

Research Paper



VEGFR-TKIs combined with chemotherapy for advanced non-small cell lung cancer: A systematic review

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Abstract

Introduction: To estimate the efficacy and safety of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) in combination with chemotherapy for patients with advanced non-small cell lung cancer (NSCLC).

Methods: We searched PubMed, PMC database, EMBASE, EBSCO-Medline, Cochrane Central Register of Controlled Trials (CENTRAL), American Society of Clinical Oncology (ASCO), International Association for the Study of Lung Cancer (IASLC) and the European Society of Medical Oncology (ESMO), http://www.clinicaltrials.gov/, CNKI, and Wanfang databases to identify primary research reporting the survival outcomes and safety of VEGFR-TKIs in patients with advanced NSCLC. A meta-analysis was conducted to generate combined hazard ratios (HRs) with 95% confidence intervals (CI) for overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and risk ratios (RRs) with 95% CI for adverse events (AEs).

Results: A total of 20 RCTs (8,366 participants) were included. The VEGFR-TKIs resulted in improved PFS (HR 0.82, 95% CI 0.78–0.87), ORR (HR 1.72, 95% CI 1.34–2.22), and DCR (1.45, 1.26–1.67) in patients with advanced NSCLC, but had no impact on OS (HR 0.94, 95% CI 0.89–1.00). The incidence of some high grade (\geq 3) AEs increased, such as hemorrhage, hypertension and neutropenia.

Conclusions: Our study demonstrated that regimens with VEGFR-TKIs combined with chemotherapy improved PFS, ORR and DCR in patients with advanced NSCLC, but had no impact on OS. VEGFR-TKIs induced more frequent and serious AEs compared with control therapies.

Key words: VEGFR-TKIs, chemotherapy, efficacy, meta-analysis, non-small cell lung cancer, safety

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, and is the primary cause of cancer deaths in men and the secondary cause in women¹. Non-small cell lung cancer (NSCLC) is found in 80% of patients with lung cancer and 75% of patients are diagnosed at an advanced stage with a poor prognosis. Most patients with advanced NSCLC progress despite therapeutic intervention due to limited treatment success^{2,3,4}. Platinum-based chemotherapy remains the standard treatment for NSCLC patients; however, epidemiologic studies suggest that its contribution has reached a therapeutic plateau⁵. Thus, new treatment strategies are required. Neovascularization of lung cancer plays an important role in cancer cell growth and metastasis⁶. Several vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) have shown clinical benefits when added to standard chemotherapy. During tumor development, the angiogenic switch is associated with the onset of expression and secretion of angiogenic factors by tumor cells. Neovasculature is crucial for the growth and survival of tumors larger than 3 mm³ in volume as it ensures the supply of oxygen and nutrients to cancer cells. In addition, it promotes metastasis by facilitating the entrance of tumor cells into the circulation system by fragile newly formed vessels7. VEGFR-TKIs inhibit the sprouting of vessels by blocking those activating signal pathways. Unlike classic cytotoxic drugs, VEGFR-TKIs have no direct cell-killing effect on lung cancer cells. It was shown in vitro that anti-VEGFR therapy contributes to normalization of tumor neovascular and enhances antitumor activity. VEGFR-TKIs in combination with chemotherapy results in cancer cell death and rapid tumor shrinkage8. However, whether VEGFR-TKIs in combination with chemotherapy can prolong survival and lower the number of adverse effects (AEs) requires further evaluation.

The use of VEGFR-TKIs in combination with chemotherapy as first-line or more than second-line agents for the treatment of patients with NSCLC has been evaluated, but the results on the efficacy and safety of such therapies are inconsistent. Nintedanib in combination with docetaxel is an effective second-line treatment for advanced lung adenocarcinoma in patients previously treated with therapy^{9,10,11}. first-line platinum-based Axitinib showed promising single agent activity with an acceptable safety profile in an open label, single arm, phase II trial in advanced NSCLC12. Vandetanib, pazopanib, cediranib, and linifanib have also demonstrated higher efficiency when combined with chemotherapy in NSCLC13,14,15. However, some negative results have been observed following treatment with VEGFR-TKIs in combination with chemotherapy for advanced NSCLC patients. Motesanib combined with carboplatin-paclitaxel in non-squamous NSCLC, failed to provide an OS benefit, while demonstrating higher grade toxicity¹⁶. Sunitinib is a small oral TKI that targets VEGFR-1/2/3. In a controlled study, data analysis showed no benefit following treatment with sunitinib in unselected or non-squamous NSCLC patients¹⁷. Many clinical trials have demonstrated that VEGFR-TKIs with chemotherapy can improve survival outcomes in NSCLC patients. However, to date, nintedanib is the only VEGFR-TKI permitted by the USA and Europe for the treatment of advanced NSCLC. Many studies have reported no clinical benefits of VEGFR-TKIs when used in combination with chemotherapy^{18,19}.

A previous meta-analysis showed that therapy consisting of chemotherapy plus VEGFR-TKIs has specific advantages over chemotherapy alone in terms of progression-free survival (PFS) and objective response rate (ORR), but the combination therapy did not prolong overall survival (OS) and disease control rate (DCR)²⁰. Thus, we performed an updated meta-analysis to summarize the efficacy and safety of VEGFR-TKIs in combination with chemotherapy for patients with advanced NSCLC.

Methods

Literature search

We searched PubMed, PMC database, EMBASE, EBSCO-Medline, Cochrane Central Register of Controlled Trials (CENTRAL), American Society of Clinical Oncology (ASCO), International Association for the Study of Lung Cancer (IASLC) and the European Society of Medical Oncology (ESMO), http://www.clinicaltrials.gov/, CNKI, Wanfang, and VIP databases using common keywords related to VEGFR-TKIs and NSCLC. The following keywords were included: VEGFR-TKI or vascular endothelial growth factor receptor tyrosine kinase inhibitors, lung cancer or NSCLC. We reviewed the bibliographies of relevant articles for additional publications.

Selection criteria

We included trials that met the following criteria: (i) the trial enrolled patients with cytologically or pathologically confirmed advanced NSCLC (males or females aged at least 18 years); (ii) the trial design was a randomized controlled trial (RCT) comparing VEGFR-TKIs in combination with chemotherapy with chemotherapy alone; (iii) the trial reported survival related outcomes, such as OS, PFS, ORR and DCR; (iv) the trial evaluated the safety of VEGFR-TKIs and reported AEs, such as hypertension, rash, nausea, vomiting, diarrhea, and neutropenia.

Data extraction and quality evaluation

Two independent investigators reviewed all the articles independently and discussed the articles until a consensus was reached. Data obtained from the studies included the first author, year of publication, patient source (region), type of study, number of patients, therapeutic regimen, survival outcomes, and safety data. The scale of risk of bias summary and risk of bias graph were used to assess the methodological quality of the included studies.

Statistical analysis

We chose OS and PFS as the endpoints in our meta-analysis. ORR and DCR are also summarized in Table 1. Safety outcomes were evaluated using STATA 14.0 (Stata Corp., College Station, TX, USA). HR was used as a measure of the prognostic value. Subgroup analyses were performed based on variables such as line of treatment. Publication bias was evaluated according to the funnel plot and Begg's and Egger's tests using Review Manager 5.3.5. Heterogeneity was assessed by the χ^2 test and expressed by the l^2 index.

Results

Characteristics of the included studies and risk of bias

In total, 20 eligible studies with information on 8,366 patients were included in this meta-analysis. A flow chart of retrieval and selection of the studies is shown in Fig. 1. Table 1 summarizes the basic characteristics of the included studies. All 20 studies were double-blinded and allocation concealment was adequate in all studies. The risk of bias items for each included study are presented in Fig. 2.



Fig. 1. Assessment of risk of bias based on the evaluation domains listed in the Cochrane Collaboration Risk of Bias Tool: risk of bias graph (A), risk of bias summary (B).

Meta-analysis of survival outcome

Progression-free survival

We identified 16 eligible trials^{11,16,17,18,21,22,23,24,25,26,} ^{27,28,29,30,31,32}, which included 8,092 patients, and investigated PFS following VEGFR-TKIs in combination with chemotherapy versus chemotherapy alone. Our meta-analysis revealed that VEGFR-TKIs in combination with chemotherapy increased PFS compared with chemotherapy alone (HR, 0.82; 95% CI, 0.78–0.87; P < 0.00001, Fig. 3A). In the subgroup analyses, both first-line treatment (HR, 0.83; 95% CI, 0.77–0.89; P < 0.00001, Fig. 4A) and more than second-line treatment (HR, 0.82; 95% CI, 0.76–0.88; P < 0.00001, Fig. 4B) prolonged PFS.

Overall survival

We identified 15 eligible trials^{11,16,17,18,21,22,23,24,25,27,} ^{28,29,30,31,32}, which included 7,379 patients, and investigated OS following **VEGFR-TKIs** in combination with chemotherapy versus chemotherapy alone. Our meta-analysis revealed that VEGFR-TKIs in combination with chemotherapy had no impact on OS compared with chemotherapy (HR, 0.94; 95% CI, 0.89–1.00; P = 0.05, Fig. 3B). In the subgroup analyses, neither first-line treatment (HR, 0.94; 95% CI, 0.86-1.02; P = 0.13, Fig. 4C) nor more than second-line treatment (HR, 0.94; 95% CI, 0.86–1.03; *P* = 0.19, Fig. 4D) prolonged OS.

Overall response rate and disease control rate

ORR Thirteen the trials reported 16,21,22,25,27,28,30,32,33,34,35,36,37,38, and ten studies reported the DCR 22,25,27,31,32,33,34,35,36,37. Our meta-analysis revealed that VEGFR-TKIs in combination with chemotherapy prolonged ORR and DCR (HR, 1.72; 95% CI, 1.34-2.22; P < 0.0001, Fig. 3C; HR, 1.45; 95% CI, 1.26–1.67; *P* < 0.00001, Fig. 3D, respectively). In the subgroup analyses, both first-line treatment (HR, 1.45; 95% CI, 1.29-1.64; P < 0.00001, Fig. 4E) and second-line treatment (HR, 1.60; 95% CI, 1.31–1.94; P < 0.00001, Fig. 4F) prolonged the ORR. In addition, only second-line treatment (HR, 1.29; 95% CI, 1.00–1.26; P < 0.00001, Fig. 4H) rather than first-line treatment (HR, 1.04; 95% CI, 0.93–1.17; P = 0.47, Fig. 4G) improved the DCR.

