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Title:

Efficacy and safety of axitinib for metastatic renal cell carcinoma: Real-world data on patients with renal impairment

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Abstract:

Objectives: Limited information is currently available on the efficacy and safety of axitinib for metastatic renal cell carcinoma (mRCC) patients with renal impairment. Therefore, the present study investigated the efficacy and toxicity of axitinib in patients with chronic kidney disease.

Methods: Post-hoc analyses were performed on a Japanese multicenter cohort study of 477 mRCC patients who received axitinib followed by 1 or 2 regimens of systemic antiangiogenic therapy between January 2012 and December 2016. Differences in clinical characteristics and the efficacy and safety of axitinib were assessed based on pretreatment renal function.

Results: Patients were categorized into the following 5 renal function groups according to baseline renal function: estimated glomerular filtration rate (eGFR) ≥60 ml/min (n=133), 45 ml/min ≤eGFR <60 ml/min (n=153), 30 ml/min ≤eGFR< 45 ml/min (n=130), eGFR <30 ml/min (n=45), and dialysis (n=16). Median progression-free survival (PFS) (95% confidence interval [CI]) in the five groups was 11 (8-16), 14 (11-19), 14 (10–19), 12 (8-24), and 6 (3-NR) months, respectively (p=0.781). After adjustments for treatment-related confounders, renal function group was not a significant prognostic factor for PFS. Objective response rates in the five groups were 22, 23, 23, 18, 20, and 38%, respectively (p=0.468). Regarding adverse events of all grades, hypertension (p=0.0006) and renal and urinary disorders (p<0.0001) were more frequently observed in the eGFR <30 ml/min group than in the other groups.

Conclusions: Since renal function at the initiation of treatment with axitinib does not adversely affect the efficacy of VEGF-TKI therapy, clinicians do not need to avoid its administration to mRCC patients with impaired renal function in consideration of the risk of progression to end-stage renal disease.

Introduction

Renal cell carcinoma (RCC) accounts for 90% of kidney cancers [1]. The outcomes of patients with metastatic renal cell carcinoma (mRCC) have markedly improved with the development of vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKI) followed by immune checkpoint inhibitors (ICIs), such as programmed cell death 1 and cytotoxic T lymphocyte–associated protein 4 and their ligands (programmed cell death ligand 1) [2, 3]. The combination of therapies has been shown to further improve survival and response rates in large phase III trials, such as CheckMate-214 (nivolumab + ipilimumab vs. sunitinib) [4, 5], KEYNOTE-426 (axitinib + pembrolizumab vs. sunitinib) [6, 7], JAVELIN Renal 101 (axitinib + avelumab, vs. sunitinib) [8, 9], CheckMate 9ER (nivolumab + cabozantinib vs. sunitinib) [10, 11], and CLEAR (lenvatinib + pembrolizumab) [12]. These trials demonstrated the superiority of combination immunotherapy over sunitinib monotherapy. Furthermore, nivolumab, cabozantinib, axitinib, and everolimus have been approved as second- and later-line therapies.

Axitinib is a TKI that has been approved as first-line therapy for mRCC in combination with ICIs and is also an option for second- and later-line therapies. The efficacy of axitinib as first-line therapy for mRCC was demonstrated in KEYNOTE-426 and JAVELIN Renal 101 and as second-line therapy for mRCC in the AXIS phase III trial [13].

The prevalence of chronic kidney disease (CKD) is increasing worldwide [14]; however, patients with CKD are excluded from pivotal clinical trials. KEYNOTE-426 and the AXIS trial

excluded patients with serum creatinine levels >1.5 fold the upper limit of the normal range. JAVELIN Renal 101 excluded patients with estimated creatinine clearance <30 mL/min calculated using the Cockcroft-Gault equation. Therefore, patients with severe renal dysfunction are not enrolled in clinical trials because they violate exclusion criteria. However, there are many real-world conditions that require the introduction of vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKIs) despite the presence of severe renal dysfunction. Real-world evidence for the efficacy of VEGFR-TKIs for patients with renal dysfunction is extremely important for clinical practice. Since axitinib plays a central role in the treatment of mRCC as first-line and second- or later-line therapies, its efficacy and safety for patients with renal dysfunction in real-world settings warrant further study.

Materials and Methods

Patients

A retrospective, descriptive analysis of the efficacy of axitinib for mRCC patients who previously received one or two regimens with VEGFR-TKIs between January 2012 and February 2019 at one of the 36 university, public, or private hospitals belonging to the Japan Urologic Oncology Group (JUOG) was performed [15]. The Institutional Review Board of each hospital approved the present study (approval number 018-0003 for Hokkaido University Hospital). Information on patient backgrounds and survival data was retrospectively collected from their

medical charts. All patients (n=590) were ≥20 years, had no previous history of treatment with ICIs; and treatment with axitinib was initiated between January 2012 and December 2016. Patients without a pathological diagnosis (n=43) or with an axitinib treatment period <4 weeks were also excluded (n=49). Twenty-one out of the remaining 498 patients were missing detailed data and, thus, were excluded. Therefore, 477 patients were ultimately examined in the final cohort. Supplementary figure 1 shows a patient flow chart.

Patients initially received axitinib twice daily at a dose of 5 mg (10 mg/day) [13]. Patients who tolerated the standard dose without adverse events (AEs) subsequently received titrated doses. Reduced doses were considered for patients who developed intolerable AEs, and the dose subsequently administered was based on the severity of AEs. CTCAE version 5.0 was used to grade the severity of AEs. AEs caused by axitinib that resulted in dose reductions or the interruption of treatment were retrieved during the review of medical charts.

Patient performance and laboratory data prior to the initiation of treatment with axitinib were collected as the baseline. The pathology was diagnosed according to the 2004 WHO classification. The institutional upper and lower limits of the normal range were used to standardize laboratory data related to the IMDC system [16]. Follow-ups with a physical examination and routine blood tests were typically conducted every 2 to 4 weeks. Patients underwent radiographic CT every 3 months. Although bone scans were not routinely scheduled, they were performed when clinically indicated. The tumor response was recorded as the best response to treatment. i.e., CR, PR, SD, or

PD, based on RECIST version 1.1 [17]. The investigators assessed the objective tumor response, and the objective response rate (ORR) was defined as the percentage of patients with PR or CR to treatment. The following formula was used to calculate the estimated glomerular filtration rate (eGFR): eGFR (ml/minute/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) [18].

