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New Drug Development and Clinical Pharmacology

A Long-Term Extension Study of Bevacizumab in Patients With Solid Tumors

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

Key Words. Bevacizumab • Cancer • Long-term treatment • Safety • Solid tumor

Abstract

Background. Bevacizumab has been studied in numerous clinical trials in multiple types of cancer; however, patients may receive bevacizumab over an extended period of time. This study assessed the long-term safety and tolerability of bevacizumab among patients with solid tumors.

Materials and Methods. Patients enrolled in a Roche/Genentech-sponsored trial who had derived benefit from bevacizumab therapy as monotherapy or in combination with anticancer drugs were eligible for continuation of bevacizumab in this long-term extension (LTE) study. The primary endpoints were the incidence of adverse events (AEs) of Common Terminology Criteria for AEs (CTCAE) grade ≥3 related to bevacizumab treatment, serious AEs (SAEs), and deaths.

Results. Ninety-five patients with the following cancer types were enrolled in the LTE: ovarian cancer or peritoneal carcinoma ($n = 41$), non-small cell lung cancer ($n = 16$), glioblastoma multiforme ($n = 14$), breast cancer ($n = 11$), colorectal cancer ($n = 7$), or renal cell carcinoma ($n = 6$). The median (range) duration of bevacizumab treatment was 15.6 (0.0–81.0) months during the LTE and 57.5 (16.4–134.9) months overall (parent trial + LTE), with three patients receiving bevacizumab for >10 years. Overall, 17 patients (17.9%) experienced SAEs, and 21 (22.1%) had a bevacizumab-related AE of CTCAE grade ≥3 (proteinuria and hypertension were the most common). Four patients died: three from disease progression and one from an AE considered unrelated to bevacizumab.

Conclusion. The safety outcomes observed support the tolerability of long-term bevacizumab in patients with various solid tumors, with a median extended treatment duration of almost 5 years overall and >10 years in some individual patients. *ClinicalTrials.gov identifier:* NCT01588184. ***The Oncologist*** 2021;26:e2254–e2264

Implications for Practice: In this long-term extension study of patients with solid tumors, the median duration of bevacizumab treatment (including parent trials) was just under 5 years, with a long-term exposure in some patients of 7 to >10 years. Grade ≥3 adverse events related to bevacizumab were consistent with the established safety profile, with proteinuria and hypertension being the most common. Patients received bevacizumab over an extended period of time (beyond the length of most clinical trials), and the overall safety outcomes observed support the tolerability of long-term bevacizumab treatment in patients with solid tumors, with clinical benefit achieved over an extended period.

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Introduction

Angiogenesis, the generation of new blood vessels sprouting from existing blood vessels, has been found to promote vascularization in the cancer setting. In normal physiology, angiogenesis is strictly controlled by a complex balance of pro- and antiangiogenic factors, yet solid tumors can take advantage of angiogenesis to promote vascularization via an "angiogenic switch" to facilitate growth [1].

Vascular endothelial growth factors (VEGFs) have been found to be key inducers of tumor angiogenesis. The binding of VEGFs to VEGF receptor (VEGFR)1–3 tyrosine kinases in endothelial cells stimulates the proliferation and survival of endothelial cells via an increase in the permeability of vessels to facilitate tumor growth [2, 3]. VEGF signaling, in particular VEGFA, has also been shown to support cancer progression via (a) promoting cancer cell migration and invasiveness through VEGFR1 signaling [1], (b) enabling stemness properties and self-renewal in cancer cells through VEGFA/neuropilin1 signaling [4], and (c) immune suppression in the tumor microenvironment through VEGFR1–3 signaling in a myriad of immune cells [5, 6].

Bevacizumab, a humanized recombinant monoclonal antibody to VEGF that blocks VEGF from binding to all VEGFA receptors [7], has been studied in numerous phase I–IV clinical trials in a multitude of cancer types, both as monotherapy or in combination with chemotherapy, and is approved for a range of solid tumor indications in 134 countries. Concomitant bevacizumab treatment with chemotherapy has been shown to improve progression-free survival (PFS) and/or overall survival (OS) in patients with metastatic colorectal cancer (CRC) [8–12], non-small cell lung cancer (NSCLC) [13–16], metastatic breast cancer (BC) [17, 18], metastatic renal cell carcinoma (RCC) [19, 20], ovarian cancer (OC) or peritoneal cancer (PC) [21–23], glioblastoma multiforme (GBM) [24–26], and cervical cancer [27, 28].

This long-term extension (LTE) study aimed to (a) provide continued bevacizumab therapy as a single agent or in combination with an anticancer drug to patients with solid tumors who derived benefit from bevacizumab while previously enrolled in a Roche/Genentech-sponsored bevacizumab trial and (b) assess the safety of long-term administration of bevacizumab.

Materials and Methods

Patient Population and Study Design

Patients with solid tumors who had derived benefit from bevacizumab as monotherapy or in combination with anticancer drugs while enrolled in a Roche/Genentech-sponsored clinical trial (parent trial) and were suitable for continuation of treatment at the end of that parent trial were eligible for inclusion in this multicenter, open-label, single-arm, phase IIIb/IV LTE study. Patients were excluded if they had evidence of disease progression while in the parent trial or if they experienced an adverse event (AE) suspected to be attributed to bevacizumab and treatment discontinuation was recommended.

All patients received bevacizumab intravenously at the same dose regimen as in the parent trial: either 7.5 or 15 mg/kg every 3 weeks or 5 or 10 mg/kg every 2 weeks. Patients continued bevacizumab and concomitant treatment until disease progression, unacceptable toxicity due to bevacizumab treatment, withdrawal of consent, death, or transition to another option for treatment with bevacizumab (Post-Trial Access Program or licensed product), whichever occurred first. The trial ended at the safety follow-up visit for the last patient, which was 30 days $\pm$ 3 days after the patient permanently discontinued treatment. This study was approved by the institutional review board and independent ethics committee of each investigational center. All patients provided written informed consent in accordance with the Declaration of Helsinki.

