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

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Background: Ramucirumab, the human immunoglobulin G1 monoclonal antibody receptor antagonist of vascular endothelial growth factor receptor 2, has been approved for treating gastric/gastroesophageal junction, non-small-cell lung, and metastatic colorectal cancers. With the completion of six global, randomized, double-blind, placebo-controlled, phase III 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 six completed phase III trials was conducted and the relative risk (RR) and associated 95% confidence intervals (CIs) were derived using fixed-effects or mixed-effects models for all-grade and high-grade adverse events (AEs) possibly related to vascular endothelial growth factor pathway inhibition. The number needed to harm was also calculable due to the placebo-controlled nature of all six 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 arm compared with the control arm.

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. Clinical Trial Numbers: NCT00917384 (REGARD), NCT01170663 (RAINBOW), NCT01168973 (REVEL), NCT01183780 (RAISE), NCT01403437 (REACH), and NCT00703326 (ROSE).

Key words: VEGF, VEGFR, ramucirumab, antiangiogenic, adverse events, meta-analysis
Introduction

Ramucirumab (CYRAMZA®, Eli Lilly and Company, Indianapolis, IN, USA) is a fully human immunoglobulin G1 monoclonal antibody with high affinity binding to the vascular endothelial growth factor receptor 2 (VEGFR-2) extracellular domain, blocking binding of multiple 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 III clinical trials with different tumor types have been published to present the efficacy and safety profile of ramucirumab [3–9] (Table 1).

The purpose of this report is to (i) examine the incidence of adverse events possibly attributed to VEGF pathway inhibition based on data from six phase III clinical trials, (ii) determine specific patient- and treatment-related factors that may be associated with an increased adverse event risk, and (iii) 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 with 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 III 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. As 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

| Trial       | Indication                      | Treatment arms                                                                 | Patients randomized per arm | Date first patient enrolled | NCI CTCAE version | Trial registry number |
|-------------|--------------------------------|--------------------------------------------------------------------------------|----------------------------|-----------------------------|-------------------|----------------------|
| REGARDb [3] | Advanced gastric or GEJ adenocarcinoma | Ramucirumab 8 mg/kg i.v. Q2W plus BSC or placebo plus BSC | RAM: n = 238; Control: n = 117 | 6 October 2009 v4.02 | NCT00917384      |
| RAINBOWb [4]| Advanced gastric or GEJ adenocarcinoma | Ramucirumab 8 mg/kg i.v. on days 1 and 15, plus paclitaxel 80 mg/m² i.v. on days 1, 8, and 15 of a 28-day cycle or placebo i.v. plus paclitaxel 80 mg/m² i.v. on days 1, 8, and 15 of a 28-day cycle | RAM: n = 330; Control: n = 335 | 23 December 2010 v4.02 | NCT01170663      |
| REVELb [5]  | Stage IV NSCLC                   | Ramucirumab 10 mg/kg i.v. plus docetaxel 75 mg/m² on day 1 of a 21-day cycle or placebo plus docetaxel 75 mg/m² on day 1 of a 21-day cycle | RAM: n = 628; Control: n = 625 | 03 December 2010 v4.0 | NCT01168973      |
| RAISEb [6]  | Metastatic CRC                   | Ramucirumab 8 mg/kg i.v. plus FOLFIRI Q2W or placebo plus FOLFIRI Q2W | RAM: n = 536; Control: n = 536 | 13 December 2010 v4.02 | NCT01183780      |
| REACHb [7]  | Advanced HCC                     | Ramucirumab 8 mg/kg i.v. Q2W plus BSC or placebo Q2W plus BSC | RAM: n = 283; Control: n = 282 | 04 November 2010 v4.0 | NCT01140347      |
| ROSEc [8]   | Metastatic breast cancer         | Ramucirumab 10 mg/kg i.v. plus docetaxel 75 mg/m² Q2W or docetaxel 75 mg/m² plus placebo Q3W | RAM: n = 759; Control: n = 385 | 11 August 2008 v3.0 | NCT00703326      |

*Intent-to-treat population.

The primary end point for these studies was overall survival.

The primary end point for this study was progression-free survival.