The primary outcome of patients with chronic renal failure according to the renal function group was progression-free survival (PFS). PFS was defined as the time from the initiation of treatment with axitinib until tumor progression or death. Patients were categorized into the following groups based on pretreatment renal function: group I (n=16) dialysis, group II (n=45) eGFR< 30 ml/min, group III (n=130) 30 ml/min ≤eGFR <45 ml/min, group IV (n=153) 45 ml/min ≤eGFR <60 ml/min, and group V (n=133) eGFR ≥60 ml/min. Potential prognostic factors for the estimation of PFS in this cohort (sex, age, the disease stage at diagnosis, a previous history of nephrectomy, histology, sarcomatoid features, the number of metastatic sites at the initiation of treatment with axitinib, the number of previous lines of TKI therapy prior to axitinib, the starting dose of axitinib, and the ECOG performance status [PS]) were also examined. The cut-off value for age was set as a median value. Time to treatment failure (TTF) was defined as the time from the initiation of treatment with axitinib to tumor progression/death or the interruption of treatment due to toxicity. Overall survival (OS) was defined as the time from the initiation of treatment with axitinib to death from any cause. Regarding each outcome, patients with no events of interest were also censored at

the date of their last medical examination. Among patients with eGFR <30 ml/min, the time to the introduction of renal replacement therapy was confirmed.

Statistical analysis

The baseline characteristics, treatment responses, and AEs of patients were examined. Categorical variables are shown as percentages and continuous variables as medians and IQR values. The Kaplan-Meier method was used to analyze PFS, TTF, and OS for which median survival and the 95% confidence interval were calculated. The bias introduced by patients with short treatment periods was removed using a 4-week landmark survival analysis. Exploratory analyses of the relationships between patient characteristics prior to the initiation of treatment with axitinib (IMDC risk group [poor, intermediate, or favorable]) and PFS were performed using Cox's model. AEs that led to dose reductions or the interruption of treatment were separately examined in each renal function group. Continuous variables were analyzed using the Mann-Whitney U test, while categorical variables were descriptively analyzed using the chi-squared test. Statistical analyses were performed using JMP version 16 (SAS Institute Inc., Cary, NC, USA), and p-values <0.05 were considered to be significant.

Results

Patient characteristics

The median follow-up for the entire population of 477 patients was 22 months. The patients included in the present study were categorized into 5 groups according to baseline renal function: eGFR ≥60 ml/min (n=133), 45 ml/min ≤eGFR <60 ml/min (n=153), 30 ml/min ≤eGFR< 45 ml/min (n=130), eGFR <30 ml/min (n=45), and dialysis (n=16) (Table 1). The characteristics of each group are summarized in Table 1. The group with an eGFR ≥60 ml/min is younger than all other groups except the dialysis group. Regarding the breakdown of the IMDC risk classification, approximately 20% of patients in the eGFR ≥60 ml/min group were at poor risk for IMDC, a higher proportion than in the other groups (approximately 10%). On the other hand, the percentage of patients with a poor risk was higher and a previous history of nephrectomy was less frequent in the eGFR ≥60 ml/min group than in the other groups. Furthermore, the number of previous lines of TKI therapy before the initiation of treatment with axitinib was higher in the eGFR <60 ml/min groups than in the dialysis and eGFR ≥60 ml/min groups.

Clinical outcomes and AEs

Table 2 shows the treatments received and clinical outcomes. Patients requiring dialysis received an initial dose of 10 mg less frequently than those in the other groups. On the other hand, ORR and the incidence of AEs were similar among the 5 groups. The duration of treatment with axitinib was slightly shorter in the dialysis group than in the other groups.

Table 3 shows axitinib-related AEs leading to dose reductions or the interruption of treatment. Regarding AEs of all grades, hypertension (p=0.0006) and renal and urinary disorders (p<0.0001) were more frequently observed in the eGFR <30 ml/min group than in the eGFR ≥30 ml/min groups. Palmar-plantar erythrodysesthesia syndrome was less frequently detected in the dialysis group (p=0.034). Regarding AEs of grade 3 or higher, renal and urinary disorders were detected in up to 10% of the renal function group with eGFR <30 ml/min. Supplementary table 1 shows the reasons for treatment discontinuation and the initiation of subsequent treatments. Supplementary table 2 lists therapies that were initiated after the treatment with axitinib. Nivolumab was the most frequently introduced agent after the treatment with axitinib. Among patients with eGFR <30 ml/min (n = 45) who were treated with axitinib, 4 (9%) required renal replacement therapy at a median of 14 (range 5-27) months after the initiation of treatment with axitinib.

PFS, treatment failure-free survival, and OS according to renal function

Figure 1 shows the Kaplan-Meier curves of PFS according to renal function. Median PFS was similar among the 5 renal function groups (p=0.7812); 11 months for eGFR ≥60 ml/min, 14 months for 45 ml/min ≤eGFR <60 ml/min, 14 months for 30 ml/min ≤eGFR <45 ml/min, 12 months for eGFR <30 ml/min, and 6 months for the dialysis group. Furthermore, TTF was similar among the 5 renal function groups (p=0.4252) (Figure 2). Median OS was as follows: 21 months for eGFR ≥60

ml/min, 39 months for 45 ml/min ≤eGFR <60 ml/min, 42 months for 30 ml/min ≤eGFR <45 ml/min, 28 months for eGFR <30 ml/min, and 43 months for the dialysis group (Figure 3).

Effects of renal function on treatment outcomes with axitinib

A univariate analysis identified the disease stage at diagnosis (p=0.0001), the number of metastatic sites at the initiation of treatment with axitinib (p<0.0001), the IMDC risk group (p=0.0023), sarcomatoid features (p=0.0025), and a previous history of nephrectomy (p=0.0002) as significant prognostic factors for PFS (Table 4). Following adjustments for these factors, renal function did not correlate with PFS (p=0.6076).

Discussion

Among the 477 patients included in the present study, 283 (59.3%) were included in the renal function group with 30 ml/min ≤ eGFR <60 ml/min and 61 (12.8%) in the renal function group with eGFR <30 ml/min. Treatment outcomes were compared among the five groups categorized according to renal function, and the results obtained revealed no significant differences in PFS, TTF, or ORR. Furthermore, renal function group was not a significant prognostic factor for PFS after adjustments for treatment-related confounders. In other words, differences in renal function at the initiation of treatment with axitinib did not have an impact on treatment effects. On the other hand, regarding OS, patients with eGFR >60 ml/min had a poorer prognosis, which may be attributed to the eGFR ≥60 ml/min group including a large number of patients with a poor risk according to the IMDC classification. Moreover, fewer patients in the eGFR ≥60 ml/min group had undergone nephrectomy than in the other groups, suggesting that there were more patients who could not have their primary tumor removed because their metastases were not controlled by the drug therapy, or their general condition was not good enough.

