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Randomized Phase II Study of Radiotherapy and Paclitaxel with Pazopanib or Placebo in Anaplastic Thyroid Cancer: NRG/RTOG 0912

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Abstract

Background: Anaplastic thyroid cancer (ATC) is a rare and aggressive cancer with no standard radiotherapy-based local treatment. Based on data suggesting synergy between pazopanib and paclitaxel in ATC, NRG Oncology conducted a double-blinded, placebo-controlled, randomized phase II clinical trial comparing concurrent paclitaxel and intensity modulated radiation therapy (IMRT) with pazopanib or placebo in the USA at 34 institutions with the aim of improving overall survival.

Methods: Eligible patients had ATC pathologic diagnosis, ≥ 18 years old, any TNM stage, Zubrod 0–2, no recent hemoptysis/bleeding, and no brain metastases. Initially, a run-in was done to establish safety. The experimental arm (pazopanib) evaluated 2–3 weeks of weekly paclitaxel (80 mg/m^2) intravenously and daily pazopanib suspension 400 mg orally followed by concurrent weekly paclitaxel (50 mg/m^2), daily pazopanib (300 mg), and IMRT 66 Gy daily fractionated. The control arm (placebo) replaced pazopanib with placebo. Patients were randomized (1:1) by permuted block randomization through NRG with stratification by metastatic disease and blinded to all. The primary endpoint was overall survival (OS) in eligible intent-to-treat randomized patients (0·15 one-sided alpha, 80% power). Safety in patients who received at least one dose

of study treatment was a secondary endpoint. This trial is registered with Clinicaltrials.gov, NCT01236547.

Findings: Run-in showed safety of the final dosing regimen based on 2 out of 9 subjects having AEs of predefined concern. Final results showed 89 patients (71 eligible; male:female 34:37) were accrued from 6/23/14–12/30/16. OS was not significantly higher with pazopanib than with placebo (hazard ratio[pazopanib/placebo]=0·86 95% CI 0·52, 1·43; p=0·28). One-year OS rates for pazopanib and placebo arms were 37·1% (95% CI 21·1, 53·2%) and 29·0% (13·2, 44·8%), respectively. The grade 3–5 treatment-related adverse event (AE) rates were 88·9% and 85·3% for the pazopanib and placebo arms, respectively (p=0·73). Most common clinically significant grade 3–4 AEs (numbers listed pazopanib;pacebo) in the 70 eligible treated patients (36;34) for toxicity were dysphagia [13(36%);10(29%)], radiation dermatitis [8(22%);13(38%)], alanine aminotransferase [12(33%);0]; aspartate aminotransferase [8(22%);0], oral mucositis [5(14%);8(24%)]. There was one grade 5 treatment-related AE on each arm (pazopanib-sepsis; placebo-pneumonitis). Treatment-related serious AEs were reported for 16 (44%) and 12 (35%) patients on pazopanib and placebo, respectively. The most common SAEs were dehydration and thromboembolic event (3 [8%] each) on pazopanib and oral mucositis (3 [8%]) on placebo.

Interpretation: This is the largest randomized ATC study that has completed accrual demonstrating feasibility in the network group setting. Although a statistically significant improvement in OS was not seen in the pazopanib arm, hypothesis-generating data was generated that may warrant further investigation.

INTRODUCTION

Anaplastic thyroid cancer (ATC) is a rare, highly aggressive cancer with an extremely poor prognosis. Given its presentation of rapidly growing neck mass, which can cause asphyxiation where local control of the neck disease is crucial, multimodality treatment consisting of surgery, chemotherapy, and radiation is often needed despite distant metastasis on presentation[1]. There has been evidence that when resectable, surgery followed by postoperative radiotherapy and chemotherapy can result in better patient outcomes than non-surgical treatment[2].

Due to its rarity, ATC had never been subject to a large completed randomized therapeutic trial, considerably limiting evidence-based therapeutic progress. The data to date are largely based on single-institution retrospective studies. Uniformly, the dose of radiation, at least 60 Gy to the thyroid, is critical to improving survival in patients even with metastatic disease, emphasizing the role of local control in oncologic outcomes[3,4]. Based on data indicating *in vitro* and *in vivo* synergy between pazopanib and paclitaxel in ATC[5], NRG Oncology accordingly organized, implemented, and completed accrual to the very first multicenter randomized phase II study for ATC, comparing outcomes resulting from concurrent paclitaxel and intensity-modulated radiotherapy (IMRT) combined with either pazopanib or placebo, following the establishment of the safety of this combination in a run-in dose-finding study.

METHODS

Study design and participants

NRG/RTOG 0912 was a multi-institutional phase II randomized, double-blinded, placebo-controlled clinical trial done in 34 institutions in USA and conducted by the National Cancer Institute's Clinical Trial Network Group NRG Oncology. Prior to the initiation of the randomized study, a safety run-in was performed to evaluate the combination of paclitaxel, pazopanib, and IMRT. Due to concerns about the pazopanib pill tolerability/delivery, and not due to toxicity concerns, the run-in was repeated twice using a pazopanib slurry.

Eligible patients had pathologically proven ATC of any TNM stage (central review required, but not necessary to start treatment), Zubrod Performance Status 0–2, adequate hematologic and liver function, normal basic metabolic panel, no active invasive malignancy (except non-melanomatous skin cancer or controlled localized prostate cancer), controlled blood pressure, no recent hemoptysis in the prior 6 months (unless clearly not from a pulmonary source), no prior overlapping radiotherapy volumes, and were 18 years or older. No prior treatment for ATC was allowed. Patients were excluded if they required heparin, had a significant cardiovascular condition in the prior 6 months, and had increased risk of gastrointestinal bleeding including inflammatory bowel disease.

Laboratory tests required to assess eligibility included serum electrolytes (sodium, potassium, chloride, carbon dioxide, BUN, creatinine, magnesium), liver function tests (serum glutamic oxaloacetic transaminase/aspartate transaminase, serum glutamic pyruvic transaminase/alanine transaminase, total bilirubin, and albumin), complete blood cell count (white blood cells, hemoglobin, platelets, absolute neutrophil count), prothrombin time/partial thromboplastin time, and spot urine for protein and creatinine.

Local IRB approval was required, and all patients had to give written informed consent.

Randomisation and masking

Eligible patients were randomly assigned (1:1) by permuted block randomization to receive pazopanib or placebo. Randomization was stratified by metastatic disease (M0 vs. M1 vs. MX). Investigators at each institution registered patients using an electronic system. Treatment assignment was centrally generated at the NRG Oncology Statistics and Data Management Center (Philadelphia, PA, USA) and provided to the institution when the patient was registered. All investigators, patients, and funders of the study were masked to group allocation. The active drug and matching placebo were identical in packaging, labelling, appearance, and schedule of administration to preserve the masking.

