Evaluation bias in objective response rate and disease control rate between blinded independent central review and local assessment: a study-level pooled analysis of phase III randomized control trials in the past seven years

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Background: In previous studies, complete-case implementation of blind independent central review has been considered unnecessary based on no sign of systematic bias between central and local assessments. In order to further evaluate its value, this study investigated evaluation status between both assessments in phase III trials of anti-cancer drugs for non-hematologic solid tumors.

Methods: Eligible trials were searched in PubMed with the date of Jan 1, 2010 to Jun 30, 2017. We compared objective response rate (ORR) and disease control rate (DCR) between central and local assessments by study-level pooled analysis and correlation analysis. In pooled analysis, direct comparison was measured by the odds ratio (OR) of central-assessed response status to local-assessed response status; to investigate evaluation bias between central and local assessments, the above calculated OR between experimental (exp-) and control (con-) arms were compared, measured by the ratio of OR.

Results: A total of 28 included trials involving 17,466 patients were included (28 with ORR, 16 with DCR). Pooled analysis showed central assessment reported lower ORR and DCR than local assessment, especially in trials with open-label design, central-assessed primary endpoint, and positive primary endpoint outcome, respectively. However, this finding could be found in both experimental [exp-ORR: OR=0.81 (95% CI: 0.76–0.87), P<0.01, I²=11%; exp-DCR: OR=0.90 (0.81–1.01), P=0.07, I²=42%] and control arms [con-ORR: OR=0.79 (0.72–0.85), P<0.01, I²=17%; con-DCR: OR=0.94 (0.86–1.02), P=0.14, I²=12%]. No sign of evaluation bias between two assessments was indicated through further analysis [ORR: ratio of OR=1.02 (0.97–1.07), P=0.42, I²=0%; DCR: ratio of OR=0.98 (0.93–1.03), P=0.37, I²=0%], regardless of mask (open/blind), sample size, tumor type, primary endpoint (central-assessed/local-

assessed), and primary endpoint outcome (positive/negative). Correlation analysis demonstrated a high-degree concordance between central and local assessments (exp-ORR, con-ORR, exp-DCR, con-DCR: r>0.90, P<0.01). **Conclusions:** Blind independent central review remained irreplaceable to monitor local assessment, but its complete-case implementation may be unnecessary.

Keywords: Blind independent central review; randomized control trials (RCTs); tumor assessment

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Introduction

The assessment for current response and progression endpoints, such as objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and time-to-progression (TTP), has to be based on investigators' professional knowledge and experience. Namely, their assessment could be influenced by subjective factors, including failure to diagnose new lesions, variability during tumor measurement, target-lesion selection, and different interpretations on non-target or immeasurable lesions (1). In addition, the knowledge of investigators regarding treatment assignment would influence their assessment as well, especially in trials with open-labelled design (2). The above subjective factors may impact the assessment for trial endpoints, and subsequently the expected outcome will over- or underestimate the true effect of the treatments from experimental arm (exp) to control arm (con), possibly causing systematic bias (3). Therefore, blinded independent central review has been increasingly implemented in recent phase III oncological randomized control trials (RCTs). During implementation, all imaging examinations are acquired as part of protocol and reviewed by independent physicians who are blinded to treatment assignments and various information of patients (4), in order to detect and control potential bias from local investigators.

In current stage, however, systematic bias between central and local assessments in phase III RCTs is out of evidence from studies. In 2011, Amit *et al.* conducted the first study on systematic bias according to 27 phase III RCTs (5). This study compared the treatment effects of PFS between central and local assessments through metaanalysis, and found no systematic bias. No evidence of systematic bias has been further verified by two subsequent meta-analyses based on 28 and 61 RCTs, respectively (6,7). Nevertheless, no evidence of systematic bias at the level of treatment effects, does not mean the evaluation concordance between central and local assessments when directly comparing response status. Further, the reliability of local assessment, as well as unnecessary implementation of central assessment could not be concluded only based on no evidence of systematic bias. For example, when comparing with central reviewers, if in experimental arm the local investigators overestimated the endpoints but in control arm they did not overestimate or even underestimated the endpoints, evaluation bias would possibly occur, even there might be no systematic bias when comparing the treatment effects between central and local assessments in the same study. Based on this assumption, central review is still valuable in clinical trials.

In order to verify the value of central assessment to local assessment, in this literature review and analyses, we investigated response status of ORR and DCR between central and local assessments among recently-published phase III RCTs on all non-hematologic solid tumors.

Methods

Search strategy and study selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (8), a PubMed search was conducted by JRZ using the dates of Jan 1, 2010 to Jun 30, 2017. The retrieval formula was: ("neoplasms"(MeSH Terms) OR "neoplasms"(All Fields) OR "cancer"(All Fields)) AND random* AND ("Phase 3" OR "Phase III") (English) (Human) (Clinical Trial, Phase III). Articles of inappropriate publication types were excluded, including reviews, systematic reviews and/or meta-analyses, guidelines, and commentaries.

Eligible articles were regarding the therapeutic efficacy of anti-cancer agents in phase III RCTs for patients with non-hematologic solid tumors. In these articles, imaging assessment for ORR and/or DCR was conducted by both central reviewers and local investigators. As some authors reported their data in more than one article, we used the name and/or clinicaltrials.gov identifier (NCT number) of eligible RCTs as search terms respectively to re-search PubMed (without the time interval limitation), to find out if there were more available articles of those trials. Endnote X7 (Thomson Reuters, New York, USA) was used in above process.

Data extraction

The process of data extraction was carried out independently and double-blindly by three reviewers working in pairs (Jianrong Zhang respectively blind to Yiyin Zhang and Shiyan Tang; in blocks of 17 articles allocated at random; discrepancies resolved by Wenhua Liang). To ensure consistency between reviewers, we used a same data extraction form, piloted the data extraction by using a sample of 16 included trials, and had discussion before and during the extraction process to confer how to properly extract and interpret the data.

Following characteristics of each trial were extracted: author, year, NCT number, mask (open/blind), sample size, tumor type, primary endpoint (central-assessed/localassessed/other), and primary endpoint outcome (positive/ negative/indeterminate). We also extracted ORR and DCR from both central and local assessments.

Statistical analysis

First, we directly compared response status between two assessments in both experimental and control arms by pooled analysis with Mantel-Haenszel method. The measurement was odds ratio (OR), defined as the ratio of central-assessed response status to local-assessed response status: ratio greater than 1 indicated central reviewers overestimated response status compared with local assessment; significant discrepancy between two assessments was shown if P<0.05. Second, we investigated evaluation bias between central and local assessments through pooled analysis with Inverse Variance method. In this procedure, above calculated ORs between experimental and control arms were compared, and the ratio of OR was the measure: regardless higher or lower than 1, P<0.05 indicated significant evaluation bias. During above two procedures, we also made subgroup analysis based on trial characteristics: mask, sample size (based on median value of all included trials), tumor type, and primary endpoint with its outcome. All mentioned procedures were conducted in Review Manager 5.3 (The Cochrane Collaboration, London, England), with initially fixed-effect model. If the corresponding p value for heterogeneity was less than 0.05 or the I² index (I²) was over 50%, we used random-effect model, in order to reduce the heterogeneity effect.

In order to investigate the concordance between two assessments, we conducted correlation analysis by using SPSS Version 23 (SPSS Software, Chicago, USA). The test for normality was completed first, followed by correlation analysis if normal distribution was indicated, we estimated the correlation by the Pearson correlation coefficient; if not, Spearman correlation was applied. Significant correlation was indicated when p value was less than 0.05.

Results

Trial searching and characteristics

Based on article identification and selection, we totally included 28 trials from 35 articles (9-30), involving 17,466 randomly assigned patients (*Figure 1*) (31-43).

Summary and detailed characteristics are presented in *Table 1* and *Table S1*. All 28 included trials reported exp- and con-ORR from two assessments, and 16 trials reported exp- and con-DCR.

Direct comparison of response status between central and local assessments

Pooled analysis presented lower response frequency of ORR and DCR in central assessment compared with local assessment (*Table 2, Figures 2* and *3*), regardless in experimental [ORR: OR=0.81 (95% CI: 0.76–0.87), P<0.01, I²=11%; DCR: OR=0.90 (0.81–1.01), P=0.07, I²=42%] or control arm [ORR: OR=0.79 (95% CI: 0.72–0.85), P<0.01, I²=17%; DCR: OR=0.94 (0.86–1.02), P=0.14, I²=12%]. During above comparison, there was no significant interaction effect of therapy allocation (experimental arm versus control arm) in both ORR (P=0.56, I²=0%) and DCR (P=0.42, I²=0%).

In subgroup analysis (*Table 2*), the discrepancy between two assessments in trials with open-label design, positive

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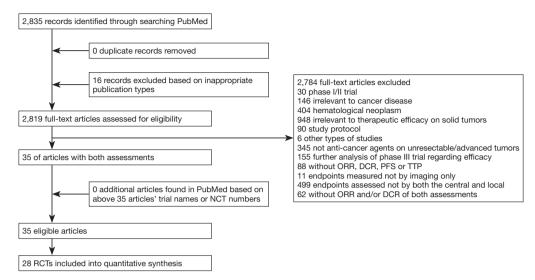


Figure 1 Flow chart of study identification and selection.

Table 1 Summary characteristics of included trials

Trial-level characteristics	Trial (N=28)	Patient (N=17,466)
Mask		
Open	22	14,133
Blind [†]	6	3,333
Sample size		
Max	-	1,110
Median	-	618.5
Min	-	185
Tumor type		
NSCLC	8	5,172
Breast	7	4,452
Renal-cell	6	3,917
Ovarian	3	1,985
Other [‡]	4	1,940
Primary endpoint		
Central-assessed [§]	16	10,668
Other ¹	7	4,465
Local-assessed ^a	5	2,333
Outcome		
Positive	18	11,328
Indeterminate ^b	1	185
Negative	9	5,953

[†], 5 double blind, and 1 single blind; [‡], 2 melanoma, 1 gastrointestinal stromal tumor, 1 pancreatic tumor; [§], 1 central-assessed objective response rate, and 15 central-assessed progression-free survival; ¹, 6 overall survival and 1 unknown-assessed objective response rate; ^a, 5 local-assessed progression-free survival; ^b, in one study, objective response rate (ORR) was the primary endpoint: significant difference in central review (P=0.03), not in local assessment (P=0.05). We consider "indeterminate" because we are unable to determine whether central- or local-assessed ORR was the primary endpoint (24). NSCLC, non-small cell lung cancer; Breast, breast cancer; Renal-cell, renal-cell carcinoma; Ovarian, ovarian cancer.

