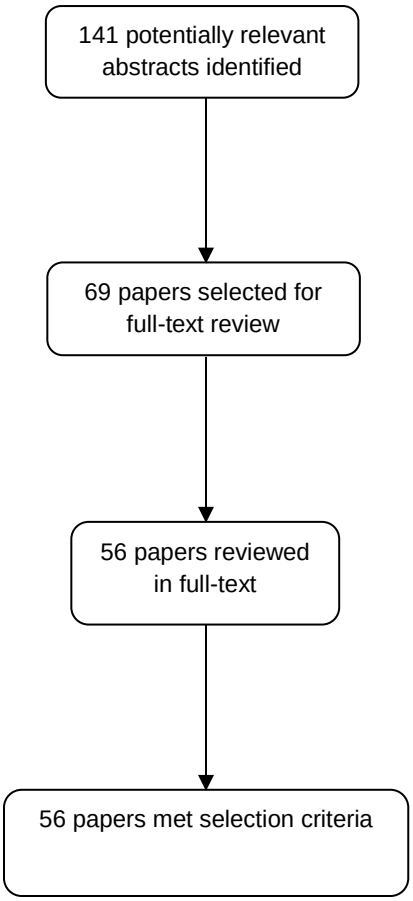
methods"[MeSH Terms] OR "epidemiologic study characteristics as topic"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms] OR "intervention studies"[MeSH Terms] OR "cross-over studies"[MeSH Terms])))) NOT (clinical trial, phase I[pt] OR "clinical trials, phase i as topic"[MeSH Terms]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) NOT review[pt] AND English[la] AND (2002/04/01[PDAT] : 2015/06/01[PDAT])

Health Disparities

(pancreatic cancer treatment) AND (((delivery of health care[MeSH:noexp] OR health behavior[MH] OR health knowledge, attitudes, practice[MH] OR health services accessibility[MH] OR health services, indigenous[MH] OR mass screening[MH] OR mass screening[TIAB] OR mass screenings[TIAB] OR health inequality[TIAB] OR health inequalities[TIAB] OR health inequities[TIAB] OR health inequity[TIAB] OR health services needs and demand[MH] OR patient acceptance of health care[MH] OR patient selection[MH] OR quality of health care[MAJR:noexp] OR quality of life[MH] OR quality of life[TIAB] OR social disparities[TIAB] OR social disparity[TIAB] OR social inequities[TIAB] OR social inequity[TIAB] OR Socioeconomic Factors[MAJR] OR socioeconomic factor[TIAB] OR socioeconomic factors[TIAB]) AND (African American[TIAB] OR African Americans[TIAB] OR African ancestry[TIAB] OR African Continental Ancestry Group[MH] OR AIAN[TIAB] OR American Native Continental Ancestry Group[MH] OR Asian continental ancestry group[MH] OR Asian[TIAB] OR Asians[TIAB] OR black[TIAB] OR blacks[TIAB] OR Caucasian[TIAB] OR Caucasians[TIAB] OR diverse population[TIAB] OR diverse populations[TIAB] OR environmental justice[TIAB] OR ethnic group[TIAB] OR ethnic groups[MH] OR ethnic groups[TIAB] OR ethnic population[TIAB] OR ethnic populations[TIAB] OR ghetto[TIAB] OR ghettos[TIAB] OR Hispanic[TIAB] OR Hispanics[TIAB] OR Indian[TIAB] OR Indians[TIAB] OR Latino[TIAB] OR Latinos[TIAB] OR Latina[TIAB] OR Latinas[TIAB] OR medically underserved area[MH] OR minority group[TIAB] OR minority groups[MH] OR minority groups[TIAB] OR minority population[TIAB] OR minority populations[TIAB] OR Native American[TIAB] OR Native Americans[TIAB] OR Oceanic Ancestry Group[MH] OR pacific islander[TIAB] OR pacific islanders[TIAB] OR people of color[TIAB] OR poverty area[MH] OR poverty area[TIAB] OR poverty areas[TIAB] OR rural health[MH] OR rural health[TIAB] OR rural health services[MH] OR rural population[MH] OR rural population[TIAB] OR rural populations[TIAB] OR slum[TIAB] OR slums[TIAB] OR urban health[MH] OR urban health services[MH] OR urban population[MH] OR urban population[TIAB] OR urban populations[TIAB] OR vulnerable populations[MH] OR vulnerable population[TIAB] OR vulnerable populations[TIAB] OR white[TIAB] OR whites[TIAB]) OR (ethnic disparities[TIAB] OR ethnic disparity[TIAB] OR health care disparities[TIAB] OR health care disparity[TIAB] OR health disparities[TIAB] OR health disparity[TIAB] OR health status disparities[MH] OR healthcare disparities[MH] OR healthcare disparities[TIAB] OR healthcare disparity[TIAB] OR minority health[MH] OR minority health[TIAB] OR racial disparities[TIAB] OR racial disparity[TIAB] OR racial equality[TIAB] OR racial equity[TIAB] OR racial inequities[TIAB] OR racial inequity[TIAB]))

OR sexual orientation[TIAB] OR sexual identity[TIAB] OR institutional racism[TIAB] OR disability[TIAB] OR special health care needs[TIAB] OR health differences[TIAB] OR social disadvantage[TIAB] OR economic disadvantage[TIAB] OR social obstacles to health[TIAB] OR economic obstacles to health[TIAB] OR social hierarchy[TIAB] OR unequal distribution[TIAB] OR ((ethnic*[tw] OR race[tw] OR racial[tw] OR disparity[tw] OR disparities[tw] OR blacks[tw] OR black[tw] OR Hispanic*[tw]) OR (population groups[mh] OR race relations[mh])))

Data Supplement 4: Quorum Diagram



Data Supplement 5: World Health Organization Definition of Palliative Care[1]

The World Health Organization has developed this definition of palliative care:

Palliative care is an approach that improves the quality of life of people with localized pancreatic cancer and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of people with localized pancreatic cancer care;
- offers a support system to help people with localized pancreatic cancer live as actively as possible until death;
- offers a support system to help the family cope during the people with localized pancreatic cancer illness and in their own bereavement;
- uses a team approach to address the needs of people with localized pancreatic cancer and their families, including bereavement counseling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as surgery and chemotherapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Data Supplement 6: Pancreatic Protocol Computerized Tomography (CT) [2,3]

To assess resectability and staging, a pancreatic protocol CT or CT angiography is performed. To perform the CT angiography:

- Bolus administration of iodinated nonionic contrast
- Imaging in arterial and venous phases
- First 30 seconds (arterial phase), maximizes attenuation of celiac axis, superior mesenteric artery, and peripancreatic arteries
- 60 to 70 seconds after start of the contrast injection (portal venous phase) provides enhancement for imaging of superior mesenteric vein, splenic and portal veins
- Portal venous phase also provides enhancement for imaging of pancreas and liver metastases
- 70 to 80 seconds after contrast injection (hepatic phase) provides enhancement for imaging of additional liver metastases

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