Procedures

Based upon the results of our safety run-in phase, all patients received paclitaxel 80 mg/m^2 intravenously weekly for 2–3 weeks, followed by weekly paclitaxel 50 mg/m^2 administered concurrently with intensity-modulated radiation therapy (IMRT) 66 Gy given in 33 daily fractions (2 Gy fractions). Subjects received either placebo (placebo) or pazopanib slurry 400 mg daily (pazopanib) administered concurrently with weekly paclitaxel (80 mg/m^2/

week) before starting IMRT, and then their corresponding treatment of pazopanib or placebo 300 mg daily was given concurrently with IMRT and weekly paclitaxel (50 mg/m^2/week for either 6–7 weeks or to the end of IMRT). Pazopanib/placebo slurry could be taken either orally or through a feeding tube. No paclitaxel or pazopanib/placebo was given after the completion of IMRT. The last dose of pazopanib/placebo was taken on the last day of IMRT. Pazopanib slurry and placebo were provided by Novartis. Paclitaxel was obtained as standard of care. Protocol treatment was discontinued due to disease progression, unacceptable treatment delays and adverse events (AEs), intercurrent illness that prevented further administration of treatment, unacceptable noncompliance per investigator's judgement, consent withdraw, or any patient's condition that render the patient unacceptable for further treatment per investigator's judgement. If protocol treatment was discontinued, follow up and data collection continued as specified in the protocol.

During treatment, laboratory tests (CBC, electrolytes) were done weekly. Liver function tests were required every other week. Patients were also required to have weekly physical exams and blood pressures. Both paclitaxel and pazopanib were allowed up to 4 dose reductions. If treatment was held more than 21 days due to an AE, they need permission from one of the study's principal investigators before deciding if they could continue on treatment.

Prior to starting treatment, imaging of the neck, chest, and abdomen were required [imaging of the neck must include contrast if computed tomography (CT) or gadolinium if magnetic resonance imaging (MRI)]. Positron emission tomography (PET) with CT was strongly recommended. Control of blood pressure (better than 140/90) and complete healing of surgical wounds were required prior to starting treatment. Suppression of the thyroid stimulating hormone during treatment was highly recommended since there could also be a component of differentiated thyroid cancer. Imaging (CT or MRI) of the brain, neck, chest, and abdomen were required 2–4 weeks after completing IMRT. Imaging (CT, MRI, or PET/CT) covering the neck, chest, and abdomen were then required every 3 months after IMRT for 2 years.

Imaging was highly recommended after 2 years. Physical exams and AE evaluations were every 3 months for 2 years, then every 6 months for the 3rd year, and then annually.

Outcomes

Since there was limited experience with pazopanib added to concurrent chemoradiation for treatment of patients with anaplastic thyroid cancer, AEs were evaluated in a nonrandomized run-in phase prior to phase II. AEs were graded with Common Terminology Criteria for Adverse Events (CTCAE) version 4. AEs rated as definitely, probably, or possibly related to treatment were considered treatment related. AE of concern was defined as treatment-related grade 4 hemorrhage, grade 4 febrile neutropenia, grade 5, or discontinuation of treatment due to toxicity (< 75% of planned radiation therapy delivered). The incidence of AE of concern was assumed to be ≤ 20% and an increase of ≥ 25% was considered unacceptable. A 2-stage design based on the binomial distribution was used. Stage 1 enrolled 11 patients (9 analyzable). If ≥ 5 patients experienced AE of concern, the study would not continue to stage 2; if ≤ 4 patients experienced AE of concern, the study would continue to stage

2. Stage 1 was repeated twice following amendments to the protocol regimen unrelated to the toxicities described above. The second stage 1 changed the mode of pazopanib delivery was from oral to oral suspension. The third stage 1 reduced the pre-radiation pazopanib dose from 600 mg daily to 400 mg daily. Stage 2 required 15 patients randomized to the pazopanib arm during phase II. With 15 more patients and a total of 24, ≤ 8 patients with AE of concern would be considered acceptable. If ≥ 9 patients had AE of concern, the trial would be stopped.

The phase II primary endpoint was overall survival (OS), defined as the time from randomization to death due to any cause. Patients alive at the time of analysis were censored at the last follow-up (administrative censoring; all patients were potentially followed for ≥ 3 years). Secondary endpoints were response to treatment, local-regional failure (LRF), AEs of concern, and other AEs. At 2–4 weeks after treatment, response in patients with baseline measurable disease was assessed via RECIST 1.1. LRF was defined as the time from randomization to local-regional relapse/progression in the thyroid bed or regional lymph nodes; death due to any cause was considered a competing risk. AEs of concern were defined as in the run-in. Other AEs were defined as treatment-related grade 3–5, excluding those in the AEs of concern endpoint defined above. Response/progression was not centrally reviewed.

Statistical analysis

The null primary hypothesis was no OS difference between the experimental and control arm, and the alternative hypothesis that the experimental improves OS. This phase II screening[6], superiority trial was designed to detect a ≥ 37·5% reduction in the death hazard rate, favoring the addition of pazopanib (*i.e.*, HR=0·625). If OS follows an exponential distribution, this equated to an improvement in 1-year OS from 19% for placebo (yearly hazard 1·66) to 35·4% for pazopanib (yearly hazard 1·04), which was deemed by the study team at the time of study design as a clinically meaningful improvement. At the time of the design of this trial, the best available data came from a population-based study that reported a 1-year survival rate of 19% with standard of care treatment[7]. With a 1-sided alpha of 0·15, the log-rank test, and 80% statistical power, 71 deaths were required from 79 eligible randomized patients. The alpha level of 0·15 was deemed consistent with the screening nature of the trial and had into consideration the lack of treatments for this aggressive disease, thus a higher false positive rate is acceptable while a higher false negative rate is not. Allowing for 10% of patients being ineligible or lost to follow-up, the total targeted enrollment was 88. Due to a higher than projected rate of ineligibility, the study team concluded that the required number of OS events for the final analysis was unlikely to be met. Therefore, the trial protocol was amended in a blinded fashion regarding clinical outcomes such that the final analysis was to be performed after all eligible randomized patients were potentially followed for 3 years. With 1-sided alpha of 0·1379, and 61 observed deaths from 71 patients, the time-driven primary efficacy analysis had 77% power. OS rates were estimated by the Kaplan-Meier method, and treatment groups were compared by 1-sided log-rank test (1-sided alpha of 0·1379 after accounting for one efficacy interim analysis). The OS analysis population was randomized and eligible patients. Hazard ratios were estimated by Cox proportional hazards models. A protocol-specified sensitivity

analysis for OS was performed on the modified intent-to-treat population limited to patients at risk for death due to ATC (*i.e.*, patients without ATC were excluded). One-year OS rates and median OS using Brookmeyer and Crowley method (post-hoc) by arm with 95% confidence intervals (CI) were also estimated.

One pre-specified interim treatment comparison (primary endpoint only) was performed at 50% of information (35 deaths; Appendix p1).

Additional analyses, not specified in the protocol, for OS included the log-rank test and Cox model stratified by M stage (stratification factor), and multivariable Cox models with M stage, gender, Zubrod performance status, prior surgery, TNM stage, and arm by M stage interaction. Proportional hazards assumption in Cox models were tested using the Kolmogorov-type supremum test. Based on the early results of the fosbretabulin study where OS did not show a significant difference, but 1-year OS was significantly different[6] and the relevance of 1-year OS when designing this trial, 1-year OS rates between arms were compared using a post-hoc analysis with a Wald-type test based on Kaplan-Meier estimates and normal approximation (0·15 one-sided significance level).