BSC, best supportive care; CRC, colorectal carcinoma; GEJ, gastroesophageal junction; FOLFIRI, leucovorin (folinic acid), fluorouracil, and irinotecan; HCC, hepatocellular carcinoma; i.v., 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; RAM, ramucirumab; v, version.
The relative risk (RR) and the associated 95% confidence interval (CI) were calculated for all-grade and severe/high-grade (grade ≥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 whether any differences in RR of an adverse event were 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 carried out in R3.1.1 [R Core Team (2016)] [15].

**Results**

A total of 4996 randomized patients received at least one dose of the 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 the supplementary Table S1, available at Annals of Oncology online. 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 3, 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 arm experienced grade ≥3 hypertension compared with 57 (2.5%) in the control arm (RR: 3.7, 95% CI 2.8–4.9). This 6.5% increase for grade ≥3 hypertension in the ramucirumab arm represents an NNH of 1 in 16 patients (Table 4). There were only two (0.07%) reported instances of grade 4 hypertensive crisis in the ramucirumab arm (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 [16].

| Table 2. Patient characteristics in the intent-to-treat population of ramucirumab double-blind randomized controlled phase III clinical trials |
|-----------------------------------------------|
| REGARD | RAINBOW | REVEL | RAISE | REACH | ROSE |
| RAM | Control | RAM | Control | RAM | Control | RAM | Control | RAM | Control | RAM | Control |
| RAM | n = 238 | Control | n = 117 | RAM | n = 330 | Control | n = 335 | RAM | n = 628 | Control | n = 625 | RAM | n = 536 | Control | n = 536 | RAM | n = 283 | Control | n = 282 | RAM | n = 759 | Control | n = 385 |
| Median age, years (range) | 60 (30–86) | 60 (24–87) | 61 (25–83) | 61 (24–84) | 62 (21–85) | 61 (25–86) | 62 (21–83) | 63 (33–87) | 64 (28–87) | 62 (25–85) | 54 (24–82) | 54 (29–81) |
| <65, n (%) | 156 (66) | 71 (61) | 204 (62) | 212 (63) | 391 (62) | 407 (65) | 324 (60) | 321 (60) | 150 (53) | 162 (57) | 629 (83) | 325 (84) |
| ≥65, n (%) | 82 (34) | 46 (39) | 126 (38) | 123 (37) | 237 (38) | 218 (35) | 212 (40) | 215 (40) | 133 (47) | 120 (43) | 130 (17) | 60 (16) |
| Gender, n (%) | | | | | | | | | | | | | |
| Male | 169 (71) | 79 (68) | 229 (69) | 243 (73) | 419 (67) | 415 (66) | 289 (54) | 326 (61) | 236 (83) | 242 (86) | 0 (0) | 0 (0) |
| Female | 69 (29) | 38 (32) | 101 (31) | 92 (27) | 209 (33) | 210 (34) | 247 (46) | 210 (39) | 47 (17) | 40 (14) | 759 (100) | 385 (100) |
| Race, n (%) | | | | | | | | | | | | | |
| White | 181 (76) | 91 (78) | 208 (63) | 199 (59) | 526 (84) | 503 (80) | 405 (74) | 410 (76) | 139 (49) | 137 (49) | 676 (89) | 341 (100) |
| Asian | 39 (16) | 17 (15) | 110 (33) | 121 (36) | 74 (12) | 86 (14) | 111 (21) | 103 (19) | 131 (46) | 135 (48) | 31 (4) | 20 (5) |
| Black | 4 (2) | 2 (2) | 6 (2) | 62 (2) | 17 (3) | 16 (3) | 14 (3) | 16 (3) | 5 (2) | 3 (1) | 27 (4) | 14 (4) |
| Other | 14 (6) | 7 (6) | 6 (2) | 9 (3) | 10 (2) | 20 (3) | 4 (1) | 2 (<1) | 8 (3) | 7 (3) | 25 (3) | 10 (3) |
| Not reported/missing | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (<1) | 0 (0) | 2 (<1) | 5 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| ECOG PS, n (%) | | | | | | | | | | | | | |
| 0 | 67 (28) | 31 (26) | 117 (35) | 144 (43) | 207 (33) | 199 (32) | 263 (49) | 259 (48) | 159 (56) | 153 (54) | 439 (58) | 240 (62) |
| 1 | 171 (73) | 85 (73) | 213 (65) | 191 (57) | 420 (67) | 425 (68) | 268 (50) | 273 (51) | 124 (44) | 129 (46) | 318 (42) | 143 (37) |
| 2 or 3 | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (<1) | 2 (<1) | 0 (0) | 0 (0) | 2 (<1) | 2 (<1) |
| Missing | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (<1) | 1 (<1) | 4 (1) | 2 (<1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

