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Gastrointestinal Cancer

The McCAVE Trial: Vanucizumab plus mFOLFOX-6 Versus Bevacizumab plus mFOLFOX-6 in Patients with Previously Untreated Metastatic Colorectal Carcinoma (mCRC)

Johanna C. Bendell,[a] Tamara Sauri,[b] Antonio Cubillo Gracián,[c] Rafael Alvarez,[c] Carlos López-López,[d] Pilar García-Alfonso,[e] Maen Hussein,[f] Maria-Luisa Limon Miron,[g] Andrés Cervantes,[h] Clara Montagut,[i] Cristina Santos Vivas,[j] Alberto Bessudo,[k] Patricia Plezia,[l] Veerle Moons,[m] Johannes Andel,[n] Jaafar Bennouna,[o] Andre van der Westhuizen,[p] Leslie Samuel,[q] Simona Rossomanno,[r] Christophe Boetsch,[r] Angelika Lahr,[s] Izolda Franjkovic,[s] Florian Heil,[s] Katharina Lechner,[s] Oliver Krieter,[s] Herbert Hurwitz,[t] for the McCAVE Study Group

[a]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, Tennessee, USA; [b]Vall d'Hebron University Hospital, Barcelona, Spain; [c]Centro Integral Oncológico Clara Campal, Hospital Madrid Norte Sanchinarro, Madrid, Spain; [d]Marqués de Valdecilla University Hospital, Santander, Spain; [e]Hospital Universitario Gregorio Maranon, Madrid, Spain; [f]Florida Cancer Specialists, Leesburg, Florida, USA; [g]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [h]Department of Medical Oncology, Biomedical Research Institute, INCLIVA, University of Valencia, Valencia, Spain; [i]Hospital del Mar, Barcelona, Spain; [j]Institut Català d'Oncologia and L'Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Spain; [k]California Cancer Associates for Research and Excellence, San Diego, California, USA; [l]Arizona Clinical Research Center, Tucson, Arizona, USA; [m]Imelda General Hospital, Bonheiden, Belgium; [n]County Hospital Steyr, Steyr, Austria; [o]Institut de Cancerologie de l'Ouest, Saint Herblain, France; [p]Calvary Mater Hospital, Newcastle, Australia; [q]Aberdeen Royal Infirmary, University of Aberdeen, Aberdeen, United Kingdom; [r]Roche Innovation Center Basel, Basel, Switzerland; [s]Roche Innovation Center Munich, Penzberg, Germany; [t]Duke University Medical Center, Durham, North Carolina, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. First-line metastatic colorectal cancer • Angiopoetin-2 • VEGF-A • Vanucizumab • Bevacizumab

Abstract

Background. Bevacizumab, a VEGF-A inhibitor, in combination with chemotherapy, has proven to increase progression-free survival (PFS) and overall survival in multiple lines of therapy of metastatic colorectal cancer (mCRC). The angiogenic factor angiopoetin-2 (Ang-2) is associated with poor prognosis in many cancers, including mCRC. Preclinical models demonstrate improved activity when inhibiting both VEGF-A and Ang-2, suggesting that the dual VEGF-A and Ang-2 blocker vanucizumab (RO5520985 or RG-7221) may improve clinical outcomes. This phase II trial evaluated the efficacy of vanucizumab plus modified (m)FOLFOX-6 (folinic acid (leucovorin), fluorouracil (5-FU) and oxaliplatin) versus bevacizumab/mFOLFOX-6 for first-line mCRC.

Patients and Methods. All patients received mFOLFOX-6 and were randomized 1:1 to also receive vanucizumab 2,000 mg or bevacizumab 5 mg/kg every other week. Oxaliplatin was given for eight cycles; other agents were continued until disease progression or unacceptable toxicity for a maximum of 24 months. The primary endpoint was investigator-assessed PFS.

Results. One hundred eighty-nine patients were randomized (vanucizumab, $n = 94$; bevacizumab, $n = 95$). The number of PFS events was comparable (vanucizumab, $n = 39$; bevacizumab, $n = 43$). The hazard ratio was 1.00 (95% confidence interval, 0.64–1.58; $p = .98$) in a stratified analysis based on number of metastatic sites and region. Objective response rate was 52.1% and 57.9% in the vanucizumab and bevacizumab arm, respectively. Baseline plasma Ang-2 levels were prognostic in both arms but not predictive for treatment effects on PFS of vanucizumab. The incidence of adverse events of grade ≥3 was similar between treatment arms (83.9% vs. 82.1%); gastrointestinal perforations (10.8% vs. 8.4%) exceeded previously reported rates in this setting. Hypertension and peripheral edema were more frequent in the vanucizumab arm.

Conclusion. Vanucizumab/mFOLFOX-6 did not improve PFS and was associated with increased rates of antiangiogenic toxicity compared with bevacizumab/mFOLFOX-6. Our results suggest that Ang-2 is not a relevant therapeutic target in first-line mCRC. ***The Oncologist*** 2020;25:e451–e459

Correspondence: Johanna C. Bendell, M.D., Sarah Cannon Research Institute, 1100 Dr. Martin Luther King Jr. Blvd., Suite 800, Nashville, Tennessee 37203, USA. Telephone: 615-320-5090; e-mail: jbendell@tnonc.com Received May 3, 2019; accepted for publication August 7, 2019; published Online First on September 30, 2019. http://dx.doi.org/10.1634/theoncologist.2019-0291

Implications for Practice: This randomized phase II study demonstrates that additional angiopoietin-2 (Ang-2) inhibition does not result in superior benefit over anti–VEGF-A blockade alone when each added to standard chemotherapy. Moreover, the performed pharmacokinetic and pharmacodynamic analysis revealed that vanucizumab was bioavailable and affected its intended target, thereby strongly suggesting that Ang-2 is not a relevant therapeutic target in the clinical setting of treatment-naïve metastatic colorectal cancer. As a result, the further clinical development of the dual VEGF-A and Ang-2 inhibitor vanucizumab was discontinued.

