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ORIGINAL RESEARCH

# ATLAS trial of adjuvant axitinib in patients with renal cell carcinoma: subgroup analyses with focus on axitinib dosing and racial groups

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**Background:** The ATLAS trial, investigating adjuvant axitinib versus placebo in renal cell carcinoma (RCC), was stopped for futility at a preplanned interim analysis. We report subgroup outcome analyses by ethnicity, time on treatment, dose modification and toxicity.

**Patients and methods:** Patient demographics, baseline characteristics, treatment duration and exposure and safety were analysed for Asian versus non-Asian patients treated with axitinib versus placebo. Disease-free survival (DFS) was analysed by ethnicity, treatment duration ($\geq$1 versus $<$1 year), dose modification and adverse event (AE) grade.

**Results:** No DFS benefit was observed for Asian {hazard ratio (HR) 0.883 [95% confidence interval (CI) 0.638-1.220]} or non-Asian [HR 0.828 (95% CI 0.490-1.400)] patients treated with axitinib or placebo. Fewer Asian versus non-Asian patients were in the highest-risk group in axitinib (51.9% versus 72.3%) or placebo (51.5% versus 66.0%) arm. Highest-risk patients in both subgroups had no DFS benefit with either treatment. More axitinib-treated Asian versus non-Asian patients had dose reductions due to AEs (58.8% versus 46.0%; $P = 0.028$). Asian patients experienced more nasopharyngitis but less fatigue or asthenia than non-Asians. Among Asian patients, proteinuria, hypothyroidism, nasopharyngitis, and hypertension were more common in Japanese patients than Korean patients and more common in Korean patients than Chinese patients. Patients receiving axitinib $>$1 year versus $\leq$1 year did not have different DFS: HR 0.572 (95% CI 0.247-1.327); $P = 0.1874$. Compared with patients on stable axitinib dose, DFS was longer in patients with dose reduction [HR 0.458 (95% CI 0.305-0.687); $P = 0.0001$], whereas DFS was not different in those with dose escalation [HR 1.936 (95% CI 0.937-3.997); $P = 0.0685$]. DFS was not different in patients experiencing grade $\geq$2 versus $<$2 AEs within 6 months of initiating axitinib: HR 0.885 (95% CI 0.419-1.869); $P = 0.7488$.

**Conclusions:** Asian versus non-Asian subgroup analysis revealed differences in AE experience and drug exposure. There were no DFS differences based on ethnicity or treatment duration, but axitinib dose reduction led to longer DFS.

**Key words:** adjuvant, Asian, ATLAS trial, axitinib, disease-free survival, renal cell carcinoma

## INTRODUCTION

Worldwide, over 400 000 cases of kidney cancer are diagnosed annually, with approximately 175 000 deaths attributed to the disease.[1] Upwards of 90% of diagnosed kidney cancers are renal cell carcinoma (RCC).[1] Patients diagnosed with American Joint Committee on Cancer (AJCC) TNM (tumour-node-metastasis) stage I/II RCC have a 5-year survival rate of 93% versus 70% for patients with TNM stage III disease, and 12% for patients with TNM stage IV disease.[2] Approximately 15% of patients with non-metastatic RCC are at high risk of recurrence, and approximately 60% of this high-risk population will experience recurrent or metastatic disease within 5 years.[3]

Surgical resection followed by observation had been the only treatment for non-metastatic RCC. However, in November 2017, sunitinib was approved by the United States Food and Drug Administration as adjuvant therapy for RCC based on disease-free survival (DFS) benefit of sunitinib versus placebo in the S-TRAC trial.[4,5] Other trials of

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targeted therapies to treat RCC in the adjuvant setting, including the ASSURE trial of sorafenib or sunitinib versus placebo,[6] did not demonstrate a clear survival benefit. The PROTECT trial reported no improvement in the primary endpoint of DFS with adjuvant pazopanib compared with placebo.[7] However, a *post hoc* analysis showed a relationship between DFS differences and higher starting dose of pazopanib.[7] In an analysis of pharmacokinetic parameters in PROTECT, higher pazopanib trough levels, observed in a subset of patients, were associated with improved DFS, adding to the evidence that increased drug exposure may contribute to outcomes in this setting.[8] None of these adjuvant tyrosine kinase inhibitors (TKIs) have provided an overall survival benefit.[5-7]

The ATLAS trial (NCT01599754) was a randomised double-blind phase III study, initiated in 2012, that compared axitinib with placebo in adult patients with locoregional RCC at high risk of recurrence post-nephrectomy.[9] Axitinib, which is in the same drug class as sunitinib,[10,11] is a selective inhibitor of the vascular endothelial growth factor receptors 1-3 approved globally for the treatment of metastatic RCC in the second-line setting. ATLAS was stopped due to futility at a preplanned interim analysis wherein results showed no difference in DFS between axitinib and placebo.[9] However, additional analysis of outcomes reported in ATLAS could help point to possible efficacy for axitinib in the adjuvant setting for some patient subgroups.