Study Assessments

The primary study endpoints were the incidence of AEs of National Cancer institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) grade ≥ 3 related to bevacizumab, serious AEs (SAEs), and death. AEs were classified by preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class, version 22.0. AEs previously described as associated with the use of bevacizumab treatment were considered to be AEs of special interest (AESIs) in this trial. Evaluation of efficacy was an exploratory objective of this LTE study; therefore, efficacy data collection was limited. Tumor assessments were performed in accordance with local standards: continuation of the same imaging technique and tumor evaluation as in the corresponding parent trial was recommended.

Statistical Analysis

The safety population, which included all enrolled patients who received at least one dose of bevacizumab in the LTE, was used for all analyses. Data are presented for all patients and by tumor type. Descriptive statistics were used for all endpoints. Clopper-Pearson 95% confidence intervals (CIs) were calculated for rates of AEs of CTCAE grade ≥ 3 related to bevacizumab and for SAE rates. PFS and OS were analyzed using a Kaplan-Meier approach. PFS and OS were exploratory endpoints, calculated until the end of the LTE from the date of first dose of bevacizumab in the LTE trial and from the parent trial. If no tumor assessment was completed for a patient in the LTE, the censoring day was calculated using a reference date of the start date of the LTE instead of day 1.

Results

Patient Disposition and Baseline Characteristics

A total of 95 patients from 17 parent trials were enrolled at 67 sites across 21 countries (Austria, Brazil, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Hungary, Italy, Korea, Mexico, The Netherlands, Romania, Russia, Slovak Republic, South Africa, Spain, Sweden, Turkey, and U.K.). The two trials with the highest enrollment numbers in the LTE were the ROSIA trial of patients with OC (NCT01239732; $n = 41$ [43.2%]) and the TAMIGA trial of patients with GBM (NCT01860638; $n = 13$ [13.7%]); the remaining 15 trials each contributed ≤ 6.5% of patients (Table 1; Fig. 1). Among all patients in the LTE, the types of cancer included OC or PC

Table 1. Number of patients enrolled in the LTE from each parent trial by indication

Parent trial			LTE						
Study number; trial acronym (enrollment)	**ClinicalTrials.gov Identifier**	**Study name**	**OC or PC ($n = 41$), n (%)**	**NSCLC ($n = 16$), n (%)**	**GBM ($n = 14$), n (%)**	**BC ($n = 11$), n (%)**	**CRC ($n = 7$), n (%)**	**RCC ($n = 6$), n (%)**	**Total ($n = 95$), n (%)**
MO22923: ROSIA ($n = 1,021$)	NCT01239732	A Study of the Addition of Avastin (Bevacizumab) to Carboplatin and Paclitaxel Therapy in Patients With Ovarian Cancer	41 (100)	—	—	—	—	—	41 (43.2)
MO28347: TAMIGA ($n = 296$)	NCT01860638	A Comparison of Continuous Bevacizumab (Avastin) Treatment or Placebo in Addition to Lomustine Followed by Standard of Care After Disease Progression in Participants With Glioblastoma	—	—	13 (92.9)	—	—	—	13 (13.7)
MO21609: BEVLIN ($n = 146$)	NCT00796757	A Study of Avastin (Bevacizumab) in Combination With Low-Dose-Interferon in Patients With Metastatic Clear Cell Renal Cell Carcinoma (RCC)	—	—	—	—	—	6 (100)	6 (6.3)
MO22089: AVAPERL1 ($n = 376$)	NCT00961415	A Study of Avastin (Bevacizumab) With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer	—	5 (31.3)	—	—	—	—	5 (5.3)
MO19390: SAIL ($n = 2,252$)	NCT00451906	A Study of Avastin (Bevacizumab) in Combination With Platinum-Containing Chemotherapy in Patients With Advanced or Recurrent Non-Squamous Cell Lung Cancer	—	5 (31.3)	—	—	—	—	5 (5.3)
MO22097: avaALL ($n = 485$)	NCT01351415	A Study of Bevacizumab in Combination With Standard of Care Treatment in Participants With Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	—	5 (31.3)	—	—	—	—	5 (5.3)
MO21926: HAX ($n = 88$)	NCT00811135	A Study of Avastin (Bevacizumab) in Combination With Herceptin (Trastuzumab) and Xeloda (Capecitabine) in Patients With HER2-Positive Breast Cancer	—	—	—	4 (36.4)	—	—	4 (4.2)
BO20231: AVEREL ($n = 424$)	NCT00391092	A Study of Avastin (Bevacizumab) in Combination With Herceptin (Trastuzumab)/Docetaxel in Patients With HER2 Positive Metastatic Breast Cancer	—	—	—	4 (36.4)	—	—	4 (4.2)

(continued)

Table 1. (continued)

