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Review

Second-line treatment in inoperable pancreatic adenocarcinoma: A systematic review and synthesis of all clinical trials☆

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ABSTRACT

There remains uncertainty regarding the optimal second-line chemotherapy in advanced pancreatic ductal adenocarcinoma (PDAC). The current recommendation of 5-fluorouracil and oxaliplatin may not be relevant in current practice, as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) has become a more popular first line therapy in fit patients. The majority of studies in this setting are

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single-arm Phase II trials with significant heterogeneity of patient populations, treatments and outcomes. In this review, we sought to systematically review and synthesise all prospective data available for the second-line treatment of advanced PDAC.

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer death in Western societies, with a 5-year survival rate of less than 5% (Siegel et al., 2014). The poor prognosis of pancreatic cancer is thought to be multi-factorial, including late diagnosis, early metastatic dissemination and limited effectiveness of chemotherapeutics in early and late stage disease (Hidalgo, 2010). Recent studies in first-line treatment of metastatic and locally advanced disease have shown an improved survival from both FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) and a combination of gemcitabine and nab-paclitaxel vs. the previous standard of care, gemcitabine (Von Hoff et al., 2013; Conroy et al., 2011). Although a significant advance, the median progression-free survival noted on the experimental arms of these studies was still only 6.4 and 5.5 months, respectively, and a median improvement in overall survival of 4 and 2 months, respectively. Efforts to identify more effective therapies in the first-line setting remain important, however, the survival of patients with this devastating disease could be improved by appropriate sequencing of systemic therapy including increased utilisation of second-line treatment. Institutional data suggests that the utilisation of second line therapy in advanced pancreatic adenocarcinoma is low (Herrmann et al., 2007a; Gebbia et al., 2007). A factor contributing to this may be the small number of controlled studies providing evidence that could guide clinicians regarding treatment options. Based on the CONKO-003 study, 5-fluorouracil (5-FU) and oxaliplatin combination treatment is recommended in both the National Cancer Care Network (NCCN) and European Society of Medical Oncology (ESMO) Clinical Practice Guidelines as second-line therapy (Pelzer et al., 2008; Seufferlein et al., 2012; Tempero et al., 2012). However, as FOLFIRINOX becomes more widely used as first-line therapy, alternative second-line options will be required. To aid decision-making and guide future study designs, we performed a systematic review and analysis of all available data from clinical trials of second-line systemic therapy in patients with unresectable pancreatic adenocarcinoma.

2. Methods

2.1. Search strategy

The review was based on a comprehensive, systematic search of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (via Ovid) from inception of each database until January 24th, 2014. Eligible studies were identified using terms and/or Medical Search Headings (MeSH terms) including pancreas AND (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or growth$ or adenocarcin$ or malig$) AND (antineoplastic or chemotherapy or therapy). Reference lists of all included studies were reviewed for additional studies. The published abstracts of the annual meetings of the American Society of Clinical Oncology and the European Society of Medical Oncology were screened from 2009 to 2013. The proceedings of the American Society of Clinical Oncology Gastrointestinal Symposium were screened from 2009 to 2013.

2.2. Inclusion and exclusion criteria

Two types of studies were included. Firstly, randomised controlled trials of first-line systemic cancer therapy (i.e. chemotherapy, hormonal therapy, molecular-targeted therapy, immunotherapy and combinations of these treatments) in metastatic or unresectable locally advanced pancreatic adenocarcinoma that published data on utilisation of second-line therapy by study participants. Secondly, all prospective trials that evaluated therapy (chemotherapy, hormonal therapy, molecular-targeted therapy, immunotherapy and combinations of these treatments) in patients with metastatic or unresectable locally advanced pancreatic adenocarcinoma that had progressed after an initial course of systemic treatment for advanced disease were also included (second-line studies). Trials were excluded if they included cancers other than pancreatic adenocarcinoma in the study unless data of a pancreatic adenocarcinoma sub-group was presented separately. The search was restricted to publications in English and no restriction was placed on date of publication.

Studies were selected in a three-step process (summarised in Fig. 1). First, all studies from the initial search were screened based on title and abstract and studies for full-text review were identified. Then the full-text articles were retrieved and screened for inclusion. Finally annual meetings and reference lists were screened.

2.3. Extraction process

We used the PRISMA statement to guide data abstraction and reporting of this systematic review (Moher et al., 2009). A structured form was used for abstraction of each study. Reviewers were not blinded to authors or journals. Data extracted included the year of publication, start date of the study, authors, journal, sample size, summary patient characteristics including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), stage of disease, treatments, response rates, median progression-free (PFS) and overall survival (OS) and utilisation of second-line therapy.

2.4. Statistical analysis

Statistical analyses were performed on extracted summarised data. Each treatment arm was studied separately. Residual survival was calculated for first-line studies by subtracting median progression-free survival from median overall survival. Basic descriptive statistics (percentages and means) were used to summarise patient and study data. Median and weighted means were calculated for outcomes across all studies. Correlations were performed using Spearman's correlation. Linear regression models were created using median progression-free survival, frequency of second-line chemotherapy, ECOG performance status, stage of disease, sex and age as covariates. All comparisons were made using the Mann–Whitney or Student's *t*-test as appropriate. Variables with a p-value < 0.05 were considered statistically significant. Statistical analysis was performed using Excel version 12.3.6 (Microsoft Corp., Redmond, WA, USA) and Stata version 13.1 (Stata Corp., College Station, TX, USA).

