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

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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 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. 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
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). 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.

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. The main mechanism of bleeding is that angiogenesis inhibitors disrupt tumor vasculature through inhibition of VEGF signaling and lead to thrombosis or bleeding.

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 (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. 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. 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 and ramucirumab was investigated in 13 trials. All of the studies included 21 colorectal cancer, 15 breast cancer, 16 lung cancer, three renal cell cancer, two pancreatic cancer, five ovarian cancer, six gastric or gastroesophageal junction adenocarcinoma, one glioblastoma, one lymphoma, one lymphocytic leukemia, two melanoma, two malignant mesothelioma, one prostate cancer, one cervical cancer, one leiomyosarcoma, two urothelial carcinoma, two hepatocellular carcinoma, and one soft tissue sarcoma. In addition, 35 trials 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 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 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 all-grade 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 (I²=74%) across the trials; we incorporated it into a random-effects model (Figure 2).

**RR of high-grade bleeding**

The RR of high-grade (≥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 (I²=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

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**Figure 1** Outline of the search flow diagram.

**Abbreviation:** RCTs, randomized controlled trials.
Table I Characteristics of studies included in the meta-analysis

| Author                  | Year | Malignancy | Phase | No. in intervention/control | Concurrent treatment                                                                 | Dose (mg/kg/week) | No. of bleeding events in intervention/control |
|-------------------------|------|------------|-------|-----------------------------|---------------------------------------------------------------------------------------|-------------------|-----------------------------------------------|
| Bevacizumab             |      |            |       |                             |                                                                                       |                   |                                               |
| Kabbinavar et al         | 2003 | CRC        | II    | 67/35                       | Fluorouracil + leucovorin                                                              | 2.5 or 5          | NR 3/0                                        |
| Hurwit et al             | 2004 | CRC        | III   | 393/397                     | Irinotecan + fluorouracil + leucovorin                                                | 2.5               | NR 12/10                                      |
| Kabbinavar et al         | 2005 | CRC        | III   | 100/104                     | Fluorouracil + leucovorin                                                              | 2.5               | NR 5/3                                        |
| Gantoni et al            | 2007 | CRC        | III   | 287/285                     | Oxaplatin + fluorouracil + leucovorin                                                  | 5                 | NR 10/1                                       |
| Saltz et al              | 2008 | CRC        | III   | 694/675                     | Cephalatin + oxaplatin/fluorouracil + folinic acid + oxaplatin                         | 2.5               | NR 13/8                                       |
| Allegra et al            | 2009 | CRC        | III   | 1,326/1,321                 | Oxaplatin + fluorouracil + leucovorin                                                  | 2.5               | NR 25/25                                      |
| Tebbutt et al            | 2010 | CRC        | III   | 157/156                     | Cephalatin                                                                            | 2.5               | 19/19                                         |
| Statopoulos et al        | 2010 | CRC        | III   | 114/108                     | Irinotecan + leucovorin                                                                | 2.5               | 0/1                                           |
| Guan et al               | 2011 | CRC        | III   | 141/70                      | Irinotecan + fluorouracil + leucovorin                                                 | 2.5               | NR 1/1                                        |
| Dotan et al              | 2012 | CRC        | II    | 12/11                       | Cephalatin + oxaplatin + cetuximab                                                     | 2.5               | 6/4                                           |
| De Gramont et al         | 2012 | CRC        | III   | 1,145/1,126                 | Oxaplatin + fluorouracil + leucovorin                                                  | 2.5               | 0/1                                           |
| Bennouna et al           | 2013 | CRC        | III   | 401/409                     | Fluorouracil/ceaplabin + oxaplatin/irinotecan                                          | 2.5               | NR 8/1                                        |
