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RESEARCH

Long-term responders to nivolumab in previously treated advanced renal cell carcinoma: a sub-analysis of meet-URO15 study

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Abstract

Background Although nivolumab prolongs overall survival (OS) in pretreated patients with metastatic renal cell carcinoma (mRCC), underlining clinical and biological features of long-term responses are still to be determined. This study aims to investigate clinical and pathological characteristics of mRCC patients who achieved long-term responses during nivolumab treatment.

Materials and methods A retrospective analysis was performed on mRCC patients receiving nivolumab as second or further therapy line between May 2016 and January 2019 in 34 Italian Oncology Centres. Outcome assessments and logistic regression were performed to evaluate factors influencing long-term responses.

Results A total of 571 patients with a median age of 61 years (range 17–85) were included in the analysis. With a median follow-up of 22.1 (1.0–89.0) months, 23.1% of patients were 2-year progression-free on treatment with nivolumab, hence they were categorized as long-term responders. Baseline characteristics, including age, gender, and histology, were similar between long- and short-term responders. Karnofsky Performance Status $\geq 80\%$ was significantly associated with long-term response ($p = 0.02$), while bone metastases ($p = 0.03$), International mRCC Database Consortium intermediate-poor risk ($p < 0.01$) and Neutrophil-to-Lymphocyte Ratio ≥ 3.2 ($p = 0.02$) were associate with short-term responses. Long-term responders exhibited a median progression-free survival of 55.0 months *versus* 4.0 months of the short-term responders. The median OS was not reached in long-term responders while it was 17.0 months for short*term responders.

Conclusion This retrospective analysis sheds light on factors associated with long-term response to nivolumab in mRCC. Understanding these clinical features will be essential for selecting patients who may mostly benefit from immunotherapy.

Keywords Metastatic renal cell carcinoma · Nivolumab · Immunotherapy · Long-term response · Prognostic factors

Introduction

In the last decades, the introduction of immune checkpoint inhibitors (ICIs) alone or in combination with vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) provided a paradigm shift in the therapeutic landscape of metastatic renal cell carcinoma (mRCC) [1–6]. Due to the survival benefit over everolimus observed in the randomized phase III Checkmate 025 trial [7], nivolumab was the first in class ICI approved in 2005 for patients with mRCC previously treated with at least a prior VEGFR-TKI.

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However, despite the survival advantage achieved with this new therapeutic strategy, mRCC is still a lethal disease accounting for a median overall survival (OS) of 25 months. mRCC is a heterogenous disease reflecting different clinical behaviors spanning from an indolent to a rapidly progressive disease. Similarly, the benefit achieved from nivolumab may vary widely from long-term disease control rate to hyperprogression [8–10]. Clinical and biological features underlining long-term response to nivolumab in mRCC are still under investigation [11, 12].

In this analysis of the multicentre retrospective Meet-URO 15 study, we attempt to evaluate the association between clinical characteristics and outcome in long-term to nivolumab among patients with mRCC previously treated with at least a prior VEGFR-TKI.

Materials and methods

Patients and treatments

This retrospective study involved patients with previously treated mRCC, who received at least one cycle of nivolumab between May 2016 and January 2019 across 34 Oncology Centers in Italy. Patients should be at least 18 years old, have a histologically confirmed diagnosis of mRCC and have received at least one completed infusion of nivolumab as a second or further treatment line, as standard clinical practice. Patients' demographics and clinical characteristics were reported. Nivolumab was initially delivered intravenously at a dose of 3 mg/kg every 2 weeks, and then at a fixed dosage of 240 mg every 2 weeks or 480 mg every 4 weeks, in line with local clinical protocols. The treatment was continued until either disease progression or intolerable toxicity. Written informed consent was obtained from each patient. Ethical sanction for this study was secured from the Ethics Regional Ethical Committee of Liguria, under registration number 068/2019, and the research adhered to the principles of the Declaration of Helsinki.

