Prognostic Impact of the Components of Progressive Disease on Survival After First-Line Tyrosine Kinase Inhibitor Therapy for Metastatic Renal Cell Carcinoma

Prognostic impact of the components of progressive disease on survival after first-line tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma

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Running header: Components of PD in TKI for mRCC

Abstract

Background: According to the Response Evaluation Criteria in Solid Tumors (RECIST) classification, progressive disease (PD) is defined as target lesion growth (TLG), unequivocal non-target lesion growth (NTLG), or new lesion appearance (NLA). The prognostic impact of the components of PD in tyrosine kinase inhibitor (TKI) therapy for metastatic renal cell carcinoma (mRCC) remains unknown.

Objective: We retrospectively evaluated the prognostic impact of these PD components on survival in patients with mRCC after first-line TKI therapy.

Patients and Methods: Patients were divided into three groups (TLG, NTLG and NLA) based on the components of PD. Progression-free survival (PFS) and overall survival (OS) after first-line TKI therapy were compared to PD components using the Kaplan-Meier method and log-rank test. The predictive impact of the PD components was evaluated using multivariate analyses.

Results: Among the 116 patients included, 80 (69.0%) were classified to the TLG group, 18 (15.5%) to the NTLG group and 69 (58.6%) to the NLA group. The mean PFS and OS were shorter for patients with than without TLG (PFS, 7.1 vs. 11.6 months, respectively, p=0.0071; OS, 18.2 vs. 25.5 months, respectively, p=0.0091). TLG was an independent predictor of PFS (hazard ratio [HR], 1.59; 95% confidence interval [CI], 1.02–2.51; p=0.0395) and OS (HR, 1.67; 95% CI, 1.02–2.83; p=0.040). NTLG and NLA were not associated with survival.

Conclusions: In this retrospective single-center study, patients with TLG had a poor survival after first-line TKI therapy for mRCC. Thus, the components of PD influence patient prognosis.

Key points

- Patient survival after first-line tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma differed according to the components of progressive disease.
- Target lesion growth was an independent predictor for poor survival in patients receiving first-line tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma.

1. Introduction

The advent of molecular-targeted therapy has notably changed the treatment strategy for metastatic renal cell carcinoma (mRCC) [1-3]. According to current guidelines, tyrosine kinase inhibitor (TKI) therapy is preferred for most patients with mRCC [2, 4, 5]. The Response Evaluation Criteria in Solid Tumors (RECIST) is a gold standard for assessing the therapeutic efficacy of cancer treatments including TKI therapy [6]. Further, several prognosticators based on RECIST have been indicated in TKI therapy for mRCC [7-11].

According to the RECIST v.1.1, progressive disease (PD) is defined as target lesion growth (TLG), unequivocal non-target lesions growth (NTLG) or new lesions appearance (NLA). Several studies have reported that oncological outcomes were significantly different among the three components of PD. Litiere et al. suggested that NTLG and NLA were worse prognostic factors in patients with breast, colon, and lung cancers [12]. Furthermore, Twelves et al. reported that NLA was significantly associated with a poor prognosis in metastatic breast cancer treated with chemotherapy [13]. It is important to understand the impacts of PD components on survivals as these can contribute to better prognostication and treatment planning. However, the prognostic impact of the components of PD in TKI therapy for mRCC remains unknown. Therefore, we retrospectively evaluated the prognostic impact of the components of PD in patients who received first-line TKI therapy for mRCC.

2. Materials and methods

2.1 Patient selection

In our department, 188 patients received first-line TKI therapy (106, sunitinib; 69, sorafenib; 13, pazopanib) between January 2007 and March 2017. Among these, we excluded 29 patients who received first-line TKI at the end of follow-up, after continuous observation of their tumor response, and another 21 patients, in whom TKI therapy was discontinued due to adverse events. Of the remaining 138 patients who had PD after TKI therapy, 1 patient who had received prior cytokine therapy, 4 patients who received TKIs for only a short duration (i.e., < four weeks), and 17 patients who received hemodialysis or kidney transplantation, were excluded. Finally, 116 patients were retrospectively evaluated (Electronic Supplementary Material 1). All patients experienced PD based on the RECIST ver. 1.1 after first-line TKI therapy initiation.

2.2 Response criteria

According to the RECIST ver. 1.1, we evaluated the tumor response for target lesions, non-target lesions and new lesions, with each classification defined as follows [6]. TLG was defined as a ≥20% increase in the sum of diameters of target lesions, taking as the reference the smallest sum observed in the study. In addition to a relative increase of 20%, the sum had to demonstrate an absolute increase of at least 5 mm. Moreover, the unequivocal progression of existing non-

target lesions (i.e. NTLG) and the appearance of new malignant lesions (i.e. NLA) were defined as disease progression.

2.3 Study design and endpoint

The Patients were divided into three groups according to PD components, namely the TLG, NTLG and NLA groups. The different components of PD were not mutually exclusive and categories could overlap in several cases.

The endpoints of this study were progression-free survival (PFS) and overall survival (OS) after first-line TKI therapy initiation. PFS was defined as the time from first-line TKI initiation to the date of progression. OS was defined as the time from the start of first-line TKI initiation to death from any cause.

2.4 Imaging methods and assessment

Baseline imaging examinations, including plain or contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis, were performed within 28 days before the start of TKI therapy. Regular scans were also performed at every 8–12 weeks of therapy, according to the patient's condition. One of the investigators (T.I.), who was blinded to all other clinical parameters and the patient outcomes, reviewed all images

for analysis.

2.5 Protocols of tyrosine kinase inhibitor regimens

The TKI regimens in our department have been previously described [14, 15]. The main agent for first-line TKI therapy is sunitinib. In the sunitinib regimen, we currently administer a 2-week-on/1-week-off schedule, based on findings from our previous study [16]. Sunitinib is orally administered at a dose of 50 mg daily and modified according to patients' condition. Based on previous research, for patients with a poor performance status or >80 years of age, either sorafenib or pazopanib were selected as these TKIs have better tolerability than sunitinib [17-20]. In the sorafenib regimen, 200 mg sorafenib is orally administered twice daily and increased up to 800 mg within 2–4 weeks to reduce any acute dermatological reactions, with a continuous dosing schedule. In the pazopanib regimen, the drug is orally initiated once daily at a dose of 800 mg with continuous dosing. The dose is reduced to 600 mg and then to 400 mg according to the severity of adverse events. In all the regimens, the drugs are administered until PD is observed or intolerable adverse events occur.

2.6 Statistical analysis

Distributions of PFS and OS were calculated using the Kaplan-Meier method and compared

using the log-rank test. The median PFS and OS along with 95% confidence intervals (CI) were reported. Univariate and multivariate analyses using Cox proportional hazards regression models were used to identify predictors of survival. All analyses were performed using JMP software (version 12.1; SAS Institute, Cary, NC, USA) and differences were considered statistically significant at p-values <0.05.