Parent trial			LTE						
Study number; trial acronym (enrollment)	**ClinicalTrials.gov Identifier**	**Study name**	**OC or PC ($n = 41$), n (%)**	**NSCLC ($n = 16$), n (%)**	**GBM ($n = 14$), n (%)**	**BC ($n = 11$), n (%)**	**CRC ($n = 7$), n (%)**	**RCC ($n = 6$), n (%)**	**Total ($n = 95$), n (%)**
MO19286: AVEX ($n = 280$)	NCT00484939	A Study of Bevacizumab (Avastin) in Combination With Capecitabine (Xeloda) in Elderly Patients With Metastatic Colorectal Cancer	—	—	—	—	2 (28.6)	—	2 (2.1)
ML18147: CRC TML ($n = 820$)	NCT00700102	A Study of Avastin (Bevacizumab) Plus Crossover Fluoropyrimidine-Based Chemotherapy in Patients With Metastatic Colorectal Cancer	—	—	—	—	2 (28.6)	—	2 (2.1)
MO29112: MODUL ($n = 609$)	NCT02291289	A Study of Biomarker-Driven Therapy in Metastatic Colorectal Cancer (mCRC) (MODUL)	—	—	—	—	2 (28.6)	—	2 (2.1)
MO19391: ATHENA ($n = 2,296$)	NCT00448591	A Study of Avastin (Bevacizumab) Plus Taxane-Based Therapy in Patients With Locally Recurrent or Metastatic Breast Cancer	—	—	—	1 (9.1)	—	—	1 (1.1)
ML18524 ($n = 306$)	NCT01131078	A Study of Avastin (Bevacizumab) in Combination Chemotherapy in Patients With Metastatic Cancer of the Colon or Rectum	—	—	—	—	1 (14.3)	—	1 (1.1)
BO17708: AVADO ($n = 736$)	NCT00333775	A Study of Bevacizumab (Avastin) in Women With HER2 Negative Metastatic Breast Cancer	—	—	—	1 (9.1)	—	—	1 (1.1)
MO22223: IMELDA ($n = 287$)	NCT00929240	A Study of Avastin (Bevacizumab) + Xeloda (Capecitabine) as Maintenance Therapy in Patients With HER2-Negative Metastatic Breast Cancer	—	—	—	1 (9.1)	—	—	1 (1.1)
ML21868: EAGLES ($n = 86$)	NCT01077713	A Study of Avastin (Bevacizumab) in Combination With Gemcitabine With or Without Cisplatin in First-Line Treatment of Elderly Patients With Non-Small Cell Lung Cancer	—	1 (6.3)	—	—	—	—	1 (1.1)
ML21965: GLARIUS ($n = 182$)	NCT00967330	A Study of Avastin (Bevacizumab) and Irinotecan Versus Temozolomide Radiochemistry in Patients With Glioblastoma	—	—	1 (7.1)	—	—	—	1 (1.1)

Patients were from the following countries: Austria ($n = 1$), Brazil ($n = 8$), Bulgaria ($n = 1$), Canada ($n = 3$), Czech Republic ($n = 2$), Estonia ($n = 1$), France ($n = 9$), Germany ($n = 2$), Hungary ($n = 1$), Italy ($n = 13$), Korea ($n = 3$), Mexico ($n = 9$), The Netherlands ($n = 3$), Romania ($n = 5$), Russia ($n = 14$), Slovak Republic ($n = 1$), South Africa ($n = 1$), Spain ($n = 12$), Sweden ($n = 2$), Turkey ($n = 1$), U.K. ($n = 3$).
Abbreviations: —, zero patients; BC, breast cancer; CRC, colorectal cancer; GBM, glioblastoma multiforme; LTE, long-term extension; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, peritoneal carcinoma; RCC, renal cell carcinoma.

($n = 41$ [43.2%]), NSCLC ($n = 16$ [16.8%]), GBM ($n = 14$ [14.7%]), BC ($n = 11$ [11.6%]), CRC ($n = 7$ [7.4%]), and RCC ($n = 6$ [6.3%]). The majority of patients were female (70.5%). At baseline, the mean (SD) and median (range) ages were 56.9 (11.4) and 56.0 (23–81) years, respectively (Table 2). The age of patients across the indication groups reflected the pathology of each disease; the oldest patients were in the CRC group (median, 72.0 years) and the youngest in the GBM group (median, 48.5 years). The mean (SD) and median (range) weights were 69.3 (13.2) and 69.7 (39–120) kg at baseline, respectively.

Overall median (95% CI) observation time was 20.7 (14.9–27.6) months during the LTE through safety follow-up. Median (95% CI) observation times were longer for patients with BC (45.4 [11.0–81.3] months) and patients with OC or PC (30.4 [15.0–49.1] months) than for patients with other indications (median duration <18 months in all other indications). The mean (SD) and median (range) durations of bevacizumab treatment during the LTE only were 22.1 (19.9) months and 15.6 (0–81.0) months, respectively. The median duration of treatment varied across the indication groups (from 4.2 months for patients with RCC to 43.6 months for patients with BC), largely reflecting the varied times that patients entered into the LTE from the various parent trials over the course of the study (i.e., patients in some studies entered into the LTE at an earlier time point based on when their parent trial ended). The mean (SD) and median (range) total treatment durations (parent trial and LTE trial combined) were 61.3 (25.7) months and 57.5 (16.4–134.9) months, respectively (Table 2). The median total treatment duration ranged from 44.3 months for patients with RCC to 98.3 months for patients with BC. Among patients with BC, three patients received bevacizumab for >10 years (range, up to 134.9 months) and another three patients for 8 years. One patient with CRC and one with NSCLC received bevacizumab for 9 years, and 1 patient with NSCLC received bevacizumab for 8 years. Ten patients with OC or PC received bevacizumab for 7 years.

The most common reasons for discontinuation of bevacizumab treatment were disease progression (30 patients [31.6%]) and AEs (25 patients [26.3%]). A total of 27 patients (28.4%) did not complete safety follow-up, with withdrawal of consent as the most frequent reason (7 patients [7.4%]). At the termination of the trial by the study sponsor, 14 patients were still receiving study treatment. Of these 14 patients, 13 transitioned to another treatment option (Post-Trial Access Program or licensed product) and 1 discontinued treatment at the investigator's decision.