Safety outcomes

The safety results related to the use of VEGFR-TKIs in combination with chemotherapy for NSCLC patients in all 20 studies are shown in Fig. 5. Patients treated with VEGFR-TKIs in combination with chemotherapy were found to have more high grade (\geq 3) AEs. Hemorrhage (RR, 8.32; 95% CI, 3.84–18.04; *P* = 0.000), hypertension (RR, 4.77; 95% CI, 2.85–7.97; P = 0.000), neutropenia (RR, 1.26; 95% CI, 1.11–1.44; *P* = 0.000), rash (RR, 6.31; 95% CI, 4.05–9.84; *P* = 0.000), vomiting (RR, 1.26; 95% CI, 1.11–1.44; *P* = 0.000), and diarrhea (RR, 2.52; 95% CI, 1.88–3.39; P = 0.000) were significantly increased in NSCLC patients treated with VEGFR-TKIs in combination with chemotherapy. The risk of anemia, nausea, and constipation were comparable between the two groups (RR, 0.80; 95% CI, 0.60-1.07; RR, 1.04; 95% CI, 0.67–1.62; RR, 1.18; 95% CI, 0.40–3.50, respectively). The RRs of all high grade (\geq 3) AEs are summarized in Fig. 5.

Publication bias

There was no evidence of publication bias following assessment by funnel plot, Egger's test (P > 0.05) and Begg's test (P > 0.05).

Author	Agents	Year	Country	Line of treatment	Phase	Regimens	Number of patients	Median OS (months)	Median PFS (months)	ORR (percentage)	DCR (percentage)
Luis Paz-Ares	Sorafenib	2012	Spain	First	III	Sorafenib + gemcitabine + cisplatin vs.	-	12.4	6	27.8	62.1
						placebo	387	12.5 (HR 0.98, <i>P</i> = 0.401)	5.5 (HR 0.83, $P = 0.008$)	25.8 (<i>P</i> = 0.11)	63.1 (<i>P</i> = 0.47)
Giorgio Scagliotti	Sorafenib	2010	Italy	First	III	Sorafenib + paclitaxel +	464	10.7	0.008) 4.6		
						carboplatin vs. placebo + paclitaxel + carboplatin	462	10.6	5.4		
						Carbopiauit		(HR 1.15, 95% CI 0.94–1.41, <i>P</i> = 0.915)	(HR 0.99, 95% CI 0.84–1.16, <i>P</i> = 0.433)		
Yan Wang	Sorafenib	2011	China	First	NR	Sorafenib + gemcitabine + cisplatin vs.	18	18	5	55.6	88.9
						placebo + gemcitabine + cisplatin	12	18	4	41.7	100
						1		(P = 0.68)	(P = 0.750)	(P = 0.905)	
Lihong Zhang	Sorafenib	2014	China	First	NR	Sorafenib + gemcitabine + cisplatin vs.	12	12.8	7.4	33.3	75
						placebo + gemcitabine + cisplatin	17	12.7	4.3	11.8	88.2
						*		(P = 0.369)	(P = 0.070)	(P = 0.172)	(P = 0.234)
John V. Heymach	Vandetanib	2008	Spain	First	Π	Vandetanib + paclitaxel + carboplatin vs.	56		6		
						placebo + paclitaxel + carboplatin	52		5.75		
								(HR 1.15, 95% CI, 0.75-1.77)	(HR 0.76, 95% CI, 0.51-1.14)		
John V. Heymach	Vandetanib	2007	Spain	Second	II	Vandetanib + docetaxel vs.	42	13.1	4.7		
						placebo + docetaxel	41	13.4 (HR 0.91, 95% CI, 0.55-1.52, P = 0.0361)	3 (HR 0.64, 95% CI, 0.38-1.05, P = 0.037)		
Prof Roy Herbst	Vandetanib	2011	USA	Second	III	Vandetanib + docetaxel vs.	694	10.3	4	17	
						docetaxel	697	9.9	3.2	10	
								(HR 0.91, 97.52% CI 0.78–1.07, <i>P</i> <0 0001)	(HR 0.79, 97.58% CI 0.70-0.90, P <0 0001)	(<i>P</i> = 0 0001)	
Richard H. de Boer	Vandetanib	2011	Australia	Second	III	Vandetanib + pemetrexed vs.	256	10.5	4.1	19	57
						placebo + pemetrexed	278	9.2	2.8	8	46
								(HR 0.86, 97.54% CI 0.65-1.13, P = 0.219)	(HR 0.86, 97.58% CI 0.69-1.06, P = 0.108)	(P < 0.001)	(<i>P</i> = 0.0116)
Gridelli	Vandetanib	2014	Italy	First	II	Vandetanib + gemcitabine vs.	61	8.7	6.1	15	72
						placebo + gemcitabine	63	10.2	5.6	13	67
Martin Reck	Nintedanib	2014	Germany	Second	III	Nintedanib + docetaxel vs.	655	10.1	3.4	35.1	73.6
						placebo + docetaxel	659	9.1 (HR 0.94, 95% CI 0.83–1.05, <i>P</i> = 0.2720)	2.7 (HR 0.79, 95% CI 0.68–0.92, <i>P</i> = 0.0019)	30.1	68.3
Hanna	Nintedanib	2013	Germany	Second	III	Nintedanib + pemetrexed vs.	353		4.4	9	61
						placebo + pemetrexed	360		3.6 (HR 0.83, 95% CI 0.70-0.99)	9	53
Chandra P Belani	Axitinib	2014	USA	First	II	Axitinib + PEM + DDP vs.	55	17	8	45.5	
						PEM + DDP	57	15.9 (HR 1.05, 95% CI, 0.65-1.69, P = 0.58)	7.1 (HR 0.89, 95% CI, 0.56-1.42, P =	26.3	

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Author	Agents	Year Country		Phase	Regimens		Median OS (months)		ORR	DCR
			treatment			of patients		(months)	(percentage)	(percentage)
								0.036)		
Giorgio Scagliotti	pazopanib	2013 Italy	First	II	pazopanib+ PEM + DDP vs.	62			14	27
					PEM + DDP	35			12	26
							(HR 1.22, 95% CI, 0.64-2.33, P = 0.5519)	(HR 0.75, 95% CI, 0.43-1.28, P = 0.2647)		
S.A. Laurie	cediranib	2014 Canada	First	III	cediranib + carboplatin + paclitaxel vs.	151	12.2	5.5		
					carboplatin + paclitaxel	153	12.1	5.5		
							(HR 0.94, 95% CI, 0.69-1.30, P = 0.72)	(HR 0.91, 95% CI, 0.71-1.18, P = 0.49)		
Glenwood D. Goss	cediranib	2010 Canada	First	II/III	Cediranib + carboplatin + paclitaxel vs.	126	10.5	5.6		
					carboplatin + paclitaxel	125	10.1	5		
							(HR 0.78, 95% CI, 0.57-1.06, <i>P</i> =	(HR 0.77, 95% CI, 0.56-1.08, <i>P</i> =		
							0.11)	0.13)		
Grace K. Dy	cediranib	2013 USA	First	II	Cediranib + carboplatin + gemcitabine vs.	58	12	6.3	19	
					carboplatin + gemcitabine	29	9.9	4.5	20	
					0		(HR 0.66, 95% CI, 0.41-1.08)	(HR 0.69, 95% CI, 0.43-1.09)		
Ramalingam	Linifanib	2015 USA	First	II	Linifanib + carboplatin + paclitaxel vs.	44	11.4	8.3		43
					placebo + carboplatin + paclitaxel	47	11.3	5.4		26
					1		(HR 1.08)	(HR 0.51)		
Heist	Sunitinib	2014 USA	Second	II	Sunitinib + pemetrexed vs.	41	6.7	3.7		
					pemetrexed	42	10.5	4.9		
							(HR 2.0, 95% CI, 1.2-3.2)	(HR 1.3, 95% CI, 0.9-2.1)		
Scagliotti	Motesanib	2012 Italy	First	III	Motesanib + carboplatin + paclitaxel vs.	541	13.5	5.6	39	
					placebo + carboplatin + paclitaxel	549	11	5.4	25	
					1		(HR 0.88, 95% CI, 0.75-1.03)	(HR 0.78, 95% CI, 0.67-0.91)		
Kubota	Motesanib	2014 Japan	First	III	Motesanib + carboplatin + paclitaxel vs.	110	20.9	7	62	91
					placebo + carboplatin +	117	14.5	5.3	27	77

Abbrevations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate.

paclitaxel

Discussion

Current treatment options for patients with advanced NSCLC are limited. Survival results and safety and tolerability findings are inconsistent in studies of various VEGFR-TKIs; thus, a statistical meta-analysis of these articles is needed. A particular focus in the treatment of NSCLC patients is survival outcome. Our results demonstrated that VEGFR-TKIs in combination with chemotherapy prolonged the PFS, ORR, and DCR, but had no impact on the OS. VEGFR-TKIs in combination with chemotherapy increased the incidence of some high grade (\geq 3) AEs, such as hemorrhage, hypertension, neutropenia, rash, vomiting, and diarrhea. With regard to the line of treatment, the efficacy of VEGFR-TKIs in combination with chemotherapy may be different in the first-line and second-line settings. Significant PFS and ORR benefits were observed in both the first-line and second-line settings. DCR benefits were observed only in second-line treatment. However, there were no OS benefits either in the first-line or the second-line setting. A previous meta-analysis also showed no OS survival benefit²⁰. It seems that although the VEGFR-TKIs have been proven to be effective in terms of the PFS, it was limited due to modest OS because of resistance during treatment. However, fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) have been found to be upregulated in patients exhibiting acquired resistance to anti-VEGF treatment and that the combination of VEGF/PDGF pathways has been proven to be more effective than single VEGF inhibition in animal models. The use of multi-targeted anti-angiogenesis TKIs in combination with chemotherapy seems to be a advanced promising strategy for NSCLC patients^{39,40,41}.

(HR 0.58, 95% CI,

0.42 - 0.79

(HR 0.669, 95% CI,

0.473 - 0.946



Fig. 2. Flowchart of computerized search and the eligible studies included in this systematic review and meta-analysis.

Several multi-targeted anti-angiogenesis TKIs, such as sorafenib, axitinib, cediranib, nintedanib, pazopanib, linifanib, motesanib are under clinical investigation and have not been approved for the treatment of patients with advanced NSCLC. The ZODIAC study demonstrated significant prolongation of PFS with vandetanib plus docetaxel versus docetaxel alone. This study showed that adding vandetanib significantly improved the ORR and delayed the time to worsening of lung cancer symptoms²⁸. In the second-line setting of NSCLC, it was previously shown that the doublet combination of single cytotoxic agents and vandetanib, was safe and demonstrated antitumor activity^{11,42}. Nintedanib improved the OS in a population of adenocarcinoma patients, particularly those with progression within 9 months after first-line treatment initiation²⁶. In a phase II trial, first-line linifanib in combination with carboplatin-paclitaxel was associated with a higher ORR, PFS, and OS³¹. However, some clinical trials have reported negative results for VEGFR-TKIs in advanced NSCLC. Axitinib is a second-generation oral TKI of VEGF receptor 1, 2 and 3, PDGFR-b and c-kit, and has shown activity against several tumors. A phase II study evaluating the combination of axitinib with chemotherapy in non-squamous NSCLC not only failed to demonstrate a survival benefit, but

also reported higher grade 3-4 toxicity²¹. Sorafenib, ceritinib, pazopanib, and motesanib also did not lead to a PFS or OS benefit in first-line treatment compared with chemotherapy alone9,16,18,22,25,29. Among the Chinese patients in phase II and phase III clinical trial, anlotinib appears to lead to prolonged overall survival and progression-free survival. Those findings suggest that anlotinib is well tolerated and is a potential third-line or further therapy for patients with advanced NSCLC^{37,38,43}. However, our object was to evaluate VEGFR-TKIs and chemotherapy in comparison with chemotherapy. Thus, studies of anlotinib don't meet our inclusion criteria and are not included in our meta-analysis.