ECOG PS, Eastern Cooperative Oncology Group Performance Status; RAM, ramucirumab.
Similar proportions of patients in both treatment arms received antihypertensive agents as concurrent therapy (Table 5), 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 arm and 70 (3.1%) patients in the control arm (RR: 3.4, 95% CI 2.6–4.3) (Table 3). Thirty-one (1.1%) patients in the ramucirumab arm experienced grade ≥3 proteinuria (including only one grade 4 and no grade 5 events) versus one (0.04%) patient in the control arm. The NNH for grade ≥3 proteinuria was 1 in 92 patients (Table 4). Twenty-seven (1.0%) patients in the ramucirumab arm and one (0.04%) patient in the control arm 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
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 with 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.

As pulmonary hemorrhage has been a concern for non-small-cell lung cancer (NSCLC) patients treated with antiangiogenic agents [17], 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 the treatment arms (squamous: ramucirumab arm all-grade = 9.6%, high-grade = 1.9%; control arm all-grade = 12.4%, high-grade = 2.4%; nonsquamous: ramucirumab arm all-grade = 7.3%, high-grade = 1.1%; control arm all-grade = 5.7%, high-grade = 0.9%) [5].

**GI perforation**

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

**Arterial thromboembolic events**

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 3, Figure 1). A total of 21 (0.8%) patients in the ramucirumab arm experienced grade ≥3 ATE versus 19 (0.8%) patients in the control arm (RR: 0.9, 95% CI 0.5–1.7). Across all trials, seven (0.3%) grade 4 events were reported in the ramucirumab arm, with four of these events not recovered or resolved, whereas four grade 4 events were reported in the control arm. Seven grade 5 ATE events were reported in the ramucirumab arm (six myocardial events and one cerebrovascular event) and 10 grade 5 ATE events were reported in the control arm (seven myocardial events and three 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**

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 arm versus 116 (5.2%) in the control arm (RR: 0.7, 95% CI 0.5–1.1) (Table 3,
Fifty-six (2.0%) patients with grade ≥3 VTEs were reported in the ramucirumab arm and 61 (2.7%) patients in the control arm (RR: 0.7, 95% CI 0.4–1.2).

Across all trials, 11 (0.4%) grade 4 VTEs were reported in the ramucirumab arm and 11 (0.5%) grade 4 VTEs were reported in the control arm. There were three grade 5 VTEs in the ramucirumab arm and six in the control arm; 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 arm, primarily due to deep vein thrombosis or PE.

Infusion-related reactions

Any-grade infusion-related reactions (IRR) was reported in 180 (6.6%) patients in the ramucirumab arm compared with 104 (4.6%) patients in the control arm (RR: 1.4, 95% CI 0.8–2.3) (Table 3). The NNH for all-grade IRR was 1 in 52 and for grade ≥3 was 1 in 227 patients (Table 4). A total of 28 (1.0%) patients in the ramucirumab arm experienced grade ≥3 IRR versus 13 (0.6%) in the control arm, with the outcome in the ramucirumab arm being either recovered or resolved. There were no grade 5 IRR reported in these trials. Twelve patients (0.4%) in the ramucirumab arm discontinued ramucirumab, whereas three (0.1%) patients in the control arm 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

Reversible posterior leukoencephalopathy syndrome (RPLS) was reported in two (0.04%) patients in these trials, one grade 2 RPLS in ramucirumab arm and one grade 2 RPLS in control arm, both in the RAISE trial. Both patients’ RPLS status was confirmed with magnetic resonance imaging. 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 arm, occurring only in the RAISE (n = 6) and ROSE (n = 8) trials (Table 3 and supplementary Table S2, available at Annals of Oncology online), and in 4 (0.2%) patients in the control arm (RR: 2.0, 95% CI 0.8–5.1). Five (0.2%) patients in the ramucirumab arm experienced grade ≥3 wound-healing complications with zero patients in the control arm. The NNH for all-grade and grade ≥3 wound-healing complication events was 1 in 302 and 1 in 550 patients in the ramucirumab and control arms, respectively (Table 4).

