# Duration of First-line Treatment with Molecular Targeted-Therapy Is a Prognostic Factor in Metastatic Renal Cell Carcinoma

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**Abstract.** *Aim: We investigated the prognostic factors associated with overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC) who received molecular targeted-therapies. Material and Methods: A total of 66 patients underwent molecular targeted-therapies at the Kurume University between May 2008 and April 2014. Medical records were retrieved and analyzed retrospectively. Results: The median OS was 25.9 [95% confidence interval (CI)=18.3-33.7] months. The median OS stratified by the Memorial Sloan Kettering Cancer Center risk classification was 49.3, 28.6 and 18.3 months for the favorable-, intermediate- and poor-risk groups, respectively. Univariate analyses for various factors revealed gender, pre-treatment C-reactive protein (CRP) level, best response to first-line treatment, the number of molecular targeted agents and the duration of first-line treatment with a median of 6 months, as prognostic variables. Multivariate analyses showed than two or more than three molecular targeted agents [two: hazard ratio (HR)=0.351, 95% CI=0.121-0.901; more than three: HR=0.193, 95% CI=0.069-0.495] and a duration of first-line treatment of more than 6 months (HR=0.203, 95% CI=0.078-0.498) to be independent prognostic factors. Conclusion: Our results suggest that the duration of first-line treatment with molecular targeted-therapies is the strongest prognostic factor in patients with mRCC.*

Renal cell carcinoma accounts for approximately 3% of adult malignancies (1) and is the fourth most common urogenitalmalignancy in Japan (2). Until recently, cytokine therapy has been mainly used in systemic treatment for metastatic RCC (mRCC). However, the response rate to interferon-alpha (IFNα) was approximately 15%, and even in combination with interleukin-2 (IL2), the effect was about 20%. For the last several years, the strategy for mRCC has been changing to administration of molecular targeted-therapies, such as the multitargeted inhibitors of tyrosine kinases (TKIs) and of the mammalian target of rapamycin (mTORIs), instead of immunotherapy as first-line therapy (3, 4).

In the cytokine era, the Memorial Sloan-Kettering Cancer Center (MSKCC) risk criteria for the kidney cancer model identified by Motzer *et al*. (5) were clinically used for the prognostic model. In the modified classification system, patients are classified into three groups based on the following five risk factors: low performance status (PS), anemia (women <11.0 g/dl, men <13.0 g/dl), high corrected serum calcium (>10 mg/dl), elevated serum lactatedehydrogenase (LDH; >1.5-fold the upper limit of normal) and time from diagnosis to therapy of less than a year.

In this era of molecular targeted-therapy, some groups have demonstrated that there are several prognostic factors for mRCC other than the MSKCC risk classification system, including the serum C-reactive protein (CRP) level (6, 7) metastasis status (8, 9) and tumor shrinkage (10). However, there have been few reports of independent prognostic factors. In the present study, we aimed to investigate the prognostic factors for patients with mRCC treated with molecular targeted agents.

## Patients and Methods

A total of 66 patients underwent molecular targeted-therapies at the Kurume University, Hospital between May 2008 and April 2014. Clinical and pathological data from medical records including age, sex, histological type of tumor, history of prior treatment, Eastern Cooperative Oncology Group performance status (ECOG PS), anemia, MSKCC risk classification, pre-treatment CRP level, the number of molecular targeted agents,

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*Key Words*: Renal cell carcinoma, molecular targeted therapy, prognostic factor, duration of first-line treatment.

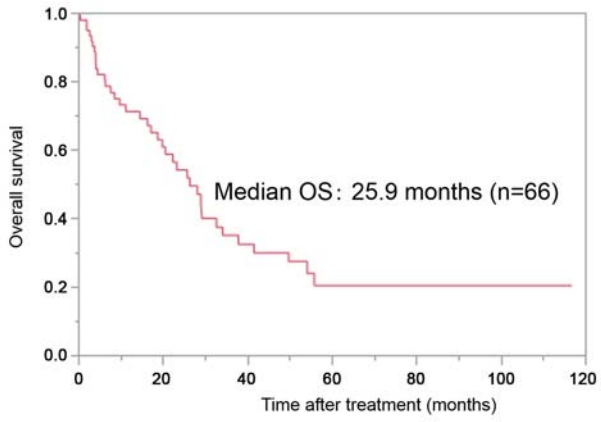


Figure 1. *Overall survival in patients with metastatic renal cell carcinoma receiving molecular targeted-therapies.*

