Treatment-free Survival After First-Line Therapies for Metastatic Renal Cell Carcinoma: An International Metastatic Renal Cell Carcinoma Database Consortium Analysis

Mehul Gupta[1], Connor Wells[2], Meredith M. Regan[3], Wanling Xie[3], Vishal Navani[1], Renee Maria Saliby[3], Naveen S. Basappa[4], Frede Donskov[5], Takeshi Yuasa[6], Kosuke Takemura[6], Christian K. Kollmannsberger[2], Megan Crumbaker[7], Aly-Khan A. Lalani[8], Thomas Powles[9], Hedyeh Ebrahimi[10], Rana McKay[11], Jae-Lyun Lee[12], Ravindran Kanesvaran[13], Toni K. Choueiri[3], Daniel Yick Chin Heng[1]

[1]Tom Baker Cancer Centre, University of Calgary; [2]BC Cancer Agency; [3]Dana-Farber Cancer Institute; [4]Cross Cancer Institute, University of Alberta; [5]University Hospital, Aarhus, Denmark, [6]Cancer Institute Hospital, Japanese Foundation for Cancer Research; [7]The Kinghorn Cancer Centre, St Vincent's Hospital; [8]Juravinski Cancer Centre, McMaster University; [9]Barts Cancer Institute; [10]Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center; [11]University of California at San Diego; [12]Asan Medical Center, University of Ulsan College of Medicine; [13]National Cancer Center of Singapore

Question

What are the treatment-free survival (TFS) outcomes of patients with metastatic renal cell carcinoma (mRCC) initiating different first-line (1L) therapy regimens?

Key Findings

3,758 patients with mRCC treated with first-line systemic therapy were included in this retrospective cohort study

IMDC favourable risk patients initiating VEGFR monotherapy had a 36-month TFS of 3.1 months, while those receiving ICB-VEGFR therapy had a 36-month TFS of 3.7 months.

IMDC Intermediate/poor risk patients receiving those regimens experienced a TFS of 2.1 months and 3.7 months relative to 5.3 months for those receiving ICB doublet therapy.

Central Conclusions

This study is the first observational analysis to report TFS outcomes for patients with mRCC receiving standard-of-care first-line therapy with VEGFR, ICB-VEGFR and doublet ICB therapy

Among IMDC favourable risk patients, despite similar overall and treatment free survival outcomes, those treated with VEGFR monotherapy spent longer on subsequent lines of treatment (17.3% vs 33.6%), while those treated with ICB-VEGFR combination therapies spent longer on first line therapies therapies (61.7% vs 44.9%).

Additionally, intermediate/poor IMDC risk patients treated with ICB doublet therapy experienced a TFS period more than twice as long as those treated with VEGFR inhibitor monotherapy over the 36-month period since therapy initiation.

Background

Novel agents targeting cancer cell growth and immune evasion have significantly improved survival for patients with mRCC. Standard of care 1L therapies include vascular endothelial growth factor receptor (VEGFR) monotherapy, immune checkpoint blockade (ICB)-VEGFR therapy, and ICB doublet therapy with ipilimumab-nivolumab

Traditional time to event endpoints fail to quantify how patients on different treatment regimens spend their time. An understanding of this is crucial to accurately counsel patients and aid in treatment decision-making given the association between time spent free of systemic therapy and quality of life

TFS quantifies the time patients spend alive and free from systemic therapies.

TFS has been explored in clinical trial settings, but this study is the first to report this outcome in patients with mRCC treated in routine practice settings. A more robust understanding of TFS outcomes in routine practice settings may help inform decision-making given the large number of therapy choices available to patients and clinicians

Methods

Patient Selection: A retrospective analysis of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), an international multi-center cohort study of consecutive patients with mRCC initiating systemic therapy between February 1, 2014, to February 1, 2023.

Primary Outcome Measure: 36-month TFS defined as the difference in restricted mean survival time between two time-to event endpoints: (1) time from 1L therapy initiation to discontinuation of therapy, death, or censor at last follow-up and (2) time from 1L therapy initiation to subsequent systemic therapy, death, or censor at last follow-up.

Secondary Outcome Measures: 36-month time spent on first-line therapy, defined as the area underneath the time to first-line therapy discontinuation curve. 36-month time spent after subsequent therapy initiation, defined as the area between the (1) overall survival and, (2) time to subsequent therapy initiation curves.

