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A multicenter open-label randomized phase II study of cediranib with or without lenalidomide in iodine 131-refractory differentiated thyroid cancer

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Disclosure

AJR reports receiving consultation fees from EMD-Serono, Nanobiotix, Astellas, Novartis, Privo, and Galectin. WMS reports Consultant (DSMB): Astra-Zeneca, Merck, Pfizer, Treadwell Therapeutics; Consultant (other): Astra-Zeneca, Calico Life Sciences, Caremark/CVS, EMA Wellness, Fortress Biotech; Speakers Bureau: CME providers (sponsorship unknown): Applied Clinical Education, Dava Oncology, Global Academy for Medical Education, OncLive, PeerView, Research to Practice, Vindico; Grant/ Research Support (to institution): Abbvie, Amgen, Astra-Zeneca, Astellas (Medivation), Bayer, Bristol-Myers-Squibb, Bellicum, Boehringer-Ingelheim, Calithera, Clovis, Corvus, Eisai, Exilixis, Genentech (Roche), Johnson & Johnson (Janssen), Merck, Novartis, Pfizer, Seattle Genetics, X4Pharmaceuticals; Stockholder: Fortress Biotech; Expert Witness: Apotex, DRL, Mylan, Sandoz; Miscellaneous/Editorial: Cancer (ACS), Up-To-Date, Kidney Cancer Journal. All remaining authors declare that they have no competing interests.

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Abstract

Background—Multi-targeted tyrosine kinase inhibitors (TKIs) of the vascular endothelial growth factor receptor (VEGFR) pathway have activity in differentiated thyroid cancer (DTC). Lenalidomide demonstrated preliminary efficacy in DTC, but its safety and efficacy in combination with VEGFR targeted TKIs is unknown. We sought to determine the safety and efficacy of cediranib, a VEGFR targeted TKI, with or without lenalidomide, in the treatment of iodine 131-refractory differentiated thyroid cancer.

Patients and Methods—In this multicenter, open-label, randomized phase II clinical trial, 110 patients were enrolled and randomized to cediranib alone or cediranib with lenalidomide. The primary endpoint was progression-free survival (PFS). Secondary endpoints included response rate, duration of response, toxicity, and overall survival. Patients (≥18 years) with DTC who were refractory to further surgical or radioactive iodine (RAI) therapy as reviewed at a multispecialty tumor board conference, and evidence of disease progression within the previous 12 months and no more than 1 prior line of systemic therapy were eligible.

Results—Of the 110 patients, 108 started therapy and were evaluable for efficacy. The median PFS was 14.8 months (95% CI 8.5 to 23.8) in the cediranib arm and 11.3 months (95% CI 8.7 to 18.9) in the cediranib with lenalidomide arm (p=0.36). The 2-year overall survival was 64.8% (95% CI 43.3–86.4) and 75.3% (95% CI 59.4–91.0), respectively (p=0.80). The serious adverse event rate was 41% in the cediranib arm and 46% in the cediranib with lenalidomide arm.

Conclusions—Single-agent therapy with cediranib showed promising efficacy in RAI refractory DTC similar to other VEGFR targeted TKIs, while the addition of lenalidomide did not result in clinically meaningful improvements in outcomes.

Clinical trial registration—Clnicaltrials.gov identifier: NCT01208051

Introduction

Differentiated thyroid cancer (DTC) accounts for approximately 90% of thyroid cancer diagnoses. Despite a favorable prognosis for the majority of patients with surgery, thyroid hormone therapy, and radioactive iodine (RAI) therapy, a subset of patients develops progressive recurrent and/or metastatic disease that is refractory to RAI and have limited treatment options.[1, 2] Historically, cytotoxic chemotherapy such as doxorubicin was associated with poor response rates, short-lived activity, and substantial treatment-related toxicity. Given the high vascularity of thyroid cancers, there has been interest in the use of tyrosine kinase inhibitors (TKIs) that target angiogenic signaling in the tumor microenvironment, particularly vascular endothelial growth factor receptor (VEGFR). At the time of study conception, no TKIs had been approved for the treatment of RAI refractory DTC. Since that time, randomized trials have demonstrated a benefit for TKIs such as lenvatinib and sorafenib associated with median PFS of 11–18 months and which are now

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Food and Drug Administration (FDA) approved in this setting.[3–5] Despite these advances, improved therapeutic strategies are needed.

Cediranib is a potent inhibitor of all three VEGF receptors (VEGFR-1, −2, and −3). Given the activity of TKIs targeting VEGFR in RAI refractory DTC, it was hypothesized that cediranib may be active in this setting. Lenalidomide, a derivative of thalidomide, has immunomodulatory properties, inhibits angiogenesis, modulates stem cell differentiation, and has anti-cancer properties particularly in the treatment of multiple myeloma. At the time of study conception, phase II data supported single-agent activity for thalidomide and lenalidomide in the treatment of DTC.[6, 7] The combination of cediranib and lenalidomide was thus seen as potentially promising and had not been evaluated in the treatment of DTC. To evaluate the safety and efficacy of cediranib and lenalidomide in RAI refractory DTC, we performed a phase I and subsequent randomized phase II study of cediranib, with or without lenalidomide.

Patients and methods

Patients

Eligible patients were ≥ 18 years of age with an Eastern Cooperative Oncology Group (ECOG) score of 0–1, a life expectancy of >12 weeks, and a histologically or cytologically confirmed differentiated thyroid cancer (papillary, follicular, papillary/follicular variant, and Hürthle cell carcinoma subtypes). Furthermore, the disease must have been radiographically measurable, with evidence of disease progression in the preceding 12 months by standard Response Evaluation Criteria of Solid Tumors (RECIST) criteria. Patients were required to have normal organ and bone marrow function, and ineligible for further curative-intent surgery and/or radioactive iodine (RAI) treatment as reviewed at a multispecialty tumor board conference.