3. Results

3.1 Patient characteristics

Eighty-two patients were men (70.7%) and the median patient age was 66.0 years. The most frequent pathological type was clear cell carcinoma (CCC) (n = 84, 72.4%). Sorafenib, sunitinib and pazopanib were administered as first-line TKI agents in 35 (30.2%), 73 (62.9%) and 8 (6.9%) patients, respectively. Among the 116 patients, 80 (69.0%) were classified to the TLG group, 18 (15.5%) to the NTLG group, and 68 (58.6%) to the NLA group. Additionally, 43 and 36 patients had TLG alone and NLA alone, respectively, whereas no patients had NTLG alone. Furthermore, 35 patients had overlapping components of PD. Among these 35 patients, two patients (1.7%) had TLG and NTLG, 17 patients (14.7%) TLG and NLA and 16 patients (13.8%) all three components. No patients had NTLG and NLA (Table 1). Electronic Supplementary Material 2 shows the PFS and OS of our entire study group, with a median PFS of 8.7 months and OS of 20.6 months.

3.2 Progression-free survival according to the individual components of progressive disease

Figure 1 shows the Kaplan-Meier curves of PFS after first-line TKI therapy according to the individual components of PD. Patients with TLG had a significantly shorter PFS compared to those without TLG (7.1 [95% CI :5.6–9.1] vs. 11.6 [95% CI: 6.3–15.1] months, p = 0.0071). Patients with NTLG had a significantly shorter PFS compared to those without NTLG (5.7 [95%

CI: 2.9–9.2] 9.0 [95% CI: 6.4–11.4] months, p = 0.0361). There was a significant difference in PFS between patients with and without NLA (7.1 [95% CI: 5.4–11.0] 9.1 [95% CI: 6.1–11.5] months, p = 0.225).

3.3 Overall survival according to individual components of progressive disease

Figure 2 shows the Kaplan-Meier curves of OS after first-line TKI therapy according to individual components of PD. Patients with TLG had a significantly shorter OS (TLG, median: 18.2 [95% CI: 13.3–23.1] no TLG, 25.5 [95% CI: 20.3–not reached] months, p = 0.0091). Patients with NTLG did not demonstrate a significant difference in OS (NTLG, 14.0 [95% CI: 8.5–31.7] no NTLG, 21.7 [95% CI: 18.2–27.4] months, p = 0.113). Patients with NLA did not show a significant difference in OS (NLA, 19.3 [95% CI: 13.7–25.6] no NLA, 21.7 [95% CI: 14.5–30.6] months, p = 0.381).

3.4 Progression-free survival and overall survival in patients with target lesion growth alone, new lesions appearance alone, and multiple components of progressive disease

To exclude the potential influences of overlapping PD components, we compared survival among patients who had a single component. Figure 3 shows that patients who had TLG alone had a significantly shorter OS than those with NLA alone (20.4 [95% CI: 13.7–27.4] vs. 29.9

[95% CI: 21.0–not reached] months, p = 0.0212). However, a trend for a shorter PFS was observed in patients with TLG alone than NLA alone (7.3 [95% CI: 5.0–11.4] vs. 10.5 [95% CI: 6.1–15.1] months, p = 0.0759).

3.5 Predictors of progression-free survival and overall survival

As shown in Table 2, univariate analysis for PFS showed that TLG, compared to no TLG, was a significant predictor of shorter PFS (p = 0.0061). Additionally, female sex, non-CCC pathological type, absence of a prior nephrectomy, and poor risk, based on MSKCC risk classification, were also significant predictors for shorter PFS (p < 0.05 for all). Multivariate analysis for PFS identified TLG as an independent predictor of shorter PFS (hazard ratio [HR]: 1.59, 95% CI: 1.02–2.51, p = 0.0395), in addition to the absence of a prior nephrectomy (HR: 2.07, 95% CI: 1.13–3.61, p = 0.0182) and poor risk, based on MSKCC risk classification, (HR: 3.22, 95% CI: 1.83–5.39, p = 0.0001).

As shown in Table 3, univariate analyses identified TLG as a significant predictor of OS (HR: 1.90, 95% CI: 1.18–3.16, p = 0.0073). Additionally, female sex, non-CCC pathological type, the absence of a previous nephrectomy, poor risk, based on MSKCC risk classification, and multiple metastasis were also significant predictors of OS (p < 0.05 for all). Multivariate analyses identified TLG as an independent predictor of OS (HR: 1.67, 95% CI: 1.02–2.83, p = 0.04), in

addition to female sex (HR: 1.73, 95% CI: 1.06–2.78, p = 0.0299), non-CCC pathological type (HR: 1.99, 95% CI: 1.15–3.38, p = 0.0144), poor risk based on MSKCC risk classification (HR: 2.74, 95% CI: 1.48–4.80, p = 0.0019), and multiple metastasis (HR: 2.19, 95% CI: 1.36–3.66, p = 0.0012).

3.6 Overall survival after first-line therapy failure according to the components of progressive disease

Further, to investigate whether TLG could affect prognosis after first-line therapy failure, we compared OS after first-line therapy failure between patients with and without TLG, as well as between patients with TLG alone and NLA alone. Consequently, patients with TLG had a significantly shorter OS after first-line therapy failure than those without TLG (8.3 [95% CI: 5.0–9.9] vs. 16.8 [95% CI: 5.7–29.5] months, p = 0.0142) (Electronic Supplementary Material 3A). However, only a trend toward a shorter OS was identified in patients with TLG alone compared to NLA alone (8.3 [95% CI: 4.9–13.1] vs. *versus* 16.8 [95% CI: 5.7–29.5] months, p = 0.0773) (Electronic Supplementary Material 3B).

4. Discussion

This study indicated that patients with TLG had a significantly poor PFS and OS and that patients with NTLG had a significantly poor PFS after first-line TKI therapy for mRCC. However, NLA was not significantly associated with PFS or OS. Multivariate analyses identified TLG as an independent predictive factor of PFS and OS. To the best of our knowledge, this is the first study evaluating the prognostic impact of components of PD after first-line TKI therapy for mRCC.

Previous studies have reported that NLA or NTLG was associated with poor patient survival after cytotoxic chemotherapies or targeted therapies for non-urological cancer [12, 13, 21, 22]. Nevertheless, TLG was a significant factor for oncological outcomes in our analysis. This difference may have been caused by different types of cancers or corresponding treatments between molecular-targeted therapy and cytotoxic chemotherapy. That is, in some patients, it is difficult to evaluate the tumor response to targeted therapy for mRCC according to the RECIST because specific morphological changes, such as necrosis, cannot be accurately reflected [23-25]. Therefore, a difference of PD interpretation may affect the analyses of outcomes according to types of treatment.

