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ORIGINAL ARTICLE

Efficacy analyses of axitinib and nivolumab in metastatic renal cell carcinoma after failure of targeted therapy: which is better?

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Summary

Purpose: *The objective of the present study was to compare the efficacy of axitinib and nivolumab in metastatic renal cell carcinoma (mRCC) previously treated with targeted therapy.*

Methods: *A total of 79 patients were enrolled (39 patients in axitinib group, 40 patients in nivolumab group). Survival outcomes of patients, progression-free survival (PFS), and overall survival (OS) were estimated using the Kaplan-Meier method and compared with the log-rank test. The associations between potential prognostic variables and OS were evaluated in univariate and multivariate Cox regression analyses.*

Results: *The median PFS and OS of all cohort were 8.1 and 36.6 months, respectively. Higher PFS and OS were evaluated in axitinib group than nivolumab group (PFS: 9.4 months vs 6.3 months, p=0.386; OS: 38.2 months vs 36.6 months, p=0.671, respectively). Patients treated with axitinib had numerically higher objective response rate (ORR) and disease control rate (DCR) than those treated with nivolumab (ORR: 43.6% vs 27.6%, p=0.157, DCR: 74.4% vs 62.5%, p=0.157, respectively). Multivariate analysis revealed that the independent predictors of OS were higher tumor grade (hazard ratio [HR]: 6.178, p=0.004), worse response to axitinib and nivolumab (HR:4.902, p=0.011), the presence of lung metastasis (HR:15.637, p=0.002) and the presence of liver metastasis (HR:12.010, p=0.001).*

Conclusion: *Comparable survival outcomes were detected in the axitinib and nivolumab groups. However, head to head comparisons are needed to highlight the relative efficacy of these therapies in mRCC..*

Key words: *axitinib, metastatic renal cell carcinoma, nivolumab, prognosis, targeted therapy*

Introduction

Kidney cancer constitutes aproximately 4% of all cancers [1]. In the recent two decades, the survival outcomes of metastatic renal cell carcinoma (mRCC) have been improved thanks to the development of targeted agents and immune check point inhibitors (ICI). Although first-line treatment of mRCC has been evolving from targeted therapy era directing vascular endotelial growth factor (VEGF) into immune check point inhibitor ICI or their combination, anti-VEGF pathway inhibitors remain preferred options as a first-line treatment [2]. Axitinib and nivolumab are the treatment al-

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ternatives of mRCC which were progressed with first-line targeted therapy, sunitinib or pazopanib.

Axitinib gained approval as a second-line therapy in mRCC patients based on the AXIS trial which showed that treatment with axitinib was significantly better than sorafenib in terms of progression-free survival (PFS) and objective response rates (ORR) [3]. Similarly, nivolumab, a human IgG4 programmed death (PD) 1 ICI antibody, was approved as a subsequent therapy in mRCC patients after progression with one or two targeted therapies based on a randomized phase 3 study in which nivolumab demonstrated better overall survival (OS) than everolimus [4]. The superiority of axitinib over nivolumab or *vice versa* has not yet been clarified due to the lack of head to head comparison of these agents in randomized trials. There are conflicting results about survival outcomes with these agents in the literature. For instance, Amzal et al reported more favorable survival outcomes with nivolumab than axitinib after previous therapy with targeted agents in a network meta-analysis [5]. However, a previous study by Suzuki et al demonstrated that treatment with axitinib was more clinically beneficial providing better tumor response rates than nivolumab [6].

The objective of the present study was to compare the efficacy of nivolumab and axitinib in mRCC patients who progressed with targeted therapy (sunitinib or pazopanib).