Patients with comorbidities who did not meet trial eligibility criteria were previously reported to have a poorer prognosis than those who met eligibility criteria [19]. On the other hand, Tatsugami et al. compared the outcomes of patients treated with sorafenib with eGFR<45 ml/min and ≥45 ml/min and found no significant differences in tumor responses or PFS between these groups [20]. Poprach et al. also compared outcomes in three groups of patients treated with sunitinib with eGFR

cut-off values of 30 and 60 ml/min. They reported no significant differences in the disease control rate, PFS, or OS according to the presence or absence of renal dysfunction, while patients with eGFR <30 ml/min had a shorter duration of drug treatment than the two other groups [21]. Since renal function at the initiation of VEGF-TKI therapy does not adversely affect its efficacy, clinicians do not need to avoid treating mRCC patients with impaired renal function.

Chen et al. examined the impact of renal dysfunction on the pharmacokinetics and safety of axitinib and reported that it may be safely administered without the need for dose adjustments regardless of renal function [22]. It is important to note that although renal function did not deteriorate with short-term VEGFR-TKI therapy [23], decreases were noted with long-term VEGFR-TKI therapy [24]. Risk factors for the deterioration of renal function include the duration of TKI treatment, a previous history of hypertension, and poor PS [25, 26]. In the present study, 9% of patients in the eGFR <30 ml/min group received renal replacement therapy at a median of 14 months after the initiation of treatment with axitinib; therefore, this needs to be considered when administering axitinib to patients with impaired renal function.

Reports on the efficacy and safety of axitinib in dialysis patients are very limited [27-29]. Thiery-Vuillemin et al. reported that they evaluated the effect of hemodialysis hemodialysis on axitinib pharmacokinetics and concluded that there is no effect of hemodialysis on axitinib blood concentrations [30]. This finding is consistent with the characterization of axitinib, its high level of protein binding (>99%), primary hepatobiliary excretion together with negligible urinary excretion

suggest that the rate of drug removal by hemodialysis would be minimal [22]. In a case series of 8 dialysis patients, the median initial dose was 8 mg (range 4-8 mg), with a reported ORR of 12.5% and median PFS of 8.12 months [29], similar to the present study. In this study, clinical outcomes in dialysis patients were similar to those in non-dialysis patients, although dialysis patients tended to receive a lower initial dose.

In the present study, the incidence of total AEs related to hypertension and renal and urinary disorders was higher in patients with impaired renal function, particularly in those with eGFR ≤30 ml/min. In addition, the incidence of severe AEs related to renal and urinary disorders was higher in patients with eGFR ≤30 ml/min than in the other groups. This result is consistent with the findings reported by Tatsugami et al. showing that renal failure/dysfunction was significantly more common in patients with renal dysfunction [20]. A previous study demonstrated that more than 30% of patients with CKD stage 4 or higher originally had proteinuria; therefore, caution is needed regarding renal and urinary disorders, including the further deterioration of renal function or proteinuria [31]. The present study showed that dialysis patients were less likely to develop hand-foot syndrome than the other groups; however, this result is not consistent with previous findings [32]. Nevertheless, this result is convincing in dialysis patients because they may be less active.

The limitations of the present study include the retrospective collection of data and the potential underreporting of AEs. Although such detailed treatment response is not available, the effect of 1st line therapy or subsequent therapies could be a potential confounder for PFS/OS.

Furthermore, detailed information was not obtained on AEs, such as renal and urinary disorders, the exacerbation of proteinuria, or elevated creatinine levels. Moreover, patient factors contributing to the deterioration of renal function were not identified due to the lack of a longitudinal follow-up of renal function. In addition, for some patients, dose titration was not strictly followed as there is no predefined protocol due to the retrospective nature of the study. Alternative dosing may be used for some patients with significant comorbidities. Other limitations include the fact that only very healthy dialysis patients can be treated with axitinib and the small number of patients and events in the dialysis group. However, the present study showed that PFS, TTF, and ORR did not significantly differ among mRCC patients with impaired renal function who were treated with axitinib irrespective of renal function. Although there are currently no established evidence-based guidelines for the management of these patients, the present results indicate that clinicians do not need to avoid the administration of axitinib to mRCC patients with impaired renal function in consideration of the risk of progression to end-stage renal disease.

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Conflicts of interest statement

Takahiro Osawa has received honoraria from Takeda. Masatoshi Eto received honoraria for lectures from ONO, BMS, Pfizer, Novartis, MSD, and Chugai, and for research funding from ONO, Pfizer, Chugai, BMS, Eisai, Bayer, and MSD. Hiroyuki Nishiyama has received honoraria from Ono and Chugai, research funds from Ono, Takeda, and Astellas, and reports scholarship endowments from MSD, Astellas, AstraZeneca, and Chugai. Takahiro Kimura received honoraria from Astellas, AstraZeneca, Bayer, Janssen, and Sanofi. Akira Yokomizo received honoraria from Pfizer and MSD. Nobuo Shinohara has received honoraria from Bayer, Ono, and Astellas and reports institutional research funding from Ono, Takeda, Sanofi, Taiho, and Astellas. Yoichi M. Ito is a statistical advisor for Nipro Corporation and an IDMC member for clinical trials of Janssen Pharmaceutical K.K. The other authors have no conflicts of interest.

References

[1] Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017;3:17009.

[2] Lalani AA, McGregor BA, Albiges L, Choueiri TK, Motzer R, Powles T, et al. Systemic Treatment of Metastatic Clear Cell Renal Cell Carcinoma in 2018: Current Paradigms, Use of Immunotherapy, and Future Directions. European urology. 2019;75:100-10.

[3] Salgia NJ, Dara Y, Bergerot P, Salgia M, Pal SK. The Changing Landscape of Management of Metastatic Renal Cell Carcinoma: Current Treatment Options and Future Directions. Current treatment options in oncology. 2019;20:41.

[4] Albiges L, Tannir NM, Burotto M, McDermott D, Plimack ER, Barthelemy P, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open. 2020;5:e001079.

[5] Motzer RJ, Rini BI, McDermott DF, Aren Frontera O, Hammers HJ, Carducci MA, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. The Lancet Oncology. 2019;20:1370-85.

[6] Powles T, Plimack ER, Soulières D, Waddell T, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. The Lancet

Oncology. 2020;21:1563-73.

[7] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380:1116-27.

[8] Choueiri TK, Motzer RJ, Rini BI, Haanen J, Campbell MT, Venugopal B, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2020;31:1030-9.

