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Outcomes for International Metastatic Renal Cell Carcinoma Database Consortium Prognostic Groups in Contemporary First-line Combination Therapies for Metastatic Renal Cell Carcinoma

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Abstract

Background: The combination of immuno-oncology (IO) agents ipilimumab and nivolumab (IPI-NIVO) and vascular endothelial growth factor targeted therapies (VEGF-TT) combined with IO (IO-VEGF) are current standard of care first-line treatments for metastatic renal cell carcinoma (mRCC).
Objective: To establish real-world clinical benchmarks for IO combination therapies based on the International mRCC Database Consortium (IMDC) criteria.
Design, setting, and participants: Patients with mRCC who received first-line IPI-NIVO, IO-VEGF, or VEGF-TT from 2002 to 2021 were identified using the IMDC database and stratified according to IMDC risk groups.
Outcome measurements and statistical analysis: Overall survival (OS), time to next treatment (TTNT), and treatment duration (TD) were calculated using the Kaplan-Meier method and compared between IMDC risk groups within each treatment cohort by the log-rank test. The overall response rate (ORR) was calculated by physician assessment of the best overall response. The primary outcome was OS at 18 mo.
Results and limitations: In total, 728 patients received IPI-NIVO, 282 IO-VEGF, and 7163 VEGF-TT. The median follow-up times for patients remaining alive were 14.3 mo for IPI-NIVO, 14.9 mo IO-VEGF, and 34.4 mo for VEGF-TT. OS at 18 mo for favorable, intermediate, and poor risk was, respectively, 90%, 78%, and 50% for those receiving IPI-NIVO; 93%, 83%, and 74% for IO-VEGF; and 84%, 64%, and 28% for VEGF-TT. ORRs in

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favorable-, intermediate-, and poor-risk groups were 41.3%, 40.6%, and 33.0% for those receiving IPI-NIVO; 60.3%, 56.8%, and 40.9% for IO-VEGF; and 39.3%, 33.5%, and 20.9% for VEGF-TT, respectively. The IMDC model stratified patients into statistically distinct risk groups for the three endpoints of OS, TTNT, and TD within each treatment cohort. Limitations of this study were the retrospective design and short follow-up.

Conclusions: This study demonstrated that the IMDC model continues to risk stratify patients with mRCC treated with contemporary first-line IO combination therapies and provided real-world survival benchmarks.

Patient summary: The International Metastatic Renal Cell Carcinoma Database Consortium model continues to stratify patients with metastatic renal cell carcinoma receiving modern combination treatments in the real-world setting.

1. Introduction

The standard first-line therapy for renal cell carcinoma (RCC) has expanded in recent years to include the combination of the immune-oncology (IO) agents ipilimumab and nivolumab (IPI-NIVO) and combinations of vascular endothelial growth factor targeted therapy (VEGF-TT) with IO agents (IO-VEGF).

The International Metastatic RCC (mRCC) Database Consortium (IMDC) prognostic model has been utilized for stratification in phase III clinical trials that established contemporary first-line combination therapies. The IMDC prognostic model was initially developed and validated in patients with mRCC receiving VEGF-TT and consists of six prognostic criteria: time from initial diagnosis to systemic therapy <1 yr, Karnofsky performance status <80, serum hemoglobin less than the lower limit of normal, platelet count greater than the upper limit of normal (ULN), absolute neutrophil count greater than the ULN, and corrected serum calcium greater than the ULN [1,2]. The IMDC model characterizes patients as having favorable (no criteria), intermediate (one or two criteria), or poor (three or more criteria) risk. The IMDC model provides essential information to guide treatment decisions and predict the effectiveness of systemic therapy.

The efficacy of current first-line combination therapies was established in phase III clinical trials. IPI-NIVO demonstrated improved OS compared with sunitinib in intermediate and poor IMDC risk patients [3]. The clinical trials that demonstrated OS benefit of IO-VEGF therapies were KEYNOTE-426 (axitinib plus pembrolizumab vs sunitinib), CHECKMATE-9ER (cabozantinib plus nivolumab vs sunitinib), and CLEAR (pembrolizumab plus lenvatinib vs everolimus plus lenvatinib vs sunitinib) [4–7]. The JAVELIN Renal 101 trial (avelumab plus axitinib vs sunitinib) demonstrated an improvement in progression-free survival, but not in overall survival (OS); however, the avelumab plus axitinib regimen is approved by the Food and Drug Administration [8].