Introduction

Colorectal cancer (CRC) is a leading cause of cancer deaths in the Western world [1]. Current first- and second-line therapies for metastatic CRC (mCRC) include a range of oxaliplatin- and irinotecan-based chemotherapy regimens; improved outcomes have been demonstrated with chemotherapy combined with therapies targeting the EGFR or VEGF-A–VEGFR signaling pathways [2]. The addition of bevacizumab, a recombinant humanized anti–VEGF-A monoclonal antibody, to standard chemotherapy improves both overall survival (OS) and progression-free survival (PFS), as well as response rates [3], providing a rationale to explore further treatment options that target angiogenic pathways.

Angiopoietin-2 (Ang-2) is overexpressed and is a negative prognostic factor in many cancers, including CRC [4]. High serum Ang-2 levels promote metastatic growth in preclinical models [5] and are associated with poor survival outcomes in patients [6]. Tumor Ang-2 overexpression is associated with lymph node metastasis, venous invasion, and high microvascular density in CRC [7].

Vanucizumab (RO5520985 or RG-7221) is a bispecific monoclonal antibody based on a human IgG1 framework, comprising two different heavy chains and two different light chains; one arm targets Ang-2 and the other arm VEGF-A. Vanucizumab showed potent tumor growth inhibition in a panel of human tumor xenograft models [8] with superior antitumor activity in larger tumors compared with the monospecific antibodies, supporting the notion that larger tumors exhibit different vessel types that do not all respond equally to anti–VEGF-A therapy [9]. The observed clinical safety profile of single-agent vanucizumab was consistent with that reported for selective inhibitors of the VEGF-A and angiopoietin-Tie2 signaling pathway and showed encouraging antitumor activity in a heterogeneous patient population [10]. The purpose of the current study, also known as BP29262 or the McCAVE trial, was to determine if concurrent target inhibition of the VEGF-A and Ang-2 axis by adding vanucizumab to standard chemotherapy can improve the treatment outcome versus bevacizumab plus chemotherapy in treatment-naïve patients with mCRC.

Patients and Methods

Participants

Adult patients (aged ≥18 years) with histologically or cytologically confirmed mCRC who had not been previously treated with chemotherapy for metastatic disease and who were not candidates for surgical resection were eligible for inclusion. Patients had to have at least one measurable metastatic lesion, as defined by RECIST version 1.1 [11]. All patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤1. Patients were excluded for any serious or uncontrolled medical disorders and any prior systemic cancer therapy before day 1 of cycle 1 or radiotherapy within 28 days prior to day 1 of cycle 1. Patients who received prior systemic adjuvant therapy for CRC were excluded if the time interval from last administration of adjuvant therapy until disease progression was less than 12 months from screening. Additional exclusion criteria included significant cardio- or cerebrovascular disease within 6 months of enrollment, history of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation or intra-abdominal abscess, clinical signs or symptoms of GI obstruction, history of pulmonary hemorrhage with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade ≥2, or gross hemoptysis.

Study Design and Treatment

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent as approved by local institutional review boards.

McCAVE (ClinicalTrials.gov identifier: NCT02141295) was a multicenter phase II trial conducted in two phases: a single-arm, open label safety run-in part followed by a randomized, double-blind parallel group study. Patients in the safety run-in phase received vanucizumab 2,000 mg followed by modified (m)FOLFOX-6 (folinic acid (leucovorin), fluorouracil (5-FU) and oxaliplatin) every two weeks (q2w) for at least two cycles to ascertain safety of the vanucizumab/mFOLFOX-6 combination. In the double-blind phase, eligible patients were randomized in a 1:1 ratio to receive either vanucizumab/mFOLFOX-6 or bevacizumab/mFOLFOX-6 (supplemental online Table 1). Patients were stratified prospectively by region (U.S. vs. rest of world [RoW]) and number of metastatic sites (one vs. more than one). Study treatment consisted of induction and maintenance therapy that was given in cycles q2w. Induction therapy comprised eight cycles of mFOLFOX-6 plus either vanucizumab or bevacizumab. Patients could switch to maintenance therapy earlier if oxaliplatin was not tolerated. After induction therapy, oxaliplatin administration was discontinued and patients received 5-fluorouracil (5-FU)/folinic acid plus either vanucizumab or bevacizumab as maintenance therapy for a maximum period of 24 months unless treatment was stopped earlier because of disease progression, unacceptable toxicity,

investigator decision, or consent withdrawal. Patients who stopped chemotherapy, either in part or in whole, could continue on vanucizumab or bevacizumab for a maximum of 24 months. Dose adjustments were prohibited for vanucizumab or bevacizumab but were allowed for mFOLFOX-6 as clinically indicated.

Study Endpoints

The primary endpoint was PFS defined as the time from randomization to the date of first documented occurrence of progression based on RECIST version 1.1 criteria, as determined by the investigator, or death from any cause on study, whichever occurred first. Death on study was defined as death from any cause within 30 days of the last study treatment. Patients without an event on study were censored at the date of the last tumor assessment when the patient was known to be progression free either during follow-up to initiation of a new cancer treatment, or during study treatment. Patients without any postbaseline assessments or with all postbaseline assessments having unknown result or response but known to be alive at the clinical cutoff for the analysis were censored at the date of randomization plus 1 day. Secondary endpoints included overall response rate (ORR) and OS; OS was calculated from the time from randomization until death from any cause. The safety and efficacy analyses were based on the randomized portion of this study only.

