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Clinical resistance predictors to first-line VEGFR-TKI monotherapy for metastatic renal cell carcinoma: a retrospective multicenter real-life case series

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Abstract

Aim: For many years, systemic treatment of metastatic Renal Cell Carcinoma (mRCC) was based on sequential targeted agent monotherapies. In this real-life case series, we evaluated easily accessible clinical factors useful for disease course prediction.

Methods: We exploited patients' clinical pathological characteristics and systemic treatment outcomes in a real-world population of 365 mRCC patients who received sequential monotherapies in the targeted therapy era, and we identified an early progressors subpopulation, resistant to first-line VEGFR-TKI monotherapy in less than 6 months.

Results: Early progressors (n = 124) show a far worse OS compared with patients progressing beyond the sixth

month of therapy (13.5 *vs.* 44.8 months, *P*-value < 0.0001, HR = 0.41, 95%CI: 0.29-0.53). However, these patients did not show far worse performance in second and third-line settings compared to first-line responders. In the univariate analysis, IMDC risk class, sarcomatoid features, and Systemic Inflammation Index (SII) were correlated with first-line therapy Progression-Free Survival (PFS1). In multivariate analysis, variables correlated with first-line outcome were IMDC risk class, histotype, and number of metastatic sites at the diagnosis.

Conclusion: Real-world data can contribute to developing easy-to-use prognostic factors associated with refractory disease that could support clinicians in identifying the most appropriate treatment strategy for each patient.

Keywords: Renal cell carcinoma, targeted therapy, tyrosine kinase inhibitor, drug resistance, early progressor, rapidly progressive, prognostic factor, real-world data

INTRODUCTION

Renal cell carcinoma (RCC) represents the vast majority (90%) of renal neoplasms, with a 5-year survival of 13% in patients with metastatic disease[1]. Only one-third of patients present at diagnosis with distant metastases, while the majority of patients present at diagnosis with a surgically curable disease. However, in at least one-third of the patients treated with surgery, the disease recurs with local and/or distant metastases[2]. From a histopathological point of view, the clear cell histotype (ccRCC) accounts for two-thirds of the diagnoses, while one-third of the cases are divided among all the other histotypes together, the so-called non-clear cell RCC (nccRCC). The fifth edition of the World Health Organization (WHO) classification of urogenital tumors (WHO "Blue Book")[3], published in 2022, identifies a total of 21 different forms of RCC, including some new molecularly-defined entities.

Metastatic RCC (mRCC) is known for being one of the few tumors that can rely on a solid prognostic algorithm. In fact, at the diagnosis of metastatic disease, RCC patients are risk stratified into favorable, intermediate, and poor risk categories using the International Metastatic RCC Database Consortium (IMDC) risk model[4]. This prognostic tool uses the interpolation of clinical data (Karnofsy Performance Status, time from diagnosis to systemic treatment) and laboratory data (Hemoglobin, Neutrophil count, Platelet count, Serum Calcium) to predict patients' prognosis. This model has been strongly corroborated by evidence over the last decade; its accuracy and reproducibility are well established in first-line targeted therapy[5] and subsequent treatment lines[6], as well as in non-clear-cell mRCC[7]. However, the prognostic role of some pathological tumor features should not be overlooked, such as sarcomatoid component and non-clear cell histotypes are predictors of poor outcomes[4]. Similarly, other indices of immune activation such as the Systemic Inflammation Index (SII) deserve more consideration. In fact, this index has been shown to correlate with poor prognosis in mRCC[8].

As for the therapy, over the last two decades, the clinical management of mRCC has radically changed. In fact, starting from a scenario comprising only high-dose interleukin 2 (IL-2) and interferon-α, with poor survival, the systemic treatment of this disease evolved towards the use of vascular endothelial growth factor receptor tyrosin-kinase inhibitors (VEGFR-TKI), mammalian target of rapamycin inhibitors (mTORi), and immune checkpoint inhibitors (ICI). As a consequence, the median overall survival for metastatic disease has increased from less than 1 year in the 1990s to more than 4 years in some recently completed trials[9]. In the current scenario, ICI combination and VEGFR-TKI plus ICI combination represent the first-choice options for the first-line treatment of mRCC[10]. Moreover, the ongoing clinical trials heavily focus on the combination of the aforementioned therapeutic principles.

We present a retrospective analysis of 365 mRCC patients who received sequential monotherapies at two Italian Oncology Reference Centres for RCC in the targeted therapy era. In our analysis, we exploit patients' clinical pathological characteristics and systemic treatment outcomes in a real-life scenario to attempt to identify clinical variables that could improve disease course prediction.