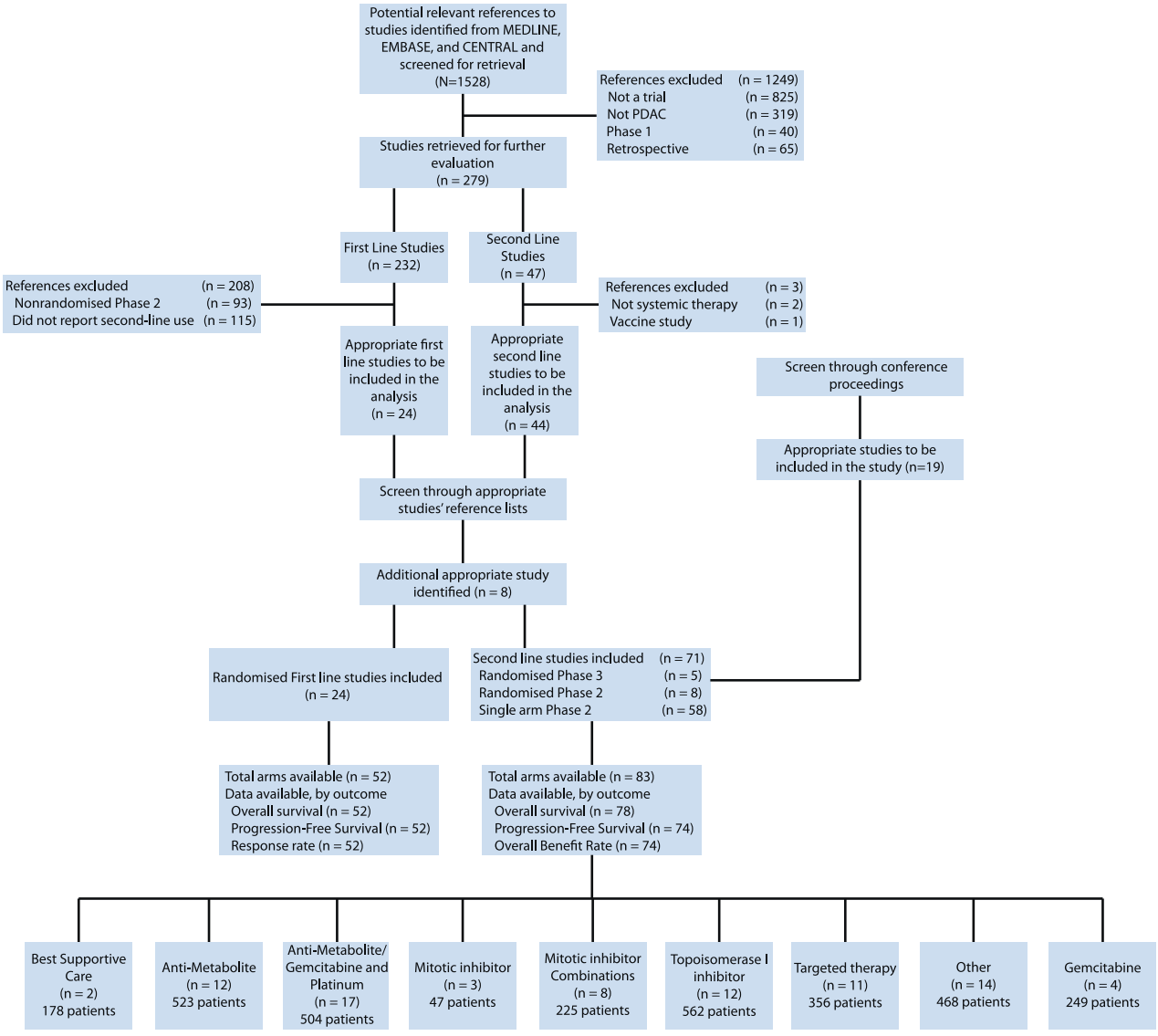

Fig. 1. Consort diagram of the systematic search.

3. Results

Our initial search yielded 1528 citations. After initial screening of titles and abstracts, 279 studies were retrieved for further evaluation. Of these 232 were first-line studies and 47 were second-line studies. Fig. 1 summarises the search strategy and reasons for study exclusions. A total of 24 first-line studies and 71 second-line studies met the inclusion criteria.

3.1. Characteristics of first-line studies

The characteristics of included first-line studies are described in Supplemental Table 1 (Von Hoff et al., 2013; Conroy et al., 2011; Bramhall et al., 2002; Maisey et al., 2002; Scheithauer et al., 2003; Rocha Lima et al., 2004; Louvet et al., 2005; Oettle et al., 2005; Reni et al., 2005; Heinemann et al., 2006; Stathopoulos et al., 2006a; Herrmann et al., 2007b; Boeck et al., 2008a; Cascinu et al., 2008; Cunningham et al., 2009; Van Cutsem et al., 2009; Colucci et al., 2010; Lohr et al., 2012; Ozaka et al., 2012; Heinemann et al., 2013; Ueno et al., 2013; Dahan et al., 2010; Poplin et al., 2013; Nakai et al., 2012). The use of second line therapy was reported in 17% (24/139) of all first-line randomised studies found during the search strategy. Studies were performed between 1998 and 2012 and comprised of 52 treatments arms in 24 studies. The utilisation of second-line chemotherapy in these arms ranged from 16% to 68% with a pooled mean of 43% (3252/7639 participants). The rate of utilisation increased from studies published pre-2007 to after 2007 (35% vs. 48%; $p = 0.0015$). The ECOG performance status (0–1) of participants in these studies was universally high (range: 71–100%).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.critrevonc.2015.07.007.

3.2. Higher rates of utilisation of second-line chemotherapy correlated with improved survival in first-line studies

Spearman correlation of frequency of second-line chemotherapy and median overall survival (Fig. 2A) and frequency of second-line chemotherapy and residual survival (Fig. 2B) showed a modest but statistically significant correlation; $r = 0.495$, $p = 0.0002$ and $r = 0.633$, $p < 0.0001$, respectively. A linear regression model of utilisation of second-line therapy suggested that studies with participants that had more advanced disease at initial study enrollment (beta-coefficient = 0.373; $p = 0.052$) were more likely to receive

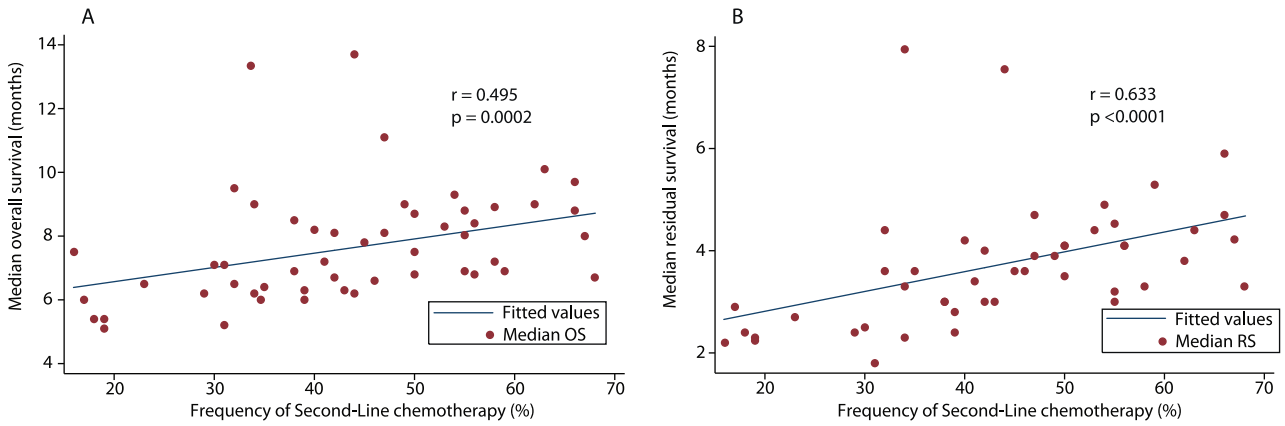

Fig. 2. Correlation between frequency of utilisation of second-line systemic therapy and survival in randomised first-line studies.

Table 1A
Linear regression of utilisation of second-line systemic therapy in first-line studies.

Utilisation of Second-line Therapy	Coefficient	Standard Error	*P*-value	Beta[a]
First-line PFS	−4.72	3.35	0.169	−0.335
First-line response rate	0.57	0.44	0.203	0.295
ECOG PS	0.28	0.36	0.454	0.166
Stage of disease	0.39	0.19	0.052	0.373
Sex	−0.19	0.40	0.64	−0.085
Age	−1.87	1.35	0.175	−0.228

Abbreviations: OS, overall survival; PFS, progression-free survival.
[a] The beta coefficients can be used to compare the relative strength of the various predictors within the model.

Table 1B
Linear regression model of median overall survival in first-line studies.