Assessments

All tumor lesions were assessed by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans and read by the local investigator. No independent, central review of imaging scans was performed. Tumor response and progression were assessed according to RECIST 1.1, with scans repeated every 8 weeks and at the end of study visit. If a patient discontinued therapy for reasons other than progression, the patient was followed by regular CT or MRI assessments until documentation of progressive disease (PD), initiation of another anticancer therapy, withdrawal of consent, or death. In the event of stable disease (SD), follow-up assessments had to have met the RECIST version 1.1 SD criteria at least once after study entry at a minimum interval of 8 weeks from treatment start. Lesions previously treated with radiotherapy were not used as target lesions for tumor assessment. Safety was assessed per NCI CTCAE version 4.03 and routine clinical laboratory assessments continuously throughout treatment and for 30 days after last dose of treatment. While the study was ongoing, patients were followed up for subsequent anticancer therapy and survival (e.g., by phone call) every 3 months until death, loss to follow-up, or study termination, whichever occurred first.

Statistical Analyses

For the safety run-in part, a minimum of six patients was considered sufficient to determine the safety and tolerability of the vanucizumab/mFOLFOX-6 combination. The emphasis of the efficacy analysis was the magnitude of treatment effect rather than hypothesis testing. Accordingly, the study was designed to allow detection of a meaningful benefit of vanucizumab/mFOLFOX-6 versus bevacizumab/mFOLFOX-6. Based on a total of 80 PFS events observed in the two treatment arms combined, there was an 80% power to detect a hazard ratio (HR) of 0.574 at a type I error of 0.05. Primary and secondary efficacy analyses included all patients who were randomized and received any dose of study treatment with patients assigned to the treatment arm to which they were randomized. The safety analysis population included all patients who had received at least one dose of study treatment (vanucizumab or bevacizumab) with patients assigned to the treatment arm, based on treatment actually received. Kaplan-Meier methods were used to estimate median PFS for each treatment arm. Stratification factors applied included number of metastatic sites (one vs. more than one) and region (U.S. vs. RoW). The stratified Cox proportional hazard model was used to estimate the hazard ratio and the corresponding 95% confidence interval. Additional stratified and nonstratified sensitivity analyses were performed using a definition of PFS including deaths occurring more than 30 days after the last dose of the study drug.

Results

Baseline Characteristics and Patient Disposition

Patients were enrolled into the study from June 2014 to May 2016 at 39 sites in the U.S., European Union, and Australia. Eight patients took part in the safety run-in part, whereas a total of 189 patients participated in the randomized part (vanucizumab, n = 94; bevacizumab, n = 95). One patient was randomized to vanucizumab but received only chemotherapy before being withdrawn from study. The clinical data cutoff for the primary analysis based on 82 PFS events was July 29, 2016, providing a median follow-up time of 17.6 months (range 2.8–20.7). The median number of cycles of vanucizumab or bevacizumab was 12.0 (range 1–47). Approximately half of the patients were aged more than 65 years. Relevant prognostic factors, including RAS and BRAF V600E status and tumor sidedness, were largely balanced between arms (Table 1). The main reason for withdrawal from the study in both treatment arms was PD. A higher proportion of patients withdrew because of PD in the bevacizumab arm compared with the vanucizumab arm (n = 38; 40.0% vs. n = 29; 31.2%). Other reasons for withdrawal included physician decision (n = 16; 17.2% in the vanucizumab arm vs. n = 12; 12.6% in the bevacizumab arm), adverse events (AEs; n = 16; 17.2% vs. n = 10; 10.5%), withdrawal of consent (n = 9; 9.7% vs. n = 4; 4.2%), and withdrawn as a result of study termination or noncompliance (n = 1 in the bevacizumab arm and n = 1 in the vanucizumab arm, respectively; supplemental online Fig. 1).

Efficacy

There was no difference in median PFS between the two treatment arms. The stratified HR was 1.00 (95% confidence interval [CI], 0.64–1.58; log-rank p = .98); the median duration of PFS in the vanucizumab and bevacizumab arms was comparable at 343 days (95% CI, 312.0–386.0) versus 334 days (95% CI, 282.0–390.0), respectively. Similarly, the number of PFS events was comparable across the vanucizumab and bevacizumab arms (n = 39; 41.5% vs. n = 43; 45.3%). The results of the nonstratified analysis were similar to those of

Table 1. Baseline patient characteristics (n = 189)

Patient characteristic	Vanucizumab (n = 94),[a] n (%)	Bevacizumab (n = 95), n (%)
Age, years		
Median (range)	64.0 (27–82)	63.0 (29–81)
<65	48.0 (51.1)	53.0 (55.8)
Male sex	56 (59.6)	38 (40.0)
Race		
White	90 (95.7)	90 (94.7)
Black	3 (3.2)	1 (1.1)
Asian	0	2 (2.1)
Other	1 (1.1)	2 (2.1)
ECOG performance status		
0	60 (63.8)	47 (49.5)
1	34 (36.2)	48 (50.5)
Primary tumor site		
Colon	73 (77.7)	77 (81.1)
Rectum	21 (22.3)	18 (18.9)
Left- or right-sided tumor		
Left	67 (75.3)	58 (61.1)
Right	26 (24.7)	37 (38.9)
Primary tumor in place		
Yes	51 (54.3)	48 (50.5)
No	43 (45.7)	47 (49.5)
Metastatic sites		
1	34 (36.2)	35 (36.8)
>1	60 (63.8)	60 (63.2)
Adjuvant treatment		
Yes	6 (6.4)	7 (7.4)
No	88 (93.6)	88 (92.6)
Plasma Ang-2		
n[b]	91	93
Median (range), ng/mL	3.01 (1.1–58.4)	2.93 (1.3–20.8)
KRAS mutation status		
n[b]	80	81
Mutant	37 (46.3)	45 (55.6)
Wild type	43 (56.8)	36 (44.4)
NRAS mutation status		
n[b]	80	81
Mutant	13 (16.3)	11 (13.6)
Wild type	67 (83.8)	70 (86.4)
BRAF mutation status		
n[b]	80	81
Mutant	7 (8.8)	5 (6.2)
Wild type	73 (91.3)	76 (93.8)