PATIENTS AND METHODS

This is a retrospective, multi-institutional analysis that includes patients with a histologically confirmed diagnosis of mRCC who received a VEGFR-TKI monotherapy as a first-line systemic therapy at two Italian Health Institutions (Translational Oncology Unit of the Istituti Clinici Scientifici Maugeri in Pavia and Medical Oncology Unit of the University Hospital Polyclinic of Bari). The collection and analysis of patient-level data for this article were approved by both institutions. Patients with a histologically confirmed diagnosis of RCC in the metastatic stage, who received at least one month of treatment and a minimum follow-up of 3 months, were included. Patients enrolled in clinical trials were excluded from this analysis. The cutoff date for data analysis was 30 June 2022.

Patient, tumor, and treatment-related variables were collected through a review of electronic medical records. Demographic data for each patient included age, gender, and race. Patient-specific variables included height, weight, IMDC risk category (i.e., favorable, intermediate, and high), and vital status as of 30 June 2022 (alive or deceased). Tumor-specific characteristics collected included histology, stage, sarcomatoid component, and metastatic sites at the time of metastatic disease evidence. Treatment-related variables included nephrectomy, surgery for metastases, radiation therapy to any site, number and type of systemic therapies beyond the first line, start and stop date of systemic therapies, neutrophils count before the first dose of first-line therapy, lymphocyte count before the first dose of first-line therapy, and platelets count before the first dose of first-line therapy.

The efficacy of systemic therapies was evaluated using several variables including overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) based on medical records or censored as of 30 June 2022. The radiological response to systemic therapies was assessed by local investigators based on the review of medical records and available imaging. PFS was defined as the time between the date of the first dose of systemic therapy and the date of the first dose of the following line of systemic therapy or the date of death. OS was defined as the time between the first dose of systemic therapies and the date of either death, last known alive, or last follow-up.

For every patient, the Systemic Inflammation Index (SII) was calculated before the beginning of the first therapy line as the product of the number of neutrophils per blood microliter and the number of platelets per blood microliter divided by the number of lymphocytes per blood microliter (as shown by Hu *et al.*)[11].

Descriptive statistics were used to summarize patient characteristics and treatment-related variables. The Kaplan-Meier method and Cox test were used to estimate and compare survival between groups. Uni- and multi-variable Cox proportional hazard models were used to correlate patient and treatment-related variables to survival (i.e., PFS and OS) on systemic therapies. All tests were two-sided and *P*-values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using R and Rstudio ("survival" package).

RESULTS

Patients' characteristics

Three hundred sixty-five patients with a histologically confirmed RCC diagnosis and at least one month of first-line therapy with VEGFR-TKI for metastatic disease were included (minimum follow-up of 3 months). The median follow-up time for patients alive on 30 June 2022 was 29.33 months (range 3.1-181.83 months). The median age at the diagnosis of RCC was 54.88 years (range 18-82 years), with the majority of patients being male (n = 293, 80%). Median BMI was 25.99 Kg/m^2 (range 17.78-46.98 Kg/m^2).

The majority of tumors were of clear cell histology (n = 200, 54.7%) followed by papillary RCC (n = 75, 20.5%), chromophobe RCC (n = 44, 12%), MiT alteration RCC (n = 12, 3.2%), unclassified RCC (n = 30, 8.2%), collecting duct RCC (n = 4, 1.4%). Sarcomatoid features were present in 25.7% of patients (n = 94).

At the time of diagnosis, 145 patients (39.7 percent) had metastatic disease, while for the other patients, the median time to the metastatic occurrence was 22.91 months (range 3.03-295.33 months). The most common metastatic sites were lungs (n = 243, 66.5%), lymph nodes (n = 168, 46.0%), bone (n = 76, 20.8%), kidney (n = 71, 19.4%), liver (n = 59, 16.1%), brain (n = 19, 5.2%), adrenal glands (n = 9, 2.4%), peritoneum (n = 7, 1.9%), muscles (n = 7, 1.9%), pancreas (n = 6, 1.6%), pleura (n = 3, 0.8%).

IMDC risk categories were calculated before the start of each systemic therapy line. At the beginning of the first therapy line, the risk groups were distributed as follows: favorable (n = 130, 35.6%), intermediate (n = 146, 40%), and poor (n = 89, 24.4%).

Median Systemic Inflammation Index (SII) was also calculated before the start of the first systemic therapy line, and the median value was 940 × 10^9/L (range 103-7,731 × 10^9/L).

Additional patient-related characteristics are summarized in Table 1.

Treatments and outcomes

As for surgical treatment, 322 patients (88.2%) received nephrectomy: 204 (55.9%) patients received nephrectomy for localized disease, and 118 (32.3%) received cytoreductive nephrectomy.

The mean number of systemic treatment lines received by the 365 patients was 2.5 (range 1-9). Globally, 302 patients (82.7%) received a second-line treatment, and 191 patients (52.3%) reached a third-line treatment.

All patients received a VEGFR-TKI as a first-line treatment. The most common agents used as first-line therapy were sunitinib (n = 231, 63.3%), pazopanib (n = 41, 11.2%) and cabozantinib (n = 18, 4.9%). For the second line of treatment, 43.3% of patients received a VEGFR-TKI, 40% an mTOR inhibitor, and 11% immunotherapy (Immune-Checkpoint inhibitors).