		Exp-ORR (central/local)	al/local)			Con-ORR (central/local)	al/local	<u> </u>		Exp-DCR (central/local)	il/local)			Con-DCR (central/local)	l/local)	
summary/subgroup -	S (n)	OR (95% CI)	_ ₽	I ^{2‡§} (%)	S (n)	OR (95% CI)	Ъ	l ^{2‡§} (%)	S (n)	OR (95% CI)	P ^a	I ^{2‡§} (%)	S (n)	OR (95% CI)	Pa	l ^{2‡§} (%)
Summary	28	0.81 (0.76–0.87) <0.01	<0.01	1	28	0.79 (0.72–0.85)	<0.01	17	16	0.90 (0.81–1.01)	0.07	42	16	0.94 (0.86–1.02)	0.14	12
Mask																
Open	22	0.80 (0.74–0.87) <0.01	<0.01	0	22	0.76 (0.69–0.83)	<0.01	75*	12	0.88 (0.77–1.02)	0.08	0	12	0.93 (0.85–1.02)	0.15	0
Blind	9	0.86 (0.73–1.01) 0.07	0.07		9	0.95 (0.78–1.17)	0.64		4	0.98 (0.83–1.15)	0.77		4	0.96 (0.80–1.16)	0.70	
Sample size																
> median (618.5)	14	0.81 (0.74–0.88) <0.01	<0.01	0	14	0.81 (0.73–0.90)	<0.01	0	10	0.89 (0.78–1.02)	0.10	0	10	0.96 (0.87–1.05)	0.34	0
< median (618.5)	14	0.82 (0.73–0.91) <0.01	<0.01		14	0.75 (0.65–0.86)	<0.01		9	0.93 (0.76–1.15)	0.52		9	0.88 (0.73–1.06)	0.17	
Tumor type																
NSCLC	œ	0.76 (0.67–0.86) <0.01	<0.01	0	œ	0.78 (0.67–0.91)	<0.01	19	4	0.95 (0.82–1.11)	0.53	62*	4	0.95 (0.80–1.13)	0.57	61*
Breast	7	0.88 (0.76–1.01) 0.07	0.07		7	0.70 (0.59–0.83)	<0.01		5	0.97 (0.75–1.27)	0.85		2J	0.96 (0.82–1.12)	0.58	
Renal-cell	9	0.82 (0.71–0.95) <0.01	<0.01		9	0.81 (0.68–0.97)	0.02		4	0.72 (0.61–0.85)	<0.01		4	0.81 (0.70–0.94)	<0.01	
Ovarian	ო	0.73 (0.59–0.90) <0.01	<0.01		ო	0.78 (0.62–0.97)	0.03		-	1.09 (0.83–1.44)	0.52		-	1.34 (1.02–1.75)	0.04	
Others	4	0.88 (0.73-1.06)	0.17		4	0.98 (0.77-1.26)	06.0		0	1.10 (0.73-1.64)	0.65		0	1.00 (0.69-1.46)	1.00	
Primary endpoint																
Central-assessed	16	0.80 (0.73–0.87) <0.01	<0.01	53	16	0.75 (0.68–0.82)	<0.01	55	10	0.86 (0.73–1.02)	0.08	22	10	0.88 (0.80–0.98)	0.02	49
Others	7	0.77 (0.67–0.89) <0.01	<0.01		7	0.94 (0.77–1.15)	0.58		5	0.95 (0.83–1.08)	0.43		5	1.02 (0.87–1.19)	0.82	
Local-assessed	Ð	0.96 (0.81–1.15)	0.68		2	0.82 (0.65–1.03)	0.08		-	1.00 (0.97–1.03)	0.96		-	1.20 (0.83–1.73)	0.34	
Primary outcome																
Positive	18	0.80 (0.73–0.87) <0.01	<0.01	0	18	0.74 (0.66–0.82)	<0.01	37	10	0.88 (0.77–1.00)	0.05	0	10	0.89 (0.79–0.99)	0.03	31
Indeterminate	-	0.79 (0.36–1.72)	0.55		-	0.64 (0.22–1.89)	0.42		F	0.83 (0.46–1.51)	0.65		-	0.87 (0.48–1.58)	0.65	
Negative	o	0.84 (0.74–0.94) <0.01	<0.01		o	0.85 (0.75–0.97)	0.01		5	0.97 (0.77–1.22)	0.77		2	1.03 (0.90–1.18)	0.68	
$^{\rm t}$, P value for the comparison between central an synthesis; $^{\rm s}$ $^{\rm l^2}$ in subgroup was for subgroup differ	mparis group	¹ , P value for the comparison between central an synthesis; [§] , 1 ² in subgroup was for subgroup differ	ntral and p differe	local a nce, reț	presen	d local assessments; P<0.05 indicated significant discrepancy; [‡] , I ² in summary outcome was for heterogeneity of data ence, representing the interaction effects between the elements of each subgroup factor; [*] , significant interaction effects	n effec	significa ts betwee	ant disc en the	d local assessments; P<0.05 indicated significant discrepancy; [‡] , l ² in summary outcome was for heterogeneity of data ence, representing the interaction effects between the elements of each subgroup factor; [*] , significant interaction effects	summa subgr	iry outc oup fac	some v stor; *,	vas for heterogen significant interac	eity of tion eff	data fects

