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Short Communication Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer: results of secondary end points analyses

A Sultana¹, C Tudur Smith^{1,2}, D Cunningham³, N Starling³, JP Neoptolemos¹ and P Ghaneh^{*,1}

¹CRUK Liverpool Cancer Trials Unit, Cancer Research Centre, 200 London Road, Liverpool, L3 9TA, UK; ²Centre for Medical Statistics and Health Evaluation, University of Liverpool, Shelley's Cottage, Brownlow Street, Liverpool L69 3GS, UK; ³Department of Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK

In advanced pancreatic cancer, level one evidence has established a significant survival advantage with chemotherapy, compared to best supportive care. The treatment-associated toxicity needs to be evaluated. This study examines the secondary outcome measures for chemotherapy in advanced pancreatic cancer using meta-analyses. A systematic review was undertaken employing Cochrane methodology, with search of databases, conference proceedings and trial registers. The secondary end points were progression-free survival (PFS)/time to progression (TTP) (summarised using the hazard ratio (HR)), response rate and toxicity (summarised using relative risk). There was no significant advantage of 5FU combinations vs 5FU alone for TTP (HR = 1.02; 95% Cl = 0.85 - 1.23) and toxicity. Progression-free survival (HR 0.78; Cl 0.70–0.88), TTP (HR = 0.85; 95% Cl = 0.72 - 0.99) and overall response rate (RR = 0.56; 95% Cl = 0.46 - 0.68) were significantly better for gemcitabine combination chemotherapy, but offset by the greater grade 3/4 toxicity thrombocytopenia (RR = 1.94; 95% Cl = 1.32 - 2.84), leucopenia (RR = 1.46; 95% Cl = 1.15 - 1.86), neutropenia (RR = 1.48; 95% Cl = 1.07 - 2.05), nausea (RR = 1.77; 95% Cl = 1.32 - 2.29), vomiting (RR = 1.64; 95% Cl = 1.24 - 2.16) and diarrhoea (RR = 2.73; 95% Cl = 1.87 - 3.98). There is no significant advantage on secondary end point analyses for administering 5FU in combination over 5FU alone. There is improved PFS/TTP and response rate, with gemcitabine-based combinations, although this comes with greater toxicity.

British Journal of Cancer (2008) **99,** 6–13. doi:10.1038/sj.bjc.6604436 www.bjcancer.com Published online 24 June 2008 © 2008 Cancer Research UK

Keywords: meta-analyses; pancreatic cancer; chemotherapy

Advanced pancreatic cancer has a poor prognosis, with a median survival of 2-6 months for metastatic disease and 6-11 months for locally advanced disease (Cancer Research, 2006). Chemotherapy with fluoropyrimidines, gemcitabine, either alone or in combination with other agents (Rocha Lima and Flores, 2006), and chemoradiation are all used in the palliative setting (Mancuso *et al*, 2006). Overall survival meta-analyses, using relative risk (Yip *et al*, 2006) or the hazard ratio (HR) (Fung *et al*, 2003; Sultana *et al*, 2007), have established a role for chemotherapy over best supportive care. Questions have arisen as to the cost at which this survival advantage is gained, in particular, the toxicity profile. Following from our previous survival meta-analysis (Sultana *et al*, 2007), we present the results of the secondary outcome measures meta-analysis.

There has only been one fully published meta-analysis evaluating secondary outcome measures, with no pooling of the results of these end points (Yip *et al*, 2006). Other published reports have assessed this only for the comparison of gemcitabine combinations *vs* gemcitabine. (Liang, 2005; Milella *et al*, 2006; Heinemann *et al*, 2006a; Xie *et al*, 2006a, b; Bria *et al*, 2007; Heinemann *et al*, 2007). To fully evaluate the risks *vs* the benefits of treatment, a comprehensive evaluation including assessment of several composite end points is required.

METHODS

Detailed description of the methodology of the systematic review has already been described (Sultana *et al*, 2007).

The secondary outcome measures evaluated were progressionfree survival (PFS – time from randomisation to progression or death) or time to progression (TTP – time from randomisation to disease progression), overall response rate (ORR – number of partial and complete responses) and toxicity (as published by the trialists, was recorded, with the most frequently reported events analysed).

Individual trial level time to event data (PFS/TTP) were summarised by the log HR and its variance was approximated using previously reported methods (Parmar *et al*, 1998; Williamson *et al*, 2002). Trial level log HRs and their variances were pooled using an inverse variance, weighted average and results presented as a HR and 95% confidence interval.

^{*}Correspondence: Dr P Ghaneh, Division of Surgery and Oncology, School of Cancer Studies, 5th Floor-UCD Building, Daulby Street, Liverpool, Merseyside L69 3GA, UK; E-mail: p.ghaneh@liv.ac.uk

Revised 28 April 2008; accepted 2 May 2008; published online 24 June 2008

Dichotomous data (ORR and toxicity) were summarised using relative risks and 95% confidence intervals and pooled using the Mantel-Haenszel method for combining trials (Deeks et al, 2001). Heterogeneity was assessed by visual inspection of the Forrest plot, the Cochran's χ^2 test (using a 10% significance level, in view of the low power of tests for heterogeneity (Paul and Donner, 1992)) and interpretation of the I² statistic (percentage of variation due to heterogeneity with higher values indicating a greater degree of heterogeneity) (Deeks et al, 2004). A fixed effect approach was adopted unless there was evidence of significant unexplained heterogeneity in which case a random effects approach was used.

RESULTS

Results are presented for the comparisons with adequate data to assess the secondary outcome measures.

5FU vs 5FU combination chemotherapy

There were five studies (Supplementary Table 1) (Kovach et al, 1974; Cullinan et al, 1985, 1990; Ducreux et al, 2002; Maisey et al, 2002) (n = 700) included in this comparison. A HR of <1 indicates a survival advantage for 5FU combination chemotherapy.

Two trials assessed TTP (Figure 1) and found no significant advantage for 5FU combinations over 5FU alone (HR = 1.02; 95% CI = 0.85 - 1.23). For PFS, 5FU combination appeared better than 5FU alone (two trials; 416 patients; HR = 0.67; 95% CI = 0.46 -0.98). The ORR (Figure 2) was superior (five trials; 700 patients; RR = 0.43; 95% CI = 0.25 - 0.74) in the 5FU combination arm. Grade 3 or 4 vomiting was significantly greater in the 5FU combination chemotherapy arm (two trials; 320 patients; RR = 3.76; 95% CI = 1.67 - 8.44). There was a higher occurrence of diarrhoea (two trials 406 patients; RR = 1.49; 95% CI = 0.58-3.84), stomatitis (three trials; 529 patients; RR = 1.29; 95% CI = 0.75 - 2.22) and thrombocytopenia (two trials; 332 patients; $RR\!=\!2.15;\,95\%$ CI $=\!0.83\!-\!5.53)$ in the combination chemotherapy arm (Figure 3). Data for leucopenia, neutropenia, anaemia and nausea are displayed in Figure 3. There was significant between trial heterogeneity in the PFS analysis, unlike for the TTP and response rate analyses.

