Invited Commentary

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# Invited commentary: When and how to initiate systemic therapy in treating favorable risk metastatic renal cell carcinoma

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Medical treatment for metastatic renal cell carcinoma (mRCC) has dramatically changed recently. Six phase 3 randomized controlled trials have shown the effectiveness of immune checkpoint inhibitors (PD-1 or PD-L1) in advanced clear cell renal cancer.[1] Dual therapy (PD-1/PD-L1 inhibitors combined with CTLA-4 signaling or VEGF-targeted therapy) has previously been compared with a standard treatment—sunitinib. While the overall survival benefits of dual therapy over sunitinib have undoubtedly been proven for patients with International Metastatic RCC Database Consortium (IMDC) intermediate or poor risk, the presence of this benefit is still being debated in the IMDC favorable risk group. The IMDC score is the most common prognostic risk score for mRCC. It includes the following risk factors: time from diagnosis to systemic therapy (ST) $<1$ year, Karnofsy performance status $<80\%$, neutrophils $>$ upper limit of normal (ULN), platelet $>$ ULN, hemoglobin $<$ lower limit of normal, and calcium $>$ ULN.[2] Patients without any of these risk factors are considered part of the IMDC favorable risk group. Recent clinical trials evaluating dual therapy versus sunitinib did not show benefits favoring the use of dual therapy in the favorable risk groups. Although the recent National Comprehensive Cancer Network guidelines recommend pembrolizumab-axitinib, pembrolizumab-levantinib, and nivolumab-cabozantinib as the preferred treatment regimens for favorable risk groups, we should consider the potential risk of overtreatment if dual therapy is used for all.[3]

Favorable risk mRCC patients mostly display an indolent and asymptomatic disease, and deaths in these patients are often delayed, regardless of treatment modalities. Furthermore, there have been rare cases of spontaneous regression without precise incidence.[4] Thus, patients with favorable risk mRCC can delay ST safely and opt for active surveillance (AS). To the best of our knowledge, few retrospective and prospective evaluations have reported on AS for mRCC. Rini et al. reported 48 patients with treatment-naïve, asymptomatic mRCC assessed radiographically at baseline and continued observation until the initiation of ST. The median time of AS from the registration in the study until ST was 14.9 months. Multivariate analysis revealed that higher numbers of IMDC adverse risk factors and metastatic disease sites were associated with a shorter surveillance period.[5] Interestingly, patients with AS in the study had fewer number of myeloid-derived suppressor cells and regulatory T cells, and a significantly greater number of interferon-γ-producing T cells compared to a separate cohort of patients with mRCC who began ST immediately.[5,6] These results potentially indicate a less immunosuppressive environment in the AS group, suggesting a relatively indolent nature of tumor growth. According to the report, favorable risk mRCC patients with oligometastatic lesions might be good candidates for AS. Recently, Harrison et al. published a prospective observational study, including 143 mRCC patients without ST (69% with present disease and 32% with no evidence of present disease) managed with AS. The median overall survival from metastatic diagnosis was 30 months in the ST cohort but was not reached in the AS cohort. Moreover, the quality of life at baseline was significantly better in patients who were managed with AS versus ST.[7] Interestingly, the IMDC risk score did not appropriately discriminate the prognosis of the AS patients in their cohort, suggesting that the risk score may not be useful for selecting patients that may be managed by AS. Identification of relevant clinical and molecular factors or biomarkers to accurately select patients who are candidates for AS is strongly required.

In the VEG105192 study evaluating 40% of patients with a favorable risk disease, the pazopanib arm did not show overall survival benefit since it allowed crossover with the pazopanib treatment after progression for patients in the control arm, which was the same situation as AS. The results indicate that AS is a more feasible treatment option for patients with a favorable risk.

In the clinical setting, we observed patients with oligometastatic mRCC without ST. If one or two metastatic lesions did not grow definitively over time, metastasectomy was selected after nephrectomy. However, we may also select metastasectomy for the growing lesion in mRCC patients with multiple metastatic sites at baseline and one abnormal growth observed after a follow-up period, suggesting that other lesions (e.g., small lung nodules) might not have been mRCC. Thus, the initial AS period in the limited cases of mRCC can help in selecting those patients for whom metastasectomy may be a good option to avoid unnecessary ST.[5]

Current treatment guidelines do not definitively indicate when and how ST should be initiated, especially in mRCC patients with favorable risk. A review of previous studies revealed that AS may be the best option for elderly patients with mRCC or

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comorbidities and with favorable risk; however, young patients with few comorbidities and with favorable risk expecting reasonable life expectancy may receive meaningful benefits from dual therapy. Checkmate 214 and Keynote-426 demonstrated a nonnegligible absolute complete response favoring dual therapy over sunitinib in the IMDC favorable risk patients.[8,9] Complete response was associated with prolonged survival outcomes, indicating that it could lead to a "potential cure". We should consider the balance between this potential benefit of prolonged survival and patient age together with comorbidities since the potential benefit with dual therapy may not be apparent until at least 54 months, when the Kaplan–Meier curve have started to cross over to favoring dual therapy over sunitinib.[9] Thus, tyrosine kinase inhibitor monotherapy is still the recommended regimen for the favorable risk group. Teishima et al. in this issue have reported on patients who will not benefit from the initial treatment with tyrosine kinase inhibitors.

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## Conflict of interest statement

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## Author contributions

None.

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