Patients who received chemotherapy or radiotherapy within 4 weeks prior to entering study, or with prior use of thalidomide or lenalidomide were excluded, as were patients with known brain metastases, poorly controlled hypertension, proteinuria >=1.5 gram protein/24 hours, any condition resulting in malabsorption, serious non-healing wound or ulcer, history of abdominal fistula or gastrointestinal perforation, history of cerebrovascular accident or transient ischemic attack, history of myocardial infarction, cardiac arrhythmias, stable or unstable angina, symptomatic congestive heart failure, or coronary or peripheral artery bypass graft or stenting within the 12 months prior to study entry. Prior treatment with VEGF pathway inhibitors or BRAF inhibitors was permissible.

Study design and conduct

This trial was designed as a phase I dose escalation with primary endpoint of maximally tolerated dose (MTD) and recommended phase 2 dose (RP2D), followed by a randomized phase II trial with a primary endpoint of progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), percent change in tumor size from baseline to the end of cycle 2, and safety and tolerability of cediranib, with or without lenalidomide. The study was conducted as a multicenter, open-label, phase

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I dose escalation and randomized phase II, comparative trial recruiting patients from twelve centers in the United States and Canada. Enrollment was performed at a participating site following approval by their respective institutional review boards, and all patients were provided written informed consent to participate.

Treatment

The phase I trial used a 3+3 design with the MTD defined as the highest dose level such that <2 of 6 patients experience dose-limiting toxicity (DLT) evaluating cediranib doses ranging from 20mg to 30mg daily, and lenalidomide doses ranging from 10mg on days 1–21 of a 28-day cycle to 20mg daily. In the phase I study of 15 evaluable patients, 4 were enrolled at the starting dose, 6 were enrolled in the +1 dose modification (cediranib 30mg daily and lenalidomide 15mg on days 1–21 of 28-day cycle), and 5 in the +2 dose modification (cediranib 30mg daily and lenalidomide 15mg daily). DLTs in the +2 dose modification were grade 3 fatigue and grade 3 mucositis. The DLT in the +1 modification was grade 3 fatigue. Since only 1 of 6 patients developed a DLT in the +1 group (cediranib 30mg daily and lenalidomide 15mg on days 1–21 of 28-day cycle) was determined as the dose schedule for the phase II portion of the trial.

In the phase II portion, patients were randomized in a 1:2 ratio to cediranib, with or without lenalidomide, stratified by prior therapy with a VEGF-pathway tyrosine kinase inhibitor (yes vs. no), and ECOG performance status (0 and 1 vs. 2). Treatment was continued until disease progression as assessed by RECIST, unacceptable toxicity, or patient or physician-initiated discontinuation.

Following the interim analysis, patients assigned to arm B discontinued lenalidomide and continued on cediranib alone.

Dose modifications for toxicities

Toxicities were evaluated using criteria from common terminology for adverse events (CTCAE) version 4.0. Dose reductions were required for grade ≥3 toxicities, with protocol management of hypertension, neutropenia, thrombocytopenia, fatigue, hand-foot-skin reaction, liver function test abnormalities, proteinuria, and venous thromboembolic events. Two dose reductions were permitted for cediranib to 20 mg and 15 mg daily, and two dose reductions were permitted for lenalidomide to 10 mg and 5 mg on days 1–21 of 28-day cycle.

Response assessment

Initial imaging evaluation was required within 28 days of enrollment. After starting treatment, disease re-evaluation occurred every 8 weeks using RECIST guidelines, and every 16 weeks after 18 cycles. Patients without evidence of anti-thyroglobulin antibodies continued to have thyroglobulin levels measured at each response assessment. All patients received thyroxine suppression therapy and thyroid stimulation hormone (TSH) levels were monitored pre-therapy and every 8 weeks during therapy. All patients included in the study were assessed for response to treatment. All patients who met eligibility criteria and started therapy were included in the main analysis of response rate.

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Statistical analysis

The primary endpoint of this study was PFS, which was estimated by the Kaplan-Meier method and compared between the two treatment arms using a stratified logrank test. PFS was calculated as the time from randomization to disease progression or death from any cause. A sample size of 110 patients (36 randomized to arm A and 74 to arm B) would have 85% power to detect a 75% improvement in median from 40 weeks (null hypothesis) to 70 weeks, corresponding to a hazard ration of 1.75, based on a one-sided test at alpha=0.10 significance level. An interim futility analysis was planned after half of the total number of projected events (40 of 80 projected events). The trial was planned to be stopped for futility if the conditional power at this time point was 15% or less, reducing the overall power of the study by 2–3%. Overall survival was analyzed in a manner similar to PFS. Objective response rates (CR or PR) were compared between the two treatment arms by chi-square test. Percent change in tumor size was compared using a nonparametric, Wilcoxon rank-sum test. Two patients who died prior to the cycle 2 were ranked at the extreme end of the distribution. Adverse event rates were tabulated by type, grade, and attribution to treatment.

Results

Patients and treatment

One hundred ten patients with RAI-refractory DTC were enrolled between 2010 and 2015 in phase II and randomized to treatment arm, 39 on arm A (cediranib alone), and 71 on arm B (cediranib with lenalidomide). Two patients withdrew consent prior to starting therapy and were considered non-evaluable, leaving 108 assessable for the primary endpoint, 39 on arm A and 69 on arm B. The futility analysis was performed after 40 events occurred, at which point a total of 39 patients had been randomized to arm A and 68 to arm B. One patient started treatment on arm B while the futility analysis was ongoing. 39 patients on arm A and 69 patients on arm B were analyzed for the final analysis (see Fig. 1).

Median age was 63 years, with a range from 24 to 86 years. Male patients were 41%, and females were 59%. 82% of patients were Caucasian. 96 patients enrolled in the United States and 12 enrolled in Canada. 23% of patients had received prior VEGF targeted therapy in both arms, and ECOG performance status was 0 or 1 in 95% and 96% in arm A and arm B, respectively.

Complete demographic data is listed in Table 1.

Response and survival

At time of futility analysis, the median PFS in arm A and arm B were 20.9 months (95% CI 10.9 to not reached) and 10.6 months (95% CI 7.3 to 14.6), respectively, with a stratified logrank test *p*-value of 0.26. The conditional power was 7.8%, reaching the futility boundary of <15%. Subsequently, patients on the combination arm discontinued lenalidomide and continued cediranib alone.

