Original Study

Overall Survival Analysis From a Randomized Phase II Study of Axitinib With or Without Dose Titration in First-Line Metastatic Renal Cell Carcinoma

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Abstract

In a randomized phase II trial in treatment-naive patients with metastatic renal cell carcinoma, axitinib dose titration was associated with significantly higher objective response rate compared with placebo dose titration. In this updated analysis, median overall survival was numerically longer with axitinib versus placebo titration (42.7 vs. 30.4 months). No new safety concerns were observed after long-term axitinib treatment.

Background: In a randomized phase II trial in metastatic renal cell carcinoma (mRCC), objective response rate was significantly higher with axitinib versus placebo titration (54% vs. 34%; 1-sided $P = .019$). **Patients and Methods:** Treatment-naive patients with mRCC (n = 213) received axitinib 5 mg twice per day (b.i.d.) for 4 weeks. Patients meeting dose titration criteria were randomized to receive axitinib 5 mg b.i.d. with axitinib or placebo titration (n = 56 each); 91 patients ineligible for randomization continued axitinib 5 mg b.i.d.; 10 discontinued before randomization. **Results:** Median overall survival (95% confidence interval [CI]) was 42.7 months (24.7-not estimable) with axitinib titration versus 30.4 months (23.7-45.0) with placebo titration (stratified hazard ratio, 0.785; 95% CI, 0.485-1.272; 1-sided $P = .162$), and 41.6 months (95% CI, 33.0-not estimable) in nonrandomized patients. Safety data were consistent with previous reports. **Conclusion:** Median overall survival was numerically longer in patients with first-line mRCC who received axitinib versus placebo titration. No new safety signal was observed after long-term axitinib treatment in first-line mRCC.

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Introduction

Axitinib, a tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor (VEGF) receptors, is approved in many countries for the treatment of advanced or metastatic renal cell carcinoma (mRCC) after failure of 1 previous systemic therapy. Patients who received the 5-mg axitinib twice daily (b.i.d.) oral starting 5-mg dose exhibited variable drug exposure,[1] and retrospective analyses indicated that higher axitinib exposure is associated with better outcomes in patients with mRCC.[2] Although other TKIs used for treatment of mRCC are prescribed at a fixed

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dose, which could be decreased, axitinib dose may be either up- or down-titrated.

To test the hypothesis that axitinib dose titration on the basis of individual tolerability would optimize plasma drug exposure and improve efficacy, a prospective phase II study compared objective response rate (ORR) in treatment-naive patients with mRCC randomized to axitinib 5 mg b.i.d. with axitinib or placebo titrated to a maximum 10 mg b.i.d. In the primary analysis,[3] ORR was significantly higher with axitinib versus placebo titration (54% vs. 34%; 1-sided $P = .019$). The hazard ratio for progression-free survival favored axitinib versus placebo titration (0.85; 95% confidence interval [CI], 0.54-1.35; 1-sided stratified $P = .24$). In this article we report updated overall survival (OS) and safety data from this study.

Patients and Methods

As previously described,[3] this randomized, double-blind, phase II trial (ClinicalTrials.gov NCT00835978) enrolled patients with clear-cell mRCC, no previous systemic therapy, measurable disease per Response Evaluation Criteria in Solid Tumors version 1.0, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, blood pressure (BP) $\leq$ 140/90 mm Hg, and adequate organ function. All patients received axitinib 5 mg b.i.d. for a 4-week lead-in period, after which patients were stratified according to ECOG PS and randomized (1:1) to receive axitinib or placebo dose titration if they met the following criteria for $\geq$2 consecutive weeks: BP $\leq$ 150/90 mm Hg, no Grade 3/4 axitinib-related toxicities, no axitinib dose reductions, and use of no more than 2 concurrent antihypertensive medications. The axitinib dose could be titrated stepwise to 7 mg b.i.d. and then to a maximum 10 mg b.i.d. Patients ineligible for dose titration continued to receive axitinib 5 mg b.i.d. (nonrandomized arm).

Tumors were assessed by investigators at screening, weeks 8, 16, and 24, and every 12 weeks thereafter. Survival status data were collected every 3 months after the follow-up study visit. Safety was assessed throughout the study, with adverse events (AEs) graded according to Common Terminology Criteria for Adverse Events version 3.0. The primary objective of the study, previously reported, was to compare ORR in the axitinib versus placebo titration arms.[3] OS and safety were secondary end points. OS estimates were computed using the Kaplan–Meier method and toxicity assessment was performed descriptively.