The use of TKIs to treat cancer in different regions and ethnic groups has delineated different disease control outcomes and side-effect profiles among these groups. Geographic differences, including demographics, genetics, lifestyle and medical practice, among other factors, may influence clinical outcomes in Asian versus non-Asian patients.[12-14] In particular, Asian patients have been reported to have polymorphic differences in cytochrome enzymes and other genetic variations in drug metabolism factors that potentially affect drug pharmacokinetics and exposure.[15-17]

To assess the potential for differential efficacy and toxicity of axitinib in patient subgroups, we conducted several preplanned, exploratory analyses of stratified data from ATLAS, including differences in baseline characteristics, outcomes and safety, by country for axitinib-treated Asian and non-Asian patients. Analyses were also carried out pooling Asian and non-Asian patients to explore the impact of axitinib and treatment duration on grade $\geq$2 adverse events (AEs) in the first 6 months of treatment, and the effects of axitinib dose increase, reduction or stable dose on DFS.

## PATIENTS AND METHODS

### *Study design*

The details of the ATLAS study have been previously described.[9] Briefly, ATLAS was a phase III, double-blind trial (NCT01599754) in patients randomised to either axitinib or placebo treatment. Patients were enrolled at 137 centres in eight countries: China (mainland and Hong Kong), France, India, Japan, Korea, Spain, Taiwan and the United States from 8 May 2012 to 1 July 2016. Patients were randomised (stratified by country and/or risk group) 1 : 1 to receive axitinib 5 mg twice a day or placebo. Patients began treatment within 7 days after randomisation. Randomisation was set to occur $>$4 and $\leq$12 weeks post-nephrectomy. Treatment was to continue for a minimum of 1 year and a maximum of 3 years. Dosage was allowed to increase or decrease based on individual tolerance.

The primary endpoint of ATLAS was to compare DFS in patients treated with axitinib versus placebo. The secondary endpoints included overall survival in the axitinib and placebo treatment arms and safety/toxicity profile in the axitinib arm. An interim analysis of efficacy and safety was planned after approximately 184 DFS events [~75% of the total number of required events as assessed by the Independent Review Committee (IRC)] had occurred. However, the trial was stopped at the preplanned interim analysis when the futility stopping boundary was crossed at 203 events, as assessed by the IRC.[9]

Inclusion/exclusion criteria for the ATLAS trial have been reported.[9] Briefly, key inclusion criteria included patients who had no evidence of macroscopic residual disease or metastatic disease post-nephrectomy and were $\geq$18 years old (aged $\geq$20 years in Japan, Korea and Taiwan or $\geq$18 years and $\leq$65 years in India). Patients had to be diagnosed with one of the following based on AJCC TNM staging (v2010) and Eastern Collaborative Oncology Group performance status (ECOG PS): (i) primary tumour stage 2 (pT2), primary tumour has not spread to lymph nodes (pN0) or regional lymph nodes cannot be assessed (pNx), no spread of tumour to distant lymph nodes or other organs (M0) and ECOG PS 0-1; (ii) primary tumour stage 3 (pT3), pN0 or pNx, M0 and ECOG PS 0-1; (iii) primary tumour stage 4 (pT4), pN0 or pNx, M0 and ECOG PS 0-1; (iv) any pT, primary tumour has spread to nearby lymph nodes (pN1), M0 and ECOG PS 0-1; patients with any Fuhrman grade were eligible.

Key exclusion criteria included the presence of any histologically undifferentiated carcinomas, sarcomas, collecting duct carcinoma, or lymphoma, or patients with any metastatic renal sites. Patients were also excluded on diagnosis of any non-RCC malignancy within 5 years from the date of randomisation, except basal cell carcinoma, squamous cell skin cancer, or *in situ* carcinoma of the cervix uteri that had been adequately treated with no evidence of recurrent disease for 12 months.

The ATLAS trial was approved by local institutional review boards and conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines and applicable local regulatory requirements and laws. All patients provided written informed consent.

### *Subgroup analysis*

**Asian versus non-Asian subgroup.** Patient demographic and baseline characteristics and baseline risk were analysed for the Asian and non-Asian subgroups. Specifically, duration

of treatment, drug exposure, and years of treatment completed were analysed. DFS for the highest-risk group (pT3 with Fuhrman grade ≥3 or pT4 and/or Nþ, any T, any Fuhrman grade), as well as drug exposure and safety events, were also analysed according to Asian and non-Asian subgroups.

**Duration of treatment, dose and toxicity effects on DFS analysis.** A landmark analysis in the pooled population, without separation of Asian and non-Asian patients, was conducted to compare patients treated with axitinib for ≤1 year versus >1 year. Patients whose disease recurred or was censored before 1 year were excluded from the analysis.

A dose increase/reduction analysis of daily-dose characteristics was undertaken to compare patients whose axitinib had dose reduction or increase (in accordance with the study design) versus those who remained on a stable dose of axitinib.

A toxicity analysis using a 6-month landmark was also conducted to determine the impact on DFS. DFS was analysed by presence or absence of grade ≥2 AE (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0) in the first 6 months of treatment in the axitinib arm.