[9] Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380:1103-15.

[10] Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. New England Journal of Medicine. 2021;384:829-41.

[11] Motzer RJ, Powles T, Burotto M, Escudier B, Bourlon MT, Shah AY, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. The Lancet Oncology. 2022;23:888-98.

[12] Motzer R, Alekseev B, Rha S-Y, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. New England Journal of Medicine. 2021;384:1289-300.

[13] Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378:1931-9.

[14] Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney international. 2019;96:1048-50.

[15] Osawa T, Kojima T, Hara T, Sugimoto M, Eto M, Takeuchi A, et al. Oncological outcomes of a multicenter cohort treated with axitinib for metastatic renal cell carcinoma. Cancer science. 2020;111:2460-71.

[16] Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27:5794-9.

[17] Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45:228-47.

[18] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2009;53:982-92.

[19] Heng DY, Choueiri TK, Rini BI, Lee J, Yuasa T, Pal SK, et al. Outcomes of patients with

metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2014;25:149-54.

[20] Tatsugami K, Oya M, Kabu K, Akaza H. Efficacy and safety of sorafenib for advanced renal cell carcinoma: real-world data of patients with renal impairment. Oncotarget. 2018;9:19406-14.

[21] Poprach A, Bortlicek Z, Melichar B, Lakomy R, Svoboda M, Kiss I, et al. Efficacy of sunitinib in patients with metastatic or unresectable renal cell carcinoma and renal insufficiency. European Journal of Cancer. 2015;51:507-13.

[22] Chen Y, Rini BI, Motzer RJ, Dutcher JP, Rixe O, Wilding G, et al. Effect of renal impairment on the pharmacokinetics and safety of axitinib. Targeted oncology. 2016;11:229-34.

[23] Oya M, Kabu K, Adachi M, Ito Y, Akaza H. Renal function in advanced renal cell carcinoma patients treated with sorafenib: Subset analyses of post-marketing surveillance in Japan with over 3,200 consecutive cases. American Society of Clinical Oncology; 2016.

[24] Takayama T, Kubo T, Yamazaki M, Takeshima S, Komatsubara M, Kameda T, et al. Sunitinib versus sorafenib for patients with advanced renal cell carcinoma with renal impairment before the immune-oncology therapy era. Japanese journal of clinical oncology. 2019;49:1164-71.

[25] Miyake H, Muramaki M, Imai S, Harada K-i, Fujisawa M. Changes in renal function of patients with metastatic renal cell carcinoma during treatment with molecular-targeted agents. Targeted Oncology. 2016;11:329-35.

[26] Launay-Vacher V, Ayllon J, Janus N, Medioni J, Deray G, Isnard-Bagnis C, et al. Evolution of

renal function in patients treated with antiangiogenics after nephrectomy for renal cell carcinoma. Urologic Oncology: Seminars and Original Investigations. 2011;29:492-4.

[27] Nishida H, Fukuhara H, Yamagishi A, Sakurai T, Shibasaki T, Kawazoe H, et al. Sequential molecularly targeted drug therapy including axitinib for a patient with end-stage renal failure and metastatic renal cell carcinoma. Hemodialysis international International Symposium on Home Hemodialysis. 2016;20:E1-4.

[28] Thiery-Vuillemin A, Orillard E, Mouillet G, Calcagno F, Devillard N, Bouchet S, et al. Hemodialysis does not impact axitinib exposure: clinical case of a patient with metastatic renal cell carcinoma. Cancer chemotherapy and pharmacology. 2017;79:1273-6.

[29] Ishihara H, Takagi T, Kondo T, Yoshida K, Okumi M, Tanabe K. Efficacy and safety of axitinib for metastatic renal cell carcinoma in patients on hemodialysis for end‐stage renal disease: Case series of eight patients. International Journal of Urology. 2019;26:1081-2.

[30] Thiery-Vuillemin A, Orillard E, Mouillet G, Calcagno F, Devillard N, Bouchet S, et al. Hemodialysis does not impact axitinib exposure: clinical case of a patient with metastatic renal cell carcinoma. Cancer chemotherapy and pharmacology. 2017;79:1273-6.

[31] Inaguma D, Imai E, Takeuchi A, Ohashi Y, Watanabe T, Nitta K, et al. Risk factors for CKD progression in Japanese patients: findings from the Chronic Kidney Disease Japan Cohort (CKD-JAC) study. Clinical and Experimental Nephrology. 2017;21:446-56.

[32] Josephs D, Hutson TE, Cowey CL, Pickering LM, Larkin JM, Gore ME, et al. Efficacy and

toxicity of sunitinib in patients with metastatic renal cell carcinoma with severe renal impairment or on haemodialysis. BJU international. 2011;108:1279-83.

Figure legends

Figure 1: Kaplan-Meier curves of PFS according to 5 renal function groups.

Figure 2: Kaplan-Meier curves of TTF according to 5 renal function groups.

Figure 3: Kaplan-Meier curves of OS according to 5 renal function groups.

Table 1: Patient characteristics.

Baseline characteristics	Dialysis (n=16)	eGFR <30 ml/min (n=45)	30 ml/min ≤ eGFR <45 ml/min (n=130)	45 ml/min ≤ eGFR <60 ml/min (n=153)	60 ml/min ≤ eGFR (n=133)	All (n=477)	
Age, median (IQR)	63 (53-68)	70 (64.5-76)	67 (63-73.3)	67 (60-74)	64 (56-71)	67 (61-73.5)	**p<0.001**
ECOG-PS							p=0.725
PS0	6 (38%)	23 (51%)	71 (55%)	101 (66%)	73 (55%)	274 (57%)	
PS1	8 (50%)	15 (33%)	42 (32%)	37 (24%)	36 (27%)	138 (29%)	
PS 2 or higher	2 (13%)	4 (9%)	11 (8%)	9 (6%)	19 (14%)	45 (9%)	
NA	0 (0%)	3 (7%)	6 (5%)	6 (4%)	5 (4%)	20 (4%)	
Sex, n (%)							p=0.266
Male	15 (94%)	31 (69%)	102 (78%)	117 (76%)	100 (75%)	365 (77%)	
Female	1 (6%)	14 (31%)	28 (22%)	36 (24%)	33 (25%)	112 (23%)	
Stage at diagnosis, n (%)							p=0.701
Localized	9 (56%)	21 (47%)	65 (50%)	84 (55%)	63 (47%)	242 (51%)	
Metastatic	7 (44%)	24 (53%)	65 (50%)	69 (45%)	70 (53%)	235 (49%)	
Risk group (IMDC), n (%)							**p=0.003**
Favorable	0 (0%)	1 (2%)	18 (14%)	22 (14%)	17 (13%)	58 (12%)	
Intermediate	13 (81%)	35 (78%)	82 (63%)	105 (69%)	73 (55%)	308 (65%)	
Poor	3 (19%)	9 (20%)	23 (18%)	20 (13%)	39 (29%)	94 (20%)	
Na	0 (0%)	0 (0%)	7 (5%)	6 (4%)	4 (3%)	17 (4%)	
Histology, n (%)							p=0.171
Clear cell carcinoma	12 (75%)	45 (100%)	113 (87%)	131 (86%)	120 (90%)	421 (88%)	
Papillary carcinoma (type 1)	0 (0%)	0 (0%)	2 (2%)	3 (2%)	2 (2%)	7 (1%)	
Papillary carcinoma (type 2)	1 (6%)	0 (0%)	7 (5%)	6 (4%)	5 (4%)	19 (4%)	
Chromophobe carcinoma	0 (0%)	0 (0%)	2 (2%)	5 (3%)	3 (2%)	10 (2%)	
Others	3 (19%)	0 (0%)	6 (5%)	8 (5%)	3 (2%)	20 (4%)	
Number of metastatic sites, n (%)							p=0.548
1	5 (31%)	23 (51%)	55 (42%)	67 (44%)	63 (47%)	213 (45%)	

