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#### ORIGINAL RESEARCH

Risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and ramucirumab: a meta-analysis of 85 randomized controlled trials

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Correspondence: Weilan Wang Department of Pharmacy, Chinese PLA General Hospital, No 28, Fuxing Rd, Beijing 100853, China Tel +86 10 6693 7243 Email 13661282643@163.com **Aim:** Bevacizumab and ramucirumab are antiangiogenic monoclonal antibodies, which target vascular endothelial growth factor-A and vascular endothelial growth factor receptor-2, respectively, used in various cancers. Bleeding events have been described with these two agents. We conducted an up-to-date meta-analysis to determine the relative risk (RR) associated with the use of antiangiogenic monoclonal antibodies, bevacizumab and ramucirumab.

**Methods:** This meta-analysis of randomized controlled trials was performed after searching PubMed, American Society for Clinical Oncology Abstracts, European Society for Medical Oncology Abstracts, and the proceedings of major conferences for relevant clinical trials. RR and 95% CIs were calculated by random-effects or fixed-effects models for all-grade and high-grade bleeding events related to the angiogenesis inhibitors.

**Results:** Eighty-five randomized controlled trials were selected for the meta-analysis, covering 46,630 patients. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade (RR: 2.38, 95% CI: 2.09–2.71, p<0.00001) and high-grade (RR: 1.71, 95% CI: 1.48–1.97, p<0.00001) bleeding compared with control arms. In the subgroup analysis, bevacizumab significantly increased the risk of all-grade (RR: 2.73, 95% CI: 2.24–3.33, p<0.00001) and high-grade bleeding (RR: 1.98, 95% CI: 1.68–2.34, p<0.00001), but ramucirumab only increased the risk of all-grade bleeding (RR: 1.94, 95% CI: 1.76–2.13, p<0.00001) and no difference was observed for the risk of high-grade bleeding (RR: 1.04, 95% CI: 0.78–1.39, p=0.79) compared with the control group. For lung cancer patients, bevacizumab significantly increased the risk of all-grade (RR: 4.72, 95% CI: 1.99–11.19, p=0.0004) and high-grade (RR: 3.97, 95% CI: 1.70–9.29, p=0.001), but no significant differences in the risk of all-grade (RR: 1.09, 95% CI: 0.76–1.57, p=0.64) and high-grade (RR: 1.22, 95% CI: 0.35–4.21, p=0.75) pulmonary hemorrhage were observed for ramucirumab. The increased risk of all-grade and high-grade bleeding was also observed in colorectal cancer or non-colorectal tumors and low-dose or high-dose angiogenesis inhibitors.

**Conclusion:** Antiangiogenic monoclonal antibodies are associated with a significant increase in the risk of all-grade and high-grade bleeding. Ramucirumab may be different from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients.

**Keywords:** bevacizumab, ramucirumab, antiangiogenic monoclonal antibodies, bleeding, meta-analysis





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# Introduction

Angiogenesis is a complex biological process that plays an important role in sustaining growth, invasion, and the metastatic potential of tumors, and this process is mainly driven by vascular endothelial growth factor (VEGF).<sup>1,2</sup> One of the VEGF family members, VEGF-A (commonly referred to as VEGF), has been demonstrated to be important in angiogenesis. Among all receptors, vascular endothelial growth factor receptor (VEGFR)-2 is widely thought to be principally linked to the stimuli of angiogenesis in malignancies. Blocking the function of VEGF-A or its receptor VEGFR-2 has been the most important antiangiogenic strategy for cancer therapy.<sup>3</sup>

Bevacizumab and ramucirumab are the most important antiangiogenic monoclonal antibodies, which target VEGF-A and its receptor VEGFR-2, respectively, used in various cancers. Bevacizumab is approved by the Food and Drug Administration (FDA) for the treatment of patients with metastatic colorectal cancer, advanced non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma, recurrent glioblastoma, advanced cervical cancer, and platinum-resistant ovarian cancer, and ramucirumab is approved by the FDA for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma, metastatic NSCLC, and advanced colorectal cancer.

Bleeding events are a kind of major adverse events reported in clinical trials of bevacizumab and ramucirumab, which may cause severe outcomes that could be even life threatening.<sup>4</sup> The main mechanism of bleeding is that angiogenesis inhibitors disrupt tumor vasculature through inhibition of VEGF signaling and lead to thrombosis or bleeding.<sup>1,5</sup>

However, the relative risk (RR) of bleeding events in patients with cancer treated with these two antiangiogenic monoclonal antibodies has yet to be defined. Therefore, we conducted an up-to-date meta-analysis of available clinical trials to determine the RR of bleeding in cancer patients treated with antiangiogenic monoclonal antibodies, bevacizumab and ramucirumab.

# Materials and methods Search strategy

This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement<sup>6</sup> (Supplementary material). We searched PubMed, American Society for Clinical Oncology Abstracts, and European Society for Medical Oncology Abstracts for relevant trials till September 2017. Moreover, we also searched the clinical trial registration website (https:// www.ClinicalTrials.gov) to obtain information on registered randomized controlled trials (RCTs). Keywords used in the search were "bevacizumab," "avastin," "ramucirumab," "IMC1121B," "LY3009806," and "randomized controlled trials." The search was limited to RCTs published in English.

## Selection of trials

Data abstraction and quality assessment were conducted independently by two reviewers. Disagreements were resolved by discussion with an independent expert. The RCTs were eligible for inclusion in our meta-analysis: 1) prospective Phase II and Phase III RCTs in patients with cancer, 2) random assignment of participants to these two antiangiogenic monoclonal antibodies treatment or control groups, 3) available data, including the event or incidence of bleeding and sample size for analysis. Phase I and single-arm phase II trials were excluded because of their lack of control groups.

#### Data extraction

We extracted details on study characteristics, treatment information, results, and safety profiles from the selected trials. Clinical endpoints were obtained from the safety profile of each clinical trial. All-grade, high-grade bleeding and all-grade, high-grade pulmonary hemorrhage in lung cancers were recorded according to the version of National Cancer Institute-Common Terminology Criteria for Adverse Events used in each trial.

#### Statistical analysis

Data were calculated by Review Manager version 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). For the outcomes, the RR was calculated for dichotomous data. Statistical heterogeneity in the results of the trials was assessed by the chi-square test, and expressed by the  $I^2$  index.<sup>7</sup> When there was no statistically significant heterogeneity, a pooled effect was calculated with a fixed-effect model. When considerable heterogeneity was found (p < 0.1, or  $I^2 > 50\%$ ), a random-effect model was employed. Subgroup analysis was conducted to examine whether the RRs of all-grade and high-grade bleeding varied by drug type, drug dosage, and cancer type.

#### **Results** Search results

We reviewed 2,045 potentially relevant articles from our initial search strategies. A total of 1,906 articles were excluded on screening abstracts and titles for the following reasons: review articles, case reports, basic researches,

Phase I or single-arm Phase II studies, irrelevant topics, and duplicate reports. The remaining 139 articles were retrieved for full evaluation, and 54 articles were excluded for unavailable data for assessment of bleeding or antiangiogenic monoclonal antibodies in both treatment and control arms. Finally, 85 RCTs were included in this meta-analysis.<sup>8–92</sup> The study search process is shown in a flow chart (Figure 1).

## Patients

A total of 85 studies and 46,630 patients were included for the analysis. Bevacizumab was investigated in 72 trials<sup>8-79</sup> and ramucirumab was investigated in 13 trials.<sup>80-92</sup> All of the studies included 21 colorectal cancer,<sup>8-26,85,86</sup> 15 breast cancer,<sup>27–39,87,88</sup> 16 lung cancer,<sup>40–52,80–82</sup> three renal cell cancer, 53,54 two pancreatic cancer, 55,56 five ovarian cancer, 57-61 six gastric or gastroesophageal junction adenocarcinoma, 62-65, <sup>89-91</sup> three glioblastoma,<sup>66-68</sup> one lymphoma,<sup>69</sup> one lymphocytic leukemia,70 two melanoma,71,72 two malignant mesothelioma,<sup>73,74</sup> one prostate cancer,<sup>75</sup> one cervical cancer,<sup>76</sup> one leiomyosarcoma,<sup>77</sup> two urothelial carcinoma,<sup>83,84</sup> two hepatocellular carcinoma,78,92 and one soft tissue sarcoma.79 In addition, 35 trials<sup>9,10,12–20,22–26,46,49,52,55,58,62–65,72,78–84,87,88</sup> were treated with low-dose drugs (28 trials for bevacizumab at 2.5 mg/kg/week, seven trials for ramucirumab at 3.3 mg/kg/ week) and 46 trials<sup>11,21,27,28,30-39,41,42,44,45,47,48,50,51,53,54,56,57,59-61,66-71,</sup> <sup>73–77,85,86,89–92</sup> were treated with high-dose drugs (40 trials for bevacizumab at 5 mg/kg/week, six trials for ramucirumab at 4 mg/kg/week). Other 4 three-arm trials<sup>8,29,40,43</sup> were two

arms of different dosage levels of bevacizumab and one arm of control. All of these RCTs were judged to be of adequate quality (Jadad score is 3–5). Baseline characteristics of the 85 RCTs are provided in Table 1.

# RR of all-grade bleeding

Forty-three RCTs were available to calculate the RR of allgrade bleeding in patients assigned to angiogenesis inhibitors arms versus control arms. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade (RR: 2.38, 95% CI: 2.09–2.71, p<0.00001) bleeding compared with control arms. There was statistically significant heterogeneity ( $I^2$ =74%) across the trials; we incorporated it into a random-effects model (Figure 2).

# RR of high-grade bleeding

The RR of high-grade ( $\geq$  grade 3) bleeding was determined in 82 RCTs. The results showed that antiangiogenic monoclonal antibodies significantly increased the risk of all-grade bleeding (RR: 1.71, 95% CI: 1.48–1.97, *p*<0.00001) with a fixed-effects models (*I*<sup>2</sup>=19%) (Figure 3).

# RR according to drug type

As an exploratory analysis, patients were stratified according to drug type. We found that bevacizumab significantly increased the risk of all-grade (RR: 2.73, 95% CI: 2.24–3.33, p < 0.00001) and high-grade bleeding (RR: 1.98, 95% CI: 1.68–2.34, p < 0.00001), but ramucirumab only increased



Figure I Outline of the search flow diagram. Abbreviation: RCTs, randomized controlled trials.