Gemcitabine vs 5FU

Two randomised controlled trials involving 197 patients were assessed (Burris et al, 1997; Cantore et al, 2004), including unpublished individual patient data (Cantore et al, 2004). A HR of <1 indicates a survival advantage for gemcitabine. Gemcitabine



Overall response rate appeared better in the gemcitabine arm; however, the wide confidence interval suggests a benefit for either gemcitabine or 5FU (one trial; 126 patients; RR = 0.14; 95% CI = 0.01 - 2.66). In the Burris trial (Burris et al, 1997), haematological toxicity was seen more frequently following gemcitabine therapy (grades 3 and 4 neutropenia in 25% of gemcitabine and 4.9% of 5FU patients; *P*<0.001).

Gemcitabine vs gemcitabine-based combination chemotherapy

Nineteen studies involving 4697 patients were included (Supplementary Table 2) (Berlin et al, 2002; Colucci et al, 2002; Wang et al, 2002; Heinemann et al, 2003; Scheithauer et al, 2003; Li and Chao, 2004; Ohkawa, 2004; Rocha Lima et al, 2004; Viret et al, 2004; Cunningham et al, 2005; Di Costanzo et al, 2005; Hermann et al, 2005; Louvet et al, 2005; Oettle et al, 2005; Reiss et al, 2005; Reni et al, 2005; Stathopoulos et al, 2005; Abou-Alfa et al, 2006; Poplin et al, 2006). Data from four of the included studies (Abou-Alfa et al, 2006; Heinemann et al, 2006b; Stathopoulos et al, 2006; Herrmann et al, 2007) were based on abstracts and extra data provided by the authors (Hermann et al, 2005; Stathopoulos et al, 2005). A HR of < 1 indicates a survival advantage for gemcitabinebased combination chemotherapy.

Progression-free survival (four trials; 864 patients; HR = 0.78; 95% CI = 0.70 - 0.88), TTP (3 trials; 559 patients; HR = 0.85; 95% CI = 0.72 - 0.99) (Figure 4) and ORR (Figure 5) (17 trials; 3577) patients; RR = 0.56; 95% CI = 0.46 - 0.68) were significantly better in the gemcitabine combination chemotherapy arm. Haematological toxicity was greater in the gemcitabine combination chemotherapy arm (Figure 6), including thrombocytopenia (18 trials; 4564 patients; RR = 1.94; 95% CI = 1.32 - 2.84), leucopenia (eight trials; 1606 patients; RR = 1.46; 95% CI = 1.15 - 1.86), neutropenia (15 trials; 3818 patients; RR = 1.48; 95% CI = 1.07-2.05) and anaemia (15 trials; 3745 patients; RR = 1.14; 95% CI = 0.82 - 1.59). Gastrointestinal side effects (Figure 7) of nausea (nine trials; 3055 patients; RR = 1.77; 95% CI = 1.37 - 2.29), vomiting (10 trials; 3471 patients; RR = 1.64; 95% CI = 1.24-2.16) and diarrhoea (14 trials; 3531 patients; RR = 2.73; 95% CI = 1.87 - 3.98) were significantly increased, with a trend towards increased stomatitis (7 trials; 2007 patients; RR=1.84; 95% CI = 0.86 - 3.92) in the gemcitabine combination chemotherapy arm. There was no significant inter-trial heterogeneity for the end points of PFS, TTP and ORR.

Study or subcategory	Log(hazard ratio) (SE)	Hazard ratio (random) 95% Cl) Weight %	Hazard ratio (random) 95% CI	
01 TTP					
Cullinan 1985	0.0900 (0.1500)		47.53	1.09 (0.82, 1.47)	
Cullinan 1990	-0.0200 (0.1200)	÷.	52.47	0.98 (0.77, 1.24)	
Subtotal (95% CI)		+	100.00	1.02 (0.85, 1.23)	
Test for heterogeneity:	χ ² =0.33, d.f.=1 (<i>P</i> =0.57), <i>I</i> ² =0%				
Test for overall effect: Z	=0.24 (<i>P</i> =0.81)				
02 PFS					
Ducreux 2002	-0.6000 (0.1500)		49.14	0.55 (0.41, 0.74)	
Maisey N 2002	-0.2100 (0.1400)	-=-	50.86	0.81 (0.62, 1.07)	
Subtotal (95% CI)		-	100.00	0.67 (0.46, 0.98)	
	$I^2 = 3.61, d.f. = 1 (P = 0.06), I^2 = 72.$	3%			
Test for overall effect: Z	=2.06 (<i>P</i> =0.04)				
	0.1	0.2 0.5 1 2	5 10		
	Fav	ours 5FU combin Favours	s 5FU		

Figure 1 5FU single agent vs 5FU-based combination chemotherapy – PFS/TTP analyses.

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Study or subcategory	5FU n/N	5FU combination n/N	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% CI
Kovach 1974	3/14	8/21		16.39	0.56 (0.18, 1.76)
Cullinan 1985	3/10	1/13		2.23	3.90 (0.47, 32.09)
Cullinan 1990	1/64	2/59		5.33	0.46 (0.04, 4.95)
Ducreux 2002	0/98	10/98		26.90	0.05 (0.00, 0.80)
Maisey N 2002	9/105	18/92	-#-	49.15	0.44 (0.21, 0.93)
Total (95% CI) Total events: 16 (5FU) Test for heterogeneity:			•	100.00	0.43 (0.25, 0.74)
Test for overall effect:	Z=3.09 (P=0.002)				
		0.0	01 0.01 0.1 1 10 10	00 1000	

Favours 5FU combin Favours 5FU

Legend: *n*=number of responses *N*=total number of patients

Figure 2 5FU single agent vs 5FU-based combination chemotherapy – response rate analyses.

Review: Treatment of advanced pancreatic cancer (Version 07; 27 june06) Comparison: 03 5FU vs 5FU combo Outcome: 04 Adverse events 5FU combo vs 5FU

