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Concomitant Drugs Prognostic Score in Patients With Metastatic Renal Cell Carcinoma Receiving Ipilimumab and Nivolumab in the Compassionate Use Program in Italy: Brief Communication

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Summary: A concomitant drug-based score was developed by our group and externally validated for prognostic and predictive purposes in patients with advanced cancer treated with immune checkpoint inhibitors (ICIs). The model considers the use of three classes of drugs within a month before initiating ICI, assigning score 1 for each between proton pump inhibitor and antibiotic administration until a month before immunotherapy initiation and score 2 in case of corticosteroid intake. In the present analysis, the drug score was validated in a prospective population of 305 patients with metastatic renal cell carcinoma treated with ipilimumab plus nivolumab in the first-line setting. The value of the model in predicting overall survival and progression-free survival was statistically significant and clinically meaningful, with an overall survival rate at 12 months of 73% vs. 44% ($P < 0.0001$), and median progression-free survival of 11.6 (95% CI: 9.1–14.1) months versus 4.8 (95% CI: 2.7–7.0) months ($P = 0.002$), respectively, for patients belonging to the favorable group (score 0–1) versus the unfavorable (score 2–4). Further development will be represented by the gut microbiome analysis according to the drug-based model classification and to the outcome of patients to ICI therapy to demonstrate the link between drug exposure and immune sensitivity.

Key Words: drug score, concomitant medications, immune checkpoint inhibitors, prognostic, renal cell carcinoma

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The issue of concomitant medications in patients with cancer undergoing immune checkpoint blockade fostered several retrospective analyses, often raising the doubt

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about the causality or casualty of the relationship between the use of self-administered drugs and the response to immune checkpoint inhibitors (ICIs).[1–3] In contrast, the predictive value of concomitant medications was demonstrated by the differential effect on patients' cohorts treated with immunotherapy or chemotherapy, suggesting an effect on the immune response to ICIs but not to other anticancer therapies with a nonimmune-mediated mechanism of action.[4] This observation was then reinforced and validated in prospective populations from randomized controlled trials comparing treatment arms with or without ICIs.[5,6] The most reliable explanation for the phenomenon was likely attributed to the gut microbiota, which modifications, in consequence of the drug's assumption, are known to influence the outcome of patients to anticancer immunotherapy.[7]

In this context, a drug-based score was developed by our group and externally validated for prognostication purposes in patients with advanced cancer treated with ICIs.[8] Our analysis demonstrated that cumulative exposure to corticosteroids, antibiotics, and pump-proton inhibitors (PPIs), three microbiota-modulating drugs, led to progressively worse outcomes during and after ICI therapy. The prognostic score was calculated using these three drug classes, assigning score 1 for each between PPI and antibiotic administration until a month before immunotherapy initiation and score 2 in case of corticosteroid intake. The final scoring defined good (score 0), intermediate (1–2), and poor (3–4) prognosis patients.[8]

Then, the model was further validated for predictive purposes in nonsmall-cell lung cancer patients, demonstrating its predictive ability for objective response rate (ORR) and stronger prognostic value for progression-free survival (PFS) and overall survival (OS) in the immunotherapy cohort versus in the chemotherapy cohort.[9]

Given the usefulness of the model as a predictive and prognostic tool in patients with advanced cancer treated with ICI immunotherapy, and considering that, in recent years, the gold standard of systemic therapy for patients with metastatic renal cell carcinoma (mRCC) shifted from anti-VEGFR inhibition to immune checkpoint blockade with ICI-based combinations,[10] we pursued the validation of the drug score in this setting.

A Compassionate Use Program (CUP) of ipilimumab and nivolumab was open in Italy from April to October 2019, prospectively enrolling patients with mRCC categorized as intermediate or poor-risk according to the International Metastatic RCC Database Consortium (IMDC) score.[11] We used the prospective CUP patient population to validate the drug score in mRCC undergoing first-line combination anti-PD-1/anti-CTLA-4 immunotherapy.

MATERIALS AND METHODS

Patients with mRCC, naive for systemic therapy, were prospectively enrolled in the Italian CUP, involving 86 institutions, from April to October 2019. All patients signed the Informed Consent before being included in the Program. Ipilimumab was infused intravenously at 1 mg/kg plus nivolumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by maintenance nivolumab (240 or 480 mg flat dose every 2 or 4 wk, respectively) until progression or unacceptable toxicity.

The multicenter retrospective study of CUP was approved by the Ethics Committee of Padova, Italy, on November 16, 2021 and then by all participating centers. The electronic case report form collected all clinical data, including any concomitant medications administrated within 1 month before immunotherapy initiation. A post-hoc analysis was conducted to validate the drug score in this patient population, with a dichotomized categorization (favorable risk with score 0–1 vs. unfavorable risk with score 2–4). We chose dichotomization of the drug score because we considered the 0–1 versus 2–4 cutoff could be easily transferred to the clinical practice.