In our meta-analysis, VEGFR-TKIs in combination with chemotherapy improved the PFS, ORR and DCR in patients with advanced NSCLC, indicating that slowing disease progression also slowed symptom progression, leading to an important palliative benefit. This improvement in PFS, ORR, and DCR raises the possibility that patients with advanced NSCLC can live with fewer symptoms for a longer periods of time. However, there was no significant effect on the OS. EGFR expression, overexpression, and mutation have been implicated in the pathogenesis of NSCLC, suggesting that EGFR positive patients may derive increased clinical benefit from EGFR-targeted treatments. Thus, absence of the selection of EGFR positive patients may be a possible explanation for the negative results obtained for OS in patients treated with VEGFR-TKIs in combination with erlotinib. An accurate understanding of the expression levels and localization of drug targets in NSCLC is necessary to elucidate the mechanism of action of drugs in the clinic and, potentially, for identifying patients who would gain most clinical benefit from VEGFR-TKIs treatment. In addition, many patients received post-progression therapy, and although the number of patients and type of therapy received were balanced between groups before progression, the possibility that differences in response to post-progression therapy cannot be excluded.

A. PFS						Hazard Ratio	Hazard	
Study or Subgroup	log[H	lazard R				IV, Fixed, 95% CI	IV, Fixed	, 95% CI
Chandra P Belani 2014				0.2364	1.3%	0.89 [0.56, 1.41]		
Giorgio Scagliotti 2010				0.0838	10.5%	0.99 [0.84, 1.17]	-	_
Giorgio Scagliotti 2013				0.2838	0.9%	0.75 [0.43, 1.31]		
Glenwood D. Goss 2010				0.1625	2.8%	0.77 [0.56, 1.06]		
Grace K. Dy 2013				0.2373	1.3%	0.68 [0.43, 1.09]		-
Hanna 2013				0.0869	9.8%	0.00 [00] 0.00]		
Heist 2014				0.2162	1.6%		1	
John V. Heymach 2007			4463	0.266	1.0%			_
John V. Heymach 2008			2744		1.8%	0.76 [0.51, 1.13]		-
Kubota 2014			5447		2.7%	0.58 [0.42, 0.80]		
Luis Paz-Ares 2012				0.0797	11.6%		-	
Martin Reck 2014			2357		12.6%			-
Richard H. de Boer 2011 Roy S Herbst 2011				0.1124 0.0617	5.8% 19.4%	0.86 [0.69, 1.07]	-	
S.A. Laurie 2014				0.1266	4.6%	0.79 [0.70, 0.89]	-	_
S.A. Laurie 2014 Scagliotti 2012				0.0776		0.91 [0.71, 1.17]		
scagnotti 2012		-0.4	2485	0.0776	12.2%	0.78 [0.67, 0.91]	-	
Total (95% CI)					100.0%	0.82 [0.78, 0.87]	•	
Heterogeneity: $Chi^2 = 19$	04 df	= 15 (P =	0.21)	$I^2 = 219$			-++	
Test for overall effect: Z							0.2 0.5 1	2 5
B. OS								Favours chemotherapy
21.00						Hazard Ratio	Hazard	
Study or Subgroup	log[H	azard Ra				IV, Fixed, 95% CI	IV, Fixed,	95% CI
Chandra P Belani 2014			488 0		1.6%	1.05 [0.65, 1.70]		-
Giorgio Scagliotti 2010			398 0			1.15 [0.94, 1.41]	1	
Giorgio Scagliotti 2013			989 0			1.22 [0.64, 2.33]	_	-
Glenwood D. Goss 2010			485	0.16		0.78 [0.57, 1.07]		_
Grace K. Dy 2013 Heist 2014			073 0			0.67 [0.41, 1.08]		
Terbe Box T			727 (943 (1.96 [1.20, 3.20]		
ohn V. Heymach 2007			398 (0.91 [0.55, 1.51]		
ohn V. Heymach 2008 Kubota 2014			021 (1.15 [0.75, 1.76]		
Luis Paz-Ares 2012			202 (3.0%	0.67 [0.47, 0.95]		
Martin Reck 2012			619 0			0.98 [0.83, 1.16]	1	
Richard H. de Boer 2011			508 0			0.94 [0.83, 1.06] 0.86 [0.65, 1.14]	-	
Roy S Herbst 2011			943 (0.91 [0.78, 1.06]		
S.A. Laurie 2014		-0.0	619 0	.1578	3.8%	0.94 [0.69, 1.28]		
		-0.0		.1578	3.8%			
S.A. Laurie 2014 Scagliotti 2012		-0.0	619 0	0.1578 0.0809	3.8% 14.5%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03]		
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI)	67 df =	-0.0 -0.1	619 (291 (0.1578 0.0809	3.8% 14.5% 100.0%	0.94 [0.69, 1.28]		
5.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22		-0.0 -0.1	0.07);	0.1578 0.0809	3.8% 14.5% 100.0%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03]	0.5 0.7 1	1.5 2
5.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z	= 1.98 (F	-0.0 -0.1 = 14 (P = P = 0.05)	619 (291 (0.07);	0.1578 0.0809 I ² = 38%	3.8% 14.5% 100.0%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00]	Favours VEGFR-TKIs	Favours chemotherapy
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z = C. ORR	= 1.98 (F	-0.0 -0.1 = 14 (P = P = 0.05) TKIs c	619 (291 (0.07); hemoti	0.1578 0.0809 I ² = 38%	3.8% 14.5% 100.0%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio	Favours VEGFR-TKIs Odd	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z C. ORR Study or Subgroup	= 1.98 (F VEGFR- Events	-0.0 -0.1 = 14 (P = P = 0.05) TKIs c Total E	619 (291 (0.07); hemoti	0.1578 0.0809 I ² = 38% herapy Total	3.8% 14.5% 100.0%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio M-H, Random, 95% CI	Favours VEGFR-TKIs Odd	Favours chemotherapy
S.Å. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014	= 1.98 (F VEGFR- Events 25	-0.0 -0.1 = 14 (P = P = 0.05) TKIs c Total E 55	619 (291 (0.07); hemotil Events 15	0.1578 0.0809 I ² = 38% herapy Total 57	3.8% 14.5% 100.0% Weight 6.3%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 [1.06, 5.16]	Favours VEGFR-TKIs Odd	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z · C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013	= 1.98 (F VEGFR- Events 25 9	-0.0 -0.1 = 14 (P = P = 0.05) TKIs c Total E	619 (291 (0.07); hemoti Events 15 4	0.1578 0.0809 I ² = 38% herapy Total	3.8% 14.5% 100.0%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 [1.06, 5.16] 1.32 [0.37, 4.63]	Favours VEGFR-TKIs Odd	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013	= 1.98 (F VEGFR- Events 25	-0.0 -0.1 = 14 (P = P = 0.05) TKIs c Total E 55 62	619 (291 (0.07); hemotil Events 15	0.1578 0.0809 I ² = 38% herapy Total 57 35	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 [1.06, 5.16] 1.32 [0.37, 4.63] 0.90 [0.29, 2.73]	Favours VEGFR-TKIs Odd M-H, Ran	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% Cl) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014	= 1.98 (F VEGFR- Events 25 9 11	-0.0 -0.1 = 14 (P = P = 0.05) TKIS C Total E 55 62 58	619 (291 (0.07); hemoti tvents 15 4 6	0.1578 0.0809 I ² = 38% merapy Total 57 35 29	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3% 4.0%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 [1.06, 5.16] 1.32 [0.37, 4.63]	Favours VEGFR-TKIs Odd M-H, Ran	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Janna 2013	= 1.98 (F VEGFR- Events 25 9 11 9	-0.0 -0.1 = 14 (P = P = 0.05) TKIs c Total E 55 62 58 61	619 (0 291 (0 0.07); hemotil Events 15 4 6 8	0.1578 0.0809 I ² = 38% herapy Total 57 35 29 63	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3% 4.0% 4.5%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03) 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95% CI 2.33 (1.06, 5.16) 1.32 (0.37, 4.63) 0.90 (0.29, 2.73) 1.19 (0.43, 3.32)	Favours VEGFR-TKIs Odd M-H, Ran	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Jorgio Scagliotti 2013 Jrace K. Dy 2013 Jrace K. Dy 2013 Jrace K. Dy 2013 Jrace J. Dy 2014 Janna 2014 Jiong Zhang 2014	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (0 291 (0 0.07); hemotil vents 15 4 6 8 32 32 32 2	0.1578 0.0809 I ² = 38% Total 57 35 29 63 360 117 17	3.8% 14.5% 100.0% 5 <u>Weight</u> 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 [1.06, 5.16] 1.32 [0.37, 4.63] 0.90 [0.29, 2.73] 1.19 [0.43, 3.32] 1.02 [0.61, 1.71] 4.30 [2.46, 7.53] 3.75 [0.56, 25.12]	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Fest for overall effect: Z - C. ORR Study or Subgroup Chandra P Belani 2014 Ciorgio Scagliotti 2013 Grace K. Dy 2013 Tridelli 2014 Janna 2013 (ubota 2014 Jihong Zhang 2014 Jin Paz-Ares 2012	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (0 291 (0 0.07); hemotil vents 15 4 6 8 32 32 2 100	0.1578 0.0809 I ² = 38% Total 57 35 29 63 360 117 17 387	3.8% 14.5% 100.0% 5 <u>Weight</u> 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95 (0.10, 0.10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Thandra P Belani 2014 Giorgio Scagliotti 2013 Gradeli 2014 Janna 2013 Cubota 2014 Lihong Zhang 2014 Linong Zhang 2014	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (291 (0.07); hemoti vents 15 4 6 8 32 32 2 2 100 22	0.1578 0.0809 I ² = 38% Total 57 355 29 63 360 117 17 387 659	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.1%	0.94 [0.69, 1.28] 0.88 [0.75, 1.03] 0.94 [0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 [1.06, 5.16] 1.32 [0.37, 4.63] 0.90 [0.29, 