Safety

A total of 79 patients (83.2%) experienced AEs, of which the most common were (number of patients [%]) proteinuria (42 [44.2]), headache (15 [15.8]), asthenia (15 [15.8]), hypertension (12 [12.6]), nausea (11 [11.6]), urinary tract infection (10 [10.5]), and diarrhea (10 [10.5]). AEs assessed as related to bevacizumab treatment were reported in 54 patients (56.8%; Table 3), the most common of which were proteinuria (39 patients [41.1%]) and hypertension (10 patients [10.5%]). AEs related to bevacizumab of CTCAE grade ≥ 3 occurred in 21 patients (22.1%; 95% CI, 14.2%–31.8%; Table 3). Grade ≥ 3 AEs (related to bevacizumab) that occurred in at least one patient were proteinuria (7 [7.4%]), hypertension (5 [5.3%]), and blood pressure increase (2 [2.1%]). No grade 4 or 5 AEs related to bevacizumab were reported. AEs that led to discontinuation of bevacizumab occurred in 25 patients (26.3%). The occurrence of proteinuria led to withdrawal of bevacizumab in 15 patients (15.8%), which was the only AE leading to withdrawal for more than one patient. Of the 42 patients who had proteinuria, 15 discontinued bevacizumab; of the 15 patients who had hypertension, 1 discontinued bevacizumab.

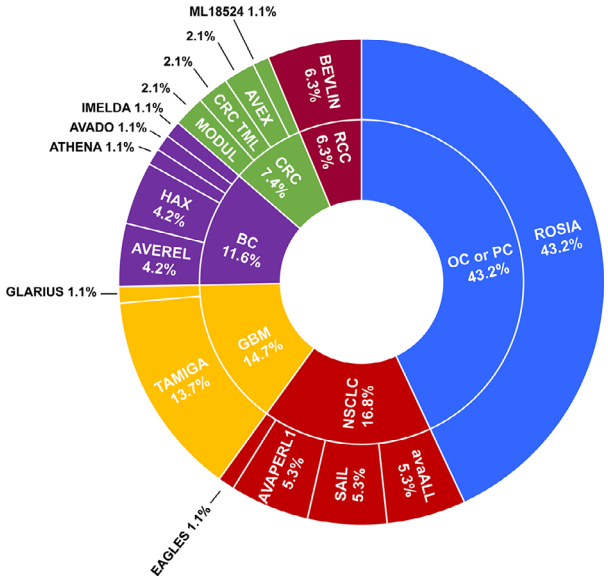

Figure 1. Proportion of patients ($n = 95$) enrolled in the LTE from each parent trial by indication.
Abbreviations: BC, breast cancer; CRC, colorectal cancer; GBM, glioblastoma multiforme; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, peritoneal carcinoma; RCC, renal cell carcinoma.

A total of 17 patients (17.9%) experienced SAEs; the most frequently reported SAEs (by MedDRA system organ class) were infections and infestations (4 patients [4.2%]); injury, poisoning, and procedural complications (3 [3.2%]); vascular disorders (3 [3.2%]); cardiac disorders (2 [2.1%]); and nervous system disorders (2 [2.1%]). No pregnancies were reported throughout the study duration. During the extension study, four deaths (4.2%) occurred; no deaths were considered related to bevacizumab. Three deaths were due to disease progression (1 patient each with RCC, NSCLC and GBM), and one death was due to an AE not related to bevacizumab (patient with BC).

AESIs were reported in 52 patients (54.7%); proteinuria and hypertension were the most common AESIs, reported in 42 patients (44.2%) and 15 patients (15.8%), respectively (Table 4). Nine patients (9.5%) experienced hemorrhages, most of which were superficial bleeds. Only one patient (1.1%) had a gastrointestinal hemorrhage, and one (1.1%) had hematemesis. Arterial and venous thromboembolic events were reported in four patients (4.2%); no overt arterial events occurred. Fistula and wound healing complications were reported in one patient each (1.1%); the event of fistula was a lacrimal gland abscess. There were no reports of gastrointestinal perforation or reversible posterior leukoencephalopathy syndrome.

Table 2. Baseline demographics and duration of treatment and exposure to bevacizumab