Response rates, rates of grade 3–5 AEs and AEs of concern were estimated along with Wilson score 95% confidence intervals, and treatment groups were compared by Fisher's exact test (0·05 significance level). Analysis of AE endpoints was limited to eligible patients who started protocol treatment and response rates were evaluated in patients with baseline measurable disease and scans 2–4 weeks after treatment. LRF rates were estimated by the cumulative incidence method, and treatment groups with randomized eligible patients were compared by 1-sided cause-specific log-rank test (0·15 significance level). LRF rates at 6 and 12 months and 95% CIs in each arm were also estimated based on the cumulative incidence method. Hazard ratios for LRF were estimated by cause-specific Cox proportional hazards models to assess the direct effect of treatment on LRF. Gray's test and Gray-Fine method were also used to supplement the cause-specific LRF analysis.

Given that this was a screening phase II trial in a rare population, no adjustments were specified in the protocol for multiple testing of secondary endpoints.

The NRG Oncology Data Monitoring Committee (DMC) evaluated the trial biannually for accrual and safety, as well as at the protocol-specified interim futility analysis. All analyses were performed in SAS version 9.4. This trial was registered with Clinicaltrials.gov, NCT01236547. The corresponding author had full access to all of the data and the final responsibility to submit for publication. All authors had access to all the data reported in the study.

Role of the funding source

The funding source of the study was the NIH and Novartis. Novartis had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Run-in stage I enrolled 11 patients between October 28, 2010 and July 6, 2011 and showed an acceptable AE of concern rate (0/9; see Appendix p2). The second stage I enrolled 11 patients between March 8, 2012 and January 18, 2013 and showed an acceptable AE of concern rate (1/9). However, additional analysis showed that 4 patients required pazopanib to be held (and eventually dose reduced) due to elevations in hepatic enzymes as specified in the protocol. Analysis of the available pharmacokinetic data showed this occurred in patients with the highest pazopanib serum levels at day 15 leading to the addition of the third stage 1. The third stage 1 enrolled 12 patients between July 31, 2013 and October 23, 2013 and showed an acceptable AE of concern rate (2/9). Accrual to the randomized phase II opened on June 23, 2014 and analysis of stage 2 showed the AE of concern rate was acceptable (2/24).

Between June 23, 2014 and December 30, 2016, 89 patients were randomized to pazopanib (n=42) or placebo (n=47). Six (14%) pazopanib patients and 12 (26%) placebo were excluded from analysis (Figure 1). Of those excluded, 15 (83%) were due to baseline labs or imaging studies not done or done outside the protocol-defined eligibility period. One eligible patient did not receive any protocol treatment. Baseline characteristics for the eligible group (pazopanib, n=36; placebo, n=35) and the total at risk for ATC death for sensitivity analysis (pazopanib, n=41; placebo, n=47) are listed in Table 1 and Appendix p3–4. Median age was 65 years (IQR 58, 68); 37 (52%) were female, 48 (68%) were white, 39 (55%) had Zubrod performance status 1–2, 48 (68%) had T4b disease, and 52 (73%) had N1 disease.

There were 61 deaths at final analysis: 31 (86%) in the pazopanib group and 30 (86%) in the placebo group; median follow-up for the remaining 10 patients was 34·7 months (IQR 0·3, 47·8) (Figure 2). Median OS was 5·7 months (95% CI 4·0, 12·8) for pazopanib and 7·3 months (95% CI 4·3, 10·6) for placebo (1-sided log-rank test p=0·28 for OS). The estimated HR (pazopanib/placebo) was 0·86 (85% lower confidence bound [LCB] 0·66; 95% CI 0·52, 1·43). Therefore, this trial did not find evidence against the null hypothesis of no OS benefit of adding pazopanib but was able to (with 85% confidence) rule out a treatment effect larger than HR=0·66, which is above the targeted HR (0.625).

Post-hoc survival analysis stratified or adjusted by M stage yielded similar results (Appendix p5). Statistical tests to assess the proportional hazards assumption in Cox models did not suggest serious violations (Appendix p6). One-year OS estimates were 37·1% (95% CI 21·1, 53·2%) for pazopanib and 29·0% (95% CI 13·2, 44·8%) for placebo. One-year OS rate for pazopanib was not significantly higher than placebo, with a difference of 8·2% (95% CI −14·3, 30·6%; 85% lower confidence bound [LCB] −3·7%, p=0·24). In multivariable analyses for OS, the only significant factor was M stage (HR[M1/MX vs. M0]=2·73; 95% CI 1·49, 5·00; p=0·0011) (Appendix p7).

Sensitivity analysis limited to 88 patients at risk for death due to ATC (Appendix p8) yielded similar results for OS: 0·82 (95% CI 0·52, 1·30); p=0·20. Median OS was 5·7 months (95% CI 4·0, 12·8) for pazopanib and 7·3 months (95% CI 4·9, 9·4) for placebo. The treatment effect HR adjusted by M stage was 0·79 (95% CI 0·50, 1·26). The only significant

prognostic factor was M stage with an HR (M1/MX/unknown vs. M0) of 2·15 (95% CI 1·30, 3·54; p=0·0027). One-year OS estimates were 36·1% (95% CI 21·0, 51·1%) for pazopanib and 23·2% (95% CI 10·7, 35·8%) for placebo (difference of 12.8%, 95% CI −6·8, 32·4%; 85% LCB 2·5%; p=0·10). Post-hoc analysis yielded HR (pazopanib/placebo) of 1·21 (95% CI 0·58, 2·52) in M1/MX patients and 0·65 (95% CI 0·32, 1·31) in M0 patients (treatment by M stage interaction p=0·23) (Appendix p9).

Post-hoc analysis of prior surgery showed no apparent differences in OS, overall or in M stage subgroups (Appendix p10–12).

LRF is shown in Figure 3. The treatment effect cause-specific HR estimate is 1·22 (95% CI 0·55, 2·67; p=0·69). The LRF rates at 6 months and 1 year were 20% (95% CI 8·6, 34·8) and 28·6% (95% CI 14·6, 44·3) for pazopanib and 27·3% (95% CI 13·3, 43·3) and 33·6% (95% CI 17·9, 50·0) for placebo, respectively. Gray's test p-value was 0·6331 with a sub-distribution HR of 1·20 (95% CI 0·55, 2·60). Except for the non-informative censoring assumption underlying the cause-specific analysis[8], which is not testable in competing risks, the assumptions on practicality of the intervention on the competing event (death) and adequate number of uncensored subjects in any level of the common risk factors were satisfied in this trial.

Grade 3–5 AE rates were not statistically significantly different between the arms (pazopanib 88·9% and placebo 85·3%; p=0·73; Table 2). There was one grade 5 AE on pazopanib (sepsis) and 1 on placebo (pneumonitis). Grade 3–4 lymphocyte count decrease and grade 3 dysphagia were common in both arms. Grade 3–4 aspartate aminotransferase increase (8 [22%]), grade 3 alanine aminotransferase increase (12 [33%]), grade 3–4 neutrophil count decrease (6 [17%]), and grade 3 white blood cell decrease (7 [19%]) were all common on pazopanib only. Grade 3 radiation dermatitis (8 [22%] on pazopanib and 13 [38%] on placebo), grade 3 oral mucositis (5 [14%] on pazopanib and 8 [24%] on placebo), and grade 3 fatigue (1 [3%] on pazopanib and 5 [15%] on placebo) were more common on placebo. Rates of AEs of concern were 2·8% (95% CI 0·5, 14·2) and 11·8% (95% CI 4·7, 26·6) on pazopanib and placebo, respectively (p=0·19). Other grade 3–5 AE rates were 86·1% (95% CI 71·3, 93·9) on pazopanib and 85·3% (95% CI 69·9, 93·6) on placebo (p=1·00). Serious AEs related to pazopanib or placebo were reported for 16 (44%) and 12 (35%) patients on pazopanib and placebo, respectively. The most common SAEs were dehydration and thromboembolic event (3 [8%] each) on pazopanib and oral mucositis (3 [8%]) on placebo.