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	ORR (Cer		ORR (L			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
5.1.1 Exp-ORR							
NCT00019682	14	91	17	91	0.5%	0.79 [0.36, 1.72]	
NCT00112294	87	338	93	338	2.2%	0.91 [0.65, 1.28]	
NCT00113607	93	337	130	337	3.1%	0.61 [0.44, 0.84]	
NCT00262990	64	412	73	412	2.0%	0.85 [0.59, 1.23]	
NCT00337103	61	554	89	554	2.6%	0.65 [0.46, 0.92]	
NCT00388726	57	508	62	508	1.8%	0.91 [0.62, 1.33]	
NCT00391092	164	216	160	216	1.3%	1.10 [0.71, 1.71]	
							_
NCT00393939	148	296	156	296	2.5%	0.90 [0.65, 1.24]	
NCT00434642	181	242	190	242	1.6%	0.81 [0.53, 1.24]	
NCT00435409	40	221	56	221	1.5%	0.65 [0.41, 1.03]	
NCT00449033	89	452	107	452	2.8%	0.79 [0.58, 1.09]	
NCT00540514	170	521	198	521	4.3%	0.79 [0.61, 1.02]	
NCT00656136	52						
		390	68	390	1.9%	0.73 [0.49, 1.08]	
NCT00678392	70	361	70	361	1.8%	1.00 [0.69, 1.45]	T
NCT00720941	171	557	186	557	4.2%	0.88 [0.69, 1.14]	-
NCT00785785	139	324	132	324	2.5%	1.09 [0.80, 1.49]	+-
NCT00844649	99	431	126	431	3.2%	0.72 [0.53, 0.98]	
NCT00863655	61	485	61	485	1.7%	1.00 [0.68, 1.46]	
NCT00883779	99	226	97	226	1.8%	1.04 [0.71, 1.50]	T
NCT00949650	129	230	159	230	2.3%	0.57 [0.39, 0.84]	
NCT01030783	86	260	92	260	2.0%	0.90 [0.63, 1.30]	-+
NCT01121393	162	242	180	242	1.9%	0.70 [0.47, 1.03]	
NCT01223027	11	284	18	284			
					0.6%	0.60 [0.28, 1.28]	<u>_</u> _
NCT01227889	93	187	99	187	1.6%	0.88 [0.59, 1.32]	T
NCT01265901	73	204	95	204	2.0%	0.64 [0.43, 0.95]	
NCT01523587	22	398	43	398	1.3%	0.48 [0.28, 0.82]	
NCT01865747	57	330	78	330	2.1%	0.67 [0.46, 0.99]	
NCT02253459	109				2.1%		
	109	270	107	270		1.03 [0.73, 1.46]	
Subtotal (95% CI)		9367		9367	59.0 %	0.81 [0.76, 0.87]	'
Total events	2601		2942				
5.1.2 Con-ORR			_				
NCT00019682	6	94	9	94	0.3%	0.64 [0.22, 1.89]	
	6 58	94 338	9 76	94 338	0.3% 2.0%	0.64 [0.22, 1.89] 0.71 [0.49, 1.05]	
NCT00019682							
NCT00019682 NCT00112294	58	338	76	338	2.0%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990	58 63 33	338 335 417	76 89 36	338 335 417	2.0% 2.3% 1.1%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103	58 63 33 63	338 335 417 548	76 89 36 109	338 335 417 548	2.0% 2.3% 1.1% 3.1%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726	58 63 33 63 10	338 335 417 548 254	76 89 36 109 16	338 335 417 548 254	2.0% 2.3% 1.1% 3.1% 0.5%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726 NCT00391092	58 63 33 63 10 136	338 335 417 548 254 208	76 89 36 109 16 144	338 335 417 548 254 208	2.0% 2.3% 1.1% 3.1% 0.5% 1.6%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726	58 63 33 63 10	338 335 417 548 254	76 89 36 109 16	338 335 417 548 254	2.0% 2.3% 1.1% 3.1% 0.5%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726 NCT00391092	58 63 33 63 10 136	338 335 417 548 254 208	76 89 36 109 16 144	338 335 417 548 254 208	2.0% 2.3% 1.1% 3.1% 0.5% 1.6%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726 NCT00381092 NCT00391092 NCT00393939	58 63 33 63 10 136 113	338 335 417 548 254 208 297	76 89 36 109 16 144 130	338 335 417 548 254 208 297	2.0% 2.3% 1.1% 3.1% 0.5% 1.6% 2.6%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726 NCT00391092 NCT0039399 NCT00434642 NCT00435409	58 63 63 10 136 113 130 36	338 335 417 548 254 208 297 242 221	76 89 109 16 144 130 139 45	338 335 417 548 254 208 297 242 221	2.0% 2.3% 1.1% 3.1% 0.5% 1.6% 2.6% 2.1% 1.2%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00387103 NCT00381092 NCT00391092 NCT00393939 NCT00434642 NCT004356409 NCT004436409	58 63 33 10 136 113 130 36 108	338 335 417 548 254 208 297 242 221 452	76 89 109 16 144 130 139 45 100	338 335 417 548 254 208 297 242 221 452	2.0% 2.3% 1.1% 3.1% 0.5% 1.6% 2.6% 2.1% 1.2% 2.5%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.64 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0038726 NCT00389726 NCT00391092 NCT0039939 NCT00434642 NCT0043642 NCT00435409 NCT00449033 NCT00540514	58 63 33 10 136 113 130 36 108 132	338 335 417 548 254 208 297 242 221 452 531	76 89 109 16 144 130 139 45 100 159	338 335 417 548 254 208 297 242 221 452 531	2.0% 2.3% 1.1% 0.5% 1.6% 2.6% 2.1% 1.2% 2.5% 3.9%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726 NCT00391092 NCT00399393 NCT00434642 NCT00435409 NCT00448033 NCT004540514 NCT005656136	58 63 33 10 136 113 30 36 108 132 132	338 335 417 548 254 208 297 242 221 452 531 195	76 89 36 109 16 144 130 139 45 100 159 1	338 335 417 548 254 208 297 242 221 452 531 195	2.0% 2.3% 1.1% 0.5% 1.6% 2.6% 2.1% 1.2% 2.5% 3.9% 0.0%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01] 1.00 [0.06, 16.10]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0038726 NCT00389726 NCT00391092 NCT0039939 NCT00434642 NCT0043642 NCT00435409 NCT00449033 NCT00540514	58 63 33 10 136 113 130 36 108 132	338 335 417 548 254 208 297 242 221 452 531	76 89 109 16 144 130 139 45 100 159	338 335 417 548 254 208 297 242 221 452 531	2.0% 2.3% 1.1% 0.5% 1.6% 2.6% 2.1% 1.2% 2.5% 3.9%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726 NCT00391092 NCT00399393 NCT00434642 NCT00435409 NCT00448033 NCT004540514 NCT005656136	58 63 33 10 136 113 30 36 108 132 132	338 335 417 548 254 208 297 242 221 452 531 195	76 89 36 109 16 144 130 139 45 100 159 1	338 335 417 548 254 208 297 242 221 452 531 195	2.0% 2.3% 1.1% 0.5% 1.6% 2.6% 2.1% 1.2% 2.5% 3.9% 0.0%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01] 1.00 [0.06, 16.10]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00388726 NCT00391092 NCT00391092 NCT00434642 NCT00435409 NCT00449033 NCT0050514 NCT00656136 NCT00678392	58 63 33 10 136 113 36 108 132 1 34 137	338 335 417 548 254 208 297 242 221 452 531 195 362 553	76 89 36 109 16 144 130 139 45 100 159 1 40 160	338 335 417 548 254 208 297 242 221 452 531 195 362 553	2.0% 2.3% 1.1% 3.1% 0.5% 1.6% 2.6% 2.1% 1.2% 3.9% 0.0% 1.2% 3.9%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01] 1.00 [0.06, 16.10] 0.83 [0.52, 1.35] 0.81 [0.62, 1.06]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00387103 NCT00381092 NCT00391092 NCT00393939 NCT00393939 NCT00434642 NCT00435409 NCT00435409 NCT00540514 NCT00656136 NCT00678392 NCT00720941 NCT00785785	58 63 33 10 136 113 130 36 108 132 1 34 137 165	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320	76 89 36 109 16 144 130 139 45 100 159 1 40 160 150	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320	2.0% 2.3% 1.1% 3.1% 0.5% 1.6% 2.6% 2.5% 3.9% 0.0% 1.2% 3.9% 2.4%	$\begin{array}{c} 0.71 & [0.49, 1.05] \\ 0.64 & [0.44, 0.92] \\ 0.91 & [0.56, 1.49] \\ 0.52 & [0.37, 0.73] \\ 0.61 & [0.27, 1.37] \\ 0.84 & [0.56, 1.27] \\ 0.79 & [0.57, 1.09] \\ 0.86 & [0.60, 1.23] \\ 0.76 & [0.47, 1.24] \\ 1.11 & [0.81, 1.51] \\ 0.77 & [0.59, 1.01] \\ 1.00 & [0.66, 16.10] \\ 0.83 & [0.52, 1.35] \\ 0.81 & [0.62, 1.06] \\ 1.21 & [0.88, 1.65] \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00387103 NCT00389726 NCT00391092 NCT003993939 NCT00393939 NCT00393939 NCT00434642 NCT00435409 NCT00435409 NCT00540514 NCT00656136 NCT006678392 NCT00785785 NCT00785785	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430	76 89 36 109 16 144 130 139 45 109 150 160 150 33	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430	2.0% 2.3% 1.1% 3.1% 0.5% 2.6% 2.5% 3.9% 0.0% 1.2% 3.9% 2.4% 1.0%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01] 1.00 [0.06, 16.10] 0.83 [0.52, 1.35] 0.81 [0.88, 1.66] 1.21 [0.88, 1.65] 0.81 [0.48, 1.37]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0038726 NCT00391092 NCT00399399 NCT00434642 NCT00435409 NCT00435409 NCT00435409 NCT004356136 NCT00540514 NCT00656136 NCT00678392 NCT00720941 NCT00785785 NCT00863655	58 63 33 10 136 113 30 368 132 1 34 137 185 27 5	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239	76 89 36 109 16 130 139 45 100 159 1 40 160 150 33 4	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239	2.0% 2.3% 1.1% 3.1% 0.5% 1.6% 2.6% 2.1% 2.5% 3.9% 0.0% 1.2% 3.9% 2.4% 1.0% 0.1%	$\begin{array}{c} 0.71 \ [0.49, 1.05] \\ 0.64 \ [0.44, 0.92] \\ 0.91 \ [0.56, 1.49] \\ 0.52 \ [0.37, 0.73] \\ 0.61 \ [0.27, 1.37] \\ 0.84 \ [0.56, 1.27] \\ 0.79 \ [0.57, 1.09] \\ 0.86 \ [0.60, 1.23] \\ 0.76 \ [0.47, 1.24] \\ 1.11 \ [0.81, 1.51] \\ 0.77 \ [0.59, 1.01] \\ 1.00 \ [0.06, 16.10] \\ 0.83 \ [0.52, 1.35] \\ 0.81 \ [0.62, 1.06] \\ 1.21 \ [0.88, 1.65] \\ 0.81 \ [0.48, 1.37] \\ 1.26 \ [0.33, 4.73] \end{array}$	
NCT00019682 NCT00112294 NCT00112607 NCT00262990 NCT0038726 NCT00391092 NCT0039399 NCT00434642 NCT00436409 NCT00448033 NCT00449033 NCT00540514 NCT00666136 NCT00678392 NCT00720941 NCT00785785 NCT00785785 NCT00843655 NCT00883655 NCT008836779	58 63 33 10 136 113 36 108 132 1 34 137 165 27 5 35	338 335 417 548 254 208 297 242 221 452 531 195 362 533 320 430 239 225	76 89 36 109 16 144 130 139 45 109 159 1 40 160 150 33 4 41	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239 225	2.0% 2.3% 1.1% 3.1% 0.5% 2.6% 2.1% 1.2% 3.9% 2.5% 3.9% 2.4% 1.0% 0.1% 1.1%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01] 1.00 [0.06, 16.10] 0.83 [0.52, 1.35] 0.81 [0.62, 1.06] 1.21 [0.88, 1.65] 0.81 [0.48, 1.37] 1.26 [0.33, 4.73] 0.83 [0.50, 1.36]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0038726 NCT00391092 NCT00399399 NCT00434642 NCT00435409 NCT00435409 NCT00435409 NCT004356136 NCT00540514 NCT00656136 NCT00678392 NCT00720941 NCT00785785 NCT00863655	58 63 33 10 136 113 30 368 132 1 34 137 185 27 5	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239	76 89 36 109 16 130 139 45 100 159 1 40 160 150 33 4	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239	2.0% 2.3% 1.1% 3.1% 0.5% 1.6% 2.6% 2.1% 2.5% 3.9% 0.0% 1.2% 3.9% 2.4% 1.0% 0.1%	$\begin{array}{c} 0.71 \ [0.49, 1.05] \\ 0.64 \ [0.44, 0.92] \\ 0.91 \ [0.56, 1.49] \\ 0.52 \ [0.37, 0.73] \\ 0.61 \ [0.27, 1.37] \\ 0.84 \ [0.56, 1.27] \\ 0.79 \ [0.57, 1.09] \\ 0.86 \ [0.60, 1.23] \\ 0.76 \ [0.47, 1.24] \\ 1.11 \ [0.81, 1.51] \\ 0.77 \ [0.59, 1.01] \\ 1.00 \ [0.06, 16.10] \\ 0.83 \ [0.52, 1.35] \\ 0.81 \ [0.62, 1.06] \\ 1.21 \ [0.88, 1.65] \\ 0.81 \ [0.48, 1.37] \\ 1.26 \ [0.33, 4.73] \end{array}$	