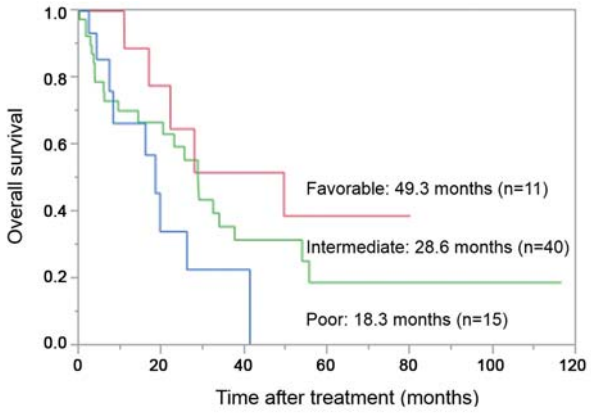


Figure 2. *Overall survival (OS) in patients with metastatic renal cell carcinoma receiving molecular targeted-therapies stratified according to Memorial Sloan Kettering Cancer Center risk classification. The OS for patients in the poor-risk group was significantly worse compared to patients in the favorable-risk group ($p<0.05$). No significant difference in OS was found between intermediate- and favorable-risk ($p=0.2745$) or poor-risk ($p=0.3029$) groups.*

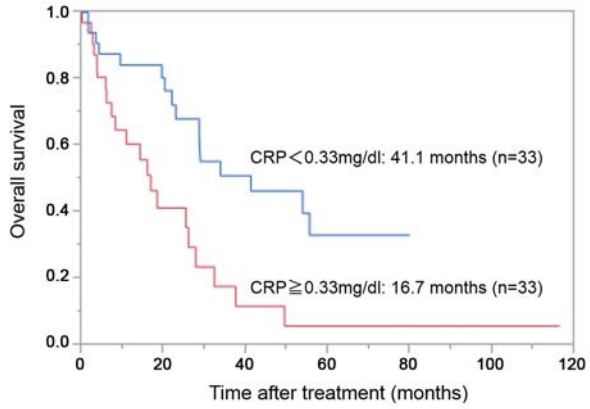


Figure 3. *Overall survival in patients with metastatic renal cell carcinoma receiving molecular targeted-therapies stratified according to C-reactive protein (CRP) level. The group with a CRP level less than 0.33 mg/dl had a significantly superior overall survival compared to the CRP ≥0.33 mg/dL group ($p<0.005$).*

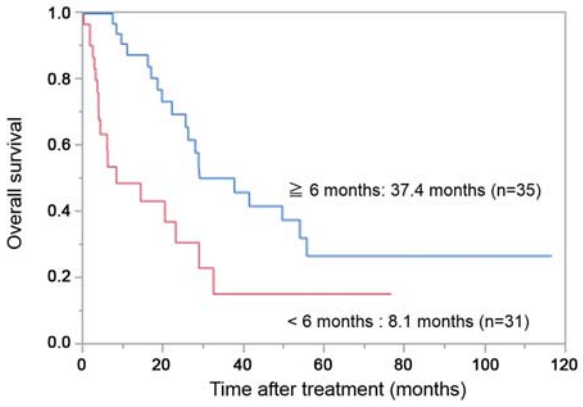


Figure 4. *Overall survival in patients with metastatic renal cell carcinoma receiving molecular targeted-therapies stratified according to the duration of first-line treatment. Patients with a duration of first-line treatment of more than 6 months had a significantly superior overall survival compared to those treated for less than 6 months ($p<0.005$).*

duration of first-line treatment and best response to first-line treatment were retrieved and analyzed retrospectively. Tumor response was evaluated as best response according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (11). Patients were stratified into three groups, with complete remission (CR) or partial response (PR); stable disease (SD); and progress disease (PD). Overall survival (OS) from the initiation of molecular targeted therapy to the date of mortality was determined using the Kaplan–Meier method, and analyzed using the log-rank test. To identify the prognostic factors associated with OS, Cox proportional hazards regression was used. Univariate and multivariate analyses were performed to identify independent prognostic factors for OS. All statistical analyses were performed using JMP version 11 (SAS Institute, Inc., Cary, NC, USA) and a value of $p<0.05$ was considered to indicate a statistically significant difference.

## Results

Patients' characteristics are summarized in Table I. Most patients were male (81.8%). The majority of patients were diagnosed with mRCC of clear cell histology. All MSKCC risk groups were represented among the patients, with 16.7% with favorable-, 60.6% with intermediate- and 22.7% with poor-risk. The median pre-treatment CRP level was 0.33 mg/dl (range=0.04-15.66 mg/dl) in all patients.

