Article Type: Meta-analysis and review

Title: Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab


¹Oncology, Instituto CUF de Oncologia (I.C.O.), Lisbon, Portugal
²Internal Medicine, Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA
³Medical Oncology Department, Vall d’Hebron University Hospital and Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Barcelona, Spain
⁴Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
⁵Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA
⁶Hematology Oncology, David Geffen School of Medicine at UCLA/Translational Research in Oncology-US Network, Santa Monica, CA, USA
⁷Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada
⁸Medical Oncology Department, Hospital Universitario Doce de Octubre, Madrid, Spain
⁹Division of Hematology Oncology, California Pacific Medical Center, San Francisco, CA, USA
¹⁰Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan
¹¹Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA
¹²Oncology, Eli Lilly and Company, Indianapolis, IN, USA
¹³Oncology, Eli Lilly and Company, Bridgewater, NJ, USA
¹⁴Department of Medicine, Royal Marsden Hospital, Sutton, UK

Corresponding Author: Dr. Dirk Arnold, Oncology, Instituto CUF de Oncologia (I.C.O.), Tv. Castro 3, Lisbon, 1350-070, Portugal, +351 926 206 726, dirk.arnold@jmellosaude.pt

Word Count: The current word count of the manuscript is below the word limit for a review article (3973/4000), as determined by Microsoft Word version 16.0.4 [32-bit], Microsoft Office Professional Plus 2016.

© The Author 2017. Published by Oxford University Press on behalf of the European Society for Medical Oncology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com.
Abstract

Background: Ramucirumab, the human IgG1 monoclonal antibody receptor antagonist of vascular endothelial growth factor receptor 2 (VEGFR-2), has been approved for treating gastric/gastroesophageal junction, non-small cell lung, and metastatic colorectal cancers. With the completion of 6 global, randomized, double-blind, placebo-controlled, phase 3 trials across multiple tumor types, an opportunity now exists to further establish the safety parameters of ramucirumab across a large patient population.

Materials and methods: An individual patient meta-analysis across the 6 completed phase 3 trials was conducted and the relative risk (RR) and associated 95% confidence intervals (CI) were derived using fixed-effects or mixed-effects models for all-grade and high-grade adverse events (AEs) possibly related to VEGF pathway inhibition. The number needed to harm (NNH) was also calculable, due to the placebo-controlled nature of all 6 registration standard trials.

Results: A total of 4996 treated patients (N = 2748 in the ramucirumab arm, and N = 2248 in the control, placebo arm) were included in this meta-analysis. Arterial thromboembolic events (ATE, all-grade, RR: 0.8, 95% CI 0.5-1.3; high-grade [Grade ≥3], RR: 0.9, 95% CI 0.5-1.7), venous thromboembolic events (VTE, all-grade, RR: 0.7, 95% CI 0.5-1.1; high-grade, RR: 0.7, 95% CI 0.4-1.2), high-grade bleeding (RR: 1.1, 95% CI 0.8-1.5), and high-grade gastrointestinal (GI) bleeding (RR: 1.1, 95% CI 0.7-1.7) did not demonstrate a definite increased risk with ramucirumab. A higher percentage of hypertension, proteinuria, low-grade (Grade 1-2) bleeding, GI perforation, infusion-related reaction and wound-healing complications were observed in the ramucirumab arms compared to control.
**Conclusions:** Ramucirumab may be distinct among antiangiogenic agents in terms of ATE, VTE, high-grade bleeding, or high-grade GI bleeding by showing no clear evidence for an increased risk of these AEs in this meta-analysis of a large and diverse patient population. Ramucirumab is consistent with other angiogenic inhibitors in the risk of developing certain AEs.

**Keywords:** VEGF, VEGFR, ramucirumab, antiangiogenic, adverse events, meta-analysis

**Key Message:** This patient level meta-analysis did not indicate an increased risk of developing ramucirumab-associated ATE, VTE, both high-grade bleeding/GI bleeding compared to placebo arms. The risk associated with ramucirumab of developing any hypertension, proteinuria, low-grade bleeding, GI perforation, IRR or wound healing complication events is consistent with those of other antiangiogenics.

**Clinical Trial Numbers:** The registered clinical trials utilized in this meta-analysis include:

NCT00917384 (REGARD), NCT01170663 (RAINBOW), NCT01168973 (REVEL), NCT01183780 (RAISE), NCT01140347 (REACH), and NCT00703326 (ROSE)
**Introduction**

Ramucirumab (CYRAMZA®, Eli Lilly and Company, Indianapolis, IN, USA) is a fully human IgG1 monoclonal antibody with high affinity binding to the vascular endothelial growth factor receptor 2 (VEGFR-2) extracellular domain, blocking binding of multiple vascular endothelial growth factor (VEGF) ligands and receptor activation. Ramucirumab has received approval for second line therapy in: gastric, lung, and colorectal cancers [1, 2].

Risk-benefit assessment is an important component of physician and patient decision-making in selecting cancer treatments. The need to minimize treatment-related toxicity while maximizing efficacy is paramount. To date, the results of six global, randomized, double-blind, placebo-controlled, phase 3 clinical trials with different tumor types has been published to present the efficacy and safety profile of ramucirumab [3-9] (Table 1).

The purpose of this report is to (1) examine the incidence of adverse events possibly attributed to VEGF pathway inhibition based on data from 6 phase 3 clinical trials; (2) determine specific patient- and treatment-related factors that may be associated with an increased adverse event risk; and (3) explore how specific observed adverse events may be managed in the clinical setting.