2.73] 1.19 [0.43, 3.32] 1.02 [0.61, 1.71] 4.30 [2.46, 7.53] 3.75 [0.56, 25.12] 1.34 [0.76, 2.36]	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Cridelli 2014 Janna 2013 Kubota 2014 Lihong Zhang 2014 Liis Paz-Ares 2012 Martin Reck 2014 Richard H. de Boer 2011	= 1.98 (F VEGFR- Events 25 9 111 9 32 68 4 107 29 49	-0.0 -0.1 -0.1 TKIS C Total E 55 62 58 62 58 63 353 110 12 385 655 256	619 (291 (0.07); hemoti vents 15 4 6 8 32 32 2 100 22 22	0.1578 0.0809 I ² = 38% Total 57 35 29 63 360 117 17 387 659 278	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.5%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95 (0.10, 0.10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Fest for overall effect: Z · C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grate K. Dy 2013 Gridelli 2014 Hanna 2013 Kubota 2014 Libong Zhang 2014 Luis Paz-Ares 2012 Martin Reck 2014 Nichard H. de Boer 2011 Noy S Herbst 2011	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (291 (0.07); hemoti <u>tvents</u> 15 4 6 8 32 32 2 100 22 22 70	0.1578 0.0809 I ² = 38% Total 57 35 29 63 3600 117 17 387 659 278 697	3.8% 14.5% 100.0% 6.3% 3.3% 4.0% 4.5% 9.8% 9.8% 1.6% 13.1% 9.1% 9.1% 9.5%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03) 0.94 (0.89, 1.00) 0.04ds Ratio 0.04ds Ratio 0.04ds Ratio 0.05 (0.65, 1.01) 1.32 (0.37, 4.63) 0.90 (0.29, 2.73) 1.19 (0.43, 3.32) 1.02 (0.64, 7.53) 3.75 (0.56, 25.12) 1.00 (0.80, 1.52) 1.34 (0.76, 2.36) 2.75 (1.61, 4.70) 1.83 (1.34, 2.52)	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z - C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grade K. Dy 2013 Gridelli 2014 Hanna 2013 Kubota 2014 Luis Paz-Ares 2012 Martin Reck 2014 Richard H. de Boer 2011 Sog Sherbst 2012 Sagliotti 2012	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118 211	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (291 (0.07); hemoti vents 15 4 6 8 32 32 2 100 22 22	0.1578 0.0809 l ² = 38% Total 57 35 29 63 360 117 17 387 659 278 659 278 659	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.1% 9.5% 13.1% 14.0%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95 (0.10, 0.10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
5.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Fest for overall effect: Z - C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Srace K. Dy 2013 Gridelli 2014 Hanna 2013 (ubota 2014 Jihong Zhang 2014 Luis Paz-Ares 2012 Martin Reck 2014 Uchard H. de Boer 2011 Stoy Sherbst 2011 Scagliotti 2012 Yan Wang 2011	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (291 (0.07); hemoti vents 15 4 6 8 32 32 2 100 22 22 70 137	0.1578 0.0809 l ² = 38% Total 57 35 29 63 360 117 387 659 278 697 549 12	3.8% 14.5% 100.0% 5 	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95 (0.10, 0.10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Fest for overall effect: Z - C. ORR Study or Subgroup Chandra P Belani 2014 Ciorgio Scagliotti 2013 Grace K. Dy 2013 Tridelli 2014 Janna 2013 (ubota 2014 Jihong Zhang 2014 Jihong Zhang 2014 Juis Paz-Ares 2012 Martin Reck 2014 Roy S Herbst 2011 Roy S Herbst 2011 Total (95% CI)	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118 211 10	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	6619 (2291 (0.07); 15 4 6 8 8 22 2 2 100 22 2 70 137 5	0.1578 0.0809 l ² = 38% Total 57 35 29 63 360 117 387 659 278 697 549 12	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.1% 9.5% 13.1% 14.0%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95 (0.10, 0.10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z i Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Hanna 2013 Subota 2014 Linong Zhang 2014 Linong Zhang 2014 Linong Zhang 2014 Richard H. de Boer 2011 Sorg Jolical Total (95% CI) Fotal events	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118 211 10 682	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	6619 (2291 (0.07); themotil Events 4 6 8 32 32 32 2 100 22 22 70 137 5 4 4 5 4 4 5 4 4 5 4 4 5 4 4 5 5 4 4 5 5 4 5 5 5 6 8 8 8 8 8 5 5 6 8 8 8 8 8 8 8 8 8 8 8 8 8	0.1578 0.0809 I ² = 38% Total 57 35 29 63 360 117 387 659 278 697 549 12 3260	3.8% 14.5% 100.0% 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.5% 13.1% 14.0% 2.5% 100.0%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00] 0.94 (0.89, 1.00] 0.95 (0.10, 10, 10, 10, 10, 10, 10, 10, 10, 10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Janna 2013 Kubota 2014 Lihong Zhang 2014 Lihong Zhang 2014 Lihong Zhang 2014 Lihong Zhang 2014 Lihong Zhang 2014 Martin Reck 2014 Scagliotti 2012 Yan Wang 2011 Total (95% CI) Total events Heterogeneity: Tau ² = 0.10	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118 211 10 682 (Chi ² = 1)	-0.0 -0.1 -0.1 TKIs c0 55 62 58 61 353 61 12 385 655 256 654 18 3260 22.4.3, df	6619 (2291 (0.07); themotil Events 4 6 8 32 32 32 2 100 22 22 70 137 5 4 4 5 4 4 5 4 4 5 4 4 5 4 4 5 5 4 4 5 5 4 5 5 5 6 8 8 8 8 8 5 5 6 8 8 8 8 8 8 8 8 8 8 8 8 8	0.1578 0.0809 I ² = 38% Total 57 35 29 63 360 117 387 659 278 697 549 12 3260	3.8% 14.5% 100.0% 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.5% 13.1% 14.0% 2.5% 100.0%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00] 0.94 (0.89, 1.00] 0.95 (0.10, 10, 10, 10, 10, 10, 10, 10, 10, 10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Janna 2013 Kubota 2014 Lihong Zhang 2014 Lihong Zhang 2014 Lihong Zhang 2014 Lihong Zhang 2014 Lihong Zhang 2014 Martin Reck 2014 Scagliotti 2012 Yan Wang 2011 Total (95% CI) Total events Heterogeneity: Tau ² = 0.10	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118 211 10 682 (Chi ² = 1)	-0.0 -0.1 -0.1 TKIs c0 55 62 58 61 353 61 12 385 655 256 654 18 3260 22.4.3, df	6619 (2291 (0.07); themotil Events 4 6 8 32 32 32 2 100 22 22 70 137 5 4 4 5 4 4 5 4 4 5 4 4 5 4 4 5 5 4 4 5 5 4 5 5 5 6 8 8 8 8 8 5 5 6 8 8 8 8 8 8 8 8 8 8 8 8 8	0.1578 0.0809 I ² = 38% Total 57 35 29 63 360 117 387 659 278 697 549 12 3260	3.8% 14.5% 100.0% 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.5% 13.1% 14.0% 2.5% 100.0%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00] 0.94 (0.89, 1.00] 0.95 (0.10, 10, 10, 10, 10, 10, 10, 10, 10, 10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z = C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Janna 2013 Kubota 2014 Lihong Zhang 2014 Lihong Zhang 2014 Linis Paz-Ares 2012 Martin Reck 2014 Roys Herbst 2011 Roys Herbst 2011 Fotal (95% CI) Total events Heterogeneity: Tau ² = 0.10 Fest for overall effect: Z =	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 49 118 211 10 682 (Chi ² = 1)	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (0 291 (0.07); hemotic vents 15 4 6 8 8 8 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	0.1578 0.0809 I ² = 38% Total 57 35 29 63 360 117 387 659 278 697 549 12 3260	3.8% 14.5% 100.0% 6.3% 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 13.1% 9.5% 13.1% 14.0% 2.5% 100.0%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00] 0.94 (0.89, 1.00] 0.95 (0.10, 10, 10, 10, 10, 10, 10, 10, 10, 10,	Favours VEGFR-TKIs Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Fest for overall effect: Z i C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Hanna 2013 Gubota 2014 Libong Zhang 2014 Libong Zhang 2014 Libong Zhang 2014 Libong Zhang 2014 Liborg Sterbst 2011 Scagliotti 2012 fan Wang 2011 Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.10 fest for overall effect: Z = i D. DCR	= 1.98 (F VEGFR- Events 25 9 9 11 9 32 68 4 107 29 49 118 211 10 682 5 (Chi ² = 2 4.19 (P <	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (0 291 (0.07); hemotic vents 15 4 6 8 8 8 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	1578 .0809 l ² = 38% trapy total 57 35 57 35 360 63 360 117 117 177 387 559 228 869 549 12 3260 3260	3.8% 14.5% 100.0% 5 100.0% 6 3.3% 4.0% 4.5% 9.8% 9.2% 1.6% 9.5% 13.1% 9.5% 13.1% 9.5% 13.1% 9.5% 13.1% 9.5% 14.0% 2.5% 100.0% 14.5% 100.0% 13.1% 13.1% 14.5% 100.0% 13.1% 13.1% 13.1% 13.1% 13.1% 13.1% 13.1% 13.1% 14.5% 13.1% 13.1% 13.1% 14.5% 13.1% 13.1% 14.5% 13.1% 14.5% 15.5	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95 (0.10, 0.10,	Favours VEGFR-TKIS Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% CI