The profiles of molecular targeted-therapy are shown in Table II. Most patients received sunitinib (50%) or sorafenib

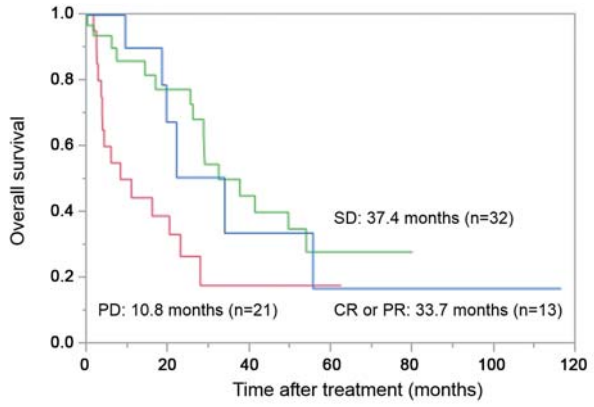


Figure 5. *Overall survival (OS) in patients with metastatic renal cell carcinoma receiving molecular targeted therapies stratified according to best response to first-line treatment. The OS for patients in the progress disease (PD) group was significantly worse compared to patients in the stable disease (SD) group ($p<0.01$) and tended to be worse compared to patients in the complete remission (CR) or partial response (PR) group ($p=0.0929$). No significant difference was found between the CR and PR group and the SD group ($p=0.7282$).*

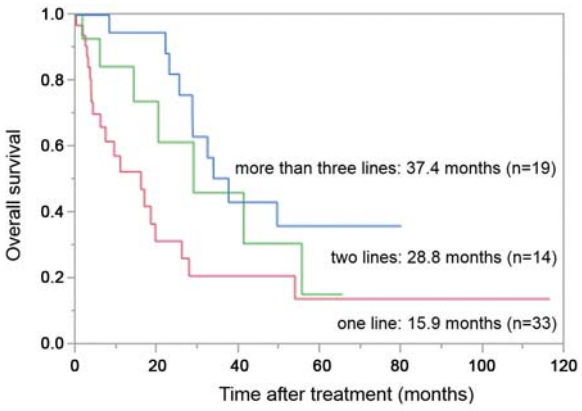


Figure 6. *Overall survival (OS) in patients with metastatic renal cell carcinoma receiving molecular targeted-therapies stratified according to the number of lines of therapy with molecular targeted agents. The OS of patients treated with more than three molecular targeted agents was significantly superior compared with that of those treated with one ($p<0.005$). There was no significant difference between those treated with one or two molecular targeted agents ($p=0.1556$), nor between those treated with two or more than three molecular targeted agents ($p=0.2917$).*

(41%) as first-line molecular targeted-therapy. The patients were stratified according to the best tumor remission on first-line treatment. Thirteen patients (19.7%) achieved objective tumor remission (CR or PR), 32 (48.5%) had SD, while 21 (31.8%) had PD. Thirty-three patients (50%) and 14 patients (21.2%) were treated with one and two molecular targeted agents, respectively. Only two patients (3%) were treated with five molecular targeted agents.

The OS curve for all patients is shown in Figure 1. The median OS from the start of first-line molecular targeted-therapy was 25.9 (95% CI=18.3-33.7) months. The median OS stratified by MSKCC risk classification was 49.3, 28.6 and 18.3 months for the favorable-, intermediate- and poor-risk groups, respectively. The OS for patients in the MSKCC poor-risk group was significantly worse compared to patients in the favorable-risk group ($p<0.05$; Figure 2). No significant difference in OS was found between MSKCC intermediate- and favorable-risk ($p=0.2745$) or poor-risk ($p=0.3029$) groups.

The pre-treatment CRP level was analyzed for an association with OS. The median OS was 41.1 months in the group with a CRP level less than 0.33 mg/dl and 16.7 months in the CRP≥0.33 mg/dL group, respectively (Figure 3). There was a significant difference in the OS rates between the two groups ($p<0.005$).

Next, the duration of first-line molecular targeted-therapy was analyzed for an association with OS. The median duration of first-line treatment was 6.0 months. Patients with a duration of first-line treatment of more than 6 months had a significantly superior OS (37.4 months) compared to those treated for less than 6 months (8.1 months) ($p<0.005$) (Figure 4). On the best response, the OS for patients in the PD group was significantly worse compared to patients in the SD group ($p<0.01$) and tended to be worse compared to patients in the CR or PR group ($p=0.0929$) (Figure 5). However, no significant difference in OS was found between the CR and PR group and the SD group ($p=0.7282$) (Figure 5). Regarding the number of lines of molecular targeted agents, the OS of patients treated with more than three molecular targeted agents was significantly superior compared to that of those treated with one ($p<0.005$) (Figure 6). There was no significant difference between those treated with one or two molecular targeted agents ($p=0.1556$), nor between those treated with two or more than three molecular targeted agents ($p=0.2917$).