The final follow-up survival analyses in the intention-to-treat population occurred after a median follow-up of 11 months, at which time there were 81 PFS events. The median PFS in

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arm A was 14.8 months (95% CI 8.5 to 23.8), and in arm B was 11.3 months (95% CI 8.7 to 18.9), logrank p=0.36. The Kaplan-Meier curves for PFS can be seen in figure 2.

The response rates were similar for cediranib alone versus cediranib with lenalidomide. In arm A with cediranib alone, 17/39 patients had a partial response corresponding to a 44% objective response rate. In arm B with cediranib plus lenalidomide, 30/69 patients had a complete (1 patient) or partial response corresponding to a 43% objective response rate (p=0.99) (see waterfall plots in figure 3.

Twenty-five patients had received prior VEGF therapy while 83 patients were first line. PFS in the two treatment arms by prior VEGF treatment is shown in Figures 4A and 4B. First-line patients fared better than second line, but there were no significant differences between the two treatment arms (p=0.11 and p=0.17, respectively). Response rates in first-line patients were 16/30 (53%) in arm A vs. 23/53 (43%) in arm B, p=0.49. For second-line patients, response rates were 1/9 (11%) and 7/16 (44%), respectively, p=0.18.

The overall survival was assessed at time of final analysis and was similar between cediranib alone versus cediranib plus lenalidomide and was associated with 2-year survival rates of 64.8% (95% CI 43.3–86.4) and 75.3% (95% CI 59.4–91.0), respectively (logrank p=0.80). Kaplan-Meier curves for overall survival for arms A and B can be observed in figure 5.

The secondary endpoint of percent change in tumor size was assessed comparing baseline to the end of cycle 2, or two months after starting therapy. 38 patients in arm A and 63 patients in arm B had assessable imaging at the 2-month time-point for this endpoint. The median percent change in tumor size in arm A with cediranib alone was −12.5% (Interquartile range [IQR] −26.0% to 0.0%), and in arm B with cediranib plus lenalidomide was −4.2% (IQR −25.0% to 0.0%), Wilcoxon p=0.83).

Toxicity

Rates and types of treatment-related adverse events (AEs) during phase II were comparable to those seen in other studies of cediranib and lenalidomide [8–10]. Table 2 lists AEs prior to the discontinuation of lenalidomide that were grade 3 or higher and at least possibly related to the study drugs. The most common grade 3 or higher treatment-related AEs included fatigue (26% in both arms), hypertension (26% in arm A and 28% in arm B), and diarrhea (15% in arm A and 12% in arm B). Notable treatment-related grade 3 or higher AEs that were more common with cediranib plus lenalidomide compared with cediranib alone included proteinuria (5.1% in arm A compared with 8.7% in arm B), generalized muscle weakness (0% in arm A compared with 5.8% in arm B), and cytopenias including neutropenia (2.6% in arm A compared with 16% in arm B), thrombocytopenia (0% in arm A compared with 4.3% in arm B), and lymphopenia (0% in arm A compared with 4.3% in arm B). In arm B, after discontinuation of lenalidomide, there was one additional grade 3 hypercalcemia, one grade 3 hyponatremia, and one grade 3 leukocytosis reported.

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Discussion

Here we report the results of a large, randomized phase II trial of cediranib, with or without lenalidomide, in RAI-refractory recurrent and/or metastatic DTC. Despite results of early phase, single-arm trials, suggesting efficacy of lenalidomide and thalidomide in RAI refractory DTC[6, 7], our randomized results did not demonstrate an improvement in PFS with the addition of lenalidomide to cediranib alone in this patient population, highlighting the importance of randomized trials in this setting.

Interestingly, our study demonstrated promising activity and tolerable safety profile for cediranib alone, which was associated with a median PFS of 14.8 months and an objective response rate of 44%. Since the completion of this study, randomized trials have demonstrated activity of multiple VEGF targeted inhibitors including lenvatinib[3, 4], sorafenib[5], and vandetanib[11]. The previously reported median PFS for lenvatinib ranges from 13 to 18 months and reported objective response rates ranging from 50% to 65%[3, 4]. Sorafenib in this patient population is associated with a median PFS of 10.8 months[5], and vandetanib is associated with a median PFS of 11.1 months[11]. Other VEGF targeted TKIs such as axitinib, pazopanib, and sunitinib have been evaluated in non-randomized studies demonstrate median PFS ranging from 12.8 months to 18.1 months, and objective response rates ranging from 22% to 49%[12–15]. Our results for cediranib demonstrating a median PFS of 14.8 months and objective response rate of 44% seems to be in similar range compared with other multitargeted TKIs including angiogenesis and, specifically, VEGFR targeted pathways.

Recently, there has been enthusiasm towards mutation specific inhibitors in a subset of RAI-refractory recurrent and/or metastatic DTC. Rearrangements of one of the neurotrophic tropomyosin receptor kinase (NTRK) 1–3 fusions can occur in approximately 1–2% of DTC[16]. Although rare, when present highly selective inhibitors of TRK kinases have demonstrated impressive objectives response rates of around 71%[17]. Other targetable changes include rearrangements involving the RET gene, particularly in papillary thyroid cancer, in approximately 6–10%, in which selective RET kinase inhibitors have demonstrated objective response rates ranging from 79% to 89%[18–20]. Interestingly, inhibitors of BRAF, with or without a MEK inhibitor in RAI-refractory DTC with BRAFV600E mutations, are associated with lower objective response rates of approximately 30% to 54%[21, 22]. Similar to other multitargeted antiangiogenic TKIs, our objective response rate of 44% with cediranib is similar to BRAF targeting and remains lower than selective inhibitors targeting NTRK and RET and therefore these remain preferred treatments in the rare subset of patients with RAI refractory DTC with these specific targets.

Yet, despite recent advances in selective targeted treatments in a rare subset of RAI-refractory DTC, improved therapeutic strategies are urgently needed. Despite meaningful responses and improvements in PFS that have been demonstrated with multitargeted antiangiogenic TKIs, complete responses continue to be rare, and are associated with toxicities which have a substantial impact on quality of life, particularly with long-term use in the setting of RAI-refractory DTC[23]. This highlights the need for investigating novel

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therapeutic strategies in RAI-refractory DTC progressed on or ineligible for VEGF targeted TKIs.