Author	Year	Malignancy	Phase	No. in	Concurrent treatment	Dose	No. of ble	No. of bleeding events
				intervention/ control		(mg/kg/week)	in interver All grade	in intervention/control All grade Grade ≥3
Bevacizumab								
Kabbinavar et al <sup>8</sup>	2003	CRC	=	67/35	Fluorouracil + leucovorin	2.5 or 5	NR	3/0
Hurwitz et al <sup>9</sup>	2004	CRC	≡	393/397	lrinotecan + fluorouracil + leucovorin	2.5	NR	12/10
Kabbinavar et al <sup>10</sup>	2005	CRC	=	100/104	Fluorouracil + leucovorin	2.5	NR	5/3
Giantonio et al <sup>11</sup>	2007	CRC	Ξ	287/285	Oxaliplatin + fluorouracil + leucovorin	S	NR	1/01
Saltz et al <sup>12</sup>	2008	CRC	≡	694/675	Capecitabine + oxaliplatin/fluorouracil +	2.5	NR	13/8
					folinic acid + oxaliplatin			
Allegra et al <sup>13</sup>	2009	CRC	≡	1,326/1,321	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	25/25
Tebbutt et al <sup>14</sup>	2010	CRC	≡	157/156	Capecitabine	2.5	19/19	2/4
Statopoulos et al <sup>15</sup>	2010	CRC	≡	114/108	Irinotecan + fluorouracil + leucovorin	2.5	3/0	NR
Guan et al <sup>16</sup>	2011	CRC	≡	141/70	lrinotecan + fluorouracil + leucovorin	2.5	NR	1/1
Dotan et al <sup>17</sup>	2012	CRC	=	12/11	Capecitabine + oxaliplatin + cetuximab	2.5	6/4	0/0
De Gramont et al <sup>18</sup>	2012	CRC	≡	1,145/1,126	Oxaliplatin + fluorouracil + leucovorin	2.5	NR	14/6
Bennouna et al <sup>19</sup>	2013	CRC	≡	401/409	Fluorouracil/capecitabine + oxaliplatin/irinotecan	2.5	NR	8/1
Cunningham et al <sup>20</sup>	2013	CRC	≡	134/136	Capecitabine	2.5	34/9	0/1
Cao et al <sup>21</sup>	2015	CRC	=	65/77	Irinotecan + fluorouracil + leucovorin	5	NR	5/0
Hegewisch-Becker et al <sup>22</sup>	2015	CRC	≡	156/158	None	2.5	14/11	0/1
Passardi et al <sup>23</sup>	2015	CRC	≡	176/194	lrinotecan + fluorouracil + leucovorin/oxaliplatin +	2.5	30/9	NR
					fluorouracil + leucovorin			
Masi et al <sup>24</sup>	2015	CRC	=	91/92	lrinotecan + fluorouracil + leucovorin/oxaliplatin +	2.5	19/2	0/0
					fluorouracil + leucovorin			
Koeberle et al <sup>25</sup>	2015	CRC	≡	131/131	None	2.5	5/1	0/0
Snoeren et al <sup>26</sup>	2017	CRC	≡	39/36	Capecitabine + oxaliplatin	2.5	NR	1/0
Miller et al <sup>27</sup>	2005	BC	≡	229/215	Capecitabine	5	66/24	1/1
Miller et al <sup>28</sup>	2007	BC	≡	365/346	Paclitaxel	5	NR	2/0
Miles et al <sup>29</sup>	2010	BC	≡	499/23 I	Docetaxel	2.5 or 5	NR	5/2
Brufsky et al <sup>30</sup>	2011	BC	≡	458/221	Capecitabine/taxane/gemcitabine/vinorelbine	5	NR	8/0
Robert et al <sup>31</sup>	2011	BC	≡	817/403	Capecitabine/taxane/anthracycline	5	NR	14/1
von Minckwitz et al <sup>32</sup>	2012	BC	≡	956/969	Epirubicin/cyclophosphamide/docetaxel	5	NR	4/3
Gianni et al <sup>33</sup>	2013	BC	≡	215/206	Docetaxel + trastuzumab	5	NR	3/1
Cameron et al <sup>34</sup>	2013	BC	≡	1,288/1,271	Anthracycline/taxane	5	NR	8/2
Coudert et al <sup>35</sup>	2014	BC	=	47/25	Trastuzumab + docetaxel	5	NR	0/0
von Minckwitz et al <sup>36</sup>	2014	BC	Ξ	245/238	Taxane/anthracycline/capecitabine/vinorelbine/	5	33/18	1/4
					gemcitabin/cyclophosphamide			
Sikov et al <sup>37</sup>	2015	BC	=	215/218	Paclitaxel $\pm$ carboplatin–doxorubicin + cyclophosphamide	5	NR	2/0
Diéras et al <sup>38</sup>	2015	BC	=	56/57	Trebananib + paclitaxel	5	29/17	0/0
Miles et al <sup>39</sup>	2017	BC	=	238/233	Paclitaxel	5	106/62	2/2
Johnson et al <sup>40</sup>	2004	LC	=	66/32	Carboplatin + paclitaxel	2.5 or 5	NR	0/9

19/3	3/1	28/6	10/7	2/0	3/0	2/0	2/1	0/0	0/0	0/0	0/0	1/11	4/1	22/16	5/4	I 4/5	9/2	2/2	15/2	6/3	6/6	1/3	12/4	2/2	15/8	4/2	5/0	8/1		0/1	2/5	1/1	4/1	2/0	35/16	10/2	1/0	3/1	2/6	(Continued)
NR	NR	NR	NR	94/18	2/0	54/22	NR	7/2	20/3	NR	NR	112/28	21/4	124/67	NR	NR	295/87	NR	170/78	140/27	NR	NR	NR	15/7	186/97	NR	NR	77/31		NR	NR	153/13	NR	91/16	NR	NR	1/2	3/1	NR	
5	5	2.5 or 5	ъ	5	2.5	ъ	S	2.5	ъ	S	2.5	5	5	2.5	5	5	2.5	S	5	5	2.5	2.5	2.5	2.5	5	S	5	5		5	5	2.5	5	5	5	5	5	2.5	2.5	
Paclitaxel + carboplatin	Docetaxel/pemetrexed	Cisplatin + gemcitabine	Erlotinib	Carboplatin + paclitaxel	Docetaxel + carboplatin $\pm$ erlotinib	Erlotinib	Carboplatin, paclitaxel	${\sf Cisplatin}+{\sf etoposide}\pm{\sf epidoxorubicin}+{\sf cyclophosphamide}$	Docetaxel	Pemetrexed	Cisplatin + etoposide	Interferon $\alpha$	Interferon $lpha$	Gemcitabine + erlotinib	Gemcitabine	Paclitaxel + carboplatin	Paclitaxel + carboplatin	PLD/paclitaxel/topotecan	Gemcitabine + carboplatin	Paclitaxel + carboplatin	Cisplatin + capecitabine	Epirubicin + cisplatin + capecitabine	Capecitabine + cisplatin	Epirubicin + cisplatin + capecitabine	Radiotherapy + temozolomide	None	Temozolomide	Rituximab + doxorubicin + vincristine +	cyclophosphamide + prednisone instead of R-CHOP	Pentostatin + cyclophosphamide + rituximab	Paclitaxel + carboplatin	None	Gemcitabine + cisplatin	Pemetrexed + cisplatin	Docetaxel + prednisone	Paclitaxel/topotecan + cisplatin	Gemcitabine + docetaxel	TACE	<pre>lfosfamide + vincristine + actinomycin-D + doxorubicin</pre>	instead of VADO/IVA/cyclophosphamide + vinorelbine
427/440	39/42	659/327	313/313	119/58	116/113	75/77	140/134	37/37	50/50	45/35	95/103	337/304	362/347	296/287	277/263	608/601	745/753	12/181	247/233	330/327	386/381	101/66	101/001	468/477	461/450	260/233	48/45	395/386		33/32	143/69	671/672	53/55	222/224	504/505	220/219	52/51	16/11	71/79	
≡	=	≡	≡	=	≡	=	≡		=	=	≡	≡	≡	≡	≡	≡	≡	≡	≡	≡	≡	11/11	≡	/	≡	≡	=	≡		=	=	≡	=	≡	≡	≡	≡	=	=	
LC	ГC	LC	ГC	ГC	ГC	ГC	ГC	ГC	ГC	ГC	ГC	RCC	RCC	PC	PC	oC	00	00	00	00	GC	CC	GC, GEJC	GEJC	Glioblastoma	Glioblastoma	Glioblastoma	Lymphoma		Lymphocytic leukemia	Melanoma	Melanoma	ΜМ	ΜМ	Prostate cancer	Cervical cancer	nLMS	HC	STSs	
2006	2007	2009	2011	2012	2013	2014	2015	2015	2016	2016	2017	2007	2010	2009	2010	2011	2011	2014	2015	2017	2011	2013	2015	2017	2014	2014	2016	2014		2016	2012	2014	2012	2016	2012	2014	2015	2015	2017	
Sandler et al <sup>41</sup>	Herbst et al <sup>42</sup>	Reck et al <sup>43</sup>	Herbst et al <sup>44</sup>	Niho et al <sup>45</sup>	Boutsikou et al <sup>46</sup>	Seto et al <sup>47</sup>	Zhou et al <sup>48</sup>	Pujol et al <sup>49</sup>	Takeda et al <sup>so</sup>	Karayama et al <sup>51</sup>	Tiseo et al <sup>52</sup>	Escudier et al <sup>53</sup>	Rini et al <sup>54</sup>	Van Cutsem et al <sup>55</sup>	Kindler et al <sup>56</sup>	Burger et al <sup>57</sup>	Perren et al <sup>58</sup>	Pujade-Lauraine et al <sup>59</sup>	Aghajanian et al <sup>60</sup>	Coleman et al <sup>61</sup>	Ohtsu et al <sup>62</sup>	Okines et al <sup>63</sup>	Shen et al <sup>64</sup>	Cunningham et al <sup>65</sup>	Chinot et al <sup>66</sup>	Gilbert et al <sup>67</sup>	Balana et al <sup>68</sup>	Seymour et al <sup>69</sup>		Kay et al <sup>70</sup>	Kim et al <sup>71</sup>	Corrie et al <sup>72</sup>	Kindler et al <sup>73</sup>	Zalcman et al <sup>74</sup>	Kelly et al <sup>75</sup>	Tewari et al <sup>76</sup>	Hensley et al $^{77}$	Pinter et al <sup>78</sup>	Chisholm et al <sup>79</sup>	

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Author	Year	Malignancy	Phase	No. in	Concurrent treatment	Dose	No. of blee	No. of bleeding events
				intervention/		(mg/kg/week)	in interven	in intervention/control
				control			All grade	Grade ≥3
Ramucirumab								
Yoh et al <sup>80</sup>	2016	ГC	=	76/81	Docetaxel	3.3	39/23	2/0
Doebele et al <sup>81</sup>	2015	LC	=	67/69	Pemetrexed + cisplatin	3.3	26/13	2/1
Garon et al <sup>82</sup>	2014	ГC	≡	627/618	Docetaxel	3.3	181/94	15/14
Petrylak et al <sup>83</sup>	2016	nc	=	46/45	Docetaxel	3.3	31/12	2/1
Petrylak et al <sup>84</sup>	2017	nc	≡	263/267	Docetaxel	3.3	67/46	8/12
Tabernero et al <sup>85</sup>	2015	CRC	≡	529/528	None	4	232/120	13/9
Moore et al <sup>86</sup>	2016	CRC	=	52/49	Oxaliplatin + fluorouracil + leucovorin	4	25/9	NR
Mackey et al <sup>87</sup>	2015	BC	≡	752/382	Docetaxel	3.3	361/85	7/7
Yardley et al <sup>88</sup>	2016	BC	=	69/65	Eribulin	3.3	13/3	1/1
Fuchs et al <sup>89</sup>	2014	GC or GEJC	≡	236/115	None	4	30/13	8/3
Wilke et al <sup>90</sup>	2014	GC or GEJC	≡	327/329	Paclitaxel	4	137/59	14/8
Yoon et al <sup>91</sup>	2016	GC, EC, or GEJC	=	82/80	Oxaliplatin + fluorouracil + leucovorin	4	36/20	5/5
Zhu et al <sup>92</sup>	2015	HC	≡	277/276	None	4	90/55	17/21

the risk of all-grade bleeding (RR: 1.94, 95% CI: 1.76–2.13, p < 0.00001) and no difference was observed for the risk of high-grade bleeding (RR: 1.04, 95% CI: 0.78–1.39, p=0.79) compared with the control group. RR of all-grade and high-grade bleeding according to drug type is summarized in Tables 2 and 3, respectively.