Outcome assessment and statistical analysis

Tumor assessments were performed every 2–4 months of treatment, according to local clinical practice, or whenever progression was clinically suspected according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [13]. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression or death whichever occurred first, while OS was defined as the duration from the beginning of nivolumab to death from any cause or to the final follow-up visit date. In this study, patients remained progression-free for > 24 months while receiving nivolumab were categorized as long-term responders.

Kaplan–Meier method was utilized to estimate both PFS and OS throughout the follow-up period. A χ^2 test was applied to compare the distribution of categorical baseline characteristics between long- and short-term responders. Quantitative data were described using median and range, while qualitative data were presented using numbers and percentages. A logistic regression model was employed to assess the influence of each clinical-pathological variable (age, gender, histological type, prior nephrectomy, Karnofsky Performance Status (KPS), International Metastatic RCC Database Consortium (IMDC) score at diagnosis and at start of nivolumab, neutrophil-to-lymphocyte ratio (NLR), sites of metastases, metastatic at diagnosis, line of nivolumab therapy and type of first line therapy) on the long-term response. Significative variables at univariate analysis were included in the multivariate model. Level of statistical significance was set to 0.05. The analyses were conducted using Stata SE version 18.

Results

Patients characteristics

This retrospective analysis included a cohort of 571 patients diagnosed with mRCC treated with nivolumab as second or further line of therapy with a median follow-up of 22.1 months.

Among these, 132 patients (23.1%) remained progression-free for > 24 months while receiving nivolumab, and they were categorized as long-term responders. Baseline characteristics according to long-term and short-term responders are detailed in Table 1. Characteristics were well-balanced among the groups in terms of median age, gender distribution, and histology, with clear cell carcinoma being the most prevalent histologic type, accounting for 84.3% of all patients. The median PFS (mPFS) and OS (mOS) for all patients were 7.0 months (95% CI, 5.0–8.0) and 25.0 months (95% CI, 21.0–30.0) respectively (Fig. 1). Long-term responders exhibited a mPFS (mPFS) of 55.0 months (95% CI: 45.0-not reached [NR]), while the median OS was NR (95% CI, 79.0-NR) (Fig. 2). Conversely, short-term responders exhibited a mPFS of 4.4 months (95% CI: 3.9–5.1) with a m OS of 17.0 months (95% CI: 14.0–19.0) (Fig. 3).

Long-term response predictors

Among long-term responders, almost 90% of the patients had previous nephrectomy, with a statistically significant predominance when compared to short-term responders (95% *vs.* 86%; $p < 0.01$). Analysis based on the IMDC risk

Table 1 Patients characteristics

	All patients ($N=571$)	PFS > 24 months ($N=132$)	PFS ≤ 24 months ($N=439$)	*P* value
Age, median (range)	61(17–85)	61(32–82)	61(17–85)	0.99
≥ 70 (%)	151(26.4%)	5(26.5%)	116(26.4%)	0.99
Gender, *n* (%)	402	90	312	0.52
Male	(70.4%)	(68.2)	(71.1%)	
Histology, *n* (%)				
Clear-cell RCC	478(84.3%)	111(84.1%)	367(84.4%)	0.30
Papillary RCC	42(7.4%)	7(5.30%)	35(7.97%)	
Chromophobe RCC	17(2.97%)	7(5.30%)	10(2.27%)	
Sarcomatoid component	30(5.25%)	7(5.30%)	23(5.32%)	
Previous nephrectomy *n* (%)	503	126	377	< 0.01
Yes	(88.1%)	(95.4%)	(85.9)%	
KPS, *n* (%)	478	125	353	< 0.01
≥ 80%	(84.4)%	(94.7)%	(81.3)%	
NLR	234	40	194	< 0.01
≥ 3.2	(41.0)%	(30.3)%	(44.2)%	
IMDC score at diagnosis, *n* (%)	333	66	267	0.02
Intermediate-poor	(66.9)%	(57.4)%	(69.7)%	
Metastatic at diagnosis				
Yes	233	46	187	0.13
	(40.8)%	(34.8)%	(42.6)%	
IMDC score at start of IT, *n* (%)*	427	78	342	< 0.01
Intermediate-poor	(76.8)%	(60.4)%	(81.7)%	
Sites of metastases, *n* (%)				
Lymph-nodal	305 (53.4%)	74 (56.1%)	231 (52.6%)	0.51
Visceral	509 (89.1%)	117 (88.6%)	392 (89.3%)	0.87
Bone	203 (35.5%)	30 (22.7%)	173 (39.4%)	< 0.01
First-line therapy, *n* (%)				
Sunitinib	350 (63.7%)	79 (62.7%)	271 (64.1%)	0.83
Pazopanib	199 (36.2%)	47 (37.3%)	152 (35.9%)	
Nivolumab line, *n* (%)				
Second line	394 (69.0%)	92 (69.7%)	302 (68.8%)	0.91
≥ Third line	177 (31.0%)	40 (30.3%)	137 (31.2%)	