Outcome: 04 Adverse	events SFU combo vs 5	FU			
Study or subcategory	5FU combination n/N	5FU alone <i>n/N</i>	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl
01 grade3 or 4 thrombocy Cullinan 1990 Maisey N 2002 Subtotal (95% Cl) Total events: 12 (5FU cor Test for heterogeneity: χ^2 Test for overall effect: Z=	8/59 4/102 161 nbination), 6 (5FU alone) = 0.00, d.f. = 1 (<i>P</i> = 0.97),	4/64 2/107 171) <i>J</i> ² =0%	•	66.28 33.72 100.00	2.17 (0.69, 6.831) 2.10 (0.39, 11.21) 2.15 (0.83, 5.53)
02 grade 3 or 4 leucopeni Cullinan 1990 Subtotal (95% Cl) Total events: 31 (5FU cor Test for heterogeneity: no Test for overall effect: Z=	31/59 59 nbination), 20 (5FU alone t applicable	20/64 64 e)	•	100.00 100.00	1.68 (1.09, 2.60) 1.68 (1.09, 2.60)
03 grade 3 or 4 neutroper Maisey N 2002 Subtotal (95% CI) Total events: 3 (5FU com Test for heterogeneity: no Test for overall effect: Z=	3/102 102 bination), 0 (5FU alone) t applicable	0/107 107		100.00 100.00	7.34 (0.38, 140.36) 7.34 (0.38, 140.36)
04 grade 3 or 4 anaemia Maisey N 2002 Subtotal (95% Cl) Total events: 8 (5FU com Test for heterogeneity: no Test for overall effect: Z=	t applicable	9/107 107	\$	100.00 100.00	0.93 (0.37, 2.32) 0.93 (0.37, 2.32)
05 grade 3 or 4 nausea Cullinan 1990 Subtotal (95% CI) Total events: 13 (5FU cor Test for heterogeneity: no Test for overall effect: Z=	t applicable	3/64 64	*	100.00 100.00	4.70 (1.41, 15.68) 4.70 (1.41, 15.68)
06 grade 3 or 4 vomiting Cullinan 1990 Ducreux 2002 Subtotal (95% CI) Total events: 25 (5FU cor Test for heterogeneity: χ^2 Test for overall effect: Z=	= 0.08, d.f. = 1 (P = 0.78),		- <u>∎-</u> 	42.22 57.78 100.00	3.25 (0.93, 11.45) 4.12 (1.43, 11.90) 3.76 (1.67, 8.44)
07 grade 3 or 4 diarrhoea Ducreux 2002 Maisey N 2002 Subtotal (95% CI) Total events: 10 (5FU cor Test for heterogeneity: χ^2 Test for overall effect: Z=	= 0.76, d.f. = 1 (P = 0.38),		•	28.75 71.25 100.00	2.58 (0.51, 12.97) 1.05 (0.31, 3.52) 1.49 (0.58, 3.84)
08 grade 3 or 4 stomatitis Cullinan 1990 Ducreux 2002 Maisey N 2002 Subtotal (95% Cl) Total events: 27 (5FU cor Test for heterogeneity: χ^2 Test for overall effect: Z=	=6.07, d.f.=2 (P=0.05),		-=- -=- •	40.41 23.04 36.55 100.00	0.36 (0.10, 1.27) 2.68 (0.99, 7.23) 1.44 (0.60, 3.44) 1.29 (0.75, 2.22)
			0.01 0.1 1 10 100 rs 5FU combin Favours 51	1000 =U	
Lonordur number of	tovicity overto				

Legend: n = number of toxicity events N = total number of patients

Figure 3 5FU single agent vs 5FU-based combination chemotherapy – toxicity analyses.

Clinical Studies

Study or subcategory	Log(hazard ratio) (SE)	Hazard ratio (fixed) 95% Cl	Weight %	Hazard ratio (fixed) 95% Cl
01 Progression-free surv	vival			
Berlin 2002	-0.2600 (0.1100)		26.59	0.77 (0.62, 0.96)
Scheithauer 2003 Di Costanzo 2005	-0.2300 (0.2400)		5.59	0.79 (0.50, 1.27) Not estimable
Hermann 2005	-0.1500 (0.1200)		22.34	0.86 (0.68, 1.09)
Louvet 2005	-0.2500 (0.1300)		19.04	0.78 (0.60, 1.00)
Reni 2005	-0.7800 (0.2800)		4.10	0.46 (0.26, 0.79)
Heinemann 2006	-0.2200 (0.1200)		22.34	0.80 (0.63, 1.02)
Subtotal (95% CI)		•	100.00	0.78 (0.70, 0.88)
Test for heterogeneity: χ	$\chi^2 = 4.34$, d.f. = 5 ($P = 0.50$), $I^2 = 0$	%		
Test for overall effect: Z	=4.31 (P<0.0001)			
	· · · ·			
02 Time to progression	· · · ·			
02 Time to progression Colucci 2002	-0.3000 (0.1400)		33.71	0.74 (0.56, 0.97)
	. ,		33.71	0.74 (0.56, 0.97) Not estimable
Colucci 2002	. ,		33.71	
Colucci 2002 Li 2004	. ,	-#	33.71	Not estimable
Colucci 2002 Li 2004 Ohkawa 2004 Reilly 2004 RochaLima 2004	. ,	-	33.71 45.89	Not estimable Not estimable Not estimable 0.90 (0.71, 1.13)
Colucci 2002 Li 2004 Ohkawa 2004 Reilly 2004 RochaLima 2004 Oettle 2005	-0.3000 (0.1400)	*		Not estimable Not estimable Not estimable 0.90 (0.71, 1.13) Not estimable
Colucci 2002 Li 2004 Ohkawa 2004 Reilly 2004 RochaLima 2004 Octtle 2005 Reiss 2005	-0.3000 (0.1400) -0.1100 (0.1200)		45.89	Not estimable Not estimable Not estimable 0.90 (0.71, 1.13) Not estimable Not estimable
Colucci 2002 Li 2004 Ohkawa 2004 Reilly 2004 RochaLima 2004 Oettle 2005 Reiss 2005 Stathoupoulos 2005	-0.3000 (0.1400)	-	45.89 20.40	Not estimable Not estimable 0.90 (0.71, 1.13) Not estimable Not estimable 0.93 (0.66, 1.33)
Colucci 2002 Li 2004 Ohkawa 2004 Reilly 2004 RochaLima 2004 Oettle 2005 Reiss 2005 Stathoupoulos 2005 Subtotal (95% CI)	-0.3000 (0.1400) -0.1100 (0.1200) -0.0700 (0.1800)	+	45.89	Not estimable Not estimable Not estimable 0.90 (0.71, 1.13) Not estimable Not estimable
Colucci 2002 Li 2004 Ohkawa 2004 Reilly 2004 RochaLima 2004 Oettle 2005 Reiss 2005 Stathoupoulos 2005 Subtotal (95% CI)	-0.3000 (0.1400) -0.1100 (0.1200) -0.0700 (0.1800) t^2 =1.42, d.f.=2 (<i>P</i> =0.49), <i>I</i> ² =05	*	45.89 20.40	Not estimable Not estimable 0.90 (0.71, 1.13) Not estimable Not estimable 0.93 (0.66, 1.33)

Favours gem combin Favours gemcitabine

Figure 4 Results for gemcitabine vs gemcitabine-based combination chemotherapy – TTP/PFS.