[a]One patient randomized to the vanucizumab arm received only chemotherapy before being withdrawn from the study.
[b]Number of patients assessed.
Abbreviations: Ang-2, angiopoietin-2; ECOG, Eastern Cooperative Oncology Group.

the stratified analysis (HR, 1.03; 95% CI, 0.67–1.59; log-rank p = .89). The overlapping Kaplan-Meier curves of PFS based on investigator assessment are shown in Figure 1. Further exploratory PFS analyses revealed no significant differences between the treatment arms for patient subgroups defined by prior adjuvant therapy, primary tumor sidedness, ECOG PS, or BRAF- and RAS- mutation status (Fig. 2). Subgroup analysis for KRAS and NRAS mutated tumors was consistent with PFS outcome for all mutant RAS (data not shown). The proportion of missing RAS data was approximately 15% (28/189). The investigator-assessed ORR was comparable between the vanucizumab and bevacizumab arms, respectively: n = 49, 52.1% (95% CI, 42.0–62.2) versus n = 55, 57.9% (95% CI, 48.0–67.8; supplemental online Table 2). At the final analysis (data cut-off February 1, 2017), the OS data were immature. There were 24 (25.5%) deaths in the vanucizumab arm and 27 (28.4%) deaths in the bevacizumab arm. After the sponsor's decision to terminate the study, the remaining ongoing patients were discontinued, and no further data on subsequent therapies after progression and survival were collected after the last patient last visit. As a result, no further analyses were performed.

Pharmacokinetics and Biomarkers

Systemic exposure of vanucizumab was assessed by noncompartmental and population pharmacokinetic (PK) analysis and was consistent with that seen after single-agent administration of vanucizumab [10] (data not shown). Likewise, PK parameters for oxaliplatin (total and free) and 5-FU were also similar to the ones previously reported [12].

Soluble Ang-2 was assessed by use of a fully validated method [13] for its potential as a candidate prognostic and predictive marker. Ang-2 at baseline could be assessed for 184 patients. Patients were classified as Ang-2 higher ("high") or Ang-2 lower or equal ("low") based on the baseline, median Ang-2 plasma concentration level as the prespecified cutoff point. Baseline Ang-2 plasma levels were prognostic but not predictive for PFS (Fig. 3). In both arms, patients with high baseline Ang-2 plasma levels had a worse outcome compared with patients with low levels. The non-stratified PFS HR (all deaths) comparing low versus high baseline Ang-2 levels was similar in each arm (vanucizumab HR 0.74 [95% CI, 0.39–1.40]; bevacizumab HR 0.67 [95% CI, 0.38–1.18]). Likewise, the HRs comparing treatment with vanucizumab versus bevacizumab were similar within each subgroup (Ang-2 high HR of 0.93 [95% CI, 0.53–1.65] and Ang-2 low HR 1.07 [95% CI, 0.52–2.02]). The stratified PFS analysis showed similar results.

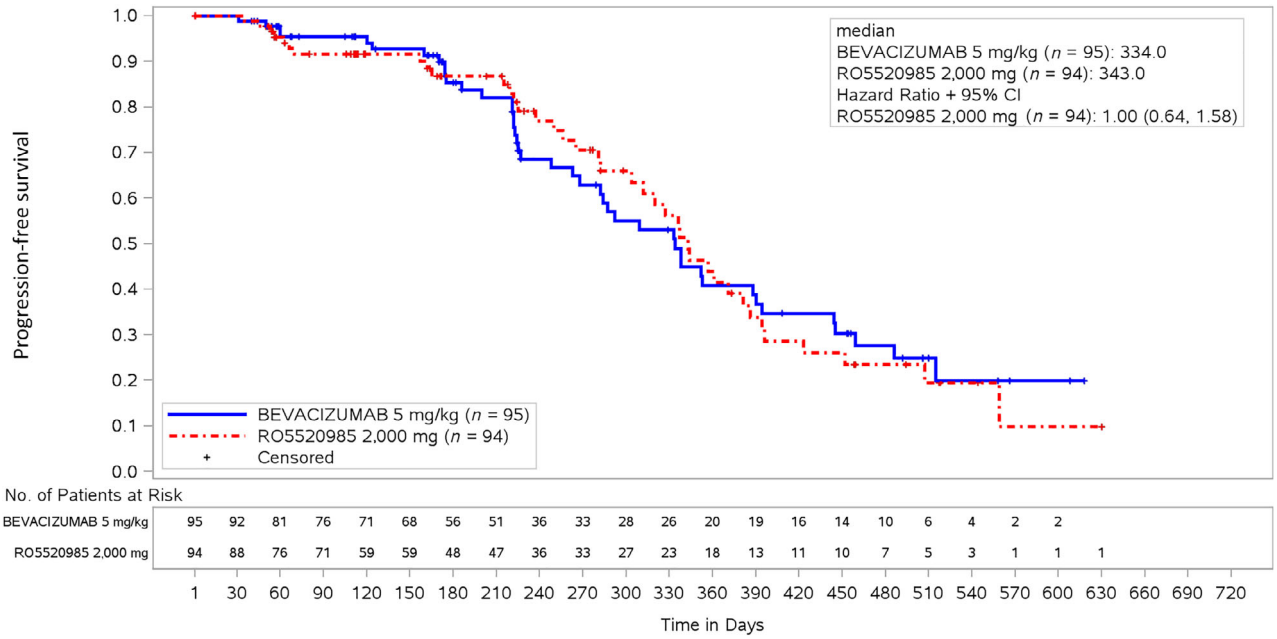

Figure 1. Kaplan-Meier plot of progression-free survival for the intent-to-treat population.
Abbreviation: CI, confidence interval.