RCC renal cell carcinoma, *KPS* Karnofsky performance status, *IMDC* international metastatic RCC database consortium, *IT* immunotherapy.*data available for a total of 556 patients: 129 patients with PFS > 24 months and 427 ≤ 24 months

group displayed a higher percentage of patients with an intermediate-poor risk status at diagnosis in the short-term response group compared to the long-term response group (69.7% *vs.* 57.4%; $p < 0.01$). A NLR ≥ 3.2 was recorded in 30.3% of patients exhibiting a long-term response versus 44.2% of those with short-term responses ($p < 0.01$).

Furthermore, a higher proportion of patients in the short-term responders group presented bone metastases compared to the long-term responders (39.4% *vs.* 22.7%; $p < 0.01$). Notably, no statistically significant differences were noted between the two groups concerning first-line therapy and the number of therapy lines of nivolumab (2nd *vs.* > 3rd line).

Logistic regression analysis was conducted on the entire cohort of 571 patients to explore the associations between clinical and pathological variables and long-term responses. Factors evaluated as potential risks included age, gender, histological type, prior nephrectomy, KPS, IMDC score at diagnosis and at start of nivolumab, NLR, sites of metastases, metastatic at diagnosis, line of nivolumab therapy and type of first line therapy. The odds ratios (OR) estimated for each variable in both univariable and multivariate analyses are presented in Tables 2 and 3.

In the univariate analyses, long-term responders displayed higher odds of having KPS ≥ 80% (OR, 4.10; 95% CI, 1.84–9.11; $p < 0.01$) (Fig. 1S) and having undergone previous nephrectomy (OR, 3.45; 95% CI, 1.46–8.18; $p = 0.01$) (Fig. 2S). Conversely, they exhibited lower odds of having bone metastases (OR, 0.45; 95% CI, 0.29–0.71;