Pooled data from these trials provide an opportunity to evaluate relatively infrequent adverse events at the individual patient level. While conditions such as thrombosis and bowel perforation may occur as part of the natural history of advanced cancers, using only registration standard placebo-controlled trials in evaluating reported adverse events permits an unbiased estimate of the number needed to trigger one additional adverse event compared to the control arm (the number needed to harm [NNH]), whereas uncontrolled trials coalesce causation and natural history.
Methods of Analysis

A meta-analysis was conducted to review reported adverse events across the six completed phase 3 ramucirumab trials. An overview of the trials and all randomized patients (intent-to-treat population) is provided in Table 1, with the data based on the primary database lock for each trial. Since all studies were placebo-controlled, the term “control arm” is used herein to pool studies with placebo and those with chemotherapy plus placebo. Adverse events possibly attributed to VEGF inhibition, based on literature review [10], were evaluated in patients receiving at least one dose of study drug (safety population). Consolidated adverse event terms are defined in the Appendix. Although only arterial thromboembolic events (ATE) are considered associated with the antiangiogenic class [10], venous thromboembolic events (VTE) are also reported along with ATE, but the association between antiangiogenic agents and VTE remains unclear [11-14]. Grading of the adverse events was based on Common Terminology Criteria for Adverse Events (CTCAE) versions 3.0 to 4.02.

The relative risk (RR) and the associated 95% confidence interval (CI) was calculated for all-grade and severe/high-grade (grade $\geq 3$) adverse events. The overall RR and 95% CI were derived using fixed-effects or mixed-effects models. In addition, for rare, severe, and fatal events, a simple pooled result or absolute risk difference without adjustment is presented. To determine consistency among studies, the meta-analyses included a statistical test of heterogeneity to determine whether any differences in RR of an adverse event were due to chance or actual differences in study results. The assumption of homogeneity was considered rejected for $P<.10$ from Cochran’s $Q$ test. Relative risks were derived using a random-effects model only if the significant heterogeneity was identified among studies. Otherwise, a fixed-
effects model based on the inverse variance weighting of the selected studies was used to pool the RR. The NNH and NNH leading to discontinuation were derived by calculating the inverse of the attributable risk; specifically, 1/(Experimental rate - Control rate). When the calculated NNH numerical value in a given section is a negative number, due to the incidence being lower in ramucirumab than in the control arm, such values are reported in data tables and not in the Results section. The statistical analysis was performed in R 3.1.1 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

**Results**

A total of 4996 randomized patients received at least one dose of study drug (safety population of 2748 received ramucirumab and 2248 received placebo). Patient characteristics and demographics are presented in Table 2, with the ramucirumab exposure being presented in Supplementary Table S1. Major inclusion criteria for study enrollment, such as adequate hematologic, hepatic, coagulation, and renal function at baseline, were similar across all trials. The following sections focus on some specific adverse events reported in these six randomized trials.

*Hypertension*

Arterial hypertension was defined as either new onset or a worsening grade of pre-existing hypertension during the trial. As shown in Table 3A, there were 585 (21.3%) and 167
(7.4%) patients with all-grade hypertension in the ramucirumab and control arms, respectively. The corresponding RR was 2.7 [95% CI 2.3, 3.2]. A total of 246 (9.0%) patients in the ramucirumab arms experienced grade ≥3 hypertension, compared with 57 (2.5%) in the control arms; RR: 3.7 [95% CI 2.8, 4.9]. This 6.5% increase for grade ≥3 hypertension in the ramucirumab arms represents a NNH of 1 in 16 patients (Table 3B). There were only 2 (0.07%) reported instances of grade 4 hypertensive crisis in the ramucirumab arms (zero in control) among these trials. There were no deaths due to hypertension. In most cases, hypertension was controlled using standard antihypertensive treatment while patients continued to receive ramucirumab therapy. Only 0.3% of patients (8/2748) discontinued ramucirumab treatment due to hypertension, or 1 in 344 patients who started ramucirumab [15].

Similar proportions of patients in both treatment arms received antihypertensive agents as concurrent therapy (Table 4); except in RAINBOW where the ramucirumab arm was 17% higher than the control arm, possibly due to a higher rate of hypertension in this trial.

**Proteinuria**

There were 259 (9.4%) patients experiencing any-grade proteinuria in the ramucirumab arms and 70 (3.1%) patients in the control arms; RR: 3.4 [95% CI 2.6, 4.3] (Table 3A). Thirty-one (1.1%) patients in the ramucirumab arms experienced grade ≥3 proteinuria (including only 1 grade 4 and no grade 5 events) versus 1 (0.04%) patient in the control arms. The NNH for grade ≥3 proteinuria was 1 in 92 patients (Table 3B). Twenty-seven (1.0%) patients in the ramucirumab arms and 1 (0.04%) patient in the control arms discontinued investigational drug due to proteinuria. The NNH for proteinuria leading to discontinuation was 1 in 107 patients. Three patients (0.1%) with nephrotic syndrome, exclusively from the RAISE trial, were
identified in the ramucirumab arms, all of whom were Asian patients with pre-existing hypertension treated with at least two antihypertensive medications.

**Hemorrhage/Bleeding**

Bleeding (all grades) was reported in 1031 (37.5%) and 426 (19.0%) patients in the ramucirumab and control arms, respectively (Table 3A, Figure 1); RR: 2.0 [95% CI 1.8, 2.2]. Low-grade (grade 1-2) epistaxis was the most frequently reported bleeding event in the ramucirumab arms (ranging from 5% [ REGARD] to 40% [ ROSE]), with the exception of three grade 3 events. Grade ≥3 bleeding was reported in 74 (2.7%) patients in the ramucirumab arms and 62 (2.8%) patients in the control arms; RR: 1.1 [95% CI 0.8, 1.5].

Gastrointestinal (GI) bleeding of any grade was reported in 186 (6.8%) patients in the ramucirumab arms versus 103 (4.6%) in the control arms; RR: 1.6 [95% CI 1.3, 2.0] (Table 3A). Grade ≥3 events were infrequent and occurred at the same rate (1.6%) in both treatment groups; RR: 1.1 [95% CI 0.7, 1.7]. Thus, no difference was observed for high-grade (grade ≥3) bleeding/GI bleeding between the ramucirumab and control arms.