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In addition, we further assessed the risk of pulmonary hemorrhage of bevacizumab and ramucirumab in all lung cancer patients. The results showed that bevacizumab significantly increased the risk of all-grade (RR: 4.72, 95% CI: 1.99–11.19, p=0.0004) and high-grade pulmonary hemorrhage (RR: 3.97, 95% CI: 1.70–9.29, p=0.001), but no significant differences in the risk of all-grade (RR: 1.09, 95% CI: 0.76–1.57, p=0.64) and high-grade (RR: 1.22, 95% CI: 0.35–4.21, p=0.75) pulmonary hemorrhage were observed for ramucirumab. RR of all-grade and high-grade pulmonary hemorrhage is shown in Figures 4 and 5, respectively.

#### RR according to drug dosage

In the subgroup analysis by dosage, the increased risk of allgrade and high-grade bleeding was observed in both low-dose and high-dose angiogenesis inhibitors.

The risks of all-grade bleeding were comparable between patients with low-dose angiogenesis inhibitors (RR: 2.46, 95% CI: 1.95–3.11) and high-dose angiogenesis inhibitors (RR: 2.34, 95% CI: 2.00–2.73) (Table 2). The risk of high-grade bleeding was more frequently observed in patients with high-dose angiogenesis inhibitors (RR: 2.17, 95% CI: 1.79–2.64) than in those with low-dose angiogenesis inhibitors (RR: 1.31, 95% CI: 1.06–1.60) (Table 3).

## RR according to tumor type

Studies were further stratified according to tumor type (colorectal cancer vs non-colorectal tumors). Increased risk of all-grade and high-grade bleeding was observed in both the colorectal cancer arm and non-colorectal tumors arm. The risks of all-grade (RRs for colorectal cancer and non-colorectal tumors were 2.24, 95% CI: 1.58–3.19 and 2.42, 95% CI: 2.09–2.80, respectively) (Table 2) and high-grade bleeding (RRs for colorectal cancer and non-colorectal tumors were 1.52, 95% CI: 1.13–2.03 and 1.77, 95% CI: 1.50–2.09, respectively) (Table 3) were comparable between patients with colorectal cancer and non-colorectal tumors.

## Publication bias

To minimize publication bias, we selected papers strictly according to the inclusion criteria. Furthermore, a funnel plot

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Study or subgroup	Experimental events	Total	Control events	Total	Weight (%)	Risk ratio M–H, random, 95% Cl	Risk ratio M–H, random, 95% Cl	
Aghajanian et al60	170	247	78	233	3.8	2.06, 1.68–2.51	-	- 2
Boutsikou et al <sup>46</sup>	7	116	0	113	0.2	14.62, 0.84–252.94		
Chinot et al <sup>66</sup>	186	461	97	450	3.8	1.87, 1.52–2.31	-	
Coleman et al <sup>61</sup>	140	330	27	327	3.1	5.14, 3.50–7.53	-	
Corrie et al <sup>72</sup>	153	671	13	672	2.4	11.79, 6.76–20.55	-	
Cunningham et al <sup>20</sup>	34	134	9	136	1.9	3.83, 1.91–7.68		
Cunningham et al <sup>65</sup>	15	468	7	477	1.4	2.18, 0.90–5.31		
Diéras et al <sup>38</sup>	29	56	17	57	2.7	1.74, 1.08–2.78		
Doebele et al <sup>81</sup>	26	67	13	69	2.3	2.06, 1.16–3.66		
Dotan et al <sup>17</sup>	6	12	4	11	1.3	1.38, 0.52–3.61		
Escudier et al53	112	337	28	304	3.1	3.61, 2.46–5.30	-	
Fuchs et al <sup>89</sup>	30	236	13	115	2.2	1.12, 0.61–2.07		
Garon et al <sup>82</sup>	181	627	94	618	3.7	1.90, 1.52–2.37	-	
Hegewisch-Becker et al <sup>22</sup>	14	156	11	158	1.7	1.29, 0.60–2.75		
Hensley et al <sup>77</sup>	1	52	2	51	0.3	0.49, 0.05–5.24		
Koeberle et al <sup>25</sup>	5	131	1	131	0.3	5.00, 0.59–42.21		_
Mackey et al <sup>87</sup>	361	752	85	382	0.3 3.8	2.16, 1.76–2.64	-	
Masi et al <sup>24</sup>	19	732 91	2	92	0.7	9.60, 2.30–40.05		_
Miles et al <sup>39</sup>	106	238	2 62	233	3.6	9.00, 2.30–40.03 1.67, 1.30–2.16		
Miller et al <sup>27</sup>	66	238 229	02 24	233 215	3.0 2.9	,	*	
Moore et al <sup>86</sup>	25	229 52	24 9	49	2.9	2.58, 1.68–3.96	-	
Niho et al <sup>45</sup>	25 94	52 119				2.62, 1.36–5.04		
Passardi et al <sup>23</sup>	94 30	176	18 9	58 194	3.0 1.9	2.55, 1.72–3.78	-	
	295	745		753		3.67, 1.79–7.52		
Perren et al <sup>58</sup>			87		3.8	3.43, 2.76–4.26	Ŧ	
Petrylak et al <sup>83</sup>	31	46	12	45	2.5	2.53, 1.50–4.27		
Petrylak et al <sup>84</sup>	67	263	46	267	3.3	1.48, 1.06–2.07	-	
Pinter et al <sup>78</sup>	3	16	1	11	0.3	2.06, 0.25–17.34		
Pujol et al <sup>49</sup>	7	37	2	37	0.6	3.50, 0.78–15.75		
Rini et al <sup>54</sup>	21	362	4	347	1.1	5.03, 1.75–14.51		
Seto et al <sup>47</sup>	54	75	22	77	3.1	2.52, 1.72–3.69	-	
Seymour et al <sup>69</sup>	77	395	31	386	3.0	2.43, 1.64–3.59	-	
Statopoulos et al <sup>15</sup>	3	114	0	108	0.2	6.63, 0.35–126.96		
Tabernero et al <sup>85</sup>	232	529	120	528	3.9	1.93, 1.60–2.32		
Takeda et al⁵⁰	20	50	3	50	1.0	6.67, 2.11–21.02		
Tebbutt et al <sup>14</sup>	19	157	19	156	2.2	0.99, 0.55–1.80		
Van Cutsem et al55	124	296	67	287	3.6	1.79, 1.40–2.30	-	
von Minckwitz et al <sup>36</sup>	33	245	18	238	2.4	1.78, 1.03–3.07		
Nilke et al <sup>90</sup>	137	327	59	329	3.6	2.34, 1.79–3.04	-	
Yardley et al <sup>88</sup>	13	69	3	65	0.9	4.08, 1.22–13.67		
Yoh et al <sup>80</sup>	39	76	23	81	3.0	1.81, 1.20–2.72		
Yoon et al <sup>91</sup>	36	82	20	80	2.8	1.76, 1.12–2.76		
Zalcman et al <sup>74</sup>	91	222	16	224	2.6	5.74, 3.49–9.44		
Zhu et al <sup>92</sup>	90	277	55	276	3.5	1.63, 1.22–2.18	-	
Total, 95% Cl		10,141		9,490	100	2.38, 2.09–2.71	•	
Total events	3,202		1,231					
Heterogeneity: $\tau^2=0.11$ ; $\chi^2$			); <i>I</i> ²=74%					
Test for overall effect: Z=1	2.95 (p<0.00001)						0.005 0.1 1 10	20
							Favors Favo	

Figure 2 RR of all-grade bleeding. Abbreviations: M–H, Mantel–Haenszel; RR, relative risk.

was used to detect publication bias and no apparent bias was found according to it for all-grade and high-grade bleeding.

# Discussion

To the best of our knowledge, this is the first and the largest meta-analysis to assess the risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and ramucirumab. The results of our meta-analysis showed a significant 2.38-fold increased all-grade bleeding risk and a 1.71-fold increased high-grade bleeding risk with these agents. A similar risk of bleeding is also associated with other VEGF receptor tyrosine kinase inhibitors.<sup>93</sup>

In order to identify potential risk factors, we performed subgroup analysis according to drug types. The results