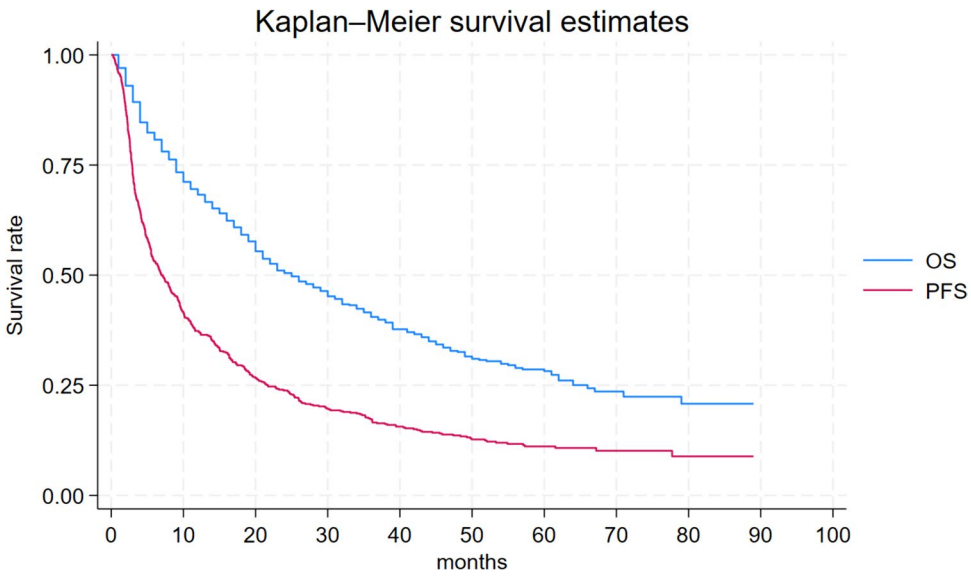

Fig. 1 Progression-free survival and overall survival and in entire population

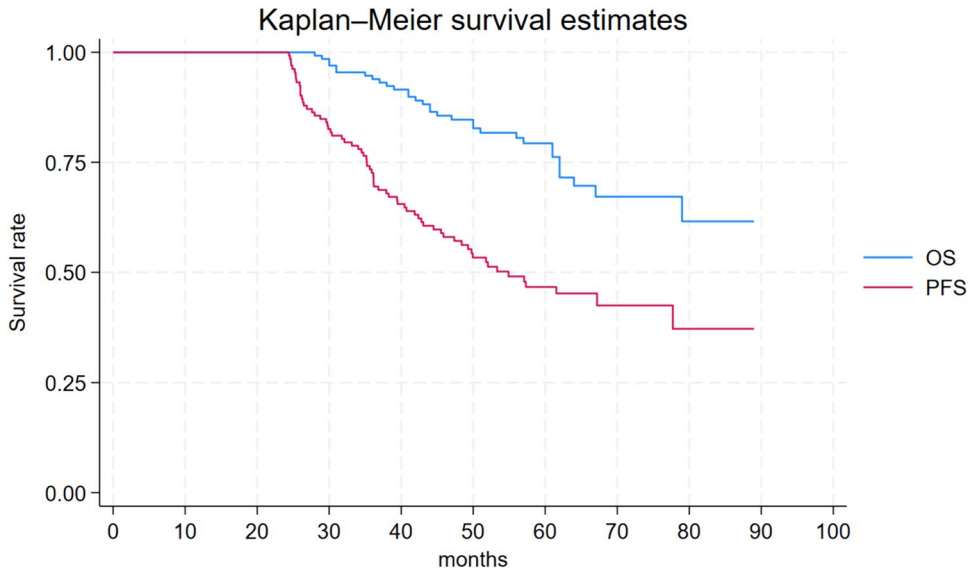

Fig. 2 Progression-free survival and overall survival in long-term responders

$p < 0.01$) (Fig. 3S), an IMDC intermediate-poor status at diagnosis (OR, 0.58; 95% CI, 0.38–0.90; $p = 0.01$) and at the onset of nivolumab treatment (OR, 0.34; 95% CI, 0.22–0.52; $p < 0.01$) (Fig. 4S), as well as an NLR ≥ 3.2 (OR, 0.56; 95% CI, 0.37–0.85; $p < 0.01$) (Fig. 5S) compared to short-term responders.

The multivariable analysis exploring the relationship between clinical-pathological variables and response group is detailed in Table 3. Patients with PFS > 24 months were more likely to have a KPS ≥ 80% (OR, 2.68; 95% CI, 1.18–6.11; $p = 0.02$) and less likely to have bone metastases (OR, 0.58; 95% CI, 0.36–0.94; $p = 0.03$), an IMDC intermediate-poor status at the start of nivolumab (OR, 0.44; 95% CI, 0.28–0.68; $p < 0.01$), and an NLR ≥ 3.2 (OR, 0.59; 95% CI, 0.38–0.92; $p = 0.02$) compared to patients with PFS ≤ 24 months.