Regarding mRCC, Stein et al. showed that NTLG and NLA, and not TLG, were significant predictors of survival using data from RECORD-1 [26]. However, the significant associations of

NTLG or NLA were not observed in the intermediate term after treatment initiation (i.e., 14–18 weeks) in their study. Therefore, the prognostic impact of the PD components may be strongly affected by the timing of PD. Stein et al. also indicated that poor OS could be predicted by the fastest growing target lesion [26]. Other studies also reported that early treatment failure was significantly associated with poor oncological outcomes [26-28]. Similarly, our previous data showed that slow tumor growth mediated by TKI therapy was associated with a favorable prognosis [14, 15]. Indeed, in the present study, 18 patients experienced PD within the initial three months after therapy initiation and their OS was significantly poorer compared to the other patients. Further, TLG was observed in 15 of these patients. In all, TLG was associated with early treatment failure and resulted in poor survival compared to the other PD components.

Importantly, the patients with TLG had a significantly shorter OS after first-line TKI therapy failure (Electronic Supplementary Material 3). In this study, conventional TKI or mammalian target of rapamycin inhibitor was administered in most patients (66 of 69 patients who received second-line therapy). Therefore, a novel treatment approach, such as the use of nivolumab and not conventional targeted therapy, may be an effective treatment option for patients who have TLG as a component of PD after first-line TKI therapy failure.

This study has several limitations. First, this study was retrospectively conducted in a single center, with a small cohort size. Thus, our results were affected by unavoidable biases of patient and

treatment selection. Second, our own TKI protocol may have influenced outcomes. That is, with regard to our use of sunitinib, a majority of patients received an alternative 2-weeks-on/1-week-off schedule. Our previous study showed no significant difference in oncological outcome between this alternative schedule and the standard 4-weeks-on/1-week-off schedule [16]; however, we cannot deny that a possible influence on outcomes, caused by the difference of the regimens, might exist. Also, we selected either sorafenib or pazopanib for patients with poor general condition and, therefore, a corresponding selection bias may exist in some cases. Third, the RECIST can assess only the change of tumor diameter and not any intratumor activity, such as necrosis, which are considered to be important morphologic changes [25]. Therefore, the efficacy of TKI therapy might not be accurately reflected in some cases using the RECIST. Finally, there might be possible diagnostic bias among the components of PD. In particular, the definition of non-target lesion growth was likely to be less strict (unequivocal progression of existing non-target lesions) compared to other components. Thus, the TLG or NLA might be over-diagnosed compared to NTLG, and this unbalanced priority of definition could affect the analyses.

5. Conclusions

This retrospective single-center study identified TLG as an independent predictor of survival in patients with mRCC who received first-line TKI therapy. This finding is valuable for physicians with regard to predicting patient survival after first-line TKI therapy.

Acknowledgments

The authors thank Editage for English language editing and Nobuko Hata for secretarial work.

Compliance with Ethical Standards

Disclosure of Conflict of Interest

Tsunenori Kondo received honoraria from Pfizer, Bayer, and Novartis. No external funding was used in the preparation of this manuscript. All other authors have no conflicts of interest to declare.

Research

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study (ID: 4518). For this type of study, formal consent is not required.

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Figure legends

Fig. 1 Progression-free survival according to the components of progressive disease

Progression-free survival was compared between patients (A) with TLG and without TLG, (B) with NTLG and without NTLG, and (C) with NLA and without NLA.

CI, confidence interval; TLG, target lesion growth; NTLG, non-target lesion growth; NLA, new lesion appearance

Fig. 2 Overall survival according to components of progressive disease

Overall survival was compared between patients (A) with TLG and without TLG, (B) with NTLG and without NTLG, and (C) with NLA and without NLA.

CI, confidence interval; TLG, target lesion growth; NTLG, non-target lesion growth; NLA, new lesion appearance

Fig. 3 Progression-free survival and overall survival in patients with target lesion growth (TLG) alone and new lesions appearance (NLA) alone (A). Progression free survival and (B) overall survival were compared between patients with TLG alone and NLA alone.

CI, confidence interval

Electronic Supplementary Material Legends

Electronic Supplementary Material 1. Flowchart of patient selection

TKI, tyrosine kinase inhibitor

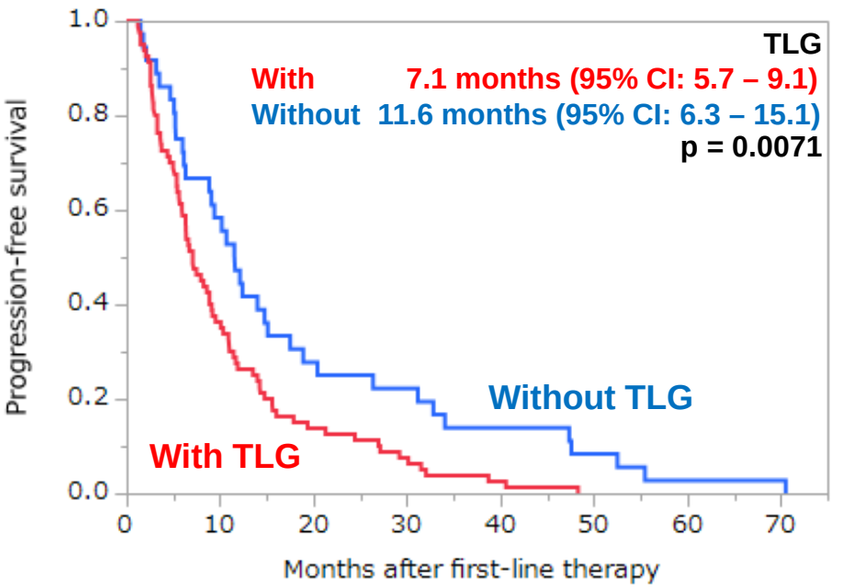
Electronic Supplementary Material 2. (A) Progression-free survival and (B) overall survival for the entire study group.

Electronic Supplementary Material 3. Overall survival after first-line therapy failure according to the components of progressive disease

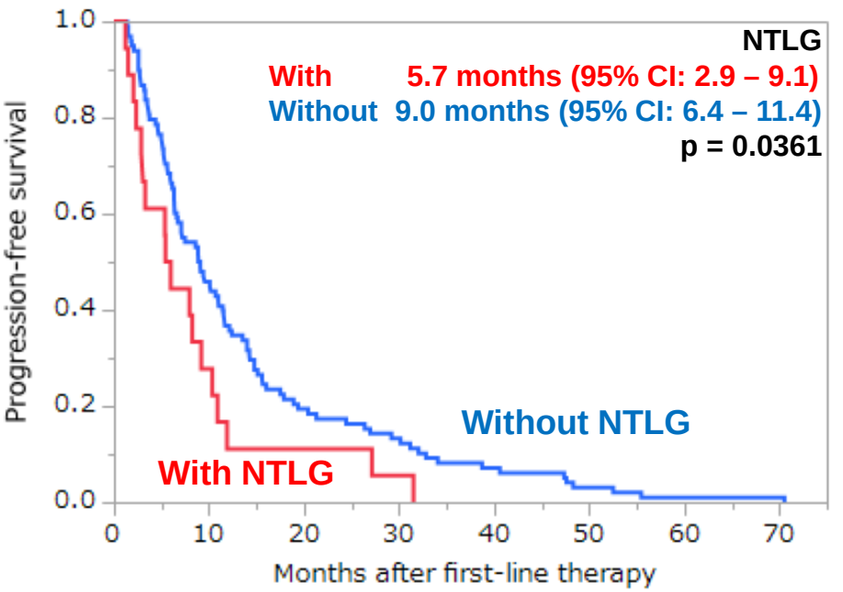
Overall survival after first-line tyrosine kinase inhibitor therapy failure was compared between patients (A) with or without TLG and (B) with TLG alone and NLA alone.