Characteristic	OC or PC ($n = 41$), *n* (%)	NSCLC ($n = 16$)	GBM ($n = 14$)	BC ($n = 11$)	CRC ($n = 7$)	RCC ($n = 6$)	Total ($N = 95$)
Female, *n* (%)	41 (100)	6 (37.5)	4 (28.6)	11 (100)	3 (42.9)	2 (33.3)	67 (70.5)
Age							
Mean (SD), yr	56.7 (11.2)	58.5 (10.5)	49.5 (10.9)	54.5 (7.3)	66.7 (13.9)	63.5 (9.8)	56.9 (11.4)
Median (range), yr	56.0 (26–75)	61.0 (41–77)	48.5 (23–66)	54.0 (42–65)	72.0 (48–81)	66.5 (46–72)	56.0 (23–81)
Weight							
Mean (SD), kg	67.7 (12.7)	73.1 (17.8)	73.6 (9.5)	65.3 (12.0)	61.4 (11.0)	77.2 (8.5)	69.3 (13.2)
Median (range), kg	69.0 (39–100)	70.9 (41–120)	73.5 (54–94)	61.5 (52–90)	63.0 (45–78)	78.2 (62–86)	69.7 (39–120)
Observation time, median (95% CI), mo[a]	30.4 (15.0–49.1)	17.7 (3.5–27.6)	9.4 (2.8–24.9)	45.4 (11.0–81.3)	12.7 (5.6–23.4)	5.6 (2.3-NA)	20.7 (14.9–27.6)
Duration of bevacizumab treatment (LTE only)[b]							
Mean (SD), mo	26.1 (20.2)	17.1 (15.0)	11.9 (10.8)	36.7 (24.9)	19.0 (23.9)	9.3 (10.5)	22.1 (19.9)
Median (range), mo	24.4 (0–57.3)	14.7 (1.4–52.5)	7.6 (1.0–30.3)	43.6 (0.7–81.0)	11.5 (4.9–71.8)	4.2 (1.4–29.3)	15.6 (0–81.0)
Duration of bevacizumab treatment (total)[c]							
Mean (SD), mo	62.2 (19.8)	56.9 (28.6)	48.5 (14.9)	94.1 (27.2)	52.1 (34.3)	48.1 (12.9)	61.3 (25.7)
Median (range), mo	59.3 (34.1–92.6)	52.2 (19.1–111.2)	46.4 (30.7–82.6)	98.3 (57.2–134.9)	45.5 (16.4–113.8)	44.3 (36.6–71.4)	57.5 (16.4–134.9)
Treatment cycles (total), *n* (%)[d]							
1–50	2 (4.9)	6 (37.5)	1 (7.1)	–	2 (28.6)	–	11 (11.6)
51–100	25 (61.0)	4 (25.0)	12 (85.7)	2 (18.2)	3 (42.9)	3 (50.0)	49 (51.6)
101–150	14 (34.1)	4 (25.0)	–	4 (36.4)	1 (14.3)	2 (33.3)	25 (26.3)
151–200	–	2 (12.5	1 (7.1)	5 (45.5)	–	1 (16.7)	9 (9.5)
201–250	–	–	–	–	1 (14.3)	–	1 (1.1)
Reason for treatment discontinuation, *n* (%)							
Disease progression	8 (19.5)	10 (62.5)	8 (57.1)	–	3 (42.9)	1 (16.7)	30 (31.6)
AE	11 (26.8)	3 (18.8)	2 (14.3)	5 (45.5)	1 (14.3)	3 (50.0)	25 (26.3)
Withdrawal of consent	8 (19.5)	–	1 (7.1)	2 (18.2)	–	1 (16.7)	12 (12.6)
Death	–	–	–	1 (9.1)	–	–	1 (1.1)
Lack of compliance	1 (2.4)	–	–	–	–	1 (16.7)	2 (2.1)
Investigator decision	6 (14.6)	2 (12.5)	–	1 (9.1)	1 (14.3)	–	10 (10.5)
Protocol violation	–	–	–	1 (9.1)	–	–	1 (1.1)
Trial termination by sponsor	7 (17.1)	1 (6.3)	2 (21.4)	1 (9.1)	2 (28.6)	–	14 (14.7)

(continued)

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Table 2. (continued)

Characteristic	OC or PC ($n = 41$), n (%)	NSCLC ($n = 16$)	GBM ($n = 14$)	BC ($n = 11$)	CRC ($n = 7$)	RCC ($n = 6$)	Total ($N = 95$)
Reason follow-up not completed							
Withdrawal of consent	4 (9.8)	–	–	2 (18.2)	–	1 (16.7)	7 (7.4)
Death	–	1 (6.3)	1 (7.1)	1 (9.1)	–	1 (16.7)	4 (4.2)
Other	3 (7.3)	–	–	–	–	1 (16.7)	4 (4.2)
Transition to another option for bevacizumab treatment	6 (14.6)	1 (6.3)	3 (21.4)	–	2 (28.6)	–	12 (12.6)

[a]Observation time was defined as the time to safety follow-up after first bevacizumab administration in extension trial based on an inverse Kaplan-Meier analysis. A patient was considered as having an event if the safety follow-up visit was completed. Summaries are based on both events and censored observations.
[b]Treatment duration of bevacizumab (extension trial) = (date of last dose of bevacizumab in extension trial – date of first dose of bevacizumab in extension trial)/30.4.
[c]Treatment duration of bevacizumab (total) = [(date of last dose of bevacizumab in extension trial – date of first dose of bevacizumab in parent trial) + 1]/30.3.
[d]Approximate number of cycles (total) = [(date of last dose of bevacizumab in extension trial – date of first dose of bevacizumab in parent trial) + 1]/(number of days in a cycle). Number of days in a cycle = 14 or 21 according to treatment schedule.
Abbreviations: –, zero patients; BC, breast cancer; CRC, colorectal cancer; GBM, glioblastoma multiforme; NA, not applicable; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, peritoneal carcinoma; RCC, renal cell carcinoma.

Efficacy

Limited efficacy data were collected because the evaluation of efficacy was not an objective of this LTE study. Moreover, patients entered into the LTE at different time points over the course of the study because of the study design, tumor assessments were in accordance with local standards, and no long-term follow-up was performed. The median (range) duration of PFS from first dose of bevacizumab in the parent study ranged from 50.8 (31.3–83.0) months for patients with GBM to 74.6 (35.0–74.6) months for patients with RCC (Fig. 2). The median PFS was not reached among patients with BC and OC or PC. The maximum duration of PFS for all patients in the study was 127.8 months from time of first dose of bevacizumab in the parent trial. The median (range) duration of OS from first dose in the parent study among patients with RCC was 74.6 (37.4–74.6) months (Fig. 3). Median OS was not reached for patients in other indication groups. The maximum duration of OS for all patients in the study was 135.3 months from time of first dose of bevacizumab in the parent trial.