Discussion

As the therapeutic landscape of advanced RCC has changed due to the development and reimbursement of new treatment combinations [1–6], a deeper understanding of clinical characteristics and baseline laboratory features affecting clinical outcomes is needed and may help clinicians in the treatment decision making. Several nomograms for mRCC were developed to better predict prognosis and are mostly based on clinical factors laboratory parameters [14, 15]. These models

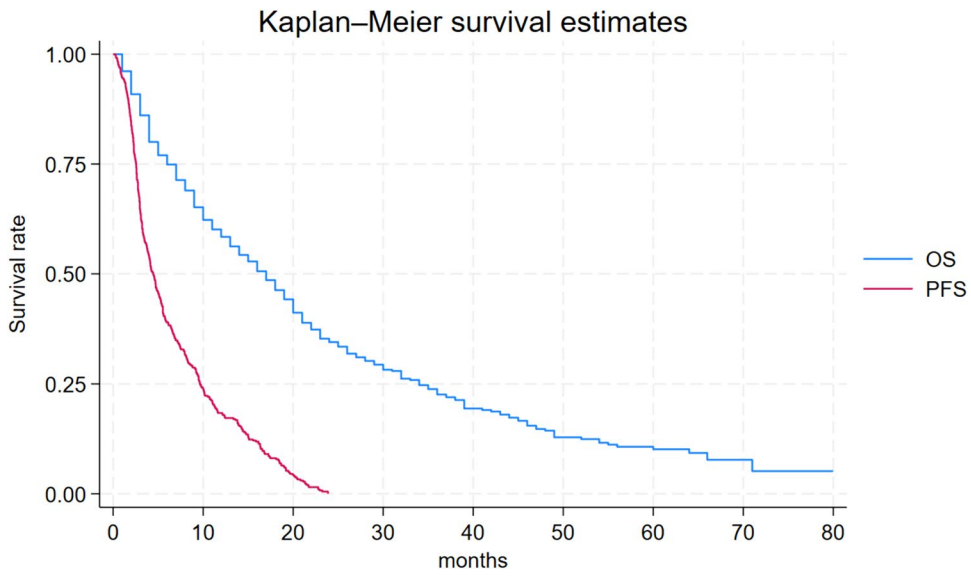

Fig. 3 Progression-free survival and overall survival of short-term responders

Table 2 Univariate analysis of the relationship of clinical-pathological variables with PFS > 24 months

Variable	Odds ratio	95% CI	*P* value
KPS (≥ 80% vs < 80)	4.10	1.84–9.11	< 0.01
Previous nephrectomy (yes vs no)	3.45	1.46–8.18	0.01
Bone metastasis (yes vs no)	0.45	0.29–0.71	< 0.01
IMDC score at diagnosis (Intermediate-poor vs good)	0.58	0.38–0.90	0.01
IMDC score at start of IT (Intermediate-poor vs good)	0.34	0.22–0.52	< 0.01
NLR(≥ 3.2 vs < 3.2)	0.56	0.37–0.85	< 0.01

KPS Karnofsky performance status, *IMDC* International metastatic RCC database consortium, *NLR* Neutrophil–Lymphocyte ratio

Table 3 Multivariate analysis of the relationship of various clinical-pathological variables with PFS > 24 months

Variable	Odds ratio	95% CI	*P* value
KPS (≥ 80% vs < 80)	2.68	1.18–6.11	0.02
Bone metastasis (yes vs no)	0.58	0.36–0.94	0.03
IMDC score at start of IT (Intermediate-poor vs good)	0.44	0.28–0.68	< 0.01
NLR (≥ 3.2 vs < 3.2)	0.59	0.38–0.92	0.02

KPS Karnofsky performance status, *IMDC* International metastatic RCC database consortium, *NLR* Neutrophil–Lymphocyte ratio

have many limitations since they have been designed before the approval of ICI and do not take into account prognostic factors such as age, site of metastases, number and duration of previous treatments and inflammatory scores [16].