Median OS	Coefficient	Standard Error	*P*-value	Beta[a]
Median PFS	1.22	0.16	<0.0001	0.70
Frequency of 2nd line chemotherapy	0.06	0.01	<0.0001	0.52
ECOG PS (0–1)	0.04	0.02	0.143	0.17
Stage of disease (% metastatic)	−0.04	0.01	0.005	−0.31
Sex	0.06	0.03	0.029	0.22
Age	0.06	0.09	0.498	0.06

Abbreviations: OS, overall survival; PFS, progression-free survival.
[a] The beta coefficients can be used to compare the relative strength of the various predictors within the model.

second-line therapy (Table 1A). Further, frequency of second-line chemotherapy was strongly predictive of median overall survival (beta-coefficient = 0.52; $p < 0.0001$) (Table 1B).

3.3. *Characteristics of second-line studies*

A total of 71 second-line therapy studies examining 83 treatment arms with 3112 participants were included in the final analysis (Pelzer et al., 2008; Heinemann et al., 2013; Dahan et al., 2010; Rothenberg et al., 1996; Sharma et al., 1997; Oettle et al., 2000; Rothenberg et al., 2002; Ulrich-Pur et al., 2003; Cantore et al., 2004; Jacobs et al., 2004; Milella et al., 2004; Ng et al., 2004; Androulakis et al., 2005; Burris et al., 2005; Hedley et al., 2005; Tsavaris et al., 2005; Demols et al., 2006; Ignatiadis et al., 2006; Mitry et al., 2006; Reni et al., 2006; Stathopoulos et al., 2006b; Blaszkowsky et al., 2007; Blaya et al., 2007; Boeck et al., 2007; Kulke et al., 2007; Togawa et al., 2007; Boeck et al., 2008b; Kindler et al., 2008; Ko et al., 2008a,b; Xiong et al., 2008; Abbruzzese et al., 2009; Blesa et al., 2009; Brell et al., 2009; Carvajal et al., 2009; Ciuleanu et al., 2009; Morizane et al., 2009; Novarino et al., 2009; Pelzer et al., 2009; Tang et al., 2009; Wolpin et al., 2009; Yi et al., 2009; Yoo et al., 2009; Bai et al., 2010; Javle et al., 2010; Messersmith et al., 2010; Nakamori et al., 2010; O'Reilly et al., 2010; Saif et al., 2010; Astsaturov et al., 2011; Cereda et al., 2011; Katopodis et al., 2011; Pelzer et al., 2011; Ramanathan et al., 2011; Rebonato et al., 2011; Sudo et al., 2011; Bodoky et al., 2012; Kim et al., 2012; Renouf et al., 2012; Shi et al., 2012; Wu et al., 2012; Zaniboni et al., 2012; El-Hadaad and Wahba, 2013; Ettrich et al., 2013; Hosein et al., 2013; Ioka et al., 2013; Ko et al., 2013a,b; Mizuno et al., 2013; Kim et al., 2009; Oh et al., 2010). 19 studies were available in abstract form while 52 were full publications. Details of the studies are provided in Table 2. Thirteen of the studies were randomised controlled trials including two cross-over studies. The remaining were single arm Phase 2 studies. Only four Phase 3 studies have been reported in this setting.

Due to the heterogeneity of treatments used in the randomised controlled trials, a meta-analysis was not possible.

The median number of participants in the included arms was 30 (range; 8–198). The ECOG PS of participants was good with a pooled mean of 81.7% of patients with an ECOG PS of 0–1. Median progression-free survival was reported in 74 arms and varied between 0.5 and 6.9 months with a median of 2.0 months. Absolute response rate (defined as % of complete and partial responders as well as participants with stable disease) was reported in 74 arms with a median of 36.5% (range of all arms; 0–83.3%). Overall survival was reported in 78 study arms and pooled analysis of all studies found that the median survival was 4.5 months (range; 0.6–16.4 months).

Table 2
Characteristics of included second-line studies.

Study	Year published	Treatment prior to study enrolment	Study regimen	Number of patients	Median age	ECOG 0–1 (%)	Median PFS (mo)	Median OS (mo)	ORR (%)
A. Randomised studies									
Astsaturov et al. (2011)	2011	At least 1 regimen of chemotherapy including gemcitabine	Bevacuzimab 10 mg/kg q2weekly, Docetaxel 35 mg/m^2 D1, D8, D15 q28days	16	56.5	100	1.6	4.1	50
		At least 1 regimen of chemotherapy including gemcitabine	Bevacuzimab 10 mg/kg q2weekly	16	67	100	1.4	5.4	25
Bodoky et al. (2012)	2012	1 regimen of Gemcitabine alone	Capecitabine 1250 mg/m^2 BD D1–D14 q21days	32	62	NR	2.2	5	38
		1 regimen of Gemcitabine alone	Selumetinib 100 mg BD	37	65	NR	2.1	5.4	38
Ciuleanu et al. (2009)	2009	1 line of gemcitabine chemotherapy	Glufosfamide 4500 mg/m^2 q21days	148	58	82	1.51	3.45	33
		1 line of gemcitabine chemotherapy	Best supportive care	155	57	84	1.41	2.76	20
Dahan et al. (2010)	2010	1 line of gemcitabine chemotherapy	Leucovorin 200 mg/m^2, 5-FU 400 mg/m^2 bolus, Cisplatin 50 mg/m2 on D1, 5-FU 2400 mg/m^2 as a 46 h infusor q2weeks	55	65	NR	5.2	NR	45
		Leucovorin 200 mg/m^2, 5-FU 400 mg/m^2 bolus, Cisplatin 50 mg/m^2 on D1, 5-FU 2400 mg/m^2 as a 46 h infusor q2weeks	Gemcitabine 1000 mg/m^2 Week 1–7 q8weeks, then D1, D8, D15 q28days	69	62	NR	3.43	NR	38
Heinemann et al. (2013)	2013	Gemcitabine 1000 mg/m^2 Wk 1–7 q8weeks, then D1, D8, D15 q28days and Erlotinib 150 mg daily	Capecitabine 1000 mg/m^2 BD D1–D14 q21days	63	65	NR	2	3.2	22
		Capecitabine 1000 mg/m^2 BD D1-D14 q21days and Erlotinib 150 mg daily	Gemcitabine 1000 mg/m^2 Wk 1–7 q8weeks, then D1, D8, D15 q28days	77	63	NR	2.5	5	36
Ioka et al. (2013) [a]	2013	1 line of gemcitabine chemotherapy	5-FU, UFT or S-1	40	NR	NR	3.7	7.4	50
		1 line of gemcitabine chemotherapy	Gemcitabine 1000 mg/m^2 D1, D8, D15 q28days	40	NR	NR	1.6	5.3	18
Jacobs et al. (2004) [a]	2004	At least 1 regimen of chemotherapy including gemcitabine	Rubitecan 1.5 mg/m^2 D1–D5 q7days	198	NR	NR	1.9	3.6	51
		At least 1 regimen of chemotherapy including gemcitabine	Physician Choice		NR	NR			
Mitry et al. (2006)	2006	Oxaliplatin 130 mg D1 q21days	Oxaliplatin 130 mg/m^2 D1, 5-FU 1000 mg/m^2 PVI D1–D4 q21days	10	55	50	0.5	0.6	10
		5-FU 1000 mg/m^2 PVI D1-D4 q21days	Oxaliplatin 130 mg/m^2 D1, 5-FU 1000 mg/m^2 PVI D1–D4 q21days	8	59	0	2.1	2.8	25
Mizuno et al. (2013)	2013	1 line of gemcitabine-based chemotherapy	S-1 80–120 mg/daily D1–D14 q28days	67	NR	100	1.9	5.8	NR
		1 line of gemcitabine-based chemotherapy	Irinotecan 100 mg/m^2 D1, D15 and S-1 80–120 mg/daily q28days	60	NR	100	3.5	6.8	NR
Pelzer et al. (2008) [a]	2008	1 line of gemcitabine chemotherapy	5FU 2000 mg/m^2, Leucovorin 200 mg/m^2 on D1, D8, D15, D22 q42days	84	NR	48	2	3.09	NR
		1 line of gemcitabine chemotherapy	5FU 2000 mg/m^2, Leucovorin 200 mg/m^2 on D1, D8, D15, D22 and Oxaliplatin 85 mg/m^2, D8, D22 q42days	76	NR	54	2.89	5.88	NR