Patients were included provided the complete availability of pharmacological information.

The clinical outcomes of interest were ORR, PFS, and OS. The cutoff date was February 1, 2021. Variables were presented using the median value for continuous variables and percentages (numbers) for categorical variables. OS was defined as the time between treatment initiation and death from any cause. PFS was defined as the time between treatment initiation and progression or death, whichever occurred first. In case of no events, both times were censored at the date of the last follow-up. Median PFS and OS were estimated by using Kaplan-Meier methods. The follow-up was estimated using the reverse Kaplan-Meier method.[12] The Cox regression model was used for univariate and multivariable analysis on survival outcomes, and data were presented as hazard ratios (HRs) and odds ratio, and their 95% CI. Logistic regression was performed to identify clinical factors associated with ORR, odds ratio, and their 95% CIs were reported. Statistical significance level was set at $P < 0.05$ for all tests. All statistical analyses were performed with IBM-SPSS version 28.0.

RESULTS

The Italian CUP for ipilimumab plus nivolumab in mRCC enrolled 324 patients; 305 had availability of pharmacological history and were included in the present analysis. Patients with nonclear cell histology were 63 (21%) (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JIT/A703). The main characteristics of the patient population are reported in Table 1.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Patients Included in the Analysis

Characteristic	Patients, n (%)
Sex	
Male	226 (74.1)
Female	79 (25.9)
Median age (range) (y)	63 (36–87)
ECOG PS	
0	167 (54.8)
1	107 (35.1)
2	31 (10.1)
Histology	
Clear cell	242 (79.3)
Nonclear cell	63 (20.7)
Sarcomatoid differentiation	56 (18.4)
Lung metastasis	218 (71.5)
Bone metastasis	98 (32.1)
Liver metastasis	57 (18.7)
Brain metastasis	23 (7.5)
IMDC prognostic risk	
Intermediate	209 (68.5)
Poor	96 (31.5)
Drug score	
0–1	234 (76.7)
2–4	71 (23.3)

ECOG PS indicates Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium.

The median follow-up for the present analysis was 16 months (interquartile range: 13–19).

The Cox regression analysis (Table 2) showed the value of the patient's performance status, histology, sarcomatoid differentiation, site of metastases, IMDC model (Supplementary Fig. S1, Supplemental Digital Content 2, http://links.lww.com/JIT/A704), and drug score for the prediction of the outcome of patients undergoing immunotherapy. The multivariable analysis confirmed the significant effect of the drug score in terms of OS and PFS, respectively, with HR 2.08 (95% CI: 1.42–3.04, $P < 0.0001$) and 1.42 (95% CI: 1.03–1.97, $P = 0.03$) for the unfavorable group (score 2–4) versus the favorable (score 0–1).

The value of the drug score in predicting OS and PFS was statistically significant, with an OS rate at 12 months of 73% versus 44% ($P < 0.0001$), and median progression-free survival of 11.6 (95% CI: 9.1–14.1) months versus 4.8 (95% CI: 2.7–7.0) months ($P = 0.002$), respectively, for patients belonging to the unfavorable group versus the favorable (Fig. 1). Moreover, the drug model was able to further stratify the prognosis within each IMDC group (Supplementary Figs. S2–S3, Supplemental Digital Content 2, http://links.lww.com/JIT/A704).

The negative prognostic effect of every single class of drugs among corticosteroids, antibiotics, and PPIs, was also confirmed, with HR for OS respectively 2.53 (95% CI: 1.74–3.70), 1.77 (95% CI: 1.02–3.11), and 1.73 (95% CI: 1.19–2.52) (Supplementary Fig. S4, Supplemental Digital Content 2, http://links.lww.com/JIT/A704). The respective effect of every single class of drug on PFS was not significant (Supplementary Fig. S5, Supplemental Digital Content 2, http://links.lww.com/JIT/A704).

DISCUSSION

The present analysis offers the validation of a clinically readily available tool for the outcome prediction in patients with mRCC undergoing ICI immunotherapy. Given the lack of reliable biomarkers in this field, clinical models have been developed for prognostication purposes and to improve a tailored selection of patients for systemic treatment.[13] Currently, the IMDC classification is the only tool for patient counseling, and its main characteristic is

TABLE 2. Cox Regression Analysis for Overall Survival, Progression-Free Survival, and Objective Response Rate