Discussion

This LTE study allowed patients with various solid tumors, including OC or PC, NSCLC, GBM, BC, CRC and RCC, who derived benefit from bevacizumab treatment in a prior parent trial to continue treatment with bevacizumab as a single agent or in combination with other anticancer drugs. The trial design allowed patients from numerous trials to continue to benefit from bevacizumab treatment while providing data on the long-term safety of bevacizumab across multiple indications. Although bevacizumab had been investigated in each of these indications separately, results from this LTE study, in which patients received bevacizumab over an extended period of time (beyond the length of most clinical trials), add to the existing data on the safety and tolerability of bevacizumab treatment. The median total duration of treatment with bevacizumab for patients in this study, including time treated with bevacizumab during the corresponding parent trials, was just under 5 years for all patients. Some patients included in this study had a very long-term exposure and benefit from bevacizumab; 16 patients received bevacizumab for 7–10 years and 3 patients (all with BC) received bevacizumab for >10 years (range up to 134.9 months).

The established safety profile for bevacizumab has been primarily based on its use in combination with standard chemotherapy regimens in multiple advanced malignancies. Based on clinical trial findings, mechanism of action, and pharmacokinetic profile, no clinically significant interactions between bevacizumab and standard chemotherapies have been observed or are expected to occur [29, 30]. Studies of the combination of bevacizumab and monoclonal antibodies (such as atezolizumab) have been consistent with the known safety profile of each individual therapy [31, 32].

Bevacizumab is most frequently associated with a dose-dependent rise in hypertension and with the development of proteinuria, which can present with varied severity ranging from asymptomatic to nephrotic syndrome [3]. Patients should be monitored closely for the occurrence of both AEs, which are generally manageable. Consistent with the established safety profile, the most frequent AESIs reported

Table 3. Principal safety outcomes among all patients and by indication

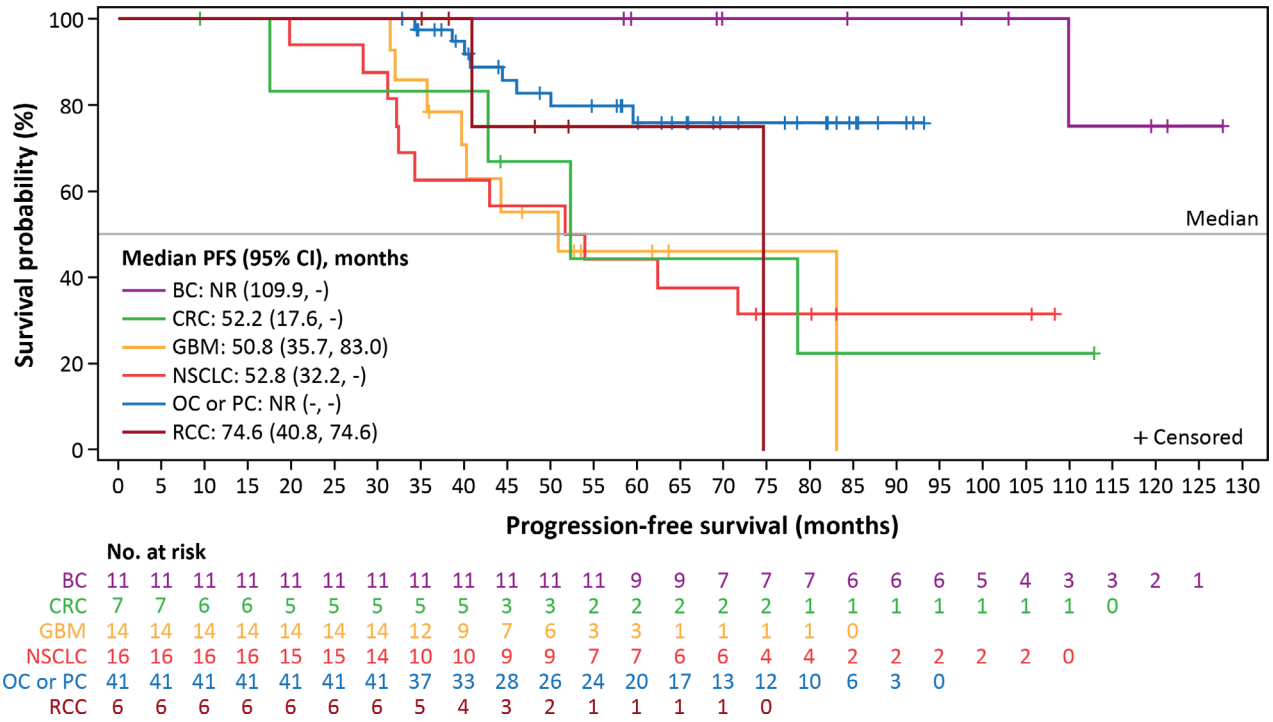
Category, *n* (%)	OC or PC (*n* = 41)	NSCLC (*n* = 16)	GBM (*n* = 14)	BC (*n* = 11)	CRC (*n* = 7)	RCC (*n* = 6)	Total (*n* = 95)
Any AE	32 (78.0)	12 (75.0)	14 (100.0)	10 (90.9)	5 (71.4)	6 (100.0)	79 (83.2)
AE related to bevacizumab	24 (58.5)	8 (50.0)	7 (50.0)	8 (72.7)	2 (28.6)	5 (83.3)	54 (56.8)
CTCAE grade ≥ 3 AE related to bevacizumab[a]	9 (22.0)	3 (18.8)	2 (14.3)	4 (36.4)	–	3 (50.0)	21 (22.1)
SAE	2 (4.9)	5 (31.3)	3 (21.4)	2 (18.2)	2 (28.6)	3 (50.0)	17 (17.9)
Death[a]	–	1 (6.3)	1 (7.1)	1 (9.1)	–	1 (16.7)	4 (4.2)
AE leading to discontinuation of bevacizumab	11 (26.8)	3 (18.8)	2 (14.3)	5 (45.5)	1 (14.3)	3 (50.0)	25 (26.3)
Proteinuria leading to discontinuation of bevacizumab	6 (14.6)	2 (12.5)	2 (14.3)	4 (36.6)	1 (14.3)	0	15 (15.8)
AE leading to discontinuation of bevacizumab/non-IMP	11 (26.8)	3 (18.8)	2 (14.3)	5 (45.5)	1 (14.3)	3 (50.0)	25 (26.3)

[a]Only 1 death was due to an AE, which was not related to bevacizumab; 3 were due to disease progression.
Abbreviations: –, zero patients; AE, adverse event; BC, breast cancer; CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Events; GBM, glioblastoma multiforme; IMP, investigational medicinal product; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, peritoneal carcinoma; RCC, renal cell carcinoma; SAE, serious adverse event.