Methods

Participants and study design

Patients treated with axitinib and nivolumab after treatment failure with targeted therapy between January, 1, 2010, and March, 1, 2021 at Hacettepe University Cancer Institute (Ankara, Turkey), a comprehensive cancer center, were enrolled in this retrospective observational study. Patients' clinical, pathological and labaratory values

Table 1. Baseline clinicopathologic characteristics of the patients stratified according to treatment groups

Characteristics	*All patients (n=79)*	*Axitinib group (n=39)*	*Nivolumab group (n=40)*	*p value*
Age (years)	59 (52-64)	55 (50-62)	60 (56-65)	0.022
Gender				0.430
Female	34.2	38.5	30	
Male	65.8	61.5	70	
Histology				0.011
Clear cell	77.9	65.8	89.7	
Non-clear cell	22.1	34.2	10.3	
Tumor grade				0.740
Grade I- II	31.5	33.3	29.7	
Grade III-IV	68.5	66.7	70.3	
Metastatic sites				
Lung	78.5	69.2	87.5	0.048
Liver	27.8	33.3	22.5	0.283
Bone	33.3	28.9	37.5	0.423
Adrenal	14.1	21.1	7.5	0.086
Brain	6.3	7.7	5	0.623
Number of metastatic sites				0.889
≤2	60.8	61.5	60	
>2	39.2	38.5	40	
IMDC risk group				0.713
Favorable	12.8	10.5	15	
Intermediate	66.7	65.8	67.5	
Poor	20.5	23.7	17.5	
Treatment group				0.060
Pazopanib	75.9	66.7	85	
Sunitinib	24.1	33.3	15	
First line PFS	10.9 (5.9-19.3)	11.5 (5.5-19.3)	9.8 (5.9-24.3)	0.927

Continuous and dichotomous characteristics are shown as median with interquartile range and percentages, respectively. IMDC: international metastatic renal cell carcinoma database consortium, PFS: progression free survival.

were recorded from the electronic records of our institute. The whole cohort was composed of patients with histologically confirmed mRCC who were previously treated with one (targeted therapy, 24.1%) or two treatment lines (immunotherapy and targeted therapy, 75.9%). All the patients have been treated with targeted therapy (sunitinib or pazopanib) before treatment with axitinib or nivolumab. In our institute, tumor grading of papillary and clear cell renal cell carcinomas (RCCs) has been evaluated with Fuhrman system [7], whereas Paner system has been used for grading of chromophobe RCC [8]. Additional necessary inclusion criteria were age ≥ 18 years and measurable disease according to RECIST version 1.1 (Response Evaluation Criteria in Solid Tumors). Patients with adverse effects requiring steroid treatment (equivalent or >10 mg of prednisone/day) were excluded. Patients' risk estimation was evaluated according to the International mRCC Database Consortium (IMDC) [9]. This study was approved by the ethics committee of Haceteppe University.

Statistics

Continuous and dichotomous variables were presented as median with interquartile range and percentages, respectively. Chi-square test and Mann-Whitney U were done to compare categorical and continuous variables in the independent groups, respectively. PFS was defined as the time interval from treatment initiation of axitinib and nivolumab to the first progression according to RECIST or death from any reason and OS was defined as the time interval from treatment initiation of these drugs to the date of death. Kaplan-Meier method was used to estimate the survival outcomes (PFS and OS) and log-rank test was used for comparison of prognostic groups. Univariate and multivariate Cox regression analyses were done to determine the associations between clinicopathologic variables and OS. Variables with a p value ≤ 0.2 in the univariate analyses were used for multivariate analyses. All the statistical analyses were performed using SPSS, version 25 (IBM Inc., Armonk, NY, USA) software and a p value<0.05 was considered statistically significant.

Results

Patient characteristics

A total of 79 patients who were treated with axitinib or nivolumab after progression with targeted therapy (pazopanib or sunitinib) were enrolled (39 patients in the axitinib group and 40 patients in the nivolumab group). Clinicopathological characteristics of the whole cohort and axitinib and nivolumab treatment groups are presented in Table 1. The median age was 59 years (25^{th}-75^{th} percentile: 52-64) and 65.8% of all cohort were male. Our cohort was mostly composed of tumors with clear cell histology (77.9%) and grade III-IV tumors (68.5%). Pazopanib was the most commonly used agent before treatment with axitinib and nivolumab (75.9%) and the median PFS with sunitinib and pazopanib was 10.9 months. The most common metastatic regions at treatment initiation with axitinib and nivolumab were lung (78.5%) followed by bone (33.3%) and liver (27.8%). Additionally, most of the patients had