There were 6 (0.2%) patients in the ramucirumab arms who experienced grade 4 bleeding events, and 4 of them were GI bleeding events. Ten (0.4%) patients in the control arms experienced grade 4 bleeding events, and 4 of them were GI bleeding events. Fatal hemorrhage/bleeding events were reported in 17 (0.6%) patients in the ramucirumab arms: GI bleeding (n = 9), pulmonary hemorrhage (n = 6), hepatic hemorrhage (n = 1), and hemorrhagic shock (n = 1). There were 14 (0.6%) fatal hemorrhage/bleeding events in the control arms: GI bleeding (n = 5), pulmonary hemorrhage (n = 6), intracranial hemorrhage (n = 2), and aortic
aneurysm rupture \( (n = 1) \). Twenty-five patients (0.9%) discontinued ramucirumab treatment due to bleeding/hemorrhage (GI bleeding \( [n = 15] \), intracranial hemorrhage \( [n = 3] \), epistaxis \( [n = 3] \), hepatic hemorrhage \( [n = 2] \), hematuria \( [n = 1] \), and hemoptysis \( [n = 1] \)) compared to 17 patients (0.8%) discontinuing placebo treatment (GI bleeding \( [n = 14] \), hepatic hemorrhage \( [n = 1] \), menorrhagia \( [n = 1] \), and hemorrhage in unknown location \( [n = 1] \)). The discontinuation rate was low and similar between the two arms.

Since pulmonary hemorrhage has been a concern for non-small-cell lung cancer (NSCLC) patients treated with antiangiogenic agents [16], we compared the incidence of all-grade pulmonary hemorrhage in both squamous and nonsquamous NSCLC histologies in the REVEL trial and showed it to be similar between treatment arms (squamous: ramucirumab arm all-grade, 9.6%, high-grade, 1.9%; control arm all-grade, 12.4%, high-grade, 2.4%; and nonsquamous: ramucirumab arm all-grade, 7.3%, high-grade, 1.1% control arm all-grade, 5.7%, high-grade 0.9%) [5].

_Gastrointestinal (GI) Perforation_

There were 30 (1.1%) patients who experienced all-grade GI perforation in the ramucirumab arms, and 7 (0.3%) patients in the control arms; RR: 3.2 [95% CI 1.5, 7.0] (Table 3A). Grade ≥3 GI perforation was reported in 28 (1.0%) patients in the ramucirumab arms versus 6 (0.3%) patients in the control arms; RR: 3.2 [95% CI 1.4, 7.3]. Ten (0.4%) patients in the ramucirumab arms experienced grade 4 GI perforation compared with 3 (0.1%) patients in the control arms. Seven (0.3%) patients in the ramucirumab arms and 1 (0.04%) patient in the control arms experienced grade 5 GI perforation. Thus, one additional grade ≥3 GI perforation
event would occur every 133 patients treated with ramucirumab (Table 3B). The fatal GI perforation rate in the ramucirumab arms was 1 in 393 treated patients, compared with 1 in 2248 in control arms. This implies an increased absolute risk of fatal GI perforation events of approximately 1 in 476 patients treated with ramucirumab.

**Arterial Thromboembolic Events (ATE)**

Overall, there were 38 (1.4%) and 40 (1.8%) cases of all-grade ATE in the ramucirumab and control arms, respectively; RR: 0.8 [95% CI 0.5, 1.3] (Table 3A, Figure 1). A total of 21 (0.8%) patients in the ramucirumab arms experienced grade ≥3 ATE versus 19 (0.8%) patients in the control arms; RR: 0.9 [95% CI 0.5, 1.7].

Across all trials, 7 (0.3%) grade 4 events were reported in the ramucirumab arms, with 4 of these events not recovered or resolved, while 4 grade 4 events were reported in the control arms. Seven grade 5 ATE events were reported in the ramucirumab arms (6 myocardial events, 1 cerebrovascular event) and 10 grade 5 ATE events were reported in the control arms (7 myocardial events, 3 cerebrovascular events). Overall, the mortality rate for ATE was low and similar between the ramucirumab (0.3%) and control arms (0.4%).

**Venous Thromboembolic Events (VTE)**

VTEs presented here include both symptomatic and non-symptomatic VTE events. Overall, 106 (3.9%) patients with all-grade VTEs were reported in the ramucirumab arms versus 116 (5.2%) in the control arms; RR: 0.7 [95% CI 0.5, 1.1] (Table 3A, Figure 1). Fifty-six (2.0%) patients with grade ≥3 VTEs were reported in the ramucirumab arms and 61 (2.7%) patients in the control arms; RR: 0.7 [95% CI 0.4, 1.2].
Across all trials, 11 (0.4%) grade 4 VTEs were reported in the ramucirumab arms and 11 (0.5%) grade 4 VTEs were reported in the control arms. There were 3 grade 5 VTEs in the ramucirumab arms and 6 in the control arms; all grade 5 VTEs in both arms were pulmonary embolism (PE). The fatal VTE rate was low and similar in both the ramucirumab (0.1%) and control arms (0.3%). Ten (0.4%) patients discontinued ramucirumab treatment due to VTEs and 15 (0.7%) patients discontinued treatment in the control arms, primarily due to deep vein thrombosis (DVT) or PE.

**Infusion-Related Reactions (IRR)**

Any-grade IRR was reported in 180 (6.6%) patients in the ramucirumab arms compared to 104 (4.6%) patients in the control arms; RR: 1.4 [95% CI 0.8, 2.3] (Table 3A). The NNH for all-grade IRR was 1 in 52 and for grade ≥3 was 1 in 227 patients (Table 3B). A total of 28 (1.0%) patients in the ramucirumab arms experienced grade ≥3 IRR versus 13 (0.6%) in the control arms; RR: 1.5 [95% CI 0.8, 2.7]. Four (0.1%) grade 4 events were reported in the ramucirumab arms and 2 (0.1%) in the control arms, with the outcome in the ramucirumab arms being either recovered or resolved. There was no grade 5 IRR reported in these trials. Twelve patients (0.4%) in the ramucirumab arms discontinued ramucirumab while 3 (0.1%) patients in the control arms discontinued placebo due to an IRR. The NNH for IRR leading to discontinuation was 1 in 330 patients treated with ramucirumab.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

RPLS was reported in 2 (0.04%) patients in these trials, 1 grade 2 RPLS in ramucirumab arms and 1 grade 2 RPLS in control arms, both in the RAISE trial. Both patients’ RPLS status
was confirmed with magnetic resonance imaging (MRI). Therefore, the incidence was approximately 1 in 2700 ramucirumab-treated patients.