S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Fest for overall effect: Z i C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Cridelli 2014 Janna 2013 Kubota 2014 Jihong Zhang 2014 Lis Paz-Ares 2012 Martin Reck 2014 Storah W. A. Geore 2011 Total (95% CI) Total events Heterogeneity: Tau ² = 0.10 Fest for overall effect: Z = 1 D. DCR Study or Subgroup Story 2013 Corglo Scagliotti 2013	= 1.98 (F VECFR- Events 25 9 11 9 32 68 4 107 29 49 118 211 10 682 0; Chi ² = 3 4.19 (P < VEGFR- VEGFR- VEGFR- VEGFR- Events 11 9 32 68 4 4 107 29 49 118 211 10 682 0; Chi ² = 4 10 0; Chi ² = 4 0; Chi ² = 4	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	619 (0 291 (0.07); hemotil (vents 15 4 4 6 8 8 2 2 2 2 2 2 2 2 70 137 5 5 5 = 12 (f	1,1578 1,0809 1 ² = 38% terapy Total 577 355 29 9 3360 1177 387 5659 12 3260 3260 * = 0.003 therapy Total	3.8% 14.5% 100.0% 5 Weight 6.3% 3.3% 4.5% 9.8% 9.2% 1.6% 9.1% 9.1% 9.5% 13.1% 14.0% 2.5% 100.0% 100.0% 1.6% 1.4%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) 0.94 (0.89, 1.00) 0.95 (0.29, 2.73) 0.90 (0.29, 2.73) 1.19 (0.43, 3.32) 1.02 (0.61, 1.71) 4.30 (2.46, 7.53) 1.37 (0.56, 25.12) 1.34 (0.66, 2.512) 1.34 (0.76, 2.56) 2.75 (1.61, 4.70) 1.83 (1.34, 2.52) 1.92 (1.48, 2.49) 1.75 (0.40, 7.66) 1.72 (1.34, 2.22) % 00dds Ratio t M-H, Fixed, 95% CI	Favours VEGFR-TKIS Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
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S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z : C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Janna 2013 Kubota 2014 Lihong Zhang 2014 Gradi (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = 0.10 Test for overall effect: Z =- D. DCR Study or Subgroup Gridelli 2014 Janna 2013	= 1.98 (F VEGFR- Events 25 9 11 9 32 68 4 107 29 32 68 4 107 29 118 211 100 682 0; Chi ² = 4.19 (P < VEGFR- VEGFR- 17 44 19	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	6619 (0 291 () 0.07); 15 4 4 6 8 8 32 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	1,1578 1,0809 1 ² = 38% 1 ³ = 38% 1 ³ = 38% 1 ³ = 38% 1 ³ = 38% 1	3.8% 14.5% 14.5% Weight 6.3% 3.3% 4.0% 4.0% 4.0% 4.0% 4.0% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 9.2% 13.1% 14.0% 2.5% 100.0% 13.1% 13.1% 14.0% 13.1% 14.0% 13.1% 13.1% 13.1% 14.0% 13.1% 13.1% 14.0% 13.1% 14.0% 13.1% 13.1% 13.1% 14.0% 13.1% 13.1% 14.0% 13.1% 13.1% 14.0% 13.1% 13.1% 14.0% 13.1% 13.1% 13.1% 13.1% 13.1% 14.0% 13.1% 13.1% 13.1% 13.1% 13.1% 13.1% 13.1% 13.1% 14.0% 13.1% 13.1% 13.1% 14.0% 13.1% 13.1% 14.0% 13.1% 14.0% 13.1% 14.0% 13.1% 13.1% 14.0% 13.1% 14.0% 13.1% 14.0% 13.1% 14.0% 13.1% 14.0% 13.1% 14.0% 13.1% 14.0% 14.0% 14.0% 14.0% 13.1% 14.0% 13.1% 14.0% 14.0% 14.0% 14.0% 14.0% 14.0% 14.0% 13.1% 14.0% 14	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) Odds Ratio M-H, Random, 95% CI 2.33 (1.06, 5.16] 1.32 (0.37, 6.63) 0.90 (0.29, 2.73) 1.10 (0.80, 1.52) 1.37 (0.56, 2.5.12) 1.37 (0.56, 2.5.12) 1.30 (0.80, 1.52) 1.34 (0.76, 2.36] 1.75 (0.40, 7.66] 1.72 [1.34, 2.22] % Odds Ratio the H-H, Fixed, 95% CI 6 1.09 (0.43, 2.80) 6 2.22 (0.91, 5.38] 2.22 (0.1, 5.38]	Favours VEGFR-TKIS Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
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S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z - C. ORR Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Cridelli 2014 Hanna 2013 Cubota 2014 Luis Paz-Ares 2012 Martin Reck 2014 Richard H. de Boer 2011 Sorg Herbst 2011 Stotal events Heterogeneity: Tau ² = 0.10 Test for overall effect: Z = D. DCR Study or Subgroup Giorgio Scagliotti 2013 Gridelli 2014 Hanna 2013 Cubota 2014 Lis Subgroup Study or Subgroup Giorgio Scagliotti 2013 Gridelli 2014 Hanna 2013 Cubota 2014 Libong Zhang 2014	= 1.98 (f VECFR- Events 25 9 11 9 32 68 4 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 107 29 49 20 20 20 20 20 20 20 20 20 20	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	6619 (0 2291 () 0.07); hemotil vents 15 4 6 8 8 32 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	1.1578 1.0809 1 ² = 38% Total 57 35 529 63 360 360 117 77 387 7549 12 3260 * = 0.003 * = 0.	3.8% 14.5% Weight 6.3% 4.0	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00) Odds Ratio M-H, Random, 95% CI 2.33 (1.06, 5.16) 1.32 (0.37, 4.63) 0.90 (0.29, 2.73) 1.19 (0.43, 3.32) 1.02 (0.61, 1.71) 4.30 (2.46, 7.53) 3.75 (0.56, 25.12) 1.10 (0.80, 1.52) 1.34 (0.76, 2.56, 25.12) 1.32 (1.48, 2.49) 1.75 (0.40, 7.66) 1.72 (1.34, 2.22] V Odds Ratio M-H, Fixed, 95% CI 4. 1.09 (0.43, 2.80) (5. 1.29 (0.60, 2.79) (6. 2.29 (0.60, 2.79) (6. 2.20 (0.61, 2.79) (6. 2.21 (0.91, 5.38) (6. 0.40 (0.64, 2.87)	Favours VEGFR-TKIS Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
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S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z = Study or Subgroup Chandra P Belani 2014 Giorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Anna 2013 Kubota 2014 Luis Paz-Ares 2012 Martin Reck 2014 Richard H. de Boer 2011 Scagliotti 2012 Yan Wang 2011 Total (95% CI) Total events Heterogeneity: Tau ² = 0.10 Test for overall effect: Z = D. DCR Study or Subgroup Giorgio Scagliotti 2013 Gridelli 2014 Hanna 2013 Kubota 2014 Liong Zhang 2014 Liong 2014 Liong 2014 Liong 2014 Liong 2014 Liong 2014	= 1.98 (F Events 25 9 11 1 9 32 268 8 4 4 4 107 29 9 118 211 107 29 9 118 211 107 29 9 107 107 29 9 107 107 29 9 107 107 29 9 107 107 107 29 9 107 107 107 107 107 107 107 107	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	6619 (291 (0.07); 15 15 4 6 8 32 32 22 20 22 22 70 0 22 22 70 137 5 4555 5 4455 5 4455 5 42 22 22 70 0 22 22 22 70 0 22 22 22 70 0 22 22 22 70 0 22 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 22 22 70 0 137 5 5 2 22 22 22 22 22 22 20 137 5 22 22 22 22 22 22 22 22 22	1.1578 1.0809 1 ² = 38% Total 757 557 299 63 360 360 117 77 387 549 12 3260 278 3260 278 3260 278 3260 278 3260 3360 360 360 360 360 360 360	3.8% 14.5% 100.0% 5 Weight 6.3% 4.0%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 [1.06, 5.16] 1.32 (0.37, 46, 5.16] 1.33 (1.34, 2.52] 1.42 (0.66, 2.512] 1.42 (0.76, 2.56] 1.72 (1.34, 2.49] 1.75 (0.40, 7.66] 1.72 (1.34, 2.49] 1.75 (0.40, 7.66] 1.72 (1.34, 2.49] 3.75 (0.60, 2.79] 4.29 (0.60, 2.79] 4.29 (0.60, 2.79] 4.20 (0.50,	Favours VEGFR-TKIS Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
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S.A. Laurie 2014 Scagliotti 2012 Total (95% CI) Heterogeneity: Chi ² = 22 Test for overall effect: Z i Study or Subgroup Chandra P Belani 2014 Glorgio Scagliotti 2013 Grace K. Dy 2013 Gridelli 2014 Hanna 2013 Cubota 2014 Liuls Paz-Ares 2012 Martin Reck 2014 Richard H. de Boer 2011 Scagliotti 2012 fan Wang 2011 Total (95% CI) Fost for overall effect: Z = D. DCR Study or Subgroup Glorgio Scagliotti 2013 Gridelli 2014 Hanna 2013 Cubota 2014 Liuls Paz-Ares 2012 Study or Subgroup Glorgio Scagliotti 2013 Gridelli 2014 Hanna 2013 Cubota 2014 Lius Paz-Ares 2012 Martin Reck 2014 Martin Reck 2014 Study and 2015 Kichard H. de Boer 2011	= 1.98 (F VECFR- Events 25 9 11 9 12 25 9 12 13 9 12 26 8 4 4 4 107 7 29 9 107 107 107 107 107 107 107 107	-0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1	6619 (291 (0.07); 15 (15 (4 4) 6 (8 3) 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	1.1578 1.0809 1 ² = 38% Total Total 77 35 29 63 32 63 33 63 33 87 77 77 77 77 77 77 77 77 77	3.8% 14.5% 100.0% 5 Weight 6.3% 4.0% 4.0% 4.0% 4.0% 4.0% 4.0% 13.1% 9.5% 9.5% 2.5% 10.0° 9.1% 9.1% 9.5% 2.5% 10.0° 11.1% 1.6%	0.94 (0.69, 1.28) 0.88 (0.75, 1.03] 0.94 (0.89, 1.00] Odds Ratio M-H, Random, 95% CI 2.33 (1.06, 5.16) 1.32 (0.37, 4.63) 0.90 (0.29, 2.73) 1.19 (0.43, 3.32) 1.02 (0.61, 1.71) 4.30 (2.46, 7.53) 3.75 (0.56, 25.12) 1.34 (0.76, 2.56) 2.75 (1.61, 4.70) 1.83 (1.34, 2.52) 1.34 (0.76, 2.56) 2.75 (1.61, 4.70) 1.83 (1.34, 2.52) 1.92 (1.48, 2.49) 1.75 (0.40, 7.66) 1.72 (1.34, 2.52) 1.72 (1.34, 2.52) 3.300 (1.38, 6.54) 4.29 (0.60, 2.79) 5.300 (1.38, 6.54) 5.300 (1.31, 2.19) 5.300 (1.31, 2.19) 5.300 (1.31, 2.19) 5.300 (1.31, 2.19) 5.300 (1.31, 2.19) 5.300 (1.31, 2.11) 5.300 (1.31,	Favours VEGFR-TKIS Odd M-H, Ran 	Favours chemotherapy s Ratio dom, 95% Cl
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Fig. 3. Meta-analysis of PFS, OS, ORR and DCR. (A) Change in PFS between VEGFR-TKIs and chemotherapy: fixed-effects model. (B) Change in OS between VEGFR-TKIs and chemotherapy: fixed-effects model. (C) Change in ORR between VEGFR-TKIs and chemotherapy: random-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Change in DCR between VEGFR-TKIs and chemotherapy: fixed-effects model.