NCT00019682 NCT00112294 NCT00112607 NCT00262990 NCT0038726 NCT00391092 NCT0039399 NCT00434642 NCT00436409 NCT00448033 NCT00449033 NCT00540514 NCT00666136 NCT00678392 NCT00720941 NCT00785785 NCT00785785 NCT00843655 NCT00883655 NCT008836779	58 63 33 10 136 113 36 108 132 1 34 137 165 27 5 35	338 335 417 548 254 208 297 242 221 452 531 195 362 533 320 430 239 225	76 89 36 109 16 144 130 139 45 109 159 1 40 160 150 33 4 41	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239 225	2.0% 2.3% 1.1% 3.1% 0.5% 2.6% 2.1% 1.2% 3.9% 2.5% 3.9% 2.4% 1.0% 0.1% 1.1%	$\begin{array}{c} 0.71 \ [0.49, 1.05]\\ 0.64 \ [0.44, 0.92]\\ 0.91 \ [0.56, 1.49]\\ 0.52 \ [0.37, 0.73]\\ 0.64 \ [0.27, 1.37]\\ 0.84 \ [0.56, 1.27]\\ 0.79 \ [0.57, 1.09]\\ 0.86 \ [0.60, 1.23]\\ 0.76 \ [0.47, 1.24]\\ 1.11 \ [0.81, 1.51]\\ 0.77 \ [0.59, 1.01]\\ 1.00 \ [0.06, 16.10]\\ 0.83 \ [0.52, 1.35]\\ 0.81 \ [0.62, 1.36]\\ 1.21 \ [0.88, 1.65]\\ 0.81 \ [0.48, 1.37]\\ 1.26 \ [0.33, 4.73]\\ 0.83 \ [0.50, 1.36]\\ 0.37 \ [0.21, 0.65]\\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0037103 NCT00381092 NCT00391092 NCT00391092 NCT00434642 NCT00435409 NCT00435409 NCT00540514 NCT00656136 NCT00678392 NCT00785785 NCT00785785 NCT00785785 NCT00844649 NCT00863655 NCT00883779 NCT00949650 NCT01030783	58 63 33 10 136 113 130 108 132 1 34 137 165 27 5 35 26 60	338 335 417 548 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257	76 89 36 106 144 130 159 1 50 159 1 40 150 33 4 4 41 51 51 79	338 335 417 548 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 0.0% 1.2% 3.9% 0.0% 1.2% 3.9% 0.1% 1.1% 1.3% 2.0%	$\begin{array}{c} 0.71 & [0.49, 1.05] \\ 0.64 & [0.44, 0.92] \\ 0.91 & [0.56, 1.49] \\ 0.52 & [0.37, 0.73] \\ 0.61 & [0.27, 1.37] \\ 0.84 & [0.56, 1.27] \\ 0.79 & [0.57, 1.09] \\ 0.86 & [0.60, 1.23] \\ 0.76 & [0.47, 1.24] \\ 1.11 & [0.81, 1.51] \\ 0.77 & [0.59, 1.01] \\ 1.00 & [0.66, 16.10] \\ 0.83 & [0.52, 1.35] \\ 0.81 & [0.62, 1.06] \\ 1.21 & [0.88, 1.65] \\ 0.81 & [0.48, 1.37] \\ 1.26 & [0.33, 4.73] \\ 0.83 & [0.50, 1.36] \\ 0.37 & [0.21, 0.65] \\ 0.69 & [0.46, 1.02] \\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0037103 NCT00389726 NCT00391092 NCT00399393 NCT00434642 NCT00435409 NCT00435409 NCT00449033 NCT00540514 NCT00656136 NCT00678392 NCT00785785 NCT00785785 NCT00884649 NCT00883655 NCT00883655 NCT00883779 NCT00949650 NCT01030783 NCT01121393	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27 5 355 26 60 28	338 335 417 548 254 208 297 242 221 195 362 531 195 362 531 320 430 239 225 115 257 122	76 89 36 109 144 130 139 45 100 159 159 150 33 4 41 51 79 38	338 335 417 548 208 297 242 221 452 531 195 362 533 320 430 239 225 115 257 257	2.0% 2.3% 3.1% 0.5% 2.6% 2.1% 1.2% 3.9% 0.0% 1.2% 3.9% 0.0% 1.2% 0.1% 1.0% 0.1% 1.3% 2.0% 1.0%	$\begin{array}{c} 0.71 & [0.49, 1.05] \\ 0.64 & [0.44, 0.92] \\ 0.91 & [0.56, 1.49] \\ 0.52 & [0.37, 0.73] \\ 0.61 & [0.27, 1.37] \\ 0.84 & [0.56, 1.27] \\ 0.79 & [0.57, 1.09] \\ 0.86 & [0.60, 1.23] \\ 0.76 & [0.47, 1.24] \\ 1.11 & [0.81, 1.51] \\ 0.77 & [0.59, 1.01] \\ 1.00 & [0.06, 16.10] \\ 0.83 & [0.52, 1.35] \\ 0.81 & [0.62, 1.06] \\ 1.21 & [0.88, 1.66] \\ 0.81 & [0.48, 1.37] \\ 1.26 & [0.33, 4.73] \\ 0.83 & [0.50, 1.36] \\ 0.37 & [0.21, 0.65] \\ 0.66 & [0.37, 1.16] \\ \end{array}$	
NCT00019682 NCT00112294 NCT00112607 NCT00262990 NCT0038726 NCT00391092 NCT0039399 NCT0043642 NCT00436409 NCT00446033 NCT00449033 NCT00678392 NCT00720941 NCT00666136 NCT00720941 NCT00785785 NCT00720941 NCT00785785 NCT00843655 NCT00843655 NCT00949650 NCT01030783 NCT01121393 NCT0123027	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27 5 35 26 60 60 28 21	338 335 417 548 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257 122 286	76 89 36 109 16 144 130 139 45 100 159 1 40 160 159 33 4 41 51 79 38 11	338 335 417 548 208 297 242 221 452 531 195 362 533 320 430 239 225 115 257 122 286	2.0% 2.3% 1.1% 3.1% 0.5% 2.6% 2.1% 1.2% 2.5% 0.0% 1.2% 3.9% 2.4% 0.1% 1.1% 1.3% 2.0% 0.3%	$\begin{array}{c} 0.71 \ [0.49, 1.05]\\ 0.64 \ [0.44, 0.92]\\ 0.91 \ [0.56, 1.49]\\ 0.52 \ [0.37, 0.73]\\ 0.61 \ [0.27, 1.37]\\ 0.84 \ [0.56, 1.27]\\ 0.79 \ [0.57, 1.09]\\ 0.86 \ [0.60, 1.23]\\ 0.76 \ [0.47, 1.24]\\ 1.11 \ [0.81, 1.51]\\ 0.77 \ [0.59, 1.01]\\ 1.00 \ [0.06, 16.10]\\ 0.83 \ [0.52, 1.35]\\ 0.81 \ [0.62, 1.06]\\ 1.21 \ [0.88, 1.65]\\ 0.81 \ [0.48, 1.37]\\ 1.26 \ [0.33, 4.73]\\ 0.83 \ [0.50, 1.36]\\ 0.37 \ [0.21, 0.65]\\ 0.69 \ [0.46, 1.02]\\ 0.66 \ [0.37, 1.16]\\ 1.00 \ [0.43, 2.34]\\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00381092 NCT00381092 NCT0039399 NCT0034642 NCT00436409 NCT00436409 NCT00449033 NCT00540514 NCT00540514 NCT00656136 NCT00656136 NCT00720941 NCT00720941 NCT00720941 NCT00785785 NCT00844649 NCT008855 NCT0084555 NCT0085555 NCT0085555 NCT00855555 NCT00855555 NCT00855555 NCT0	58 63 33 10 136 113 130 36 108 132 134 137 165 27 5 35 26 60 28 11 4	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257 1226 63	76 89 36 109 16 144 130 159 40 160 150 33 4 41 51 79 38 11 21	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 2395 115 257 122 286 63	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 0.0% 1.2% 3.9% 2.4% 1.0% 0.1% 1.3% 2.0% 1.3% 2.0% 1.3% 0.3% 0.4%	$\begin{array}{c} 0.71 & [0.49, 1.05] \\ 0.64 & [0.44, 0.92] \\ 0.91 & [0.56, 1.49] \\ 0.52 & [0.37, 0.73] \\ 0.61 & [0.27, 1.37] \\ 0.84 & [0.56, 1.27] \\ 0.79 & [0.57, 1.09] \\ 0.86 & [0.60, 1.23] \\ 0.76 & [0.47, 1.24] \\ 1.11 & [0.81, 1.51] \\ 0.77 & [0.59, 1.01] \\ 1.00 & [0.06, 16.10] \\ 0.83 & [0.52, 1.35] \\ 0.81 & [0.62, 1.06] \\ 1.21 & [0.88, 1.65] \\ 0.81 & [0.48, 1.37] \\ 1.26 & [0.33, 4.73] \\ 0.83 & [0.51, 1.66] \\ 0.37 & [0.21, 0.65] \\ 0.69 & [0.46, 1.02] \\ 0.66 & [0.37, 1.16] \\ 1.00 & [0.43, 2.34] \\ 0.29 & [0.09, 0.95] \\ \end{array}$	
NCT00019682 NCT00112294 NCT00112607 NCT00262990 NCT0038726 NCT00391092 NCT0039399 NCT0043642 NCT00436409 NCT00446033 NCT00449033 NCT00678392 NCT00720941 NCT00666136 NCT00720941 NCT00785785 NCT00720941 NCT00785785 NCT00843655 NCT00843655 NCT00949650 NCT01030783 NCT01121393 NCT0123027	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27 5 35 26 60 60 28 21	338 335 417 548 208 297 242 221 452 531 195 362 320 430 239 225 115 257 122 286 3135	76 89 36 109 16 144 130 159 100 159 100 150 33 4 41 51 79 38 11 257	338 335 417 548 208 297 242 221 452 531 195 362 533 320 430 239 225 115 257 122 286	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 0.0% 1.2% 2.5% 3.9% 0.0% 1.0% 0.1% 1.1%	$\begin{array}{c} 0.71 & [0.49, 1.05] \\ 0.64 & [0.44, 0.92] \\ 0.91 & [0.56, 1.49] \\ 0.52 & [0.37, 0.73] \\ 0.61 & [0.27, 1.37] \\ 0.84 & [0.56, 1.27] \\ 0.79 & [0.57, 1.09] \\ 0.86 & [0.60, 1.23] \\ 0.76 & [0.47, 1.24] \\ 1.11 & [0.81, 1.51] \\ 0.77 & [0.59, 1.01] \\ 1.00 & [0.66, 16.10] \\ 0.83 & [0.52, 1.35] \\ 0.81 & [0.62, 1.06] \\ 1.21 & [0.88, 1.65] \\ 0.81 & [0.48, 1.37] \\ 1.26 & [0.33, 4.73] \\ 0.83 & [0.50, 1.36] \\ 0.37 & [0.21, 0.66] \\ 0.69 & [0.46, 1.02] \\ 0.66 & [0.37, 1.16] \\ 1.00 & [0.49, 0.95] \\ 0.97 & [0.60, 1.57] \\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00381092 NCT00381092 NCT0039399 NCT0034642 NCT00436409 NCT00436409 NCT00449033 NCT00540514 NCT00540514 NCT00656136 NCT00656136 NCT00720941 NCT00720941 NCT00720941 NCT00785785 NCT00844649 NCT008855 NCT0084555 NCT0085555 NCT0085555 NCT00855555 NCT00855555 NCT00855555 NCT0	58 63 33 10 136 113 130 36 108 132 134 137 165 27 5 35 26 60 28 11 4	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257 1226 63	76 89 36 109 16 144 130 159 40 160 150 33 4 41 51 79 38 11 21	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 2395 115 257 122 286 63	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 0.0% 1.2% 3.9% 2.4% 1.0% 0.1% 1.3% 2.0% 1.3% 2.0% 1.3% 0.3% 0.4%	$\begin{array}{c} 0.71 & [0.49, 1.05] \\ 0.64 & [0.44, 0.92] \\ 0.91 & [0.56, 1.49] \\ 0.52 & [0.37, 0.73] \\ 0.61 & [0.27, 1.37] \\ 0.84 & [0.56, 1.27] \\ 0.79 & [0.57, 1.09] \\ 0.86 & [0.60, 1.23] \\ 0.76 & [0.47, 1.24] \\ 1.11 & [0.81, 1.51] \\ 0.77 & [0.59, 1.01] \\ 1.00 & [0.06, 16.10] \\ 0.83 & [0.52, 1.35] \\ 0.81 & [0.62, 1.06] \\ 1.21 & [0.88, 1.65] \\ 0.81 & [0.48, 1.37] \\ 1.26 & [0.33, 4.73] \\ 0.83 & [0.51, 1.66] \\ 0.37 & [0.21, 0.65] \\ 0.69 & [0.46, 1.02] \\ 0.66 & [0.37, 1.16] \\ 1.00 & [0.43, 2.34] \\ 0.29 & [0.09, 0.95] \\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0037103 NCT00381092 NCT00391092 NCT00393939 NCT00434642 NCT00436409 NCT00449033 NCT00540514 NCT0066136 NCT00678392 NCT00785785 NCT0084649 NCT00863655 NCT00883779 NCT00843650 NCT00883779 NCT00843650 NCT00883779 NCT00949650 NCT01030783 NCT01121393 NCT011223027 NCT01223027 NCT01223027 NCT01223027 NCT01223027	58 63 33 10 136 113 130 108 132 1 34 137 165 27 5 35 26 60 28 11 4 56 11	338 335 417 548 208 297 242 221 195 362 531 195 362 533 220 430 239 225 115 257 122 286 63 397	76 89 36 109 16 144 130 139 45 100 159 16 33 4 41 51 79 38 11 127 36 157 16	338 335 417 548 264 208 297 242 221 452 531 452 531 452 533 320 430 239 225 115 257 122 286 63 135 397	2.0% 2.3% 3.1% 0.5% 1.6% 2.6% 2.6% 3.9% 0.0% 1.2% 3.9% 0.0% 1.2% 3.9% 0.1% 1.0% 0.1% 1.3% 0.3% 0.3% 0.3%	$\begin{array}{c} 0.71 & [0.49, 1.05] \\ 0.64 & [0.44, 0.92] \\ 0.91 & [0.56, 1.49] \\ 0.52 & [0.37, 0.73] \\ 0.61 & [0.27, 1.37] \\ 0.84 & [0.56, 1.27] \\ 0.79 & [0.57, 1.09] \\ 0.86 & [0.60, 1.23] \\ 0.76 & [0.47, 1.24] \\ 1.11 & [0.81, 1.51] \\ 0.77 & [0.59, 1.01] \\ 1.00 & [0.66, 16.10] \\ 0.83 & [0.52, 1.35] \\ 0.81 & [0.62, 1.06] \\ 1.21 & [0.88, 1.65] \\ 0.81 & [0.48, 1.37] \\ 1.26 & [0.33, 4.73] \\ 0.83 & [0.50, 1.36] \\ 0.37 & [0.21, 0.65] \\ 0.69 & [0.46, 1.02] \\ 0.66 & [0.37, 1.16] \\ 1.00 & [0.43, 2.34] \\ 0.29 & [0.09, 0.95] \\ 0.97 & [0.60, 1.57] \\ 0.68 & [0.31, 1.48] \\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00381092 NCT00391092 NCT00399399 NCT00434642 NCT00435409 NCT00435409 NCT00540514 NCT00656136 NCT00678392 NCT00785785 NCT00844649 NCT00883655 NCT00883675 NCT00844649 NCT00883675 NCT00949650 NCT01949650 NCT0123027 NCT01227899 NCT01227899 NCT01225387 NCT01865747	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27 5 35 26 60 28 11 4 56 11	338 335 417 548 254 208 297 242 221 195 362 531 195 362 531 320 430 239 225 115 257 122 286 63 135 397 328	76 89 36 109 144 130 139 45 100 159 1 40 150 33 4 41 51 79 38 11 12 57 16 14	338 335 417 548 264 208 297 242 221 195 362 531 320 430 239 225 115 257 122 286 63 135 397 328	2.0% 2.3% 3.1% 0.5% 2.6% 2.1% 1.2% 3.9% 0.0% 1.2% 3.9% 0.1% 1.0% 0.1% 1.3% 0.3% 0.3% 0.4% 1.0%	$\begin{array}{c} 0.71 & [0.49, 1.05]\\ 0.64 & [0.44, 0.92]\\ 0.91 & [0.56, 1.49]\\ 0.52 & [0.37, 0.73]\\ 0.61 & [0.27, 1.37]\\ 0.84 & [0.56, 1.27]\\ 0.79 & [0.57, 1.09]\\ 0.86 & [0.60, 1.23]\\ 0.76 & [0.47, 1.24]\\ 1.11 & [0.81, 1.51]\\ 0.77 & [0.59, 1.01]\\ 1.00 & [0.06, 16.10]\\ 0.83 & [0.52, 1.35]\\ 0.81 & [0.62, 1.06]\\ 1.21 & [0.88, 1.66]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.43, 2.34]\\ 0.29 & [0.09, 0.95]\\ 0.97 & [0.60, 1.57]\\ 0.68 & [0.31, 1.44]\\ 0.78 & [0.35, 1.74]\\ \end{array}$	