TLG, target lesion growth; NLA, new lesion appearance

(A)


TLG
With 7.1 months (95% CI: 5.7 – 9.1)
Without 11.6 months (95% CI: 6.3 – 15.1)
p = 0.0071
Without TLG
With TLG
Progression-free survival
Months after first-line therapy

(B)


NTLG
With 5.7 months (95% CI: 2.9 – 9.1)
Without 9.0 months (95% CI: 6.4 – 11.4)
p = 0.0361
Without NTLG
With NTLG
Progression-free survival
Months after first-line therapy

(C)

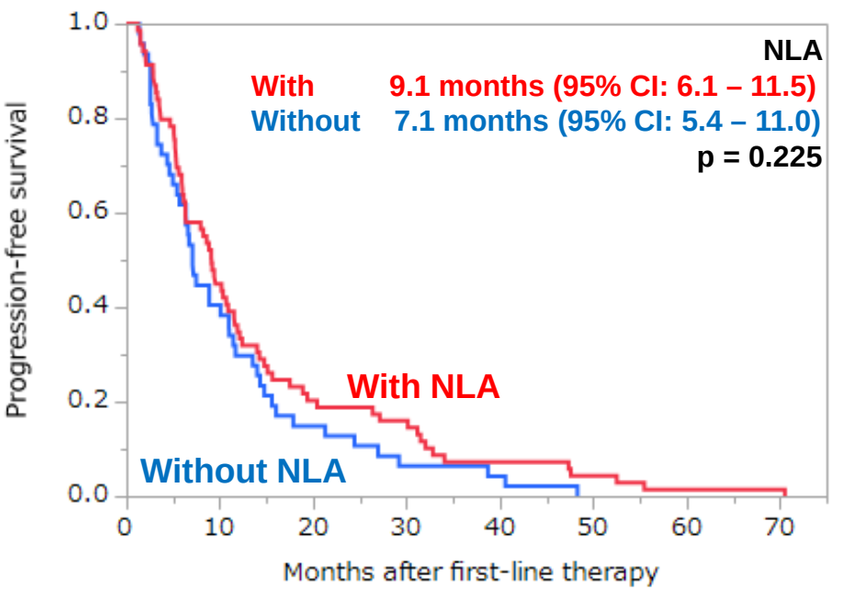

NLA
With 9.1 months (95% CI: 6.1 – 11.5)
Without 7.1 months (95% CI: 5.4 – 11.0)
p = 0.225
With NLA
Without NLA
Progression-free survival
Months after first-line therapy

Figure 1

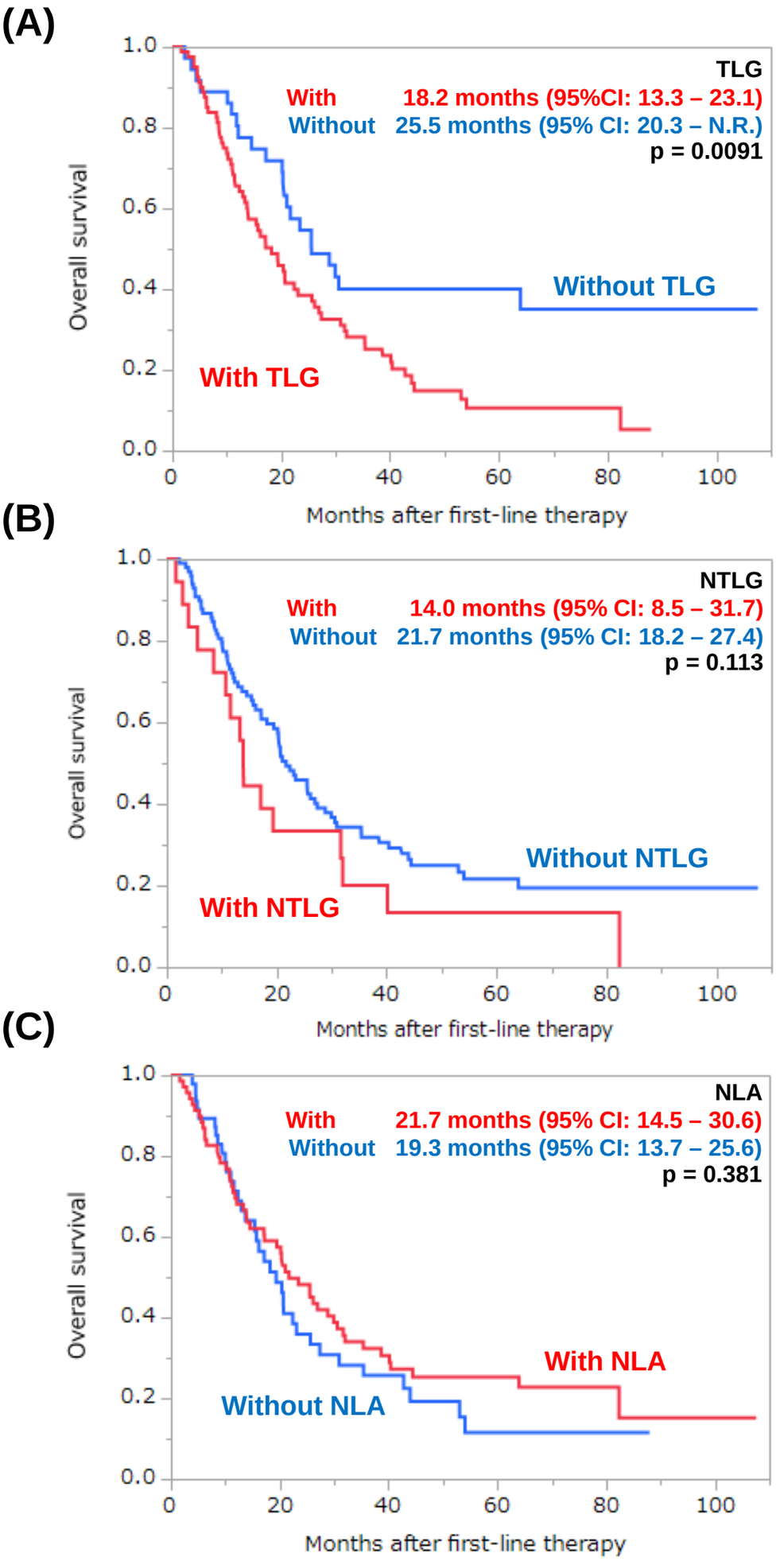
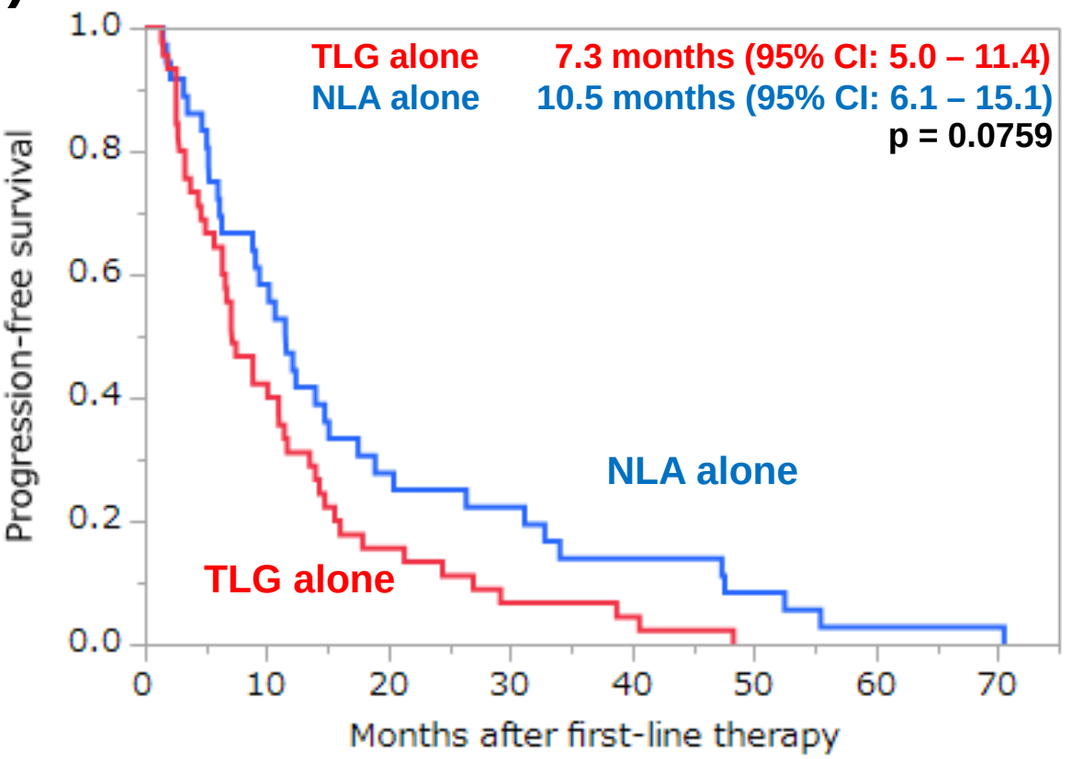