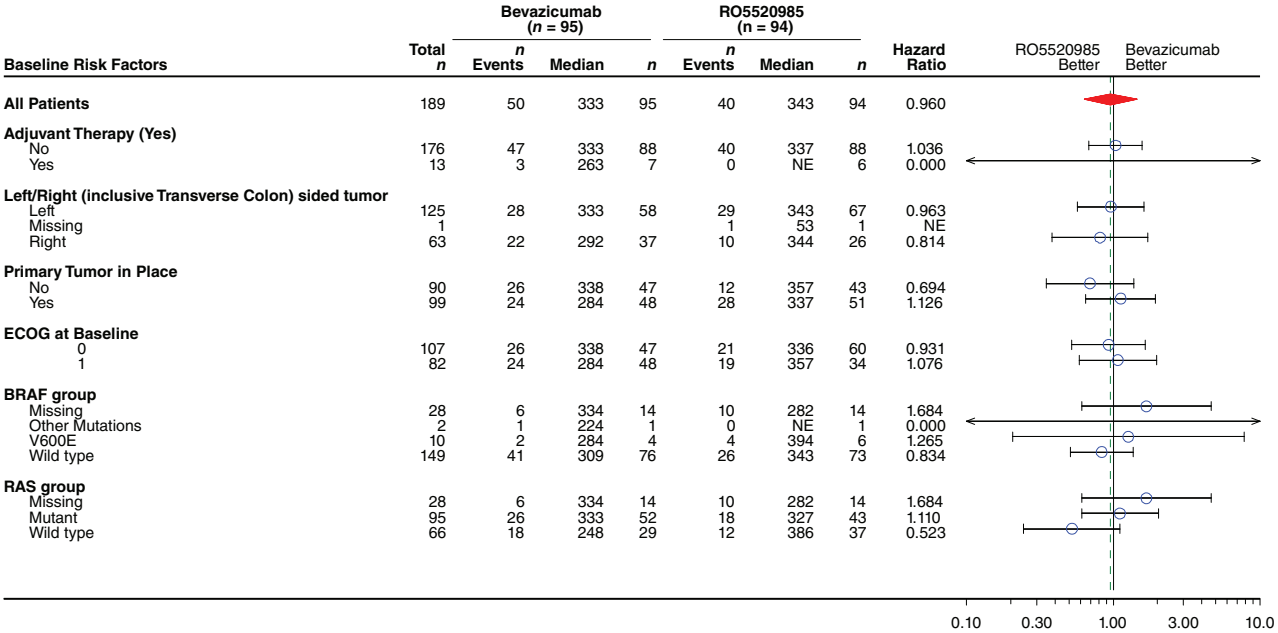

Figure 2. Forest plot of progression-free survival hazard ratio by subgroups, including death outside of 30-day window. Mutation K601Q is artifact only; therefore, it is displayed under "wild type." Mutation D594G is displayed under "other mutations."
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NE, not evaluable.

As in the previous study of single-agent vanucizumab [10], free Ang-2 levels in plasma rapidly decreased after vanucizumab dosing, whereas levels of total (free plus drug-bound) Ang-2 increased (Fig. 4). There was no effect of bevacizumab on soluble Ang-2 levels.

Safety

Adverse events of any grade were reported in all patients, with a similar proportion of patients experiencing severe AEs (SAEs) in the vanucizumab and bevacizumab arms, respectively (Table 2). Similar proportions of patients experiencing grade ≥3 AEs were also seen across the vanucizumab and bevacizumab arms. The most common grade ≥3 AEs (occurring in ≥5% of patients) were neutropenia, hypertension, diarrhea, and asthenia; a higher proportion (37.6% vs. 18.9%) of patients were diagnosed with grade ≥3 hypertension (HTN) in the vanucizumab arm compared with in the bevacizumab arm. Sixteen (17.2%) and ten (10.5%) patients were withdrawn from the study treatment because of AEs in the vanucizumab and bevacizumab

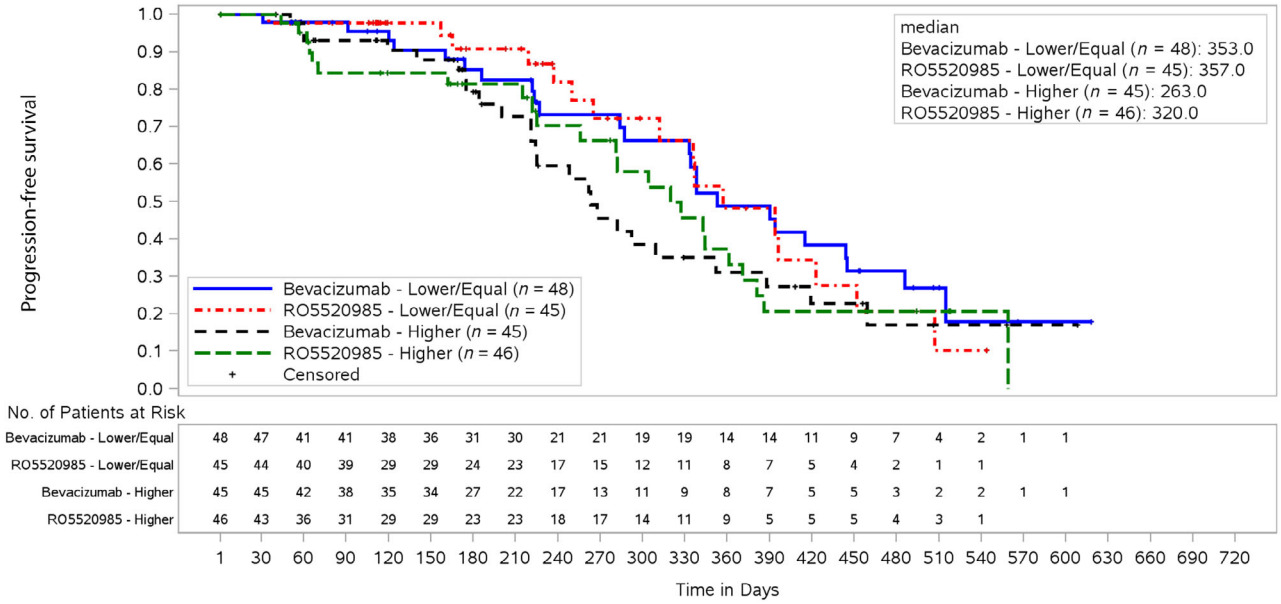

Figure 3. Kaplan-Meier plot of progression-free survival by plasma angiopoietin-2 baseline levels.