NCT00019682 NCT00112294 NCT00112607 NCT00262990 NCT00387103 NCT00388726 NCT00391092 NCT0039399 NCT00434642 NCT00436409 NCT00436403 NCT00449033 NCT00540514 NCT00658136 NCT00658392 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00245785 NCT00245650 NCT011225027 NCT01227889 NCT01225897 NCT01225877 NCT01225877 NCT012253459	58 63 33 10 136 113 130 108 132 1 34 137 165 27 5 35 26 60 28 11 4 56 11	338 335 417 548 254 208 297 242 531 195 362 553 320 430 239 225 115 257 1226 63 135 397 328 135	76 89 36 109 16 144 130 139 45 100 159 16 33 4 41 51 79 38 11 127 36 157 16	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257 122 286 63 135 397 328 135	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 2.4% 1.2% 3.9% 2.4% 1.0% 0.1% 1.3% 2.0% 1.3% 0.1% 0.3% 0.4% 1.1%	$\begin{array}{c} 0.71 & [0.49, 1.05]\\ 0.64 & [0.44, 0.92]\\ 0.91 & [0.56, 1.49]\\ 0.52 & [0.37, 0.73]\\ 0.61 & [0.27, 1.37]\\ 0.84 & [0.56, 1.27]\\ 0.79 & [0.57, 1.09]\\ 0.86 & [0.60, 1.23]\\ 0.76 & [0.47, 1.24]\\ 1.11 & [0.81, 1.51]\\ 0.77 & [0.59, 1.01]\\ 1.00 & [0.06, 16.10]\\ 0.83 & [0.52, 1.36]\\ 0.81 & [0.42, 1.06]\\ 1.21 & [0.88, 1.65]\\ 0.81 & [0.48, 1.37]\\ 1.26 & [0.33, 4.73]\\ 1.26 & [0.37, 1.16]\\ 0.37 & [0.21, 0.65]\\ 0.69 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.43, 1.37]\\ 1.00 & [0.43, 2.34]\\ 0.29 & [0.09, 0.95]\\ 0.97 & [0.60, 1.57]\\ 0.68 & [0.35, 1.74]\\ 0.70 & [0.40, 1.22]\\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00381092 NCT00381092 NCT0039399 NCT0043642 NCT00436409 NCT00436409 NCT00449033 NCT00540514 NCT00540514 NCT00656136 NCT00656392 NCT00720941 NCT00785785 NCT00844649 NCT00863655 NCT00843655 NCT00843655 NCT00843655 NCT00843655 NCT00843655 NCT00843655 NCT00843655 NCT002949650 NCT01121393 NCT01227889 NCT01227889 NCT01227889 NCT01225857 NCT01523587 NCT01265901 NCT01523587 NCT02263459 Subtotal (95% CI)	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27 5 5 26 60 28 11 4 56 11 11 11 29	338 335 417 548 254 208 297 242 221 195 362 531 195 362 531 320 430 239 225 115 257 122 286 63 135 397 328	76 89 36 109 16 144 130 159 40 160 150 33 41 51 79 38 11 52 57 16 14 38	338 335 417 548 264 208 297 242 221 195 362 531 320 430 239 225 115 257 122 286 63 135 397 328	2.0% 2.3% 3.1% 0.5% 2.6% 2.1% 1.2% 3.9% 0.0% 1.2% 3.9% 0.1% 1.0% 0.1% 1.3% 0.3% 0.3% 0.4% 1.0%	$\begin{array}{c} 0.71 & [0.49, 1.05]\\ 0.64 & [0.44, 0.92]\\ 0.91 & [0.56, 1.49]\\ 0.52 & [0.37, 0.73]\\ 0.61 & [0.27, 1.37]\\ 0.84 & [0.56, 1.27]\\ 0.79 & [0.57, 1.09]\\ 0.86 & [0.60, 1.23]\\ 0.76 & [0.47, 1.24]\\ 1.11 & [0.81, 1.51]\\ 0.77 & [0.59, 1.01]\\ 1.00 & [0.06, 16.10]\\ 0.83 & [0.52, 1.35]\\ 0.81 & [0.62, 1.06]\\ 1.21 & [0.88, 1.66]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.48, 1.65]\\ 0.81 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.43, 2.34]\\ 0.29 & [0.09, 0.95]\\ 0.97 & [0.60, 1.57]\\ 0.68 & [0.31, 1.44]\\ 0.78 & [0.35, 1.74]\\ \end{array}$	
NCT00019682 NCT00112294 NCT00112607 NCT00262990 NCT00387103 NCT00388726 NCT00391092 NCT0039399 NCT00434642 NCT00436409 NCT00436403 NCT00449033 NCT00540514 NCT00658136 NCT00658392 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00720941 NCT00245785 NCT00245650 NCT011225027 NCT01227889 NCT01225897 NCT01225877 NCT01225877 NCT012253459	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27 5 35 26 60 28 11 4 56 11	338 335 417 548 254 208 297 242 531 195 362 553 320 430 239 225 115 257 1226 63 135 397 328 135	76 89 36 109 144 130 139 45 100 159 1 40 150 33 4 41 51 79 38 11 12 57 16 14	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257 122 286 63 135 397 328 135	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 2.4% 1.2% 3.9% 2.4% 1.0% 0.1% 1.3% 2.0% 1.3% 0.1% 0.3% 0.4% 1.1%	$\begin{array}{c} 0.71 & [0.49, 1.05]\\ 0.64 & [0.44, 0.92]\\ 0.91 & [0.56, 1.49]\\ 0.52 & [0.37, 0.73]\\ 0.61 & [0.27, 1.37]\\ 0.84 & [0.56, 1.27]\\ 0.79 & [0.57, 1.09]\\ 0.86 & [0.60, 1.23]\\ 0.76 & [0.47, 1.24]\\ 1.11 & [0.81, 1.51]\\ 0.77 & [0.59, 1.01]\\ 1.00 & [0.06, 16.10]\\ 0.83 & [0.52, 1.36]\\ 0.81 & [0.42, 1.06]\\ 1.21 & [0.88, 1.65]\\ 0.81 & [0.48, 1.37]\\ 1.26 & [0.33, 4.73]\\ 1.26 & [0.33, 4.73]\\ 0.83 & [0.50, 1.36]\\ 0.37 & [0.21, 0.65]\\ 0.69 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.43, 1.37]\\ 1.00 & [0.43, 2.34]\\ 0.29 & [0.09, 0.95]\\ 0.97 & [0.60, 1.57]\\ 0.68 & [0.35, 1.74]\\ 0.70 & [0.40, 1.22]\\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT0037103 NCT00381092 NCT00391092 NCT00393939 NCT00434642 NCT00436409 NCT00436409 NCT00540514 NCT00656136 NCT00678392 NCT00785785 NCT0084649 NCT00863655 NCT00883779 NCT0084650 NCT00883779 NCT00843650 NCT010863655 NCT00883779 NCT00283779 NCT01223027 NCT01223027 NCT01223027 NCT01225387 NCT01225387 NCT01265901 NCT01523587 NCT01865747 NCT012263459 Subtotal (95% CI) Total events	58 63 33 10 136 113 130 36 108 132 1 34 132 1 34 132 27 5 35 60 28 11 4 56 11 11 29 1528 : 32.68, df=	338 335 417 548 254 208 297 242 221 452 531 195 362 531 320 430 239 225 115 257 122 286 63 135 397 328 135 8099	76 89 36 109 16 144 130 139 45 100 159 1 40 150 150 33 4 41 51 79 38 11 12 57 16 14 38 1797 0.21); I ^a	338 335 417 548 264 208 297 242 221 452 531 195 362 533 320 430 239 225 115 257 122 286 63 3135 397 328 135 8099	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 2.4% 1.2% 3.9% 2.4% 1.0% 0.1% 1.3% 2.0% 1.3% 0.1% 0.3% 0.4% 1.1%	$\begin{array}{c} 0.71 & [0.49, 1.05]\\ 0.64 & [0.44, 0.92]\\ 0.91 & [0.56, 1.49]\\ 0.52 & [0.37, 0.73]\\ 0.61 & [0.27, 1.37]\\ 0.84 & [0.56, 1.27]\\ 0.79 & [0.57, 1.09]\\ 0.86 & [0.60, 1.23]\\ 0.76 & [0.47, 1.24]\\ 1.11 & [0.81, 1.51]\\ 0.77 & [0.59, 1.01]\\ 1.00 & [0.06, 16.10]\\ 0.83 & [0.52, 1.36]\\ 0.81 & [0.42, 1.06]\\ 1.21 & [0.88, 1.65]\\ 0.81 & [0.48, 1.37]\\ 1.26 & [0.33, 4.73]\\ 1.26 & [0.33, 4.73]\\ 0.83 & [0.50, 1.36]\\ 0.37 & [0.21, 0.65]\\ 0.69 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.43, 1.37]\\ 1.00 & [0.43, 2.34]\\ 0.29 & [0.09, 0.95]\\ 0.97 & [0.60, 1.57]\\ 0.68 & [0.35, 1.74]\\ 0.70 & [0.40, 1.22]\\ \end{array}$	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00381092 NCT00381092 NCT0039399 NCT00434642 NCT00436409 NCT00436409 NCT00449033 NCT00540514 NCT00540514 NCT00656136 NCT00656392 NCT00720941 NCT00720941 NCT00785785 NCT00844649 NCT008455 NCT008455 NCT008455 NCT008455 NCT008455 NCT008455 NCT008455 NCT008455 NCT008479 NCT0123789 NCT01227889 NCT0122789 NCT01225957 NCT0122587 NCT0122587 NCT01225459 Subtotal (95% CI) Total events Heterogeneity: Chi ^z = Test for overall effect	58 63 33 10 136 113 130 36 108 132 1 34 137 165 27 5 35 26 60 28 11 4 56 11 11 129 252,68, df = Z = 5,67 (F	338 335 417 548 254 208 297 242 221 452 531 195 362 553 320 430 239 225 115 257 122 286 63 135 397 328 135 8099 27 (P =	76 89 36 109 16 144 130 139 45 100 159 1 40 150 150 33 4 41 51 79 38 11 12 57 16 14 38 1797 0.21); I ^a	338 335 417 548 254 208 297 242 221 452 531 195 362 53 320 430 239 225 115 257 122 286 63 135 397 328 135 8099 = 17%	2.0% 2.3% 1.1% 3.1% 1.6% 2.6% 2.5% 3.9% 2.4% 1.2% 3.9% 2.4% 1.0% 0.1% 1.3% 2.0% 1.1% 0.3% 0.4% 1.1% 0.5% 0.4% 1.1%	0.71 [0.49, 1.05] 0.64 [0.44, 0.92] 0.91 [0.56, 1.49] 0.52 [0.37, 0.73] 0.61 [0.27, 1.37] 0.84 [0.56, 1.27] 0.79 [0.57, 1.09] 0.86 [0.60, 1.23] 0.76 [0.47, 1.24] 1.11 [0.81, 1.51] 0.77 [0.59, 1.01] 1.00 [0.06, 16.10] 0.83 [0.52, 1.35] 0.81 [0.62, 1.06] 1.21 [0.88, 1.65] 0.81 [0.48, 1.37] 1.26 [0.33, 4.73] 0.83 [0.50, 1.36] 0.37 [0.21, 0.65] 0.69 [0.46, 1.02] 0.66 [0.37, 1.16] 1.00 [0.43, 2.34] 0.29 [0.09, 0.95] 0.97 [0.60, 1.57] 0.68 [0.31, 1.48] 0.78 [0.35, 1.74] 0.79 [0.72, 0.85]	
NCT00019682 NCT00112294 NCT00113607 NCT00262990 NCT00337103 NCT00381092 NCT00393939 NCT0043642 NCT00435409 NCT00435409 NCT00449033 NCT00540514 NCT00540514 NCT00666136 NCT006678392 NCT00720941 NCT00785785 NCT00844649 NCT00863655 NCT00843655 NCT00843655 NCT00843655 NCT00863655 NCT00843655 NCT00843655 NCT00843655 NCT00843655 NCT00843655 NCT01230783 NCT01121393 NCT0112393 NCT011227889 NCT01227889 NCT01227889 NCT012253459 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	58 63 33 10 136 113 130 36 108 132 1 32 1 34 137 165 27 5 5 26 60 28 11 4 56 11 11 129 26 8,00 28 11 2,268,df= 2,368,df= 3,368,df= 3,368	338 335 417 548 254 208 297 242 221 452 531 195 362 531 320 430 239 225 115 257 122 286 63 135 397 328 135 8099	76 89 36 109 16 144 130 159 1 100 159 1 1 40 150 33 4 41 51 79 38 11 51 79 38 11 12 57 16 14 38 179 70 38 112 57 16 14 38 179 38 112 57 16 16 16 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 159 100 150 100 10	338 335 417 548 254 208 297 242 221 452 531 195 362 53 320 430 239 225 115 257 122 286 63 135 397 328 135 8099 = 17%	2.0% 2.3% 1.1% 3.1% 2.6% 2.6% 2.5% 3.9% 2.4% 1.2% 3.9% 2.4% 1.0% 0.1% 1.3% 2.0% 1.3% 0.1% 0.3% 0.4% 1.1%	$\begin{array}{c} 0.71 & [0.49, 1.05]\\ 0.64 & [0.44, 0.92]\\ 0.91 & [0.56, 1.49]\\ 0.52 & [0.37, 0.73]\\ 0.61 & [0.27, 1.37]\\ 0.84 & [0.56, 1.27]\\ 0.79 & [0.57, 1.09]\\ 0.86 & [0.60, 1.23]\\ 0.76 & [0.47, 1.24]\\ 1.11 & [0.81, 1.51]\\ 0.77 & [0.59, 1.01]\\ 1.00 & [0.06, 16.10]\\ 0.83 & [0.52, 1.36]\\ 0.81 & [0.42, 1.06]\\ 1.21 & [0.88, 1.65]\\ 0.81 & [0.48, 1.37]\\ 1.26 & [0.33, 4.73]\\ 1.26 & [0.33, 4.73]\\ 0.83 & [0.50, 1.36]\\ 0.37 & [0.21, 0.65]\\ 0.69 & [0.46, 1.02]\\ 0.66 & [0.37, 1.16]\\ 1.00 & [0.43, 1.37]\\ 1.00 & [0.43, 2.34]\\ 0.29 & [0.09, 0.95]\\ 0.97 & [0.60, 1.57]\\ 0.68 & [0.35, 1.74]\\ 0.70 & [0.40, 1.22]\\ \end{array}$	
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Figure 2 Forest plot for direct comparison of ORR between central and local assessments. ORR, objective response rate.