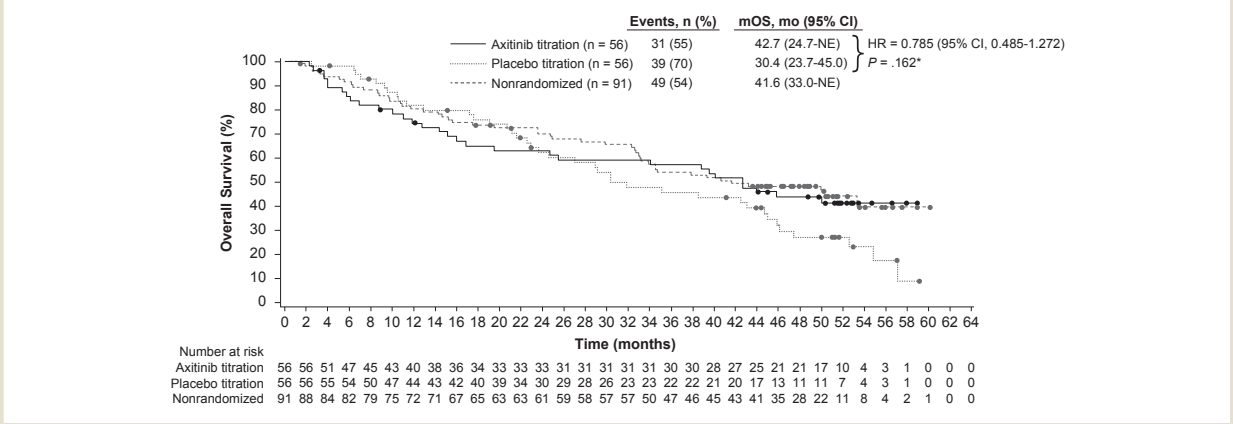
Results

Of 213 patients enrolled, 112 met the randomization criteria and were randomly assigned to receive axitinib or placebo dose titration (n = 56 each); 91 patients continued in the nonrandomized arm, and 10 withdrew during the lead-in period.[3] In all patients, median age (range) was 62 (28-87) years, 67% (n = 143) were male, 64% (n = 136) had ECOG PS 0, and 86% (n = 183) had previous nephrectomy. Memorial Sloan Kettering Cancer Center and Heng risk classification data were not captured in this study. There was a higher proportion of Asian patients in the nonrandomized (36%; n = 33) versus the 2 randomized (11%; n = 6 each) arms. As of the data cutoff date for the present analyses (November 4, 2014; ie, after treatment periods >3.5 years), 9 (16%), 1 (2%), and 10 (11%) patients continued treatment in the axitinib titration, placebo titration, and nonrandomized arms, respectively.

A total of 123 deaths (58% of patients) was reported, including 31 (55%) in the axitinib titration, 39 (70%) in the placebo titration, and 49 (54%) in the nonrandomized arms, and 4 patients (40%) who had discontinued during the lead-in period. The main cause of death was disease progression, which occurred in 29, 35, 43, and 4 patients in the axitinib titration, placebo titration, nonrandomized arms, and those discontinued before randomization, respectively. There were no deaths due to study treatment toxicity.

Median OS (95% CI) was 42.7 months (24.7-not estimable) in the axitinib titration versus 30.4 months (23.7-45.0) in the placebo titration arms (stratified hazard ratio, 0.785; 95% CI, 0.485-1.272; 1-sided $P = .162$; Figure 1). The first 25% of deaths occurred earlier in the axitinib versus placebo titration arm (by approximately 12 vs. approximately 19 months), whereas after approximately 20 months, deaths occurred more rapidly in the placebo versus axitinib

Figure 1 Kaplan-Meier Estimates of Overall Survival From First Dose of Axitinib or Placebo. *P Value Is From a 1-Sided Log-Rank Test Stratified According to Eastern Cooperative Oncology Group Performance Status Used in Randomization



Abbreviations: HR = hazard ratio; mOS = median overall survival; NE = not estimable.