Table 2 (*Continued*)

Study	Year published	Treatment prior to study enrolment	Study regimen	Number of patients	Median age	ECOG 0–1 (%)	Median PFS (mo)	Median OS (mo)	ORR (%)
Pelzer et al. (2011)	2011	1 line of gemcitabine chemotherapy	Best Supportive Care	23	61	NR	NR	2.3	NR
		1 line of gemcitabine chemotherapy	5-FU 2000 mg/m^2, Leucovorin 200 mg/m^2 D1, D8, D15, D22 and Oxaliplatin 85 mg/m^2 D8, D22 q42days	23	60	NR	NR	4.82	NR
Ulrich-Pur et al. (2003)	2003	1 line of gemcitabine-based chemotherapy	Ralitrexed 3 mg/m^2 D1 q21days for a total of 6 cycles	19	60	NR	2.5	4.3	37
		1 line of gemcitabine-based chemotherapy	Ralitrexed 3 mg/m^2 and Irinotecan 200 mg/m^2 D1 q21days for a total of 6 cycles	19	63	NR	4	6.5	48
Yoo et al. (2009)	2009	1 line of gemcitabine-based chemotherapy	Oxaliplatin 85 mg/m^2 D1 and Leucovorin 400 mg/m^2 D1 and 5-FU 2000 mg/m^2 over 46 h q14days	30	55	97	1.38	3.44	17
		1 line of gemcitabine-based chemotherapy	Irinotecan 70 mg/m^2 D1, D3 and Leucovorin 400 mg/m^2 D1, and 5-FU 2000 mg/m^2 over 46 h q14days	31	55	100	1.92	3.83	23
B. Anti-metabolite studies									
Abbruzzese et al. (2009) [a]	2009	1 line of gemcitabine-based chemotherapy	S-1 30 mg/m^2 BD D1–D14 q21days	45	NR	NR	1.4	3.1	37
Boeck et al. (2008b)	2008	At least 1 regimen of chemotherapy including Gemcitabine	Capecitabine 1250 mg/m^2 BD D1–D14 q21days	39	63	95	2.3	7.6	39
Morizane et al. (2009)	2009	1 line of gemcitabine-based chemotherapy	S-1 80–120 mg/daily D1–D14 q28days	40	62	100	2	4.5	58
Rothenberg et al. (2002)	2002	1 line of chemotherapy	5-FU 20 mg/m^2/d oral D2–D6 and Eniluracil 50 mg D1–D7	48	59	77	NR	3.4	NR
Saif et al. (2010) [a]	2010	1 line of gemcitabine-based chemotherapy	Capecitabine 750 mg/m^2 BD D1–D7, PHY906 800 mg D1–D4 q2weeks	25	60	96	2.31	2.77	48
Sudo et al. (2011)	2011	1 line of gemcitabine chemotherapy	S-1 80–120 mg/daily D1–D28 q42days	21	64	71	4.1	6.3	53
C. Anti-metabolite or Gemcitabine and platinum combination studies									
Blesa et al. (2009) [a]	2009	1 regimen of gemcitabine alone	Capecitabine 1000 mg/m^2 D1–D14, Oxaliplatin 100 mg/m^2 D1 q21days	15	NR	NR	4.1	5.4	40
Demols et al. (2006)	2006	1 regimen of chemotherapy including gemcitabine	Gemcitabine 1000 mg/m^2 D1, Oxaliplatiin 100 mg/m^2 D2 q14days	33	57	88	4.2	6	62
El-Hadaad and Wahba (2013)	2013	1 line of gemcitabine chemotherapy	Oxaliplatin 85 mg/m^2 D1, D15, Leucovorin 20 mg/m^2 D1, D8, D15, 5-FU 500 mg/m^2 D1, D8, D15 q21days	32	63	78	3	5.08	27
Kim et al. (2012)	2012	1 line of gemcitabine-based chemotherapy	S-1 40–60 mg BD D1–D14 q21days, Cisplatin 60 mg/m^2 D1	11	56	82	1.4	2.7	9
Novarino et al. (2009)	2009	1 line of gemcitabine chemotherapy	Oxaliplatin 40 mg/m^2, Leucovorin 250 mg/m^2, bolus 5-FU 500 mg/m^2 D1, D8, D15 q28days for a total of 6 cycles	23	61	74	2.7	3.9	24
Pelzer et al. (2009)	2009	1 line of gemcitabine chemotherapy	5FU 2600 mg/m^2, Leucovorin 500 mg/m^2 on D1, D8, D15, D22 and Oxaliplatin 85 mg/m^2, D8, D22 q42days	37	NR	NR	2.8	5.1	49