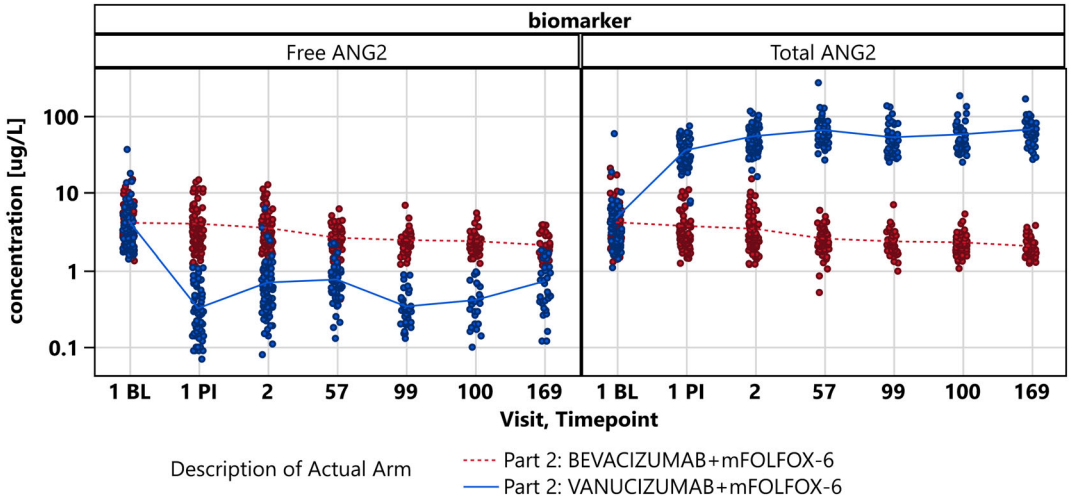

Figure 4. Free and total angiopoietin-2 plasma levels.
Abbreviations: ANG2, angiopoietin-2; BL, baseline; PI, postinfusion.

arms, respectively. Sixteen (17.2%) deaths were reported in the vanucizumab arm: 13 of these were due to PD, 2 due to SAEs with fatal outcome (intestinal perforation and cardiac arrest). In the bevacizumab arm, 21 deaths (22.1%) were reported, including 12 due to PD and 2 due to SAEs with fatal outcome (septic shock and intestinal perforation). Other adverse events identified as being of special interest (Table 3) revealed that a higher proportion (38.9%) of patients in the bevacizumab arm experienced hemorrhages versus the vanucizumab arm (24.7%); most of these events were grade 1–2. Eleven patients (11.9%) in the vanucizumab arm and nine patients (9.5%) in the bevacizumab arm experienced grade 3–4 venous (6.5% vs. 2.1%) or arterial (1.1% vs. 3.2%) thromboembolic events. Thirteen (14%) patients in the vanucizumab arm had peripheral edema (all grade 1–2), compared with five (5.3%) in the bevacizumab arm. The proportion of patients with gastrointestinal perforations (including GI fistula and abdominal abscess) was comparable across the treatment arms: ten patients (10.7%) in the vanucizumab arm (GI perforation [*n* = 8], GI fistula [*n* = 1], abdominal abscess [*n* = 1]) and eight patients (8.4%) in the bevacizumab arm (*n* = 6, 2, and 0).

Three patients developed antidrug antibodies (ADAs) to vanucizumab after treatment (two in the safety lead-in and one in the randomized portion). Four patients presented ADA titers before start of dosing, three of whom were ADA negative after treatment.

Discussion

Antiangiogenetic agents targeting the VEGF-A–VEGFR pathway are currently the standard of care in patients with mCRC [14]. Angiopoetin-2 biology appears VEGF-A dependent and

Table 2. Adverse events including grade ≥3 AEs with an incidence of ≥5% in either arm

Adverse event	Vanucizumab (*n* = 93), *n* (%)	Bevacizumab (*n* = 95), *n* (%)
Patients with any AEs	93 (100)	95 (100)
AEs (any grade)	1,734 (100)	1,928 (100)
AEs leading to discontinuation of vanucizumab or bevacizumab	22 (23.7)	17 (17.9)
SAEs	41 (44.1)	40 (42.1)
Death (including due to PD)	16 (17.2)	21 (22.1)
NCI CTCAE v.4.03 grade ≥3 AEs	78 (83.9)	78 (82.1)
Arterial hypertension	35 (37.6)	18 (18.9)
Neutropenia	28 (30.1)	34 (35.8)
GI perforation	10 (10.7)	8 (8.4)
Thromboembolism	7 (7.6)	5 (5.3)
Asthenia	6 (6.5)	6 (6.3)
Diarrhea	5 (5.4)	11 (11.6)

Abbreviations: AE, adverse event; GI, gastrointestinal; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; SAE, severe adverse event.