Limitations of his study include that mutational status for patients was not known and there was no alternative antiangiogenic TKI as the backbone. Nevertheless, our study contributes to the expanding body of literature regarding the efficacy of VEGFR inhibitors in RAI-refractory DTC. The lack of improved efficacy with the addition of immunomodulatory agent lenalidomide, despite promising data regarding potential single-agent activity, highlights the need for investigating novel therapeutic strategies to improve patient outcomes in this setting in RAI-refractory recurrent and/or metastatic DTC.

Conclusion

Antiangiogenic TKIs are reaffirmed as the standard of care treatment approach in RAI-refractory DTC while the addition of immunomodulatory agents does not improve progression-free survival, demonstrating alternative combinatorial approaches warrant evaluation in large multicenter studies.

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Highlights

- This randomized phase II trial demonstrated promising activity of cediranib with a median PFS of 14.8 months and an objective response rate of 44%.
- The addition of lenalidomide to cediranib alone did not improve progression-free or overall survival.
- This highlights the activity of antiangiogenic TKIs in RAI-refractory differentiated thyroid carcinoma, and the need for novel combinatorial therapeutic strategies in this disease.

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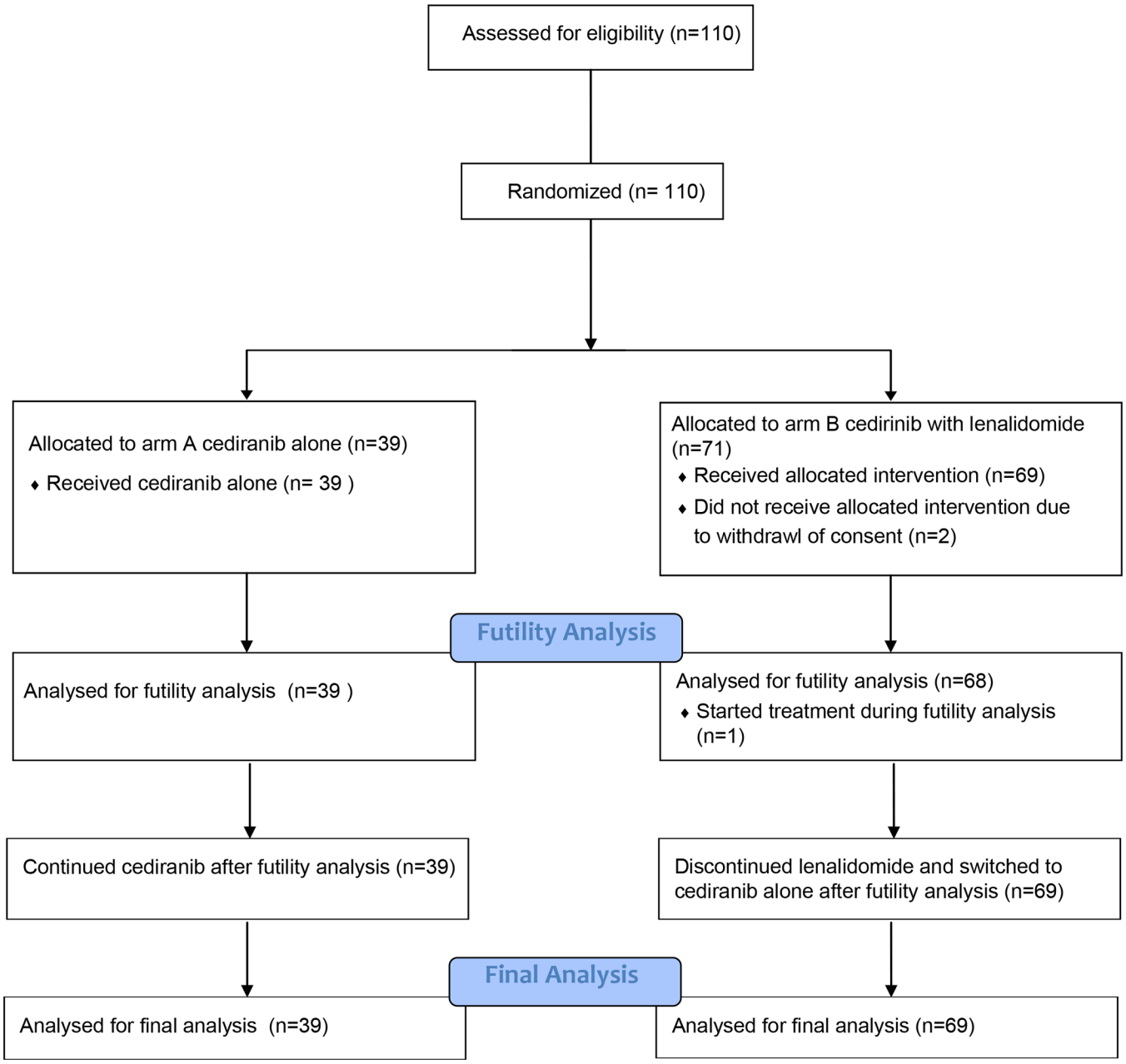

Figure 1:
CONSORT diagram demonstrating patient flow through enrollment, randomization, assigned treatment, futility analysis, and final analysis.