The median OS of the overall population was 29.36 months (95%CI: 27.6-36.5 months, range: 1.8-181.83 months). At the time of the data cutoff, death occurred in 306 patients (83.8%). The first-line treatment PFS was 9.1 months (95%CI: 8.1-13.7 months, range 1.4-152.3 months), the ORR 28% and the DCR 83%. A median second-line PFS of 5.1 months is reported (95%CI: 4.6-5.8 months, range 1.1-116.8 months), along with an ORR of 15% and a DCR of 63%, without clinically relevant differences among the different treatment groups. In the third line setting, 51.8% of patients received an antiangiogenic drug, 34.5% an mTOR inhibitor, and 7.8% immunotherapy. Median third-line PFS was 5.2 months (95%CI: 4.2-6.9 months, range 1.03-53.6 months), with an ORR of 13% and a DCR of 63%, without clinically relevant differences

Table 1. Patient characteristics

Variable	Number of patients (% of the total number = 365)
Age at diagnosis:	
Under 50	116 (31.7%)
50-70	215 (58.9%)
Over 70	34 (9.4%)
Gender:	
Male	293 (80%)
Female	72 (20%)
BMI:	
< 25 Kg/m^2	155 (42.4%)
≥ 25 Kg/m^2	210 (57.6%)
Histology:	
Clear cell	200 (54.7%)
Papillary	75 (20.5%)
Chromophobe	44 (12.0%)
MiT alteration	12 (3.2%)
Unclassified	30 (8.2%)
Collecting duct	4 (1.4%)
Sarcomatoid features:	
Present	271 (74.3%)
Absent	94 (25.7%)
Stage at diagnosis:	
I-III	220 (60.3%)
IV	145 (39.7%)
Nephrectomy:	322(88.2%)
For localized disease	204 (55.9%)
Cytoreductive	118 (32.3%)
Onset metastatic sites:	
Lung	243 (66.5%)
Lymph nodes	168 (46.0%)
Bone	76 (20.8%)
Kidney	71 (19.4%)
Liver	59 (16.1%)
Brain	19 (5.2%)
Adrenal gland	9 (2.4%)
Peritoneum	7 (1.9%)
Muscles	7 (1.9%)
Pancreas	6 (1.6%)
Pleura	3 (0.8%)
IMDC (before the first therapy line):	
Favourable	146 (40%)
Intermediate	130 (35.6%)
Poor	89 (24.4%)
First-line systemic therapy	365 (100%)
Sunitinib	241 (66.0%)
Sorafenib	49 (13.4%)
Pazopanib	45 (12.3%)
Cabozantinib	22 (6.0%)
Tivozanib	8 (2.3%)

Second-line systemic therapy	302 (82.7%)
Axitinib	19 (5.2%)
Cabozantinib	13 (3.6%)
Everolimus	117 (32.1%)
Nivolumab	45 (12.3%)
Pazopanib	7 (1.9%)
Sorafenib	50 (13.7%)
Sunitinib	45 (12.3%)
Temsirolimus	6 (1.6%)
Third-line systemic therapy	191(52.3%)
Axitinib	4 (1.1%)
Cabozantinib	16 (4.4%)
Dovitinib	5 (1.4%)
Everolimus	70 (19.2%)
Nivolumab	18 (4.9%)
Sorafenib	46 (12.6%)
Sunitinib	25 (6.8%)
Temsirolimus	4 (1.1%)
Tivozanib	3 (0.8%)

among the different treatment groups. Finally, the median time between the stop of active therapies and death was 68 days.

IMDC score calculated before the start of the first line therapy was found to be a favorable predictor of Disease Control Rate (DCR) and OS. In fact, the median OS was 64.3 months (range 19.03-181.83 months, 95%CI: 57.5-72.0) for favorable prognosis patients, 28.3 months (range 2.4-124.83 months, 95%CI: 26.8-30.2) for intermediate prognosis patients, and 10 months (range 1.8-41.56 months, 95%CI: 8.1-11.8) for poor prognosis patients (Cox proportional hazard regression *P*-value < 0.0001, Supplementary Figure 1). Moreover, a higher proportion of favorable risk patients experienced disease control (CR + PR + SD) compared to intermediate and poor-risk patients in first-line therapy (93.8% *vs.* 77.0%; $P < 0.0001$ by Fisher's exact test), in second-line therapy (80.1% *vs.* 51.3%; $P < 0.0001$ by Fisher's exact test), and in third-line therapy (73.2% *vs.* 51.6%; $P = 0.02$ by Fisher's exact test).

"Early progressors" population: definition and clinical characteristics

The time to first-line therapy progression (PFS1) was found to be strongly correlated with OS (Cox proportional hazard regression *P*-value < 0.0001). We furthermore observed that patients with a PFS1 under 6 months ($n = 124$) had a notably worse OS than those who progressed after 6 months (13.5 *vs.* 44.8 months, Cox proportional hazard regression *P*-value < 0.0001, HR = 0.41, 95%CI: 0.29-0.53, Figure 1). These patients were labeled as "early progressors", in opposition to the "responders", who remained in first-line treatment for more than 6 months.