| Cunningham et al         | 2013 | CRC        | III   | 134/136                     | Cephalatin                                                                            | 2.5               | 34/9                                          |
| Cao et al                | 2015 | CRC        | II    | 65/77                       | Irinotecan + fluorouracil + leucovorin                                                 | 5                 | NR 5/0                                        |
| Hegewisch-Becker et al   | 2015 | CRC        | III   | 156/158                     | None                                                                                    | 2.5               | 14/11                                         |
| Passardi et al           | 2015 | CRC        | III   | 176/194                     | Irinotecan + fluorouracil + leucovorin/oxaplatin + fluorouracil + leucovorin           | 2.5               | 30/9                                          |
| Masi et al               | 2015 | CRC        | III   | 91/92                       | Irinotecan + fluorouracil + leucovorin/oxaplatin + fluorouracil + leucovorin           | 2.5               | 19/2 0/0                                      |
| Koeberle et al           | 2015 | CRC        | III   | 131/131                     | None                                                                                    | 2.5               | 5/1 0/0                                       |
| Snoeren et al            | 2015 | CRC        | III   | 39/36                       | Cephalatin + oxaplatin                                                                  | 2.5               | NR 0/1                                        |
| Miller et al             | 2005 | BC         | III   | 229/215                     | Cephalatin                                                                            | 5                 | 66/24                                         |
| Miller et al             | 2007 | BC         | III   | 365/346                     | Paclitaxel                                                                            | 5                 | NR 2/0                                        |
| Miles et al              | 2010 | BC         | III   | 499/231                     | Docetaxel                                                                             | 2.5 or 5          | NR 5/2                                        |
| Bruisky et al            | 2011 | BC         | III   | 458/221                     | Cephalatin/taxane/gemcitabine/vinorelbine                                             | 5                 | NR 8/0                                        |
| Robert et al             | 2011 | BC         | III   | 817/403                     | Cephalatin/taxane/anthracycline                                                       | 5                 | NR 14/1                                       |
| von Minckwitz et al       | 2012 | BC         | III   | 956/969                     | Epirubicin/anthracycline/oxaplatin                                                     | 5                 | NR 4/3                                        |
| Gianni et al             | 2013 | BC         | III   | 215/206                     | Docetaxel + trastuzumab                                                               | 5                 | NR 3/1                                        |
| Cameron et al            | 2013 | BC         | III   | 1,288/1,271                 | Anthracycline/taxane                                                                   | 5                 | NR 8/2                                        |
| Coudert et al            | 2014 | BC         | II    | 7/25                        | Trastuzumab + docetaxel                                                               | 5                 | NR 0/0                                        |
| von Minckwitz et al       | 2014 | BC         | III   | 245/238                     | Taxane/anthracycline/ceaplabin/vinorelbine/gemcitabine/cyclophosphamide              | 5                 | 33/18                                         |
| Sikov et al              | 2015 | BC         | II    | 215/218                     | Paclitaxel ± carboplatin ± doxorubicin + cyclophosphamide                             | 5                 | NR 7/0                                        |
| Diéras et al             | 2015 | BC         | II    | 56/57                       | Trebananib + paclitaxel                                                              | 5                 | 29/17                                         |
| Miles et al              | 2017 | BC         | III   | 238/233                     | Paclitaxel                                                                            | 5                 | 106/62                                       |
| Johnson et al            | 2004 | LC         | II    | 66/32                       | Carboplatin + paclitaxel                                                             | 2.5 or 5          | NR 6/0                                        |
| Reference         | Year | Tissue or Disease | Stage | Treatment 1 | Treatment 2 | Treatment 3 | Treatment 4 | Toxicity | Dose | Comments                        |
|-------------------|------|-------------------|-------|-------------|-------------|-------------|-------------|----------|------|---------------------------------|
| Sandler et al.     | 2006 | LC                | III   | Paclitaxel  | Carboplatin |             |             |          | 5    | NR                              |
| Herbst et al.      | 2007 | LC                | II    | Paclitaxel  | Carboplatin |             |             |          | 9    | 19/3                            |
| Reck et al.        | 2009 | LC                | III   | Docetaxel   | Carboplatin |             |             |          | 5    | NR                              |