The phase 3 CheckMate 025 trial showed longer median OS with nivolumab (25 months) compared with everolimus (19.6 months) in previously treated patients with advanced RCC [7]. This benefit was sustained across all the subgroups, including Memorial Sloan Kettering Cancer Center (MSKCC) and IMDC risk groups, number and sites of metastases, age < 65 and ≥ 65 years, number, and duration of prior therapies[15]. The safety and efficacy observed in the CheckMate 025 trial were consistent with those reported in real-world setting major series, showing a good correspondence from the results in clinical trials and those in clinical practice [15, 17]. As such, further investigations of clinical predictive factors that could more accurately define the outcome of advanced RCC in the current treatment landscape from clinical practice remains a clinical need.

The multicentre retrospective Meet-URO 15 study [18] explored the prognostic role of baseline peripheral blood inflammatory indices and clinical factors in advanced RCC patients receiving nivolumab as second or further line to develop a prognostic score that could better predict survival outcome and overcome the limitations of previous analyses in short series with nomograms [14, 15]. Inflammatory indexes as neutrophil–lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic inflammation index (SII), and systemic inflammation response index (SIRI) have been recently developed and confirmed for outcome prediction in pre-treated mRCC [16, 19, 20]. The MeetURO-Score included

priori and recent biomarkers showing a prognostic impact for NLR, IMDC score, and bone metastases identifying five different prognostic groups: group 1 (mOS not reached), group 2 (mOS 43.9 months), group 3 (mOS 22.4 months), group 4 (mOS 10.3 months) and group 5 (mOS 3.2 months).

However, although nivolumab provided a survival benefit in pretreated advanced RCC patients [21], usually only a small proportion of them achieves a long-term benefit [8].

In the present analysis of Meet-URO 15 we attempted to define the clinical characteristics that correlate with longer response to nivolumab. At multivariable analysis we found out that patients with PFS > 24 months were more likely to have a KPS ≥ 80% and less likely to have bone metastases, an IMDC intermediate-poor status, and an NLR ≥ 3.2.

Our data are like that reported in a previous long-term response study of sunitinib and pazopanib with accordance to the general characteristics of mRCC patients [22–24].

Age < 65 years, previous nephrectomy, absence of bone or lung metastases and favorable MSKCC risk status were the factors associated with long-term responses in mRCC patients receiving TKI as first line therapy [22–24]. Accordingly with previous studies, NLR is significantly associated with poorer OS and PFS, and lower rates of response and clinical benefit, after ICI therapy across multiple cancer types [25]. We acknowledge several limitations of the study including the retrospective design, and the numbers of previous treatment received. However, we believe that our study provides the rationale for prospectively exploring the presented putative biomarkers of prolonged response to ICI. Given the lack of validated biomarkers, the identification of prognostic and predictive clinical and biochemical features would allow to identify patients that could most benefit from immunotherapy. Moreover, these data are extremely punctual since several ongoing phase III clinical trials are exploring the efficacy of ICI combinations in patients previously progressed to first line ICI-based therapy [26, 27].