Table 4. AESIs across all patients by category and preferred term

AESI category/preferred term, *n* (%)	OC or PC (*n* = 41), *n* (%)	NSCLC (*n* = 16), *n* (%)	GBM (*n* = 14), *n* (%)	BC (*n* = 11), *n* (%)	CRC (*n* = 7), *n* (%)	RCC (*n* = 6), *n* (%)	Total (*n* = 95)
Any AESI	23 (56.1)	8 (50.0)	6 (42.9)	8 (72.7)	2 (28.6)	5 (83.3)	52 (54.7)
Proteinuria	20 (48.8)	8 (50.0)	5 (35.7)	6 (54.5)	2 (28.6)	1 (16.7)	42 (44.2)
Proteinuria	20 (48.8)	8 (50.0)	5 (35.7)	6 (54.5)	2 (28.6)	1 (16.7)	42 (44.2)
Nephrotic syndrome	1 (2.4)	–	–	–	–	–	1 (1.1)
Hypertension	7 (17.1)	2 (12.5)	2 (14.3)	2 (18.2)	–	2 (33.3)	15 (15.8)
Hypertension	7 (17.1)	1 (6.3)	–	2 (18.2)	–	2 (33.3)	12 (12.6)
Blood pressure increased	–	–	2 (14.3)	–	–	–	2 (2.1)
Hypertensive crisis	–	1 (6.3)	–	–	–	–	1 (1.1)
Retinopathy hypertensive	1 (2.4)	–	–	–	–	–	1 (1.1)
Hemorrhage[a]	3 (7.3)	2 (12.5)	3 (21.4)	1 (9.1)	–	–	9 (9.5)
Epistaxis	1 (2.4)	2 (12.5)	2 (14.3)	1 (9.1)	–	–	6 (6.3)
Gingival bleeding	1 (2.4)	–	2 (14.3)	–	–	–	3 (3.2)
Conjunctival hemorrhage	–	–	1 (7.1)	–	–	–	1 (1.1)
Contusion	1 (2.4)	–	–	–	–	–	1 (1.1)
Gastrointestinal hemorrhage	1 (2.4)	–	–	–	–	–	1 (1.1)
Hematemesis	1 (2.4)	–	–	–		–	1 (1.1)
Arterial and venous thromboembolic events	1 (2.4)	2 (12.5)	–	–		1 (16.7)	4 (4.2)
Embolism venous	–	1 (6.3)	–	–		–	1 (1.1)
Ischemic stroke	–	1 (6.3)	–	–		–	1 (1.1)
Subclavian vein thrombosis	1 (2.4)	–	–	–		–	1 (1.1)
Transient ischemic attack	–	–	–	–		1 (16.7)	1 (1.1)
Congestive heart failure	–	–	–	1 (9.1)		1 (16.7)	2 (2.1)
Cardiac failure	–	–	–	–		1 (16.7)	1 (1.1)
Ejection fraction decreased	–	–	–	1 (9.1)		–	1 (1.1)

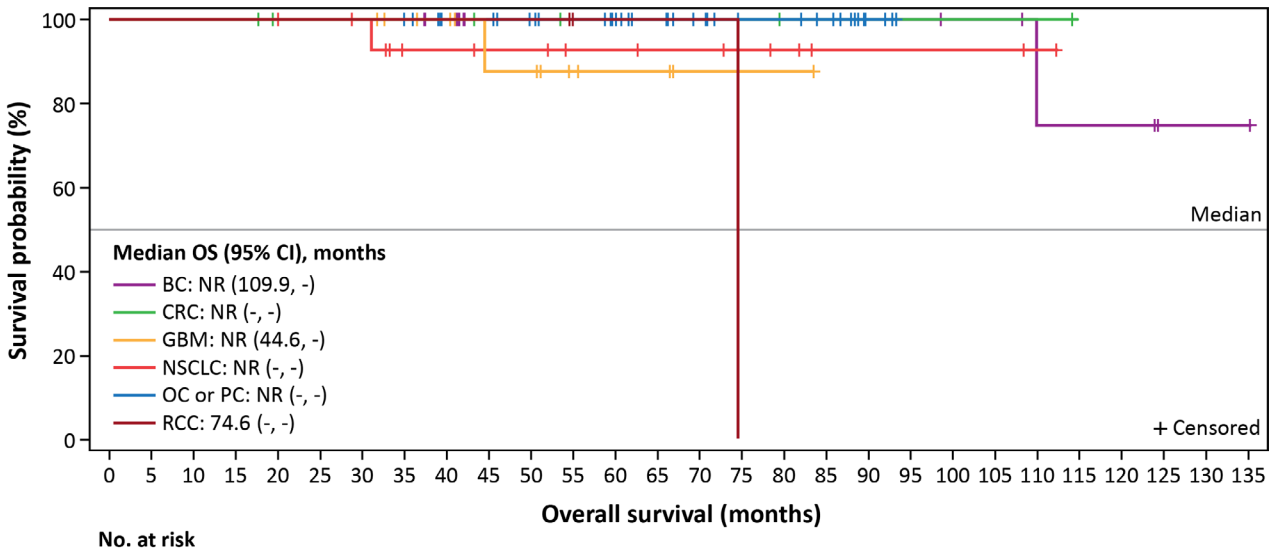
AEs previously described as associated with the use of bevacizumab treatment were considered to be AESIs in this trial. Medical Dictionary for Regulatory Activities version 22.0 was used to classify AESIs. A patient with multiple occurrences of an AE was counted only once in each AESI category and/or preferred term. A preferred term could contribute to >1 AESI category.
[a]Hemorrhage with a focus on hemoptysis and central nervous system bleeding.
Abbreviations: –, zero patients; AESI, adverse event of special interest; BC, breast cancer; CRC, colorectal cancer; GBM, glioblastoma multiforme; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, peritoneal carcinoma; RCC, renal cell carcinoma.