Treatment of advanced pancreatic cancer

Study	Gemcitabine	Gem combination	RR (fixed)	Weight	RR (fixed)
or subcategory	n/N	n/N	95% Cl	%	95% CI
Berlin 2002	9/162	11/160		4.26	0.81 (0.34, 1.90)
Colucci 2002	5/48	14/45		5.57	0.33 (0.13, 0.85)
Wang 2002	1/16	2/18		0.73	0.56 (0.06, 5.63)
Scheithauer 2003	6/42	7/41		2.73	0.84 (0.31, 2.28)
Li 2004	3/25	2/21		0.84	1.26 (0.23, 6.85)
Abou-Alfa 2006	11/174	14/175		5.38	0.79 (0.37, 1.69)
Ohkawa 2004	3/9	0/10		0.18	7.70 (0.45, 131.36)
RochaLima 2004	8/180	29/180		11.17	0.28 (0.13, 0.59)
Viret F 2004	2/41	3/42		1.14	0.68 (0.12, 3.88)
Cunningham D 2005	19/266	38/267		14.61	0.50 (0.30, 0.85)
Di Costanzo 2005	4/48	5/43		2.03	0.72 (0.21, 2.50)
Hermann 2005	12/152	15/148		5.85	0.78 (0.38, 1.61)
Louvet 2005	27/156	42/157	-=-	16.13	0.65 (0.42, 0.99)
Oettle 2005	20/282	42/283	-#-	16.15	0.48 (0.29, 0.79)
Reiss 2005	0/1	0/1			Not estimable
Reni 2005	4/47	20/52		7.31	0.22 (0.08, 0.60)
Stathoupoulos 2005	4/50	5/42		2.09	0.67 (0.19, 2.34)
Heinemann 2006	8/97	10/98		3.83	0.81 (0.33, 1.96)
Poplin 2006	0/1	0/1			Not estimable
Total (95% CI)	1797	1784		100.00	0.56 (0.46, 0.68)
Total events: 146 (gemcitat	oine). 259 (aem comb	pination)			
Test for heterogeneity: $\chi^2 =$					
Test for overall effect: $Z=5$.					
	, ,	0.00	1 0.01 0.1 1 10 10	00 1000	
			urs gem combin Favours		
Legend: n=number of re	esponses	Tave	ars gen complitier avours	gem	

N=total number of patients

Review:

Comparison: 04 Gem vs Gem combo

Figure 5 Results for gemcitabine vs gemcitabine-based combination chemotherapy – response rate.

Examination of the funnel plots revealed evidence of bias, possibly publication bias, but this is difficult to interpret in view of the small number of studies within each comparison.

DISCUSSION

5FU combinations did not prolong TTP over 5FU alone, despite significantly better response rate with the former. The study of Yip *et al* (2006) assessed the parameters described in our analyses, but did not pool the results unlike our approach. In the two trials that had assessed PFS, the overall summary estimate favoured 5FU combination chemotherapy, but there was significant inter-trial

heterogeneity. This may be due to the differences in dosing. The dose of 5FU administered was lower in the Maisey *et al* (2002) study ($300 \text{ mg m}^{-2} \text{ day}^{-1}$ in both arms) compared to the Ducreux *et al* (2002) study ($500 \text{ mg m}^{-2} \text{ day}^{-1}$ used in the single-agent arm and 1000 mg m^{-2} used in the combination arm).

As overall survival is a better indicator of efficacy than response rate (Maisey *et al*, 2002), the evidence from these end points, interpreted alongside the overall survival result (Sultana *et al*, 2007), do not support the use of 5FU combinations over 5FU single agent.

Meta-analyses of the secondary end points were not possible in the gencitabine vs 5FU comparison, as these results were only available for one randomised trial.