| Herbst et al.      | 2011 | LC                | III   | Cisplatin   | Gemcitabine |             |             |          | 5    | 1/31                            |
| Niho et al.        | 2012 | LC                | II    | Erlotinib   |             |             |             |          | 5    | 10/7                            |
| Boutsikou et al.   | 2013 | LC                | III   | Docetaxel   | Carboplatin | Erlotinib   |             |          | 7/0  | 3/0                            |
| Seto et al.        | 2014 | LC                | II    | Carboplatin | Paclitaxel  |             |             |          | 5    | 4/22                            |
| Zhou et al.        | 2015 | LC                | II-III| Cisplatin   | Epitaxorubicin + Cyclophosphamide |            |          |          | 5    | 2/1                            |
| Pujol et al.       | 2015 | LC                | II-III| Docetaxel   |             |             |             |          | 20/3 | 0/0                            |
| Takeda et al.      | 2016 | LC                | II    | Pemtrexed   |             |             |             |          | 5    | 0/0                            |
| Karayama et al.    | 2016 | LC                | II    | Carboplatin | Interferon  |             |             |          | 5    | 1/1                            |
| Tiseo et al.       | 2017 | LC                | III   | Cisplatin   | Interferon  |             |             |          | 5    | 21/4                            |
| Escudier et al.    | 2007 | RCC               | III   | Gemcitabine + Erlotinib |            |             |          | 2.5    | 124/67 | 22/16                           |
| Rini et al.        | 2010 | RCC               | III   | Gemcitabine |             |             |             |          | 5    | 5/4                            |
| Van Cutsem et al.  | 2009 | PC                | II    | Paclitaxel  |             |             |             |          | 2.5  | 14/7                            |
| Kinder et al.      | 2010 | PC                | II    | Paclitaxel  |             |             |             |          | 5    | 14/7                            |
| Burger et al.      | 2011 | OC                | II    | Paclitaxel  |             |             |             |          | 5    | 14/7                            |
| Perren et al.      | 2011 | OC                | II    | Paclitaxel  |             |             |             |          | 5    | 14/7                            |
| Pujade-Lauraine et al. | 2014 | OC                | II    | Paclitaxel  |             |             |             |          | 5    | 14/7                            |
| Aghajanian et al.  | 2015 | OC                | II    | Paclitaxel  |             |             |             |          | 5    | 14/7                            |
| Coleman et al.     | 2017 | OC                | II    | Paclitaxel  |             |             |             |          | 5    | 14/7                            |
| Ohtsu et al.       | 2011 | GC                | III   | Cisplatin   |             |             |             |          | 5    | 9/9                            |
| Okines et al.      | 2013 | GC                | VI    | Epirubicin + Cisplatin + Capetitabine |            |          |          | 2.5    | 2/12 | 1/3                            |
| Shen et al.        | 2015 | GC, GEJC          | III   | Cisplatin   |             |             |             |          | 5    | 15/7                            |
| Cunningham et al.  | 2017 | GEJC              | VI    | Epirubicin + Cisplatin + Capetitabine |            |          |          | 2.5    | 15/7 | 2/2                            |
| Chino et al.       | 2014 | Gioblastoma       | III   | Radiotherapy + Temozolomide |            |          |          | 5      | 186/97 | 15/8                           |
| Gilbert et al.     | 2014 | Gioblastoma       | III   | Cisplatin   |             |             |             |          | 5    | 4/2                            |
| Balana et al.      | 2016 | Gioblastoma       | II    | Temozolomide |            |          |          | 5      | 5/0                            |
| Seymour et al.     | 2014 | Lymphoma          | III   | Rituximab + Doxorubicin + Vinristine + Cyclophosphamide + Prednisone instead of R-CHOP | 77/31 | 8/1   |
| Kay et al.         | 2016 | Lymphocytic leukemia | II | Pentostatin + Cyclophosphamide + Rituximab | 5 | NR | 1/0 | 2/5 |
| Kim et al.         | 2012 | Melanoma          | II    | Paclitaxel  |             | Gemcitabine | None        | 5    | 13/13 | 2/5 |
| Corrie et al.      | 2012 | Melanoma          | II    | Paclitaxel  | Gemcitabine | None        | 2.5    | 15/16 | 1/1 |
| Kinder et al.      | 2012 | MM                | II    | Gemcitabine | Pemtrexed   | Docetaxel  | Docetaxel  | 5    | 91/16 | 2/0 |
| Zalcman et al.     | 2016 | MM                | II    | Pemtrexed   |             | Docetaxel  |             | 5    | NR | 35/16 |
| Kelly et al.       | 2012 | Prostate cancer   | III   | Docetaxel   | Pemtrexed   | Docetaxel  |             | 5    | NR | 10/2 |
| Tewari et al.      | 2014 | Cervical cancer   | III   | Paclitaxel/topotecan + Cisplatin |            |          |          | 5    | NR | 2/6 |
| Hensley et al.     | 2015 | uLMS              | II    | Gemcitabine + Docetaxel |             |          |          | 2.5    | 3/1 | 3/1 |
| Pinter et al.      | 2015 | HC                | II    | IFSamide + vinristine + actinomycin-D + Doxorubicin instead of VADO/IVACyclophosphamide + Vinorelbine | 178/174 | 3/1 |
| Chisholm et al.    | 2017 | STSs              | II    | TACE        |             |          |          | 5      | 3/1 | 3/1 |