Table 2. Response evaluation of the patients stratified according to treatment groups

Response	*Axitinib (n=39)* *n (%)*	*Nivolumab (n=41)* *n (%)*
CR	1 (2.6)	1 (2.5)
PR	16 (41)	10 (25)
SD	12 (30.8)	14 (35)
PD	10 (25.6)	15 (37.5)
ORR	17 (43.6)	11 (27.5)
DCR	18 (74.4)	4 (62.5)

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; ORR: overall response rate; DCR: disease control rate.

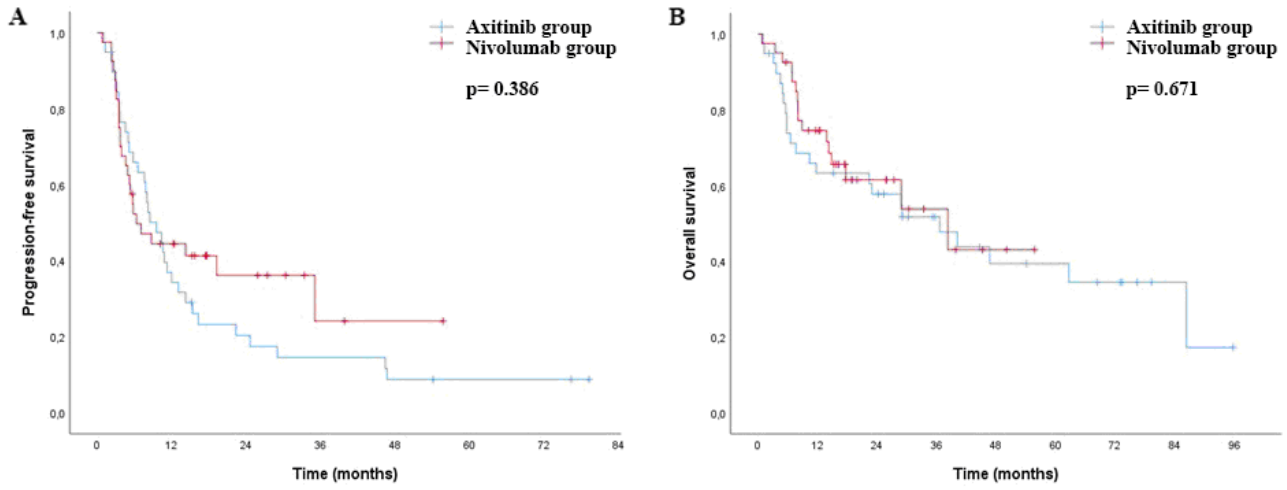

Figure 1. A: Median PFS in patients treated with axitinib and nivolumab. **B:** Median OS in patients treated with axitinib and nivolumab.

one or two metastatic sites (60.8%) and patients in both of the treatment groups were categorized in intermediate IMDC risk group (65.8% in the axitinib group, 67.5% in the nivolumab group).

Survival outcomes

The median follow-up time was 17.4 months. The median PFS and OS of all patients were 8.1 months (95% confidence interval [CI], 4.6 to 11.6) and 36.6 months (95% CI, 25.6 to 47.6), respectively. The median PFS of patients treated with axitinib was higher than those treated with nivolumab (9.4 months, 95% CI: 5.9 to 13 vs 6.3 months, 95% CI: 2.2 to 10.3, p=0.386, respectively) (Figure 1A), whereas the median OS of patients treated with nivolumab was higher than those treated with axitinib (38.2 months, 95% CI: 10.6 to 65.8 vs 36.6 months, 95% CI: 16 to 57.2, p=0.671, respectively) (Figure 1B). The best response to axitinib and nivolumab is presented in Table 2. Partial responses were determined in 16 patients (41%) in the axitinib group and in 10 patients (25%) in the nivolumab group. In both of the treatment groups, complete response was determined in one patient (2.6% in the axitinib group, 2.5% in the nivolumab group). The ORR and disease control rate (DCR) were higher with axitinib than nivolumab (ORR: 43.6% vs 27.5%, p=0.157; DCR: 74.4% vs 62.5%, p=0.326).