Response rates (CR+PR) for evaluable patients were 30·4% (95% CI 15·6, 50·9) on pazopanib and 33·3% (95% CI 18·6, 52·2) on placebo (p=1·00) (Appendix p13).

Three (8%) pazopanib patients and 4 (11%) placebo patients did not receive IMRT. On pazopanib, 26 (72%) patients received ≥ 95% of the planned IMRT dose of 66 Gy, compared to 24 (69%) on placebo. Study chairs scored the overall radiotherapy delivery as per protocol or with acceptable variation in 26 (72%) pazopanib and 25 (71%) placebo patients.

One (3%) patient on placebo did not receive paclitaxel. Patients on pazopanib received a median of 7·5 cycles (Q1 5, Q3 9) and 413·8 mg/m^2 (Q1 305·1, Q3 506·1), compared to 9

cycles (Q1 7, Q3 9) and 474·3 mg/m^2 (Q1 416·4, Q3 512·6) on placebo. Study chairs scored the pre-IMRT/concurrent paclitaxel delivery as per protocol or with acceptable variation in 36 (100%)/28 (78%) pazopanib and 32 (91%)/29 (83%) placebo patients.

Two patients (6%) on each arm did not receive pazopanib or placebo. Of treated patients, 19 (56%) completed pazopanib and 21 (64%) completed placebo; 21 (62%) and 11 (33%) required dose modifications to pazopanib and placebo, and 9 (26%) and 4 (12%) discontinued pazopanib and placebo due to AEs (Appendix p14). Median total pazopanib dose was 12,775 mg (Q1 9200, Q3 17450) and median total placebo dose was 17,600 mg (Q1 10800, Q3 20700). Study chairs scored the pre-IMRT/concurrent pazopanib or placebo delivery as per protocol or with acceptable variation in 33 (92%)/29 (81%) pazopanib and 31 (89%)/28 (80%) placebo patients.

Treatment delivery for ineligible patients is summarized in Appendix p15.

Eighteen pazopanib patients (50%) and 16 placebo patients (46%) received second-line (non-protocol) treatment, including 6 (17%) and 4 (11%) receiving targeted therapy on the pazopanib and placebo arms, respectively (Appendix p16).

DISCUSSION

We report the results of what is to our knowledge the first ever fully accrued multicenter randomized therapeutic trial in ATC. This study demonstrates the ability of cooperative groups to complete multicenter international complex multimodality therapy trials even in very rare cancers. In terms of the primary endpoint of OS, the results did not show a statistically significant benefit of adding pazopanib to the IMRT/paclitaxel regimen. In M0 patients we saw encouraging survival rates favoring the pazopanib arm starting around 6 months from randomization in an unplanned, exploratory analysis (Appendix p9). In the M1/MX group, 1-year OS rates were similar between arms, and there were no 2-year survivors. Additionally, we demonstrated that the combination of IMRT with concurrent paclitaxel and pazopanib can be safely and effectively administered in ATC patients. While on face value the amount of grade 4–5 AEs seems high, something expected in any ATC population due to the disease, the majority were related to grade 4 lymphopenia, an AE that is unlikely to have a significant effect in quality of life or mortality. Only elevations of hepatic enzymes and decreases in white blood count/neutrophils seem to stand out as more likely to occur in the pazopanib study arm, most of which were grade 3. What, then, additionally was learned from this trial?

We interpret the above results as indicating: 1) our study was underpowered to demonstrate a smaller treatment effect (larger HR) compared to the hypothesized HR for OS in the overall population and 2) the apparent benefit associated with pazopanib appears to occur primarily among M0 patients and seems to be more of a delayed effect (e.g., after 6 months). Regarding 1), the study was designed to detect a 16·4% absolute difference in OS at year 1, compared to an estimate of 8·1%. Interestingly, in a post-hoc analysis with all 88 subjects at risk of death from ATC, there does appear to be a significant benefit in 1-year OS with the addition of pazopanib. The study included a heterogenous population: patients with any

metastatic stage were allowed, prior surgery was allowed (although post-hoc analysis did not show an OS difference based on prior surgery), and performance status ranged from 0 to 2. One must question the assumption that patients with M0 and M1 disease would have improved outcomes with more aggressive treatment to the primary and regional nodal disease. Regarding the behavior of the OS curves, we should not be surprised that the survival curves are tight in the beginning but start to separate later. A common clinical observation is that a subset of ATC is so aggressive that it is unlikely that any treatment would affect their aggressive disease course. Therefore, it is likely that the "less aggressive" ATC tumors were the ones that benefited from treatment intensification. While this is purely a hypothesis, as there is a paucity of randomized trials in ATC, the OS curve seen in the randomized study with fosbretabulin (FACT study) has a similar separation[10]. Alternative analytic strategies have been proposed to increase the statistical power with crossing survival curves or delayed treatment effects, which should be considered in the design of future trials.

Although we would expect a better outcome for patients who underwent a total thyroidectomy (or even a partial thyroidectomy), especially since this should be a surrogate for better baseline disease, a post-hoc analysis did not indicate differences in OS, even in the M0 population. Of course, the study was not powered and designed to test these differences, so this result should be considered hypothesis-generating.

Our study had several limitations. First, the design assumed that there would only be a 10% ineligibility rate. Unfortunately, 18 (20%) of 89 patients were ineligible, almost all of which were due to lab or imaging studies not being done or done outside the protocol eligibility limits. This is likely related to the need to put ATC patients on treatment as quickly as possible. The protocol-specified OS analysis with eligible randomized patients (i.e., allowing exclusions after randomization) could have led to potential selection bias. Although the ineligibility reasons are unlikely to be related to the risk of dying from ATC, these exclusions could still be problematic as they defeat the purpose of randomisation. To overcome this limitation, a sensitivity analysis for OS using a modified ITT approach, which is expected to preserve the integrity of the randomization, was also performed with similar results as the primary endpoint analysis. In the future, inclusion/exclusion criteria should be much less restrictive, especially windows for lab and imaging studies, to minimize ineligibility since it is unlikely loosening these requirements would have any effect on the outcome of the study based on our sensitivity analysis. A main problem with any ATC study is that it is a very rare disease, aggressive enough that any protocol needs to be flexible to get patients on quickly. Second, HRs in Cox models have been shown to suffer from built-in selection bias[11,12]. The design of future clinical trials should consider the use of alternative efficacy measures and modeling frameworks that admit causal inference interpretations. Also, although the test for the proportionality assumption in Cox models did not suggest serious departures for the treatment factor, the behavior of survival curves in Figure 2 suggests that the HR of 0·86 for OS in favor of pazopanib could be seen as a weighted average of time-varying HRs, which seems to be close to 1 during the first months of follow-up and declined later. However, the sample size limitation in this trial does not allow for a rigorous assessment using alternative modeling approaches.