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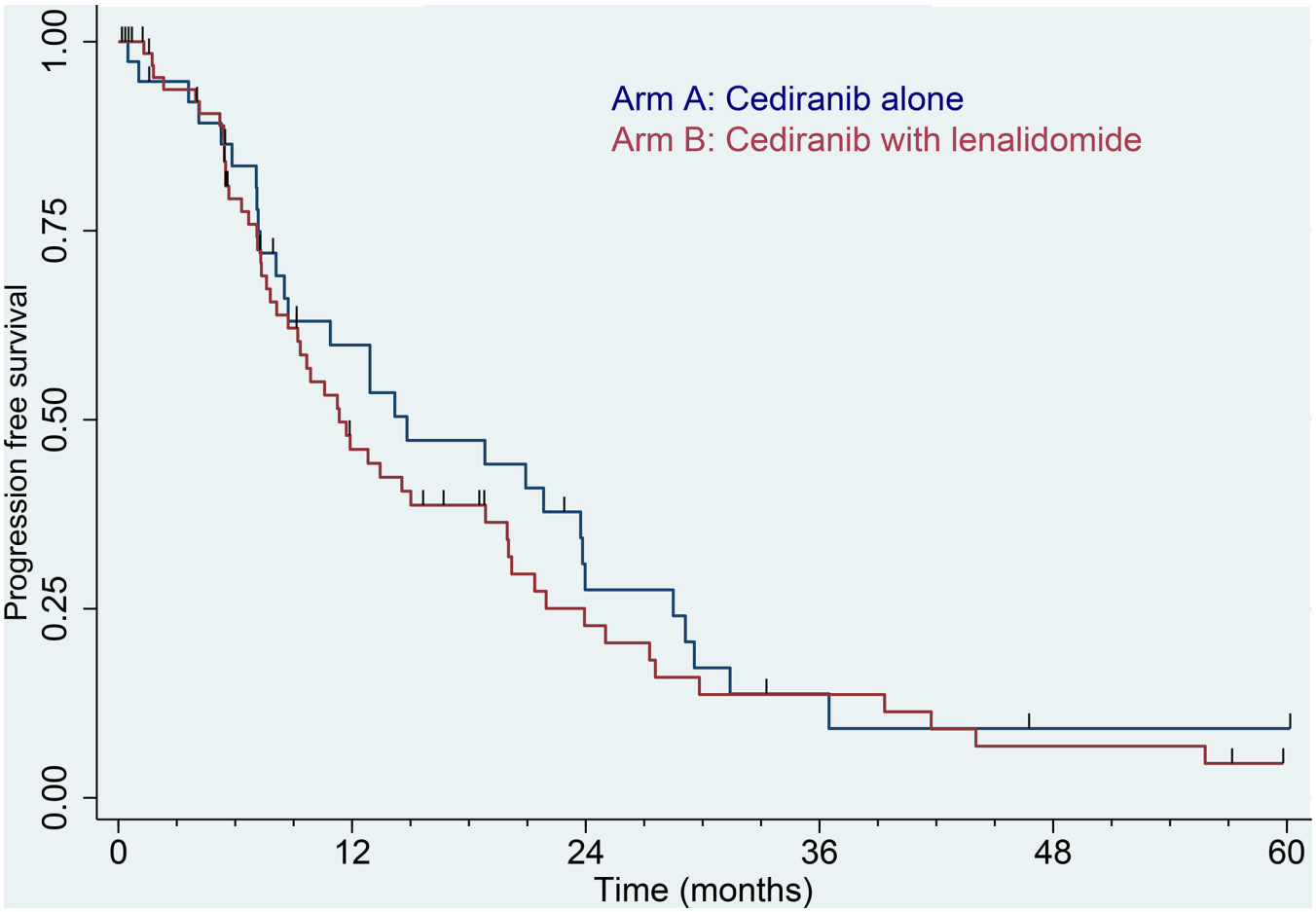

Figure 2:

Kaplan–Meier curve for progression-free survival by RECIST. Blue: Arm A (cediranib alone), N = 39. Red: Arm B (cediranib with lenalidomide), N = 69. ECIST = Response Evaluation Criteria in Solid Tumors. Tic marks denote censored observations.

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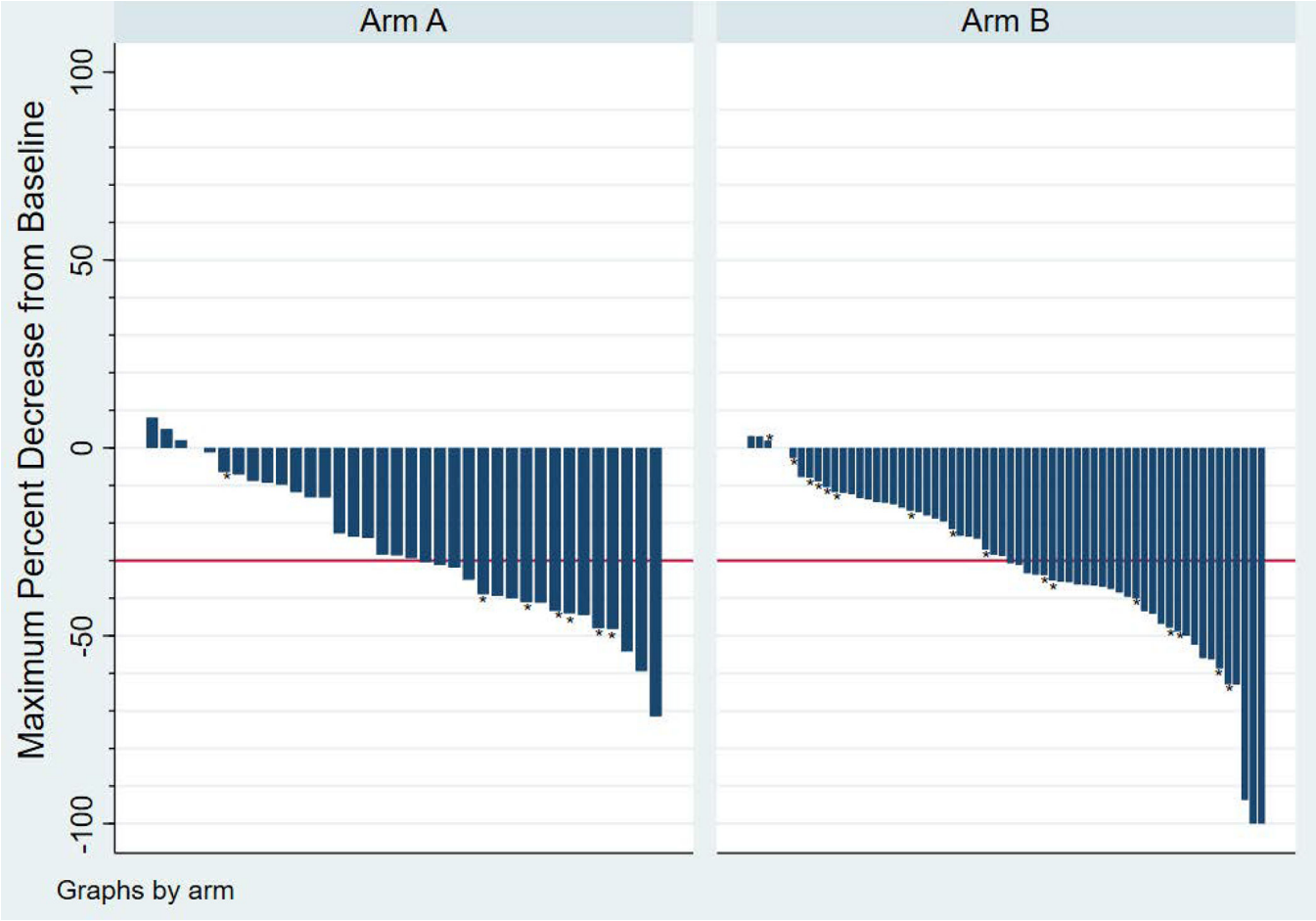