### *Statistical analyses*

The preplanned, exploratory analyses included differences in baseline characteristics, outcomes and safety by country for axitinib-treated Asian and non-Asian patients. Additional *post hoc* analyses in the axitinib-treated patients included the impact of axitinib and treatment duration on grade ≥2 AEs in the first 6 months of treatment, and the effects of axitinib dose increase, reduction or stable dose on DFS. The DFS estimates were based on the IRC review of tumour assessments (by imaging or by pathology reports in the absence of IRC imaging confirmation) and were used for the primary endpoint in ATLAS. The intent-to-treat (ITT) population, which included all randomised patients, was used to evaluate all efficacy endpoints and patient characteristics. The "as-treated" population, all patients who received at least one dose of study drug, was used to evaluate all safety endpoints. The median DFS along with corresponding 95% confidence interval (CI) were estimated for each arm using Kaplan—Meier methods. The hazard ratio (HR) was estimated using proportional hazard regression. All subgroups were compared using a two-sided unstratified log-rank test. All *P* values are nominal and provided for descriptive purposes. Statistical analysis was carried out using SAS version 9.4 (SAS Institute Inc, Cary, NC).

## RESULTS

### *Patients*

Patient data for the ATLAS trial as reported at the time of discontinuation have been previously described.[9] Briefly, 724 patients were randomised to axitinib ($n = 363$) or placebo ($n = 361$). Of these, 356 and 359 patients, respectively, received at least one treatment.

The trial was stopped due to futility at a preplanned interim analysis at 203 of the required 245 DFS (IRC assessment) events for the final analysis. Asian patients were a large percentage (73%) of the randomised population, and over half of these patients had highest-risk cancer (56%; pT3 with Fuhrman grade ≥3 or pT4 and/or N+, any T, any Fuhrman grade). In all, 724 patients were included in the subgroup analyses ($n = 526$ and 198, Asian and non-Asian patients, respectively).

### *Subgroups analyses*

The analysis of patient demographic/baseline characteristics revealed that fewer Asian patients were overweight or obese versus non-Asian patients: 32.8% versus 78.2% treated with axitinib and 37.1% versus 79.4% with placebo (Table 1). Median time from diagnosis to study entry was also shorter in Asian versus non-Asian patients: 8.7 versus 10.3 weeks treated with axitinib and 8.6 versus 10.0 weeks with placebo (Table 1).

Analysis of baseline risk indicated there were fewer Asian patients in the highest-risk group versus non-Asians, 51.9% versus 72.3%, respectively, treated with axitinib and 51.5% versus 66.0%, respectively, with placebo (Table 1). The analysis of DFS highest-risk group for Asian versus non-Asian subgroups did not show a difference in treatment effect over placebo for either subgroup. HR was 0.731 (95% CI: 0.486-1.102) in the Asian subgroup and 0.755 (95% CI: 0.418-1.365) in the non-Asian subgroup (Figure 1).

Asian patients had a longer median duration of treatment versus non-Asians [25.3 versus 15.6 months ($P = 0.0147$) treated with axitinib and 27.0 versus 22.9 months ($P = 0.2095$) with placebo] and more Asian patients completed 3 years of treatment (31.5% versus 15.0%; $P = 0.0015$ with axitinib and 31.1% versus 15.6%; $P = 0.0035$ with placebo; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100105).

Analysis of drug exposure showed that Asian patients had a lower median daily dose compared with non-Asians: 6.6 versus 8.6 mg ($P < 0.001$) treated with axitinib and 9.9 versus 10.0 mg with placebo, with a similar trend seen for median daily dose at 6 and 12 months (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100105).

In the assessment of safety experience, more Asian versus non-Asian patients treated with axitinib had an AE that resulted in permanent discontinuation of study drug: 27.3% versus 15.0%, respectively ($P = 0.014$) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100105). Also, more Asian versus non-Asian patients in the axitinib arm had dose reductions due to AEs (58.8% versus 46.0%, respectively; $P = 0.028$) compared with the placebo arm (7.6% versus 10.4%, respectively). Asian patients treated with axitinib had higher frequencies of proteinuria and nasopharyngitis and lower frequencies of fatigue and asthenia compared with non-Asian patients (Table 2). Among the major Asian ethnicities, proteinuria, hypothyroidism, nasopharyngitis and