Fortunately, several important factors were verified by the study. Most importantly, a randomized study in ATC is feasible in the cooperative group setting. The randomized portion of the study completed accrual 14 months earlier than expected (Appendix p17). Furthermore, over the final 6 months of the study, an average of 3·3 patients were accrued per month. This should help with the planning of future studies. Second, the study was able to successfully use a central review process without delaying start of treatment. The accurate diagnosis of ATC is difficult. All pathology was confirmed by a designated study pathologist (Dr. Ronald Ghossein), although patients were allowed to start treatment based on local review. Only one of the 89 patients was found to have a different diagnosis, indicating that the clinical scenario and pathology are typically adequate for diagnosis at the local level.

Since this study was completed, the landscape for the management of ATC has also changed. Molecular sequencing has become standard and is now included in the recommendations of the NCCN guidelines. Significant activity in metastatic disease has been shown in ATC with BRAFV600E mutations[13], TRK fusion genes[14], and RET fusion genes[15] (although all studies have been small and, in some cases, equivalent to case reports) which have led to FDA-approval for treatment with dabrafenib+trametinib, entrectinib/larotrectinib, and selpercatinib, respectively. Other potential targets include TSC1/TSC2 mutations[16] and ALK-fusion genes[17]. However, these treatments have been mainly approved for the treatment of distant disease and not for long-term control of local disease, although there is very promising data reported in a small single institution series evaluating the use of dabrafenib and trametinib followed by surgery in the neck[18]. Considering the high expression of PD-1/PD-L1 in ATC[19] immunotherapy may be a promising approach. There have been several promising small studies of immunotherapy alone or in combination with other agents[20–23], but these approaches need to be better evaluated and validated. In addition, there are concerns about the safety of using immunotherapy with radiation therapy in ATC[24]. Efficacy issues with the addition of immunotherapy to radiation therapy have been reported in other cancers[25], so it is unlikely that the addition of immunotherapy to radiation will be the best approach. However, the use of immunotherapy in the neoadjuvant and/or adjuvant setting may hold more promise.

While the current study did not demonstrate statistically significantly improved OS for pazopanib over placebo, the OS results in the M0 population, are intriguing and set the stage for a future randomized trial with the same treatment arms in only M0 ATC patients. However, the issue that would exist is the feasibility of doing such a study in a subset of a rare population since 56% of patients had M0 disease. The rarity of the disease makes it more challenging to study a truly homogenous population (i.e., only M0 disease) unless we believe the treatment benefit will be sufficiently large. Furthermore, the percentages of grade 3–4 toxicities suggest that the addition of pazopanib did not significantly change the toxicity of the treatment, showing that paclitaxel and pazopanib can be safely administered with IMRT for ATC. While further exploration of pazopanib would be reasonable, more contemporary approaches with targeted therapies and/or immunotherapy are likely to be more promising. Finally, this study serves as a model for future randomized ATC studies in terms of what can and perhaps what cannot be accomplished.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing:

All deidentified participant data and data dictionary from this paper will be available upon request within 6 months of publication in accordance with NRG Oncology's data sharing policy, which can be found at https://www.nrgoncology.org/Resources/Ancillary-Projects-Data-Sharing-Application (accessed on 25 August 2022).

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Research in context

Evidence before this study

Anaplastic thyroid cancer is rare, and at the time of study initiation, there were no proven standard treatment options. We searched PUBMED using the terms “anaplastic thyroid cancer” and “randomized controlled trial”. There were no relevant studies (in any language) published prior to the start of NRG/RTOG 0912 (prior to December 1, 2009). Since the start of NRG/RTOG 0912, only two relevant studies were found. The first was a randomized study of carboplatin/paclitaxel with and without fosbretabulin. This study was stopped early due to poor accrual (accrued 80 out of the planned 180 patients). No benefit was seen in terms of median overall survival, the primary outcome, but analysis of one-year overall survival suggested a possible benefit in the fosbretabulin arm (26% vs 9%). The second study was a randomized study of paclitaxel with or without valproic acid. Only a total of 25 patients were randomized in the study, and no differences were found between either arm. Data using pazopanib with paclitaxel and pazopanib with radiation therapy as well as pazopanib to treat anaplastic thyroid cancer was based on unpublished data at the time of study conception.

Added value of this study

To our knowledge, NRG/RTOG 0912 is the largest randomized study in anaplastic thyroid cancer and the only randomized study ever done with radiation therapy in anaplastic thyroid cancer. While the primary endpoint of overall survival was not met, an unplanned analysis suggests that any potential benefit would be found only in patients without distant metastatic disease at the time of diagnosis, the first time this has ever been suggested in anaplastic thyroid cancer (where it is believed that local control will have effects on overall survival). This will inform future clinical trials. In addition, likely due to the need to get these patients on treatment as quickly as possible, a larger number than expected patients were found to be ineligible. This highlights the need in future studies to limit eligibility requirements or be more flexible in the timing of tests since these patients need to get on treatment as quickly as possible.

Implications of all available evidence

In this study, we concluded that adding pazopanib to paclitaxel and radiation therapy did not benefit patients with anaplastic thyroid cancer when all stages were evaluated together. Hypothesis-generating results suggest that more intense treatment with the addition of pazopanib may benefit patients without evidence of distant metastases at presentation and could be given safely with standard chemotherapy and radiation therapy, and warrants further investigation.