**Wound-Healing Complications**

All-grade wound-healing complications were reported in 14 (0.5%) patients in the ramucirumab arms, occurring only in the RAISE ($n = 6$) and ROSE ($n = 8$) trials (Table 3A and Supplementary Table S2), and in 4 (0.2%) patients in the control arms; RR: 2.0 [95% CI 0.8, 5.1]. Five (0.2%) patients in the ramucirumab arms experienced grade $\geq 3$ wound-healing complications with zero patients in the control arms. The NNH for all-grade and grade $\geq 3$ wound-healing complication events was 1 in 302 and 1 in 550 patients in the ramucirumab and control arms, respectively (Table 3B).
**Discussion and Clinical Implications**

This meta-analysis represents one of the largest individual patient meta-analyses of an antiangiogenic drug and has some notable findings. First, similar to the published safety data for other antiangiogenics as a “class effect”, we observed a higher percentage of low-grade bleeding, GI perforation, wound-healing complications, hypertension, and proteinuria in the ramucirumab arms compared to control. The rates and severity of these events are consistent with those seen in other antiangiogenic trials [10, 17-19]. In addition, the safety profile described here is consistent with the ramucirumab labels [1, 2].

Ramucirumab may differ from other antiangiogenics in relation to bleeding and thromboembolism, as no evidence for increased risk of ATE, VTE, high-grade bleeding, or high-grade GI bleeding was found in this meta-analysis. The lack of an increased risk of ATE, VTE, or high-grade bleeding differs from published studies with other antiangiogenics [11, 12, 20-24]. The mechanisms underlying these differences remain unclear, although it cannot be ruled out that differences in the incidence of these adverse events between ramucirumab and other antiangiogenics may be related to differences in the patient populations.

Arterial **hypertension** is recognized as a common adverse event associated with antiangiogenic therapies [25, 26]. The mechanisms of hypertension associated with VEGF inhibition are thought to include decreased production of nitric oxide (NO) in the wall of arterioles and other resistance vessels [27], increased activation of the endothelin-1 system [28], and/or capillary rarefaction [29]. Once detected, hypertension is readily managed with antihypertensives, and rarely delays or stops cancer treatment. Pre-existing hypertension should be controlled before starting ramucirumab treatment, and monitoring of blood pressure is
recommended during therapy [1]. Although hypertension was common and required treatment, only 1 out of 344 ramucirumab patients in these trials discontinued therapy due to hypertension.

**Proteinuria** has been reported with antiangiogenic agents that block the effects of VEGF-A [30-32]; however, the underlying mechanism is not well understood. Inhibition of VEGF-dependent interactions between podocytes and glomerular endothelial cells lessens the integrity of the filtration barrier, leading to proteinuria [33-35]. Most patients enrolled in our trials had adequate renal function at baseline, and the incidence of high-grade proteinuria in the ramucirumab arms was 1.1% [RR: 8.3; 95% CI 2.9, 24.1] (Table 3A). During ramucirumab therapy, the clinician should monitor for the development or worsening of proteinuria [1]. In most cases, proteinuria was manageable during ramucirumab therapy. Only 3 (0.1%) patients in the ramucirumab arms reported nephrotic syndrome.

A meta-analysis of patients from 16 randomized trials with bevacizumab reported a proteinuria incidence of 2.2% and a significantly increased risk for high-grade proteinuria [RR: 4.79; 95% CI 2.71, 8.46, \( P < .001 \)] [31]. This same study also reported a 0.8% incidence of patients with nephrotic syndrome as well as a RR of 7.78 [95% CI 1.80, 33.62, \( P = .006 \)] [31].

The pathogenesis of antiangiogenic-associated **bleeding** is not well understood. Tumor-infiltrated vascular walls or injured mucosal membranes, which exhibit high VEGF dependence, may have an enhanced propensity to bleed [36]. Preclinical data demonstrate capillaries with endothelial fenestrations are dependent on VEGF signaling [33, 37]. Thus, tumors with fenestrated capillaries, such as those arising in endocrine glands or the GI tract, may be particularly sensitive to anti-VEGF pathway agents, and more likely to develop capillary damage leading to hemorrhage.
Overall, the incidence rate of all-grade bleeding and GI bleeding events with ramucirumab was higher than the control arms. However, 72% of bleeding events (739/1031) in the ramucirumab arms were low-grade epistaxis requiring no intervention. Most importantly, the incidence rates of severe bleeding and GI bleeding (grade ≥3) were low and similar between the two treatment arms. Results from the REVEL NSCLC trial also demonstrated that, despite higher rates of all-grade pulmonary hemorrhage in both treatment arms in squamous histology patients (9.6% ramucirumab arm, 12.4% control arm) compared to nonsquamous histology (7.3% ramucirumab arm, 5.7% control arm), the incidence rate of pulmonary hemorrhage was similar between the two treatment arms within each histology [5].

**Gastrointestinal perforation** is a rare but serious adverse event, and can be fatal due to severe peritonitis [18, 38]. Patients receiving ramucirumab in these studies had a low (1.0%) incidence of grade ≥3 GI perforation with an increased absolute risk of 0.7%. Despite this low incidence, patients and physicians should be aware of GI perforation, and consider this in the differential diagnosis of patients with unexplained abdominal symptoms.