Among the early progressors, we described the patients who progressed in less than 3 months from therapy start ($n = 67$, "primary refractory" population) and patients who progressed between 3 and 6 months ($n = 56$, "primary resistant" population) from the therapy start. Notably, no clinically relevant differences in OS were noted between primary refractory and primary resistant (13.1 *vs.* 16.8 months, Cox proportional hazard regression *P*-value = 0.10, HR = 0.79, 95%CI: 0.56-1.01, Figure 1).

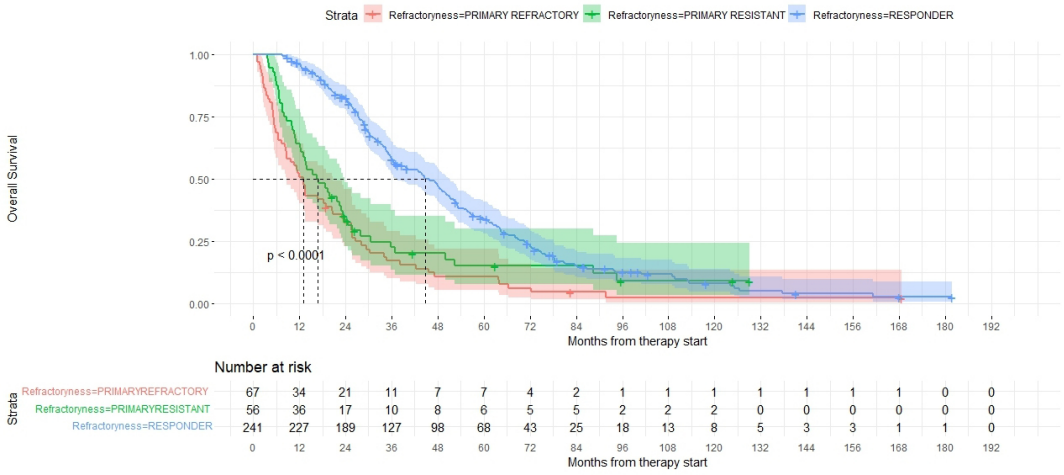

Figure 1. Overall Survival probability according to time after therapy initiation in the study population, divided by time to first-line VEGFR-TKI monotherapy failure. Patients who progressed in less than 3 months from therapy start are labeled "primary refractory", patients who progressed between 3 and 6 months are labeled "primary resistant", and patients who progressed beyond 6 months from therapy start are labeled "responder".

The population of early progressors was prevalently male (76%) with a median age of 61.25 years at the diagnosis (17% under-50, 71% with an age between 50 and 70, and 12% over 70). The median BMI of early progressors was 25.86 Kg/m^2 (range 18.67-36.59 Kg/m^2). Most tumors were of clear cell histology (52.4%) followed by papillary RCC (22.6%), chromophobe RCC (12.0%), MiT alteration RCC (3.0%), and unclassified RCC (10.0%). Sarcomatoid features were present in 34.7% of patients (n = 43). Fifty-two percent of them (n = 59) were diagnosed in a metastatic stage, while the remaining part of the population developed metastases after a median time of 21.8 months (range 3.2-201.8 months). The distribution of the onset metastatic sites was similar to the one observed in the global population. IMDC risk categories were calculated before the start of the first systemic therapy line and included poor (n = 64, 51.6%), intermediate (n = 39, 31.4%), and favorable (n = 21, 17.0%). Median Systemic Inflammation Index (SII) was also calculated before the start of the first systemic therapy line, and the median value was 969 × 10^9/L (range 188-3,772 × 10^9/L).

Additional patient-related characteristics of early progressor patients and responder patients are summarized in Table 2.

Furthermore, we searched if any of the main clinical variables could significantly correlate with the "early progressor" status. We found that the presence of sarcomatoid features, the SII value above the median of the general population, and the IMDC score correlated significantly with early progressions (Fisher exact test P-value = 0.005, 0.006, and < 0.0001, respectively).

"Early progressor" population: clinical behavior

We further analyzed the clinical behavior of early progressors compared with other patients. In the second-line setting, these patients showed a slightly lower PFS than first-line responders (3.85 *vs.* 5.67 months, Cox proportional hazard regression P-value = 0.44, HR = 0.90, 95%CI: 0.77-1.03, Supplementary Figure 2). A similar difference was observed for the progression-free survival at the third therapy line (4.20 *vs.* 6.07 months, Cox proportional hazard regression P-value = 0.06, HR = 0.72, 95%CI: 0.55-0.99, Supplementary Figure 3). No statistically significant differences between early progressor and other patients were observed either in the different therapy groups in second and third-line settings (immunotherapy *vs.* antiangiogenics *vs.* mTOR inhibitors).