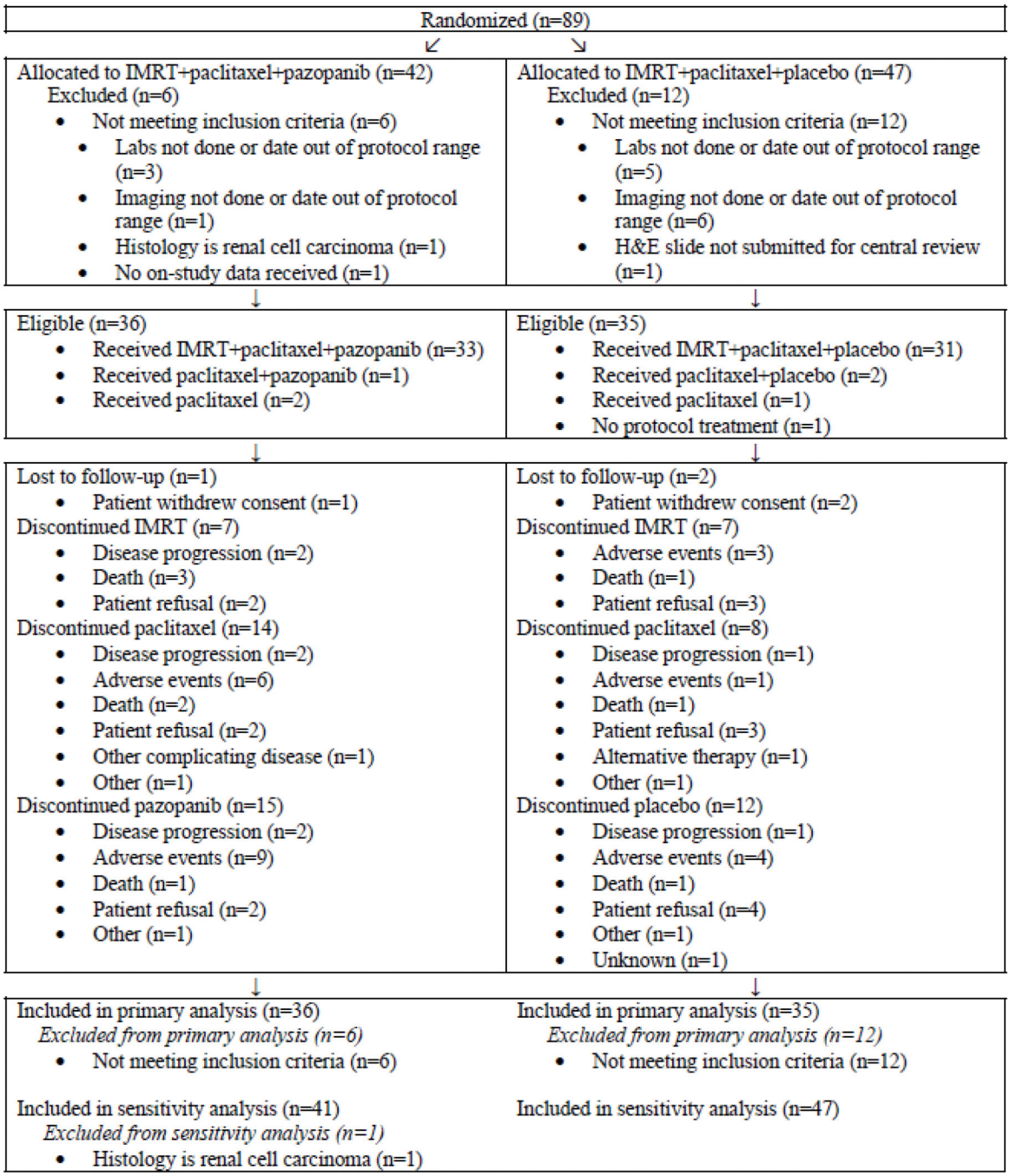

Figure 1.
CONSORT Flow Diagram for NRG Oncology RTOG 0912.

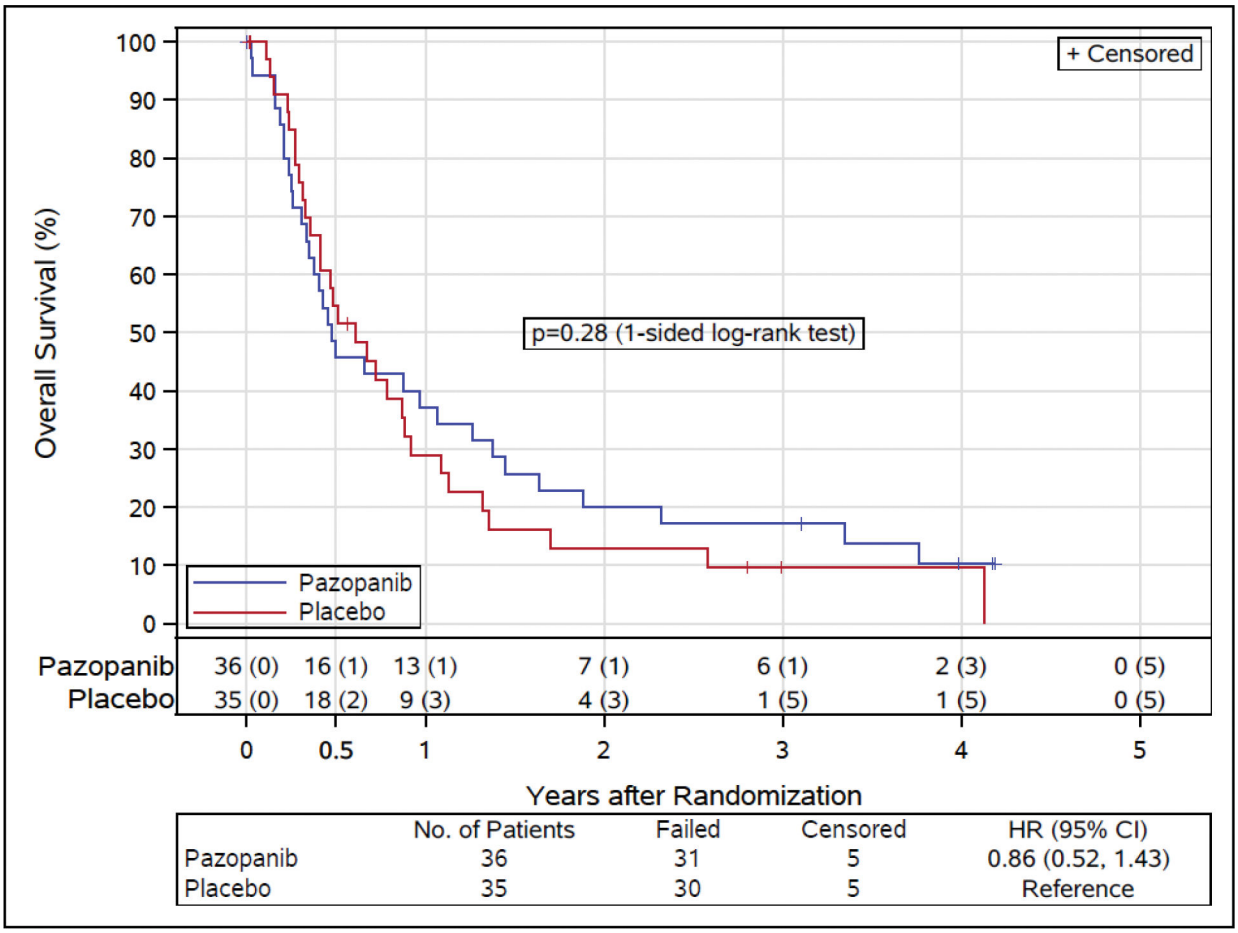

Figure 2.

Overall survival for NRG Oncology RTOG 0912 eligible population by assigned treatment. The p-value for the 1-sided log-rank test was 0·2831 and median survival was 5·7 months (95% CI 4·0, 15·2) for pazopanib and 7·3 months (95% CI 4·9, 10·6) for placebo.