ubujonjo         Potel	Oto da ca			<b>a</b>				Bill of the training
Weigen at all         25         1.328         25         1.321         8.5         1.00.088-1.73	Study or subgroup				Total			
alama et al" 5 48 0 46 0 2 103. 0.59-191.54	Aghajanian et al <sup>60</sup>	15	247		233		7.07, 1.64-30.60	
Bernoma all <sup>11</sup> 5 401 1 460 0.3 B. B. 1, 106-6494 4 4 4 4 4 4 4 4 5 4 4 5 4 4 5 4 4 4 5 4 5 4 4 4 5 4 5 4 4 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4 5 5 4 5 4 5 4 5 4 5 4 5 5 4 5 4 5 4 5 4 5 5 4 5 4 5 4 5 5 4 5 4 5 4 5 5 4 5 4 5 5 4 5 4 5 5 4 5 4 5 5 4 5 4 5 5 4 5 5 4 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	Allegra et al <sup>13</sup>							-
Society of at <sup>16</sup> 3         116         0         113         0.2         8.82, 0.38-190, 67           Society of at <sup>16</sup> 6         6         0         211         0.2         8.82, 0.48-14, 81           Society of at <sup>16</sup> 5         6.65         0         77         0.2         8.82, 0.48-14, 81           Society of at <sup>16</sup> 5         6.65         0         77         0.2         130, 0.78-427           Society of at <sup>16</sup> 5         6.65         0         77         0.2         130, 0.78-427           Society of at <sup>16</sup> 6         6.6         0         77         0.2         0.50, 0.07-427           Society of at <sup>16</sup> 0         6.7         0         0.00, 0.05-15, 8								
backsy et al <sup>20</sup> 8         468         0         221         0.2         82.2         0.4-14.18           American et al <sup>20</sup> 1.28         0.27         1.28         0.07-764								
Jager et al <sup>27</sup> , 14 4 500 5 001 1,7 2,77, 10,7-7.4 4 4 4 1,7 2,77, 10,7-7.4 4 4 4 1,7 2,8 2,7 1,0 7,8 4 4 4 1,7 2,7 1,0 7,8 4,7 1,0 1,0 8,0,5 7,8 6 4 4 4 1,7 1,0 7,9 1,0 1,0 8,0,0 7,8 6 4 4 4 1,7 1,0 7,9 1,0 1,0 8,0,0 7,8 6 4 4 4 1,0 1,0 7,2 1,0 1,0 8,0,0 7,8 6 4 4 4 1,0 1,0 7,2 1,0 1,0 8,0,0 7,8 6 4 4 4 1,0 1,0 7,2 1,0 1,0 8,0,0 7,8 6 4 4 4 1,0 1,0 7,2 1,0 1,0 8,0,0 7,8 6 4 4 4 1,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 1,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 2,0 1,0 7,1 1,0 1,0 1,0 1,0 1,0 1,0 1,0 1,0 1,0 1								
Damber of all         6         1.288         2         1.271         0.7         33.06.0.8-18.55           Dance of all         5         6         6         0         77         0.2         133.0.79-427           Camber of all         6         6.30         3.27         10.0         133.0.79-427           Camber of all         6         6.30         3.27         10.0         10.0.05-786           Camber of all         6         7.7         0.5         Not estimable           Consolid et all         0         7.7         0.5         Not estimable           Consolid et all         0         7.7         0.5         0.52.0.0.1-7.21           Consolid et all         1.144         1.6         0.7         Not estimable           Consolid et all         1.126         2.2         0.2.2.0.0.1-2.21								
Date data <sup>11</sup> 5         65         0         77         0.2         13.00.073-23.07           Date data <sup>11</sup> 15         451         5         65         0         77         0.2         13.00.073-23.07           Date main         15         15         15         15         150.00-7.65         150.00-7.65           Date data <sup>11</sup> 1         671         1         672         0.3         10.00.00-7.82.07           Date data <sup>11</sup> 1         671         1         672         0.3         10.00.00-7.82.07           Date data <sup>11</sup> 0         47         0         257         0.00.00-1.82.1           Date data <sup>11</sup> 0         434         1.145         6         1.126         21         2.28.0.08-5.95           Date data <sup>11</sup> 0         1.33         1.1         1.4         1.30.0.35-4.81	Cameron et al34		1,288					· · · ·
Diaboline at all         2         71         6         79         1.9         0.37, 0.50-178           Control at all         6         330         3         327         1.0         1.00, 0.50-158           Control at all         1         0.71         0.72         0.3         1.00, 0.50-158           Control at all         1         138         0.5         0.44, 0.00-162.2           Control at all         1.128         1.128         1.22, 0.14-7.21           Data at all         1.128         1.128         1.128         1.128           Data at all         1.128         1.128         1.128         1.128         1.128           Data at all         1.128         1.128         1.128         1.128         1.128         1.128         1.128         1.128         1.128         1.128         1.128	Cao et al <sup>21</sup>	5	65	0	77	0.2	13.00, 0.73-230.76	+
Johanna rafi"       6       330       3       327       1.0       1.88, 0.59-7.86         Concert at all*       1       672       0.3       1.00, 0.00-15.98         Journingham at all*       2       445       2       1.00, 0.00-15.98         Journingham at all*       2       445       2       1.00, 0.00-15.98         Joachert at all*       1.4       1.145       6       1.126       2.1       2.230, 0.85-5.95         Joachert at all*       0       56       0.7       Not estimable	Chinot et al66							+
Scrie et al <sup>10</sup> 0       071       0       072       0.3       100.006-15.98         Jurningham et al <sup>10</sup> 0       34       1       136       0.5       0.44.001-8.23         Jurningham et al <sup>10</sup> 0       34       1       136       0.5       0.44.001-8.23         Join and tal <sup>10</sup> 0       88       0       97.0       Not estimable         Join and tal <sup>10</sup> 0       12       0       11       Not estimable         Join and tal <sup>10</sup> 1       2.0       11       Not estimable	Chisholm et al <sup>79</sup>							
Dodefit et al <sup>a</sup> 0         47         0         25         Not estimable           Durningham et al <sup>an</sup> 0         134         1         136         0.5         0.34         0.01-8.23           Durningham et al <sup>an</sup> 2         468         2         477         0.7         102         0.01-8.23           Darbie et al <sup>an</sup> 14         1145         6         10.26         0.01-8.23         0.00-8.23           Darbie et al <sup>an</sup> 1         37         1         0.40         0.4         9.32         1.20-84.14           Darbie et al <sup>an</sup> 1         37         1         304         0.4         9.32         1.20-78.14           Darbie et al <sup>an</sup> 1         0.27         1         605         4.3         120.03-8.41         1.4           Darbie et al <sup>an</sup> 1         0.27         1         265         0.3         9.63.128-77.01         1.4         10.3         120.7         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-97.01         1.70.03-								
Lunningham et al <sup>10</sup> Lunningham et al <sup>10</sup> the Gamort et al <sup>10</sup> the Gamort et al <sup>10</sup> the Gamort et al <sup>10</sup> the Gamort et al <sup>10</sup> Cobbe et al <sup>11</sup> Cobbe et al <sup>11</sup>				-		0.3		
Junningham et all <sup>16</sup> 2 458 2 477 0.7 120.014-721 been at all <sup>17</sup> 0 58 0 57 been at all <sup>17</sup> 1 141 1 70 consolid tall <sup>17</sup> 144 11 70 consolid tall <sup>17</sup> 144 0 59 1 15 been at all <sup>17</sup> 144 11 70 consolid tall <sup>17</sup> 144 0 59 1 15 been at all <sup>18</sup> 1 144 1 70 consolid tall <sup>17</sup> 144 0 58 0 5 consolid tall <sup>17</sup> 145 0 7 consolid tall <sup>17</sup> 15 consolid tall <sup>17</sup> 145 0 7 consolid tall <sup>17</sup> 15 consolid tall <sup>17</sup>						0.5		
be Grammet al <sup>11</sup> 14 1,145 6 1,126 2,1 222,0.88–5.96								
Defense tal <sup>an</sup> O       S8       O       S7       Not estimable         Defan et al <sup>an</sup> 0       12       0       11       Not estimable         Defan et al <sup>an</sup> 1       327       13       16       0.14       9.32       1.52-78.41         Samon et al <sup>an</sup> 15       207       14       161       4.4       9.32       1.52-78.41								
December are         2         67         1         69         0.3         2006. [0 + 22: 18           Scouder et all <sup>21</sup> 1         337         1         304         0.4         9.32. [2:0.75:41           Scouder et all <sup>21</sup> 8         227         3         116         14         9.32. [2:0.75:41           Signific et all <sup>21</sup> 3         257         14         206         0.3         9.37. [2:0.75:41           Signific et all <sup>21</sup> 10         287         1         266         0.3         9.37. [2:0.75:41           Signific et all <sup>21</sup> 10         287         1         266         0.3         9.37. [2:0.75:41           Signific et all <sup>21</sup> 1         10         33         0.7         17.0         0.3         0.57:0.00-7.82           Signific et all <sup>21</sup> 1         11         10         0.3         0.34. 0.12-82	Diéras et al <sup>38</sup>							
Johan et al <sup>17</sup> 0       12       0       11       Not estimable         Under et al <sup>18</sup> 5       237       3       15       1       130       0.35       2.120-76       14         Simol et al <sup>18</sup> 3       255       1       265       0.3       2.97       17         Simol et al <sup>18</sup> 10       267       1       265       0.3       9.93, 128-77.07         Simol et al <sup>18</sup> 1       41       1       70       0.3       0.57, 0.03-9.70         Simol et al <sup>18</sup> 1       41       1       70       0.3       0.50, 0.00-7.82         Simol et al <sup>18</sup> 1       141       1       70       0.3       0.50, 0.00-7.82         Simol et al <sup>18</sup> 10       133       7       133       2.4       143, 0.55-37.7         Simol et al <sup>18</sup> 10       133       10       317       2.4       143, 0.55-2.77         Simolog al <sup>18</sup> 6       6       0       32       0.2       0.40, 0.37-110, 2.0-80.70         Simolog al <sup>18</sup> 1       0       1.5       1.6       50       5.4       1.6       50       5.4       1.6       50       5.4       1.6	Doebele et al <sup>81</sup>					0.3		
Scader al <sup>ab</sup> 11         337         1         304         0.4         9.32, 120-78.41           Gran at al <sup>ab</sup> 15         627         14         618         4.8         1.06, 0.67-217           Samon at al <sup>ab</sup> 15         627         14         618         4.8         1.06, 0.67-217           Samon at al <sup>ab</sup> 10         257         11         206         0.3         2.67, 0.30-27.41           Samon at al <sup>ab</sup> 10         257         11         206         0.3         2.67, 0.30-27.41           Samon at al <sup>ab</sup> 10         270         12         233         0.7         17, 0.03-30-970           Samon at al <sup>ab</sup> 10         156         1         158         0.5         0.34, 0.01-8.22           Samon at al <sup>ab</sup> 10         127         137         2.2         0.26, 0.00-7.82           Samon at al <sup>ab</sup> 10         0.52         1.5         0.5         0.33, 0.01-7.05           Samon at al <sup>ab</sup> 10         0.3         2.2         0.22         0.20-7.02           Samon at al <sup>ab</sup> 10         1.33         0.2         2.71, 0.20-6.07           Samon at al <sup>ab</sup> 10         1.33	Dotan et al17			0				