Figure 3:
Waterfall plots demonstrating best overall response by RECIST in Arm A and Arm B respectively. Two additional patients who died prior to two months are excluded (both Arm A). * denotes patients who had a new lesion.

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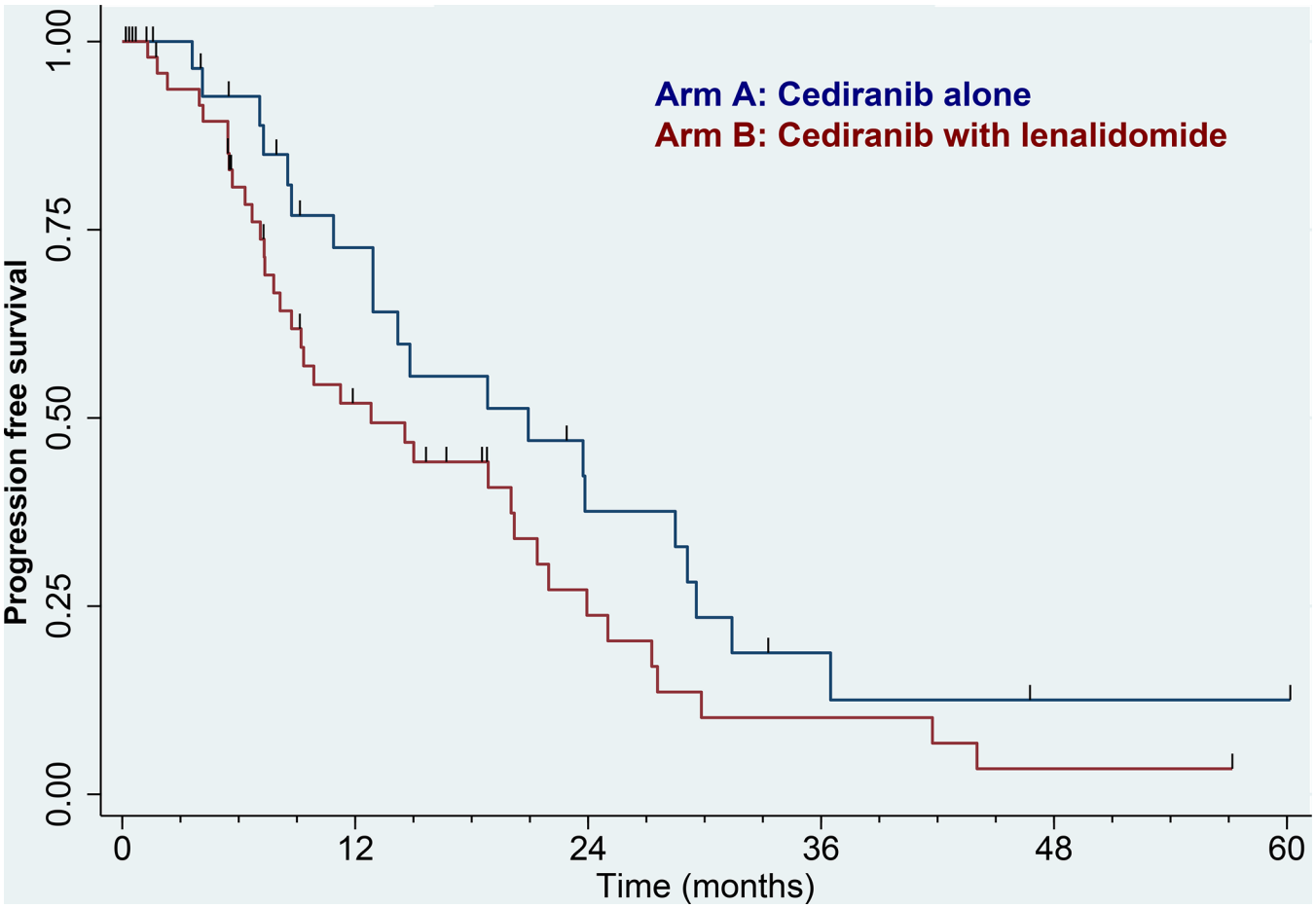