Validation of the IMDC prognostic model in real-world mRCC patient cohorts in the context of contemporary first-line combination therapies and characterization of real-world clinical benchmarks by prognostic group have not yet been reported in the literature. Establishing clinical benchmarks may inform prognosis and expectations of therapy.

2. Patients and methods

2.1. Study design and patient selection

A retrospective analysis was conducted using the IMDC database to identify patients with mRCC treated with first-line IPI-NIVO, IO-VEGF, or VEGF-TT from 2002 to 2021 with available IMDC criteria. The IMDC database (www.imdconline.com) includes 13 056 consecutive patients treated at 40 international centers with a data cutoff of January 1, 2022. Data were collected from hospital and pharmacy records using uniform database collection templates. Institutional review board approval was obtained from each participating center. This study included only approved contemporary treatment regimens representative of clinical practice and thus defined IO-VEGF as follows: axitinib plus pembrolizumab, cabozantinib plus nivolumab, lenvatinib plus pembrolizumab, or axitinib plus avelumab. The regimens defined as VEGF-TT were sunitinib or pazopanib. Patients were excluded if they received any other treatment in the first line or if IMDC prognostic category could not be calculated due to missing data (Supplementary Fig. 1).

2.2. Outcome measurement

Patients were stratified into favorable-, intermediate-, and poor-risk groups based on the IMDC prognostic criteria. The primary endpoint of this study was OS at 18 mo. The secondary endpoints were OS at 12 mo, time to next treatment (TTNT), treatment duration (TD), and overall response rate (ORR). OS was calculated from the time of initiation of first-line systemic therapy to death from any cause or censored at the time of last follow-up. TTNT was calculated from the time of initiation of first-line systemic therapy to the time of initiation of second-line therapy or death or censored at the time of last follow-up. TD was calculated from the time of initiation of first-line systemic therapy until discontinuation for any reason or censored at the time of last follow-up. TTNT and TD were chosen as secondary endpoints over progression-free survival or time to treatment failure because the IO treatment effect can persist beyond discontinuation of the IO agent and physicians may treat beyond first progression. Complete response (CR), partial response (PR), stable disease, and progressive disease were determined by physician assessment of the best response using RECIST v1.1 principles [9]. ORR was calculated as the proportion (%) of patients with CR or PR as their best response to first-line systemic therapy.

2.3. Statistical analysis

Patient outcomes were compared between IMDC risk groups within treatment groups. OS, TTNT, and TD were calculated using the Kaplan-Meier method with significant log-rank $p < 0.05$. Patient demographics and baseline characteristics were described as proportions (%) for cate-

gorical variables and medians (interquartile range) for continuous variables. Differences in baseline characteristics between risk groups of IPI-NIVO and IO-VEGF compared with the VEGF-TT cohort were assessed using the chi-square test with significance of $p < 0.05$. SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to perform the statistical analysis.

3. Results

3.1. Patient characteristics

Overall, 8171 patients with mRCC were identified who received IPI-NIVO, IO-VEGF, or VEGF-TT in the first-line setting and for whom IMDC prognostic criteria were known. The total numbers of patients who received IPI-NIVO, IO-VEGF, and VEGF-TT were 728, 282, and 7163, respectively. The median follow-up times for patients remaining alive were 14.3 mo for IPI-NIVO (517/728 patients remaining alive), 14.9 mo for IO-VEGF (222/282 patients remaining alive), and 34.4 mo for VEGF-TT (2071/7163 patients remaining alive). The median follow-up times for all patients were 17.8 mo (95% confidence interval [CI], 16.4–19.7) for IPI-NIVO, 18.0 mo (95% CI, 15.6–21.9) for IO-VEGF, and 61.3 mo (95% CI, 58.9–64.0) for VEGF-TT.