B         236         3         115         1.4         1.30         0.35-481           Jann et al <sup>10</sup> 3         215         1         206         0.3         2.47         0.30         0.55-41           Jann et al <sup>10</sup> 3         215         1         206         0.3         2.47         0.30         0.51-27         1           Jann et al <sup>10</sup> 1         227         1         225         0.3         0.51         2.27         1           Jann et al <sup>10</sup> 1         156         1         158         0.5         0.33         0.01-7.82           Jann et al <sup>10</sup> 0         52         1         51         0.5         0.33         0.01-7.82           Herolst et al <sup>10</sup> 0         53         2.2         0.33         0.01-7.82	Escudier et al53			1		0.4		
Jamie ta <sup>124</sup> 3 215 1 206 0.3 247 (30-27.41 jilient et al <sup>16</sup> 4 250 2 233 0.7 17,0 (33-9.70 jilient et al <sup>16</sup> 4 250 2 233 0.7 17,0 (33-9.70 jilient et al <sup>16</sup> 1 141 1 70 0.3 0.35 (0.20-7.82 jilient et al <sup>16</sup> 1 141 1 70 0.3 0.35 (0.20-7.82 jilient et al <sup>16</sup> 1 141 1 70 0.3 0.35 (0.20-7.85 0.3 0.91-7.85 0.3 0.91-7.85 0.4 0.93-7.110.25 0.2 0.27,10 20-85,70 0.4 0.93-7.110.25 0.2 0.27,10 20-85,70 0.4 0.93-7.110.25 0.2 0.27,10 20-85,70 0.4 0.93-7.110.25 0.4 0.93-7.110.25 0.4 0.93-7.110.25 0.4 0.93-7.10.25 0.4 0.95 0.4 0.95	Fuchs et al <sup>89</sup>	8	236	3	115	1.4	1.30, 0.35-4.81	
Sanchon et al" 10 287 1 285 0.3 9.33, 128-7.77 Juan et al" 4 250 2 23 0.7 179, 0.35-8.70 ternsley et al" 0 52 1 51 0.5 0.33, 0.00-7.82 ternsley et al" 0 52 1 51 0.5 0.33, 0.01-7.85 70 ternsley et al" 0 52 1 51 0.5 0.33, 0.01-7.85 70 ternsley et al" 12 0.33 17 413 0.55-77 1 turwize tal" 12 0.33 10 397 3.4 121, 052-77 0 dabinaver et al" 3 67 0 35 0.2 3.71, 02-09.79 dabinaver et al" 3 67 0 35 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 3.71, 02-09.79 dabinaver et al" 1 5 34 0.0 26 0.2 4.2 3.0 11, 0.10-4, 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0 4.0 0.0	Garon et al <sup>82</sup>	15	627	14	618	4.8	1.06, 0.51-2.17	
Silbert et al <sup>m</sup>	Gianni et al33							
Juan et al <sup>16</sup> 1 1 11 1 70 0.3 0.50, 00-7.82 tensiey et al <sup>77</sup> 0 52 1 55 0.5 0.33, 00-7.82 tensiey et al <sup>77</sup> 0 52 1 55 0.5 0.33, 00-7.82 tensiey et al <sup>77</sup> 0 52 1 51 0.5 0.33, 00-7.82 tensiey et al <sup>77</sup> 1 0 313 7 313 2.4 1.43, 055-7.71 tensies et al <sup>47</sup> 1 2 393 10 397 3.4 112, 055-7.71 tensies et al <sup>47</sup> 1 2 393 10 397 3.4 1.12, 055-7.72 tensies et al <sup>47</sup> 1 3 30 0 22 0.2 371, 02-0679 tensies et al <sup>47</sup> 1 3 30 0 22 0.2 371, 02-0679 tensies et al <sup>47</sup> 1 3 30 0 22 0.2 371, 02-0679 tensies et al <sup>47</sup> 1 3 30 0 22 0.2 2 371, 02-0679 tensies et al <sup>47</sup> 1 3 35 0.04 16 506 5.4 2.19, 1.23-3.91 tensies et al <sup>47</sup> 2 1.43 5 69 2.3 0.19, 0.04-0.97 tensies et al <sup>47</sup> 2 1.43 5 69 2.3 0.19, 0.04-0.97 tensies et al <sup>47</sup> 2 1.43 5 69 2.3 0.7 0.98, 0.14-6.85, 0.5 tensies et al <sup>47</sup> 0 1.31 0 1.31 Note estimate tensies et al <sup>47</sup> 1 2.29 1 1.31 Note estimate tensies et al <sup>47</sup> 1 2.29 1 1.31 Note estimate tensies et al <sup>47</sup> 1 2.29 1 1.31 Note estimate tensies et al <sup>47</sup> 1 2.29 1 1.31 Note estimate tensies et al <sup>47</sup> 1 2.29 1 2.15 0.4 0.98, 0.14-6.89 tensies et al <sup>47</sup> 1 2.29 1 2.15 0.4 0.98, 0.04-4.82 tensies et al <sup>47</sup> 1 0 0 3 101 10 0.34, 0.04-3.22 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.22 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.22 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.24 tensies et al <sup>47</sup> 2 1.50 0 4.60 9.02-2.46 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 3.101 10 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 3.102 0.102 0.207 0.1 1.50, 0.02-2.07 tensies et al <sup>47</sup> 1 0.9 0.9 0.22.1734 tensies et al <sup>47</sup> 1 0.9 0.101 1.0 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 0.101 1.0 0.34, 0.04-3.24 tensies et al <sup>47</sup> 1 0.9 0.50 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	Giantonio et al11							·
bigewisch-Becker et al <sup>12</sup> 0         156         1         158         0.5         0.34, 0.01-8.25           refolst et al <sup>12</sup> 3         39         1         42         0.3         3.23, 0.35-29.77           refolst et al <sup>12</sup> 12         393         10         397         3.4         1.21, 0.55-2.77           refolst et al <sup>12</sup> 12         393         10         397         3.4         1.21, 0.52-27.7           refolst et al <sup>13</sup> 1         12         393         10         397         3.4         1.21, 0.22-87.79           refolst et al <sup>14</sup> 6         6         0         32         0.2         2.10, 10.2-49.79           dabinxare et al <sup>16</sup> 6         6         0         15         10.1         11.10.17.06           Grapt al <sup>11</sup> 1         3         0         2.2         2.3         0.19, 0.40-9.71           Grapt al <sup>11</sup> 2         143         5         69         2.3         0.19, 0.40-9.71           Grapt al <sup>11</sup> 2         143         5         0.3         4.15, 0.48-35.05         0.5           Grapt al <sup>11</sup> 7         752         7         382         2.2         0								
tendel et all <sup>27</sup> 0         62         1         51         0.5         0.33, 0.01-7.85           terbat et all <sup>27</sup> 10         313         7         313         2.4         1.43, 0.55-3.71           terbat et all <sup>28</sup> 10         397         3.4         1.21, 0.55-3.71								
ierbst er al <sup>m</sup> 3       39       1       42       0.3       323, 0.35-29.77         turwitz et al <sup>m</sup> 12       393       10       397       3.4       1.14, 0.65-3.71         turwitz et al <sup>m</sup> 6       65       0       32       0.2       371, 0.20-69.79         diabinavar et al <sup>m</sup> 3       67       0       352       0.2       371, 0.20-69.79         diabinavar et al <sup>m</sup> 0       46       0       36       0.2       2.19, 0.23.91         diapinate et al <sup>m</sup> 0       46       0       36       0.2       2.19, 0.23.91         diapinate et al <sup>m</sup> 1       5       60       2.3       0.19, 0.04-0.97         Ginde et al <sup>m</sup> 0       131       0       131       Not estimable         diackey et al <sup>m</sup> 7       752       7       382       3.2       0.51, 0.10-1.44         diackey et al <sup>m</sup> 1       2.29       1       2.15       0.4       0.94, 0.06-14.82         differet al <sup>m</sup> 2       2.35       0.7       4.66, 0.24-56.02								
idenset at all*       10       313       7       313       2.4       1.43       0.55-3.71         industry at all*       6       65       0       32       0.2       6.40       0.37-110.26         isobinavar et all*       6       65       0       32       0.2       6.40       0.37-110.26         isobinavar et all*       6       100       3       104       10       1.73       0.43-7.06         isobinavar et all*       6       100       3       104       10       1.73       0.43-7.06         isobinavar et all*       0       466       0.86       1.14       1.18       0.24-2.81       1.4         isobinavar et all*       1       33       0       226       2.21       1.91       0.19       0.19         isobinavar et all*       0       131       0       131       0.3       Not estimable         isobinavar et all*       0       91       0       92       Not estimable       Not estimable         isobinavar et all*       0       91       0       92       0.51       0.10-1.44       9         isobinavar et all*       0       91       0       92       0.90       0.90								
Unvike et al"       12       333       10       397       3.4       1.21, 0.53-277         Gabbiavar et al"       3       67       0       35       0.2       37, 10, 20-66, 79         Gabbiavar et al"       0       46       0       36       Not estimable         Garayama et al"       0       46       0       36       Not estimable         Garayama et al"       0       46       0       36       Not estimable         Garayama et al"       0       46       0       36       Not estimable         Kinder et al"       1       33       0.2       2.2       2.10, 10, 12-44, 55         Kinder et al"       0       131       0       131       Not estimable         Gabetia et al"       0       131       0       131       Not estimable         Gabetia et al"       0       99       0       92       100       100       144       46.80         Gabetia et al"       2       235       0       346       0.2       244       0.44.80       0.44.80         Gabetia et al"       2       19       0       68       0.2       246       0.42-50.30       0.44       0.44.80       0.44.80 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>								
boheson et al <sup>®</sup> 6 65 0 32 0.2 6.40, 0.37-110.26 dabbiavar et al <sup>®</sup> 5 100 3 104 1.0 173, 0.43-7.06 dabbiavar et al <sup>®</sup> 5 100 3 104 1.0 173, 0.43-7.06 dabbiavar et al <sup>®</sup> 5 100 3 104 1.0 173, 0.43-7.06 dabbiavar et al <sup>®</sup> 5 504 16 506 5.4 219, 123-3.81 								
Gabinary et ali <sup>a</sup> 3       67       0       35       0.2       37.1       0.20-60.79         Grayama et al <sup>in</sup> 0       46       0       36       Not estimable         Grayama et al <sup>in</sup> 1       33       0.2       2.91       0.12-0.49.55         Gely et al <sup>in</sup> 35       504       16       506       5.4       2.19       1.22-0.49.55         Gindler et al <sup>in</sup> 2       1.33       0.93       0.04-0.97								
Gabhiavar et all*       5       100       3       104       1.0       1.73, 0.43-7.06         Kay et all*       1       33       0       22       0.2       2.91, 0.12-0.495         Kay et all*       2       143       5       650       5.4       2.19, 1.2-0.495         Kin et all*       2       143       5       650       2.3       0.19, 0.04-0.97         Kin et all*       2       143       5       69       2.3       0.4       1.0, 0.42-3.05         Kinder et all*       0       131       0       131       Not estimable       Not estimable         dacks yet all*       7       752       7       382       3.2       0.51, 0.10-1.44       4         daset all*       1       0.92       1.15, 0.22-5.92        Not estimable         differet all*       1       2.29       1       2.15       0.4       0.94, 0.06-14.92         differet all*       1       2.90       3.10       1.0       0.40-2.46          differet all*       1       0.60       3       101       0.70       0.34, 0.04-3.26          differet all*       1       0.60       3       101	Kabbinavar et al <sup>8</sup>							
Cap et al <sup>16</sup> 1       33       0       22       0.2       2.91       0.12-04.95         Gind et al <sup>16</sup> 5       64       2.15       0.13       0.12-04.95         Gind et al <sup>16</sup> 5       277       4       283       1.4       1.39       0.04-0.97         Gindle et al <sup>16</sup> 0       131       0       131       Not estimable         Mackey et al <sup>17</sup> 7       752       7       382       3.2       0.51       0.10-1.44         Mass et al <sup>16</sup> 0       91       0       92       Not estimable         Miles et al <sup>18</sup> 2       233       0.7       0.98       0.14-8.69         Miles et al <sup>16</sup> 2       386       2.2       33       0.7       0.98       0.02-3.93         Miles et al <sup>16</sup> 2       119       0       68       0.2       2.4%       0.02-4.92       0.00-4.04         Sinus et al <sup>16</sup> 2       150       0.3       101       0.94.04-2.46       0.06-3.92       0.00-0.00       0.00-0.00-0.00       0.00-0.00-0.00       0.00-0.00-0.00       0.00-0.00-0.00       0.00-0.00-0.00       0.00-0.00-0.00       0.00-0.00-0.00       0.00-0.00-0.00-0.00       0.00-0.00-0.00-0.00 <th< td=""><td>Kabbinavar et al<sup>10</sup></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<>	Kabbinavar et al <sup>10</sup>							