2	5 (31%)	9 (20%)	38 (29%)	51 (33%)	32 (24%)	135 (28%)	
3 or more (range: 3-6)	6 (38%)	13 (29%)	37 (28%)	35 (23%)	38 (29%)	129 (27%)	
Site of metastases, n (%)							
Lung	11 (69%)	36 (80%)	95 (73%)	106 (69%)	87 (65%)	335 (70%)	
Liver	5 (31%)	5 (11%)	17 (13%)	20 (13%)	27 (20%)	74 (16%)	
Bone	6 (38%)	10 (22%)	34 (26%)	40 (26%)	54 (41%)	144 (30%)	
Brain	0 (0%)	0 (0%)	3 (2%)	7 (5%)	13 (10%)	23 (5%)	
Lymph node	5 (31%)	15 (33%)	37 (28%)	43 (28%)	34 (26%)	134 (28%)	
Adrenal gland	4 (25%)	3 (7%)	11 (8%)	6 (4%)	3 (2%)	27 (6%)	
Pancreas	0 (0%)	3 (7%)	13 (10%)	13 (8%)	8 (6%)	37 (8%)	
Others	4 (25%)	10 (22%)	29 (22%)	29 (19%)	19 (14%)	91 (19%)	
Prior nephrectomy, n (%)	16 (100%)	44 (98%)	122 (94%)	141 (92%)	110 (83%)	433 (91%)	**p=0.002**
Number of previous lines of TKI therapy before axitinib, n (%)							**p=0.003**
1 line	16 (100%)	37 (82%)	106 (82%)	129 (84%)	125 (94%)	413 (87%)	
2 lines	0 (0%)	8 (18%)	24 (18%)	24 (16%)	8 (6%)	64 (13%)	
First-line therapy, n (%)							p=0.383
Sorafenib	5 (31%)	10 (22%)	36 (28%)	36 (24%)	26 (20%)	113 (24%)	
Sunitinib	9 (56%)	30 (67%)	84 (65%)	104 (68%)	102 (77%)	329 (69%)	
Pazopanib	2 (13%)	5 (11%)	10 (8%)	13 (9%)	5 (4%)	35 (7%)	
Second-line therapy, n (%)							**p=0.029**
Sorafenib	0 (0%)	3 (7%)	9 (7%)	7 (5%)	2 (2%)	21 (4%)	
Sunitinib	0 (0%)	3 (7%)	10 (8%)	15 (10%)	6 (5%)	34 (7%)	
Pazopanib	0 (0%)	2 (4%)	5 (4%)	2 (1%)	0 (0%)	9 (2%)	
Sarcomatoid features, n (%)	1 (6%)	5 (11%)	7 (5%)	13 (9%)	16 (12%)	42 (9%)	p=0.383

Table 2: Treatment received and clinical outcomes.

Treatment received	Dialysis (n=16)	eGFR <30 ml/min (n=45)	30 ml/min ≤ eGFR <45 ml/min (n=130)	45 ml/min ≤ eGFR <60 ml/min (n=153)	60 ml/min ≤ eGFR (n=133)	All (n=477)	
Axitinib duration (months) median (IQR)	5 (3.25-22.75)	9 (5-23)	8 (3.75-18.25)	10 (5-24.5)	7 (3-16.5)	8 (4-20)	p=0.105
Initial dose of 10 mg, n (%)	7 (44%)	33 (73%)	115 (88%)	124 (81%)	117 (88%)	396 (83%)	**p<0.001**
Dose escalation, n (%)	0 (0%)	4 (9%)	16 (12%)	23 (15%)	21 (16%)	64 (13%)	p=0.160
Dose reduction, n (%)	2 (13%)	10 (22%)	28 (22%)	34 (22%)	28 (21%)	102 (21%)	p=0.918
Clinical outcomes							
Best response							p=0.468
Complete response, n (%)	0 (0%)	1 (2%)	3 (2%)	4 (3%)	2 (2%)	10 (2%)	
Partial response, n (%)	6 (38%)	8 (18%)	21 (16%)	31 (20%)	28 (21%)	94 (20%)	
Stable disease, n (%)	7 (44%)	30 (67%)	77 (59%)	87 (57%)	69 (52%)	270 (57%)	
Progression of disease, n (%)	3 (19%)	6 (13%)	26 (20%)	28 (18%)	34 (26%)	97 (20%)	
Not assessed, n (%)	0 (0%)	0 (0%)	3 (2%)	3 (2%)	0 (0%)	6 (1%)	
Toxicity, Adverse events, n (%)							
All grades	10 (3%)	26 (9%)	77 (27%)	85 (30%)	90 (31%)	288 (60%)	p=0.323
Grade 3 or higher	4 (3%)	15 (12%)	37 (30%)	31 (25%)	38 (30%)	125 (26%)	p=0.423

Table 3: Axitinib-related adverse events leading to dose reductions or treatment interruption