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$ \begin{array}{c clusters} C = 0.116 0 = 2244 & 1.38 & 0.89 (0.56, 1.41) \\ Clusters Scapiton 2010 & -0.317 & 0.2481 & 0.56 & 0.91 (0.41, 1.13) \\ Clusters Scapiton 2011 & -0.347 & 0.2481 & 0.56 & 0.91 (0.41, 1.13) \\ Clusters Scapiton 2011 & -0.347 & 0.2481 & 0.56 & 0.91 (0.41, 1.13) \\ Clusters C = 0.116 & 0.2474 & 0.167 & 2.76 & 0.58 & 0.91 (0.41, 1.13) \\ Clusters C = 0.116 & 0.2474 & 0.167 & 2.76 & 0.58 & 0.91 (0.41, 1.13) \\ Clusters C = 0.116 & 0.2474 & 0.167 & 2.76 & 0.58 & 0.24 & 0.080 \\ Clusters C = 0.2474 & 0.047 & 2.76 & 0.58 & 0.24 & 0.080 \\ Clusters C = 0.2474 & 0.047 & 2.76 & 0.58 & 0.24 & 0.080 \\ Clusters C = 0.2474 & 0.047 & 2.76 & 0.58 & 0.24 & 0.080 \\ Clusters C = 0.2474 & 0.047 & 2.76 & 0.58 & 0.24 & 0.080 \\ Clusters C = 0.2474 & 0.047 & 0.247 & 2.248 & 0.276 & 0.280 \\ Clusters C = 0.2474 & 0.0201 & 0.0180 & 0.0270 & 2.80 \\ Clusters C = 0.2474 & 0.0201 & 0.0180 & 0.0270 & 2.80 \\ Clusters C = 0.2474 & 0.0201 & 0.0180 & 0.0270 & 2.80 \\ Clusters C = 0.2474 & 0.0201 & 0.0180 & 0.0270 & 0.280 \\ Clusters C = 0.0270 & 0.018 & 0.0270 & 0.028 & 0.021 \\ Clusters C = 0.018 & 0.00001 & 0.00001 & 0.0180 & 0.0270 & 0.028 \\ Clusters C = 0.018 & 0.00001 & 0.00001 & 0.028 & 0.0270 & 0.028 \\ Clusters C = 0.018 & 0.00001 & 0.00001 & 0.028 & 0.0270 & 0.028 \\ Clusters C = 0.018 & 0.0486 & 0.2471 & 1.68 & 0.056 & 1.701 \\ Clusters C = 0.018 & 0.0486 & 0.2471 & 1.68 & 0.056 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.056 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.056 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.056 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.056 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.0501 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.0501 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.0501 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.0501 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.0501 & 1.701 \\ Clusters C = 0.018 & 0.0488 & 0.2471 & 1.68 & 0.0501 & 1.701 \\ Clusters C = 0.028 & 0.028 & 0.07$
$ \frac{\text{Clemend D}}{\text{Cores C}, D \ge 201} \qquad -0.2614 0.1625 2.86 6.71 \\ \text{Cores C}, D \ge 201 \qquad -0.2744 0.263 \\ \text{Cores C}, D \ge 201 \qquad -0.2744 0.263 \\ \text{Cores C}, D \ge 201 \qquad -0.2744 0.263 \\ \text{Cores C}, D \ge 201 \qquad -0.2744 0.263 \\ \text{Cores C}, D \ge 201 \qquad -0.2744 0.263 \\ \text{Cores C}, D \ge 201 \qquad -0.284 \\ \text{Cores C}, D \ge 201 \\ $
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Lubots 2014 -0.547 0.167 2.76 0.58 0.021 0.001 Lub R Parkers 2012 -0.046 0.077 1.16 0.83 0.71 0.71 S.A. Lumi 2014 -0.046 0.077 1.16 0.83 0.71 0.71 Stabulard 1935 -0.166 0.078 1.16 0.83 0.71 0.93 Hetrogenetry: CM* = 1.15.0, df = 9 P = 0.24; l* = 228 Test for ovail diffect 2 = 4.38 P = 0.00011 -0.2357 0.0073 1.28 0.79 0.98 Hetrogenetry: CM* = 7.37, df = 5 P = 0.39; l* = 228 Test for ovail diffect 2 = 7.30 P = 0.300011 -0.2357 0.057 1.00.05 0.82 0.078 0.83 0.081 0.
S.A. Lanie 2014
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $
$ \begin{aligned} & \text{Hetrogeneity: } Ch^4 = 11.60, d^4 = 9 P = 0.24; l^4 = 228 \\ \text{Test for overall effect: 2 = 4.88 P < 0.00001 \\ \hline \text{Hetrogeneity: } Ch^4 = 10.40, d^4 = 15 P = 0.21; l^4 = 228 \\ \text{Hetrogeneity: } Ch^4 = 10.445 = 0.248 \\ \hline Loss of the loss$
Test for overall effect $Z = 4.8 \text{ (} P < 0.0001)$ H = 75 2 accord line H = 75 2 acc
Hama 2013 Heat 2014 Hest 2014 Hest 2014 Matrin Rek 2014 Autrin Rek 2014 Hest 2014
Heat 2014 Deby V. Hymach 2007 -0.4463 0.264 1.08 0.64 [0.58, 1.08] Martin Reck 2014 $-0.2357 0.076 1.266 0.79 [0.68, 0.92] Rock and H. Ber 2011 -0.2357 0.076 1.266 0.67 [0.68, 0.97]Reck 2014-0.2357 0.076 1.266 0.67 [0.68, 0.97]Reck 2014-0.2357 0.076 1.266 0.67 [0.68, 0.97]Reck 2014-0.2357 0.061 1.10 0.050 0.82 [0.76, 0.87]Hereorgenetic, Ch2 = 19.04, df = 15 (P = 0.21); l2 = 218Test for overall effect: 2 = 5.30 (P < 0.00001)Total (95% C)Hereorgenetic, Ch2 = 19.04, df = 15 (P = 0.21); l2 = 218Test for overall effect: 2 = 5.30 (P < 0.00001)Total (95% C)Hereorgenetic, Ch2 = 19.04, df = 15 (P = 0.21); l2 = 218Test for overall effect: 2 = 5.30 (P < 0.00001)Total (95% C)Hereorgenetic, Ch2 = 19.04, df = 15 (P = 0.21); l2 = 218Test for subgroup differences: Ch2 = 0.04, df = 16 - 0.78); l2 = 08Hereorgenetic, Ch2 = 19.04, df = 15 (P = 0.21); l2 = 218Test for subgroup differences: Ch2 = 0.04, df = 16 - 0.78); l2 = 08Hereorgenetic, Ch2 = 19.04, df = 15 (P = 0.21); l2 = 218Test for subgroup differences: Ch2 = 0.04, df = 16 - 0.78); l2 = 08Hereorgenetic, Ch2 = 19.04, df = 15 (P = 0.018); l2 = 08Hereorgenetic, Ch2 = 19.04, df = 0.028 (0.162, 1.07)Def Station 20100.198 (0.102) 0.055 (1.70)Def Station 2010Def Station 2010Def Station 2011Def Station 2010Def Station 2011Def Station 2011Def Station 2011Def Station 2011Def Station 2014Def St$
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Boy Stebular 2011 -0.257 0.617 19.48 0.79 0.28 0.76 0.88 Heterogeneity: $Ch^2 = 7.37$, $df = 5$ $0 = 0.051$; $f^2 = 326$ Test for overall effect: $2 = 3.00$ 100005 0.82 0.76 0.83 Test for overall effect: $2 = 7.20$ (P < 0.00001) Test for overall effect: $2 = 7.20$ (P < 0.00001) Hazard Ratio Hearogeneity: Ch ² = 7.20 (P < 0.00001) Hazard Ratio Hazard Ratio Study of Subgroup log(Hazard Ratio) St Weight IV, Fixed, 955C CI Hazard Ratio Condra P Bata 2014 0.0488 0.2471 1.060 0.55 0.70 Circuity Scalineti 2010 0.1988 0.129 0.057 0.75 0.75 Garea K, Dy 2013 0.0497 0.2471 1.060 0.75 0.75 0.75 0.75 Subject 2014 -0.0420 0.0848 0.270 0.95 0.027 0.94 0.027 0.95 0.027 0.95 0.07 0.75 0.75 0.75 0.75 0.75 0.75 0.75 0.75 0.75 0.75 0.75 0.75 <
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Test for overall effect: $2 = 5.30$ (P < 0.0001) Total (95% C) Test for volume of fifteness: Chr = 15, 0, 0 = 0.21; 1 ² = 21% Test for volume of fifteness: Chr = 0.08, df = 1, 0 = 0.78; 1 ² = 0.05 Test for volume of fifteness: Chr = 0.08, df = 1, 0 = 0.78; 1 ² = 0.05 CO 5ff tis Chardra P Relation 2014 Congols Scapilont 2013 Congols Scapilont 2014 Congols Scapilont 2014 Congols Scapilont 2015 Congols Scapilont 2015 Congols Scapilont 2017 Congols Scapilont 2017 Cong
Heterogenetry: $Ch^2 = 19.04$, $df = 15 (P = 0.21)$; $l^2 = 218$ Test for varial fields: $2 = 7.20 (P < 0.0001)$ Test for varial fields: $2 = 7.20 (P < 0.0001)$ Test for varial fields: $2 = 7.20 (P < 0.0001)$ Test for varial fields: $2 = 7.20 (P < 0.0001)$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 0.08$, $df = 1 (P = 0.28)$, $l^2 = 0.08$ CoS fields: $2 = 0.08$, $df = 0.08$, $df = 0.08$, $l^2 = 0.0$
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Test for volgram effects: $2 - 22.6 \text{ p}^{2} - 0.00013$ Test for volgram g differences: $Ch^{2} = 0.78, h^{2} = 0.6$ Study or Subgroup leg[Hazard Ratio S Study or Subgroup leg[Hazard Ratio S Subject Status 2014 C or Sinst line C hand a P lean 2
Hazard Ratio Hazard Ratio Stew vor Meght IV. Fixed, 95% CI V. Fixed, 95% CI C OS first line C OS first line C OS first line C OS first line Control 0.0488 0.2447 1.06 II. 105 [0.65, 1.70] Control 0.0488 0.2447 1.06 II. 105 [0.65, 1.70] Control 0.05 2010 0.2485 0.132 [0.64, 1.23] Control 0.05 2010 -0.2485 0.05 [0.57, 1.07] Control 0.057 1.078 0.05 (0.75, 1.76] Mathematics 2014 -0.06710 2.058 (0.75, 1.03] Subtoal (95% CI D 05 2 second line Heterogeneity: Chi ² = 1.38 (F = 9 (P = 0.14); I ² = 33% Test for subgradial effect: 2 = 1.30 (P = 0.05); I ² = 38% Test for subgradial effect: 2 = 1.30 (P = 0.05); I ² = 38% Test for subgradial effect: 2 = 1.30 (P = 0.05); I ² = 38% Test for subgradial effect: 2 = 1.30 (P = 0.05); I ² = 38% Test for subgradial effect: 2 = 1.30 (P = 0.05);
Study or Subgroup log[Hazard Ratio] SE Weight IV, Fixed, 95% CI IV, Fixed, 95% CI C OS first line
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Clemendo D. Goss 2010 Grave K. Dy 2013 -0.4073 0.2471 1.66 0.67 [0.41, 1.08] John V. Heymach 2008 0.1398 0.2181 2.0% 1.15 [0.75, 1.76] Kubota 2014 -0.4020 0.0484 13.2% 0.98 [0.83, 1.16] Scalioti 2012 -0.0202 0.0484 13.2% 0.98 [0.75, 1.03] Subtotal (95% CD) D OS 2 second line Heist 2014 -0.0619 0.0635 23.6% 0.94 [0.63, 1.06] Kichard H. de Bor 2011 -0.1508 0.128 15.4% 0.91 [0.55, 1.51] Martin Reck 2014 -0.0619 0.0635 23.6% 0.94 [0.83, 1.06] Subtotal (95% CD) Total (95% CD) Total (95% CD) EVECFR-TKis Chemotherapy Kick Ratio Chard P. Hein 2014 -0.01 d -1 (P = 0.04); t ² = 50K Test for overall effect: 2 = 1.30 (P = 0.19) Total (95% CD) EVECFR-TKis Chemotherapy Kick Ratio Chard P. Hein 2014 -0.01 d -1 (P = 0.94); t ² = 00K Test for overall effect: 2 = 1.30 (P = 0.19) Total (95% CD) EVECFR-TKis Chemotherapy Kick Ratio Chard P. Hein 2014 -0.01 d -1 (P = 0.94); t ² = 00K -0.05 0.27 1.5 2 Favours VECFR-TKis Favours chemotherapy Kick Ratio Chard P. Hein 2014 -0.01 d -1 (P = 0.94); t ² = 00K -0.05 0.27 1.5 2 Favours VECFR-TKis Favours chemotherapy Kick Ratio Chard P. Hein 2014 -0.01 d -1 (P = 0.94); t ² = 00K -0.05 0.27 1.5 2 Favours VECFR-TKis Favours chemotherapy Kick Ratio -0.5 0.7 1.5 2 Favours VECFR-TKis Favours chemotherapy -0.5 0.7 1.5 2
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Kubora 2014 -0.4021 0.1768 3.08 0.67 0.47,0.95 Luis Paz-Ares 2012 -0.0200 0.0484 13.28 0.98 0.81 1.16 S.A. Laurie 2014 -0.0619 0.1578 3.88 0.94 0.66.1.28 Scapiont 2012 -0.1291 0.0409 1.55 3.88 0.94 0.66.1.28 Subtotal (95% C) 53.4% 0.94 0.66.1.02 53.4% 0.94 0.66.1.02 Hetrogenetic: Ch ² = 1.3.48, df = 6 (P = 0.1.3) 0.6727 0.2502 1.5% 1.96 1.20 D O 5 2 second line -0.0619 0.653 2.86 0.94 0.81 1.065 Narrin Rek 2014 -0.0510 0.0432 4.7% 0.86 10.55 1.16 Subtotal (95% C) -0.0510 1.024 4.66% 0.94 0.85 1.065 Hetrogenetic: Ch ² = 2.01 -0.051; r ² = 56X 1.06 1.055 1.061 -0.57; r ¹ = 38% 5.07 Favours VEGR-TKis Favours Chemotherapy Test for overall effect: Z = 1.30 (P = 0.05) 100.056 0.94 0.89, 1.061 0.5, 0.7