Table 2. Characteristics of responder and early progressor patients

Variable	Number of responder patients (% of the total number = 241)	Number of early progressor patients (% of the total number = 124)
Age at diagnosis		
Under 50	75 (31.1%)	42 (33.9%)
50-70	150 (62.2%)	65 (52.0%)
Over 70	16 (6.7%)	18 (14.1%)
Gender		
Male	188 (78%)	105 (84.7%)
Female	53 (22%)	19 (15.3%)
BMI		
< 25 Kg/m^2	104 (43.2%)	51 (42.4%)
≥ 25 Kg/m^2	137 (56.8%)	73 (57.6%)
Histology		
Clear cell	137 (56.8%)	65 (52.4%)
Papillary	54 (22.4%)	21 (16.9%)
Chromophobe	29 (12.0%)	15 (12.1%)
MiT alteration	4 (1.6%)	8 (6.4%)
Unclassified	14 (5.8%)	16 (12.9%)
Collecting duct	3 (1.2%)	1 (0.8%)
Sarcomatoid features		
Present	190 (78.8%)	81 (65.3%)
Absent	51 (21.2%)	43 (34.7%)
Stage at diagnosis		
I-III	193 (80.1%)	89 (71.8%)
IV	48 (19.9%)	35 (28.2%)
Onset metastatic sites		
Lung	166 (68.9%)	77 (62.1%)
Lymph nodes	106 (44.0%)	62 (50.0%)
Kidney	47 (19.5%)	24 (19.3%)
Bone	39 (16.2%)	37 (29.8%)
Liver	36 (14.9%)	23 (18.5%)
Brain	11 (4.6%)	8 (6.4%)
Adrenal gland	7 (2.9%)	2 (1.6%)
Peritoneum	7 (2.9%)	0 (0%)
Pancreas	4 (1.7%)	2 (1.6%)
Muscles	3 (1.2%)	4 (3.2%)
Pleura	2 (0.8%)	1 (0.8%)
IMDC (before the first therapy line)		
Favourable	109 (45.2%)	21 (16.9%)
Intermediate	107 (44.3%)	39 (31.5%)
Poor	25 (10.5%)	64 (51.6%)

Factors associated with poorer PFS1

Since early progressors at the first treatment line (VEGFR-TKI) were observed to perform much worse in this cohort of patients, we determined the factors that are associated with a shorter PFS at the first therapy line (PFS1).

The IMDC risk class showed a significant correlation with PFS1 (17.05 months for favorable risk *vs.* 9.23 months for intermediate risk *vs.* 3.70 months for poor risk, Cox proportional hazard regression *P*-value < 0.0001, Figure 2).

As for the histological characteristics, the presence of a sarcomatoid component was strongly correlated with decreased PFS1 (6.42 *vs.* 10.20 months, Cox proportional hazard regression *P*-value < 0.0001, HR = 1.63, 95%CI: 1.51-1.75, Figure 3).

Finally, we searched for a lab-test variable that could impact PFS1. We chose to determine the impact of the Systemic Inflammation Index (SII) of PFS1 in our population, as it could be considered a bonafide representation of the immune system status. Overall SII, calculated at the first administration of the first-line therapy, showed a significant correlation with PFS1 (Cox proportional hazard regression *P*-value = 0.002). Patients with SII below the median had a better PFS1 than those with SII above the median (10.07 *vs.* 8.68 months, Cox proportional hazard regression *P*-value = 0.025, HR = 1.27, 95%CI: 1.16-1.38, Figure 4).

As for the other tested variables, the non-clear cell histology (Cox proportional hazard regression *P*-value = 0.54), the young age (under-50) at the diagnosis (Cox proportional hazard regression *P*-value = 0.97), the gender (Cox proportional hazard regression *P*-value = 0.88), the Body Mass Index (BMI) at the diagnosis (Cox proportional hazard regression *P*-value = 0.15), the time to metastases onset (Cox proportional hazard regression *P*-value = 0.079), the time to systemic therapy initiation (Cox proportional hazard regression *P*-value = 0.085), the number of metastatic sites at diagnosis (Cox proportional hazard regression *P*-value = 0.11), the presence of brain metastases (Cox proportional hazard regression *P*-value = 0.50), liver metastases (Cox proportional hazard regression *P*-value = 0.61), and bone metastases (Cox proportional hazard regression *P*-value = 0.79) did not show a significant impact over PFS1.

Multivariate analysis

We performed a Cox Multivariate Analysis to evaluate the combined impact of IMDC, SII, presence of sarcomatoid, non-clear cell histology, age at the diagnosis, gender, Body Mass Index (BMI) at the diagnosis, time to metastases onset, time to systemic therapy initiation, number of metastatic sites at diagnosis, presence of brain metastases, presence of liver metastases, presence of bone metastases. Among all the variables, IMDC score (HR = 2.71 ± 0.18, 95%CI: 1.92-3.83, $P < 0.0001$) and non-clear cell histology (HR = 1.43 ± 0.16, 95%CI: 1.04-1.96, $P = 0.0266$) showed and the number of metastatic sites (HR = 0.87 ± 0.07, 95%CI: 0.72-1.01, $P = 0.078$) showed correlation with PFS1 [Supplementary Figure 4]. The proportional hazard assumption was met for all three aforementioned variables.