(A)
TLG
With 18.2 months (95%CI: 13.3 – 23.1)
Without 25.5 months (95% CI: 20.3 – N.R.)
p = 0.0091
Without TLG
With TLG
Overall survival
Months after first-line therapy
(B)
NTLG
With 14.0 months (95% CI: 8.5 – 31.7)
Without 21.7 months (95% CI: 18.2 – 27.4)
p = 0.113
Without NTLG
With NTLG
Overall survival
Months after first-line therapy
(C)
NLA
With 21.7 months (95% CI: 14.5 – 30.6)
Without 19.3 months (95% CI: 13.7 – 25.6)
p = 0.381
With NLA
Without NLA
Overall survival
Months after first-line therapy

Figure 2

(A)


TLG alone
7.3 months (95% CI: 5.0 – 11.4)
NLA alone
10.5 months (95% CI: 6.1 – 15.1)
p = 0.0759
NLA alone
TLG alone
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
Months after first-line therapy

(B)

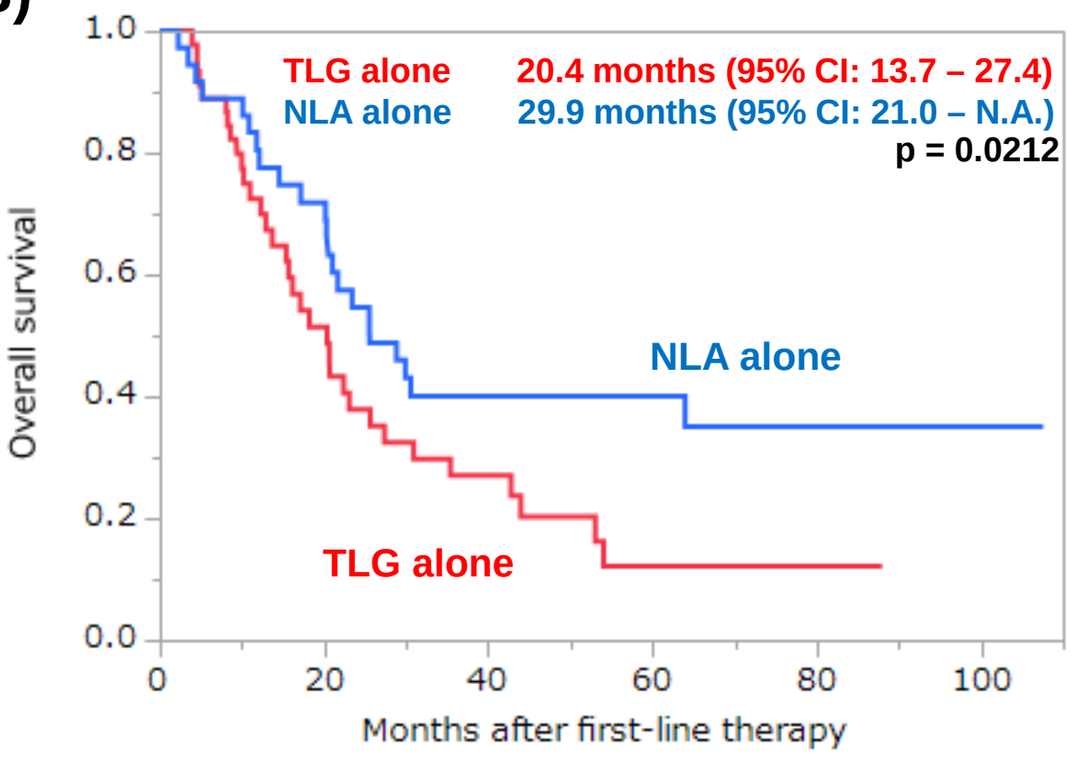

TLG alone
20.4 months (95% CI: 13.7 – 27.4)
NLA alone
29.9 months (95% CI: 21.0 – N.A.)
p = 0.0212
NLA alone
TLG alone
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Months after first-line therapy