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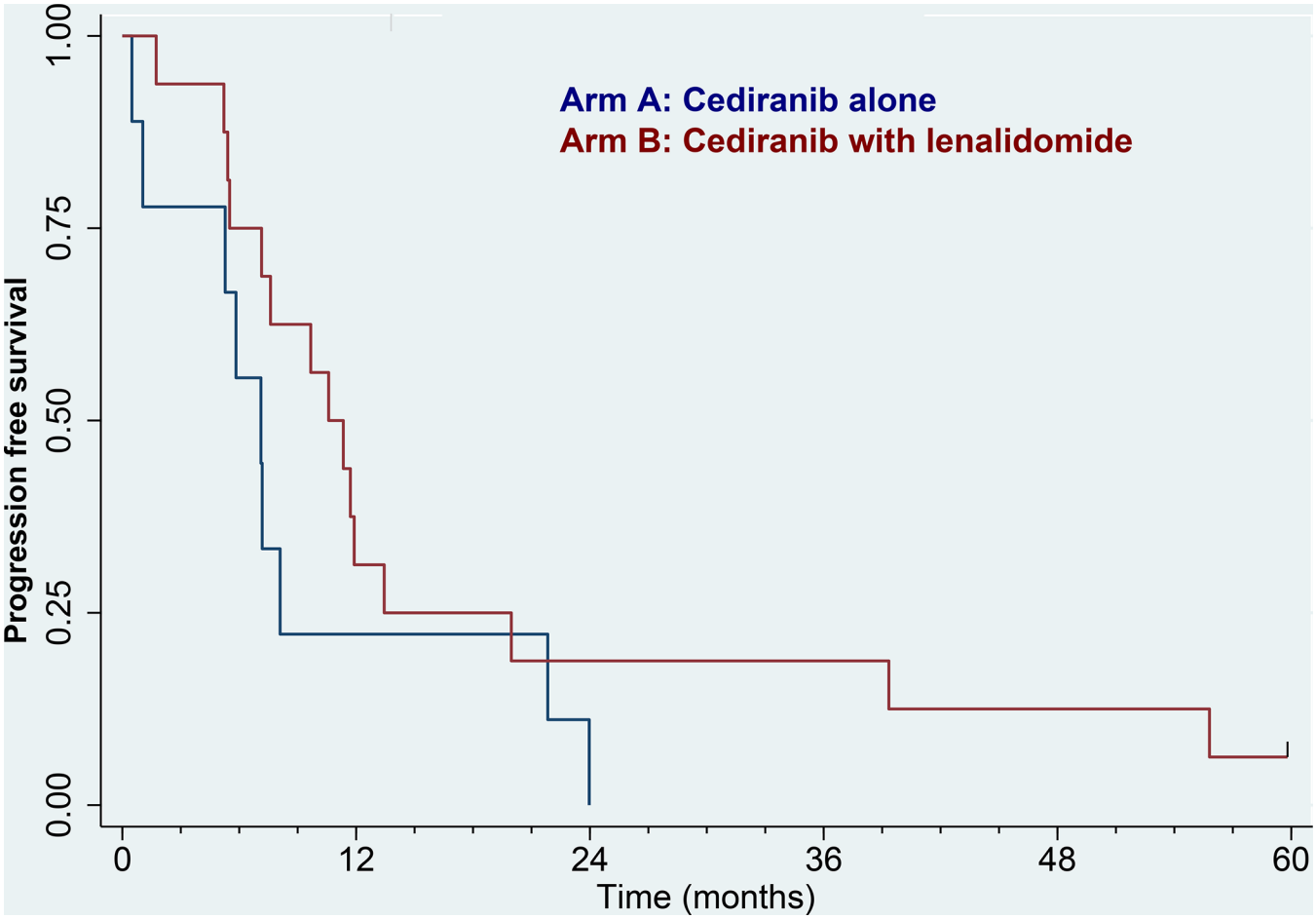

Figure 4:

Kaplan–Meier curve for progression-free survival by RECIST. 4A) No prior VEGF therapy. Blue: Arm A (cediranib alone), N = 30. Red: Arm B (cediranib with lenalidomide), N = 53. 4B) Prior VEGF therapy. Blue: Arm A (cediranib alone), N = 9. Red: Arm B (cediranib with lenalidomide), N = 16. Tic marks denote censored observations.

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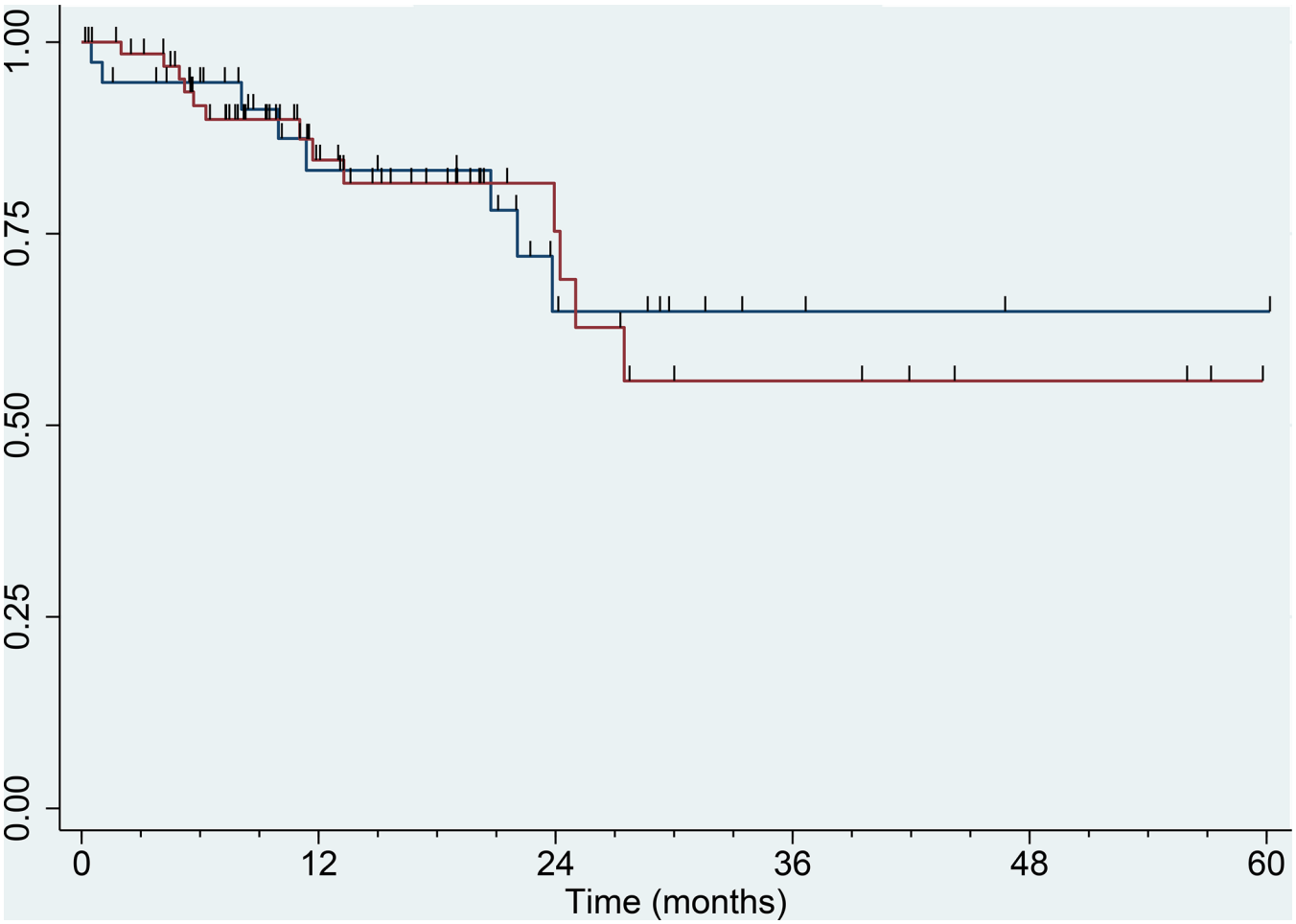