(Continued)
Table 1 (Continued)

| Author          | Year | Malignancy      | Phase | No. in intervention/control | Dose Concurrent treatment | No. of bleeding events in intervention/control | Grade | All grade | Grade $^3$ |
|-----------------|------|-----------------|-------|-----------------------------|---------------------------|-----------------------------------------------|-------|-----------|-----------|
| Ramucirumab     | 2016 | LC              | II    | 76/81                        | Docetaxel                 | 6/76/18                                       | 0.00001 | 1.94      | 1.76–2.13 |
| Yoh et al.      | 2015 | LC              | III   | 68/84                        | Docetaxel                 | 15/14                                        | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Doebele et al.  | 2014 | LC              | III   | 67/69                        | Docetaxel                 | 11/18                                        | 0.00001 | 1.99–11.19| 1.76–2.13 |
| garon et al.    | 2014 | LC              | III   | 627/618                      | Docetaxel                 | 5/12                                         | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Petrylak et al. | 2015 | Uc              | II    | 46/45                        | Docetaxel                 | 5/12                                         | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Petrylak et al. | 2016 | Uc              | III   | 263/267                      | Docetaxel                 | 9/12                                         | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Tabernero et al.| 2015 | CRC             | III   | 529/528                      | None                       | 13/9                                         | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Moore et al.    | 2016 | CRC             | II    | 52/49                        | Oxaliplatin + fluorouracil + leucovorin | 5/12                                         | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Yardley et al.  | 2016 | CRC             | III   | 752/382                      | Docetaxel                 | 26/13                                        | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Mackey et al.   | 2015 | Bc              | III   | 752/382                      | Docetaxel                 | 26/13                                        | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Fuchs et al.    | 2014 | Bc              | III   | 26/13                        | Erbitin                    | 1/1                                          | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Wilke et al.    | 2016 | Bc              | III   | 26/13                        | Paclitaxel                | 14/8                                         | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Yoon et al.     | 2016 | Bc              | III   | 26/13                        | Oxaliplatin + fluorouracil + leucovorin | 5/12                                         | 0.00001 | 1.99–11.19| 1.76–2.13 |
| Zhu et al.      | 2015 | Bc              | III   | 26/13                        | None                       | 1/1                                          | 0.00001 | 1.99–11.19| 1.76–2.13 |

Abbreviations: CRC, colorectal cancer; Bc, breast cancer; lc, lung cancer; rcc, renal cell carcinoma; Pc, pancreatic cancer; Oc, ovarian cancer; gc, gastric cancer; MM, malignant mesothelioma; ulMs, uterine leiomyosarcoma; Uc, urothelial carcinoma; ec, esophagus cancer; geJc, gastroesophageal junction cancer; hc, hepatocellular carcinoma; sTss, soft tissue sarcomas; nr, not reached; Tace, transarterial chemoembolization.