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Study or subcategory	Gem combin n/N	Gem alone <i>n/N</i>	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
01 grade 3 or 4 thromboo	cvtopenia				
Berlin 2002	30/158	17/158	-	9.99	1.76 (1.02, 3.07)
Colucci 2002	1/51	1/53		1.39	1.04 (1.07, 16.18)
Scheithauer 2003	0/40	1/39		1.07	0.33 (1.01, 7.75)
_i 2004	5/21 30/175	1/25 7/174		2.27 7.80	5.95 (0.75, 47.04)
Abou-Alfa 2006 Dhkawa 2004	1/10	0/9		1.12	4.26 (1.92, 9.44) 2.73 (0.12, 59.57)
RochaLima 2004	34/173	34/169	-	10.70	1.38 (0.86, 2.23)
/iret F 2004	14/42	5/41		6.78	2.73 (1.08, 6.90)
Cunningham D 2005	8/267	5/266		5.59	1.59 (0.53, 4.81)
Di Costanzo 2005	0/41	0/49			Not estimable
Hermann 2005	8/155	7/153		6.33	1.13 (0.42, 3.03)
₋ouvet 2005 Dettle 2005	22/157 49/273	5/156 17/273	-	6.64 10.25	4.37 (1.70, 11.25) 2.88 (1.70, 4.88)
Reiss 2005	30/230	17/236		9.86	1.81 (1.03, 3.19)
Reni 2005	30/52	1/47		2.49	27.12 (3.85, 191.14)
Stathoupoulos 2005	3/57	0/69		1.22	8.45 (0.45, 160.24)
leinemann 2006	4/95	10/95		5.48	0.40 (0.13, 1.23)
Poplin 2006 Subtotal (95% CI)	31/276 2273	39/271 2291		11.04 100.00	0.80 (0.52, 1.25)
Fotal events: 300 (gem c			•	100.00	1.94 (1.32, 2.84)
Test for heterogeneity: χ^2	2 =45.56 d f = 16 (P=	$0.0001)$ $l^2 = 64.9\%$			
Fest for overall effect: Z =		0.0001), 1 = 01.070			
	· · · · ·				
2 grade 3 or 4 leucoper		25/158	-	01.64	1 0/ (1 10 0 /0)
Berlin 2002 Colucci 2002	46/158 2/51	25/158 2/53		21.64 4.98	1.84 (1.19, 2.48) 1.04 (0.15, 7.10)
Scheithauer 2003	4/40	3/39		4.98 7.80	1.30 (0.31, 5.44)
Dhkawa 2004	2/10	3/9		6.97	0.60 (0.13, 2.82)
RochaLima 2004	45/173	25/169	-=	21.52	1.76 (1.13, 2.73)
Di Costanzo 2005	1/41	1/49		2.71	1.20 (0.08, 18.52)
Reiss 2005	28/230	28/236	ŧ	20.60	1.03 (0.63, 1.68)
Heinemann 2006	10/95	8/95		13.80	1.25 (0.52, 3.03)
Subtotal (95% CI) Fotal events: 138 (gem c	798 2000 (app along	808	•	100.00	1.46 (1.15, 1.86)
Test for heterogeneity: χ					
Fest for overall effect: Z =		52), 7 = 070			
	, ,				
03 grade 3 or 4 neutrope		E/1E0		4.10	1 40 (0 45 4 00)
Berlin 2002	7/158 9/51	5/158 5/53		4.13 4.61	1.40 (0.45, 4.32) 1.87 (0.67, 5.21)
Colucci 2002 Scheithauer 2003	4/40	3/39		3.02	1.30 (0.31, 5.44)
_i 2004	4/21	2/25		2.58	2.38 (0.48, 11.74)
Abou-Alfa 2006	53/175	26/174	+	8.49	2.03 (1.33, 3.08)
21.1	1/10	1/9		1.14	0.90 (0.07, 12.38)
Dhkawa 2004					1.18 (0.88, 1.57)
RochaLima 2004	65/173	54/169	-	9.30	
RochaLima 2004 /iret F 2004	65/173 24/42	16/41	-	8.18	1.46 (0.92, 2.33)
RochaLima 2004 /iret F 2004 Cunningham D 2005	65/173 24/42 45/267	16/41 29/266	*	8.18 8.38	1.46 (0.92, 2.33) 1.55 (1.00, 2.39)
RochaLima 2004 /iret F 2004 Cunningham D 2005 Hermann 2005	65/173 24/42 45/267 34/155	16/41 29/266 30/153		8.18 8.38 8.36	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73)
RochaLima 2004 /iret F 2004 Cunningham D 2005	65/173 24/42 45/267	16/41 29/266	*	8.18 8.38	1.46 (0.92, 2.33) 1.55 (1.00, 2.39)
RochaLima 2004 /iret F 2004 Cunningham D 2005 Hermann 2005 Jouvet 2005 Dettle 2005 Reni 2005	65/173 24/42 45/267 34/155 32/157 123/273 43/52	16/41 29/266 30/153 43/156 35/273 14/47		8.18 8.38 8.36 8.62 9.04 8.23	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38)
RochaLima 2004 Viret F 2004 Cunningham D 2005 Hermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005	65/173 24/42 45/267 34/155 32/157 123/273 43/52 15/57	16/41 29/266 30/153 43/156 35/273 14/47 11/69		8.18 8.38 8.36 9.04 8.23 6.55	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31)
AochaLima 2004 /iret F 2004 Lunningham D 2005 Hermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006	65/173 24/42 45/267 34/155 32/157 123/273 43/52 15/57 61/276	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279		8.18 8.38 8.62 9.04 8.23 6.55 9.38	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31) 0.67 (0.51, 0.88)
RochaLima 2004 /iret F 2004 Junningham D 2005 Jermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI)	65/173 24/42 45/267 34/155 32/157 123/273 43/52 15/57 61/276 1907	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911	• • • • •	8.18 8.38 8.36 9.04 8.23 6.55	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31)
RochaLima 2004 Viret F 2004 Cunningham D 2005 Jermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Total events: 520 (gem c	65/173 24/42 45/267 34/155 32/157 123/273 43/52 15/57 61/276 1907 combin), 366 (gem alou	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne)	* * * * * *	8.18 8.38 8.62 9.04 8.23 6.55 9.38	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31) 0.67 (0.51, 0.88)
AochaLima 2004 Viret F 2004 Lunningham D 2005 Jermann 2005 Joutet 2005 Aeni 2005 Reni 2005 Poplin 2006 Subtotal (95% CI) Fotal events: 520 (gem c Fest for heterogeneity: χ'	65/173 24/42 45/267 34/155 32/157 123/273 43/52 15/57 61/276 1907 combin), 366 (gem alou 2 =81.15, d.f.=14 (<i>P</i> <	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne)	* * * * * * * *	8.18 8.38 8.62 9.04 8.23 6.55 9.38	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31) 0.67 (0.51, 0.88)
AochaLima 2004 Viret F 2004 Cunningham D 2005 Hermann 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) fotal events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z=	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ \text{combin}, 366 (gem aloo\\ ^2=81.15, d.f.=14 (P<\\ =2.38 (P=0.02)\\ \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne)	*	8.18 8.38 8.62 9.04 8.23 6.55 9.38	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31) 0.67 (0.51, 0.88)
AochaLima 2004 /iret F 2004 /iret F 2004 Junningham D 2005 Hermann 2005 Jouth 2005 Jouth 2005 Jouth 2005 Stathoupoulos 2005 Joplin 2006 Subtotal (95% CI) Fost levents: 520 (gem c) Fest for heterogeneity: x/ Fest for overall effect: Z= 04 grade 3 or 4 anaemia	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gem alor\\ ^2=81.15, d.f.=14 (P<\\ =2.38 (P=0.02) \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), I ² =82.7%	*	8.18 8.38 8.36 8.62 9.04 8.23 6.55 9.38 100.00	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31) 0.67 (0.51, 0.88) 1.48 (1.07, 2.05)