DISCUSSION

In recent years, ICI-based combination regimens have shown better oncological results than VEGFR-TKI therapies alone[10]. However, VEGFR-TKI monotherapy should be considered a first-choice treatment option for patients with a favorable risk profile, a low metastatic disease burden or ineligible for ICI[12]. Clinical trials with agents targeting the VEGF pathway showed PFS improvement in both first- and second-line therapy[13]. Outside randomized controlled clinical trials, the understanding of the targeted therapies' effectiveness for mRCC is limited.

The aim of our study is to exploit real-world retrospective data from two mRCC referral centers for evaluating target therapy efficacy in clinical practice and to identify readily available prognostic factors that could be considered in designing an individual patient's treatment strategy.

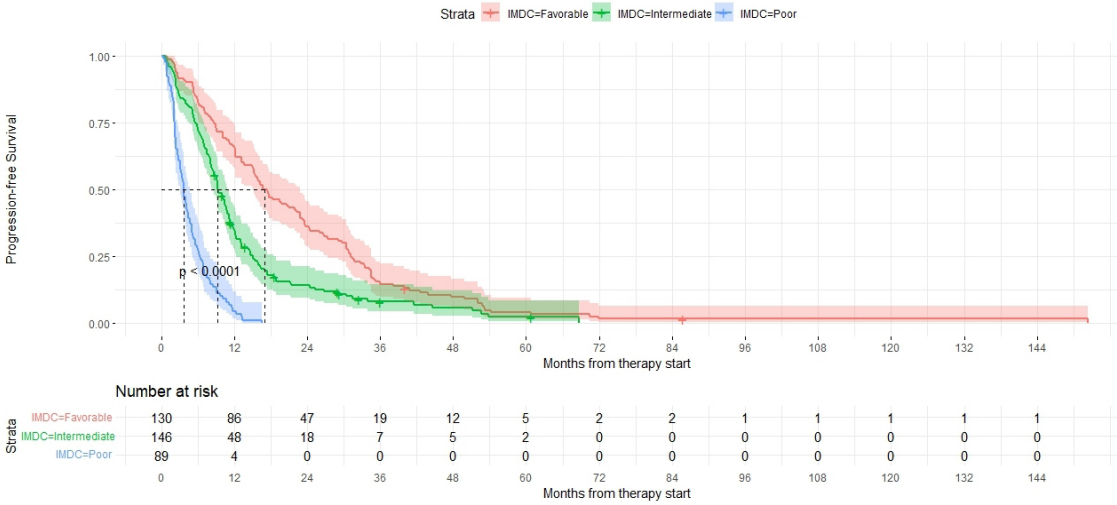

Figure 2. Progression-Free Survival probability to VEGFR-TKI monotherapy in first-line according to time after therapy initiation in the study population, divided by IMDC risk class.

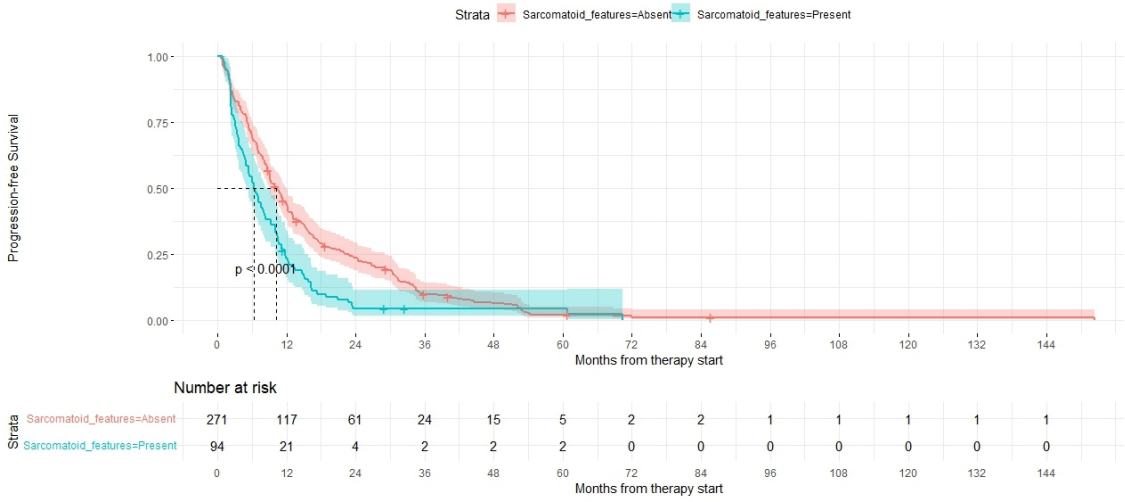

Figure 3. Progression-Free Survival probability to VEGFR-TKI monotherapy in first-line according to time after therapy initiation in the study population, divided by presence/absence of sarcomatoid features.