	OS		PFS		ORR	
	HR (95% CI) (Univariate)	HR (95% CI) (Multivariable)	HR (95% CI) (Univariate)	HR (95% CI) (Multivariable)	OR (95% CI) (Univariate)	OR (95% CI) (Multivariable)
Sex	$P = 0.49$		$P = 0.73$		$P = 0.17$	
Male	0.87 (0.58–1.30)		1.06 (0.77–1.46)		1.47 (0.84–2.59)	
Female	1.00		1.00		1.00	
Age (y)	$P = 0.66$		$P = 0.06$	$P = 0.02$*	$P = 0.56$	
	1.00 (0.98–1.01)		0.99 (0.98–1.00)	0.98 (0.97–1.00)	1.01 (0.99–1.03)	
ECOG PS	$P < 0.0001$*		$P = 0.06$		$P < 0.0001$*	$P = 0.002$*
0	1.00		1.00		1.00	1.00
1	1.99 (1.34–2.95)		1.36 (1.01–1.82)		0.36 (0.21–0.63)	0.42 (0.24–0.73)
2	2.51 (1.41–4.49)		1.53 (0.95–2.47)		0.30 (0.12–0.77)	0.31 (0.12–0.81)
Histology	$P = 0.036$*		$P = 0.022$*	$P = 0.005$*1	$P = 0.055$	
Clear cell	0.64 (0.42–0.97)		0.67 (0.48–0.94)	0.60 (0.42–0.86)	1.86 (0.99–3.52)	
Nonclear cell	1.00		1.00		1.00	
Sarcomatoid differentiation	$P = 0.07$	$P = 0.049$*	$P = 0.39$		$P = 0.98$	
Yes	1.49 (0.97–2.30)	1.54 (1.00–2.37)	1.17 (0.82–1.67)		0.99 (0.54–1.83)	
No	1.00	1.00	1.00		1.00	
Bone mets	$P < 0.0001$*	$P = 0.009$*	$P < 0.0001$*	$P = 0.007$*	$P = 0.002$*	$P = 0.01$*
Yes		1.65 (1.13–		1.50 (1.12–2.02)	0.41 (0.23–	0.48 (0.27–0.86)
No	2.04 (1.41–		1.70 (1.28–	1.00		1.00
Liver mets	$P = 0.02$*		$P < 0.0001$*	$P = 0.001$*	$P = 0.002$*	$P = 0.008$*
Yes	1.64 (1.06–2.52)		1.81 (1.30–2.52)	1.77 (1.26–2.50)	0.30 (0.14–0.64)	0.35 (0.16–0.76)
No	1.00		1.00	1.00	1.00	1.00
Brain mets	$P = 0.03$*		$P = 0.03$*	$P = 0.029$	$P = 0.20$	
Yes	1.89 (1.06–3.36)		1.67 (1.05–2.65)	1.74 (1.06–2.87)	0.51 (0.18–1.43)	
No	1.00		1.00	1.00	1.00	
Lung mets	$P = 0.21$		$P = 0.90$		$P = 0.72$	
Yes	1.32 (0.86–2.02)		1.02 (0.75–1.38)		0.91 (0.54–1.53)	
No	1.00		1.00		1.00	
IMDC	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P = 0.003$*	
Intermediate	1.00	1.00	1.00	1.80	1.00	
Poor	3.61 (2.50–5.21)	3.11 (2.14–4.52)	1.95 (1.46–2.62)	1.94 (1.34–2.42)	0.42 (0.24–0.74)	
Drug score	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P = 0.036$*	$P = 0.08$	
Favorable group (0–1)	1.00	1.00	1.00	1.00	1.00	
Unfavorable group (2–4)	2.56 (1.76–3.72)	2.11 (1.44–3.08)	1.75 (1.28–2.38)	1.41 (1.02–1.95)	0.58 (0.32–1.06)	

*P value considered statistically significant if <0.05.

ECOG PS indicates Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; mets, metastases; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