Table 3. Adverse events of special interest

	Vanucizumab (*n* = 93), *n* (%)		Bevacizumab (*n* = 95), *n* (%)	
Adverse event	Any grade	≥G3 AEs	Any grade	≥G3 AEs
Patients with any AEs of special interest	79 (84.9)	52 (56.0)	69 (72.6)	31 (32.7)
Gastrointestinal perforation	10 (10.7)	10 (10.7)	8 (8.4)	8 (8.4)
Hemorrhage	23 (24.7)	2 (2.2)	37 (38.9)	1 (1.1)
Arterial hypertension	41 (44.1)	35 (37.6)	27 (28.4)	18 (18.9)
Thromboembolism	11 (11.9)	7 (7.6)	9 (9.5)	5 (5.3)
ATE	1 (1.1)	1 (1.1)	4 (4.2)	3 (3.2)
VTE	10 (10.8)	6 (6.5)	5 (5.3)	2 (2.1)
Congestive heart failure	1 (1.1)	0	0	0
Peripheral edema	13 (14.0)	0	5 (5.3)	0
Proteinuria	12 (12.9)	0	9 (9.5)	0
Wound healing	2 (2.2)	0	4 (4.2)	1 (1.1)
Neutropenia	40 (43.0)	28 (30.1)	43 (45.3)	34 (35.8)
Infusion related reaction	19 (20.4)	4 (4.3)	12 (12.6)	2 (2.1)

Abbreviations: AE, adverse event; ATE, arterial thromboembolism; G3, grade 3; VTE, venous thromboembolism.

downregulated in response to anti–VEGF-A therapy [15]; indeed, in patients receiving bevacizumab-containing treatment, low Ang-2 baseline levels correlated with better PFS and OS [15, 16]. These observations suggested that Ang-2 suppression may be a predictor of benefit from an anti–VEGF-A containing therapy but also underscored the potential value of simultaneous targeting of VEGF-A and Ang-2 [17–19]. The McCAVE trial demonstrates that vanucizumab/mFOLFOX-6 treatment was associated with modulation of the primary target Ang-2 and systemic exposures of vanucizumab/mFOLFOX-6, consistent with those previously reported [10, 12, 20]. However, our results found no improvement in either PFS or ORR for vanucizumab compared with bevacizumab in patients with mCRC treated in combination with mFOLFOX-6. Moreover, exploratory biomarker analysis revealed no patient subgroups that would be likely to benefit from the dual Ang-2–VEGF inhibition. To this point and consistent with recent findings from other trials exploring the angiopoietin-Tie2 signaling pathway in mCRC, soluble Ang-2 levels at baseline were prognostic in both arms but not predictive for treatment response to vanucizumab [21, 22]. Likewise, other prognostic factors, including RAS and BRAF mutation status and tumor sidedness, were largely balanced between arms and did not result in significantly different PFS outcomes across treatment arms. The overall treatment outcomes in both arms also matched the historical performance of front-line bevacizumab/mFOLFOX-6 [23, 24], thereby making it highly implausible that the therapeutic potency of vanucizumab was confounded by the study conduct adversely interfering with delivery or efficacy of the regimens. Similarly, other emerging antiangiogenic approaches to potentiate the anti–VEGF-A effect of bevacizumab in the first-line setting of mCRC by targeting the mesenchymal-epithelial transition receptor with onartuzumab [25] or the vascular-restricted, extracellular matrix protein epidermal growth factor-like domain 7 with parsatuzumab [26] were also unsuccessful.

The overall incidence of AEs, grade ≥3 AEs, serious AEs, and AEs leading to discontinuation were similar for both treatment arms. No new safety signals were identified for vanucizumab. The distinct toxicities in the vanucizumab arm matched those reported in previous studies exploring vanucizumab as a single agent [10]. Consistent with its mode of action, peripheral edema formation (all grade ≤2) was more frequent in patients receiving vanucizumab/mFOLFOX-6, thereby also supporting respective observations with other selective inhibitors of the angiopoietin-Tie2 axis [22, 27, 28]. Furthermore, the incidence of HTN grade 3–4 was doubled in the vanucizumab arm and appeared to be mainly induced by the VEGF-A inhibitory component of the bispecific antibody given at a biweekly dose of 2,000 mg (or 30 mg/kg). HTN is a common complication of anti–VEGF-A treatment that appears to depend on dose, tumor type, and interaction with other antineoplastic drugs [29, 30]. Bevacizumab added to first-line chemotherapy in mCRC is associated with HTN grade 3–4 ranging from 3% to 25% [23, 31, 32], with highest incidence rates being reported for high dose bevacizumab at 10 mg/kg q2w [33]. On the contrary, blocking the angiopoietin-Tie2 signaling pathway in combination with low-dose bevacizumab (7.5 mg/kg q3w) or chemotherapy in the setting of first- and second-line mCRC did not result in greater incidence of high-grade HTN [22, 34]. The incidence rates of GI perforations (including GI fistula and abscess) were similar in the two treatment arms

but higher than previously reported with bevacizumab in mCRC [23, 35]. The exact reason for this is unknown but likely related to the presence of primary tumors in place for the majority of affected patients or other known risk factors such as prior radiotherapy, intestinal stent implants, and/or recent colonoscopy [36, 37].

Conclusion

In conclusion, and by demonstration of Ang-2 target modulation and adequate systemic exposure of vanucizumab, our data suggest that additional Ang-2 inhibition does not provide additional benefit over anti–VEGF-A blockade alone when added to standard chemotherapy for first-line treatment of mCRC. As a result, further clinical development of the dual VEGF-A–Ang-2 inhibitor vanucizumab was discontinued.