Reni et al. (2006)	2006	At least 1 regimen of chemotherapy including gemcitabine	Raltitrexed 3 mg/m^2 D1 and Oxaliplatin 130 mg/m^2 D1 q21days	41	61	NR	1.8	5.2	51
Stathopoulos et al. (2006b)	2006	1 line of gemcitabine-based chemotherapy	Lipoplatin 25–125 mg/m^2 D1, D15 and Gemcitabine 1000 mg/m^2 D1, D15 q28days	24	66	50	NR	4	66
Togawa et al. (2007)	2007	1 line of gemcitabine chemotherapy	S-1 80 mg/d D1–21, Cisplatin 40 mg/m^2 D8 q35days	17	59.5	NR	NR	9	41
Tsavaris et al. (2005)	2005	1 line of gemcitabine chemotherapy	Oxaliplatin 50 mg/m^2, Leucovorin 50 mg/m^2, 5-FU 500 mg/m^2 D1, D8, D15, D22, D29, D36 q8weeks	30	63	33	5.08	5.77	54
Xiong et al. (2008)	2008	1 line of chemotherapy	Oxaliplatin 130 mg/m^2 D1, Capecitabine 750 mg/m^2 BD D1–D14 q21days	39	62	71	2.28	5.31	29
D. Mitotic inhibitor studies									
Carvajal et al. (2009)	2009	1 regimen of chemotherapy including Gemcitabine	Docetaxel 35 mg/m^2, Flavopiridol 80 mg/m^2 D1, D8, D15 q 28days	10	64	90	1.8	4.2	33
Hosein et al. (2013)	2013	1 regimen of chemotherapy including Gemcitabine	nab-Paclitaxel 100 mg/m^2 D1, D8, D15 q28days	19	61	79	1.7	7.3	37
Oettle et al. (2000)	2000	At least 1 regimen of chemotherapy including gemcitabine	Paclitaxel 50 mg/m^2 weekly for 6 weeks with a 1 week break	18	59	NR	3.2	4	33
E. Mitotic inhibitor combination studies									
Blaszkowsky et al. (2007) [a]	2007	At least 1 regimen of chemotherapy including gemcitabine	Docetaxel 40 mg/m^2 D1, D8 and Gefitinib 250 mg daily q21days	15	60	100	NR	NR	60
Blaya et al. (2007) [a]	2007	At least 1 regimen of chemotherapy including gemcitabine	Capecitabine 800 mg/m^2 BD D1–D14, Docetaxel 30 mg/m^2 D1, D8 q21days	24	65	71	NR	NR	83
Brell et al. (2009)	2009	1 regimen of chemotherapy including Gemcitabine	Docetaxel 60 mg/m^2 q3weekly, Gefitinib 250 mg daily	41	64	93	1.8	4.5	48
Ettrich et al. (2013) [a]	2013	1 regimen of chemotherapy including Gemcitabine	Docetaxel 75 mg/m^2 D1, Oxaliplatin 80 mg/m^2 D2 q22days	44	NR	NR	1.6	8.3	48
Ignatiadis et al. (2006)	2006	1 regimen of chemotherapy including Gemcitabine	Docetaxel 75 mg/m^2 D1 q21days, Gefitinib 250 mg daily	26	65	92	2.1	2.9	19
Katopodis et al. (2011)	2011	1 line of gemcitabine-based chemotherapy	Docetaxel 75 mg/m^2 D1, Capecitabine 800 mg/m^2 BD D1–D14 q21days	31	63	94	2.37	6.3	32
Kim et al. (2009)	2009	At least 1 regimen of chemotherapy including gemcitabine	5-Fluorouracil 1000 mg/m^2 over 72 h and paclitaxel 175 mg/m^2 D1 q28days	28	NR	46	2.5	7.6	30
F. Topoisomerase I inhibitor studies									
Burris et al. (2005)	2005	At least 1 regimen of chemotherapy but not just Gemcitabine alone	Rubitecan 1.5 mg/m^2 D1–5 q7days for 8 weeks	58	62.5	NR	1.9	3	23
Cantore et al. (2004)	2004	1 regimen of chemotherapy including Gemcitabine	Oxaliplatin 60 mg/m^2 D1, D15 and Irinotecan 60 mg/m^2 D1, D8, D15 q 28 days	30	59.7	70	4.1	5.9	33
Ko et al. (2008b)	2008	At least 1 regimen of chemotherapy including gemcitabine	Docetaxel 65 mg/m^2 D1, Irinotecan 160 mg/m^2 D1 q21 days	14	54	93	1.61	4.41	21
Ko et al. (2013a)	2013	At least 1 regimen of chemotherapy including gemcitabine	PEP02 (liposomal irinotecan sucrosofate) 120 mg/m^2 D1 q21days	40	NR	75	2.4	5.2	50

Table 2 (*Continued*)

Study	Year published	Treatment prior to study enrolment	Study regimen	Number of patients	Median age	ECOG 0–1 (%)	Median PFS (mo)	Median OS (mo)	ORR (%)
Ng et al. (2004) [a]	2004	1 line of chemotherapy	Irinotecan 180 mg/m^2 D1 and Leucovorin 125 mg/m^2 and 5-Fluorouracil 400 mg/m^2 and 1200 mg/m^2 q48 h q2weeks	15	60	NR	2.5	3.19	38
Oh et al. (2010)	2010	At least 1 regimen of chemotherapy	Oxaliplatin 85 mg/m^2 D1, and irinotecan 150 mg/m^2 q14days	14	65.5	71	1.4	4.1	50
Yi et al. (2009)	2009	1 line of gemcitabine-based chemotherapy	Irinotecan 150 mg/m^2 D1 q14days	33	59	94	2	6.6	48
Zaniboni et al. (2012)	2012	1 line of gemcitabine-based chemotherapy	Irinotecan 180 mg/m^2 D1 and Leucovorin 200 mg/m^2 D1, D2 and 5-FU 400 mg/m^2 D1, D2 and 600 mg/m^2 over 22 h D1 q14days	50	63	100	3.27	5	36
G. Targeted therapy studies									
Hedley et al. (2005) [a]	2005	1 line of chemotherapy	Perifosine 525 mg D1, D2 and 150 mg D3–D21	19	NR	NR	1.6	3.1	12
Javle et al. (2010)	2010	At least 1 regimen of chemotherapy including gemcitabine	Everolimus 30 mg weekly, Erlotinib 150 mg daily	16	NR	NR	1.61	2.86	NR
Ko et al. (2008a) [a]	2008	At least 1 regimen of chemotherapy including gemcitabine	Bevacuzimab 15 mg/kg D1, Erlotinib 150 mg daily q21days	26	60	100	1.3	3.4	32
Ko et al. (2013b) [a]	2013	At least 1 regimen of chemotherapy	Erlotinib 100 mg daily and selumetinib 100 mg daily	46	67	100	2.6	7.4	46
Messersmith et al. (2010) [a]	2010	1 line of gemcitabine-based chemotherapy	Saracatinib 175 mg/d	19	62	100	1.60	2.50	NR
O'Reilly et al. (2010)	2010	1 line of gemcitabine-based chemotherapy	Sunitinib 50 mg D1–D28 q6weeks	77	65	88	1.31	3.68	22
Ramanathan et al. (2011)	2010	At least 1 regimen of chemotherapy including gemcitabine	PX-12 54 mg/m^2 or 128 mg/m^2	17	69	100	0.9	3.2	12
Tang et al. (2009) [a]	2009	1 line of gemcitabine chemotherapy	Erlotinib 150–300 mg/daily	50	61	92	1.6	4.1	35
Wolpin et al. (2009)	2009	1 line of gemcitabine-based chemotherapy	Everolimus 10 mg/d	33	61	100	1.8	4.5	21
H. Other therapy studies									
Androulakis et al. (2005)	2005	At least 1 regimen of chemotherapy including gemcitabine	Oxaliplatin 130 mg/m^2 q3weekly	18	61	73	NR	3.5	17
Bai et al. (2010) [a]	2010	1 line of gemcitabine-based chemotherapy	Pemetrexed 500 mg/m^2 D1 q21days	17	NR	NR	1.94	NR	50
Boeck et al. (2007)	2007	1 regimen of chemotherapy including Gemcitabine	Pemetrexed 500 mg/m^2 q3weekly	52	62.5	94	1.6	4.6	23
Cereda et al. (2011)	2011	At least 1 regimen of chemotherapy including gemcitabine	Mitomycin C 8 mg/m^2 D1, Ifosfamide 2500 mg/m^2 D1–D3, Mesna 3000 mg/m^2 D1–D3 q28days for a max of 6 cycles	20	56	NR	1.7	3.7	15
Kindler et al. (2008)	2012	1 line of gemcitabine-based chemotherapy	Arsenic trioxide 0.3 mg/kg D1–5 q28days for 2 cycles	13	61	85	1.6	3.8	0
Kulke et al. (2007)	2007	1 line of gemcitabine-based chemotherapy	Capecitabine 1000 mg/m^2 BD D1–D14, Erlotinib 150 mg daily q21days	32	60	100	3.4	6.5	10
Milella et al. (2004)	2004	1 line of gemcitabine-based chemotherapy	Celecoxib 400 mg BD, 5FU 200 mg/m^2 PVI continuously for 9 months	17	60	94	1.8	3.5	25