In the subgroup analysis by dosage, the increased risk of all-grade 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...
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. In order to identify potential risk factors, we performed subgroup analysis according to drug types. The results

| Study or subgroup | Experimental events | Control events | Total | Weight (%) | Risk ratio M–H, random, 95% CI | Risk ratio M–H, random, 95% CI |
|-------------------|---------------------|----------------|-------|------------|-------------------------------|-------------------------------|
| Aghajanian et al | 170                 | 247            | 78    | 233        | 3.8                           | 2.06, 1.68–2.51               |
| Boutsikou et al  | 7                   | 116            | 0     | 113        | 0.2                           | 14.62, 0.84–252.94            |
| Chiot et al      | 186                 | 461            | 97    | 450        | 3.8                           | 1.87, 1.52–2.31               |
| Coleman et al    | 140                 | 330            | 27    | 327        | 3.1                           | 5.14, 3.50–7.53               |
| Corrie et al     | 153                 | 671            | 13    | 672        | 2.4                           | 11.79, 6.76–20.55             |
| Cunningham et al | 34                  | 134            | 9     | 136        | 1.9                           | 3.83, 1.91–7.68               |
| Cunningham et al | 15                  | 468            | 7     | 477        | 1.4                           | 2.18, 0.90–5.31               |
| Diéras et al     | 29                  | 56             | 17    | 57         | 2.7                           | 1.74, 1.08–2.78               |
| Doebele et al    | 26                  | 67             | 13    | 69         | 2.3                           | 2.06, 1.16–3.66               |
| Dotan et al      | 6                   | 12             | 4     | 11         | 1.3                           | 1.38, 0.52–3.61               |
| Escudier et al   | 112                 | 337            | 28    | 304        | 3.1                           | 3.61, 2.46–5.30               |
| Fuchs et al      | 30                  | 236            | 13    | 229        | 2.2                           | 1.12, 0.61–2.07               |
| Garon et al      | 181                 | 627            | 94    | 618        | 3.7                           | 1.90, 1.52–2.37               |
| Hegewisch-Becker et al | 14 | 156            | 11    | 158        | 1.7                           | 1.29, 0.60–2.75               |
| Hensley et al    | 7                   | 52             | 2     | 51         | 0.3                           | 0.49, 0.05–5.24               |
| Koebeler et al   | 5                   | 131            | 1     | 131        | 0.3                           | 5.00, 0.59–42.21              |
| Mackey et al     | 361                 | 752            | 85    | 382        | 3.8                           | 2.16, 1.76–2.64               |
| Masi et al       | 19                  | 91             | 2     | 92         | 0.7                           | 9.60, 2.30–40.05              |
| Miles et al      | 106                 | 238            | 62    | 233        | 3.6                           | 1.67, 1.30–2.16               |
| Miller et al     | 66                  | 229            | 24    | 215        | 2.9                           | 2.58, 1.68–3.96               |
| Moore et al      | 25                  | 52             | 9     | 43         | 2.1                           | 2.62, 1.36–5.04               |
| Nish et al       | 94                  | 119            | 18    | 88         | 3.0                           | 2.55, 1.72–3.78               |
| Passardi et al   | 30                  | 176            | 9     | 194        | 1.9                           | 3.67, 1.79–7.52               |
| Perren et al     | 295                 | 745            | 87    | 735        | 3.8                           | 3.43, 2.76–4.26               |
| Petrylak et al   | 31                  | 46             | 12    | 45         | 2.5                           | 2.53, 1.50–4.27               |
| Petrylak et al   | 67                  | 263            | 46    | 267        | 3.3                           | 1.48, 1.06–2.07               |
| Pinter et al     | 3                   | 16             | 1     | 11         | 0.3                           | 2.06, 0.25–17.34              |
| Pujol et al      | 7                   | 37             | 2     | 37         | 0.6                           | 3.50, 0.78–15.75              |
| Rini et al       | 21                  | 362            | 4     | 347        | 1.1                           | 5.03, 1.75–14.51              |
| Seto et al       | 54                  | 75             | 22    | 77         | 3.1                           | 2.52, 1.72–3.69               |
| Seymour et al    | 77                  | 395            | 31    | 386        | 3.0                           | 2.43, 1.64–3.59               |
| Statopoulos et al| 3                   | 114            | 0     | 108        | 0.2                           | 6.63, 0.35–126.96             |
| Taberner et al   | 232                 | 529            | 120   | 528        | 3.9                           | 1.93, 1.60–2.32               |
| Takeda et al     | 20                  | 50             | 3     | 50         | 1.0                           | 6.67, 2.11–21.02              |
| Tebbutt et al    | 19                  | 157            | 19    | 156        | 2.2                           | 0.99, 0.55–1.80               |
| Van Cutsen et al | 124                 | 296            | 67    | 287        | 3.6                           | 1.79, 1.40–2.30               |
| von Minckwitz et al | 33 | 245         | 18    | 238        | 2.4                           | 1.78, 1.03–3.07               |
| Wilke et al      | 137                 | 327            | 59    | 326        | 3.6                           | 2.34, 1.79–3.04               |
| Yardley et al    | 13                  | 69             | 3     | 65         | 0.9                           | 4.08, 1.22–13.67             |
| Yoh et al        | 39                  | 76             | 23    | 81         | 3.0                           | 1.81, 1.20–2.72               |
| Yoon et al       | 36                  | 82             | 20    | 80         | 2.8                           | 1.76, 1.12–2.76               |
| Zalcman et al    | 91                  | 222            | 16    | 224        | 2.6                           | 5.74, 3.49–9.44               |
| Zhu et al        | 90                  | 277            | 55    | 276        | 3.5                           | 1.63, 1.22–2.18               |