To identify the prognostic factors associated with OS, we performed univariate and multivariate analyses using the Cox proportional hazards model (Table III). Univariate analyses for various factors revealed gender, pre-treatment CRP level, best response to first-line treatment, the number of molecular targeted agents and the duration of first-line treatment of a median of 6 months as prognostic variables. Multivariate analyses showed treatment with two or more than three molecular targeted agents (two: HR 0.351, 95% CI=0.121-0.901, $p=0.0286$; more than three: HR=0.193, 95% CI=0.069-0.395, $p=0.0005$) and duration of first-line treatment of more than 6 months (HR 0.203, 95% CI=0.078-0.498, $p=0.0004$) to be independent prognostic factors.

Table I. *Characteristics of 66 patients with metastatic renal cell carcinoma who underwent molecular targeted-therapy.*

| | N |
|---|---|
| Total | 66 |
| Gender | |
| Male | 54 |
| Female | 12 |
| Age, years | |
| Median (range) | 66 (21-78) |
| Histological type | |
| Clear cell type | 40 |
| Papillary type | 7 |
| Chromophobe type | 1 |
| MTSCC | 1 |
| Unclassified | 1 |
| Unknown | 16 |
| Pre-treatment | |
| Nephrectomy | 53 |
| IFN | 15 |
| IL2 | 1 |
| MSKCC risk classification | |
| Favorable | 11 |
| Intermediate | 40 |
| Poor | 15 |
| Anemia | |
| Yes | 37 |
| No | 29 |
| Pre-treatment CRP level, mg/dl | |
| Median (range) | 0.33 (0.04-15.66) |
| ≥0.33 mg/dl | 33 |
| <0.33 mg/dl | 33 |

MTSCC: Mucinous tubular and spindle cell carcinoma; IFN: interferon-alpha; IL2: interleukin-2; CRP: C-reactive protein.

Table II. *Profile of molecular targeted-therapy.*

| | | N |
|---|---|---|
| Total | | 66 |
| Duration of first-line treatment, months | Median (range) | 6.0 (1.1-116.2) |
| First-line treatment | Sunitinib | 33 |
| | Sorafenib | 27 |
| | Pazopanib | 2 |
| | Axitinib | 2 |
| | Temsirolimus | 2 |
| | Everolimus | 0 |
| Best response to first-line treatment | CR or PR | 13 |
| | SD | 32 |
| | PD | 21 |
| No. of lines of molecular targeted agents | 1 | 33 |
| | 2 | 14 |
| | 3 | 10 |
| | 4 | 7 |
| | 5 | 2 |

CR: Complete remission; PR: partial response; SD: stable disease; PD: progress disease.

## Discussion

Current estimates for median OS in patients with mRCC may be in the range of 22.9-26.4 months (12, 13). Molecular targeted-therapies have significantly prolonged survival of patients with mRCC compared to that in the cytokine era. In the current era, several studies have investigated clinical prognostic factors. However, there have been few reports of independent prognostic factors. Therefore, establishing an enhanced risk classification for patients with mRCC is important.

The OS of 25.9 months presented in our study is equivalent to that in other reports. Although MSKCC risk classification was based on data of patients with mRCC treated during the cytokine era, several researchers suggest that it is also useful in the molecular targeted-therapy era. In our study, the poor-risk group was significantly worse compared to patients in the favorable-risk group in OS, while there was no significant difference between intermediate- and favorable- or poor-risk groups. Furthermore, MSKCC risk classification itself did not remain an independent prognostic factor in multivariate analysis.

Some researchers have demonstrated that the serum CRP level is one of the most important prognostic factors for advanced RCC (14, 15). Yasuda *et al*. suggested that the pre-treatment CRP level is a significant prognostic factor in patients treated for mRCC with TKIs (7). While the pre-treatment CRP level was associated with a worse OS in univariate analyses in our study, the pre-treatment CRP level did not remain significant in multivariate analyses.