Nakamori et al. (2010) [a]	2010	1 line of gemcitabine chemotherapy	S-1 80 mg/m^2/d D1–D5, D8–D12 and Gemcitabine 1000 mg/m^2 D6, D13 q21days	29	67	NR	3.5	12.3	62
Rebonato et al. (2011) [a]	2011	1 line of gemcitabine chemotherapy	Intra-arterial Epirubicin 35 mg/m^2, Cisplatin D1 and Gemcitabine 1000 mg/m^2 D2 and Capecitabine 650 mg/m^2 D2–D15 q28days	45	NR	NR	6.9	16.4	66
Renouf et al. (2012)	2012	At least 1 regimen of chemotherapy including gemcitabine	Eribulin 1.4 mg/m^2 D1, D8 q21days	15	62	87	1.4	6.1	42
Sharma et al. (1997)	1997	1 line of 5-FU based chemotherapy	Flutamide 250 mg TDS	14	NR	NR	NR	4.7	0
Shi et al. (2012)	2012	1 line of gemcitabine-based chemotherapy	Thalidomide 100 mg/d and Capecitabine 1250 mg/m^2 BD D1–D14 q21days	31	59.5	94	2.7	6.1	42
Wu et al. (2012) [a]	2012	1 line of gemcitabine-based chemotherapy	Capecitabine 1000 mg/m^2 BD D1–D14 q21days and Lapatinib 1250 mg daily	17	NR	NR	2.08	5.77	24
I. Gemcitabine studies									
Rothenberg et al. (1996)	1996	1 line of 5-FU based chemotherapy	Gemcitabine 1000 mg/m^2 Week 1–7 q8weeks, then D1, D8, D15 q28days	63	62	27	2.53	3.85	41

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, overall response rate (sum of complete responses, partial responses and stable disease); NR, not reported.

[a] Abstract only.

3.4. Comparison of treatment arms

Correlation of response rates with progression-free survival and progression-free survival with overall survival with a line of best fit demonstrated a modest relationship between reported end-points (Supplementary Fig. 1A and B). This provided supportive evidence that comparison of summary end-points across non-randomised studies may provide useful insights. It also highlighted any studies that had an unusual relationship between response and PFS or PFS and OS. The outliers in this analysis highlighted that one study (Rebonato 2011 in Supplementary Fig. 1A) had a high absolute response rate (66%) and PFS (6.9 months): this study assessed celiac axis intra-arterial epirubicin and only included patients that had cancer limited to the abdomen (Rebonato et al., 2011). Also, a second study of combination S-1 and gemcitabine (Nakamori 2010 in Supplementary Fig. 1B) had a modest PFS of 3.5 months and an absolute response rate of 62% but a high OS of 12.3 months. The study has only been presented in abstract form. Data regarding the characteristics of included patients and subsequent therapies have not been published (Nakamori et al., 2010).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.critrevonc.2015.07.007.

Each treatment arm was grouped based on the type of treatment allocated resulting in nine treatments groups; Best supportive care (BSC; $n=2$) (Ciuleanu et al., 2009; Pelzer et al., 2011), Anti-metabolite (5-fluorouracil or similar treatment alone; $n=12$) (Pelzer et al., 2008; Heinemann et al., 2013; Rothenberg et al., 2002; Ulrich-Pur et al., 2003; Boeck et al., 2008b; Abbruzzese et al., 2009; Morizane et al., 2009; Saif et al., 2010; Sudo et al., 2011; Bodoky et al., 2012; Ioka et al., 2013; Mizuno et al., 2013), Anti-metabolite or gemcitabine and platinum combination ($n=17$) (Pelzer et al., 2008; Dahan et al., 2010; Tsavaris et al., 2005; Demols et al., 2006; Mitry et al., 2006; Reni et al., 2006; Stathopoulos et al., 2006b; Togawa et al., 2007; Xiong et al., 2008; Blesa et al., 2009; Novarino et al., 2009; Pelzer et al., 2009; Yoo et al., 2009; Pelzer et al., 2011; Kim et al., 2012; El-Hadaad and Wahba, 2013), Mitotic inhibitors (paclitaxel or similar; $n=3$) (Oettle et al., 2000; Carvajal et al., 2009; Hosein et al., 2013), Mitotic inhibitor combinations ($n=8$) (Ignatiadis et al., 2006; Blaszkowsky et al., 2007; Blaya et al., 2007; Brell et al., 2009; Astsaturov et al., 2011; Katopodis et al., 2011; Ettrich et al., 2013; Kim et al., 2009), Topoisomerase I inhibitors (irinotecan or similar in combination or alone; $n=12$) (Ulrich-Pur et al., 2003; Cantore et al., 2004; Jacobs et al., 2004; Ng et al., 2004; Burris et al., 2005; Ko et al., 2008b; Yi et al., 2009; Yoo et al., 2009; Zaniboni et al., 2012; Ko et al., 2013a; Mizuno et al., 2013; Oh et al., 2010), Targeted therapy (defined as therapies that target tyrosine kinases, growth factors, or receptors; $n=11$) (Hedley et al., 2005; Ko et al., 2008a; Tang et al., 2009; Wolpin et al., 2009; Javle et al., 2010; Messersmith et al., 2010; O'Reilly et al., 2010; Astsaturov et al., 2011; Ramanathan et al., 2011; Bodoky et al., 2012; Ko et al., 2013b), Other therapies ($n=14$) (Sharma et al., 1997; Milella et al., 2004; Androulakis et al., 2005; Boeck et al., 2007; Kulke et al., 2007; Kindler et al., 2008; Ciuleanu et al., 2009; Bai et al., 2010; Nakamori et al., 2010; Cereda et al., 2011; Rebonato et al., 2011; Renouf et al., 2012; Shi et al., 2012; Wu et al., 2012), and gemcitabine ($n=4$) (Heinemann et al., 2013; Dahan et al., 2010; Rothenberg et al., 1996; Ioka et al., 2013). The individual treatment arms and respective end-points are summarised in Fig. 3 and Table 3.