Baseline characteristics are described in Table 1. Of note, in the IPI-NIVO cohort, fewer patients received nephrectomies than in the VEGF-TT cohort ($p < 0.00001$ in each risk group); however, there was no statistically significant difference in nephrectomies between the IO-VEGF and VEGF-TT cohorts. Similarly, more patients in the IPI-NIVO cohort had pathology with sarcomatoid features than in the VEGF-TT cohort ($p < 0.001$ in each risk group). More patients in the IO-VEGF intermediate-risk cohort had sarcomatoid features than in the VEGF-TT intermediate-risk cohort ($p = 0.004$). There were no other substantial differences between baseline characteristics of the IO combination cohorts and the VEGF-TT cohort.

Table 1 – Baseline characteristics of patients in the IPI-NIVO, IO-VEGF and VEGF-TT treatment cohorts

IMDC risk (*n*)	IPI-NIVO (*n* = 728)			IO-VEGF (*n* = 282)			VEGF-TT (*n* = 7163)		
	Favorable[a] (67)	Intermediate (421)	Poor (240)	Favorable (95)	Intermediate (130)	Poor (57)	Favorable (1293)	Intermediate (3983)	Poor (1887)
Age (yr), median (IQR)	62.1 (56.0–67.3)	62.7 (55.7–69.3)	62.0 (55.6–68.6)	62.2 (53.7–69.9)	63.6 (58.2–59.3)	62.6 (55.4–70.5)	64.0 (56.8–70.8)	63.7 (55.7–70.8)	62.2 (54.7–69.8)
Male	76.1% (51/67)	73.6% (310/421)	67.9% (163/240)	79.0% (75/95)	71.5% (93/130)	73.7% (42/57)	71.5% (925/1293)	72.2% (2877/3983)	71.1% (1342/1887)
IMDC criteria									
KPS <80%	0 (0/67)	7.8% (32/413)	38.0% (87/229)	0 (0/95)	6.3% (8/126)	35.2% (19/54)	0 (0/1293)	11.5% (435/3777)	54.7% (960/1755)
Dx to Tx <1 yr	0 (0/67)	74.5% (313/420)	96.7% (231/239)	0 (0/95)	71.3% (92/129)	93.0% (53/57)	0 (0/1293)	61.4% (2441/3974)	90.5% (1707/1886)
Ca >ULN	0 (0/67)	4.2% (17/407)	39.0% (89/228)	0 (0/95)	6.6% (8/122)	39.3% (22/56)	0 (0/1293)	6.6% (249/3775)	31.9% (554/1739)
Hb <LLN	0 (0/67)	46.0 (193/420)	92.5% (222/240)	0 (0/95)	38.0% (49/129)	91.2% (52/57)	0 (0/1293)	49.8% (1982/3980)	90.5% (1706/1886)
Plt >ULN	0 (0/67)	4.1% (17/417)	58.9% (139/236)	0 (0/95)	5.4% (7/130)	59.6% (34/57)	0 (0/1293)	5.1% (204/3976)	51.3% (956/1865)
Neut >ULN	0 (0/67)	6.3% (26/416)	38.8% (92/237)	0 (0/95)	4.6% (6/130)	38.2% (21/55)	0 (0/1293)	8.6 (336/3920)	42.7% (779/1826)
Nephrectomy	91.0%[b] (61/67)	67.0%[b] (281/419)	39.6%[b] (95/240)	98.9% (94/95)	80.0% (104/130)	45.6% (26/57)	98.3% (1269/1291)	82.2% (3266/3975)	57.1% (1074/1882)
Non–clear cell	12.7% (7/55)	11.4% (36/315)	18.0% (32/178)	11.1% (9/81)	10.6% (11/104)	11.6% (5/43)	11.0% (118/1076)	12.2% (406/3315)	15.1% (234/1549)
Papillary	8.6% (5/58)	4.8% (17/357)	4.3% (8/185)	5.4% (5/93)	1.7% (2/116)	4.4% (2/45)	6.2% (64/1038)	8.7% (266/3059)	8.5% (117/1376)
Chromophobe	4.1% (2/49)	2.0% (6/303)	2.4% (4/169)	3.8% (3/80)	3.0% (3/99)	0 (0/40)	3.5% (34/965)	2.5% (69/2815)	1.8% (24/1321)
Collecting duct	0 (0/57)	0.3% (1/356)	2.8% (5/181)	0 (0/93)	0 (0/116)	0 (0/45)	0.2% (2/1046)	0.3% (10/3076)	0.8% (11/1390)
Unclassified	1.8% (1/57)	3.9% (14/357)	9.8% (18/184)	2.2% (2/93)	3.4% (4/117)	2.2% (1/46)	1.4% (15/1049)	3.1% (96/3086)	6.7% (94/1397)
Sarcomatoid	9.8%[b] (5/51)	20.9%[b] (63/301)	30.9%[b] (51/165)	1.3%[b] (1/80)	22.6%[b] (24/106)	22.5% (9/40)	6.2% (61/982)	13.1% (408/3121)	19.5 (285/1459)
Site of metastasis									
Lung	72.3% (47/65)	69.7% (287/412)	73.5% (172/234)	69.1% (65/94)	69.3% (88/127)	73.7% (42/57)	65.6% (806/1229)	67.1% (2571/3832)	70.6% (1285/1820)
Brain	1.6% (1/61)	6.7% (27/404)	11.5% (26/226)	5.3% (5/94)	2.4%[b] (3/125)	3.6% (2/56)	6.7% (82/1218)	8.0% (307/3820)	8.9% (162/1821)
Bone	31.3% (20/64)	32.0% (130/406)	42.7% (99/232)	20.0% (19/95)	28.8% (36/125)	48.2% (27/56)	24.1% (294/1219)	31.0 % (1189/3831)	42.6% (774/1818)
Liver	14.8% (9/61)	15.7% (63/402)	24.8% (56/226)	13.8% (13/94)	12.0% (15/125)	21.4% (12/56)	15.8% (192/1218)	17.0% (652/3827)	25.1% (455/1816)