We report a cohort of 365 patients with a histologically confirmed mRCC diagnosis who received at least one month of VEGFR-TKI monotherapy as a first-line systemic therapy. Patients' characteristics and treatment sequences are consistent with other real-life case series published in this setting[14-17]. Of note, over 80% of patients received second-line treatment and over 50% third-line treatment. The median OS in the entire cohort was 29.36 months (95% confidence interval [CI] ranging from 1.8 to 181.83 months), thus aligned with the literature data. Patients with IMDC favorable risk had better OS than those with intermediate and poor risk. This finding confirms that VEGFR-TKI monotherapy did not have sufficient efficacy in intermediate and poor risk patients[10].

In our further analyses, we focused on the early progressor patients (34%, n = 124/365), a subgroup of patients who progress to first-line VEGFR-TKI monotherapy in less than 3 months (54%, n = 67/124,

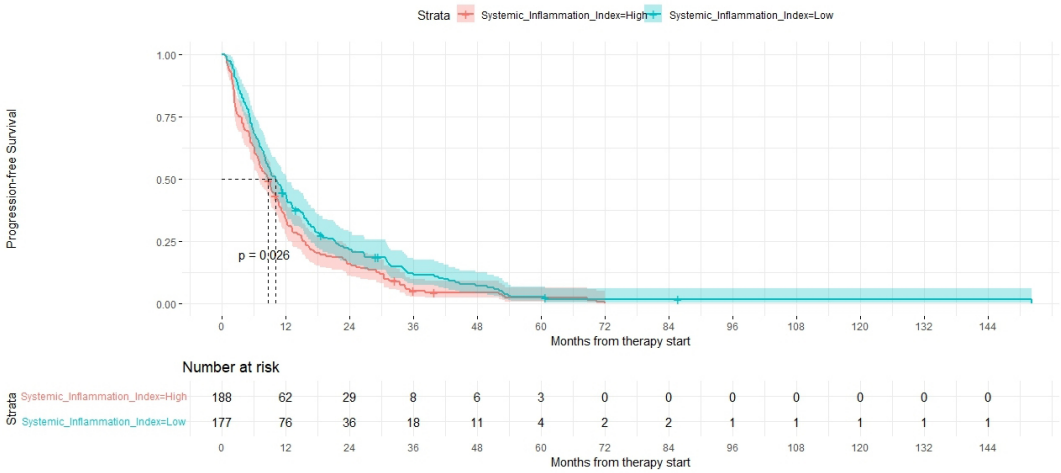

Figure 4. Progression-Free Survival probability to VEGFR-TKI monotherapy in first-line according to time after therapy initiation in the study population, divided by Systemic Inflammation Index (SII).

"primary refractory" population) or between 3 and 6 months (46%, *n* = 56/124, "primary resistant" population) from therapy start. This population shows a far worse OS compared with patients progressing beyond the sixth month of therapy (13.5 *vs.* 44.8 months, Cox proportional hazard regression *P*-value < 0.0001, HR = 0.41, 95%CI: 0.29-0.53, Figure 1). Most early progressors to first-line treatment with VEGFR-TKIs had a sarcomatoid component[18] and a high Systemic Inflammation Index (SII)[19].

Unfortunately, a proportion of patients do not respond to first-line targeted agents, mainly due to intrinsic resistance. The primary resistance rate was around 20% in first-line pivotal phase III trials with VEGFR-TKI monotherapy[20-22] and between 18 and 26% in retrospective case series focusing on this subpopulation[23,24]. In contrast, in our case series, 34% of patients showed early progressive disease. The median OS of early progressors in our case series (13.5 months) was consistent with those from Busch *et al.* and better than other retrospective cohorts reported[24,25] (6.8 months and 7.4 months, respectively)[23]. However, these patients do not show far worse performance in second and third-line settings compared with first-line responders. This observation is congruent with the evidence that an alternative VEGFR-TKI, cabozantinib, or an ICI, nivolumab, can provide benefits regardless of primary resistance to first-line TKIs[26,27]. The biological basis of resistance to these targeted therapies and the subsequent clinical approach should be further explored. Emerging preclinical evidence suggests that resistance is mediated by tumor and environmental changes, which permit sustained perfusion and less VEGF-dependent tumor growth. Upstream elements of VEGFR blockade, such as hypoxia-inducible factor (HIF), and VEGF-independent pathways could drive tumor growth. These considerations provide a rational basis for sequential or combination therapy targeting these targets[28].