	DCR (Ce		DCR (L			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
7.1.1 Exp-DCR							
NCT00019682	34	91	38	91	1.0%	0.83 [0.46, 1.51]	
NCT00262990	245	412	236	412	4.1%	1.09 [0.83, 1.44]	+
NCT00337103	374	554	421	554	5.8%	0.66 [0.50, 0.85]	-
NCT00388726	265	508	281	508	5.7%	0.88 [0.69, 1.13]	
NCT00435409	152	221	150	221	2.0%	1.04 [0.70, 1.56]	
NCT00449033	235	452	239	452	4.9%	0.97 [0.74, 1.25]	-
NCT00656136	227	390	236	390	4.2%	0.91 [0.68, 1.21]	
NCT00678392	250	361	277	361	3.6%	0.68 [0.49, 0.95]	
NCT00720941	387	557	417	557	5.4%	0.76 [0.59, 0.99]	
NCT00785785	264	324	251	324	2.0%	1.28 [0.87, 1.88]	<u>+</u>
NCT00863655	417	485	407	485	2.4%	1.18 [0.83, 1.67]	
NCT01121393	224	242	225	242	0.7%	0.94 [0.47, 1.87]	
NCT01223027	158	284	182	284	3.4%	0.70 [0.50, 0.98]	
NCT01523587	201	398	203	398	4.3%	0.98 [0.74, 1.29]	
NCT01865747	273	330	287	330	2.1%	0.72 [0.47, 1.10]	
NCT02253459	243	270	230	270	1.0%	1.57 [0.93, 2.63]	
Subtotal (95% CI)		5879		5879	52.8%	0.89 [0.82, 0.97]	•
Total events	3949		4080				
Heterogeneity: Chi² =				= 42%			
Test for overall effect:	: Z = 2.71 (ł	P = 0.00	7)				
7.1.2 Con-DCR							
NCT00019682	31	94	34	94	1.0%	0.87 [0.48, 1.58]	
NCT00262990	234	417	204	417	3.8%	1.34 [1.02, 1.75]	
NCT00337103	366	548	387	548	5.5%	0.84 [0.65, 1.08]	
NCT00388726	106	254	112	254	2.8%	0.91 [0.64, 1.29]	
NCT00435409	155	221	146	221	1.9%	1.21 [0.81, 1.80]	
NCT00449033	235	452	244	452	5.0%	0.92 [0.71, 1.20]	
NCT00656136	36	195	42	195	1.5%	0.82 [0.50, 1.36]	
NCT00678392	231	362	253	362	3.9%	0.76 [0.56, 1.04]	
NCT00720941	379	553	399	553	5.4%	0.84 [0.65, 1.09]	
NCT00785785	284	320	281	320	1.3%	1.09 [0.68, 1.77]	
NCT00863655	155	239	145	239	2.2%	1.20 [0.83, 1.73]	
NCT01121393	93	122	92	122	0.9%	1.05 [0.58, 1.88]	
NCT01223027	160	286	184	286	3.5%	0.70 [0.50, 0.99]	
NCT01523587	157	397	156	397	4.0%	1.01 [0.76, 1.34]	+
NCT01865747	214	328	219	328	3.2%	0.93 [0.68, 1.29]	
NCT02253459	91	135	97	135	1.3%	0.81 [0.48, 1.36]	
Subtotal (95% CI)		4923		4923	47.2%	0.94 [0.86, 1.02]	•
Total events	2927		2995				
Heterogeneity: Chi ² = Test for overall effect:	•	•		= 12%			
Total (95% CI)		10802		10802	100.0%	0.92 [0.86, 0.97]	•
Total events	6876	10002	7075	10002	.00.070	0.02 [0.00, 0.07]	·
Heterogeneity: Chi ² =		- 31 (P -		- 20%			
Test for overall effect:				2070			0.01 0.1 1 10 100
Test for subaroup dif				(P = 0.4	2). I² = 09	6	DCR (Central) DCR (Local)