RochaLima 2004 /iret F 2004 Lunningham D 2005 Hermann 2005 Joutet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Total events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z= 24 grade 3 or 4 anaemia Berlin 2002	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ 2^{2}=81.15, d.f.=14 \ (P<=2.38 \ (P=0.02)\\ 16/158\end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), I ² =82.7%	*	8.18 8.36 8.62 9.04 8.23 6.55 9.38 100.00	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31) 0.67 (0.51, 0.88) 1.48 (1.07, 2.05)
AochaLima 2004 Viret F 2004 Cunningham D 2005 Hermann 2005 Joutet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Total events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z= J4 grade 3 or 4 anaemia Berlin 2002	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ \text{combin}, 366 (gem aloo\\ ^2=81.15, d.f.=14 (P<\\ =2.38 (P=0.02)\\ & \\ 16/158\\ 3/51 \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), / ² =82.7%		8.18 8.36 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27	$\begin{array}{c} 1.46\ (0.92\ 2.33)\\ 1.55\ (1.00,\ 2.39)\\ 1.12\ (0.72,\ 1.73)\\ 0.74\ (0.50,\ 1.10)\\ 3.51\ (2.51,\ 4.92)\\ 2.78\ (1.76,\ 4.38)\\ 1.65\ (0.82,\ 3.31)\\ 0.67\ (0.51,\ 0.88)\\ 1.48\ (1.07,\ 2.05)\\ \end{array}$
AochaLima 2004 /iret F 2004 Lunningham D 2005 Hermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Fotal events: 520 (gem C Fest for heterogeneity: χ' Fest for overall effect: Z= 04 grade 3 or 4 anaemia Berlin 2002 Scheithauer 2003	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gem aloi \\ 2=81.15, d.f. = 14 (P < = 2.38 (P = 0.02) \\ \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), / ² = 82.7%		8.18 8.38 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29	1.46 (0.92, 2.33) 1.55 (1.00, 2.39) 1.12 (0.72, 1.73) 0.74 (0.50, 1.10) 3.51 (2.51, 4.92) 2.78 (1.76, 4.38) 1.65 (0.82, 3.31) 0.67 (0.51, 0.88) 1.48 (1.07, 2.05) 1.00 (0.52, 1.93) 1.56 (0.27, 8.95) 4.88 (0.24, 98.47)
AochaLima 2004 Viret F 2004 Viret F 2004 Cunningham D 2005 Hermann 2005 Joutet 2005 Pottle 2005 Reni 2005 Pottle 2005 Optim 2006 Subtotal (95% CI) Fotal events: 520 (gem c Fest for overall effect: Z= P4 grade 3 or 4 anaemia Berlin 2002 Scheithauer 2003 Lolucci 2002 Scheithauer 2003 Li 2004	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ \text{combin}, 366 (gem aloo\\ ^2=81.15, d.f.=14 (P<\\ =2.38 (P=0.02)\\ & \\ 16/158\\ 3/51 \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), / ² =82.7% 16/158 2/53 0/39 2/25 22/169		8.18 8.36 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36	$\begin{array}{c} 1.46\ (0.92\ 2.33)\\ 1.55\ (1.00,\ 2.39)\\ 1.12\ (0.72,\ 1.73)\\ 0.74\ (0.50,\ 1.10)\\ 3.51\ (2.51,\ 4.92)\\ 2.78\ (1.76,\ 4.38)\\ 1.65\ (0.82,\ 3.31)\\ 0.67\ (0.51,\ 0.88)\\ 1.48\ (1.07,\ 2.05)\\ \end{array}$
AochaLima 2004 /iret F 2004 Lunningham D 2005 Hermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Fotal events: 520 (gem C Fest for heterogeneity: χ' Fest for overall effect: Z= 04 grade 3 or 4 anaemia Berlin 2002 Scheithauer 2003 i 2004 RochaLima 2004 Jiret F 2004	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gem alor\\ 2=81.15, d.f.=14 (P<=2.38 (P=0.02)\\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 28/173\\ 16/42\\ \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), / ² = 82.7% 16/158 2/53 0/39 2/25 22/169 12/41		8.18 8.38 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36	$\begin{array}{c} 1.46 \ (0.92, 2.33) \\ 1.55 \ (1.00, 2.39) \\ 1.12 \ (0.72, 1.73) \\ 0.74 \ (0.50, 1.10) \\ 3.51 \ (2.51, 4.92) \\ 2.78 \ (1.76, 4.38) \\ 1.65 \ (0.82, 3.31) \\ 0.67 \ (0.51, 0.88) \\ 1.48 \ (1.07, 2.05) \end{array}$
RochaLima 2004 /iret F 2004 /iret F 2005 Lunningham D 2005 Jermann 2005 Jouth 2005 Dottle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Total events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z= 204 grade 3 or 4 anaemia Berlin 2002 Colucci 2002 Scheithauer 2003 i 2004 RochaLima 2004 Viret F 2004 Lunningham D 2005	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gen aloo\\ 2^2=81.15, d.f.=14 (P<\\ =2.38 (P=0.02)\\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 28/173\\ 16/42\\ 3/267\\ \end{array}$	$\begin{array}{c} 16/41\\ 29/266\\ 30/153\\ 43/156\\ 35/273\\ 14/47\\ 11/69\\ 92/279\\ 1911\\ ne)\\ 0.00001), \ l^2 = 82.7\%\\ \end{array}$		8.18 8.36 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44	$\begin{array}{c} 1.46\ (0.92\ 2.33)\\ 1.55\ (1.00,\ 2.39)\\ 1.12\ (0.72,\ 1.73)\\ 0.74\ (0.50,\ 1.10)\\ 3.51\ (2.51,\ 4.92)\\ 2.78\ (1.76,\ 4.38)\\ 1.65\ (0.82,\ 3.31)\\ 0.67\ (0.51,\ 0.88)\\ 1.48\ (1.07,\ 2.05)\\ \end{array}$
AochaLima 2004 Viret F 2004 Lunningham D 2005 Hermann 2005 Jouvet 2005 Dettle 2005 Poplin 2006 Subtotal (95% CI) Fotal events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z= 14 grade 3 or 4 anaemia Berlin 2002 Scheithauer 2003 Li 2004 RochaLima 2004 Viret F 2004 Cunningham D 2005 Di Costanzo 2005	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ \text{combin}, 366 (gem alou \\ ^2=81.15, d.f.=14 (P<\\ =2.38 (P=0.02)\\ \end{array}$	$\begin{array}{c} 16/41\\ 29/266\\ 30/153\\ 43/156\\ 35/273\\ 14/47\\ 11/69\\ 92/279\\ 1911\\ \text{ne})\\ 0.00001), \ l^2 = 82.7\%\\ \end{array}\\ \\ \begin{array}{c} 16/158\\ 2/53\\ 0/39\\ 2/25\\ 22/169\\ 12/41\\ 5/266\\ 3/49\\ \end{array}$		8.18 8.36 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44 2.20	$\begin{array}{c} 1.46\ (0.92\ 2.33)\\ 1.55\ (1.00,\ 2.39)\\ 1.12\ (0.72,\ 1.73)\\ 0.74\ (0.50,\ 1.10)\\ 3.51\ (2.51,\ 4.92)\\ 2.78\ (1.76,\ 4.38)\\ 1.65\ (0.82,\ 3.31)\\ 0.67\ (0.51,\ 0.88)\\ 1.48\ (1.07,\ 2.05)\\ \end{array}$
AochaLima 2004 /iret F 2004 /iret F 2005 Jermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Fost al events: 520 (gem C Fest for heterogeneity: χ' Fest for overall effect: Z= 04 grade 3 or 4 anaemia Berlin 2002 Colucci 2002 Scheithauer 2003 i 2004 RochaLima 2004 Uriet F 2004 Cunningham D 2005 Di Costanzo 2005 Hermann 2005	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gem alor\\ 2=81.15, d.f.=14 (P<=2.38 (P=0.02)\\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 28/173\\ 16/42\\ 3/267\\ 1/41\\ 9/155\\ \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), / ² = 82.7% 16/158 2/53 0/39 2/25 22/169 12/41 5/266 3/49 9/153	* * * * * * * * * * *	8.18 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44 2.20 7.69	$\begin{array}{c} 1.46 \left(0.92, 2.33 \right) \\ 1.55 \left(1.00, 2.39 \right) \\ 1.12 \left(0.72, 1.73 \right) \\ 0.74 \left(0.50, 1.10 \right) \\ 3.51 \left(2.51, 4.92 \right) \\ 2.78 \left(1.76, 4.38 \right) \\ 1.65 \left(0.82, 3.31 \right) \\ 0.67 \left(0.51, 0.88 \right) \\ 1.48 \left(1.07, 2.05 \right) \\ \end{array}$