Recent reports have shown that patients with insufficient response to first-line treatment have a worse prognosis (16, 17). Seidel *et al*. suggested that early tumor shrinkage is a prognostic tool and superior tumor shrinkage relates to a favorable prognosis (10). Patients in their analysis were stratified into five groups according to the change of tumor size on first-treatment evaluation, but we stratified patients into three groups according to the best response to first-line treatment. In our study, the PD group had the worst prognosis among the other groups. However, there was no significant difference by best response to first-line treatment in OS from the initiation of molecular targeted therapy. This result suggests that the clinical response rate might not reflect the survival time.

In our study, patients who received two or more lines of molecular targeted-therapy had a longer OS compared with those receiving only one line. Furthermore, first-line

Table III. *Univariate and multivariate analyses of overall survival.*

| Parameter | Category | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *p*-Value | HR (95% CI) | *p*-Value |
| Age, years | | | | | |
| | <66 | 1 | | | |
| | ≥66 | 1.006 (0.524-1.937) | 0.9863 | | |
| Gender | | | | | |
| | Men | 1 | | 1 | |
| | Women | 0.351 (0.104-0.895) | 0.0263 | 0.462 (0.125-1.335) | 0.1628 |
| MSKCC risk classification | | | | | |
| | Favorable | 1 | | | |
| | Intermediate | 1.746 (0.716-5.214) | 0.2341 | | |
| | Poor | 2.739 (0.922-9.1329 | 0.0699 | | |
| PS | | | | | |
| | 0, 1 | 1 | | | |
| | ≥2 | 1.993 (0.927-4.038) | 0.0756 | | |
| Anemia | | | | | |
| | No | 1 | | | |
| | Yes | 1.878 (0.970-3.803) | 0.0617 | | |
| Pre-treatment CRP level | | | | | |
| | <0.33 mg/dl | 1 | | 1 | |
| | ≥0.33 mg/dl | 2.609 (1.337-5.149) | 0.0051 | 1.559 (0.755-3.288) | 0.2304 |
| No. of lines of molecular targeted agents | | | | | |
| | 1 | 1 | | 1 | |
| | 2 | 0.535 (0.209-1.214) | 0.1388 | 0.351 (0.121-0.901) | 0.0286 |
| | ≥3 | 0.346 (0.153-0.734) | 0.0054 | 0.193 (0.069-0.495) | 0.0005 |
| Duration of first-line treatment | | | | | |
| | <6 Months | 1 | | 1 | |
| | ≥6 Months | 0.346 (0.178-0.678) | 0.0023 | 0.203 (0.078-0.498) | 0.0004 |
| Best response to first-line treatment | | | | | |
| | PD | 1 | | 1 | |
| | SD | 0.367 (0.177-0.762) | 0.0078 | 0.617 (0.275-1.375) | 0.2361 |
| | CR or PR | 0.423 (0.150-1.046) | 0.063 | 0.537 (0.165-1.589) | 0.2645 |

MSKCC: Memorial Sloan-Kettering Cancer Center; PS: performance status; CRP: C-reactive protein; CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease.

treatment of more than 6 months was associated with good prognostic outcomes. Ko *et al*. demonstrated that patients with mRCC who were able to receive more lines of molecular targeted therapy lived longer, with better progression-free survival (18). Seidel *et al*. suggested that progression-free survival with first-line treatment of more than 6 months is an independent prognostic marker (19). To date, four TKIs, sunitinib, sorafenib, axitinib and pazopanib, and two mTORIs, temsirolimus and everolimus, have been approved in Japan. The better use of these molecular targeted agents might contribute to good prognosis of patients with mRCC.

Currently, multiple candidate predictive and prognostic biomarkers, such as vascular endothelial growth factor A, IL6, IL8, hepatocyte growth factor, phosphatase and tensin homolog, AKT and phosphorylated AKT, have been evaluated (20-26). However, the relationship between OS and these biomarkers was not examined in these studies. The utility of these molecular biomarkers for predicting clinical outcomes in the molecular targeted-therapy era needs to be further studied.

Our study has several weaknesses, including its retrospective design and the limited number of patients from a single Institution. Prospective investigation of clinical and molecular features in a large number of patients with mRCC is required.

In conclusion, our results suggest that the duration of first-line treatment with molecular targeted therapies is the strongest prognostic factor in patients with mRCC. Additionally, these results show that sequential therapy with molecular targeted agents prolongs the survival of patients with mRCC. These results suggest that the selection of first-line drug might be very important and more information will be required on the stratification of molecular targeted agents

by using some biomarkers in patients with mRCC. We demonstrated that it is important to maintain first-line treatment in order to suppress tumor progression and maintain sequential therapy. Additional studies are required in order to validate our findings.

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