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Author Contributions

Conception/design: Carlos López-López, Maria-Luisa Limon Miron, Clara Montagut, Cristina Santos Vivas, Alberto Bessudo, Patrizia Plezia, Veerle Moons, Johannes Andel, Jaafar Bennouna, Simona Rossomanno, Angelika Lahr, Florian Heil, Katharina Lechner, Oliver Krieter, Herbert Hurwitz

Provision of study material or patients: Johanna Bendell, Tamara Sauri, Antonio Cubillo Gracián, Rafael Alvarez, Carlos López-López, Pilar García-Alfonso, Maen Hussein, Maria-Luisa Limon Miron, Andrés Cervantes, Clara Montagut, Cristina Santos Vivas, Alberto Bessudo, Patrizia Plezia, Veerle Moons, Johannes Andel, Jaafar Bennouna, Andre van der Westhuizen, Leslie Samuel, Simona Rossomanno, Christophe Boetsch, Angelika Lahr, Izolda Franjkovic, Florian Heil, Katharina Lechner, Oliver Krieter, Herbert Hurwitz

Collection and/or assembly of data: Johanna Bendell, Tamara Sauri, Antonio Cubillo Gracián, Rafael Alvarez, Carlos López-López, Pilar García-Alfonso, Maen Hussein, Maria-Luisa Limon Miron, Andrés Cervantes, Clara Montagut, Cristina Santos Vivas, Alberto Bessudo, Patrizia Plezia, Veerle Moons, Johannes Andel, Jaafar Bennouna, Andre van der Westhuizen, Leslie Samuel, Florian Heil, Katharina Lechner, Herbert Hurwitz

Data analysis and interpretation: Johanna Bendell, Antonio Cubillo Gracián, Carlos López-López, Maen Hussein, Maria-Luisa Limon Miron, Clara Montagut, Cristina Santos Vivas, Alberto Bessudo, Patrizia Plezia, Veerle Moons, Johannes Andel, Jaafar Bennouna, Leslie Samuel, Simona Rossomanno, Christophe Boetsch, Angelika Lahr, Izolda Franjkovic, Florian Heil, Katharina Lechner, Oliver Krieter, Herbert Hurwitz

Manuscript writing: Johanna Bendell, Tamara Sauri, Antonio Cubillo Gracián, Rafael Alvarez, Carlos López-López, Pilar García-Alfonso, Maen Hussein, Maria-Luisa Limon Miron, Andrés Cervantes, Clara Montagut, Cristina Santos Vivas, Alberto Bessudo, Patrizia Plezia, Veerle Moons, Johannes Andel, Jaafar Bennouna, Andre van der Westhuizen, Leslie Samuel, Simona Rossomanno, Christophe Boetsch, Angelika Lahr, Izolda Franjkovic, Florian Heil, Katharina Lechner, Oliver Krieter, Herbert Hurwitz

Final approval of manuscript: Johanna Bendell, Tamara Sauri, Antonio Cubillo Gracián, Rafael Alvarez, Carlos López-López, Pilar García-Alfonso, Maen Hussein, Maria-Luisa Limon Miron, Andrés Cervantes, Clara Montagut, Cristina Santos Vivas, Alberto Bessudo, Patrizia Plezia, Veerle Moons, Johannes Andel, Jaafar Bennouna, Andre van der Westhuizen, Leslie Samuel, Simona Rossomanno, Christophe Boetsch, Angelika Lahr, Izolda Franjkovic, Florian Heil, Katharina Lechner, Oliver Krieter, Herbert Hurwitz

Disclosures

Johanna C. Bendell: Gilead, Genentech-Roche, Bristol-Myers Squibb, Five Prime, Eli Lilly & Co., Merck, MedImmune, Celgene, EMD Serono, Taiho, Macrogenics, GlaxoSmithKline, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Koltan, SynDevRex, Forty Seven, AbbVie, Array, Onyx, Sanofi, Takeda, Eisai, Celldex, Agios, Cytomx, Nektar, ARMO, Boston Biomedical, Ipsen, Merrimack, Tarveda, Tyrogenex, Oncogenex, Marshall Edwards, Pieris, Mersana, Calithera, Blueprint, Evelo, FORMA, Merus, Jacobio, Effector, Novocare, Arrys, Tracon, Sierra, Innate, Arch, Prelude, Unum, Vyriad, Harpoon, ADC, Amgen, Pfizer, Millennium, Imclone, Acerta, Rgenix, Bellicum (RF—to institution), C/A to institution: Gilead, Genentech-Roche, Bristol-Myers Squibb, Five Prime, Eli Lilly & Co., Merck, MedImmune, Celgene, Taiho, Macrogenics, GlaxoSmithKline, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Array, Sanofi, ARMO, Ipsen, Merrimack, Oncogenex, FORMA, Arch Oncology, Prelude Therapeutics, Phoenix Bio, Cyteir, Molecular Partners, Innate, Torque, Tizona, Janssen, Tolero, TD2 (Translational Drug Development), Amgen, Seattle Genetics, Moderna Therapeutics, Tanabe Research Laboratories, Beigene, Continuum Clinical (C/A—to institution); **Carlos López-López:** Roche, Sanofi, Merck, Servier (SAB), Roche, Sanofi, Amgen, Merck, Servier, Merck Sharp & Dohme, Bristol-Myers Squibb (RF), Roche, Sanofi, Amgen, Merck, Servier (H); **Pilar García-Alfonso:** Roche, Amgen, Merck, Sanofi, Servier (SAB); **Maen Hussein:** Bristol-Myers Squibb, BI, Herron, Incyte, AMAG, Pfizer (H); **Andrés Cervantes:** Roche, Genentech (RF, C/A); **Clara Montagut:** Roche, Merck, Amgen, Sanofi (C/A); **Jaafar Bennouna:** Roche, Boehringer, AstraZeeca, Bayer, Merck Sharp & Dohme, Servier (SAB, H); **Leslie Samuel:** Amgen, Pierra Fabre (C/A), Array, Mologen, Roche, Merck (RF); **Simona Rossomanno:** F. Hoffmann-La Roche (E); **Christophe Boetsch:** F. Hoffmann-La Roche (E); **Angelika Lahr:** Roche (E); **Florian Heil:** Roche Diagnostics GmbH (E, OI); **Katharina Lechner:** Roche Diagnostics GmbH (E); **Oliver Krieter:** F. Hoffmann-La Roche (E); **Herbert Hurwitz:** Genentech-Roche (RF, SAB, E/O). The other authors indicated no financial relationships.

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