Figure 3 Forest plot for direct comparison of DCR between central and local assessments. DCR, disease control rate.

primary outcome, and central assessed primary endpoints, was larger than the discrepancy in trials with blind design, negative primary outcome, and local-assessed primary endpoints, respectively. Correspondingly significant interaction effect was only found in con-ORR (P=0.04, I^2 =75%) between the mask pattern (open versus blind).

Evaluation bias between central and local assessments

No evidence of evaluation bias between central and local assessments was indicated by pooled analysis. Of ORR, the ratio of OR was 1.02 (0.97-1.07) (P=0.42); of DCR, the ratio of OR was 0.98 (0.93-1.03) (P=0.37). Subgroup analysis further verified no sign of evaluation bias, including the mask pattern and primary endpoint outcomes (*Table 3*).

Concordance between central and local assessments

Correlation analysis presented high-degree concordance between two assessments. The outcome (r) was 0.985 (P<0.01), 0.962 (P<0.01), 0.962 (P<0.01) and 0.926 (P<0.01) of exp-ORR, con-ORR, exp-DCR and con-DCR, respectively (*Figure 4*).

Discussion

As we acknowledge, this is the largest study to investigate response status between central and local assessments in recent 28 phase III oncological clinical trials on different advanced solid tumors, and it is the first study involving DCR for this topic. Based on pooled analysis, we found even though local assessment estimated higher treatment efficacy than the efficacy of central assessment, this phenomenon existed in both experimental and control arms. In other words, both response statuses of central and local assessments between two arms were concordant. This was verified by correlation analysis. More importantly, there was no sign of evaluation bias between two assessments after further pooled analysis.

Comparing with two previous meta-analyses, first, our study further confirms their results. In Lima *et al.* study based on 13 RCTs on metastatic colorectal cancer (44), local assessment had higher ORR than central assessment; this higher-estimated finding was not just in experimental arm [OR=1.16 (1.09–1.22), P<0.001], but also in control arm [OR=1.16 (1.09–1.25), P<0.001]. Parallel with our research, there was no significant interaction effect between therapy allocation (P=0.81), and also no evidence

of evaluation bias by their further analysis [ratio of OR=0.97 (0.90-1.04), P=0.35]. According to the results, Lima et al. concluded that, the need of complete-case central assessment should be reappraised (44). In another meta-analysis based on 21 trials with different tumors, Tang et al. investigated the variability according to the difference of ORR and median PFS between central and local assessments (18 trials with ORR, 8 trials with PFS) (45). Comparing with central reviewers, local investigators overestimated ORR [estimated mean difference =4.57% (2.95–6.19%)], but did not overestimate median PFS [estimated mean difference =-0.19 (-0.68 to 0.29) months]. No evaluation bias was indicated by further analysis regardless of ORR (P=0.54) or PFS (P=0.31). Tang et al. concluded, due to the variability between central and local assessments, central review should be considered when the primary endpoint is based on response or progression assessment in oncological clinical trials (45).

The difference between our research and the above two studies is, we included larger RCTs which are recently published from 2010 to 2017, and involved DCR for analysis. Additionally, we found lower treatment response of central assessments especially in trials with open-label design, central-assessed primary endpoint, and positive primary endpoint outcome. Namely, assessment by central reviewers seemed more "conservative" in open-label studies, or in trials whose primary endpoint was based on central assessment. However, no evaluation bias could be found regardless of summary synthesis or subgroup analysis, including above-mentioned subgroup circumstances of open-labelled versus blind design, central-assessed primary endpoint versus local-assessed primary endpoint, and positive primary endpoint outcome versus negative primary endpoint outcome.

According to no evidence of systematic bias (5,6), as well as high-degree concordance without evaluation bias between central and local assessment in previous and our meta-analysis, we consider, the implementation of central assessment for all enrolled patients is unnecessary in clinical trials. Instead, we are looking forward to understanding the usage of sample-based central review as an audit strategy in future trials (1,2,5,6,46). Its value deserves further investigation.

Our research has several limitations. First, the finding of our research may be not completely generalizable to all phase III clinical trials on advanced solid tumors, in that our included trials were implemented with both assessments' response endpoints. Accordingly, we are

0	ORR (Exp/Con)					DCR (Exp/C	on)	
Summary/subgroup	S (n)	OR (95% CI)	P^{\dagger}	l ^{2‡§} (%)	S (n)	OR (95% CI)	P ^a	l ^{2‡§} (%)
Summary	28	1.02 (0.97–1.07)	0.42	0	16	0.98 (0.93–1.03)	0.37	0
Mask								
Open	22	1.03 (0.98–1.09)	0.23	30	12	0.97 (0.91–1.02)	0.25	0
Blind	6	0.95 (0.84–1.08)	0.43		4	1.01 (0.91–1.13)	0.79	
Sample size								
> median (618.5)	14	1.00 (0.94–1.06)	0.99	1	10	0.96 (0.91–1.02)	0.21	0
< median (618.5)	14	1.05 (0.97–1.14)	0.20		6	1.03 (0.92–1.15)	0.63	
Tumor type								
NSCLC	8	1.01 (0.93–1.10)	0.81	0	4	1.01 (0.91–1.12)	0.85	0
Breast	7	1.08 (0.98–1.20)	0.13		5	0.98 (0.89–1.07)	0.62	
Renal-cell	6	1.01 (0.91–1.12)	0.86		4	0.95 (0.87–1.05)	0.35	
Ovarian	3	0.98 (0.85–1.12)	0.72		1	0.91 (0.77–1.09)	0.32	
Others	4	1.00 (0.86–1.15)	0.99		2	1.04 (0.83–1.30)	0.73	
Primary endpoint								
Central-assessed	16	1.04 (0.98–1.10)	0.22	50	10	0.97 (0.91–1.04)	0.37	0
Others	7	0.92 (0.83–1.03)	0.16		5	0.99 (0.90–1.08)	0.76	
Local-assessed	5	1.08 (0.94–1.24)	0.28		1	0.99 (0.80–1.23)	0.93	
Primary outcome								
Positive	18	1.04 (0.98–1.11)	0.23	0	10	0.99 (0.93–1.06)	0.76	0
Indeterminate	1	1.10 (0.61–1.95)	0.76		1	0.98 (0.68–1.42)	0.92	
Negative	9	0.99 (0.92–1.07)	0.84		5	0.96 (0.88–1.04)	0.30	

Table 3 Evaluation bias between central versus local assessments

[†], P value for the comparison between central and local assessments; P<0.05 indicated significant discrepancy; [‡], I² in summary outcome was for heterogeneity of data synthesis; [§], I² in subgroup was for subgroup difference, representing the interaction effects between the elements of each subgroup factor. Exp, experimental arm; Con, control arm; ORR, objective response rate; DCR, disease control rate; OR, odds ratio; S, study.

unclear for the reliability of either assessment in trials which were only implemented or reported according to the result of one assessment. Second, even though we included trials with different solid tumors, heterogeneity analysis indicated, trials with different tumor types could have inconsistent findings when directly comparing DCR between two assessments. For example, in trials on non-small cell lung cancer, breast cancer and renal-cell carcinoma, central assessment underestimated treatment benefit on DCR compared with local assessment, but in trials on ovarian cancer, central assessment did not underestimate. However, regardless of above higher or lower treatment benefit, the OR of trials on different tumors represented same direction in both experimental and control arms. Given further analysis on evaluation bias, as well as following correlation analysis, these findings represented evaluation concordance between both assessments. Third, this meta-analysis was conducted based on study-level analysis, instead of individual-level analysis.

In conclusion, according to the finding that local assessment estimated higher treatment efficacy than the efficacy of central assessment in our direct comparison, we believe blind independent central review remains an

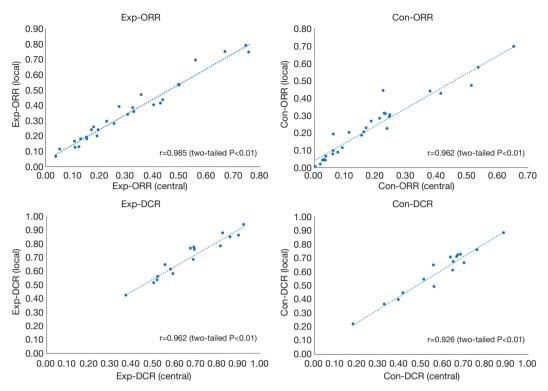


Figure 4 Scatterplot for the correlation between central and local assessments. ORR, objective response rate; DCR, disease control rate.

irreplaceable method to monitor local assessment. However, we don't believe its implementation for all patients is necessary in all trials, due to no evaluation bias between central and local assessments, as well as their high-degree evaluation concordance.

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Footnote

Conflicts of Interest: Some data of this research has been presented at ESMO 2016 Annual Meeting.