Conclusion

In this large retrospective Meet-URO 15 analysis, we identified, among patients with mRCC suitable for nivolumab treatment, the prognostic role of clinical factors and inflammatory indices that may predict long response to nivolumab in real life setting. Future perspectives include the external validation of these findings in the International multicenter real-world REGistry for patients with metastatic renAL cell carcinoma—Meet-URO 33 study (REGAL study) [28].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-024-03741-2.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MM, UDG, PP, AS, PAZ, CM, EN, GP, MM, FC, LF, SP, RR, SP, VM, MS, VP, FA, MDN, MM, FM, GP, FN, AM, MT, FV, AC, AS, GLB, PR, SB, SER, and GF. The first draft of the manuscript was written by CM, MC, GR, AG, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest *Sebastiano Buti:* has received honoraria for speaking at scientific events and advisory roles from AstraZeneca, Bristol Myers Squibb, Ipsen, Astellas, Merck, Eisai, MSD, Novartis, and Pfizer and research funding from Novartis and Pfizer, outside the present work. *Giuseppe Luigi Banna:* Speaker bureau: Astellas, Astrazeneca, Amgen. Patents: n. 4 patents with ST Microelectronics. Travel, Accommodations for scientific conferences: Merck, Janssen. *Ugo De Giorgi:* services as advisory/board member of Astellas, Bayer, BMS, IPSEN, Janssen, Merck, Pfizer, Sanofi, received research grant/funding to the institution from AstraZeneca, Roche, Sanofi, and travel/accommodations/expenses from BMS BMS, IPSEN, Janssen, Pfizer. *Mariella Sorarù*: honoraria as consultant or advisory role from Janssen; grant for participation at scientific events: Astellas Pharma, Sanofi, Roche Novartis, Ipsen, Janssen, Bristol Myers Squibb, Pfizer; research funding: Roche, Merck, Janssen.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Liguria number 068/2019.

Consent to participate Informed consent was obtained from all individual participants included in the study.

References

1. Motzer RJ, Tannir NM, McDermott DF et al (2018) Nivolumab plus Ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 378:1277–1290. https://doi.org/10.1056/nejmoa1712126
2. Motzer RJ, Penkov K, Haanen J et al (2019) Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 380:1103–1115. https://doi.org/10.1056/nejmoa1816047