**Arterial thromboembolic events** have been associated with some antiangiogenic therapeutic agents, particularly in the context of combination regimens including anti-VEGF antibodies and cytotoxic chemotherapy. Scappaticci et al. [12] reported the risk of ATE was increased with chemotherapy plus bevacizumab versus chemotherapy alone (hazard ratio [HR] = 2.0, 95% CI 1.05, 3.75, \( P = .031 \)). Cancer patients have an intrinsically increased risk for thrombosis [22, 39]. The prevention and treatment of thromboembolic events is important, since they are the second most frequent cause of death in cancer patients [40]. The RRs from our results were 0.8 [95% CI 0.5, 1.3] for all-grade ATEs, and 0.9 [95% CI 0.5, 1.7] for grade ≥3 ATEs. We cannot rule out whether the patient population included in our trials was better
selected to reduce ATE risk factors due to prior knowledge of the potential risks for arterial embolic events. Since patients with any ATE (including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack) within 6-12 months prior to randomization were excluded in all trials reported here except ROSE, the risk of developing ramucirumab-associated ATE for the patients with a recent history of ATE remains unclear. In aggregate, our data suggests that ramucirumab does not increase the risk of developing ATE.

Venous thrombosis is a common complication in patients with cancer [41, 42]. Compared to patients without cancer, thrombosis in patients with cancer is significantly more likely to be fatal [43]. Cancer patients with active malignancy have a 4- to 7-fold higher incidence of symptomatic VTE than the general population [41, 44, 45]. Venous thromboembolic events have been reported with antiangiogenic therapies [11, 22-24, 46, 47], but this association is still controversial [11-14]. Our data demonstrated ramucirumab did not increase the risk of VTE compared with the control arms (Table 3A) [all-grade RR: 0.7 (95% CI 0.5, 1.1), high-grade RR: 0.7 (95% CI 0.4, 1.2)].

Monoclonal antibodies may cause infusion-related reactions [48, 49]. The incidence of all-grade and high-grade IRR was very low for both treatment groups across these 6 trials (Tables 3A and B), with the outcome of most reported IRR being either recovered or resolved, and no fatal IRR events were observed.

Despite previous reports of reversible posterior leukoencephalopathy syndrome associated with antiangiogenic drug therapy [50, 51], in this meta-analysis there were single events in both treatment and control populations. Due to the extreme rarity of RPLS, a much larger patient population will be needed in order to further define this risk. Based on the evidence to date, it remains uncertain whether ramucirumab contributes to RPLS development.
VEGF mediates three effects for **wound-healing**: vasodilation to facilitate nutrient delivery and waste removal, increased vascular permeability for fibrinogen and plasminogen extravasation (providing a substrate for tissue growth), and angiogenesis for tissue formation and remodeling [52]. Clinical data on the effect of angiogenesis inhibitors on wound healing are limited. The risk of developing wound-healing complications with bevacizumab has been reported by Scappaticci et al. [53]. Patients experiencing major surgery concurrent with bevacizumab treatment demonstrated increased wound-healing complications, while no increased risk of wound-healing complications was observed in those given 5-fluorouracil/leucovorin-based chemotherapy plus bevacizumab 28-60 days post-surgical intervention versus chemotherapy-only treatment [53]. In the current study, the rate of the wound-healing complications was low overall in the ramucirumab arms (all-grade 0.5%).

A strength of this meta-analysis is that it represents one of the largest meta-analyses at the patient level of an antiangiogenic therapy, having evaluated 2748 ramucirumab-treated and 2248 placebo-treated patients. This permits the differentiation of study drug-related adverse events from toxicities of other anticancer therapy, and the natural history of the disease.

One limitation of this meta-analysis is that despite a population of approximately 5000 patients, not all rare events may be observed. However, the 90% confidence interval upper bound for the unobserved events rate in the current study population is less than 1/1000. Another (potential) limitation is that most trials reported here represented unique tumor types (with both REGARD and RAINBOW being gastric/GEJ cancer); but, Supplementary Table S2 provides a summary of the incidence rate of a given AE in a given tumor type. Furthermore, while patients enrolled in these trials met study inclusion/exclusion criteria, had adequate organ function and acceptable concurrent morbidities and medications, they may not reflect the general
patient population receiving cancer treatment. Another concern in principle when combining data from multiple studies is the emergence of the so-called Simpson’s Paradox, in which a trend appears in different groups of data but disappears or reverses when these groups are combined [54, 55]. However, this is specifically a concern when studies are combined in which the randomization ratios differ substantially [56], which was not the case in the present meta-analysis: 4 out of the 6 studies had a common randomization of 1:1, and only the REGARD and ROSE trials, representing about 30% of the total analysis population, had a ratio of 2:1. Similarly, the presence/absence of chemotherapy, or differences in the chemotherapy regime itself between studies is relevant on its own, particularly in the context of different proportions of patients receiving placebo in different studies.

The safety signal for all therapeutics develops over time. Four additional phase 3 global, registrational, placebo-controlled trials with ramucirumab are underway (https://clinicaltrials.gov/). These ongoing controlled trials will add an additional 1500-2000 patients to the overall ramucirumab-treated population, and will allow further analysis of ramucirumab safety at the patient level.

**Conclusions**

The importance of our results for clinical practice is that the risk of developing hypertension, proteinuria, all-grade bleeding, GI perforation, IRR, RPLS, and wound-healing delay are consistent with reported adverse events associated with the angiogenesis inhibitor class. However, we do not observe an increased risk associated with ramucirumab for developing ATE, VTE, high-grade bleeding, or high-grade GI bleeding across these trials. Also, the majority of adverse events are low-grade and manageable.
Acknowledgements

We thank the patients and their caregivers who participated in the trials, and the investigators and their support staff who conducted the trials comprising this analysis. Additional thanks to Jennifer Meyer Harris (Lilly USA, LLC, Indianapolis, IN, USA) for diligent contributions to the drafting, design, and critical revisions of this manuscript. Writing and editorial assistance, funded by Eli Lilly and Company, was provided by Matthew R. Distasi (Eli Lilly and Company, Indianapolis, IN, USA) and Melissa A. Wolferz (Eli Lilly and Company, Bridgewater, NJ, USA).

Funding

This work was supported by Eli Lilly and Company, Indianapolis, IN, USA, and no grant number is applicable.