**Table 1. Patient demographics and baseline characteristics**

| *n* (%)[a] | Axitinib | | Placebo | |
|---|---|---|---|---|
| | Asian *n* = 262 | Non-Asian *n* = 101 | Asian *n* = 264 | Non-Asian *n* = 97 |
| Age, years | | | | |
| <65 | 188 (71.7) | 67 (66.3) | 177 (67.0) | 70 (72.2) |
| ≥65 | 74 (28.2) | 34 (33.7) | 87 (33.0) | 27 (27.8) |
| Mean (SD) | 58.1 (10.38) | 57.4 (11.84) | 58.5 (11.70) | 57.1 (10.27) |
| Median (range) | 58.0 (25-82) | 60.0 (21-84) | 59.0 (21-85) | 56.0 (31-79) |
| Sex | | | | |
| Male | 201 (76.7) | 79 (78.2) | 179 (67.8) | 71 (73.2) |
| Female | 61 (23.3) | 22 (21.8) | 85 (32.2) | 26 (26.8) |
| Race | | | | |
| Asian[b] | 262 (100) | 2 (2.0) | 264 (100) | 3 (3.1) |
| White | — | 91 (90.1) | — | 90 (92.8) |
| Black | — | 3 (2.8) | — | 1 (1.0) |
| Other | — | 5 (5.0) | — | 3 (3.1) |
| Body mass index, kg/m$^2$ | | | | |
| Normal weight (≥18.5, <25) | 168 (64.1) | 19 (18.9) | 154 (58.3) | 19 (19.6) |
| Overweight (≥25, <30) | 74 (28.2) | 41 (40.6) | 87 (33.0) | 37 (38.1) |
| Obese (≥30) | 12 (4.6) | 38 (37.6) | 11 (4.2) | 40 (41.2) |
| Underweight (<18.5) | 6 (2.3) | 1 (1.0) | 12 (4.5) | — |
| Duration since histopathic diagnosis | | | | |
| Mean (SD) | 8.57 (1.92) | 10.92 (7.32) | 8.51 (2.06) | 9.75 (2.00) |
| Median (range) | 8.7 (4.0-16.3) | 10.3 (4.1-79.3) | 8.6 (3.3-16.0) | 10.0 (3.9-13.6) |
| Body site of disease at diagnosis | | | | |
| Right kidney | 125 (47.7) | 58 (57.4) | 132 (50.0) | 49 (50.5) |
| Left kidney | 137 (52.3) | 43 (42.6) | 130 (49.2) | 48 (49.5) |
| Both kidneys | — | — | 2 (0.8) | — |
| Fuhrman grade | | | | |
| 1 | 9 (3.4) | 1 (1.0) | 13 (4.9) | 3 (3.1) |
| 2 | 87 (33.2) | 27 (26.7) | 91 (34.4) | 31 (32.0) |
| 3 | 114 (43.5) | 48 (47.5) | 105 (39.8) | 35 (36.1) |
| 4 | 42 (16.0) | 25 (24.8) | 39 (14.8) | 28 (28.9) |
| Missing | 10 (3.8) | — | 16 (6.1) | — |
| Risk group,[c] *n* (%) | | | | |
| (a) pT2, pN0 or pNx, M0 and ECOG PS 0-1 | 39 (14.9) | 4 (4.0) | 36 (13.6) | 1 (1.0) |
| (b) pT3, pN0 or pNx, M0 and ECOG PS 0-1 | 205 (78.2) | 91 (90.1) | 206 (78.0) | 91 (93.8) |
| (c) pT4, pN0 or pNx, M0 and ECOG PS 0-1 | 5 (1.9) | 2 (2.0) | 7 (2.7) | 1 (1.0) |
| (d) Any pT, pN1, M0 and ECOG PS 0-1 | 13 (5.0) | 4 (4.0) | 15 (5.7) | 4 (4.1) |
| Highest risk (b with Fuhrman grade 3 or 4) + c + d | 136 (51.9) | 73 (72.3) | 136 (51.5) | 64 (66.0) |
| Lower risk [a + (b with Fuhrman grade 1 or 2)] | 118 (45.0) | 28 (27.7) | 116 (43.9) | 33 (34.0) |

ECOG PS, Eastern Cooperative Oncology Group performance score; M0, no spread of tumour to distant lymph nodes or other organs; SD, standard deviation; TNM, tumour, nodes, and metastasis.

[a] Unless otherwise indicated.

[b] Patient classification of Asian is based on country of enrolment.

[c] TNM staging. pT2, primary tumour stage 2; pN0, primary tumour has not spread to lymph nodes; pNx, regional lymph nodes cannot be assessed; pT3, primary tumour stage 3; pT4, primary tumour stage 4; pN1, primary tumour has spread to nearby lymph nodes.

hypertension were more common in Japanese patients than Korean patients and more common in Korean patients than Chinese patients (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100105).

Overall, there was no DFS benefit observed for either Asian [HR 0.883 (95% CI 0.638-1.220)] or non-Asian [HR 0.828 (95% CI 0.490-1.400)] patients receiving axitinib compared with placebo (Figure 2).

The treatment duration in the landmark analysis that compared all patients treated with axitinib for ≤1 year versus >1 year included 264 axitinib-treated patients from the ATLAS study who remained disease-free at 1 year and were not censored. Of these, 42 patients were treated for ≤1 year and 222 patients for >1 year. Patients who remained on axitinib ≤1 year versus >1 year did not have different DFS: HR 0.572 (95% CI 0.247-1.327); $P = 0.1874$ (Figure 3).

Patients with axitinib dose reduction had longer DFS than those who received a stable dose: HR 0.458 (95% CI 0.305-0.687); $P = 0.0001$. However, patients with dose increase of axitinib ($n = 19$) did not have significantly different DFS than patients who maintained a stable dose: HR 1.936 (95% CI 0.937-3.997); $P = 0.0685$ (Figure 3). Patients who had dose reduction had longer mean and median treatment times (21.5 and 22.1 months) than patients with dose increase (18.0 and 18.8 months) or stable dose (16.8 and 15.6 months). A summary of time on axitinib treatment of the different dosing groups in the dose increase/reduction analysis is presented in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2021.100105.