Subsequently, we assessed whether progression-free survival at first-line therapy (PFS1) is a reliable predictor of overall survival. We analyzed those clinical variables that correlate with better or worse PFS1. In our univariate analysis, three clinical variables showed an impact on the time to progression at the first-line VEGFR-TKI-based monotherapy: the presence of sarcomatoid features, the IMDC risk category, and a high pre-treatment SII value. Among the other variables tested in the univariate analysis, we found a tendency towards statistical significance for the time between initial diagnosis and systemic therapy start and the time between initial diagnosis and clinical evidence of metastases, with shorter times predicting worse PFS1. Another parameter associated with better PFS1 was a BMI over 25 Kg/m^2, which seems to corroborate the

existence of the so-called obesity paradox, which has already been described and analyzed in RCC[29]. On the other hand, no significant impact on PFS1 was observed from the localization of metastases in bone, liver, or brain.

In the multivariate analysis section, we analyzed the combined impact on PFS1 of all the factors tested in the univariate analysis. The final model that emerges from this analysis is based on the IMDC risk class, whose prognostic role in mRCC is widely consolidated[4], the non-clear cell histology[30], and the number of metastatic sites at the diagnosis of metastatic disease[31]. It is interesting to note that this model selected, besides the IMDC risk class, a histopathological variable and a radiological parameter. In the elaboration of future prognostic models, the inclusion of factors beyond pure clinical (such as performance status) and laboratory data (i.e. neutrophil count or platelet count) should be considered.

Among the biases that affect this retrospective analysis, the large time of accrual is probably the most impacting. In fact, many radical changes in the clinical management of RCC took place over time: the development of new VEGFR-TKI, the introduction of ICI, and the introduction of VEGFR-TKI plus ICI combinations. Moreover, this leads to a time-related bias, since patients who started therapy in the early years of our observation period will inevitably have longer follow-up time and thus longer overall survival. Conversely, patients recently enrolled will have shorter follow-up times and many of them will still be ongoing on their treatment. Another considerable limitation relies on the fact that both the Centers, in their respective period of enrollment, were reference high-volume centers for the Oncological management of RCC. This inevitably selects fitter patients and those patients with rare clinical-pathological variants of the disease. This explains the overrepresented under-50 population and the relatively high number of nccRCC histotypes (especially papillary and chromophobe histotypes) and poorer prognosis diseases (metastatic de novo and MiT alteration RCC). Finally, As it has already been demonstrated, the patients with mRCC treated at higher volume facilities have longer survival compared with those treated at lower volume facilities, and our analysis seems to support this finding[30].

The strengths of our analysis are the large multicenter database focusing on patients with mRCC who received first-line VEGFR-TKI monotherapy and the real-life context. On large case series such as ours, it is possible to ascertain the prognostic role of clinical factors recognized to impact patient survival. While the presence of sarcomatoid features and IMDC score have been confirmed as unfavorable prognostic factors, in concordance with consolidated literature data[4], the finding on the SII as a predictor of PFS1 makes an addition to a more recent - but constantly growing - body of evidence[19]. Given the nature of SII, a full blood count-based algorithm trying to describe the systemic inflammation status, this index should be considered in the design of future prognostic and predictive models.

Real-world evidence can contribute to the optimal management of available drugs and establish benchmarks for investigational drugs[32]. Moreover, in an era of multiple treatment options, further real-life evidence on the easy-to-use prognostic factors associated with refractory disease could support clinicians in identifying the most appropriate treatment strategy for each patient.

DECLARATIONS

Authors' contributions

Conceptualization: Rizzo M, Pezzicoli G
Statistical Analysis: Pezzicoli G, Quaglini S, Tibollo V
Revision: Rizzo M, Quaglini S, Pezzicoli G
All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from Quaglini S upon reasonable request.

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None.

Conflicts of Interest

Mimma Rizzo received, outside the present work, honoraria as a speaker/consultant by Pfizer, Novartis, MSD, Astra Zeneca, Bristol-Myers Squibb (BMS) and Merck. Melissa Bersanelli received, outside the present work, institutional research funding from Roche S.p.A., Pfizer, Seqirus UK, Novartis, Bristol Myers Squibb (BMS), Astra Zeneca, Sanofi; personal honoraria as a speaker at scientific events by BMS, MSD, IPSEN, Novartis, Astra Zeneca, Pierre Fabre, and Pfizer; personal honoraria for advisory role by IPSEN, Novartis, Sanofi, Pierre-Fabre, and Merck; personal fees for copyright transfer by Sciclone Pharmaceuticals, Pierre-Fabre, MSD, IPSEN, Pfizer, and Sanofi. Camillo Porta received, outside the present work, honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, General Electric, Ipsen and MSD and acted as a Protocol Steering Committee Member for BMS, Eisai and MSD. The other authors declared that there are no conflicts of interest.

Ethical Approval and Consent to Participate

We confirm that our research was performed in accordance with the Declaration of Helsinki and approved by an appropriate ethics committee, as detailed below: Ethics Committee of Translational Oncology Unit of the Istituti Clinici Scientifici Maugeri in Pavia; Approvation n° 2421 (April 23, 2020); Ethics Committee of Medical Oncology Unit of the University Hospital Polyclinic of Bari: Approvation n° 64783 (July 7, 2021).

Consent for Publication

Not applicable.

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