Disclosure

D.A. reports honoraria/consultancy from Bayer, Biocompatibles, Boehringer Ingelheim, Eli Lilly and Company, Roche, Sanofi, and Servier; as well as honoraria presentations for Bayer, Eli Lilly and Company, Roche, and Servier. C.F. has had consultant roles for Entrinsic Health, Genetech, Merck, Gilead Sciences, Sanofi, Dicerna, Five Prime Therapeutics, Merrimack, Bayer, Agios, Taiho, Kew, and Eli Lilly and Company. J.T. has had consultant/advisory roles for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Imclone, Eli Lilly and Company, MSD, Merck
Serono, Novartis, Roche, Sanofi, Symphogen, and Taiho. A.O. reports a grant from BMS. A.X.Z. reports research support to his institution from Eli Lilly and Company. E.B.G. reports grants to his institution from Eli Lilly and Company, AstraZeneca, Boehringer Ingelheim, BMS, Genentech, Merck, Mirati, Novartis, and Pfizer. J.R.M has had advisory roles for Eli Lilly and Company, Roche, and Pfizer, and holds shares in Pacylex Pharmaceuticals. L.P.A. has had advisory roles for Eli Lilly and Company, Roche, MSD, BMS, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Clovis, and Amgen. A.D.B. declared no conflicts of interest. T.O. has had an editor role, research grant, and honoraria from Novartis; reports research grants and honoraria from Pfizer, Taiho, Bayer, Chugai, Eli Lilly and Company, Yakuruto Honsha, Ono Pharmaceutical, AstraZeneca, Merck Serono, Baxter, Nobelpharma Co.; and research grants from Nippon Boehringer Ingelheim, Dainippon Simitomo Pharma, Eisai Co., OncoTherapy Science Inc., Kyowa Hakko Kirin Co., Shizuoka Industry, Nano Carrier Co., Zeria Pharmaceutical Co., and Glaxo Smith Kline. T.Y. reports grants from Boehringer Ingelheim GmbH. and GlaxoSmithKline. H.H.Y. reports grants to his institution from Eli Lilly and Company. M. D., D. F., Y. Z., Y. L., P. B., and A. S. are all employees and shareholders of Eli Lilly and Company. I.C. reports advisory board roles at: Sanofi Oncology, Eli Lilly and Company, Bristol Meyers Squibb, MSD, Bayer, Roche, Five Prime Therapeutics; honorarium from: Taiho, Pfizer, Amgen, Eli Lilly and Company, Gilead Science; research funding from: Janssen-Cilag, Sanofi Oncology, Merck-Serono, Novartis; and would like to acknowledge National Health Service funding to the National Institute for Health Research Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research.
References

5. Garon EB, Ciuleanu TE, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384 (9944): 665-673.


Table and Figure Legends

Table 1. Ramucirumab Double-Blind Randomized Controlled Phase 3 Clinical Trials

*Intent-to-treat population; the primary endpoints for these studies were overall survival or progression-free survival.

Abbreviations: BSC = best supportive care; CRC = colorectal carcinoma; GEJ = gastroesophageal junction; FOLFIRI = leucovorin (folinic acid), fluorouracil, and irinotecan; HCC = hepatocellular carcinoma; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non-small-cell lung cancer; Q2W = every two weeks; Q3W = every 3 weeks; v = version; RAM = ramucirumab

Table 2. Patient Characteristics in the Intent-to-Treat Population of Ramucirumab Double-Blind Randomized Controlled Phase 3 Clinical Trials

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; RAM = ramucirumab

Table 3A. Summary of the Incidence and Relative Risk of Adverse Events across the Six Completed Phase 3 Ramucirumab Clinical Trials

* = Random-effects analysis model utilized due to significant identified heterogeneity. # = For rare events (events that were not observed in at least one treatment arm in any study), the relative risk might not be reliable due to large variability.

Abbreviations: CI = confidence interval; RAM = ramucirumab; GI = gastrointestinal

Table 3B. The Number Needed to Harm (NNH)* in each Adverse Event from the Six Completed Phase 3 Ramucirumab Clinical Trials

* = NNH calculated via the following formula: 1/(Ramucirumab rate - Control rate). Negative values indicate that the incidence of the given adverse event was higher in the Control than in the Ramucirumab arms.

Abbreviations: ATE = arterial thromboembolic events; GI = gastrointestinal; IRR = infusion-related reactions; N/C = not calculable; RAM = ramucirumab; VTE = venous thromboembolic events

Table 4. Antihypertensive Agents used in the Completed Phase 3 Ramucirumab Clinical Trials
Concurrent antihypertensive therapy includes any antihypertensive therapy received between treatment start date and 30 days after treatment end, including therapies that may have started prior to treatment start date. Antihypertensive therapies included diuretics, peripheral vasodilators, beta-blocking agents, calcium channel antagonists, renin angiotensin agents, and other antihypertensive therapy. Patient is only counted once for each category.

Abbreviation: RAM = ramucirumab

Figure 1. Forest Plots of the Incidence and Relative Risk of ATE, VTE and Bleeding Adverse Events in Completed Phase 3 Ramucirumab Clinical Trials