As shown in Table 3, the univariate Cox regression analyses revealed that the significant variables associated with OS were the presence of liver metastasis at treatment initiation with nivolumab and axitinib (hazard ratio [HR], 2.068; 95% CI, 1.087 to 3.936; p=0.027) and the response to these agents (HR, 2.609; 95% CI, 1.246 to 5.460; p=0.011). However, the potential variables associated with OS

Table 3. Univariate analyses determining the associations between clinicopathological parameters and OS

Variables	*HR (95% CI)*	*95% CI*		*p value*
		Lower	*Upper*	
Age, years < 65 vs ≥ 65	0.986	0.956	1.017	0.384
Gender, Female vs male	1.214	0.607	2.426	0.584
Tumor grade, I-II vs III-IV	1.588	0.761	3.315	0.218
Histology, Clear cell vs Non-clear cell	1.499	0.724	3.106	0.276
IMDC risk group				0.053
Favorable	Reference			
Intermediate	0.735	0.249	2.167	0.577
Poor	1.776	0.570	5.531	0.322
First-line treatment type, Sunitinib vs pazopanib	0.678	0.341	1.349	0.268
First-line treatment duration, >median vs ≤median	0.803	0.424	1.520	0.500
Response to second line treatment, CR, PR vs SD, PD	2.609	1.246	5.460	0.011
Second line therapy, axitinib vs nivolumab	0.755	0.378	1.509	0.426
Lung metastasis, absent vs present	2.054	0.854	4.944	0.108
Liver metastasis, absent vs present	2.068	1.087	3.936	0.027
Bone metastasis absent vs present	1.623	0.845	3.118	0.146
Brain metastasis absent vs present	2.387	0.722	7.896	0.154
Adrenal metastasis absent vs present	0.721	0.255	2.040	0.538

IMDC: international metastatic renal cell carcinoma database consortium; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

Table 4. Multivariate analyses determining independent parameters in predicting OS

Variables	*HR (95% CI)*	*95% CI*		*p value*
		Lower	*Upper*	
Tumor grade, I-II vs III-IV	6.178	1.769	21.573	0.004
Response to second line treatment , CR, PR vs SD, PD	4.902	1.445	16.634	0.011
Lung metastasis, absent vs present	15.637	2.676	91.366	0.002
Liver metastasis, absent vs present	12.010	2.677	53.879	0.001

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

were tumor grade (p=0.218), the presence of lung metastasis (p=0.108), bone metastasis (p=0.146), brain metastasis (p=0.154) and IMDC scoring system (p=0.053). As shown in Table 4, the multivariate Cox regression analyses that were performed with the significant and potential variables detected in the univariate analyses showed that the independent variables for prediction of OS were higher tumor grade (HR: 6.178, p=0.004), presence of lung metastasis (HR:15.637, p=0.002), presence of liver metastasis (HR: 12.010, p=0.001) and poorer response to axitinib and nivolumab (HR: 4.902, p=0.011).

Discussion

According to recent randomized trials, the combination of ICI and targeted therapy or ICIs have consisted of the cornerstone of previosly untreated mRCC because of the gained survival improvement over sunitinib [10,11]. However, given the longer experience with targeted therapy agents than ICIs, targeted therapy seems an effective alternative to these combination therapies. Addditionally, after progression with these agents, treatment sequencing is well-established in starting treatment with targeted therapy. Regarding the cost of these therapies, there is an additional concern with the use of ICI-based regimens [12]. Therefore, the present study was conducted to provide further knowledge about the efficacy of an ICI, nivolumab, and a second generation VEGF receptor inhibitor, axitinib, in mRCC after failure of systematic treatment.