Gely et all <sup>16</sup> 35       504       16       56       5.4       2.19, 1.23-31         Gindle et all <sup>16</sup> 5       2.77       4       23       0.19, 1.04-0.97         Gindle et all <sup>16</sup> 5       2.77       4       23       0.19, 1.04-0.97         Gindle et all <sup>16</sup> 0       131       0       131       Not estimable         Mackey et all <sup>16</sup> 0       91       0       92       Not estimable         Miles et all <sup>16</sup> 0       91       0       92       Not estimable         Miles et all <sup>16</sup> 2       2.38       2       231       0.9       1.15, 0.23-5.92         Miles et all <sup>16</sup> 2       190       0       68       0.2       4.74, 0.23-98.32         Miller et all <sup>16</sup> 2       190       0       68       0.2       2.47, 0.23-98.32         Petropic at all <sup>16</sup> 9       3.46       8       201       3.1       0.99, 0.40-2.46         Miller et all <sup>16</sup> 9       3.46       1.45       0.3       1.96, 0.82-2.16       4.66         Petropic at all <sup>16</sup> 1       10       0.3, 0.43-34       1.4       4.56, 0.92-0.096       4.56, 0.92-0.096       4.56, 0.92-0.096	Karayama et al <sup>51</sup>							
Kim et al <sup>11</sup> 2       143       5       669       2.3       0.19, 0.04-0.97         Kindle et al <sup>12</sup> 4       53       1       55       0.3       4.15, 0.48-3505         Kindle et al <sup>12</sup> 7       752       7       382       3.2       0.51, 0.10-1.44         Masie tal <sup>14</sup> 0       91       0       92       Notestimable         Miles et al <sup>12</sup> 2       233       0.7       0.98, 0.14-6.89         Miller et al <sup>17</sup> 1       229       1       215       0.4       0.94, 0.02-1.492         Miller et al <sup>16</sup> 2       365       0       346       0.2       2.46, 0.12-0.39         Miller et al <sup>18</sup> 2       119       0       68       0.2       2.46, 0.12-0.39         Vihos et al <sup>18</sup> 9       746       2       753       0.7       4.56, 0.99-20.50         Petrylak et al <sup>18</sup> 2       166       1       11       0.4       2.06, 0.28-1.63         Vipde-Laurine et al <sup>18</sup> 9       746       2       75       0       0.66, 0.28-1.63         Vipde-Laurine et al <sup>18</sup> 0       37       0       37       0.383, 0.43-3.414         Vipde-Laurine e	Kay et al <sup>70</sup>	1	33	0	22	0.2	2.91, 0.12-04.95	
Kindler et al <sup>16</sup> 5       277       4       283       1.4       1.39, 0.32–37         Goberne et al <sup>16</sup> 0       131       0       131       Not estimable         Mackey et al <sup>16</sup> 0       91       0       92       Not estimable         Males et al <sup>16</sup> 0       91       0       92       Not estimable         Males et al <sup>16</sup> 0       91       0       92       Not estimable         Males et al <sup>16</sup> 2       238       2       231       0.7       0.88, 014-6.89         Miller et al <sup>16</sup> 2       355       0       346       0.2       2.46, 012-50.39         Sines et al <sup>16</sup> 9       346       8       201       3.1       0.99, 0.40-2.46         Terrare tal <sup>16</sup> 9       746       2       753       0.7       4.66, 0.92-0.90         Terrare tal <sup>16</sup> 9       746       2       753       0.7       1.06, 0.25-17.34         Terrare tal <sup>16</sup> 1       92       46       1       450       0.25, 0.27-17.34         Terrare tal <sup>16</sup> 2       650       5       327       7       2.2, 0.07-55.4         Terrare tal <sup>16</sup> 3	Kelly et al <sup>75</sup>	35	504	16	506	5.4		
Kindle rel <sup>12</sup> 4       53       1       55       0.3       4.15, 0.48-35.05, 0.51, 0.10-1.44         Mackey rel <sup>147</sup> 7       752       7       382       3.2       0.51, 0.10-1.44         Masie tal <sup>14</sup> 0       91       0       92       Not estimable         Miles et al <sup>16</sup> 2       233       0.7       0.98, 0.14-6.89	Kim et al <sup>71</sup>							
Cobber et al <sup>66</sup> 0       131       0       131       Not estimable         Masi et al <sup>67</sup> 0       91       0       92       Not estimable         Masi et al <sup>67</sup> 5       499       2       231       0.9       115, 0.23-5.92         Miles et al <sup>67</sup> 2       238       2       233       0.7       0.88, 0.14-6.89         Miler et al <sup>67</sup> 1       2.29       1       215       0.4       0.94, 0.06-1.49.2         Miler et al <sup>67</sup> 2       355       0       346       0.2       4.46, 0.12-50.39         Difus et al <sup>66</sup> 2       119       0       68       0.21       3.1       0.98, 0.14-2.46         Difus et al <sup>66</sup> 9       346       8       201       3.1       0.98, 0.14-3.25         Perron et al <sup>66</sup> 9       7.6       2       75.3       0.7       4.56, 0.92-0.96         Perron et al <sup>66</sup> 2       75.3       0.7       4.56, 0.28-1.63								
Mackey et all <sup>67</sup> 7       752       7       382       3.2       0.51, 0.10-1.44         Miles et all <sup>67</sup> 5       499       2       231       0.9       1.15, 0.23-592         Miles et all <sup>67</sup> 1       229       1       215       0.4       0.048, 0.14-6.89         Miller et all <sup>67</sup> 1       229       1       215       0.4       0.049, 0.06-1.49.2         Miller et all <sup>67</sup> 2       119       0       68       0.2       2.46, 0.12-50.39         Ohnsu et all <sup>68</sup> 9       3.46       8       201       3.1       0.99, 0.40-2.46         Ohnsu et all <sup>68</sup> 9       3.46       1       45       0.3       1.66, 0.18-20.53         Petrylak et all <sup>68</sup> 2       7.73       0.7       4.56, 0.28-20.86						0.3		
Mase it al <sup>16</sup> 0       91       0       92       Not estimable         Miles et al <sup>16</sup> 5       499       2       231       0.9       115, 0.23-5.92         Miles et al <sup>16</sup> 2       238       2       233       0.7       0.88, 0.14-6.89         Miller et al <sup>16</sup> 2       355       0       346       0.2       4.74, 0.23-98.32         Miller et al <sup>16</sup> 9       346       8       2.01       1.0       0.94, 0.04-2.46         Shicu et al <sup>16</sup> 9       346       8       2.01       1.0       0.34, 0.04-2.46         Shicu et al <sup>16</sup> 9       746       2       753       0.7       4.66, 0.99-20.96         Vertrylak et al <sup>16</sup> 8       263       1.2       267       4.0       0.06, 0.28-1.63         Vipide-Lauraine et al <sup>16</sup> 2       179       2       181       0.7       1.01, 0.14-7.10         Vipide ta <sup>16</sup> 8       263       12       277       7.232, 0.07-5.54								
Miles et al <sup>10</sup> 5       499       2       231       0.9       115, 023-592         Miller et al <sup>17</sup> 1       229       1       215       0.4       0.94, 0.07-4.82         Miler et al <sup>17</sup> 1       229       1       215       0.4       0.94, 0.07-4.82         Miler et al <sup>16</sup> 2       315       0.4       0.94, 0.07-4.92       0.07-4.92         Mine et al <sup>16</sup> 2       346       8       201       31       0.99, 0.40-2.46         Dista et al <sup>16</sup> 1       90       3       101       10       0.34, 0.04-325         Terren et al <sup>16</sup> 2       46       1       45       0.3       196, 0.18-20.63         Terright et al <sup>16</sup> 3       16       1       11       0.4       206, 0.25-17.34         Tujdot Lauraine et al <sup>169</sup> 3       36       327       2.7       2.32, 0.97-5.4       4.00         Tujdot et al <sup>161</sup> 3       66       5       327       2.7       2.2, 0.20-5.24       4.00         Short et al <sup>116</sup> 4       652       1       346       0.5       0.21-5.23.8       4.01         Short et al <sup>116</sup> 1       4       0.5       0.77 <td></td> <td></td> <td></td> <td></td> <td></td> <td>3.2</td> <td></td> <td></td>						3.2		
Alles et al <sup>10</sup> 2       238       2       233       0.7       0.98, 0.14-6.89         Aller et al <sup>10</sup> 2       355       0       346       0.2       47.4, 0.23-86.32         Aller et al <sup>10</sup> 2       355       0       346       0.2       47.4, 0.23-86.32         Dhtsu et al <sup>10</sup> 9       346       8       201       3.1       0.99, 0.40-2.46         Skines et al <sup>10</sup> 9       746       2       753       0.7       4.56, 0.99-20.66         Terren et al <sup>10</sup> 9       746       2       276       4.0       0.66, 0.28-16.3         "Inter et al <sup>10</sup> 2       179       2       181       0.7       1.01, 0.14-7.10         Vigide Lauraine et al <sup>10</sup> 2       179       2       181       0.7       1.03, 0.34, 3.41         Vigide ta <sup>14</sup> 4       352       1       347       0.3       3.83, 0.43, 4.14         Vigide ta <sup>14*</sup> 28       650       5       327       2.7       2.32, 0.97-5.54         Sinder et al <sup>14*</sup> 13       694       8       675       2.4       1.56, 0.66-3.79         Sinder et al <sup>14*</sup> 14       617       1       400 <t< td=""><td></td><td></td><td></td><td></td><td></td><td>0.0</td><td></td><td></td></t<>						0.0		
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Aller et al <sup>16</sup> 2       355       0       346       0.2       47.0 (23-96.32)         Wine et al <sup>16</sup> 9       346       8       201       3.1       0.99, 0.40-2.46         Dhtsu et al <sup>16</sup> 9       346       8       201       3.1       0.99, 0.40-2.46         Perren et al <sup>16</sup> 9       746       2       753       0.7       4.56, 0.99-2.096         Petrylak et al <sup>16</sup> 2       46       1       45       0.3       1.96, 0.28-1.73.4         Pinter et al <sup>16</sup> 3       16       1       11       0.4       2.06, 0.28-1.63.5         Pinter et al <sup>16</sup> 3       16       1       11       0.4       2.06, 0.28-1.63.5         Vijde-Lauraine et al <sup>169</sup> 2.179       2       181       0.7       1.01, 0.14-7.10         Vijde-Lauraine et al <sup>169</sup> 2.86       650       5       327       2.7       2.32, 0.97-5.54         Statz et al <sup>17</sup> 1.4       617       1       400       0.5       6.91, 0.91-52.33         Sandler et al <sup>161</sup> 1.9       427       3       440       1.0       6.53, 1.95-25.89         Seymouret al <sup>166</sup> 3.955       1       388       0.3								
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Dhise et al <sup>16</sup> 9       346       8       201       3.1       0.90, 40-2.46         Shines et al <sup>16</sup> 9       746       2       753       0.7       4.56, 0.99-20.96         Perren et al <sup>16</sup> 9       746       2       753       0.7       4.56, 0.99-20.96         Perren et al <sup>16</sup> 2       46       1       45       0.3       1.96, 0.18-20.53         Perren et al <sup>16</sup> 2       179       2       181       0.7       1.01, 0.14-7.10         Vigide-Laurine et al <sup>169</sup> 2       179       2       181       0.7       1.01, 0.14-7.10         Vigide-Laurine et al <sup>161</sup> 2       179       2       181       0.7       1.01, 0.14-7.10         Vigide-Laurine et al <sup>161</sup> 2       165       327       2.7       2.32, 0.97-5.54         Vigide-Laurine et al <sup>161</sup> 4       650       5       327       2.7       0.3       38, 0.43-34.14         Sobert et al <sup>171</sup> 19       427       3       440       1.0       6.53, 1.95-25.89         Sandler et al <sup>161</sup> 12       100       4       101       1.4       303, 1.01-0.06         Show et al <sup>172</sup> 7       2.10       2.13	Niho et al45							