Figure 3

Prognostic impact of the components of progressive disease on survival after first-line tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma

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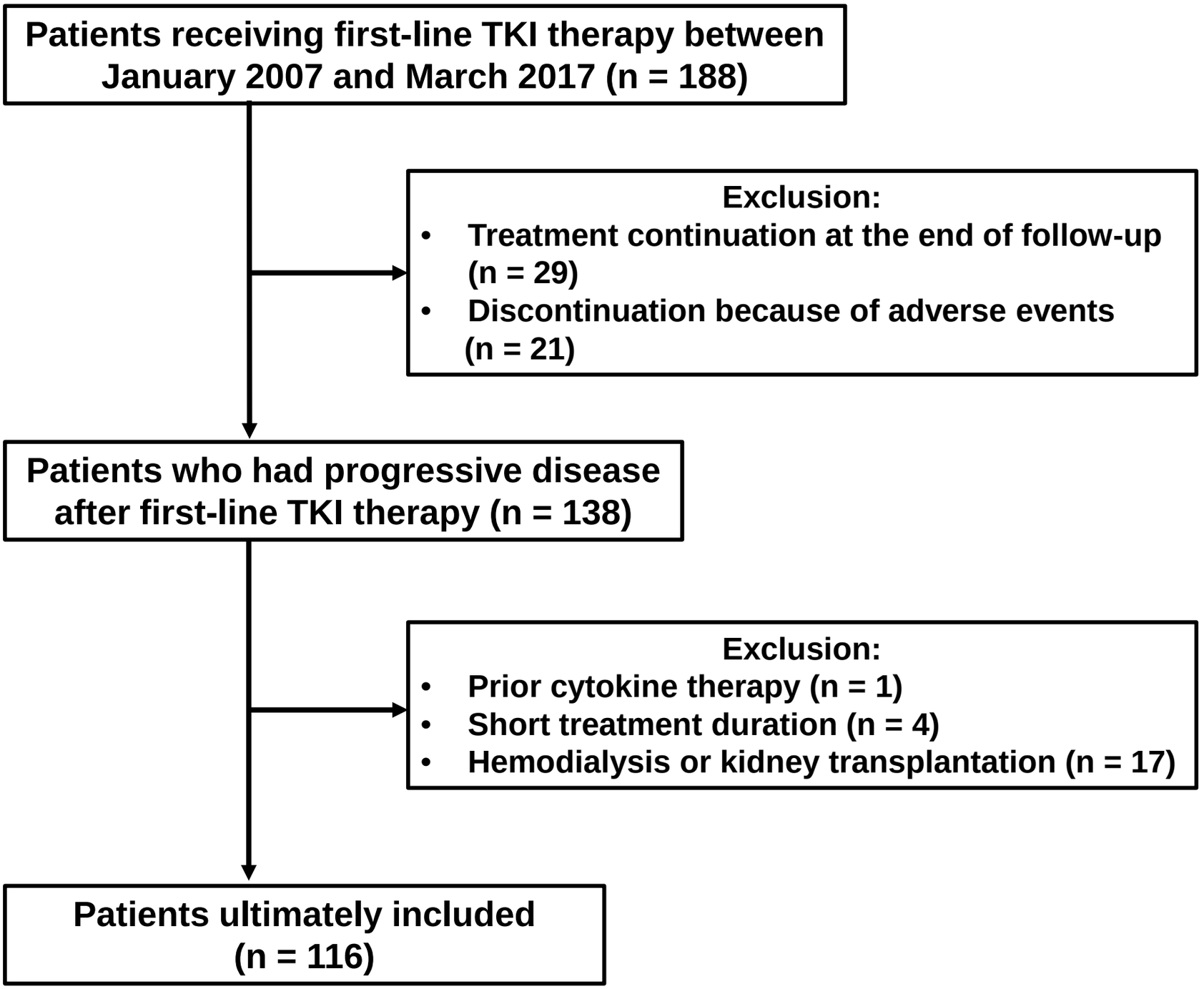
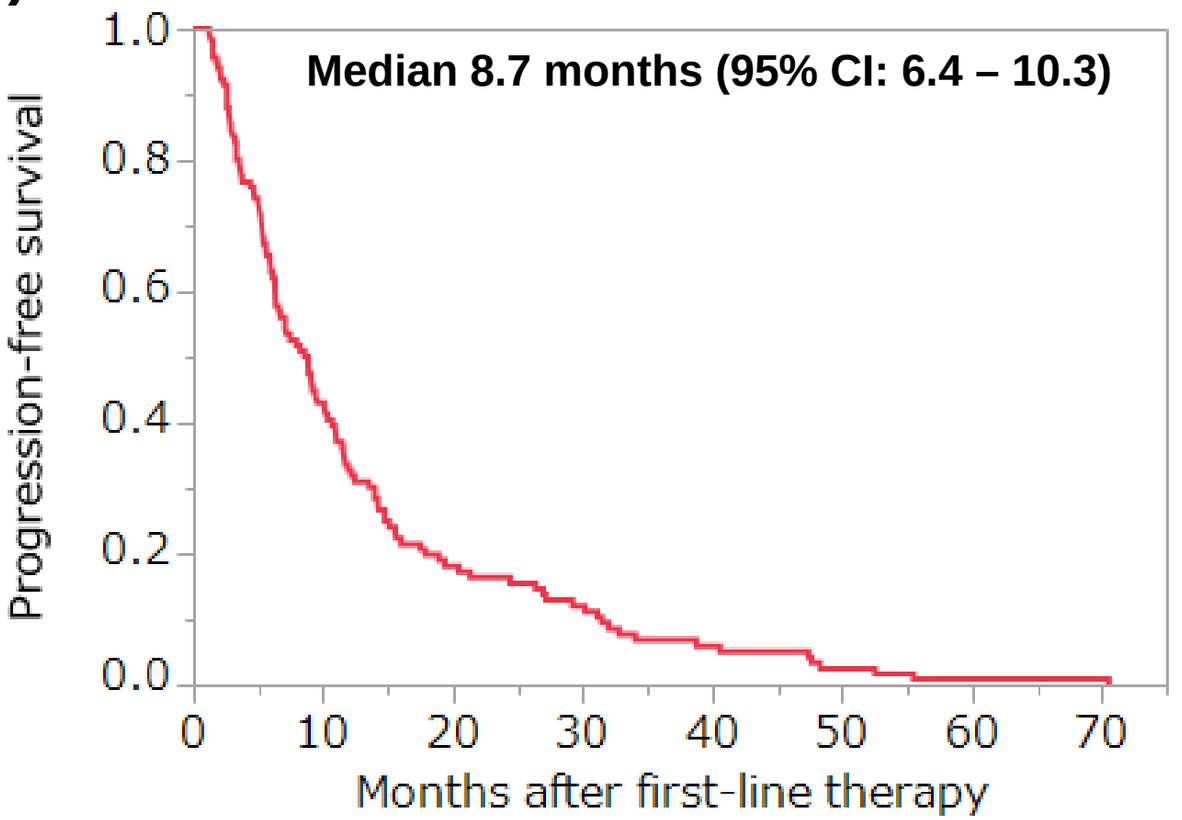
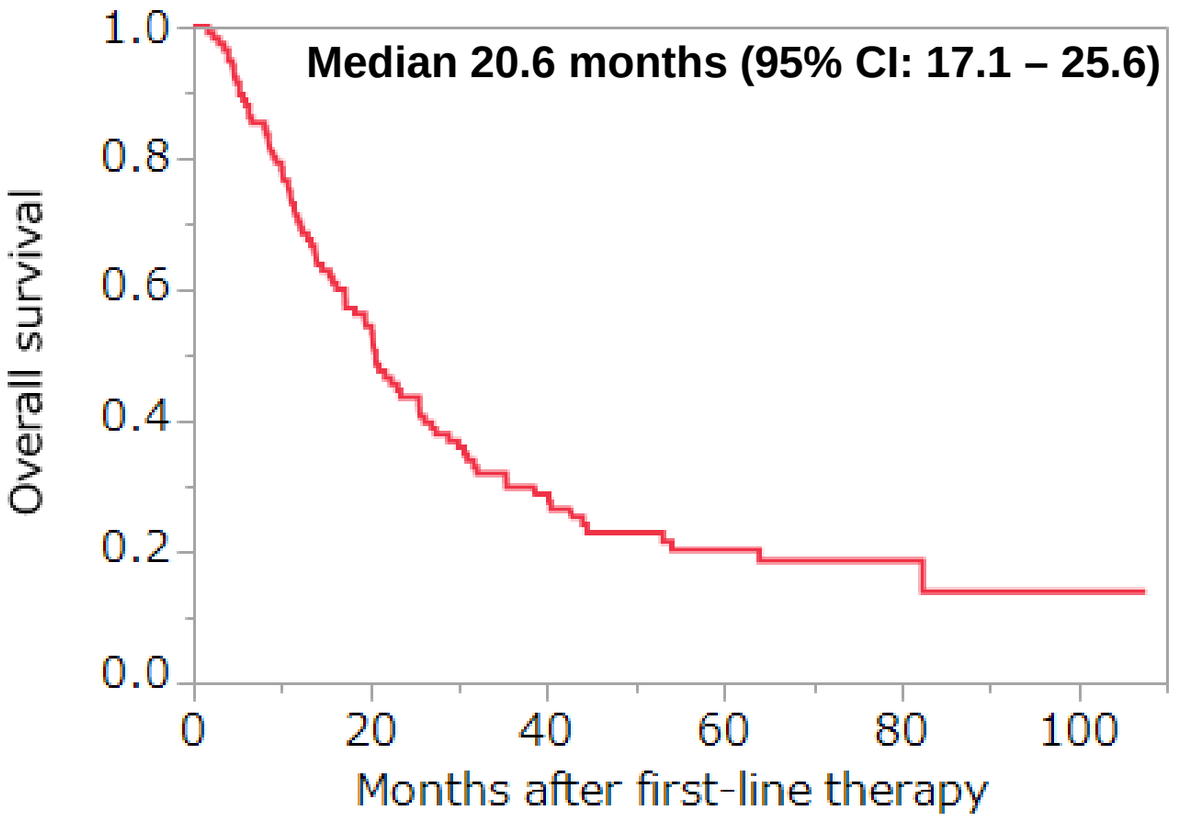