Luis Raz-Ares 2012 -0.0202 0.0448 13.2% 0.38 [0.83, 1.16] S.A. Laurie 2014 -0.0619 0.1578 3.8% 0.94 [0.65, 1.28] Staplicit 2012 -0.1291 0.0809 14.5% 0.38 [0.75, 1.03] Subtotal (95% C) S.1.4% 0.94 [0.36, 1.02] Heterogeneity: Ch ² = 13.48, df = 9 ($P = 0.14$); $l^2 = 33\%$ Test for overall effect: 2 = 1.50 ($P = 0.13$) D OS 2 second line Heist 2014 0.6727 0.2502 1.5% 1.96 [1.20, 3.20] John V. Heymath 2007 -0.0943 0.2569 1.4% 0.91 [0.57, 1.51] Martin Reck 2014 0.0612 2.5% 0.428 4.7% 0.36 [0.65, 1.14] Roy 5 Herbst 2011 -0.1508 0.1428 4.7% 0.36 [0.65, 1.14] Roy 5 Herbst 2011 -0.0943 0.0786 15.4% 0.91 [0.78, 1.06] Subtotal (95% C) 4.6% 0.128 1.4% 0.91 [0.78, 1.06] Heterogeneity: Ch ² = 2.2.67, df = 14 ($P = 0.07$); $l^2 = 38\%$ Test for overall effect: 2 = 1.30 ($P = 0.19$) Total (95% C) 100.0% 0.94 [0.89, 1.00] Heterogeneity: Ch ² = 2.2.67, df = 14 ($P = 0.07$); $l^2 = 38\%$ Test for overall effect: 2 = 1.30 ($P = 0.19$) Total (95% C) VECFR-TKis Chemotherapy Risk Ratio E ORF risk ine VECFR-TKis Chemotherapy Risk Ratio E ORF risk ine C Chardra P Belani 2014 25 55 15 57 3.2% 1.73 [1.02, 2.93] Craadra P Belani 2014 25 55 15 57 3.2% 1.73 [1.02, 2.33] Craadra P Belani 2014 4.12 2 17 0.4% 2.83 [0.61, 3.36] Heterogeneity: Ch ² = 2.10 0.73 fi 15 6.2 29 1.8% 0.52 (0.38, 2.23] Craadra P Belani 2014 6.8 101 32 117 6.8% 2.26 [1.63, 3.14] Kubota 2014 6.8 100 327 21.9% 1.08 [0.85, 1.36] Luis Raz-Ares 2012 107 335 100 387 21.9% 1.08 [0.85, 1.36] Total events 454 309 Heterogeneity: Ch ² = 6.06 ($P < 0.0001$) F ORF zecond line Hanao 2013 Martin Reck 2014 22 52 2559 4.45% 1.13 [0.77, 2.28] Richard H, de foor 2011 49 256 22 275 4.46% 2.42 [1.51, 3.88] Martin Reck 2014 228 51 146 Hanao 2014 99 50 1999 31.8% 1.60 [1.31, 1.94] F ORF zecond line Hanao 2013 Martin Reck 2014 22 28 166 Hanao 2014 4.12 22 17 0.46% 2.28 [1.62, 2.23] Heterogeneity: Ch ² = 6.06% ($P < 0.0001$) F ORF zecond line Hanao 2013 Martin Reck 2014 22 35 13 2.2 (1.59% 1.56] [1.54% 1.54] Hanao 2013 Martin Reck 2
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Subtotal (95% C) Heterogenerity: Ch ² = 1.3.8, df = 9 (p = 0.14); t ² = 33% Test for overall effect: Z = 1.50 (p = 0.13) D GS 2 second line Heist 2014 0.6727 0.2502 1.5% 1.96 [1.20, 3.20] John V. Heymach 2007 -0.0943 0.2569 1.4% 0.91 [0.75, 1.51] Marrin Rek 2014 -0.0619 0.0635 2.36% 0.94 [0.8.3, 1.06] Richard H. de Boer 2011 -0.01508 0.1428 4.7% 0.86 [0.65, 1.14] Reby S Herbs 2011 -0.0943 0.0786 15.4% 0.91 [0.76, 1.06] Subtotal (95% C) Heterogenerity: Ch ² = 2.91, df = 4 (p = 0.00); t ² = 56% Test for overall effect: Z = 1.30 (p = 0.19) Total (95% C) Heterogenerity: Ch ² = 2.92, f, df = 14 (p = 0.07); t ² = 38% Test for overall effect: Z = 1.98 (p = 0.00); t ² = 56% Test for overall effect: Z = 1.30 (p = 0.19) Total (95% C) Heterogenerity: Ch ² = 2.267, df = 14 (p = 0.07); t ² = 38% Test for overall effect: Z = 1.30 (p = 0.07); t ² = 38% Test for overall effect: Z = 1.30 (p = 0.01, df = 1 (p = 0.94), t ² = 0% Total events Total Events Total Weight: M=H, Fixed, 95% Cl Heterogenerity: Ch ² = 2.267, df = 14 (p = 0.091, t ² = 0% Total events Total Events Total Weight: M=H, Fixed, 95% Cl Heterogenerity: Ch ² = 2.021 1.5 4 Study or Subgroup Events Total Events Total Weight: M=H, Fixed, 95% Cl Heterogenerity: Ch ² = 2.026 (A, 2, 3.83) Grade K, Dy 2013 11 5 8 6 29 1.8% 0.92 (0.38, 2.33] Grade K, Dy 2013 11 5 8 6 29 1.8% 0.92 (0.38, 2.33] Grade K, Dy 2013 11 5 8 6 29 1.8% 0.92 (0.38, 2.33] Grade K, Dy 2013 11 5 8 1.0 32 117 6.8% 2.26 [1.63, 3.14] Huong Zhang 2014 4 12 2 2 17 0.6% 2.26 [1.63, 3.14] Huong Zhang 2014 4 12 2 2 120 6.5% 2.26 [1.63, 3.14] Total events 454 309 Heterogenerity: Ch ² = 1.6.6% (p = 0.0001): F ORR 2 excond line Huana 2013 32 35 33 32 600 7.0% 1.02 (0.64, 1.63] Huana 2014 32 32 459 4.48% 1.310 (0.7, 2.28] Richard H. de loer 2011 49 255 22 275 4.6% 7.4% 1.50 [1.63, 1.34] F ORR 2 second line Huana 2013 32 353 32 460 F ORR 2 second line Huana 2014 32 32 353 12 466 Heterogenerity: Ch ² = 1.6.6% (
Test for overall effect: $Z = 1.50$ ($P = 0.13$) D 05 2 second line Heist 2014 0.6727 0.2502 1.5% 1.96 [1.20, 3.20] John V. Heymach 2007 -0.0943 0.2569 1.4% 0.91 [0.55, 1.51] Marrin Reck 2014 -0.0619 0.0635 2.36K 0.94 [0.83, 1.06] Richard H. de Boer 2011 -0.01508 0.1428 4.7% 0.86 [0.65, 1.14] Recy 5 Herbs 2011 -0.0943 0.0786 115.4% 0.91 [0.78, 1.06] Subtoal (95% CD) 46.5% 0.94 [0.83, 1.06] Heterogenetic; Ch ² = 2.92, df = 4 ($P = 0.00$); t ² = 56% Test for overall effect: $Z = 1.30$ ($P = 0.19$) Total (95% CD) 100.0% 0.94 [0.89, 1.00] Heterogenetic; Ch ² = 2.57, df = 14 ($P = 0.07$); t ² = 38% Test for overall effect: $Z = 1.98$ ($P = 0.0.0$); t ² = 56% Test for overall effect: $Z = 1.30$ ($P = 0.07$); t ² = 38% Test for overall effect: $Z = 1.30$ ($P = 0.07$); t ² = 38% Test for overall effect: $Z = 1.30$ ($P = 0.07$); t ² = 38% Test for subgroup differences: Ch ² = 0.20, 1, df = 1 ($P = 0.94$), t ² = 0% E ORR first line Chardra P Belani 2014 25 55 15 57 3.2% 1.73 [1.02, 2.91] Grade K. Oy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.3] Grade K. Oy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.3] Grade K. Oy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.3] Grade K. Oy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.3] Grade K. Oy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.3] Grade K. Oy 2013 11 58 10 32 117 6.8% 2.281 (6.13, 3.14] Hana 2014 4 12 2 17 0.4% 2.83 (0.61, 3.93] Value and the de a 10 0 307 21.9% 1.08 (0.85, 1.36] Total events 454 309 Heterogenetic; Ch ² = 1.66, K, P < 0.0001) F ORR 2 second line Hana 2013 12 21 541 137 549 29.9% 1.56 (1.31, 1.87] Tabe and H de low 7.011 49 255 22 25 55 4458 1.131 (0.77, 2.28] Rohard H, de low 7.011 49 255 12 22 25 57 4.45% 1.128, 1.28] Wototal (95% CO) 1955 1994 31.8% 1.60 [1.31, 1.54] F ORR 2 second line Hana 2013 12 21 954 1099 31.8% 1.60 [1.31, 1.54] Total events 228 146
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Bitchard H, de Boer 2011 -0.1508 0.1428 -4.7% 0.36 [0.65; 1.14] Swy S Herbs 2011 -0.0943 0.0786 15.4% 0.91 [0.78, 1.06] Subtotal (95% C) 46.6% 0.94 [0.88, 1.00] Heterogeneity: Ch ² = 2.91, df = 4 (P = 0.06); t ² = 56X Test for overall effect: Z = 1.30 (P = 0.07); t ² = 38X Test for overall effect: Z = 1.30 (P = 0.07); t ² = 38X Test for subgroup differences: Ch ² = 0.01, df = 1 (P = 0.94), t ² = 0% Test for subgroup differences: Ch ² = 0.01, df = 1 (P = 0.94), t ² = 0% Test for subgroup differences: Ch ² = 0.01, df = 1 (P = 0.94), t ² = 0% Test for subgroup differences: Ch ² = 0.01, df = 1 (P = 0.94), t ² = 0% Test for subgroup differences: Ch ² = 0.13, df = 1 (P = 0.94), t ² = 0% Test for subgroup differences: Ch ² = 2.28 For Rins line Chardra P Belani 2014 25 55 15 57 3.28 1.73 [1.02, 2.91] Grade K, Dy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.31] Grade K, Dy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.31] Grade K, Dy 2012 107 385 100 387 21.9% 1.86 (0.85, 1.36] Luine Raz-ares 2012 107 385 100 387 22.9% 1.56 (1.33, 1.41] Yan Wang 2012 11 54 37 549 2.9% 1.56 (1.33, 1.41] Total events 454 309 Heterogeneity: Ch ² = 1.66.5, df = 80 = 0.049
Subtotal (05% C) 46.6% 0.94 [0.86, 1.03] Heterogeneity: Ch ² = 2.91, df = 4 (P = 0.06); t ² = 56% 100.0% 0.94 [0.89, 1.00] Test for overall effect: Z = 1.30 (P = 0.19) 100.0% 0.94 [0.89, 1.00] Heterogeneity: Ch ² = 2.67, df = 14 (P = 0.07); t ² = 38%. 0.5 0.5 0.7 Test for overall effect: Z = 1.98 (P = 0.03) 100.0% 0.94 [0.89, 1.00] Favours VEGFR-TKs Fetrogeneity: Ch ² = 2.67, df = 14 (P = 0.07); t ² = 38%. 0.5 0.5 0.7 1.5 2 Study or Subgroup Gffererces: Ch ² = 2.00, l, df = 1 (P = 0.94), l ² = 0% Favours VEGFR-TKs Favours VEGFR-TKs Favours VEGFR-TKs Favours VEGFR-TKs Chardra P Belani 2014 25 55 15 57 3.2% 1.73 [1.02, 2.91] 1.6 Grade K, Oy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.31) 1.6 Grade K, Oy 2013 11 58 6 29 1.8% 1.31 (0.2, 9.91] 1.6 1.6 1.7% 1.6 (0.48, 1.31) 1.6 1.6 1.6 1.6 1.6 1.6
$\betterogeneticy: Chi^2 = 9.19, df = 4 (P = 0.05); t^2 = 56\% \\ Test for overall effect: 2 = 1.30 (P = 0.19) \\ \hline \betterogeneticy: Chi^2 = 22.67, df = 14 (P = 0.07); t^2 = 38\% \\ \hline \betterogeneticy: Chi^2 = 22.67, df = 14 (P = 0.07); t^2 = 38\% \\ \hline \betterogeneticy: Chi^2 = 22.67, df = 14 (P = 0.07); t^2 = 38\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.01, df = 1 (P = 0.94), t^2 = 0\% \\ \hline \betterogeneticy: Chi^2 = 0.02, t^2 = 0.01, df = 0.02, t^2 $
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Test for overall effect: Z = 1.98 (P = 0.05) For overall effect: Z = 1.98 (P = 0.05) For overall effect: Z = 1.98 (P = 0.05) Test for subgroup differences: Chi = 0.01, df = 1 (P = 0.94), P = 0% Fask Ratio Fask Ratio Study or Subgroup Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl E ORR first line Chardra P Belani 2014 25 55 15 57 3.2% 1.73 (1.02, 2.91) Grade K, Dy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.23) Grade K, Dy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.23) Grade K, Dy 2013 11 58 6 29 1.8% 0.92 (0.38, 2.31) Linong Zhang 2014 4 12 17 0.4% 2.83 (0.61, 1.36) Linong Zhang 2012 107 385 100 387 2.19% 1.56 (0.51, 2.63) Staglionti 2012 107 385 126 (0.65% 1.45 (1.26, 1.36) + Year Ares 2012 107 385 1.28 (0.51, 2.63) + + Year Ares 2012 107 385 100 387 (2.1, 381)
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Total events 228 146
Heterogeneity: $Chi^{-} = 7.11$, $dt = 3$ ($t = 0.07$); $t^{-} = 58\%$
Test for overall effect: Z = 4.67 (P < 0.00001)
Total (95% Cl) 3260 3260 100.0% 1.50 [1.35, 1.66] ♦ Total events 682 455
Heterogeneity: Chi ² = 24.03, df = 12 (P = 0.02); l ² = 50%
Test for overall effect: Z = 7.66 (P < 0.00001) Test for subgroup differences: Chi ² = 0.62, df = 1 (P = 0.43), i ² = 0%
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Fig. 4. Meta-analysis of subgroup. (A) Subgroup of first line of treatment on PFS between VEGFR-TKIs and chemotherapy: fixed-effects model. (B) Subgroup of second line of treatment on PFS between VEGFR-TKIs and chemotherapy: fixed-effects model. (C) Subgroup of first line of treatment on OS between VEGFR-TKIs and chemotherapy: fixed-effects model. (D) Subgroup of second line of treatment on OS between VEGFR-TKIs and chemotherapy: fixed-effects model. (E) Subgroup of first line of treatment on OR between VEGFR-TKIs and chemotherapy: fixed-effects model. (E) Subgroup of first line of treatment on DCR between VEGFR-TKIs and chemotherapy: fixed-effects model. (G) Subgroup of first line of treatment on DCR between VEGFR-TKIs and chemotherapy: random-effects model. (H) Subgroup of second line of treatment on DCR between VEGFR-TKIs and chemotherapy: random-effects model. (H) Subgroup of second line of treatment on DCR between VEGFR-TKIs and chemotherapy: random-effects model. (H) Subgroup of second line of treatment on DCR between VEGFR-TKIs and chemotherapy: random-effects model. (H) Subgroup of second line of treatment on DCR between VEGFR-TKIs and chemotherapy: random-effects model. (H) Subgroup of second line of treatment on DCR between VEGFR-TKIs and chemotherapy: random-effects model. (H) Subgroup of second line of treatment on DCR between VEGFR-TKIs and chemotherapy: random-effects model.