In the toxicity analysis of the 6-month landmark analysis, there was no difference in DFS in patients who experienced grade ≥2 AEs versus grade <2 AEs within 6 months of start

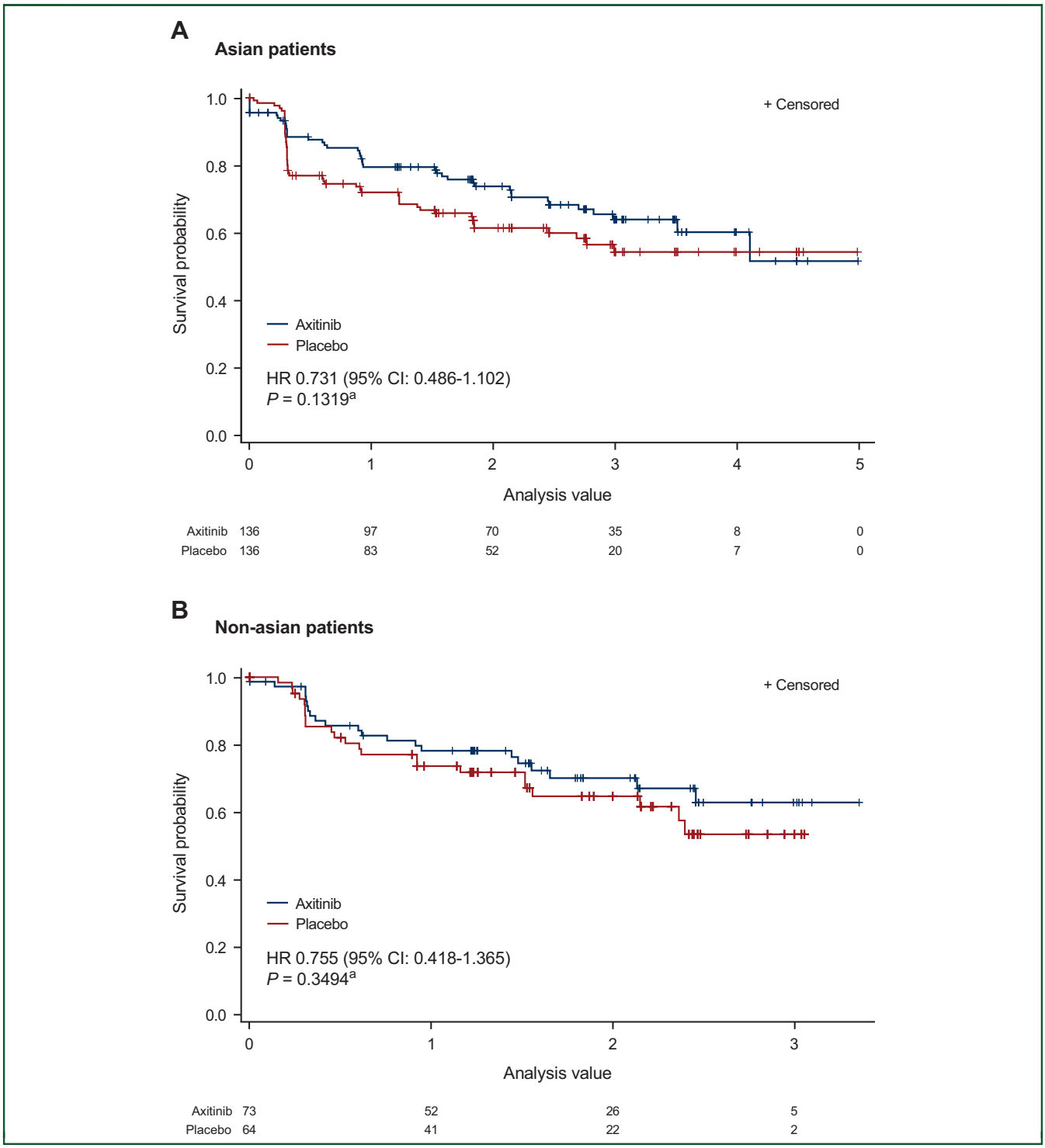


**Figure 1. Disease-free survival in patients in highest-risk group.**
[a] Log-rank.
CI, confidence interval; HR, hazard ratio.

of axitinib treatment: HR 0.885 (95% CI 0.419-1.869); $P = 0.7488$ (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100105). Patients who experienced grade $\geq$3 AEs within 6 months of start of axitinib had numerically shorter DFS compared with those who experience a grade <3 AE within 6 months of start of axitinib: HR 1.643 (95% CI 0.963-2.801); $P = 0.0653$ (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100105).