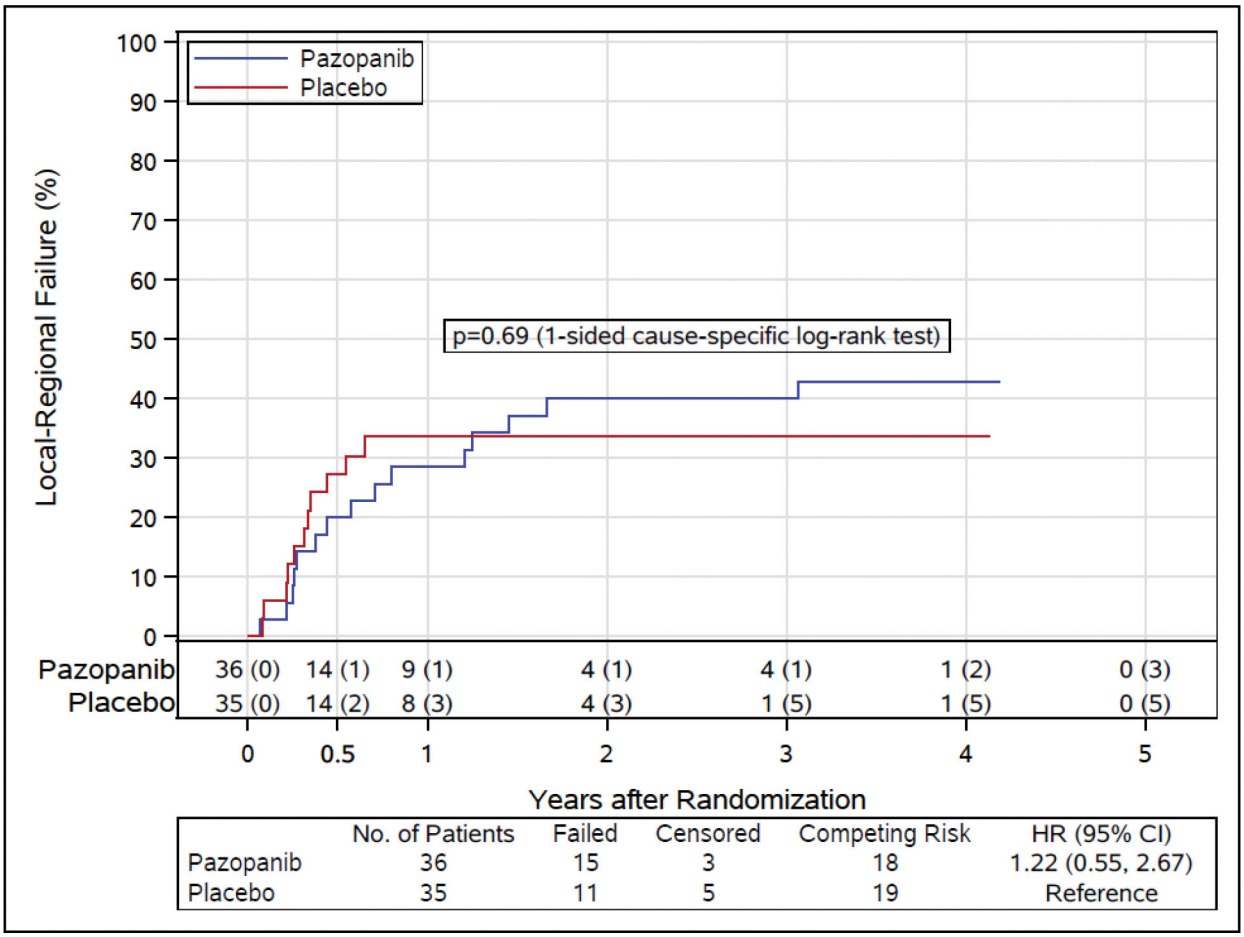

Figure 3.

Local-regional failure for NRG Oncology RTOG 0912 eligible population by assigned treatment. The p-value for the 1-sided cause-specific log-rank test was 0·6880.

Table 1.

Patient and Tumor Characteristics for NRG Oncology RTOG 0912 Eligible Patients

	Pazopanib (n=36)		Placebo (n=35)		Total (n=71)	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age (years)						
≤ 49	5	14	4	11	9	13
50 – 59	5	14	7	20	12	17
60 – 69	19	53	14	40	33	46
≥ 70	7	19	10	29	17	24
Gender						
Male	18	50	16	46	34	48
Female	18	50	19	54	37	52
Race						
American Indian/Alaska Native	1	3	0	0	1	1
Asian	2	6	1	3	3	4
Black or African American	2	6	2	6	4	6
Native Hawaiian or Other Pacific Islander	0	0	1	3	1	1
White	23	64	25	71	48	68
Unknown or not reported	8	22	6	17	14	20
Ethnicity						
Hispanic or Latino	1	3	3	9	4	6
Not Hispanic or Latino	29	81	24	69	53	75
Unknown	6	17	8	23	14	20
Zubrod performance status						
0	17	47	15	43	32	45
1	17	47	16	46	33	46
2	2	6	4	11	6	8
Prior surgery for study cancer						
None	14	39	16	46	30	42
Total thyroidectomy	15	42	11	31	26	37
Partial thyroidectomy	7	19	8	23	15	21
T stage (AJCC 7th Edition)						
T4a	11	31	12	34	23	32
T4b	25	69	23	66	48	68
N stage (AJCC 7th Edition)						
N0	8	22	6	17	14	20
N1a	10	28	5	14	15	21
N1b	14	39	23	66	37	52
NX	4	11	1	3	5	7
M stage (AJCC 7th Edition)						
M0	19	53	21	60	40	56
M1	13	36	13	37	26	37

	Pazopanib (n=36)		Placebo (n=35)		Total (n=71)	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
MX	4	11	1	3	5	7

Table 2.

Treatment-Related Adverse Events in NRG Oncology RTOG 0912

Term	Pazopanib (n=36) n (%) by grade				Placebo (n=34) n (%) by grade			
	1–2	3	4	5	1–2	3	4	5
Overall highest grade	1 (3)	19 (53)	12 (33)	1 (3)	4 (12)	19 (56)	9 (26)	1 (3)
Abdominal pain	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Alanine aminotransferase increased	4 (11)	12 (33)	0 (0)	0 (0)	3 (9)	0 (0)	0 (0)	0 (0)
Alkaline phosphatase increased	7 (19)	2 (6)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Allergic reaction	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	1 (3)	0 (0)	0 (0)
Alopecia	4 (11)	0 (0)	0 (0)	0 (0)	3 (9)	0 (0)	0 (0)	0 (0)
Anemia	12 (33)	2 (6)	0 (0)	0 (0)	9 (26)	3 (9)	0 (0)	0 (0)
Anorexia	8 (22)	2 (6)	0 (0)	0 (0)	6 (18)	4 (12)	0 (0)	0 (0)
Aspartate aminotransferase increased	9 (25)	7 (19)	1 (3)	0 (0)	4 (12)	0 (0)	0 (0)	0 (0)
Aspiration	1 (3)	2 (6)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)
Blood bilirubin increased	5 (14)	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Colitis	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	4 (11)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)
Cough	3 (8)	0 (0)	0 (0)	0 (0)	4 (12)	1 (3)	0 (0)	0 (0)
Dehydration	4 (11)	4 (11)	0 (0)	0 (0)	4 (12)	2 (6)	0 (0)	0 (0)
Depression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
Dermatitis radiation	14 (39)	8 (22)	0 (0)	0 (0)	12 (35)	13 (38)	0 (0)	0 (0)
Diarrhea	13 (36)	0 (0)	0 (0)	0 (0)	3 (9)	0 (0)	0 (0)	0 (0)