RochaLima 2004 /iret F 2004 /iret F 2005 Hermann 2005 Journingham D 2005 Hermann 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Total events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z= 14 grade 3 or 4 anaemia Berlin 2002 Colucci 2002 Scheithauer 2003 Li 2004 RochaLima 2004 /iret F 2004 Dunningham D 2005 Di Costanzo 2005 Hermann 2005 Jouvet 2005	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gen aloo)\\ e^2=81.15, d.f.=14 (P<\\ =2.38 (P=0.02)\\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 28/173\\ 16/42\\ 3/267\\ 1/41\\ 9/155\\ 10/157\\ \end{array}$	$\begin{array}{c} 16/41\\ 29/266\\ 30/153\\ 43/156\\ 35/273\\ 14/47\\ 11/69\\ 92/279\\ 1911\\ ne)\\ 0.00001), \ l^2 = 82.7\%\\ \end{array}$		8.18 8.36 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44 2.20 7.69 9.00	$\begin{array}{c} 1.46 \ (0.92, 2.33) \\ 1.55 \ (1.00, 2.39) \\ 1.12 \ (0.72, 1.73) \\ 0.74 \ (0.50, 1.10) \\ 3.51 \ (2.51, 4.92) \\ 2.78 \ (1.76, 4.38) \\ 1.65 \ (0.82, 3.31) \\ 0.67 \ (0.51, 0.88) \\ 1.48 \ (1.07, 2.05) \\ \end{array}$
AochaLima 2004 /iret F 2004 /iret F 2005 Jermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Fost al events: 520 (gem C Fest for heterogeneity: χ' Fest for overall effect: Z= 04 grade 3 or 4 anaemia Berlin 2002 Colucci 2002 Scheithauer 2003 i 2004 RochaLima 2004 Uriet F 2004 Cunningham D 2005 Di Costanzo 2005 Hermann 2005	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gem alor\\ 2=81.15, d.f.=14 (P<=2.38 (P=0.02)\\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 28/173\\ 16/42\\ 3/267\\ 1/41\\ 9/155\\ \end{array}$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), / ² = 82.7% 16/158 2/53 0/39 2/25 22/169 12/41 5/266 3/49 9/153		8.18 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44 2.20 7.69	$\begin{array}{c} 1.46 \left(0.92, 2.33 \right) \\ 1.55 \left(1.00, 2.39 \right) \\ 1.12 \left(0.72, 1.73 \right) \\ 0.74 \left(0.50, 1.10 \right) \\ 3.51 \left(2.51, 4.92 \right) \\ 2.78 \left(1.76, 4.38 \right) \\ 1.65 \left(0.82, 3.31 \right) \\ 0.67 \left(0.51, 0.88 \right) \\ 1.48 \left(1.07, 2.05 \right) \\ \end{array}$
AochaLima 2004 Viret F 2004 Lunningham D 2005 Hermann 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Total events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z= 204 grade 3 or 4 anaemia Berlin 2002 Scheithauer 2003 1 2004 NochaLima 2004 Viret F 2004 Lunningham D 2005 Di Costanzo 2005 Hermann 2005 Jouvet 2005 Dettle 2005 Reni 2005 Stathoupoulos 2005	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ 50mbin), 366 (gem alou\\ ^2=81.15, d.f.=14 (P<=2.38 (P=0.02)\\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 28/173\\ 16/42\\ 3/267\\ 1/41\\ 9/155\\ 10/157\\ 38/273\\ 7/52\\ 2/57\\ \end{array}$	$\begin{array}{c} 16/41\\ 29/266\\ 30/153\\ 43/156\\ 35/273\\ 14/47\\ 11/69\\ 92/279\\ 1911\\ ne)\\ 0.00001), \ l^2 = 82.7\%\\ \end{array}$	***** ********************************	8.18 8.36 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44 2.20 7.69 9.00 9.05 5.78 3.25	$\begin{array}{c} 1.46 \ (0.92, 2.33) \\ 1.55 \ (1.00, 2.39) \\ 1.12 \ (0.72, 1.73) \\ 0.74 \ (0.50, 1.10) \\ 3.51 \ (2.51, 4.92) \\ 2.78 \ (1.76, 4.38) \\ 1.65 \ (0.82, 3.31) \\ 0.67 \ (0.51, 0.88) \\ 1.48 \ (1.07, 2.05) \\ \end{array}$
AcchaLima 2004 Viret F 2004 Viret F 2004 Junningham D 2005 Jermann 2005 Jouvet 2005 Jouret 2005 Stathoupoulos 2005 Joplin 2006 Subtotal (95% CI) Total events: 520 (gem c Fest for heterogeneity: χ'_i Fest for overall effect: Z= 04 grade 3 or 4 anaemia Berlin 2002 Scheithauer 2003 J. 2004 AcchaLima 2004 Viret F 2004 Cunningham D 2005 Di Costanzo 2005 Hermann 2005 Joutet 2005 Stathoupoulos 2005 Hermann 2005 Joutet 2005 Stathoupoulos 2005	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ \text{combin}, 366 (gem aloo 2^2=81.15, d.f.=14 (P<=2.38 (P=0.02))\\ \hline \\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 2/40\\ 2/21\\ 2/41\\ 3/267\\ 1/41\\ 9/155\\ 10/157\\ 38/273\\ 7/52\\ 2/57\\ 13/95\\ \end{array}$	$\begin{array}{c} 16/41\\ 29/266\\ 30/153\\ 43/156\\ 35/273\\ 14/47\\ 11/69\\ 92/279\\ 1911\\ ne)\\ 0.00001), \ l^2 = 82.7\%\\ \end{array}$	• • • • • • • • • • • • • • • • • • •	8.18 8.36 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44 2.20 7.69 9.00 9.05 5.78 3.25 8.77	$\begin{array}{c} 1.46 \left(0.92, 2.33 \right) \\ 1.55 \left(1.00, 2.39 \right) \\ 1.12 \left(0.72, 1.73 \right) \\ 0.74 \left(0.50, 1.10 \right) \\ 3.51 \left(2.51, 4.92 \right) \\ 2.78 \left(1.76, 4.38 \right) \\ 1.65 \left(0.82, 3.31 \right) \\ 0.67 \left(0.51, 0.88 \right) \\ 1.48 \left(1.07, 2.05 \right) \\ \end{array}$
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AochaLima 2004 Viret F 2004 Viret F 2004 Lunningham D 2005 Hermann 2005 Joutet 2005 Dettle 2005 Stathoupoulos 2005 Poplin 2006 Subtotal (95% CI) Total events: 520 (gem c Fest for heterogeneity: χ' Fest for overall effect: Z= P4 grade 3 or 4 anaemia Berlin 2002 Scheithauer 2003 J 2004 AochaLima 2004 Viret F 2004 Cunningham D 2005 Di Costanzo 2005 Vertle 2005 Stathoupoulos 2005 Jerlin 2005 Di Costanzo 2005 Stathoupoulos 2005 Stathoupoulos 2005 Jerlin 2005 Subtotal (95% CI)	$\begin{array}{c} 65/173\\ 24/42\\ 45/267\\ 34/155\\ 32/157\\ 123/273\\ 43/52\\ 15/57\\ 61/276\\ 1907\\ combin), 366 (gem alor\\ 2=81.15, d.f.=14 (P<=2.38 (P=0.02)\\ 16/158\\ 3/51\\ 2/40\\ 2/21\\ 28/173\\ 16/42\\ 3/267\\ 1/41\\ 9/155\\ 10/157\\ 38/273\\ 7/52\\ 2/57\\ 13/95\\ 17/276\\ 1858\\ combin), 141 (gem alor\\ 2=25.52, d.f.=14 (P<2)\\ 3/25\\ 2=25.52, d.f.=14 (P<2)\\ 3/25\\ 2=25.52, d.f.=14 (P<2)\\ 3/25\\$	16/41 29/266 30/153 43/156 35/273 14/47 11/69 92/279 1911 ne) 0.00001), / ² = 82.7% 16/158 2/53 0/39 2/25 22/169 12/41 5/266 3/49 9/153 17/156 8/273 4/47 3/69 10/95 28/279 1872 ne)	**** ***** ***************************	8.18 8.38 8.36 8.62 9.04 8.23 6.55 9.38 100.00 9.91 3.27 1.29 2.93 11.36 10.36 4.44 2.20 7.69 9.00 9.05 5.78 3.25 5.78 3.25 5.77 10.71	$\begin{array}{c} 1.46 \ (0.92, 2.33) \\ 1.55 \ (1.00, 2.39) \\ 1.12 \ (0.72, 1.73) \\ 0.74 \ (0.50, 1.10) \\ 3.51 \ (2.51, 4.92) \\ 2.78 \ (1.76, 4.38) \\ 1.65 \ (0.82, 3.31) \\ 0.67 \ (0.51, 0.88) \\ 1.48 \ (1.07, 2.05) \\ \end{array}$