References

- Amit O, Bushnell W, Dodd L, et al. Blinded independent central review of the progression-free survival endpoint. Oncologist 2010;15:492-5.
- Dodd LE, Korn EL, Freidlin B, et al. Blinded independent central review of progression-free survival in phase III clinical trials: important design element or unnecessary expense? J Clin Oncol 2008;26:3791-6.
- 3. Stone AM, Bushnell W, Denne J, et al. Research outcomes and recommendations for the assessment of progression in cancer clinical trials from a PhRMA working group. Eur J Cancer 2011;47:1763-71.
- 4. Dancey JE, Dodd LE, Ford R, et al. Recommendations for the assessment of progression in randomised cancer treatment trials. Eur J Cancer 2009;45:281-9.
- 5. Amit O, Mannino F, Stone AM, et al. Blinded independent

central review of progression in cancer clinical trials: results from a meta-analysis. Eur J Cancer 2011;47:1772-8.

- Zhang JJ, Chen H, He K, et al. Evaluation of Blinded Independent Central Review of Tumor Progression in Oncology Clinical Trials: A Meta-analysis. Ther Innov Regul Sci 2013;47:167-74.
- Liang W, Zhang J, He Q, et al. Comparison of assessments by blinded independent central reviewers and local investigators: An analysis of phase III randomized control trials on solid cancers (2010-2015). Ann Oncol 2016;27:abstr 316P. doi:10.1093/annonc/mdw366.1
- 8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
- 9. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-9.
- Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2dagger. Ann Oncol 2014;25:2357-62.
- 11. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30:870-84.
- 12. Beaver JA, Park BH. The BOLERO-2 trial: the addition of everolimus to exemestane in the treatment of postmenopausal hormone receptor-positive advanced breast cancer. Future Oncol 2012;8:651-7.
- Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377:914-23.
- Bergh J, Bondarenko IM, Lichinitser MR, et al. Firstline treatment of advanced breast cancer with sunitinib in combination with docetaxel versus docetaxel alone: results of a prospective, randomized phase III study. J Clin Oncol 2012;30:921-9.
- 15. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.
- Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6):

analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141-51.

- Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic nonsmall-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.
- Gianni L, Romieu GH, Lichinitser M, et al. AVEREL: a randomized phase III Trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer. J Clin Oncol 2013;31:1719-25.
- Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552-62.
- 20. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011;378:1931-9.
- 21. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol 2010;28:911-7.
- 22. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-65.
- 23. Motzer RJ, Porta C, Vogelzang NJ, et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:286-96.
- 24. Schwartzentruber DJ, Lawson DH, Richards JM, et al. gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. N Engl J Med 2011;364:2119-27.
- Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
- Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. Lancet Oncol 2013;14:777-86.
- 27. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med

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2013;369:722-31.

- 28. Kaufman PA, Awada A, Twelves C, et al. Phase III openlabel randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015;33:594-601.
- 29. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
- Crown JP, Dieras V, Staroslawska E, et al. Phase III trial of sunitinib in combination with capecitabine versus capecitabine monotherapy for the treatment of patients with pretreated metastatic breast cancer. J Clin Oncol 2013;31:2870-8.
- Paz-Ares LG, Biesma B, Heigener D, et al. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the firstline treatment of advanced, nonsquamous non-small-cell lung cancer. J Clin Oncol 2012;30:3084-92.
- 32. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013;31:3791-9.
- 33. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012;30:2055-62.
- 34. Aghajanian C, Goff B, Nycum LR et al. Independent radiologic review: bevacizumab in combination with gemcitabine and carboplatin in recurrent ovarian cancer. Gynecol Oncol 2014;133:105-10.
- 35. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039-45.
- 36. Colombo N, Kutarska E, Dimopoulos M, et al. Randomized, open-label, phase III study comparing patupilone (EPO906) with pegylated liposomal doxorubicin in platinum-refractory or -resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer. J Clin Oncol 2012;30:3841-7.
- 37. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: overall survival analysis. Eur J

Cancer 2012;48:2361-8.

- Monk BJ, Herzog TJ, Kaye SB, et al. Trabected in plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010;28:3107-14.
- 39. Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol 2015;16:897-907.
- Rini BI, Stenzl A, Zdrojowy R, et al. IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicentre, openlabel, randomised, controlled, phase 3 trial. Lancet Oncol 2016;17:1599-611.
- Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-27.
- 42. Blay JY, Shen L, Kang YK, et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol 2015;16:550-60.
- 43 Zhang P, Sun T, Zhang Q, et al. Utidelone plus capecitabine versus capecitabine alone for heavily pretreated metastatic breast cancer refractory to anthracyclines and taxanes: a multicentre, open-label, superiority, phase 3, randomised controlled trial. Lancet Oncol 2017;18:371-83.
- 44. Lima JP, de Souza FH, de Andrade DA, et al. Independent radiologic review in metastatic colorectal cancer: systematic review and meta-analysis. Radiology 2012;263:86-95.
- 45. Tang PA, Pond GR, Chen EX. Influence of an independent review committee on assessment of response rate and progression-free survival in phase III clinical trials. Ann Oncol 2010;21:19-26.
- Zhang JJ, Zhang L, Chen H, et al. Assessment of audit methodologies for bias evaluation of tumor progression in oncology clinical trials. Clin Cancer Res 2013;19:2637-45.

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Supplementary

Table S1 Characteristics of included trials

No. Author & year	NCT number	P (Exp)	P (Con)	Funding source	Mask	Tumor type	Study design	Primary endpoint (outcome)
1 Baselga <i>et al.</i> 2012 (9)	NCT00863655	485	239	Pharmaceutical	Double	BC	Super	L-PFS (+)
2 Piccart <i>et al.</i> 2014 (10)								
3 Yardley et al. 2013 (11)								
Beaver et al. 2012 (12)								
5 Cortes <i>et al.</i> 2011 (13)	NCT00388726	508	254	Pharmaceutical	Open	BC	Super	OS (+)
6 Bergh <i>et al.</i> 2012 (14)	NCT00393939	296	297	Pharmaceutical	Open	BC	Super	C-PFS (–)
Wu et al. 2014 (15)	NCT01121393	242	122	Pharmaceutical	Open	NSCLC	Super	C-PFS (+)
Yang et al. 2015 (16)								
Miller et al. 2012 (17)	NCT00656136	390	195	Pharmaceutical	Double	NSCLC	Super	OS (+)
0 Gianni <i>et al.</i> 2013 (18)	NCT00391092	216	208	Pharmaceutical	Open	BC	Super	L-PFS (–)
1 Motzer <i>et al.</i> 2013 (19)	NCT00678392	361	362	Pharmaceutical	Open	RCC	Super	C-PFS (+)
2 Rini <i>et al.</i> 2011 (20)								
3 Lynch et al. 2010 (21)	NCT00112294	338	338	Pharmaceutical	Open	NSCLC	Super	C-PFS (-)
4 Hauschild <i>et al.</i> 2012 (22)	NCT01227889	187	63	Pharmaceutical	Open	Μ	Super	L-PFS (+)
5 Motzer <i>et al.</i> 2014 (23)	NCT01223027	284	286	Pharmaceutical	Open	RCC	Super	C-PFS (+)
6 Schwartzentruber et al. 2011 (24) NCT00019682	91	94	Academic	Single	Μ	Super	$ORR(\pm^{\dagger})$
7 Von Hoff <i>et al.</i> 2013 (25)	NCT00844649	431	430	Pharmaceutical	Open	PT	Super	OS (+)
8 Wu et al. 2013 (26)	NCT00883779	226	225	Pharmaceutical	Double	NSCLC	Super	L-PFS (+)
9 Motzer <i>et al.</i> 2013 (27)	NCT00720941	557	553	Pharmaceutical	Open	RCC	Non	C-PFS (+)
0 Kaufman <i>et al.</i> 2015 (28)	NCT00337103	554	548	Pharmaceutical	Open	BC	Super	C-PFS + OS (-)
1 Sequist <i>et al.</i> 2013 (29)	NCT00949650	230	115	Pharmaceutical	Open	NSCLC	Super	C-PFS (+)
Yang et al. 2015 (16)								
2 Crown et al. 2013 (30)	NCT00435409	221	221	Pharmaceutical	Open	BC	Super	C-PFS (-)
3 Paz-Ares <i>et al.</i> 2012 (31)	NCT00449033	452	452	Pharmaceutical	Double	NSCLC	Super	OS (–)
4 Motzer <i>et al.</i> 2013 (32)	NCT01030783	260	257	Pharmaceutical	Open	RCC	Super	C-PFS (+)
5 Socinski <i>et al.</i> 2012 (33)	NCT00540514	521	531	Pharmaceutical	Open	NSCLC	Non	C-ORR (+)
6 Aghajanian <i>et al.</i> 2014 (34)	NCT00434642	242	242	Pharmaceutical	Double	OC	Super	L-PFS (+)
7 Aghajanian <i>et al.</i> 2012 (35)								
8 Colombo <i>et al.</i> 2012 (36)	NCT00262990	412	417	Pharmaceutical	Open	OC	Super	OS (–)
9 Monk <i>et al.</i> 2010 (37)	NCT00113607	337	335	Pharmaceutical	Open	OC	Super	C-PFS (+)
0 Monk <i>et al.</i> 2012 (38)								
1 Soria <i>et al.</i> 2015 (39)	NCT01523587	398	397	Pharmaceutical	Open	NSCLC	Super	C-PFS (+)
2 Rini et al. 2016 (40)	NCT01265901	204	135	Pharmaceutical	Open	RCC	Super	OS (–)
3 Choueiri <i>et al.</i> 2016 (41)	NCT01865747	330	328	Pharmaceutical	Open	RCC	Super	C-PFS (+)
Blay <i>et al.</i> 2015 (42)	NCT00785785	324	320	Pharmaceutical	Open	GST	Super	C-PFS (–)
35 Zhang <i>et al.</i> 2017 (43)	NCT02253459	270	135	Pharmaceutical	Open	BC	Super	C-PFS (+)

[†], in one study, objective response rate (ORR) was the primary endpoint: significant difference in central review (P=0.03), not in local assessment (P=0.05). We consider "indeterminate" because we are unable to determine whether central- or local-assessed ORR was the primary endpoint (24). P, patients; Criteria, assessment criteria for tumor response or progression; BC, breast cancer; OC, ovarian cancer; NSCLC, non-small-cell lung cancer; RCC, renal-cell cancer; M, melanoma; PT, pancreatic tumor: GST, gastrointestinal stromal tumor; Super, superiority; Non, noninferiority; C-, central-assessed; L-, local-assessed; ORR, objective response rate; PFS, progression-free survival; OS, overall survival. +, positive; –, negative.