Abbreviations: ATE = arterial thromboembolic events; CI = confidence interval; VTE = venous thromboembolic events; RR = relative risk
<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Treatment Arms</th>
<th>Patients Randomized per Arm</th>
<th>Date 1st Patient Enrolled</th>
<th>NCI CTCAE</th>
<th>Trial Registry Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGARD†,‡, I4T-IE-JVBD</td>
<td>Advanced gastric or GEJ adenocarcinoma</td>
<td>Ramucirumab 8 mg/kg IV Q2W plus BSC or placebo plus BSC</td>
<td>RAM: n = 238</td>
<td>6 Oct. 2009</td>
<td>v4.02</td>
<td>NCT00917384</td>
</tr>
<tr>
<td>RAINBOW†,‡, I4T-IE-JVBE</td>
<td>Advanced gastric or GEJ adenocarcinoma</td>
<td>Ramucirumab 8 mg/kg IV on Days 1 and 15, plus paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15 of a 28-day cycle or placebo IV plus paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15 of a 28-day cycle</td>
<td>RAM: n = 330</td>
<td>23 Dec. 2010</td>
<td>v4.02</td>
<td>NCT01170663</td>
</tr>
<tr>
<td>REVEL†,‡, I4T-MC-JVBA</td>
<td>Stage IV NSCLC</td>
<td>Ramucirumab 10 mg/kg IV plus docetaxel 75 mg/m^2 on Day 1 of a 21-day cycle or placebo plus docetaxel 75 mg/m^2 on Day 1 of a 21-day cycle</td>
<td>RAM: n = 628</td>
<td>03 Dec. 2010</td>
<td>v4.0</td>
<td>NCT01168973</td>
</tr>
<tr>
<td>RAISE†,‡, I4T-MC-JVBB</td>
<td>Metastatic CRC</td>
<td>Ramucirumab 8 mg/kg IV plus FOLFIRI Q2W or placebo plus FOLFIRI Q2W</td>
<td>RAM: n = 536</td>
<td>13 Dec. 2010</td>
<td>v4.02</td>
<td>NCT01183780</td>
</tr>
<tr>
<td>REACH†,‡, I4T-IE-JVBF</td>
<td>Advanced HCC</td>
<td>Ramucirumab 8 mg/kg IV Q2W plus BSC or placebo Q2W plus BSC</td>
<td>RAM: n = 283</td>
<td>04 Nov. 2010</td>
<td>v4.0</td>
<td>NCT01140347</td>
</tr>
<tr>
<td>ROSE†,‡, I4T-IE-JVBC</td>
<td>Metastatic breast cancer</td>
<td>Ramucirumab 10 mg/kg IV plus docetaxel 75 mg/m^2 Q3W or docetaxel 75 mg/m^2 plus placebo Q3W</td>
<td>RAM: n = 759</td>
<td>11 Aug. 2008</td>
<td>v3.0</td>
<td>NCT00703326</td>
</tr>
</tbody>
</table>

*Intent-to-treat population; the primary endpoints for these studies were overall survival or progression-free survival.

Abbreviations: BSC = best supportive care; CRC = colorectal carcinoma; GEJ = gastroesophageal junction; FOLFIRI = leucovorin (folic acid), fluorouracil, and irinotecan; HCC = hepatocellular carcinoma; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non-small-cell lung cancer; Q2W = every two weeks; Q3W = every 3 weeks; v = version; RAM = ramucirumab
### Table 2. Patient Characteristics in the Intent-to-Treat Population of Ramucirumab Double-Blind Randomized Controlled Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>REGARD</th>
<th>RAINBOW</th>
<th>REVEL</th>
<th>RAISE</th>
<th>REACH</th>
<th>ROSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM</td>
<td>Control</td>
<td>RAM</td>
<td>Control</td>
<td>RAM</td>
<td>Control</td>
</tr>
<tr>
<td>n = 238</td>
<td>n = 117</td>
<td>n = 330</td>
<td>n = 335</td>
<td>n = 628</td>
<td>n = 625</td>
</tr>
<tr>
<td><strong>Median age, yrs. (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65, n (%)</td>
<td>156 (66)</td>
<td>71 (61)</td>
<td>204 (62)</td>
<td>212 (63)</td>
<td>391 (62)</td>
</tr>
<tr>
<td>≥65, n (%)</td>
<td>82 (34)</td>
<td>46 (39)</td>
<td>126 (38)</td>
<td>123 (37)</td>
<td>237 (38)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>169 (71)</td>
<td>229 (69)</td>
<td>243 (73)</td>
<td>419 (67)</td>
<td>415 (66)</td>
</tr>
<tr>
<td>Female</td>
<td>69 (29)</td>
<td>101 (31)</td>
<td>92 (27)</td>
<td>209 (33)</td>
<td>210 (34)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>181 (76)</td>
<td>208 (63)</td>
<td>199 (59)</td>
<td>526 (84)</td>
<td>503 (80)</td>
</tr>
<tr>
<td>Asian</td>
<td>39 (16)</td>
<td>110 (33)</td>
<td>121 (36)</td>
<td>74 (12)</td>
<td>86 (14)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (2)</td>
<td>6 (2)</td>
<td>17 (3)</td>
<td>16 (3)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (6)</td>
<td>9 (3)</td>
<td>10 (2)</td>
<td>20 (3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>Not reported/ Missing</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>67 (28)</td>
<td>117 (35)</td>
<td>144 (43)</td>
<td>207 (33)</td>
<td>199 (32)</td>
</tr>
<tr>
<td>1</td>
<td>171 (72)</td>
<td>213 (65)</td>
<td>191 (57)</td>
<td>420 (67)</td>
<td>425 (68)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ECOG PS = Eastern Cooperative Oncology Group Performance Status; RAM = ramucirumab
<table>
<thead>
<tr>
<th>Safety Population</th>
<th>Hypertension (HTN), ( n (%) )</th>
<th>Proteinuria, ( n (%) )</th>
<th>Bleeding, ( n (%) )</th>
<th>GI Bleeding, ( n (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grade</td>
<td>Grade ≥3</td>
<td>All grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>RAM</td>
<td>( N = 2748 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>585 (21.3)</td>
<td>246 (9.0)</td>
<td>259 (9.4)</td>
<td>31 (1.1)</td>
</tr>
<tr>
<td></td>
<td>167 (7.4)</td>
<td>57 (2.5)</td>
<td>70 (3.1)</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Control</td>
<td>( N = 2248 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>167 (7.4)</td>
<td>57 (2.5)</td>
<td>70 (3.1)</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>[95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAM</td>
<td>2.7 [2.3, 3.2]</td>
<td>3.7 [2.8, 4.9]</td>
<td>8.3 [2.9, 24.1]</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.4 [2.6, 4.3]</td>
<td>8.3 [2.9, 24.1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Perforation, ( n (%) )</td>
<td>All grade</td>
<td>Grade ≥3</td>
<td>All grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>RAM</td>
<td>30 (1.1)</td>
<td>28 (1.0)</td>
<td>106 (3.9)</td>
<td>56 (2.0)</td>
</tr>
<tr>
<td>Control</td>
<td>40 (1.8)</td>
<td>19 (0.8)</td>
<td>116 (5.2)</td>
<td>61 (2.7)</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>[95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.2 [1.5, 7.0]</td>
<td>3.2 [1.4, 7.3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial Thromboembolic Events (ATE), ( n (%) )</td>
<td>All grade</td>
<td>Grade ≥3</td>
<td>All grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>RAM</td>
<td>0.8 [0.5, 1.3]</td>
<td>0.9 [0.5, 1.7]</td>
<td>0.7 [0.4, 1.2]</td>
<td>1.4 [0.8, 2.3]</td>
</tr>
<tr>
<td>Control</td>
<td>0.7 [0.3, 1.1]</td>
<td>0.9 [0.5, 1.7]</td>
<td>0.7 [0.4, 1.2]</td>
<td>1.4 [0.8, 2.3]</td>
</tr>
<tr>
<td>Venous Thromboembolic Events* (VTE), ( n (%) )</td>
<td>All grade</td>
<td>Grade ≥3</td>
<td>All grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>RAM</td>
<td>36 (1.6)</td>
<td>14 (0.6)</td>
<td>14 (0.5)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Control</td>
<td>7 (0.3)</td>
<td>4 (0.2)</td>
<td>4 (0.2)</td>
<td>0 (0)#</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>[95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.4 [1.6, 7.5]</td>
<td>3.2 [1.4, 7.3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-Related Reactions (IRR), ( n (%) )</td>
<td>All grade</td>
<td>Grade ≥3</td>
<td>All grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>RAM</td>
<td>0.8 [0.5, 1.3]</td>
<td>0.9 [0.5, 1.7]</td>
<td>0.7 [0.4, 1.2]</td>
<td>1.4 [0.8, 2.3]</td>
</tr>
<tr>
<td>Control</td>
<td>0.7 [0.3, 1.1]</td>
<td>0.9 [0.5, 1.7]</td>
<td>0.7 [0.4, 1.2]</td>
<td>1.4 [0.8, 2.3]</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>[95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.4 [1.6, 7.5]</td>
<td>3.2 [1.4, 7.3]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = Random-effects analysis model utilized due to significant identified heterogeneity. # = For rare events (events that were not observed in at least one treatment arm in any study), the relative risk might not be reliable due to large variability. Abbreviations: CI = confidence interval; RAM = ramucirumab; GI = gastrointestinal
### Table 3B. The Number Needed to Harm (NNH) in each Adverse Event from the Six Completed Phase 3 Ramucirumab Clinical Trials