All grades

	Dialysis (n=16)	eGFR <30 ml/min (n=45)	30 ml/min ≤ eGFR <45 ml/min (n=130)	45 ml/min ≤ eGFR <60 ml/min (n=153)	60 ml/min ≤ eGFR (n=133)	All (n=477)	
Diarrhea	3 (19%)	4 (9%)	29 (19%)	37 (28%)	28 (22%)	101 (21%)	p=0.395
Proteinuria	0 (0%)	9 (20%)	24 (16%)	26 (20%)	15 (12%)	74 (16%)	p=0.332
Malaise	3 (19%)	5 (11%)	15 (10%)	25 (19%)	19 (15%)	67 (14%)	p=0.888
Anorexia	1 (6%)	6 (13%)	18 (12%)	12 (9%)	18 (13%)	55 (12%)	p=0.625
Palmar-plantar erythrodysesthesia syndrome	0 (0%)	2 (4%)	5 (3%)	21 (16%)	18 (14%)	46 (10%)	**p=0.034**
Gastrointestinal disorder	2 (13%)	4 (9%)	12 (8%)	9 (7%)	9 (7%)	36 (8%)	p=0.935
Hypertension	2 (13%)	8 (18%)	7 (5%)	8 (6%)	2 (2%)	27 (6%)	**p=0.006**
Mucositis oral	0 (0%)	2 (4%)	4 (3%)	12 (9%)	6 (5%)	24 (5%)	p=0.592
Renal and urinary disorders	0 (0%)	10 (22%)	6 (4%)	7 (5%)	0 (0%)	23 (5%)	**p<0.001**
Hypothyroidism	0 (0%)	2 (4%)	7 (5%)	2 (2%)	10 (8%)	21 (4%)	p=0.243
Blood and lymphatic system disorders	1 (6%)	1 (2%)	4 (3%)	6 (5%)	8 (6%)	20 (4%)	p=0.911
Infections and infestations	2 (13%)	2 (4%)	1 (1%)	7 (5%)	7 (5%)	19 (4%)	p=0.367
General disorders and administration site conditions	0 (0%)	2 (4%)	6 (4%)	8 (6%)	2 (2%)	18 (4%)	p=0.742
Respiratory, thoracic, and mediastinal disorders	0 (0%)	0 (0%)	2 (1%)	1 (1%)	7 (5%)	10 (2%)	p=0.179
Hepatobiliary disorders	0 (0%)	1 (2%)	2 (1%)	4 (3%)	2 (2%)	9 (2%)	p=0.981
Musculoskeletal and connective tissue disorders	0 (0%)	0 (0%)	3 (2%)	2 (2%)	2 (2%)	7 (1%)	p=0.956
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	2 (1%)	3 (2%)	2 (2%)	7 (1%)	p=0.967
Hoarseness	0 (0%)	0 (0%)	2 (1%)	4 (3%)	0 (0%)	6 (1%)	p=0.626
Nervous system disorders	0 (0%)	0 (0%)	3 (2%)	1 (1%)	2 (2%)	6 (1%)	p=0.905
Cardiac disorders	1 (6%)	0 (0%)	2 (1%)	0 (0%)	2 (2%)	5 (1%)	p=0.834
Others	0 (0%)	0 (0%)	6 (4%)	3 (2%)	2 (2%)	11 (2%)	p=0.631

Grade 3 or higher

	Dialysis (n=16)	eGFR<30 ml/min (n=45)	30 ml/min ≤eGFR <45 ml/min (n=130)	45 ml/min ≤eGFR <60 ml/min (n=153)	eGFR ≥60 ml/min (n=133)	All (n=477)	
Proteinuria	0 (0%)	2 (4%)	7 (5%)	14 (9%)	5 (4%)	28 (6%)	p=0.498
Diarrhea	0 (0%)	2 (4%)	7 (5%)	8 (5%)	7 (5%)	24 (5%)	p=0.997
Anorexia	0 (0%)	2 (4%)	5 (4%)	3 (2%)	7 (5%)	17 (4%)	p=0.840
Hypertension	1 (6%)	4 (9%)	5 (4%)	3 (2%)	1 (1%)	14 (3%)	p=0.233
Blood and lymphatic system disorders	0 (0%)	0 (0%)	3 (2%)	5 (3%)	5 (4%)	13 (3%)	p=0.952
Malaise	0 (0%)	1 (2%)	2 (2%)	5 (3%)	5 (4%)	13 (3%)	p=0.960
Infections and infestations	2 (12%)	2 (4%)	0 (0%)	3 (2%)	5 (4%)	12 (3%)	p=0.196
Palmar-plantar erythrodysesthesia syndrome	0 (0%)	1 (2%)	0 (0%)	3 (2%)	7 (5%)	11 (2%)	p=0.176
Gastrointestinal disorder	0 (0%)	1 (2%)	2 (2%)	2 (1%)	5 (4%)	10 (2%)	p=0.818
Renal and urinary disorders	0 (0%)	4 (9%)	3 (2%)	3 (2%)	0 (0%)	10 (2%)	p=0.058
Mucositis oral	0 (0%)	0 (0%)	0 (0%)	2 (1%)	4 (3%)	6 (1%)	p=0.499
Others	1 (6%)	1 (2%)	7 (5%)	9 (6%)	9 (7%)	27 (6%)	p=0.940