## DISCUSSION

The ATLAS study was stopped at a preplanned interim analysis due to futility. The primary endpoint of DFS

**Table 2. Adverse events, by type and sub-population**

| | Axitinib | | Placebo | |
|---|---|---|---|---|
| | Asian $n = 260$ | Non-Asian $n = 100$ | Asian $n = 264$ | Non-Asian $n = 96$ |
| Hypertension | 164 (63.1) | 67 (67.0) | 54 (20.5) | 37 (38.5) |
| Diarrhoea | 114 (43.8) | 56 (56.0) | 26 (9.8) | 26 (27.1) |
| Dysphonia | 114 (43.8) | 35 (35.0) | 13 (4.9) | 8 (8.3) |
| PPE[a] | 90 (34.6) | 25 (25.0) | 12 (4.5) | 5 (5.2) |
| Proteinuria[b] | 74 (28.5) | 10 (10.0) | 23 (8.7) | 2 (2.1) |
| Fatigue[c] | 45 (17.3) | 30 (30.0) | 22 (8.3) | 22 (22.9) |
| Hypothyroidism | 58 (22.3) | 15 (15.0) | 17 (6.4) | 5 (5.2) |
| Arthralgia | 35 (13.5) | 24 (24.0) | 18 (6.8) | 18 (18.8) |
| Nasopharyngitis[b] | 53 (20.4) | 4 (4.0) | 48 (18.2) | 14 (14.6) |
| Increased TSH | 38 (14.6) | 10 (10.0) | 5 (1.9) | — |
| Headache | 31 (11.9) | 17 (17.0) | 24 (9.1) | 16 (16.7) |
| Stomatitis | 34 (13.1) | 12 (12.0) | 6 (2.3) | 3 (3.1) |
| Back pain | 27 (10.4) | 19 (19.0) | 34 (12.9) | 20 (20.8) |
| Rash | 38 (14.6) | 8 (8.0) | 9 (3.4) | 6 (6.3) |
| Decreased appetite | 30 (11.5) | 15 (15.0) | 4 (1.5) | 3 (3.1) |
| Dizziness | 33 (12.7) | 9 (9.0) | 29 (11.0) | 5 (5.2) |
| Asthenia[b] | 8 (3.1) | 33 (33.0) | 1 (0.4) | 21 (21.9) |
| Nausea | 17 (6.5) | 19 (19.0) | 18 (6.8) | 17 (17.7) |

PPE, palmar-plantar erythrodysesthesia syndrome; TSH, thyroid-stimulating hormone.
[a] $P = 0.022$ for axitinib-treated Asian versus non-Asian patients.
[b] $P < 0.0001$ for axitinib-treated Asian versus non-Asian patients.
[c] $P = 0.0038$ for axitinib-treated Asian versus non-Asian patients.

improvement for axitinib treatment of RCC in the adjuvant setting versus placebo was not reached.[9] There are numerous ongoing/unreported adjuvant or neo-adjuvant trials in RCC involving single immuno-oncology agents or combinations, including atezolizumab, nivolumab alone and with ipilimumab, pembrolizumab, durvalumab and tremelimumab.[18] Final efficacy and safety data from these trials are not yet available. Sunitinib is currently the only agent for adjuvant treatment of RCC approved by the US Food and Drug Administration,[4] but has not been approved by any other regulatory authority. Because of the poor prognosis for patients who experience recurrence and metastatic disease, there is still a need for adjuvant treatment options with potential to delay or prevent recurrence for patients with high-risk, non-metastatic disease post-nephrectomy.[19]

The current exploratory analyses were carried out to assess the possibility that DFS benefit versus placebo may be different for a subgroup of axitinib-treated patients in the ATLAS trial. A group of analyses in this study examined the possible impact of ethnic differences on DFS in the adjuvant setting investigated in ATLAS. The subgroup analysis of DFS by Asian versus non-Asian subgroups did not indicate a DFS benefit over placebo for either subgroup. Patients in the Asian versus non-Asian subgroup had a lower median daily dose of axitinib whereas there were no differences in the placebo group. Furthermore, Asian patients had more frequent dose reductions versus non-Asian patients. Although patients with axitinib dose reductions had longer DFS versus patients with stable dose or dose increase, the frequent dose reduction in Asian patients did not translate to DFS benefit. This is potentially because Asian patients were also more likely to have AEs leading to dose reductions of axitinib and drug discontinuation versus the non-Asian cohort. This is consistent with previously reported subgroup analyses of axitinib efficacy in the metastatic RCC setting of the AXIS trial in Asian versus non-Asian patients, wherein there was no progression-free survival benefit in the Asian subgroup.[20-22]

The 6-month landmark in axitinib-treated patients experiencing grade $\geq$2 AEs versus grade $<$2 AEs also did not show any difference in DFS between subgroups and suggests there is no relationship between toxicity and DFS. There were notable differences in AEs between Asian and non-Asian patients as well as among Japanese, Korean and Chinese patients. This suggests that national and ethnic differences could lead to different AE experiences that could impact management strategies. Differences in axitinib tolerability between Asian and non-Asian patients were seen in the assessment of safety and similar differences have been reported for axitinib in other trials with Asian and non-Asian patients[22] and also with sunitinib in an analysis of data from 1059 patients treated for RCC pooled from six trials.[23]