Perene tal <sup>66</sup> 9 746 2 753 0.7 4.66, 0.99-20.96 Petrylak et al <sup>66</sup> 2 46 1 45 0.3 1.96, 0.18-20.53 Petrylak et al <sup>67</sup> 3 16 1 11 0.4 2.66, 0.25-17.34 Pujole et al <sup>67</sup> 3 16 1 11 0.4 2.06, 0.25-17.34 Pujole et al <sup>67</sup> 0 37 0 37 N 0.57 2.4 0.0.66, 0.25-17.34 Pujole et al <sup>67</sup> 0 37 0 37 N 0.57 2.23 0.97-5.54 Rini et al <sup>64</sup> 4 352 1 347 0.3 3.83, 0.43-34.14 Sobert et al <sup>61</sup> 14 617 1 400 0.5 6.91, 0.91-52.33 Sandler et al <sup>61</sup> 19 427 3 440 1.0 6.63, 1.95-25.89 Sandler et al <sup>61</sup> 19 427 3 440 1.0 6.53, 1.95-25.89 Selo et al <sup>67</sup> 7 7 10 77 0.2 0.13, 0.25-105.14 Seymour et al <sup>66</sup> 5 395 1 388 0.3 7.02, 0.01-62.21 Shen et al <sup>67</sup> 12 100 4 101 1.4 3.03, 1.01-0.08 Show et al <sup>67</sup> 7 7 125 0 216 0.2 15.21, 0.07-254.64 Show et al <sup>67</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 13 529 9 528 3.1 144, 0.62-3.34 Fabermero et al <sup>66</sup> 10 20 2 2 219 0.7 4.98, 1.10-22.45 Faborero et al <sup>66</sup> 10 20 2 2 219 0.7 4.98, 1.10-22.45 Faborero et al <sup>66</sup> 13 529 9.7 1.76, 0.76-4.14 Faborero et al <sup>66</sup> 14 227 8 329 2.7 1.76, 0.76-4.14 Faborero et al <sup>66</sup> 12 27 0.0 0.71; <i>F</i> =20% Faborero et al <sup>67</sup> 1 0.81, 0.44-1.50 Faborero et al <sup>67</sup> 10 0.81, 0.44-1.50 Faborero et al <sup>66</sup> 276 Faborero et al <sup>66</sup> 276 Faborero et al <sup>67</sup> 2 40.00, 0.1 1 10 2 Faborero 50.0 0.1 1 1 10 2	Ohtsu et al62	9	346	8	201	3.1	0.99, 0.40-2.46	
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Duple tal <sup>46</sup> 0       37       0       37       Not estimable         Reck et al <sup>43</sup> 28       650       5       327       2.7       2.32, 0.97-5.54         Note stimable       3       38.0, 0.43-34.14								
Teck et alsa       28       650       5       327       2.7       2.32, 0.97-5.54         Nini et alsa       4       352       1       347       0.3       3.83, 0.43-34.14         Sobert et alsa       617       1       400       0.5       6.91, 0.91-52.33         Saltz et alsa       13       694       8       675       2.4       1.56, 0.66-3.79         Sander et alsa       19       427       3       440       1.0       6.53, 1.95-26.89         Seto et alsa       2       75       0       77       0.2       0.13, 0.25-105.14         Sepmour et alsa       0       395       1       388       0.3       7.02, 0.01-62.21         Shove et alsa       12       1001       1.4       3.03, 1.01-0.08       4.00         Shove et alsa       13       529       9       528       3.1       1.44, 0.62-3.34         Taked et alsa       0.5       0.31, 0.01-7.34       4.00       0.50, 0.09-2.67       4.00       4.00       0.00, 0.9-2.67         Terwari et alsa       10       220       2       219       0.7       4.98, 1.10-22.45       4.024       4.024       4.024       4.024       0.05       0.09-2.67       4.0						0.7		
Nine tell <sup>24</sup> 4       352       1       347       0.3       3.88, 0.43 - 34.14         Robert et al <sup>21</sup> 13       694       8       675       2.4       1.56, 0.66 - 3.79         Sandler et al <sup>21</sup> 13       694       8       675       2.4       1.56, 0.66 - 3.79         Sandler et al <sup>21</sup> 19       427       3       440       1.0       6.53, 1.95 - 25.89         Selo et al <sup>27</sup> 2       75       0       77       0.2       0.13, 0.25 - 105.14         Seymour et al <sup>26</sup> 5       395       1       388       0.3       7.02, 0.01 - 62.21         Shon et al <sup>26</sup> 7       2.15       0       218       0.2       15.21, 0.07 - 254.64         Shon et al <sup>26</sup> 0       39       1       36       0.5       0.31, 0.01 - 7.34         Takeda et al <sup>26</sup> 0       528       3.1       1.44, 0.62 - 3.34       4         Fewari et al <sup>26</sup> 0       9       528       1.3       1.44, 0.62 - 3.44         Greeval et al <sup>26</sup> 0       9       1.38       1.4       0.20, 0.9 - 2.67         Tewari et al <sup>26</sup> 0       9       1.66       0.30, 0.1 - 2.49       4						27		
Sobert et al <sup>11</sup> 14       617       1       400       0.5       6.91       0.91-52.33         Saltz et al <sup>12</sup> 13       694       8       675       2.4       1.56       0.66-3.79         Saltz et al <sup>12</sup> 19       427       3       440       1.0       6.53.195-25.89         Send et al <sup>141</sup> 19       427       3       440       1.0       6.53.195-25.89         Semour et al <sup>166</sup> 5       395       1       388       0.3       7.02, 0.01-62.21         Shore et al <sup>164</sup> 12       100       4       101       1.4       3.03, 1.01-0.08         Shore et al <sup>164</sup> 12       100       4       101       1.4       0.0, 0.9-26.67         Shore et al <sup>165</sup> 13       529       9       528       3.1       1.44, 0.62-3.34         Saltz et al <sup>160</sup> 0       50       0       60       Not estimable         Febbutt et al <sup>164</sup> 2       157       4       158       1.4       0.02, 0.09-2.67         Grewari et al <sup>167</sup> 10       220       2       219       0.7       4.98, 1.10-2.2.45         Grewari et al <sup>167</sup> 10       220       2       296								
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Sandler et al <sup>41</sup> 19       427       3       440       1.0       6.53, 195–25.89         Send et al <sup>47</sup> 2       75       0       77       0.2       0.13, 0.25–105.14         Semour et al <sup>66</sup> 5       395       1       388       0.3       7.02, 0.01–62.21         Shoe et al <sup>66</sup> 12       100       4       101       1.4       3.03, 1.01–0.08         Sikov et al <sup>77</sup> 7       215       0       218       0.2       15.21, 0.07–254.64         Snoeren et al <sup>66</sup> 0       39       1       36       0.5       0.31, 0.01–7.34         Takeda et al <sup>69</sup> 0       50       0       60       Not estimable         Tebutit et al <sup>145</sup> 10       220       2       219       0.7       4.98, 1.10–22.45         Tere et al <sup>169</sup> 0       96       0       103       Not estimable	Saltz et al <sup>12</sup>							
Seymour et all**       5       395       1       388       0.3       7.02, 0.01-62.21         Shen et alf**       12       100       4       101       1.4       3.03, 1.01-0.08         Shon et alf**       7       215       0       218       0.2       15.21, 0.07-254.64         Shon et alf**       0       39       1       36       0.5       0.31, 0.01-7.34         Tabernero et alf**       0       50       0       60       Not estimable         Fewari et alf**       10       220       219       0.7       4.98, 1.10-22.45         Gread et alf**       0       96       0       103       Not estimable         or Minckwitz et alf**       0       96       0       103       Not estimable         on Minckwitz et alf**       12       246       4       238       1.4       0.24, 0.03-2.16         of Minckwitz et alf**       1       246       4       238       1.4       0.24, 0.03-2.16         of Minckwitz et alf**       1       59       1       65       0.3       0.94, 0.06-14.75         of het alf**       2       222       0       224       0.2       5.04, 0.24-104.49         of het al	Sandler et al41							
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Tiseo et all <sup>52</sup> 0       96       0       103       Not estimable         Van Cutsem et all <sup>55</sup> 22       296       16       287       5.5       1.33, 0.71–2.49         oro Minckwitz et all <sup>22</sup> 4       958       3       289       1.0       1.35, 0.30–0.02         oro Minckwitz et all <sup>26</sup> 1       246       4       238       1.4       0.24, 0.03–2.16         Wilk et all <sup>56</sup> 14       327       8       329       2.7       1.76, 0.76–4.14         Gradley et all <sup>56</sup> 1       5       9       1       65       0.3       0.94, 0.06–14.75         (ardley et all <sup>56</sup> 2       76       0       81       0.2       5.32, 0.26–109, 15         (fon et all <sup>51</sup> 5       82       5       80       1.7       0.98, 0.29–3.24         (Zalcman et all <sup>24</sup> 2       244       0.2       5.04, 0.24–104.49								
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foon et al <sup>β1</sup> 5     82     5     80     1.7     0.98, 0.29-3.24       Zalcman et al <sup>β4</sup> 2     222     0     224     0.2     5.04, 0.24-104.49       Thu et al <sup>β2</sup> 17     277     21     276     7.1     0.81, 0.44-1.50       Total 95% CI     24,062     21,855     100     1.71, 1.48-1.97       Total events     626     276       febrogeneity: χ²=90.19, df=72 (ρ=0.07); β²=20%     Γavors     Favors       Feavors     Favors     Favors	Yardley et al <sup>88</sup>							
Załoman et al <sup>74</sup> 2       222       0       224       0.2       5.04, 0.24-104.49         Zhou et al <sup>48</sup> 2       140       1       134       0.3       1.91, 0.18-20.87         Zhu et al <sup>42</sup> 17       277       21       276       7.1       0.81, 0.44-1.50         Fotal, 95% Cl       24,062       21,855       100       1.71, 1.48-1.97         fotal events       626       276       276       0.005       0.1       1       10       2         fest for overall effect: Z=7.38 (p<0.0001)	Yoh et al <sup>80</sup>							
2 140     1     134     0.3     1.91, 0.18-20.87       Chu et al <sup>162</sup> 17     277     21     276     7.1     0.81, 0.44-1.50       Total, 95% CI     24,062     21,855     100     1.71, 1.48-1.97       Total events     626     276       Teberogeneity: χ <sup>2</sup> =90.19, df=72 (ρ=0.07); P=20%     0.005     0.1     1     10       Fest for overall effect: Z=7.38 (ρ<0.00001)								
2 <sup>h</sup> u et al <sup>122</sup> 17     277     21     276     7.1     0.81, 0.44–1.50       Total, 95% CI     24,062     21,855     100     1.71, 1.48–1.97       Total events     626     276       leterogeneity: χ <sup>2</sup> =90.19, df=72 (p=0.07); l <sup>2</sup> =20%     276       fest for overall effect: Z=7.38 (p<0.00001)     0.005     0.1     1     10     276       Favors								
Fotal, 95% CI         24,062         21,855         100         1.71, 1.48–1.97           fotal events         626         276           Heterogeneity: χ²=90.19, df=72 (p=0.07); l²=20%         0.005         0.1         1         10         2           fest for overall effect: Z=7.38 (p<0.00001)								
Total events         626         276           leterogeneity: $\chi^2$ =90.19, $df$ =72 ( $p$ =0.07); $l^2$ =20%         0.005         0.1         1         10         2           fest for overall effect: Z=7.38 ( $p$ <0.00001)	Zinu et di-	17	211	21	210	1.1	0.01, 0.44-1.50	-
Total events         626         276           leterogeneity: $\chi^2$ =90.19, $df$ =72 ( $p$ =0.07); $l^2$ =20%         0.005         0.1         1         10         2           fest for overall effect: Z=7.38 ( $p$ <0.00001)	Total 95% CI		24 062		21 855	100	1 71 1 48-1 97	
Heterogeneity: χ²=90.19, df=72 (p=0.07); l²=20%         0.005         0.1         1         10         2           fest for overall effect: Z=7.38 (p<0.00001)		626	24,002	276	21,000	100	1.71, 1.40-1.37	
Test for overall effect: Z=7.38 (p<0.00001) 0.005 0.1 1 10 2 Favors Favors Favors			7): /2=20%	210				-ttttt
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								(experimental) (control)