No. at risk

BC	11	11	11	11	11	11	11	11	11	11	11	11	9	9	7	7	7	6	6	6	5	4	3	3	2	1
CRC	7	7	6	6	5	5	5	5	5	3	3	2	2	2	2	2	1	1	1	1	1	1	1	0		
GBM	14	14	14	14	14	14	14	12	9	7	6	3	3	1	1	1	1	0								
NSCLC	16	16	16	16	15	15	14	10	10	9	9	7	7	6	6	4	4	2	2	2	2	2	0			
OC or PC	41	41	41	41	41	41	41	37	33	28	26	24	20	17	13	12	10	6	3	0						
RCC	6	6	6	6	6	6	6	5	4	3	2	1	1	1	1	0										

Figure 2. PFS by indication calculated from first dose of bevacizumab in parent trial.
Abbreviations: BC, breast cancer; CRC, colorectal cancer; GBM, glioblastoma multiforme; NR, not reached; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, peritoneal carcinoma; PFS, progression-free survival; RCC, renal cell carcinoma.



No. at risk

BC	11	11	11	11	11	11	11	11	11	11	11	11	11	10	9	7	7	7	6	6	5	5	3	3	3	1	1	1
CRC	7	7	7	7	5	5	5	5	5	4	3	2	2	2	2	2	1	1	1	1	1	1	1	0				
GBM	14	14	14	14	14	14	14	12	10	7	7	4	3	3	1	1	1	0										
NSCLC	16	16	16	16	16	15	14	10	10	9	9	7	7	6	6	5	4	2	2	2	2	2	1	0				
OC or PC	41	41	41	41	41	41	41	41	35	32	27	25	22	19	15	12	10	4	0									
RCC	6	6	6	6	6	6	6	6	5	3	3	1	1	1	1	0												

Figure 3. OS by indication calculated from first dose of bevacizumab in parent trial.
Abbreviations: BC, breast cancer; CRC, colorectal cancer; GBM, glioblastoma multiforme; NR, not reached; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; PC, peritoneal carcinoma; RCC, renal cell carcinoma.

in this LTE were proteinuria (44.2%) and hypertension (15.8%); however, they were manageable when following the protocol-specified side-effect management plan, which was dependent on the grade of AE and may have included medical management and/or temporary discontinuation of bevacizumab.

Gastrointestinal perforations, hemorrhage, and arterial thromboembolism are the most common SAEs occurring with

bevacizumab treatment [33]. Among patients in this LTE, there were no reports of gastrointestinal perforations, nine patients (9.5%) experienced hemorrhage (mostly superficial bleeds), and four patients (4.2%) experienced arterial and venous thromboembolic events.

Efficacy results may not be representative and should be interpreted with caution because of the limited efficacy data collected during the LTE and the fact that patients rolled over at different time points. The median duration of PFS from first dose of bevacizumab in the parent study ranged from 50.8 months in patients with GBM to 74.6 months in patients with RCC; median PFS was not reached in patients with BC and OC or PC. The median duration of OS from first dose of bevacizumab was 74.6 months in patients with RCC and not reached in any of the other indication groups. These limited efficacy results provide information in addition to that provided by the extended duration of bevacizumab received by multiple patients in this study.

Conclusion

The overall safety outcomes observed support the tolerability of long-term bevacizumab treatment in patients with various solid tumors, with clinical benefit achieved over an extended period.

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Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Disclosures

Amit M. Oza: AstraZeneca (RF—institution, outside the submitted work), AstraZeneca, Clovis (C/A), AstraZeneca, GlaxoSmithKline (SAB), AstraZeneca, GlaxoSmithKline, Clovis (RF-principal investigator); **Claudio Zamagni:** Roche, Eisai, Novartis, AstraZeneca, Pfizer, PharmaMar, Amgen, Tesaro, QuintilesIMS, Eli Lilly & Co, Celgene (SAB), Roche, Novartis, AstraZeneca, Pfizer, Tesaro, SeattleGenetics, Pierre Fabre, Istituto Gentili, Takeda, TEVA, Medivation, AbbVie, Array BioPharma, Morphotek, Synthon (RF), Roche, Novartis, Pfizer, PharmaMar, Tesaro, Pierre Fabre, Istituto Gentili, Celgene (Other—congresses travel accommodation); **Sonja Nick:** F. Hoffmann-La Roche Ltd (E); **Natsumi Irahara:** Roche (E); **Nicoletta Colombo:** Roche, PharmaMar, AstraZeneca, Merck Sharp & Dohme/Merck, Clovis Oncology, Tesaro, GlaxoSmithKline, Novartis, Pfizer, Takeda, BIOCAD, Immunogen, Mersana, Eisai, Oncxerna (SAB, H), Ellipses.life (C/A). The other authors indicated no financial relationships.

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