<table>
<thead>
<tr>
<th>Safety Population</th>
<th>SUMMARY Control</th>
<th>REGARD Control</th>
<th>RAINBOW Control</th>
<th>REVEL Control</th>
<th>RAISE Control</th>
<th>REACH Control</th>
<th>ROSE Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 2748</td>
<td>N = 2248</td>
<td>n = 236</td>
<td>n = 327</td>
<td>n = 627</td>
<td>n = 529</td>
<td>n = 277</td>
<td>n = 752</td>
</tr>
<tr>
<td>NNH All grade</td>
<td>7</td>
<td>16</td>
<td>12</td>
<td>5</td>
<td>17</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>NNH Grade ≥3</td>
<td>10</td>
<td>20</td>
<td>5</td>
<td>8</td>
<td>29</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Proteinuria</td>
<td>20</td>
<td>5</td>
<td>8</td>
<td>17</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Bleeding</td>
<td>GI Bleeding</td>
<td>46</td>
<td>2768</td>
<td>372</td>
<td>25</td>
<td>91</td>
<td>18</td>
</tr>
<tr>
<td>GI Perforation</td>
<td>ATE</td>
<td>128</td>
<td>133</td>
<td>-4523</td>
<td>109</td>
<td>158</td>
<td>88</td>
</tr>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRR</td>
<td>Wound-Healing</td>
<td>52</td>
<td>227</td>
<td>-76</td>
<td>46</td>
<td>116</td>
<td>35</td>
</tr>
</tbody>
</table>

* = NNH calculated via the following formula: 1/(Ramucirumab rate - Control rate). Negative values indicate that the incidence of the given adverse event was higher in the Control than in the Ramucirumab arms. Abbreviations: ATE = arterial thromboembolic events; GI = gastrointestinal; IRR = infusion-related reactions; N/C = not calculable; RAM = ramucirumab; VTE = venous thromboembolic events.
### Table 4. Antihypertensive Agents used in the Completed Phase 3 Ramucirumab Clinical Trials

<table>
<thead>
<tr>
<th>Patients Receiving Concurrent Anti-Hypertensive Therapies</th>
<th>RAM n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGARD</td>
<td>101 (42.8)</td>
<td>46 (40.0)</td>
</tr>
<tr>
<td>RAINBOW</td>
<td>180 (55.0)</td>
<td>124 (37.7)</td>
</tr>
<tr>
<td>REVEL</td>
<td>159 (25.4)</td>
<td>109 (17.6)</td>
</tr>
<tr>
<td>RAISE</td>
<td>329 (62.2)</td>
<td>286 (54.2)</td>
</tr>
<tr>
<td>REACH</td>
<td>223 (80.5)</td>
<td>201 (72.8)</td>
</tr>
<tr>
<td>ROSE</td>
<td>379 (50.4)</td>
<td>167 (43.7)</td>
</tr>
</tbody>
</table>

*a Concurrent antihypertensive therapy includes any antihypertensive therapy received between treatment start date and 30 days after treatment end, including therapies that may have started prior to treatment start date.

*b Antihypertensive therapies included diuretics, peripheral vasodilators, beta-blocking agents, calcium channel antagonists, renin angiotensin agents, and other antihypertensive therapy.

Patient is only counted once for each category.

Abbreviation: RAM = ramucirumab
Figure 1. Forest Plots of the Incidence and Relative Risk of ATE, VTE and Bleeding Adverse Events in Completed Phase 3 Ramucirumab Clinical Trials

325x591mm (300 x 300 DPI)