Axitinib and nivolumab were effective approved therapies in mRCC after progression with first-line targeted therapies. In an Asian multicenter study, which compared axitinib with sorafenib as a second-line therapy following progression with sunitinib or cytokine-based regimen showed that axitinib was associated with better ORR than sorefenib (%23.7, 95% CI, 16.8%-31.8% vs 10.1%, 95% CI 4.2%-19.8%, respectively) [13]. Similarly, a European study investigated the effect of axitinib as a second-line therapy in comparision to everolimus in mRCC patients previously treated with multiple agents including VEGF pathway inhibitors, m-TOR pathway inhibitor, or the combination of interferon and bevacizumab and they reported that axitinib showed numerically but not significantly higher DCR than everolimus (73% vs 69%, respectively) [14]. Consistent with these reports, the present study demonstrated that the percents of ORR and DCR in patients treated with axitinib were 43.6%, and 74.4%, respectively. In previous studies, it was demonsrated that PD-ligand 1 (PD-L1) expression is related to inferior survival outcomes in RCC patients, probably due to its immunosuppressive effect [15,16]. However, it has been speculated that patients with PD-L1 expression had improved OS than those with no expression in several cancers treated with nivolumab because of the improvement of anti-tumor immunity mediated by immune check point blockage of nivolumab [17]. In the pivotal study of nivolumab as a subsequent therapy after failure of one or two anti-angiogenic therapies, nivolumab showed significant activity across all PD-L1 sub-groups over everolimus [4]. Yip et al reported the tumor responses to ICIs at different therapy lines using the IMDC database, and they demonstrated that the ORR and DCR in mRCC treated with nivolumab as a second line therapy were 22% and 54%, respectively [18]. Similar to these results, we found that the ORR and DCR were 26.7%, and 60.8%, respectively. While both axitinib and nivolumab are effective in the treatment of mRCC after first-line treatment failure with targeted therapies according to the studies mentioned above, there is a limited knowledge in the literature in respect to head to head comparison of these agents. First direct comparison of nivolumab and axitinib as a second-line therapy was evaluated in an Asian study by Suzuki et al who found that there was a tendency favoring axitinib over nivolumab for PFS, whereas no significant difference was reported for OS (PFS: 10.3 months versus 7.3 months, p=0.067; OS: both not reached, p=0.581, respectively). Smilar to this study, our results showed that treatment with axitinib or nivolumab had no significant effect for PFS and OS (p=0.386 for PFS; p=0.671 for OS).

It is not clear whether response duration of targeted therapies has an effect on survival outcomes with axitinib and nivolumab. The AXIS trial showed that patients treated with axitinib who had previously received longer treatment duration with sunitinib had better OS compared to those with shorter treatment duration [19]. However, an Italian real life study reported that longer treatment duration with sunitinib compared to shorter duration did not affect the OS of patients treated with second-line axitinib [20]. Addditionally, Suzuki et al demonstrated that PFS with previous agents, targeted therapy and mTOR inhibitor were not determined as independent predictors of OS in patients treated with second-line axitinib or nivolumab [6]. In the present study, we found that the median PFS of targeted therapy (sunitinib and pazopanib) in the whole cohort were 10.9 months, and the duration of targeted therapy was not associated with OS of patients treated with axitinib and nivolumab.

There are other treatment options in mRCC after failure of targeted therapy. According to a phase II trial, lenvatinib and everolimus combination is

favored over everlolimus alone for PFS in patients previously treated with one targeted therapy [21]. However, the lack of definitive OS outcomes limits the use of this combination as a preferable option in patients after treatment failure with targeted therapy. The phase III METEOR trial compared the efficacy of cabozantinib over everolimus and demonstrated that cabozantinib was superior to everolimus in terms of ORR, PFS and OS [22,23]. While nivolumab and cabozantinib ere prefered category 1 treatment options, axitinib and the combination of everolimus and lenvatinib are other recommended category 1 options for second-line treatment according to the National Comprehensive Cancer Network [24]. In selecting treatment options after treatment failure with targeted therapy, clinicians must think about several conditions; comorbidities, cost effectiveness, prior treatments and quality of life improvements with these agents.

