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LETTER TO THE JOURNAL

Sunitinib in metastatic renal cell carcinoma: clinical outcomes across risk groups in a Turkish Oncology Group Kidney Cancer Consortium

Renal cell carcinoma (RCC) is responsible for an estimated 434,419 new cases and 155,702 deaths, which amounts to 2.2% of all new cancer globally [1]. Despite the advent of new combination therapies, the 3-year overall survival (OS) in metastatic RCC (mRCC) remains around 60% [2–4]. To stratify the patients according to their prognosis, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model and the Memorial Sloan Kettering Cancer Center (MSKCC) model, are well developed and used before the initiation of the treatment. Sunitinib was the standard of care after showing superiority over interferon alfa in mRCC until immunotherapy (IO) combinations gained approval [5]. While IO and anti-vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) combinations are recommended first-line, they have not shown a significant OS benefit in patients with IMDC favorable risk and remain costly, limiting access in resource-constrained settings. This study evaluates clinical outcomes of mRCC patients treated with first-line sunitinib and aims to identify factors impacting these outcomes.

We conducted a retrospective cohort study using data from the Turkish Kidney Cancer Consortium (TKCC) database. The study included patients aged 18 and older diagnosed with mRCC and treated with sunitinib as a first-line therapy. The primary objectives were to evaluate time to treatment failure (TTF) across risk groups and identify factors affecting TTF. Secondary objectives included assessing OS by risk group, factors affecting OS, and objective response rate (ORR). TTF was defined as the time from treatment start to discontinuation due to any cause, while OS was defined as the time from treatment start to death. ORR represented the percentage achieving complete response (CR) or partial response (PR).

Statistical analyses were performed using IBM SPSS Statistics Version 24.0. Survival curves were estimated with the Kaplan-Meier method, and multivariate analyses included variables with $P \leq 0.20$ in univariate analyses. Cox regression calculated hazard ratios (HRs) with 95% confidence intervals (CIs), with $P < 0.05$ considered statistically significant.

A total of 531 patients with median age of 57.3 (interquartile range = 12.5) years were included the study. Baseline characteristics and of patients were summarized in Supplementary Table S1. Median TTF was 10.25 (95% CI = 8.94-11.55) months (Figure 1A). Median TTF was 10.12 (95% CI = 8.55-11.69) months for clear cell histology and 10.86 (95% CI = 8.14-13.21) months for non-clear cell histology ($P = 0.653$). TTF was 15.70 (95% CI = 11.76-19.64), 11.36 (95% CI = 9.89-12.84), and 4.89 (95% CI = 3.83-5.95) months for IMDC favorable, intermediate and poor risk groups, respectively. There was no difference in TTF between patients with IMDC favorable risk and IMDC intermediate risk with 1 risk factor (15.70 months vs. 12.25 months, $P = 0.321$) (Figure 1B). TTF was 14.94 months (95% CI = 12.46-17.43), 10.74 months (95% CI = 9.08-12.39), and 4.17 months (95% CI = 2.75-5.58) in patients with MSKCC favorable, intermediate, and high groups, respectively. There was no significant difference in TTF between patients with MSKCC favorable risk and those with MSKCC intermediate risk with 1 risk factor (14.94 months vs. 12.52 months, $P = 0.287$) (Figure 1C). The univariate and multivariate analysis for TTF was presented in Supplementary Table S2.

Median OS was 31.01 (95% CI = 25.38-36.64) months for all population (Figure 1D). Median OS was 34.63 (95% CI = 28.16-41.09) and 22.80 (95% CI = 16.77-28.84) months for clear cell and non-clear cell histology, respectively

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immunotherapy; IQR, Interquartile range; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; RCC, renal cell carcinoma; TKCC, Turkish Kidney Cancer Consortium; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure; VEGF, vascular endothelial growth factor.