Although more Asian patients had dose reductions and a longer median duration of treatment versus non-Asians, DFS did not vary based on duration of axitinib treatment of both Asian and non-Asian subgroups. This is consistent with the observed outcomes in the overall ATLAS population.[9] It is possible that improved DFS with dose reduction was due to pharmacokinetic-pharmacodynamic factors, leading to greater toxicity, but the results from the current study do not confirm a relationship between toxicity and DFS. The differences in DFS among dose subgroups does suggest there is a relationship between axitinib exposure and DFS, as was reported with sunitinib in the metastatic RCC setting[24] and with pazopanib in the adjuvant PROTECT study.[8]

Limitations of this study include the limited sample size of the group of patients who were treated for $\leq$1 year and the possibility that longer treatment might be a surrogate

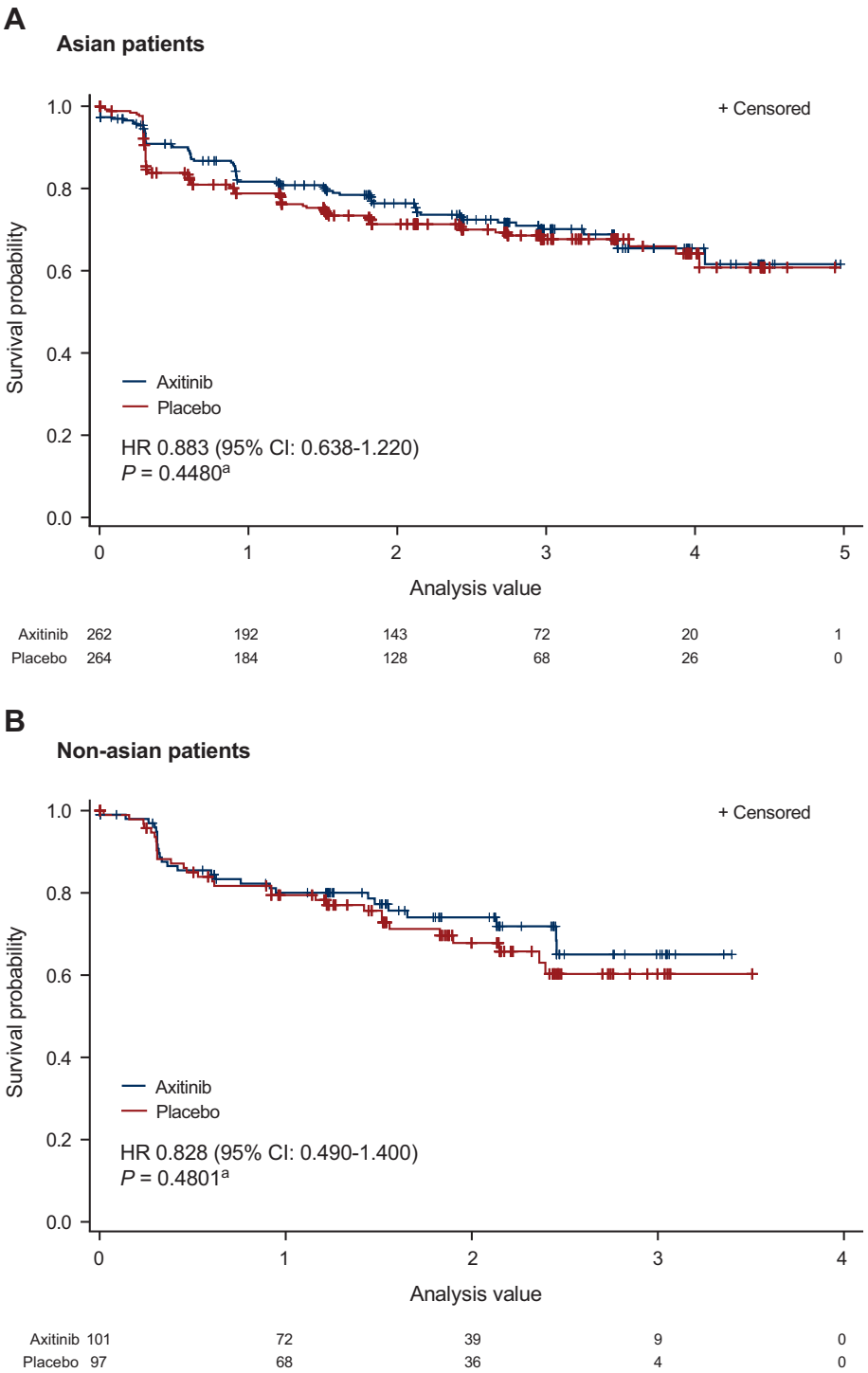


**Figure 2. Disease-free survival in Asian versus non-Asian patients.**
[a] Log-rank.
CI, confidence interval; HR, hazard ratio.

marker for prognostically favourable-risk patients. In addition, pharmacokinetic specimen collection and analysis were not included in ATLAS, making pharmacokinetic comparisons with other trials not possible.[8]

## *Conclusions*

The analysis of data by Asian versus non-Asian subgroups in the ATLAS trial revealed differences in AE experience and drug exposure between the subgroups; however, this did not translate to an impact on DFS. Further, the landmark analysis comparing subgroups of patients treated with axitinib $\leq$1 year versus $>$1 year did not show a difference in DFS between the Asian and non-Asian subgroups. The toxicity analysis using a 6-month landmark in axitinib-treated patients experiencing grade $\geq$2 AEs versus grade $<$2 AEs also did not show any difference in DFS between subgroups.