#### Figure 3 RR of high-grade bleeding. Abbreviations: M–H, Mantel–Haenszel; RR, relative risk.

showed that ramucirumab differed from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients. The mechanisms underlying these differences remained unclear. A possible explanation was that bevacizumab, as an anti-VEGF-A agent, specified both VEGFR-1 and VEGFR-2, whereas ramucirumab was only specified for VEGFR-2. VEGFR-2 was the major mediator

Table 2 RR of all-grade bleeding	g associated with angiogenesis	s inhibitors in the subgroup analysis
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Bleeding	No. of	No. of events/total (%)		RR, 95% CI
	trials	Treatment	Control	
Type of drug				
Bevacizumab	30	1,934/6,738 (28.7)	679/6,586 (10.3)	2.73, 2.24–3.33
Ramucirumab	13	1,268/3,403 (37.3)	552/2,904 (19.0)	1.94, 1.76–2.13
Drug dosage				
Low dose	22	1,452/5,220 (27.8)	508/4,863 (10.4)	2.46, 1.95–3.11
High dose	21	1,750/4,921 (35.6)	723/4,627 (15.6)	2.34, 2.00–2.73
Tumor types				
Colorectal cancer	10	387/1,552 (24.9)	184/1,563 (11.8)	2.24, 1.58–3.19
Non-colorectal cancer	33	2,815/8,589 (32.8)	1,047/7,927 (13.2)	2.42, 2.09–2.80

Abbreviation: RR, relative risk.

of VEGF-driven responses in endothelial cells. The precise function of VEGFR-1 was not entirely established and some studies showed that VEGFR-1 could also regulate proliferation and survival of endothelial cells.94-97 Increased level of tumor VEGFR-1 expression has been shown to be associated with high tumor angiogenesis.<sup>96</sup> VEGF/VEGFR-1 signalingmediated tumor cell monocyte chemoattractant protein-1 expression could represent a mechanism responsible for the tumor angiogenic switch.<sup>97</sup> Therefore, bevacizumab increased the risk of bleeding by inhibiting both VEGFR-1 and VEGFR-2. Squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, which is the main risk factor of pulmonary hemorrhage.98 The difference in the risk of pulmonary hemorrhage caused bevacizumab to be used only for non-squamous NSCLC and ramucirumab to be used for any tumor histology of NSCLC.

Our study also demonstrated that both low-dose and high-dose angiogenesis inhibitors increased the risk of bleeding. The risk of high-grade bleeding was more frequently observed in patients with high-dose angiogenesis inhibitors, suggesting that the risk may be dose-dependent and close supervision and careful management should be emphasized especially in patients with high dosage.

In a meta-analysis of bevacizumab, patients with colorectal cancer were found to have the highest risk of bleeding compared to other tumors.<sup>99</sup> For colorectal cancer patients, high-grade bleeding such as perforation was commonly fatal and life threatening.<sup>100</sup> Therefore, we performed a subgroup analysis according to colorectal cancer and non-colorectal tumors in order to identify the potential risk factors. Results showed that the risk of all-grade and high-grade bleeding was comparable between patients with colorectal cancer and non-colorectal tumors, suggesting that the increased risk of bleeding is associated with many tumor types.

#### Limitations

There are several limitations in this meta-analysis. First, we performed stratification analysis only for colorectal cancer and non-colorectal tumor types because too many tumor types were included in the analysis and assessment was difficult. Second, we did not evaluate the risk of pulmonary hemorrhage between bevacizumab and ramucirumab in

Bleeding	No. of	No. of events/total (%	)	RR, 95% CI
	trials	Treatment	Control	
Type of drug				
Bevacizumab	70	432/20,731 (2.1)	194/19,000 (1.0)	1.98, 1.68–2.34
Ramucirumab	12	94/3,351 (2.8)	82/2,855 (2.9)	1.04, 0.78–1.39
Drug dosage				
Low dose	37	203/10,569 (1.9)	149/10,089 (1.5)	1.31, 1.06–1.60
High dose	49	323/13,513 (2.4)	135/12,391 (1.1)	2.17, 1.79–2.64
Tumor types				
Colorectal cancer	18	111/5,868 (1.9)	71/5,747 (1.2)	1.52, 1.13–2.03
Non-colorectal cancer	64	415/18,214 (2.3)	205/16,108 (1.3)	1.77, 1.50–2.09

Abbreviation: RR, relative risk.

Study or subgroup	Experime events	ental Total	Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% Cl		Risk ratio fixed, 95	,	
Bevacizumab										
Boutsikou et al46	7	116	0	113	0.9	14.62, 0.84–252.94	4	+		
Karayama et al <sup>51</sup>	1	45	1	35	1.9	0.78, 0.05–12.00				
Niho et al45	26	119	3	58	6.9	4.22, 1.33–13.38		-		
Seto et al47	6	75	1	77	1.7	6.16, 0.76–49.95		+		-
Subtotal, 95% CI		355		283	11.3	4.72, 1.99–11.19			•	
Total events	40		5							
Heterogeneity: $\chi^2$ =	2.37, df=3 (	o=0.50); /2	<sup>2</sup> =0%							
Test for overall effe	ct: Z=3.52 (	p=0.0004)								
Ramucirumab										
Garon et al <sup>82</sup>	49	627	46	618	78.8	1.05, 0.71–1.55				
Yoh et al <sup>80</sup>	8	76	6	81	9.9	1.42, 0.52–3.91				
Subtotal, 95% CI		703		699	88.7	1.09, 0.76–1.57		•		
Total events	57		52							
Heterogeneity: $\chi^2$ =	0.30, <i>df</i> =1 (	0=0.58); / <sup>2</sup>	<sup>2</sup> =0%							
Test for overall effe	ct: Z=0.47 (	o=0.64)								
Total, 95% CI		1,058		982	100	1.50, 1.09–2.07				
Total events	97	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	57			,				
Heterogeneity: $\chi^2 =$	10.81, <i>df</i> =5	(p=0.06);	/²=54%				-+		-	E.
Test for overall effe	,	u ,,					0.005	0.1 1	10	200
Test for subgroup of	4	,	f=1 (p=0.002	2); /²=89.4	%		E	avors	Favor	
<b>U</b> 1	,	- /						rimental)	(contro	-

Figure 4 RR of all-grade pulmonary hemorrhage.

Abbreviations: M–H, Mantel–Haenszel; RR, relative risk.

Study or subgroup	Experim events	ental Total	Control events	Total	Weight (%)	Risk ratio M–H, fixed, 95% Cl	Risk ratio M–H, fixed, 95% Cl
Bevacizumab							
Boutsikou et al46	3	116	0	113	4.4	6.82, 0.36–130.57	
Herbst et al42	2	39	0	42	4.2	5.38, 0.27–108.58	
Herbst et al44	3	313	1	313	8.7	3.00, 0.31–28.68	
Johnson et al40	6	66	0	32	5.8	6.40, 0.37–110.26	——
Karayama et al⁵¹	0	45	0	35		Not estimable	
Niho et al45	1	119	0	58	5.8	1.48, 0.06–35.66	
Pujol et al49	0	37	0	37		Not estimable	
Reck et al43	8	659	2	327	23.2	1.98, 0.42–9.29	
Sandler et al41	8	427	1	440	8.6	8.24, 1.04–65.63	
Seto et al47	0	75	0	77		Not estimable	
Takeda et al⁵⁰	0	50	0	50		Not estimable	
Tiseo et al52	0	95	0	103		Not estimable	
Zhou et al48	0	140	0	134		Not estimable	
Subtotal, 95% CI		2,181		1,761	60.8	3.97, 1.70-9.29	•
Total events Heterogeneity: $\chi^2=1$ Test for overall effect			4 =0%				
Ramucirumab							
Garon et al <sup>82</sup>	4	627	4	618	35.0	0.99, 0.25–3.92	_ <b>_</b>
Yoh et al <sup>80</sup>	1	76	0	81	4.2	3.19, 0.13–77.25	
Subtotal, 95% CI		703		699	39.2	1.22, 0.35–4.21	-
Total events Heterogeneity: $\chi^2=0$ Test for overall effect			4 =0%				
Total, 95% CI		2,884		2,460	100	2.89, 1.46–5.72	•
Total events	36		8				-
Heterogeneity: $\chi^2=4$ Test for overall effect	ct: Z=3.05 (p	=0.002)					0.005 0.1 1 10 20
Test for subgroub di	fferences: $\chi$	<sup>2</sup> =2.37, df	=1 (p=0.12)	; /²=57.7%	, D		Favors Favors (experimental) (control)

Figure 5 RR of high-grade pulmonary hemorrhage. Abbreviations: M–H, Mantel–Haenszel; RR, relative risk. lung squamous cell carcinoma patients due to the small sample size or absence of original data. Finally, our literature search was limited to articles published in English leading to some selection bias.

# Conclusion

Despite the limitations of our meta-analysis, we conclude that antiangiogenic monoclonal antibodies are associated with a significant increase in the risk of all-grade and high-grade bleeding. Ramucirumab may be different from bevacizumab in terms of the risk of high-grade bleeding and the risk of all-grade and high-grade pulmonary hemorrhage in lung cancer patients. Clinicians should be aware of this adverse effect and ensure close monitoring, especially in patients at high risk.

# Acknowledgment

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# Disclosure

The authors report no conflicts of interest in this work.

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# Supplementary material

# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	I.	Identify the report as a systematic review, meta-analysis, or both.	I.
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I <sup>2</sup> ) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	7,8

(Continued)

# ERIS MA

PRISMA 2009 Checklist (Continued)

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	7,8
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	11

Notes: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. For more information, visit: <u>www.prisma-statement.org</u>.

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