The best supportive care group had the lowest median overall survival of 2.5 months while the pooled median overall survival of studies in the anti-mitotic combination group was highest at 5.4 months. The pooled median OS of all other groups ranged from 4 to 5.1 months. The pooled median PFS of the best supportive care group was lowest at 1.4 months and the highest median PFS (2.7 months) was seen in the combination anti-metabolite

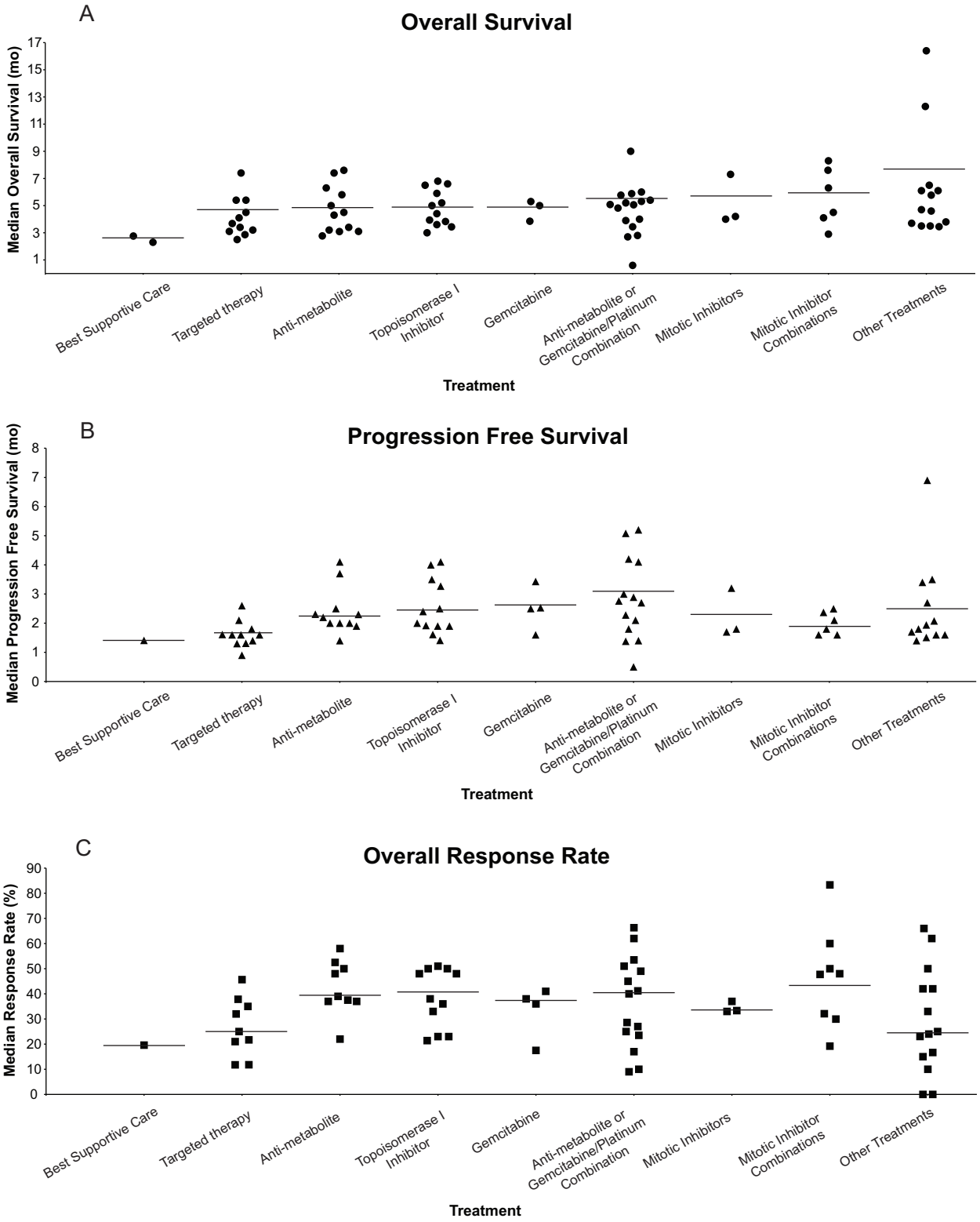

Fig. 3. Overall survival (A), progression-free survival (B) and response rate (C) in studies of second-line systemic therapy. Each symbol denotes one therapy type. The horizontal lines represent the weighted means of each sub-group.

or gemcitabine and platinum group. The pooled median absolute response rate of the anti-metabolite or gemcitabine and platinum combination group was 40% however the highest response rate was noted in the mitotic inhibitor combination treatment group (48%; range; 19–83%). As expected, the median response rates in the targeted therapy group were low (25%).

An exploratory analysis was performed to compare median survivals between studies of best supportive care vs. active treatment and showed that median overall survival was significantly longer with active treatment compared to best supportive care (4.6 vs. 2.5 months; Mann–Whitney U test; $p = 0.02$). Further, a comparison of single agent vs. combination therapy studies suggested

Table 3
Summary statistics of treatment arms in second-line systemic therapy studies.

	n	OS (months)		PFS (months)		ORR (%)	
		Median	Range	Median	Range	Median	Range
Best supportive care	2	2.53	2.30–2.76	1.41		20	
Anti-metabolites	12	4.40	2.77–7.60	2.20	1.40–4.10	39	22–58
Anti-metabolite or Gemcitabine and platinum	17	5.07	0.60–9.00	2.73	0.50–5.20	40	9–66
Anti-mitotic	3	4.20	4.00–7.30	1.80	1.70–3.20	33	33–37
Anti-mitotic combinations	8	5.40	2.90–8.30	1.95	1.60–2.50	48	19–83
Topoisomerase I inhibitors	12	4.70	3.00–6.80	2.20	1.40–4.10	38	21–51
Targeted therapy	11	3.97	2.50–7.40	1.60	0.90–2.60	25	12–46
Other types of therapy	14	4.70	3.45–16.40	1.87	1.40–6.90	25	0–66
Gemcitabine	4	5.00	3.85–5.30	2.52	1.60–3.43	37	18–41

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, overall response rate (sum of complete responses, partial responses and stable disease); *n*, number of treatment arms.

that delivering combination therapy results in an improvement in progression-free survival (1.9 vs. 2.5 months; $p = 0.018$) but not overall survival (4.3 vs. 5.1 months; $p = 0.169$). There was no difference in median age ($p = 0.07$) or ECOG performance status ($p = 0.34$) between BSC, single agent or combination treatment groups.

3.5. Survival of participants on study over time

The median overall survival was examined over time based on the date that studies were initiated and increased from August, 1992 (3.9 months) to January, 2011 (7.4 months) (Fig. 4A). Concurrently, the percentage (%) of participants with ECOG PS of 0 or 1 that were included on studies also increased from 27% to 100% (Fig. 4B). However the median PFS and response rates have not increased from 1992 to 2011 (Supplementary Fig. 2A and B).

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4. Discussion

Pancreatic cancer has had a poor prognosis for nearly 50 years and minimal progress has been made. Studies in the population of patients who progress after first-line therapy are difficult to conduct in this disease, as patients are often older, unwell and their condition can deteriorate rapidly (Hidalgo, 2010). Thus a focused approach is needed to investigate new therapies in this setting.

To the best of our knowledge, this is the most comprehensive systematic review focusing on second-line therapy in pancreatic adenocarcinoma. Seventy-one studies of 3112 patients examining 62 different treatments have been conducted. The reviewed studies highlight the diverse range of treatments that have been studied in this setting and suggest that the expected median progression-free and overall survival of good performance patients in this setting are 2.0 and 4.4 months, respectively. This provides a benchmark for clinicians and investigators.