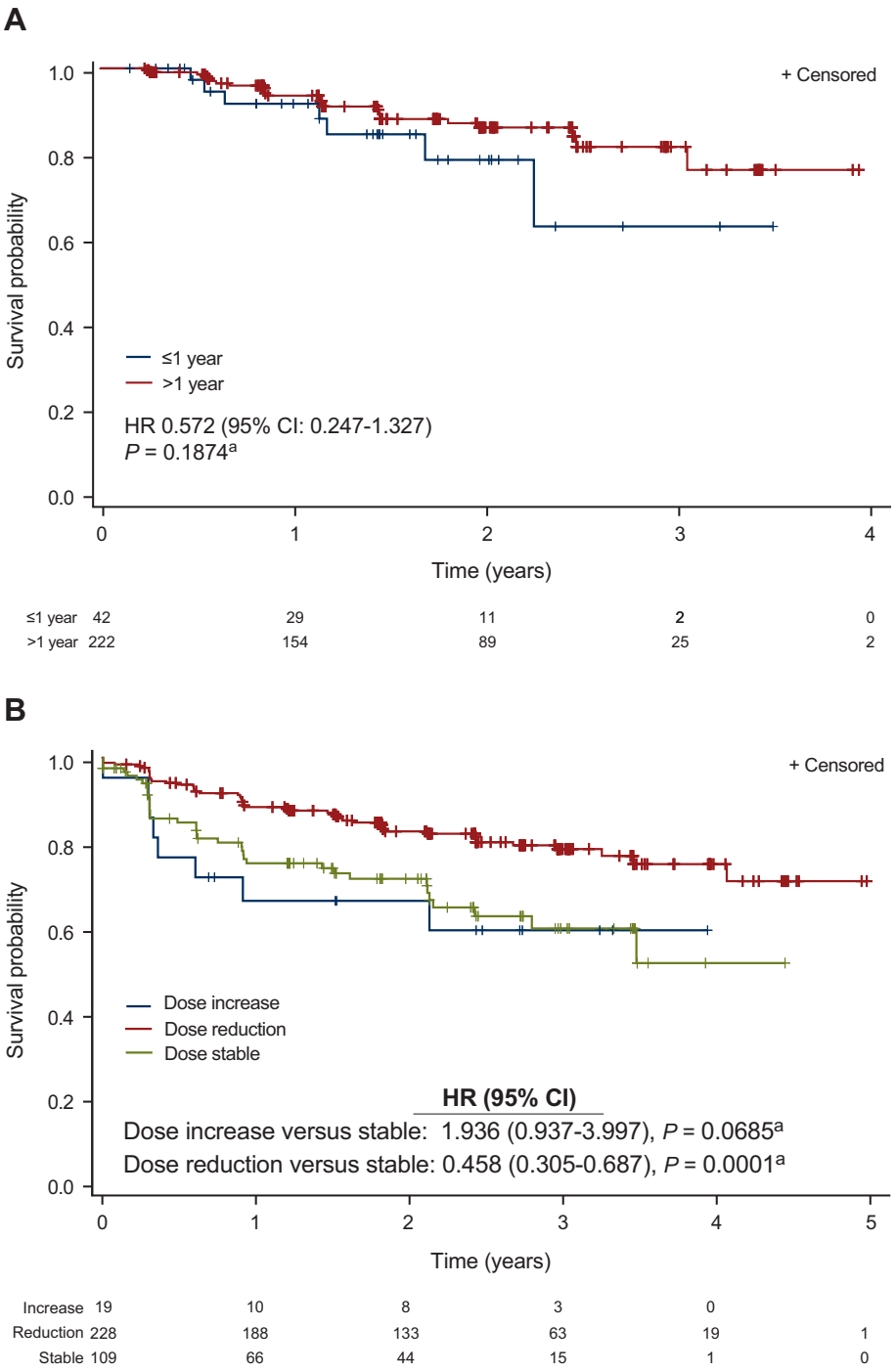


**Figure 3. Disease-free survival in patients remaining on axitinib (A) >1 year versus ≤1 year, (B) at stable dose versus dose reduction or dose increase.**
[a] Log-rank.
CI, confidence interval; HR, hazard ratio.

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## DISCLOSURE

DIQ has provided advisory board services for Pfizer, Bayer, Novartis, Bristol-Myers Squibb, Merck, Exelixis, Genentech, Roche, AstraZeneca and Astellas. CFN has consulted for and/or participated in speakers bureau for Boston Scientific, Janssen, Ferring and Astellas, and has received research funding for Ferring, Astellas, Janssen and Olympus. ME has received honoraria from Bristol-Myers Squibb, Pfizer, Novartis and Ono Pharmaceuticals. EG has received

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## DATA SHARING

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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