Term	Pazopanib (n=36) n (%) by grade				Placebo (n=34) n (%) by grade			
	1–2	3	4	5	1–2	3	4	5
Dizziness	2	0	0	0	2	1	0	0
	(6)	(0)	(0)	(0)	(6)	(3)	(0)	(0)
Dry mouth	13	0	0	0	13	2	0	0
	(36)	(0)	(0)	(0)	(38)	(6)	(0)	(0)
Dysgeusia	14	0	0	0	10	0	0	0
	(39)	(0)	(0)	(0)	(29)	(0)	(0)	(0)
Dysphagia	12	13	0	0	13	10	0	0
	(33)	(36)	(0)	(0)	(38)	(29)	(0)	(0)
Dyspnea	3	0	1	0	2	1	0	0
	(8)	(0)	(3)	(0)	(6)	(3)	(0)	(0)
Ejection fraction decreased	0	0	1	0	0	0	0	0
	(0)	(0)	(3)	(0)	(0)	(0)	(0)	(0)
Electrocardiogram QT corrected interval prolonged	1	0	0	0	1	1	0	0
	(3)	(0)	(0)	(0)	(3)	(3)	(0)	(0)
Esophageal fistula	0	1	0	0	0	0	0	0
	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
Esophageal pain	2	0	0	0	0	1	0	0
	(6)	(0)	(0)	(0)	(0)	(3)	(0)	(0)
Esophagitis	2	1	0	0	0	2	0	0
	(6)	(3)	(0)	(0)	(0)	(6)	(0)	(0)
Fatigue	24	1	0	0	17	5	0	0
	(67)	(3)	(0)	(0)	(50)	(15)	(0)	(0)
Gastrointestinal disorders - Other	5	1	0	0	1	0	0	0
	(14)	(3)	(0)	(0)	(3)	(0)	(0)	(0)
General disorders and administration site conditions - Other	7	0	0	0	1	0	0	0
	(19)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
Headache	0	1	0	0	2	0	0	0
	(0)	(3)	(0)	(0)	(6)	(0)	(0)	(0)
Hoarseness	7	1	0	0	7	1	0	0
	(19)	(3)	(0)	(0)	(21)	(3)	(0)	(0)
Hyperglycemia	4	0	0	0	1	0	0	0
	(11)	(0)	(0)	(0)	(3)	(0)	(0)	(0)
Hyperkalemia	4	0	0	0	2	0	0	0
	(11)	(0)	(0)	(0)	(6)	(0)	(0)	(0)
Hypermagnesemia	0	1	0	0	0	0	0	0
	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
Hypertension	7	1	0	0	8	1	0	0
	(19)	(3)	(0)	(0)	(24)	(3)	(0)	(0)
Hypertriglyceridemia	0	1	0	0	0	0	0	0

Term	Pazopanib (n=36) n (%) by grade				Placebo (n=34) n (%) by grade			
	1–2	3	4	5	1–2	3	4	5
	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
Hypoalbuminemia	4	0	0	0	5	0	0	0
	(11)	(0)	(0)	(0)	(15)	(0)	(0)	(0)
Hypocalcemia	5	2	0	0	4	1	1	0
	(14)	(6)	(0)	(0)	(12)	(3)	(3)	(0)
Hyponatremia	4	2	0	0	5	1	0	0
	(11)	(6)	(0)	(0)	(15)	(3)	(0)	(0)
Hypophosphatemia	2	1	0	0	0	0	0	0
	(6)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
Hypoxia	0	1	0	0	0	0	0	0
	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
Infections and infestations - Other	1	0	0	0	1	1	0	0
	(3)	(0)	(0)	(0)	(3)	(3)	(0)	(0)
Laryngeal mucositis	0	0	0	0	1	2	0	0
	(0)	(0)	(0)	(0)	(3)	(6)	(0)	(0)
Lung infection	1	1	0	0	0	1	0	0
	(3)	(3)	(0)	(0)	(0)	(3)	(0)	(0)
Lymphocyte count decreased	1	5	8	0	1	7	6	0
	(3)	(14)	(22)	(0)	(3)	(21)	(18)	(0)
Metabolism and nutrition disorders - Other	3	1	1	0	2	0	0	0
	(8)	(3)	(3)	(0)	(6)	(0)	(0)	(0)
Mucositis oral	13	5	0	0	9	8	0	0
	(36)	(14)	(0)	(0)	(26)	(24)	(0)	(0)
Musculoskeletal and connective tissue disorder - Other	4	0	0	0	0	0	0	0
	(11)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Nausea	16	4	0	0	15	4	0	0
	(44)	(11)	(0)	(0)	(44)	(12)	(0)	(0)
Neck pain	9	0	0	0	4	1	0	0
	(25)	(0)	(0)	(0)	(12)	(3)	(0)	(0)
Neutrophil count decreased	7	5	1	0	2	0	0	0
	(19)	(14)	(3)	(0)	(6)	(0)	(0)	(0)
Oral pain	3	1	0	0	5	0	0	0
	(8)	(3)	(0)	(0)	(15)	(0)	(0)	(0)
Pain	5	0	0	0	8	1	0	0
	(14)	(0)	(0)	(0)	(24)	(3)	(0)	(0)
Peripheral sensory neuropathy	6	1	0	0	2	0	0	0
	(17)	(3)	(0)	(0)	(6)	(0)	(0)	(0)
Pharyngeal mucositis	5	0	0	0	4	1	0	0
	(14)	(0)	(0)	(0)	(12)	(3)	(0)	(0)

Term	Pazopanib (n=36) n (%) by grade				Placebo (n=34) n (%) by grade			
	1–2	3	4	5	1–2	3	4	5
Platelet count decreased	8	0	1	0	3	0	0	0
	(22)	(0)	(3)	(0)	(9)	(0)	(0)	(0)
Pneumonitis	1	1	0	0	0	0	0	1
	(3)	(3)	(0)	(0)	(0)	(0)	(0)	(3)
Radiation recall reaction (dermatologic)	1	0	0	0	0	1	0	0
	(3)	(0)	(0)	(0)	(0)	(3)	(0)	(0)
Respiratory failure	0	0	0	0	0	0	2	0
	(0)	(0)	(0)	(0)	(0)	(0)	(6)	(0)
Respiratory, thoracic and mediastinal disorders - Other	1	2	0	0	0	0	0	0
	(3)	(6)	(0)	(0)	(0)	(0)	(0)	(0)
Salivary gland infection	0	0	0	0	0	1	0	0
	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)
Sepsis	0	0	1	1	0	0	0	0
	(0)	(0)	(3)	(3)	(0)	(0)	(0)	(0)
Skin and subcutaneous tissue disorders - Other	6	0	1	0	4	1	0	0
	(17)	(0)	(3)	(0)	(12)	(3)	(0)	(0)
Skin infection	0	1	0	0	0	1	0	0
	(0)	(3)	(0)	(0)	(0)	(3)	(0)	(0)
Sore throat	1	1	0	0	2	2	0	0
	(3)	(3)	(0)	(0)	(6)	(6)	(0)	(0)
Stridor	0	0	0	0	0	1	0	0
	(0)	(0)	(0)	(0)	(0)	(3)	(0)	(0)
Syncope	0	0	0	0	0	2	0	0
	(0)	(0)	(0)	(0)	(0)	(6)	(0)	(0)
Thromboembolic event	0	3	0	0	2	0	0	0
	(0)	(8)	(0)	(0)	(6)	(0)	(0)	(0)
Upper respiratory infection	0	1	0	0	0	0	0	0
	(0)	(3)	(0)	(0)	(0)	(0)	(0)	(0)
Voice alteration	2	2	0	0	1	0	0	0
	(6)	(6)	(0)	(0)	(3)	(0)	(0)	(0)
Vomiting	9	1	0	0	8	0	0	0
	(25)	(3)	(0)	(0)	(24)	(0)	(0)	(0)
Weight loss	9	0	0	0	10	2	0	0
	(25)	(0)	(0)	(0)	(29)	(6)	(0)	(0)
White blood cell decreased	10	7	0	0	6	0	0	0
	(28)	(19)	(0)	(0)	(18)	(0)	(0)	(0)

Adverse events were graded with CTCAE version 4.

Limited to grade 1–2 incidence of at least 10% on either arm and all grade 3–5.

Treatment-related is defined as definitely, probably, or possibly related.