The analysis of first-line studies demonstrates that the use of second-line therapy in a highly selected population is only 43%. Importantly, a high number of patients enrolled on these studies had an excellent ECOG performance status of 0 or 1. We expected that utilisation rates in community cohorts would be lower. Consistent with this hypothesis, single institution experiences have demonstrated utilisation rates of as low as 25% (Herrmann et al., 2007a). We also show that there is a correlation between utilisation of second-line therapy and overall survival in these studies and that the rate of utilisation has increased since 2007. Although our study design does not allow a direct causative link between increased use of second line chemotherapy and overall survival to be demonstrated, a clear association is seen. Together with our analysis that treatment improves survival compared to best supportive care, our conclusion that increased delivery of second-line therapy may improve the overall outcome for patients with pancreatic cancer seems reasonable.

The design of Phase 3 trials in this setting highlights the lack of consensus regarding the standard of care. Two studies, CONKO-003 and Ciuleanu et al. used BSC as their control arms (Ciuleanu et al., 2009; Pelzer et al., 2011). CONKO-003 was unable to recruit due to the lack of acceptance of BSC and was redesigned with 5-FU/leucovorin as the control arm (Pelzer et al., 2008). Jacobs et al. (2004) most pragmatically of all, allowed physician choice of treatment as the control arm. Interestingly, 89% of patients received chemotherapy and only 11% were offered BSC in this study. Our analysis demonstrates that overall survival with best supportive care was low. Based on the results of CONKO-003, current guidelines recommend 5-FU and oxaliplatin as the preferred option for second-line therapy (Seufferlein et al., 2012; Tempero et al., 2012). Our review provides some support to this recommendation as the group of studies with gemcitabine or anti-metabolites e.g. 5-Fluorouracil in combination with platinum had a higher median and mean overall survival (5.1 and 5.1 months, respectively) than other study groups (Fig. 3). However, as FOLFIRINOX is now considered a standard of care as first-line therapy, the next best treatment is unknown. The benefit of gemcitabine second-line is small with a pooled response rate of only 6.8% and a pooled mean overall survival of 4.7 months. Less commonly used treatments including anti-mitotic agents and Topoisomerase 1 inhibitors result in similar overall response rates and survival. The survival seen in studies of combination therapies was noted to be higher than studies of single agent therapies. In particular the pooled response rate and overall survival of mitotic inhibitor combinations was high at 48% and 5.4 months, respectively.

Analysis of published data shows that the overall survival of patients enrolled on second-line studies has increased over time, however, progression-free survival and response rates have remained stable. The positive trend for ECOG PS over the same period suggests that selection bias may be a contributing factor to the improved overall survival seen in these patients rather than therapeutic efficacy. Further, unlike colon cancer, a correlation between progression-free survival and overall survival has not been found in pancreatic adenocarcinoma (Rahma et al., 2013).

Although there have been previous reviews on second-line therapy in pancreatic adenocarcinoma, these have not included as many studies as this review (Rahma et al., 2013; Almhanna and Kim, 2008; Custodio et al., 2009; Petrelli et al., 2010). A similar analysis by Rahma et al. found a decline in PFS and no change in OS over time, however that review incorporated a smaller number of studies and did not explore ECOG performance status in their included studies. Strengths of this review include the systematic methodology used to identify relevant studies, inclusion of multiple databases and inclusion of studies regardless of first-line therapy used. We

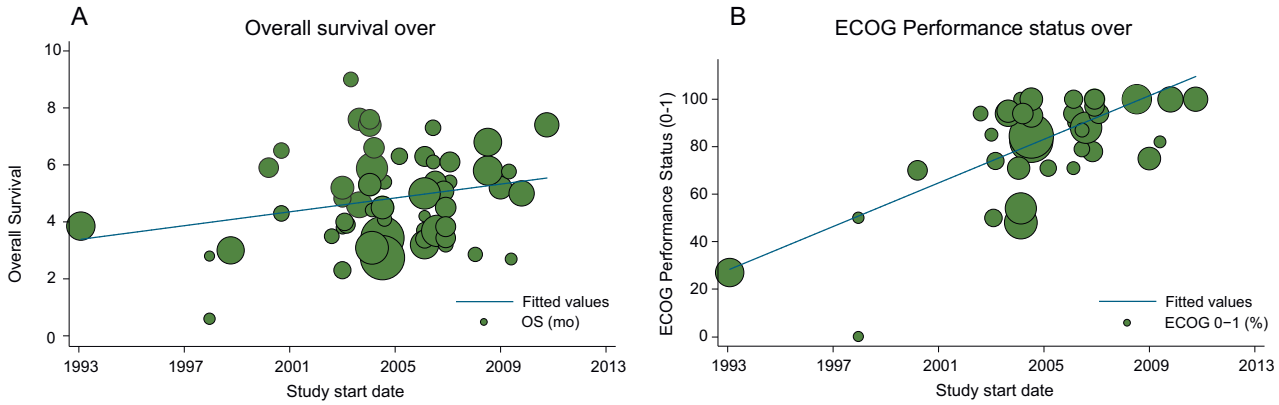

Fig. 4. Change in survival (A) and ECOG performance status (B) over time in studies of second-line systemic therapy.

also attempted to reduce the risk of publication bias by also searching through conference abstracts. However, limitations include the large number of studies that were only available in abstract format, and limitation to studies published in English. Additionally, we were unable to perform a meta-analysis due to the heterogeneity of randomised studies while the statistical comparisons of summary data can only be described as exploratory. This heterogeneity is likely a reflection of the lack of consensus of a standard for second-line therapy in this disease. Nonetheless, this summary provides clinicians with a practical overview of the evaluated treatments. A question that remains unanswered from our analysis is what factors predict benefit from second-line therapy. An individual patient data analysis of second-line studies could further clarify this important issue.

In conclusion, the reported use of second-line systemic therapy in pancreatic adenocarcinoma studies has increased over time and correlates with survival, but is not reported in the majority of published studies. Although a large number of therapies have been explored in this setting, no particular therapy can be universally recommended. Studies of targeted therapies have been primarily performed in unselected populations and outcomes have been disappointing. Future studies need to include significant translational components so that predictive biomarkers can be assessed. The survival of patients in second-line studies has increased over time but that may not correlate with an improved effect of the treatment used. Future studies relying on comparisons to historical outcomes may not be reliable. As randomised studies are therefore required, it is imperative that consensus regarding standard therapy is reached. Studies currently available in the literature do not provide clear support for any specific therapy. Options that are listed in the NCCN guidelines currently include gemcitabine, 5-FU, capecitabine and oxaliplatin. Based on this review, anti-mitotic agents such as docetaxel and Topoisomerase I inhibitors e.g. irinotecan could also be considered as viable options.

Conflict of interest statement

The authors have declared no conflicts of interest.

Authors' contribution

All authors have contributed to the conception and design of the review, acquisition of data, and analysis and interpretation of data, drafting the article or revising it critically for important intellectual content. All authors provided final approval of the version to be submitted.

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