Analysis Groups: Analysis was conducted by IMDC risk group and by type of 1L treatment received including VEGFR inhibitor monotherapy (sunitinib or pazopanib), combination ICB-VEGFR therapy (avelumab-axitinib, pembrolizumab-axitinib, nivolumab-cabozantinib, or pembrolizumab-lenvatinib), or ICB doublet therapy (ipilimumab-nivolumab)

Results

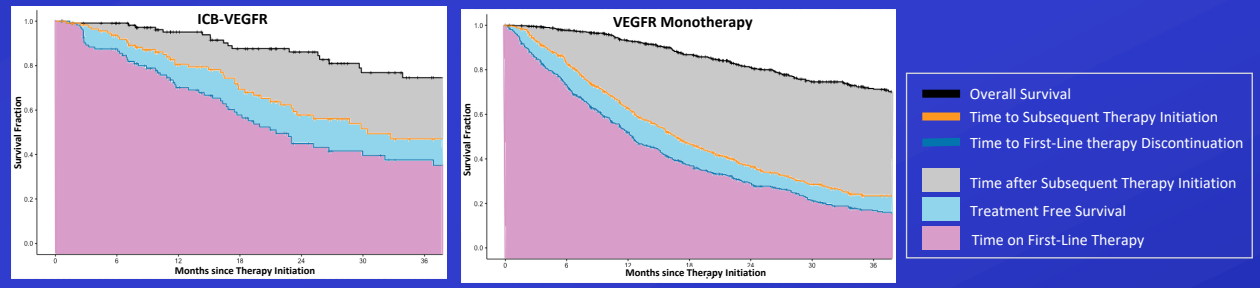
3,758 patients with mRCC were included with a median follow-up time of 33.2 months. Among patients with favourable risk, 118 (19.0%) received ICB-VEGFR therapy and 504 (81.0%) received VEGFR monotherapy. Among intermediate/poor risk patients 769 (24.5%) received ICB doublet therapy, 236 (7.5%) received ICB-VEGFR therapy, and 2,131 (68.0%) received VEGFR monotherapy

Among IMDC favourable risk patients, the TFS period for ICB-VEGFR therapy was 3.7 months (95% CI 0.2-7.2) relative to 3.1 months (95% CI 1.5-4.6) for VEGFR monotherapies, corresponding to a total of 10.1% and 8.5% of the 36-month period spent free from systemic therapy.

Among IMDC intermediate/poor risk patients, the TFS period for 5.3 months (95% CI 3.8-6.8) for ICB doublet therapy, 3.7 months (95% CI 1.0-6.4) for ICB-VEGFR therapies, and 2.1 months (95% CI 1.4-2.8) for VEGFR monotherapies, corresponding to 14.6%, 10.3%, and 5.9% of the 36-month period spent free from systemic therapy.

Figure 1. Treatment-free survival time and other survival states over the 36-month period since first-line therapy initiation, according to treatment and IMDC Risk Group

IMDC Favourable Risk



IMDC Intermediate/Poor Risk

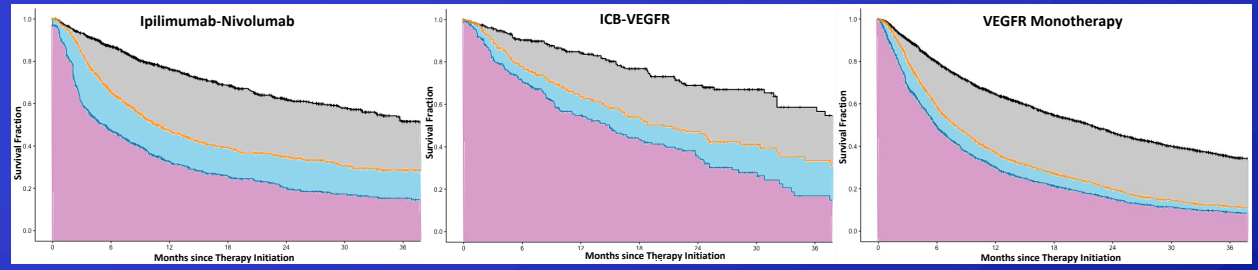


Table 1. Summary of treatment-free survival and other survival states over the 36-month period since first-line therapy initiation, according to treatment and IMDC Risk Group

Over 36-Month Study Period	IMDC Favourable Risk		IMDC Intermediate/Poor Risk		
	ICB-VEGFR n= 118	VEGFR Monotherapy n=504	Ipilimumab-Nivolumab n=769	ICB-VEGFR n=236	VEGFR Monotherapy n=2131
Time spent on First-Line Therapy months (95% CI)	22.2 (19.6 - 24.7)	16.2 (15.0 - 17.3)	11.6 (10.6 - 12.6)	17.2 (15.3 - 19.1)	10.6 (10.1 - 11.1)
Treatment Free Survival months (95% CI)	3.7 (0.2 - 7.2)	3.1 (1.5 - 4.6)	5.3 (3.8 - 6.8)	3.7 (1.0 - 6.4)	2.1 (1.4 - 2.8)
Time after Subsequent Therapy Initiation months (95% CI)	6.2 (3.3 - 9.2)	12.1 (10.7 - 13.5)	8.8 (7.3 - 10.3)	7.0 (4.3 - 9.6)	8.5 (7.7 - 9.2)
Overall Survival months (95% CI)	32.1 (30.4 – 33.8)	31.3 (30.5 - 32.1)	25.7 (24.6 – 26.7)	27.9 (26.1 - 29.6)	21.2 (20.6 - 21.8)