Total, 95% CI 10,141 9,490 100 2.38, 2.09–2.71

Figure 2 RR of all-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 of VEGFR-1 and VEGFR-2, whereas ramucirumab was only specified for VEGFR-2.
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. Increased level of tumor VEGFR-1 expression has been shown to be associated with high tumor angiogenesis. VEGF/VEGFR-1 signaling-mediated tumor cell monocyte chemoattractant protein-1 expression could represent a mechanism responsible for the tumor angiogenic switch. 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. 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. For colorectal cancer patients, high-grade bleeding such as perforation was commonly fatal and life threatening. 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 colorectal cancer patients.
### Table 1: Weighted Risk Ratio for All-Grade Pulmonary Hemorrhage

| Study or subgroup | Experimental events | Control events | Total | Weight (%) | Risk ratio M–H, fixed, 95% CI |
|------------------|---------------------|----------------|-------|------------|-----------------------------|
| **Bevacizumab**  |                     |                |       |            |                             |
| Boutsikou et al<sup>41</sup> | 7                   | 116            | 0     | 113        | 0.9                         | 14.62, 0.84–252.94 |
| Karayama et al<sup>51</sup> | 1                   | 45             | 1     | 35         | 1.9                         | 0.78, 0.05–12.00 |
| Nihno et al<sup>55</sup> | 26                  | 119            | 3     | 58         | 6.9                         | 4.22, 1.33–13.38 |
| Seto et al<sup>57</sup> | 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:** χ²=2.37, df=3 (p=0.50); I²=0% |
| **Test for overall effect:** Z=3.52 (p=0.0004) |