Conclusion

In summary, we presented the comparison of axitinib and nivolumab in mRCC after failure of targeted therapy. We found that axitinib and nivolumab can be effectively used for the treatment of mRCC patients who were previously treated with targeted therapy. We also determined that high tumor grade, response to axitinib and nivolumab, the presence of lung and liver metastasis were independent predictors of OS. Prospective studies with head to head comparison and determination of predictive molecular and clinical factors are needed for better individualized treatment of mRCC patients who progressed with targeted therapy.

Conflict of interests

The authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. Motzer RJ, Jonasch E, Michaelson MD et al. NCCN Guidelines Insights: Kidney Cancer, Version 2.2020. J Natl Compr Canc Netw 2019;17:1278-85.
3. Rini B, Escudier B, Tomczak P et al. Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): Results of phase III AXIS trial. J Clin Oncol 2011;29:4503-4503.
4. Motzer RJ, Escudier B, McDermott DF et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
5. Amzal B, Fu S, Meng J, Lister J, Karcher H. Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: A network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma. PLoS One 2017;12:e0184423.
6. Suzuki K, Terakawa T, Furukawa J et al. Clinical outcomes of second-line treatment following prior targeted therapy in patients with metastatic renal cell carcinoma: a comparison of axitinib and nivolumab. Int J Clin Oncol 2020;25:1678-86.
7. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6:655-63.
8. Paner GP, Amin MB, Alvarado-Cabrero I et al. A novel tumor grading scheme for chromophobe renal cell carcinoma: prognostic utility and comparison with Fuhrman nuclear grade. Am J Surg Pathol 2010;34:1233-40.
9. Ko JJ, Xie W, Kroeger N et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. Lancet Oncol 2015;16:293-300.
10. Motzer RJ, Tannir NM, McDermott DF et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-90.
11. Rini BI, Plimack ER, Stus V et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1116-27.
12. Bach PB. New Math on Drug Cost-Effectiveness. N Engl J Med 2015;373:1797-9.
13. Qin S, Bi F, Jin J et al. Axitinib versus sorafenib as a second-line therapy in Asian patients with metastatic renal cell carcinoma: results from a randomized registrational study. Onco Targets Ther 2015;8:1363-73.
14. Guida A, Albiges L, Derosa L et al. Everolimus Versus Axitinib as Second-line Therapy in Metastatic Renal Cell Carcinoma: Experience From Institut Gustave Roussy. Clin Genitourin Cancer 2017;15:e1081-88.
15. Thompson RH, Gillett MD, Cheville JC et al. Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci U S A 2004;101:17174-9.
16. Choueiri TK, Fishman MN, Escudier B et al. Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma. Clin Cancer Res 2016;22:5461-71.
17. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
18. Yip SM, Wells C, Moreira R et al. Checkpoint inhibitors in patients with metastatic renal cell carcinoma: results from the international metastatic renal cell carcinoma database consortium. Cancer 2018;124:3677-83.
19. Escudier B, Michaelson M, Motzer R et al. Axitinib

versus sorafenib in advanced renal cell carcinoma: subanalyses by prior therapy from a randomised phase III trial. Br J Cancer 2014;110:2821-8.

20. D'Aniello C, Vitale MG, Farnesi A et al. Axitinib after Sunitinib in Metastatic Renal Cancer: Preliminary Results from Italian "Real-World" SAX Study. Front Pharmacol 2016;7:331.
21. Motzer RJ, Hutson TE, Glen H et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015;16:1473-82.
22. Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814-23.
23. Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-27.
24. Motzer RJ, Jonasch E, Boyle S et al. NCCN Guidelines Insights: Kidney Cancer, Version 1.2021: Featured Updates to the NCCN Guidelines. J Natl Compr Canc Netw 2020;18:1160-70.