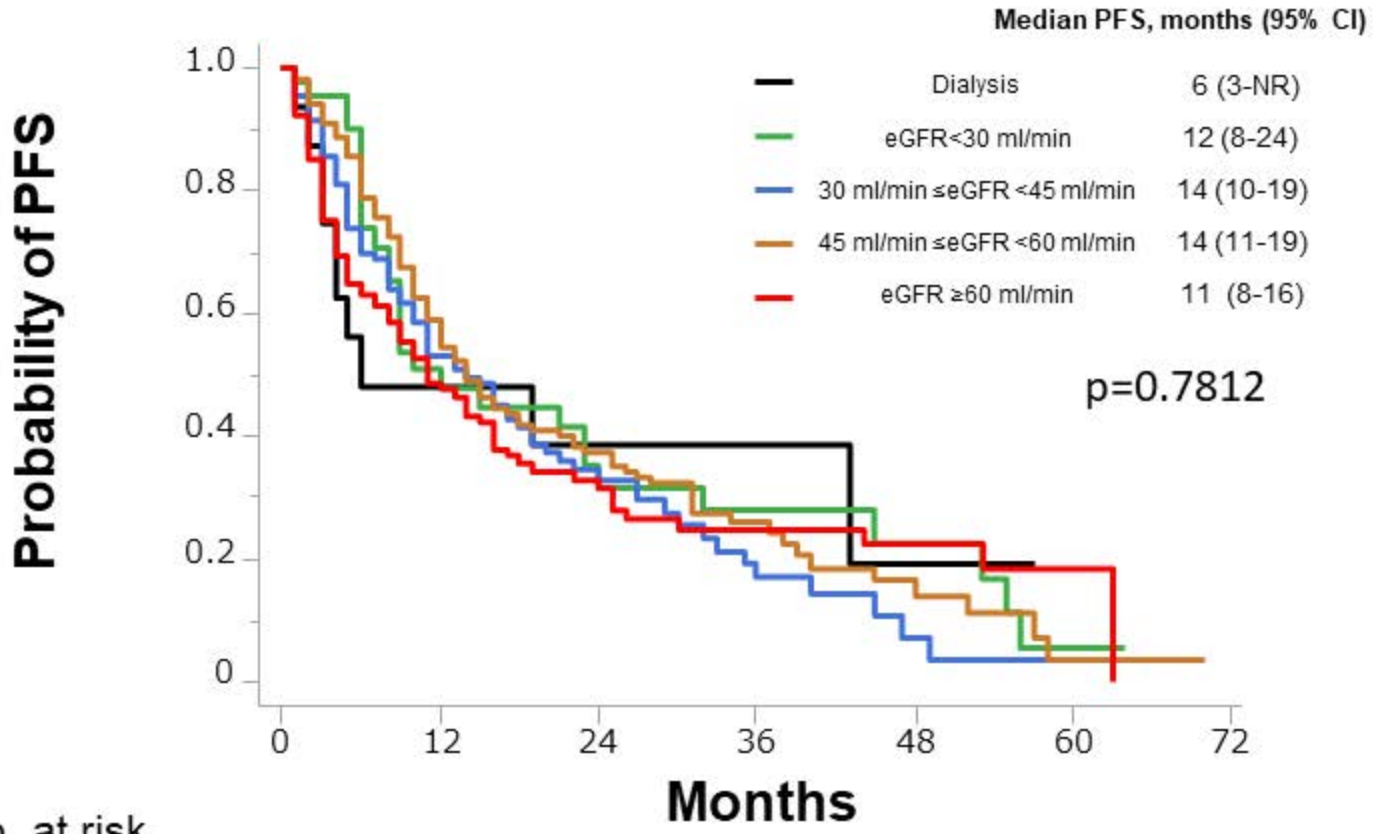
Table 4: Univariate and multivariable analyses of progression-free survival; A 1-month landmark analysis

		HR	95% CI		p-value	HR	95% CI		p-value
Age	<67	1			0.1282				
	>67	0.837907	0.667188	1.052309					
Sex	Male	1			0.6635				
	Female	1.061824	0.810414	1.391229					
ECOG PS	0, 1	1			0.0552				
	2 or more	1.449734	0.991694	2.119333					
Stage at diagnosis	localized	1			0.0001*	1			0.0242*
	metastasized	1.571678	1.249124	1.977524		1.336241	1.038609	1.719166	
No. of metastatic sites at the time of axitinib therapy	1	1			<.0001*	1			0.0003*
	2 or more	1.651041	1.301597	2.094301		1.576806	1.234397	2.014196	
IMDC risk	Poor	1			0.0023*	1			0.0837
	Favorable	2.16163	1.404692	3.326457	0.0005*	1.67759	1.075446	2.616877	0.0226*
	Intermediate	1.49403	1.116919	1.998468	0.0068*	1.325019	0.977679	1.795757	0.0696
Histology	Other	1							
	Clear cell carcinoma	0.922751	0.645336	1.319421	0.6595				
Sarcomatoid features	No	1			0.0025*	1			0.0047*
	Yes	1.769805	1.22239	2.562365		1.743594	1.185484	2.564456	
Prior nephrectomy	Yes	1			0.0002*	1			0.0554
	No	2.020786	1.403135	2.910324		1.492161	0.99082	2.247172	
Number of previous lines of TKI therapy before axitinib	1 line	1			0.6922				
	2 lines	1.067124	0.773598	1.472021					
Starting dose of axitinib	less than 10 mg	1			0.6282				
	10 mg	1.149041	0.842392	1.567316	0.3804				
	more than 10 mg	0.868077	0.269835	2.792659	0.8124				
Renal function (eGFR: ml/min/1.73 m^2)	Dialysis	1			0.7938	1			0.6076

eGFR<30 ml/min (n=45)	1.137921	0.554054	2.337073	0.7249	1.249347	0.606821	2.572202	0.5457
30 ml/min ≤eGFR <45 ml/min (n=130)	0.962914	0.497756	1.862766	0.9106	1.022558	0.524869	1.992166	0.9477
45 ml/min ≤eGFR <60 ml/min (n=153)	1.115507	0.580866	2.142246	0.7427	1.232857	0.637246	2.385164	0.5341
eGFR ≥60 ml/min (n=133)	0.959623	0.497468	1.85113	0.9021	1.014874	0.519103	1.984132	0.9656

Progression free survival

Figure 1 :