Electronic Supplementary Material 1

(A)

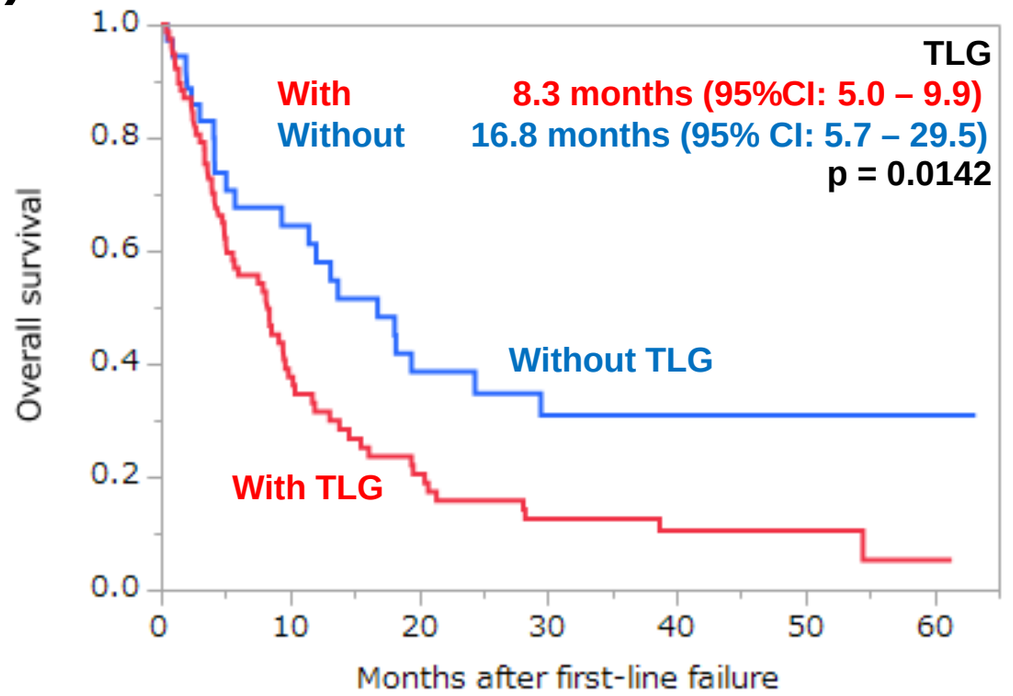


(B)