Favours gem combin Favours gem alone

Legend: *n*=number of toxicity events *N*=total number of patients

Figure 6 Results for gemcitabine vs gemcitabine-based combination chemotherapy - haematological toxicity.

Previous meta-analyses of secondary end points evaluating gemcitabine-based combinations vs gemcitabine employed differing survival analyses methodology (Liang, 2005; Heinemann *et al*, 2006a; Milella *et al*, 2006; Xie *et al*, 2006a). In contrast to these reports, our survival analyses were conducted using the HR, which is the ideal measure for time-to-event analyses, as it accounts for both censoring of data and the time it takes for the event (such as death or progression) to occur (Parmar *et al*, 1998).

For gemcitabine-based chemotherapy vs gemcitabine alone, our findings of improved PFS/TTP are in agreement with the metaanalyses of Xie *et al* (2006b). Better ORR with the combination regimens was in keeping with the studies of Xie *et al* and Milella

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Study or subcategory	Gem combin n/N	Gem alone n/N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl
05 grade 3 or 4 nausea					
Berlin 2002	7/158	5/158		5.90	1.40 (0.45, 4.32)
RochaLima 2004	29/173	17/169	+	20.29	1.67 (0.95, 2.92)
Viret F 2004	6/42	2/41	+	2.39	2.93 (0.63, 13.68)
Hermann 2005	8/155	5/153	-+	5.94	1.58 (0.53, 4.72)
Louvet 2005	16/157	9/156	t=-	10.65	1.77 (0.80, 3.88)
Oettle 2005 Reiss 2005	9/273 32/230	8/273 17/236		9.44 19.80	1.13 (0.44, 2.87) 1.93 (1.10, 3.38)
Stathoupoulos 2005	1/57	2/69		2.13	0.61 (0.06, 6.51)
Poplin 2006	42/276	20/279	-	23.47	2.12 (1.28, 3.52)
Subtotal (95% CI)	1521	1534	•	100.00	1.77 (1.37, 2.29)
Total events: 150 (gem con Test for heterogeneity: χ^2 = Test for overall effect: Z=4	=293, d.f. = 16 (<i>P</i> =0.94), <i>I</i> ² =0%			
06 grade 3 or 4 vomiting					
Berlin 2002	11/158	13/158		17.32	0.85 (0.39, 1.83)
Abou-Alfa 2006	19/175	9/174		12.02	2.10 (0.98, 4.51)
RochaLima 2004	24/173	14/169		18.87	1.67 (0.90, 3.13)
Viret F 2004	3/42	1/41		1.35	2.93 (0.32, 27.02)
Cunningham D 2005	3/267	5/266		6.67	0.60 (0.14, 2.48)
Hermann 2005	6/155	3/153		4.02	1.97 (0.50, 7.75)
Louvet 2005 Oettle 2005	14/157 9/273	5/156 10/273		6.68 13.32	2.78 (1.03, 7.54) 0.90 (0.37, 2.18)
Stathoupoulos 2005	1/57	1/69		1.21	1.21 (0.08, 18.93)
Poplin 2006	33/276	14/279		18.55	2.38 (1.30, 4.35)
Subtotal (95% CI)	1733	1738	•	100.00	1.64 (1.24, 2.16)
Total events: 123 (gem con Test for heterogeneity: χ^2 = Test for overall effect: Z=3	=9.86, d.f. =9 (P=0.36)	, <i>I</i> ² =8.8%			
07 grade 3 or 4 diarrhoea					
Berlin 2002	16/158	6/158		16.76	2.76 (1.07, 6.64)
Colucci 2002	2/51	0/53		1.37	5.19 (0.26, 105.59)
Scheithauer 2003	2/40	0/39		1.41	4.88 (0.24, 98.47)
Ohkawa 2004	1/10	0/9		1.46	2.73 (0.12, 59.57)
RochaLima 2004	32/173	3/169		8.48	10.42 (3.25, 33.38)
Cunningham D 2005	3/267 0/41	3/266	-	8.39	1.00 (0.20, 4.89)
Di Costanzo 2005 Hermann 2005	8/155	0/49 3/153		8.43	Not estimable 2.63 (0.71, 9.74)
Louvet 2005	9/157	2/156		5.60	4.47 (0.98, 20.36)
Oettle 2005	8/273	2/273		5.59	4.00 (0.86, 18.67)
Reiss 2005	9/230	9/236	-+-	24.81	1.03 (0.41, 2.54)
Reni 2005	1/52	0/47		1.47	2.72 (0.11, 65.12)
Stathoupoulos 2005	2/57	2/69		5.05	1.21 (0.18, 8.33)
Heinemann 2006	3/95	4/95		11.17	0.75 (0.17, 3.26)
Subtotal (95% CI) Total events: 96 (gem com	1759 (gem alone)	1772	•	100.00	2.73 (1.87, 3.98)
Test for heterogeneity: χ^2 =		(6) $l^2 = 23.7\%$			
Test for overall effect: $Z=5$		0), 1 = 20.1 /0			
08 grade 3 or 4 stomatitis	0// 50	0/152		00.05	0.07 (0.11.0.04)
Berlin 2002 Scheithauer 2003	2/158	3/158 0/39		29.65	0.67 (0.11, 3.94)
Scheithauer 2003 Cunningham D 2005	1/40 0/267	0/266		5.00	2.93 (0.12, 69.74) Not estimable
Hermann 2005	0/155	1/153	· · · · · · · · · · · · · · · · · · ·	14.92	0.33 (0.01, 8.02)
Oettle 2005	8/273	3/273		29.65	2.67 (0.72, 9.95)
Reni 2005	7/52	2/47		20.77	3.16 (0.69, 14.48)
Stathoupoulos 2005	0/57	0/69			Not estimable
Subtotal (95% CI) Total events: 18 (gem com		1005	•	100.00	1.84 (0.86, 3.92)
Test for heterogeneity: χ^2 = Test for overall effect: Z=1		, / = 0 /0			
				+	
	0.001 0.01 0.1 1 10 100 1000				
logondin number -f	toviaity avents	Favours	gem combin Favours ger	n alone	
Legend: n=number of	loxicity events				

N=total number of patients

Figure 7 Results for gemcitabine vs gemcitabine-based combination chemotherapy – gastrointestinal toxicity.

et al (Xie *et al*, 2006b), while increased toxicity profile was noted by Xie *et al* (2006b). The meta-analyses that examined gemcitabine plus a platinum agent *vs* gemcitabine alone found better PFS/TTP in the combination arm (Xie *et al*, 2006a; Heinemann *et al*, 2007), significant improvement in ORR (Heinemann *et al*, 2007) and greater toxicity (Xie *et al*, 2006a).

We have done our utmost to cover most reported end points in the randomised controlled trials. We could not address quality of life due to the different methods used for reporting quality of life. Although we have pooled the response rate and adverse events data across studies to permit a clinically relevant analysis, reporting of these parameters varied. Response rates were reported using clinical parameters, the WHO and RECIST criteria, whereas the CTC, WHO and ECOG scales were used for toxicity data.

To conclude, there is insufficient evidence to suggest a TTP, response rate and toxicity advantage in administering 5FU in combination with other chemotherapy agents over 5FU alone. There is a small but significant TTP/PFS advantage, as well as improved response rate, with gemcitabine-based combinations, and this provides a justification for the use of these agents, despite their greater toxicity. An area for further randomised controlled trials to assess is which gemcitabine-based combination chemotherapy regimens are least toxic, while retaining all the other advantages of the combination approach.



ACKNOWLEDGEMENTS

This study was supported by Cancer Research UK.

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