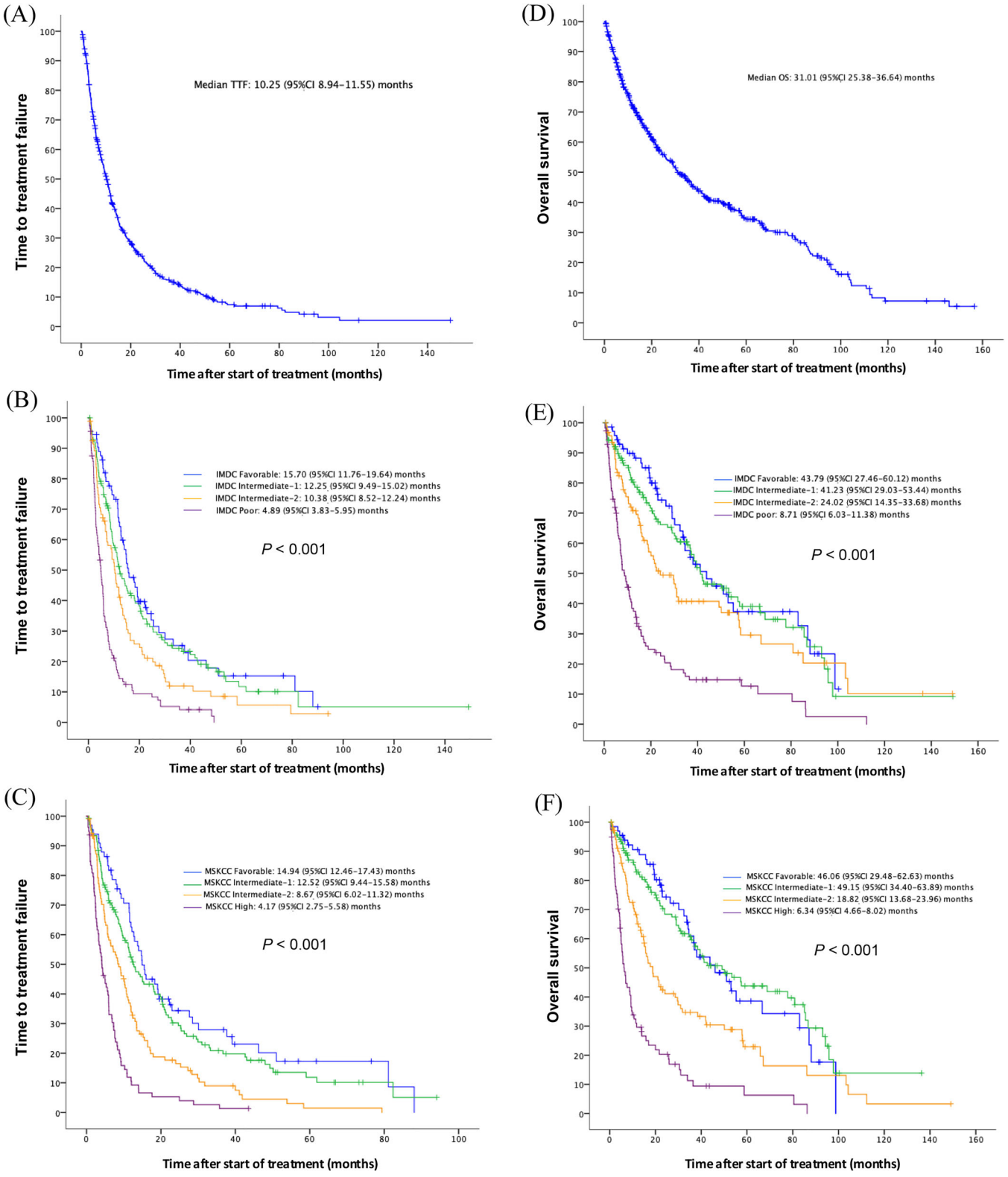

FIGURE 1 Kaplan-Meier curve for time to treatment failure for all population (A), IMDC risk groups (B) and MSKCC risk groups (C), and for overall survival for all population (D), IMDC risk groups (E) and MSKCC risk groups (F). Abbreviations: CI, Confidence interval; HR, Hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center.

($P = 0.247$). OS was 43.79 (95% CI = 27.46-60.12), 37.29 (95% CI = 29.57-46.00) and 8.71 (95% CI = 6.03-11.38) months for IMDC favorable, intermediate and poor risk groups, respectively. The median OS was 41.23 (95% CI = 29.03-53.44) for patients with IMDC intermediate risk with one risk factor, and there was no difference with patients with IMDC favorable risk ($P = 0.579$) (Figure 1E). The median OS was 46.06 (95% CI = 29.46-62.63), 31.77 (95% CI = 24.02-39.51), and 6.34 (95% CI = 4.66-8.02) months in MSKCC favorable, intermediate, and high-risk groups, respectively. There was no significant difference in OS between patients with MSKCC favorable risk and those with MSKCC intermediate risk with one risk factor (46.06 months vs. 49.15 months, $P = 0.827$) (Figure 1F). The univariate and multivariate analysis for TTF was presented in Supplementary Table S3.