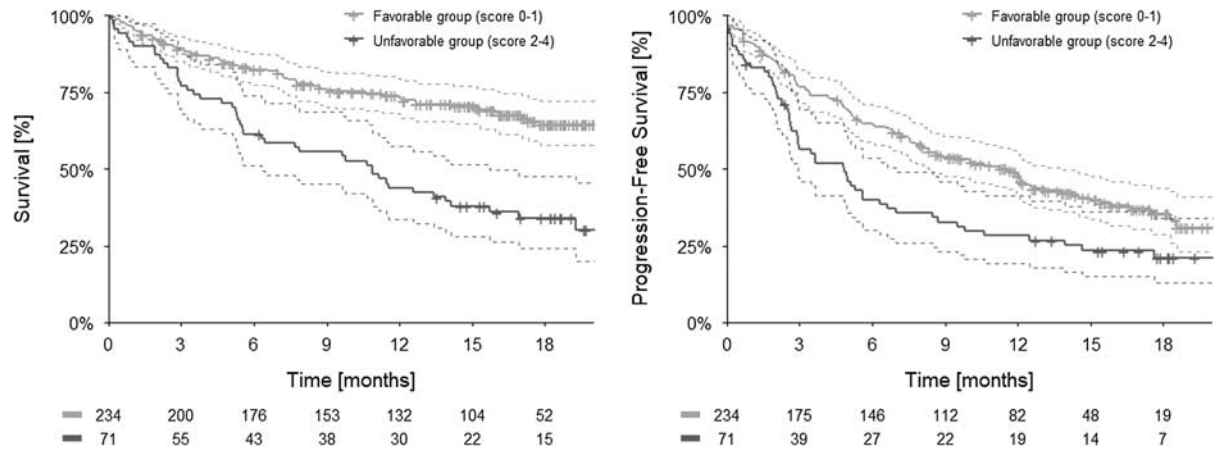

FIGURE 1. Overall survival and progression-free survival according to the drug model (drug score 0–1 = favorable group; drug score 2–4 = unfavorable group).

represented by its invariability, given the lack of possibilities to act on the model's variables.[14,15]

The drug score represents a double-faced coin to spend with our patients. First, it can be easily used for the outcome prediction before proposing immunotherapy-based therapy in mRCC patients, relying on the availability of simple information from the recent medical history of patients. This model allows a finer prognostic stratification even within the IMDC groups. Second, it can be helpful as a critical concept, suggesting avoiding using certain drugs for patients who are candidates for immunotherapy. More than a 1-month drug washout before ICI initiation, not often feasible because of the frequent priority of anticancer treatment start, the drug model should suggest extreme caution when prescribing common medications to patients with cancer. Indeed, drugs as antibiotics, and even more PPIs, are too often chronically prescribed both by general practitioners and oncologists as prophylactic tools, without a strong rationale and, mostly, without real need.

The OS and PFS stratification offered by the drug-based model is undoubtedly clinically meaningful, showing an absolute 1-year survival gain of 29% in the favorable group and a median progression-free survival difference of 6.8 months, versus the unfavorable classification.

Among the analyzed factors, only the IMDC model, bone metastases, and drug score were significantly related both to OS and PFS at the multivariable analysis in the study population, suggesting the strength of the new prognostic tool regardless of other well-known prognostic factors (ie, eastern cooperative oncology group performance, liver, and brain metastases).

Of interest, the characteristics of the CUP patient population included in the present analysis were almost entirely overlapped to those of patients enrolled in the Checkmate-214 pivotal trial in this setting, except for 7.5% of patients with brain metastases in our population.[14] This element renders the drug score validity even more reliable in a real-life population, encouraging its use in everyday practice.

The main limitation of the present work is its retrospective nature and the lack of a case-matched control cohort treated with TKIs or other non-ICI therapies, preventing the verification of the model's predictive value in a mRCC population. Further development of the project will be represented by the gut microbiome analysis according to the drug-based model classification to demonstrate the link between drug exposure and ICI sensitivity.

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Conflicts of Interest/Financial Disclosures

M.B. received honoraria as a speaker at scientific events by Bristol-Myers Squibb (BMS), Novartis, AstraZeneca, Pierre Fabre, and Pfizer and as a consultant for advisory role by Novartis, BMS, IPSEN, and Pfizer; she also received fees for copyright transfer by Sciclone Pharmaceuticals and research funding by Roche S.P.A., Seqirus UK, Pfizer, Novartis, BMS, AstraZeneca, and Sanofi Genzyme. S.B. received honoraria as a speaker at scientific events and advisory role by Bristol-Myers Squibb (BMS), Pfizer; MSD, Ipsen, AstraZeneca, and Novartis; he also received research funding from Novartis. A.C. received speaker's fees from AstraZeneca, Novartis and EISAI and grant consultancies from MSD, Astrazeneca, BMS and Roche. U.D.G. received honoraria for advisory boards or invited speaker fees from Pfizer, BMS, MSD, PharmaMar, Astellas, Bayer, Ipsen, Novartis, Roche, Clovis, AstraZeneca, institutional research grants from AstraZeneca, Sanofi, and Roche. M.M. received honoraria as a consultant for advisory role by Bristol-Myers Squibb, IPSEN, Pfizer, MSD, Merck-Serono, Janssen Cilag, and Astellas. C.P. acted as a remunerated consultant and/or speaker for Angelini Pharma, AstraZeneca, BMS, Eisai, EUSA Pharma, General Electric, Ipsen, Janssen, Merck, MSD, Novartis, and Pfizer, as an Expert Testimony for EUSA Pharma and Pfizer and as a Protocol Steering Committee Member for MSD, BMS, Eisai, and EUSA Pharma; finally he received travel support from Roche. All remaining authors have declared there are no financial conflicts of interest with regard to this work.

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