Figure 5.

Kaplan–Meier curve for overall survival. Blue: Arm A (cediranib alone), N = 39. Red: Arm B (cediranib with lenalidomide), N = 69. Tic marks denote censored observations.

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Table 1:

Patient demographics

	Arm A (cediranib alone)	Arm B (cediranib with lenalidomide)	Total
	No. (overall %, n=39)	**No. (overall %, n=69)**	**No. (overall %, n=108)**
Sex			
Male	24 (62%)	40 (58%)	64 (59%)
Female	16 (38%)	29 (42%)	44 (41%)
Age, years	**Median (range)**	**Median (range)**	**Median (range)**
	62 (27 to 86)	64 (24–83)	63 (24–86)
ECOG PS			
0 or 1	37 (95%)	66 (96%)	103 (95%)
2	2 (5%)	3 (4%)	5 (5%)
Race			
White	30 (77%)	59 (86%)	89 (82%)
Asian	3 (8%)	4 (6%)	7 (6%)
Black or African American	5 (13%)	2 (3%)	7 (6%)
American Indian or Alaskan native	1 (3%)	0 (0%)	1 (1%)
More than one race	0 (0%)	1 (1%)	1 (1%)
Unknown or not reported	0 (0%)	3 (4%)	3 (3%)
Region of enrollment			
United States	34 (87%)	62 (90%)	96 (89%)
Canada	5 (13%)	7 (10%)	12 (11%)
Prior VEGF targeted therapy			
Yes	9 (23%)	16 (23%)	25 (23%)
No	30 (77%)	53 (77%)	83 (77%
Thyroid cancer subtype			
Papillary	19 (73%)	26 (44%)	45 (64%)
Follicular	1 (4%)	7 (16%)	8 (11%)
Squamous cell	2 (8%)	1 (2%)	3 (4%)
Adenocarcinoma	0 (0%)	2 (5%)	2 (3%)
Not otherwise specified	4 (15%)	8 (18%)	12 (17%)
Missing	13	25	

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Table 2:

Adverse events that were grade 3 or higher and at least possibly related to study drug(s).

	Arm A (cediranib alone), n (%)	Arm B (cediranib with lenalidomide) (%)
Fatigue	10 (26)	18 (26)
Hypertension	10 (26)	19 (28)
Diarrhea	6 (15)	8 (12)
Hand foot syndrome	6 (15)	5(7.2)
Oral mucositis	3 (7.7)	3 (4.3)
Proteinuria	2 (5.1)	6 (8.7)
Generalized muscle weakness	0 (0)	4 (5.8)
Anorexia	3 (7.7)	2 (2.9)
Syncope	2 (5.1)	1 (1.4)
Vomiting	0 0)	1 (1.4)
Hypophosphatemia	1 (2.6)	4 (5.8)
Hypokalemia	1 (2.6)	3 (4.3)
Thromboembolic event	1 (2.6)	2 (2.9)
Neutropenia	1 (2.6)	11 (16)
Thrombocytopenia	0 (0)	3 (4.3)
White blood cell count decreased	0 (0)	3 (4.3)
Stroke	0 (0)	1 (1.4)
Sinus bradycardia	0 (0)	1 (1.4)
Rash maculo-papular	0 (0)	2 (2.9)
Pneumothorax	0 (0)	1 (1.4)
Pharyngolaryngeal pain	0 (0)	1 (1.4)
Pancreatitis	0 (0)	1 (1.4)
Oral dysesthesia	0 (0)	1 (1.4)
Nausea	0 (0)	1 (1.4)
Muscle weakness upper limb	0 (0)	1 (1.4)
Lung infection	0 (0)	1 (1.4)
Leukocytosis	0 (0)	1 (1.4)
Hypophosphatemia	0 (0)	4 (5.8)
Hypokalemia	0 (0)	3 (4.3)
Hypocalcemia	0 (0)	3 (4.3)
Hypercalcemia	0 (0)	1 (1.4)
Hepatobiliary disorder-other	0 (0)	1 (1.4)
Fall	0 (0)	1 (1.4)
Ejection fraction increased	0 (0)	1 (1.4)
Ear pain	0 (0)	1 (1.4)
Dyspnea	0 (0)	2 (2.9)
Dizziness	0 (0)	1 (1.4)

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	Arm A (cediranib alone), n (%)	Arm B (cediranib with lenalidomide) (%)
Delirium	0 (0)	1 (1.4)
Dehydration	0 (0)	2 (2.9)
Creatinine increased	0 (0)	1 (1.4)
Colitis	0 (0)	1 (1.4)
Blood bilirubin increased	0 (0)	2 (2.9)
Aspartate aminotransferase increased	0 (0)	1 (1.4)
Anemia	0 (0)	1 (1.4)
Weight loss	1 (2.6)	3 (4.3)
Lymphocyte count decreased	2 (5.1)	3 (4.3)
Hyponatremia	1 (2.6)	1 (1.4)
Lymphopenia	0 (0)	3 (4.3)
Alanine aminotransferase increased	0	3 (4.3)
Peripheral ischemia	1 (2.6)	0 (0)
Abdominal pain	1 (2.6)	1 (1.4)