Another focus of the treatment of NSCLC patients is safety and tolerability. VEGFR-TKIs in combination with chemotherapy resulted in more high grade (\geq 3) AEs than chemotherapy alone, such as rash, hemorrhage, neutropenia, hypertension, and diarrhea. Hypertension is a well-known AE of VEGFR-TKIs. It is known that VEGFR-TKIs induce vasoconstriction bv inhibiting flow-mediated dilation⁴⁷. Interestingly, the occurrence of treatment-related hypertension is associated with the benefit of VEGFR-TKIs⁴⁸. The VEGF signal pathway plays an important role in hematopoiesis. Therefore, VEGFR-TKIs may lead to neutropenia. Furthermore, the increased overall incidence of AEs probably reflects the additive effects of the drug combination, for example, the addition of vandetanib to docetaxel resulted in higher rates of grade 3-4 diarrhea, neutropenia, and rash ²⁸. In addition, another reason for these AEs may be the antiangiogenic effects in normal tissues that could destroy the network of capillaries in healthy lung tissues. VEGFR-TKIs change tumor vessel physiology, resulting in increased intratumoral uptake of drugs⁴⁹. The body grows new blood vessels during wound healing, and as collateral circulation around blocked or atherosclerotic blood vessels. One concern is that VEGFR-TKIs may interfere with these normal processes, and worsen conditions such as coronary artery disease or peripheral artery disease. The risk of anemia, nausea, and constipation were comparable between the two groups. One possible explanation for this is the potential benefit of VEGFR-TKIs in

reducing tumor growth. Another explanation might be the increase in erythropoietin induced by the antiangiogenic effect⁵⁰. However, the mechanism has not been fully evaluated and further studies are required. In addition, the lower rate of treatment-related toxic effects indicated that the treatment was tolerable and manageable.

Our study has important limitations. Despite the RCT design, there were slight imbalances in sex and prior lines of therapy in the included trials. Differences between groups in the use of and response to post-progression therapies may confound the DCR and OS outcome. The outcome estimates were taken from published data; thus, systematic biases could not be minimized and the data in some cases were incomplete. Thus, further research should focus on high quality studies and clinical features in patients with comprehensive evaluation to obtain a more standardized study design and more accurate conclusions.

Clearly, there is an urgent need for a better understanding of the complex nature of tumor angiogenesis and how VEGFR-TKIs affect tumor vasculature and cellular components within the tumor microenvironment⁵¹.

Conclusions

The results of this meta-analysis showed that VEGFR-TKIs in combination with chemotherapy prolonged the PFS, ORR, and DCR in patients with advanced NSCLC, but had no impact on the OS.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Authors' contributions

LL collected the references, analyzed the data and wrote the manuscript, JY modified and approved it. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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