### Table 2: Weighted Risk Ratio for High-Grade Pulmonary Hemorrhage

| Study or subgroup | Experimental events | Control events | Total | Weight (%) | Risk ratio M–H, fixed, 95% CI |
|------------------|---------------------|----------------|-------|------------|-----------------------------|
| **Bevacizumab**  |                     |                |       |            |                             |
| Boutsikou et al<sup>41</sup> | 3                   | 116            | 0     | 113        | 4.4                         | 6.82, 0.36–130.57 |
| Herbst et al<sup>42</sup> | 2                   | 39             | 0     | 42         | 4.2                         | 5.38, 0.27–108.58 |
| Herbst et al<sup>42</sup> | 3                   | 313            | 1     | 313        | 8.7                         | 3.00, 0.31–28.68 |
| Johnson et al<sup>42</sup> | 6                   | 66             | 0     | 32         | 5.8                         | 6.40, 0.37–110.26 |
| Karayama et al<sup>51</sup> | 0                   | 45             | 0     | 35         | Not estimable                |                |
| Nihno et al<sup>55</sup> | 1                   | 119            | 0     | 58         | 5.8                         | 1.48, 0.06–35.66 |
| Pujol et al<sup>51</sup> | 0                   | 37             | 0     | 37         | Not estimable                |                |
| Reck et al<sup>53</sup> | 8                   | 659            | 2     | 327        | 23.2                        | 1.98, 0.42–9.29 |
| Sandler et al<sup>51</sup> | 8                   | 427            | 1     | 440        | 8.6                         | 8.24, 1.04–65.63 |
| Seto et al<sup>57</sup> | 0                   | 75             | 0     | 77         | Not estimable                |                |
| Takeda et al<sup>51</sup> | 0                   | 50             | 0     | 50         | Not estimable                |                |
| Tiseo et al<sup>52</sup> | 0                   | 95             | 0     | 103        | Not estimable                |                |
| Zhou et al<sup>50</sup> | 0                   | 140            | 0     | 134        | Not estimable                |                |
| **Subtotal, 95% CI** |                    |                | 2,181 | 1,761      | 60.8                        | 3.97, 1.70–9.29 |
| **Total events** |                    |                | 31    | 4          |                             |                |
| **Heterogeneity:** χ²=1.96, df=6 (p=0.92); I²=0% |
| **Test for overall effect:** Z=3.18 (p=0.001) |

### Table 3: Weighted Risk Ratio for High-Grade Pulmonary Hemorrhage

| Study or subgroup | Experimental events | Control events | Total | Weight (%) | Risk ratio M–H, fixed, 95% CI |
|------------------|---------------------|----------------|-------|------------|-----------------------------|
| **Ramucirumab**  |                     |                |       |            |                             |
| Garon et al<sup>22</sup> | 4                   | 627            | 4     | 618        | 35.0                        | 0.99, 0.25–3.92 |
| Yoh et al<sup>51</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** |                    |                | 5     | 4          |                             |                |
| **Heterogeneity:** χ²=0.44, df=1 (p=0.51); I²=0% |
| **Test for overall effect:** Z=0.32 (p=0.75) |

| **Total events** |                    |                | 36    | 8          |                             |                |
| **Heterogeneity:** χ²=4.50, df=8 (p=0.81); I²=0% |
| **Test for subgroup differences:** χ²=2.37, df=1 (p=0.12); I²=57.7% |

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**Figure 4** RR of all-grade pulmonary hemorrhage.
**Abbreviations:** M–H, Mantel-Haenszel; RR, relative risk.

**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.

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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**                   | 1 | Identify the report as a systematic review, meta-analysis, or both.             | 1                  |
| **Abstract**                | 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**            | 3,4| 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**                 | 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. | 5                  |
| Protocol and registration   | 6 | Specify study characteristics (eg, PICO, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4,5                |
| Eligibility criteria        | 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                  |
| Information sources         | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4                  |
| Search                      | 9 | State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5                  |
| Study selection             | 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 collection process     | 11| List and define all variables for which data were sought (eg, PICO, funding sources) and any assumptions and simplifications made. | 5                  |
| Data items                  | 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                  |
| Risk of bias in individual studies | 13| State the principal summary measures (eg, risk ratio, difference in means). | 5                  |
| Summary measures            | 14| Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I²) for each meta-analysis. | 5                  |
| Synthesis of results        | 15| Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies). | 5                  |
| Risk of bias across studies | 16| Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5                  |
| Additional analyses         | 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                  |
| Results                     | 18| For each study, present characteristics for which data were extracted (eg, study size, PICO, follow-up period) and provide the citations. | 6                  |
| Study selection             | 19| Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 6                  |
| Study characteristics       | 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                |
| Risk of bias within studies | 21| Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 7,8                |
| Results of individual studies | 22| Present results of any assessment of risk of bias across studies (see item 15). | 7,8                |

(Continued)
### 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: [www.prisma-statement.org](http://www.prisma-statement.org).