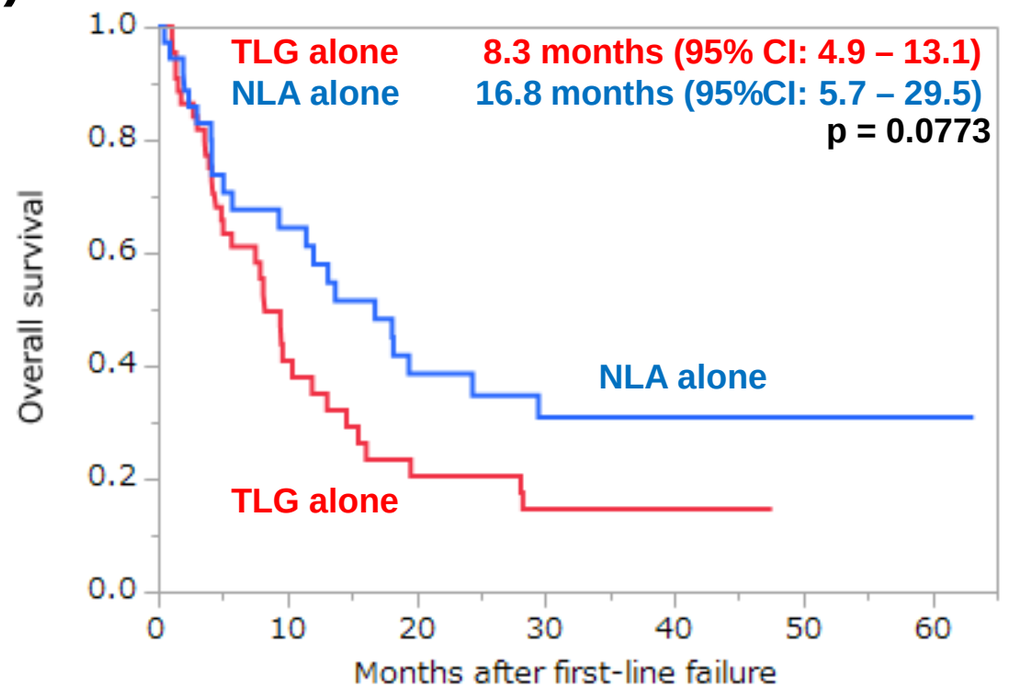


Electronic Supplementary Material 2

(A)



(B)



Electronic Supplementary Material 3

Table 1: Patient and tumor characteristics

Parameter	N = 116 (%)
Sex	
Male (ref. female)	82 (70.7)
*Age	66 (60-71)
Pathology	
Clear cell carcinoma	84 (72.4)
Papillary renal cell carcinoma type 2	8 (6.9)
Clear cell carcinoma with spindle cell	8 (6.9)
Others/unknown	16 (13.8)
First-line agent	
Sorafenib	35 (30.2)
Sunitinib	73 (62.9)
Pazopanib	8 (6.9)
Components of progression	
TLG	80 (69.0)
NTLG	18 (15.5)
NLA	69 (58.6)
Only TLG	45 (37.9)
Only NTLG	0 (0)
Only NLA	36 (31.0)
With TLG and NTLG but not NLA	2 (1.7)
With TLG and NLA but not NTLG	17 (14.7)
With NTLG and NLA but not TLG	0 (0)
With TLG, NTLG, and NLA	16 (13.8)
Prior nephrectomy	
With	98 (84.5)
Without	18 (15.5)
MSKCC risk classification	
Favorable	17 (14.7)
Intermediate	81 (70.0)
Poor	18 (15.3)
Metastatic lesions	
Solitary	
Multiple	40 (34.5)
*Follow-up, months	19.4 (10.2-36.2)

* Median and interquartile range

MSKCC, Memorial Sloan Kettering Cancer Center; TLG, target lesion growth; NTLG, non-target

lesion growth; NLA, new lesion appearance

Table 2: Univariate and multivariate analyses for progression-free survival

Variable	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Sex				
Male	Ref.	-	Ref.	-
Female	1.73 (1.13-2.61)	0.0121	1.45 (0.92-2.23)	0.1059
*Age, years	0.997 (0.98-1.01)	0.8		
Pathology				
CCC	Ref.	-	Ref.	-
Non-CCC/unknown	2.25 (1.44-3.46)	0.0005	1.71 (1.04-2.75)	0.0526
First-line agent				
Sunitinib/Pazopanib	Ref.	-		
Sorafenib	0.79 (0.52-1.68)	0.2406		
Components of progression				
Without TLG	Ref.	-	Ref.	-
With TLG	1.77 (1.17-2.70)	0.0061	1.59 (1.02-2.51)	0.0395
Without NTLG	Ref.	-	Ref.	-
With NTLG	1.71 (1.00-2.78)	0.0515	1.73 (0.97-2.95)	0.0615
Without NLA	Ref.	-		
With NLA	0.79 (0.55-1.16)	0.2306		
Prior nephrectomy				
With	Ref.	-	Ref.	-
Without	2.48 (1.43-4.07)	0.0018	2.07 (1.13-3.61)	0.0182
MSKCC outcome classification				
Favorable/intermediate	Ref.	-	Ref.	-
Poor	3.01 (1.74-4.95)	0.0002	3.22 (1.83-5.39)	0.0001
Metastatic lesions				
Solitary	Ref.	-	Ref.	-
Multiple	1.48 (0.98-2.14)	0.0649	1.34 (0.89-2.06)	0.1645

* Continuous variable

CCC, clear-cell carcinoma; HR, hazard ratio; CI, confidence interval; Ref, reference

TLG, target lesion growth; NTLG, non-target lesion growth; NLA, new lesion appearance; MSKCC, Memorial Sloan Kettering Cancer Center

Table 3: Univariate and multivariate analyses for overall survival

Variable	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Sex				
Male	Ref.	-	Ref.	-
Female	1.92 (1.21-3.02)	0.0066	1.73 (1.06-2.78)	0.0299
*Age, years	0.997 (0.98-1.01)	0.8		
Pathology, %				
CCC	Ref.	-	Ref.	-
Non-CCC/unknown	2.23 (1.35-3.60)	0.0023	1.99 (1.15-3.38)	0.0144
First-line agent, %				
Sunitinib/Pazopanib	Ref.	-		
Sorafenib	0.84 (0.52-1.34)	0.4875		
Components of progression				
Without TLG	Ref.	-	Ref.	-
With TLG	1.90 (1.18-3.16)	0.0073	1.67 (1.02-2.83)	0.04
Without NTLG	Ref.	-		
With NTLG	1.54 (0.87-2.60)	0.1331		
Without NLA	Ref.	-		
With NLA	0.82 (0.54-1.28)	0.385		
Prior nephrectomy				
With	Ref.	-	Ref.	-
Without	2.18 (1.17-3.76)	0.0157	1.22 (0.62-2.28)	0.5468
MSKCC outcome classification				
Favorable/intermediate	Ref.	-	Ref.	-
Poor	2.73 (4.15-4.65)	0.0014	2.74 (1.48-4.80)	0.0019
Metastatic lesions				
Solitary	Ref.	-	Ref.	-
Multiple	2.40 (1.50-3.97)	0.0002	2.19 (1.36-3.66)	0.0012

* Continuous variable

CCC, clear-cell carcinoma; HR, hazard ratio; CI, confidence interval; Ref, reference

TLG, target lesion growth; NTLG, non-target lesion growth; NLA, new lesion appearance; MSKCC, Memorial Sloan Kettering Cancer Center