3. Rini BI, Plimack ER, Stus V et al (2019) Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 380:1116–1127. https://doi.org/10.1056/nejmoa1816714
4. Rini BI, Powles T, Atkins MB et al (2019) Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet 393:2404–2415. https://doi.org/10.1016/S0140-6736(19)30723-8
5. Choueiri TK, Powles T, Burotto M et al (2021) Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 384:829–841. https://doi.org/10.1056/nejmoa2026982
6. Motzer R, Alekseev B, Rha S-Y et al (2021) Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 384:1289–1300. https://doi.org/10.1056/nejmoa2035716
7. Motzer RJ, Escudier B, McDermott DF et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803–1813. https://doi.org/10.1056/NEJMOA1510665
8. McDermott DF, Choueiri TK, Puzanov I et al (2015) Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. J Clin Oncol 33:2013–2020. https://doi.org/10.1200/JCO.2014.58.1041
9. Caner B, Ertas H, Ocak B, Cubukcu E (2022) Hyperprogression and hypercalcemia after nivolumab treatment in three cases with renal cell carcinoma. J Oncol Pharm Pract 28:1645–1649. https://doi.org/10.1177/10781552221077418
10. Dionese M, Pierantoni F, Maruzzo M et al (2021) Fatal hyperprogression induced by nivolumab in metastatic renal cell carcinoma with sarcomatoid features: a case report. Anticancer Drugs 32:222–225. https://doi.org/10.1097/CAD.0000000000000991
11. Rebuzzi SE, Perrone F, Bersanelli M et al (2020) Prognostic and predictive molecular biomarkers in metastatic renal cell carcinoma patients treated with immune checkpoint inhibitors: a systematic review. Expert Rev Mol Diagn 20:169–185. https://doi.org/10.1080/14737159.2019.1680286
12. Catalano M, Rebuzzi SE, Maruzzo M et al (2023) Sodium levels and outcomes in patients with metastatic renal cell carcinoma receiving nivolumab. JAMA Netw Open 6:e2345185–e2345185. https://doi.org/10.1001/JAMANETWORKOPEN.2023.45185
13. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247. https://doi.org/10.1016/J.EJCA.2008.10.026
14. Heng DYC, Xie W, Regan MM et al (2009) Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 27:5794–5799. https://doi.org/10.1200/JCO.2008.21.4809
15. Motzer RJ, Bacik J, Schwartz LH et al (2004) Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 22:454–463. https://doi.org/10.1200/JCO.2004.06.132
16. Santoni M, De Giorgi U, Iacovelli R et al (2013) Pre-treatment neutrophil-to-lymphocyte ratio may be associated with the outcome in patients treated with everolimus for metastatic renal cell carcinoma. Br J Cancer 109:1755. https://doi.org/10.1038/BJC.2013.522
17. Velev M, Dalban C, Chevreau C et al (2023) Efficacy and safety of nivolumab in bone metastases from renal cell carcinoma: results of the GETUG-AFU26-NIVOREN multicentre phase II study. Eur J Cancer 182:66–76. https://doi.org/10.1016/J.EJCA.2022.12.028
18. Rebuzzi SE, Signori A, Banna GL et al (2021) Inflammatory indices and clinical factors in metastatic renal cell carcinoma patients treated with nivolumab: the development of a novel prognostic score (Meet-URO 15 study). Ther Adv Med Oncol 13:17588359211019642–17588359211019642. https://doi.org/10.1177/17588359211019642
19. Rebuzzi SE, Cerbone L, Signori A et al (2022) Application of the Meet-URO score to metastatic renal cell carcinoma patients treated with second- and third-line cabozantinib. Ther Adv Med Oncol. https://doi.org/10.1177/17588359221079580
20. Jeyakumar G, Kim S, Bumma N et al (2017) Neutrophil lymphocyte ratio and duration of prior anti-angiogenic therapy as biomarkers in metastatic RCC receiving immune checkpoint inhibitor therapy. J Immunother Cancer 5:1–8. https://doi.org/10.1186/S40425-017-0287-5
21. Motzer RJ, Escudier B, McDermott DF et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803–1813. https://doi.org/10.1056/NEJMOA1510665/SUPPL_FILE/NEJMOA1510665_DISCLOSURES.PDF
22. Erman M, Biswas B, Danchaivijitr P et al (2021) Correction to: prospective observational study on pazopanib in patients treated for advanced or metastatic renal cell carcinoma in countries in Asia Pacific, North Africa, and Middle East regions: PARACHUTE study (BMC Cancer, (2021), 21, 1, (1021), 10.118. BMC Cancer 21:1–10. https://doi.org/10.1186/s12885-021-08848-8
23. Catalano M, De Giorgi U, Maruzzo M et al (2022) Long-term response to tyrosine kinase inhibitors for metastatic renal cell carcinoma. Biomedicines 10:1–12. https://doi.org/10.3390/biomedicines10102444
24. Odegaard JI, Chawla A (2008) 基因的改变NIH public access. Bone 23:1–7. https://doi.org/10.1016/j.clgc.2013.04.001.Long-Term
25. Valero C, Lee M, Hoen D et al (2021) Pretreatment neutrophil-to-lymphocyte ratio and mutational burden as biomarkers of tumor response to immune checkpoint inhibitors. Nat Commun 12:1–9. https://doi.org/10.1038/s41467-021-20935-9
26. Pal SK, Albiges L, Tomczak P et al (2023) Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. Lancet (London, England) 402:185–195. https://doi.org/10.1016/S0140-6736(23)00922-4
27. TiNivo-2: A phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following one or two lines of therapy where one line has an immune checkpoint inhibitor - UROONCO Kidney Cancer. https://kidney.uroonco.uroweb.org/publication/tinivo-2-a-phase-3-randomized-controlled-multicenter-open-label-study-to-compare-tivozanib-in-combination-with-nivolumab-to-tivozanib-monotherapy-in-subjects-with-renal-cell-carcinoma-who-have-pr/. Accessed 25 Feb 2024
28. (PDF) International multicenter real-world REGistry for patients with metastatic renAL cell carcinoma – Meet-URO 33 study (REGAL study). https://www.researchgate.net/publication/374659008_International_multicenter_real-world_REGistry_for_patients_with_metastatic_renAL_cell_carcinoma_-_Meet-URO_33_study_REGAL_study. Accessed 25 Feb 2024

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