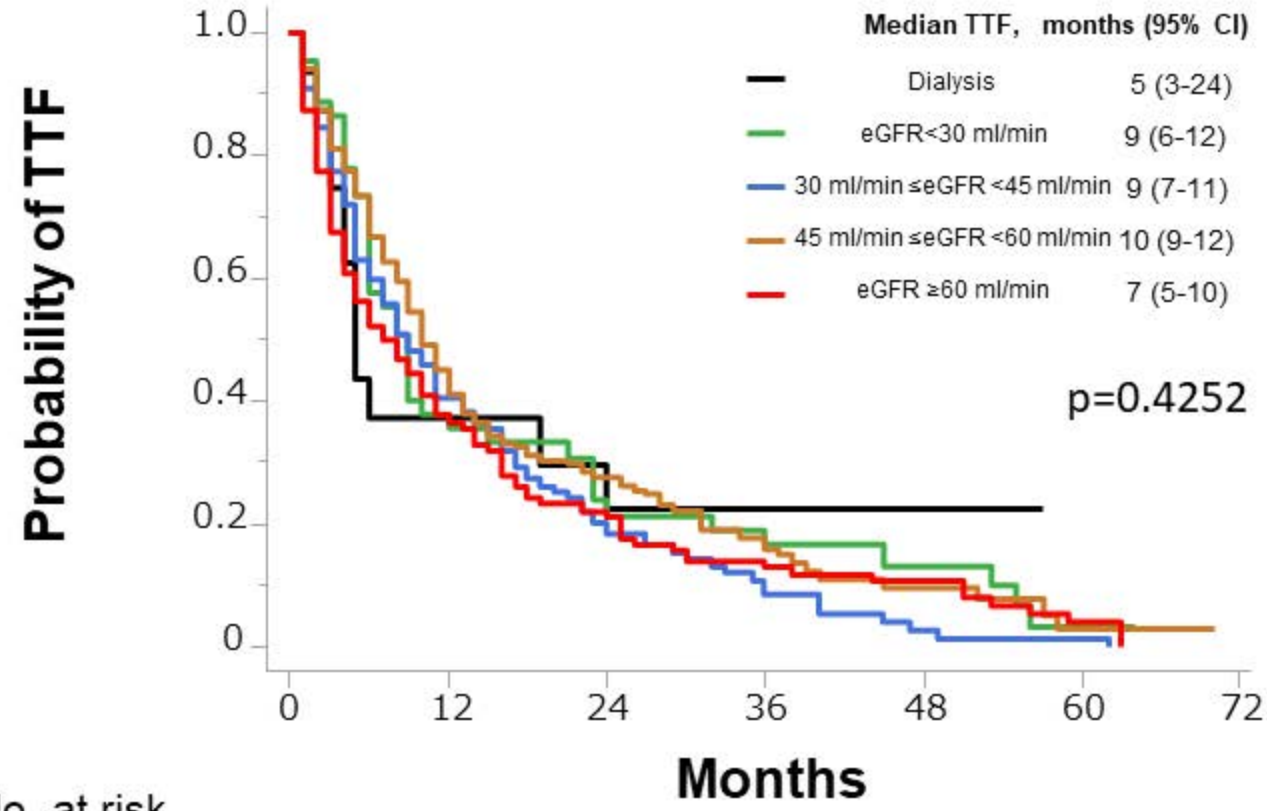


No. at risk

Month	0	12	24	36	48	60
Hemodialysis	16	6	5	4	2	0
eGFR≤30ml/min	45	17	10	8	5	2
30ml/min≤eGFR<45ml/min	130	54	22	9	3	1
45ml/min≤eGFR<60ml/min	153	68	39	19	6	2
60ml/min≤eGFR	133	48	25	14	9	4

Time to treatment failure

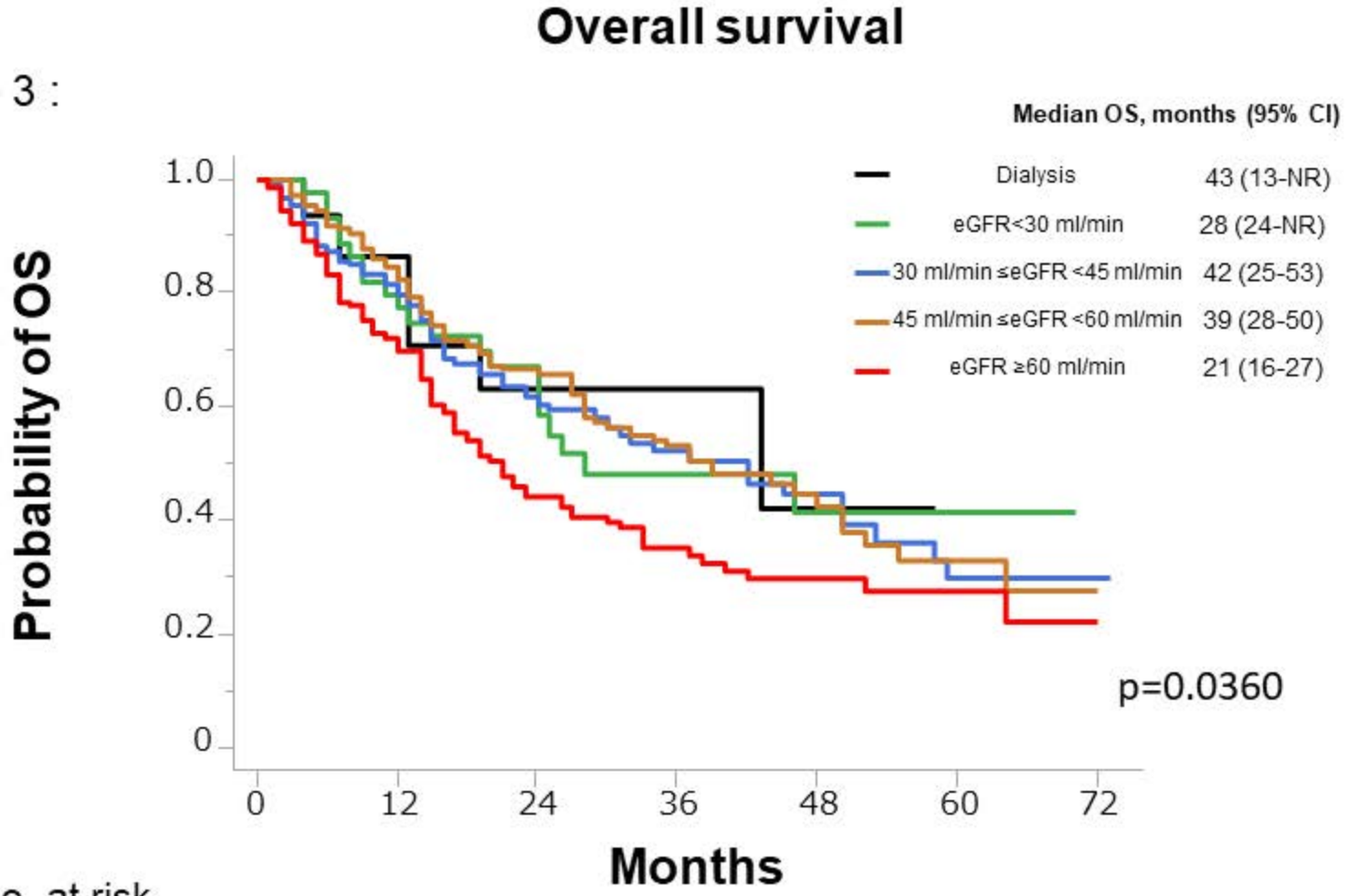
Figure 2 :



No. at risk

Month	0	12	24	36	48	60
Hemodialysis	16	6	4	3	3	0
eGFR<30ml/min	45	17	10	8	5	2
30ml/min≤eGFR<45ml/min	130	54	22	9	3	2
45ml/min≤eGFR<60ml/min	153	67	39	18	6	2
60ml/min≤eGFR	133	47	25	14	9	4

Figure 3 :



No. at risk

Month	0	12	24	36	48	60	72
Hemodialysis	16	12	7	4	2	0	0
eGFR<30ml/min	45	33	23	12	7	3	0
30ml/min≤eGFR<45ml/min	130	90	56	31	21	9	2
45ml/min≤eGFR<60ml/min	153	124	89	47	21	9	1
60ml/min≤eGFR	133	90	50	29	17	10	1