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 arm compared with the control arm. The rates and severity of these events are consistent with those seen in other antiangiogenic trials [10, 18–20]. In addition, the safety profile described here is consistent with the ramucirumab labels [1, 2].
increased risk of ATE, VTE, or high-grade bleeding differs from published studies with other antiangiogenics [11, 12, 21–25]. 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 [26, 27]. The mechanisms of hypertension associated with VEGF inhibition are thought to include decreased production of nitric oxide in the wall of arterioles and other resistance vessels [28], increased activation of the endothelin-1 system [30], and/or capillary rarefaction [29]. Once detected, hypertension is readily managed with antihypertensives and rarely delays or stops cancer treatment. Preexisting 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 [31–33]; 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 [34–36]. Most patients enrolled in our trials had adequate renal function at baseline, and the incidence of high-grade proteinuria in the ramucirumab arm was 1.1% (RR: 8.3, 95% CI 2.9–24.1) (Table 3). During ramucirumab therapy, the clinician should monitor for the development of worsening or proteinuria [1]. In most cases, proteinuria was manageable during ramucirumab therapy. Only three (0.1%) patients in the ramucirumab arm 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 < 0.001) [32]. This same study also reported a 0.8% incidence of patients with nephrotic syndrome as well as an RR of 7.78 (95% CI 1.80–33.62; P = 0.006) [32].

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 [37]. Preclinical data demonstrate that capillaries with endothelial fenestrations are dependent on VEGF signaling [34, 38]. 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 arm. However, 72% of bleeding events (739/1031) in the ramucirumab arm 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 with 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].

GI perforation is a rare but serious adverse event and can be fatal due to severe peritonitis [19, 39]. 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.

ATEs 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 that the risk of ATE was increased with chemotherapy plus bevacizumab versus chemotherapy alone (hazard ratio = 2.0, 95% CI 1.05–3.75, P = 0.031). Cancer patients have an intrinsically increased risk for thrombosis [23, 40]. The prevention and treatment of thromboembolic events is important, because they are the second most frequent cause of death in cancer patients [41]. 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 suggest that ramucirumab does not increase the risk of developing ATE.

Venous thrombosis is a common complication in patients with cancer [42, 43]. Compared with patients without cancer, thrombosis in patients with cancer is significantly more likely to be fatal [44]. Cancer patients with active malignancy have a four- to seven-fold higher incidence of symptomatic VTE than the general population [42, 45, 46]. VTEs have been reported with antiangiogenic therapies [11, 23–25, 47, 48], but this association is still controversial [11–14]. Our data demonstrated that ramucirumab did not increase the risk of VTE compared with the control arm (Table 3) (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 IRR [49, 50]. The incidence of all-grade and high-grade IRR was low for both treatment groups across these six trials (Tables 3 and 4), with the outcome of most reported IRR being either recovered or resolved, and no fatal IRR events were observed.

Despite previous reports of RPLS associated with antiangiogenic drug therapy [51, 52], 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 repair.
formation and remodeling [53]. 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. [54]. Patients experiencing major surgery concurrent with bevacizumab treatment demonstrated increased wound-healing complications, whereas 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 [54]. In the current study, the rate of the wound-healing complications was low overall in the ramucirumab arm (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% CI 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/gastroesophageal junction cancer), but supplemental Table S2, available at *Annals of Oncology* online, provides a summary of the incidence rate of a given AE in a given tumor type. Furthermore, although 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 [55, 56]. However, this is specifically a concern when studies are combined in which the randomization ratios differ substantially [57], which was not the case in the present meta-analysis: four out of the six 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 III global, registrational, placebo-controlled trials with ramucirumab are under way (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 the 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.

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