Among the patients, 3.1% achieved a CR, 35.2% had a PR, 36.9% had stable disease (SD), and 24.8% experienced progressive disease (PD). ORR was 50.1% (6.3% CR and 43.8% PR), 42.9% (2.3% CR and 40.6% PR), and 22.4 (2.0% CR and 20.4 PR) for IMDC favorable, intermediate, and poor risk groups, respectively. ORR was 60.0% (7.5% CR and 52.5% PR), 40.6% (2.1% CR and 38.5% PR), and 20.6 (0% CR and 20.6 PR) for MSKCC favorable, intermediate, and high-risk groups, respectively.

Our study provides valuable real-world evidence on the clinical outcomes of mRCC patients treated with first line sunitinib, stratified by IMDC and MSKCC risk groups We found no significant difference in TTF and OS between IMDC favorable-risk patients and intermediate-risk patients with one risk factor. Intermediate-risk patients, the largest subgroup in mRCC, show heterogeneity in clinical characteristics. There may be a need to further refine the IMDC intermediate-risk category, as has been done for favorable risk [6]. Retrospective analysis of pivotal phase-III trial data of sunitinib by Rini et al. reported median PFS of 14.1, 10.7, and 2.4 months for the IMDC favorable, intermediate, and poor risk groups. Median OS was not reached for the IMDC favorable group; it was 23.0 months for intermediate-risk and 5.1 months for poor-risk groups [7]. In our study, OS in the IMDC groups was longer than in the pivotal sunitinib trial, which aligns with recent studies showing improved survival when sunitinib is used as a comparator increased [2, 3, 8]. Differences in patients' characteristics, and more available post-progression treatments may explain the slight differences in outcomes.

VEGF plays an important role in tumor progression by promoting angiogenesis and fostering an immune-suppressive environment. Though combining IO with anti-VEGF TKIs shows higher ORR in favorable-risk patients than sunitinib alone, this has not translated into improved OS [2, 3, 8, 9]. In patients with favorable risk mRCC, the expression levels of angiogenic genes and specific targets for TKIs are higher, and a higher angiogenesis gene signature is associated with a better response to sunitinib monotherapy. TKI monotherapy may still be a viable option for patients in the IMDC favorable risk group who are asymptomatic, have a low disease burden, and live in resource-limited settings with restricted access to IO and TKI combinations.

Our study highlights that sunitinib monotherapy continues to yield meaningful clinical outcomes, especially for patients in the favorable risk group. There is a need for the development of predictive biomarkers to identify which patients are more likely to benefit from monotherapy as opposed to combination regimens. Looking forward, future research should focus on integrating molecular and genetic markers into clinical practice to better personalize treatment plans for mRCC patients.

AUTHOR CONTRIBUTIONS

Conceptualization: Hatice Bolek, Emre Yekeduz, and Yuksel Urun. *Methodology*: Hatice Bolek, Emre Yekeduz, and Yuksel Urun. *Formal analysis*: Hatice Bolek and Emre Yekeduz. *Investigation*: Hatice Bolek. *Data Curation*: Hatice Bolek, Omer Faruk Kuzu, Elif Sertesen Camoz, Saadet Sim, Serhat Sekmek, Hilal Karakas, Selver Isık, Murad Guliyev, and Aysun Fatma Akkus. *Visualization*: Hatice Bolek. *Writing-Original Draft*: Hatice Bolek and Emre Yekeduz. *Writing-Review & Editing*: Deniz Tural, Cagatay Arslan, Sema Sezin Goksu, Ozlem Nuray Sever, Nuri Karadurmus, Cengiz Karacin, Mehmet Ali Nahit Sendur, and Yuksel Urun. *Project administration*: Yuksel Urun.

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CONFLICT OF INTEREST STATEMENT

Yuksel Urun declared research funding (Institutional and personal) from Turkish Oncology Group. Yuksel Urun has served on the advisory board for Abdi-İbrahim, Astellas, AstraZeneca, Bristol Myers-Squibb, Eczacıbası, Gilead, Janssen, Merck, Novartis, Pfizer, Roche. Yuksel Urun received honoraria or has served as a consultant for Abdi-İbrahim, Astellas, Bristol Myers-Squibb, Eczacıbasi, Janssen, Merck, Novartis, Pfizer, Roche. All remaining authors have declared no conflicts of interest.

FUNDING INFORMATION

This study was sponsored by Pfizer.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Ankara University Faculty of Medicine Clinical Research Ethics Committee (approval no: 16-1068-18) and by the T.C. Ministry of Health Turkish Medicines and Medical Devices Agency (approval no: 66175679-514.05.01-E.48666) which determined that informed consent was not required due to the retrospective nature of the research and the anonymization of patient data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.