Ca = corrected serum calcium; Dx = initial diagnosis of renal cell carcinoma; Hb = hemoglobin concentration; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO-VEGF = immuno-oncology agent plus vascular endothelial growth factor targeted therapy; IPI-NIVO = ipilimumab plus nivolumab; IQR = interquartile range; KPS = Karnofsky performance scale; LLN = lower limit of normal; Plt = platelet count; Neut = neutrophil count; Tx = initiation of first-line treatment for renal cell carcinoma; ULN = upper limit of normal; VEGF-TT= vascular endothelial growth factor targeted therapy.

[a] IPI-NIVO is not indicated in favorable risk and therefore must be interpreted with caution.

[b] Statistically different from VEGF-TT by chi-square ($p < 0.05$).

Within the IO-VEGF cohort, 59 (21.0%) received avelumab plus axitinib, 27 (9.6%) received nivolumab plus cabozantinib, 127 (61.4%) received pembrolizumab plus axitinib, and 23 (8.2%) received pembrolizumab plus lenvatinib. Within the VEGF-TT cohort, 1696 (23.7%) received pazopanib and 5467 (76.3%) received sunitinib.

3.2. Clinical outcomes

The IMDC prognostic model stratified patients into three statistically distinct prognostic groups based on OS, TD, and TTNT within each treatment cohort (Figs. 1–3). The primary endpoints of OS at 18 mo for favorable, intermediate, and poor risk were, respectively, 90%, 78%, and 50% for those receiving IPI-NIVO (log-rank $p < 0.0001$); 93%, 83%, and 74% for IO-VEGF (log-rank $p = 0.0012$); and 84%, 64%, and 28% for VEGF-TT (log-rank $p < 0.0001$). The OS, TD, TTNT, and ORR for IPI-NIVO and IO-VEGF are numerically higher than those for VEGF-TT, which is to be expected and in keeping with clinical trials (Tables 2 and 3). As the intermediate-risk group was quite large and heterogeneous, we conducted an exploratory subgroup analysis of intermediate-risk patients and demonstrated a significant difference in OS for those with one versus two IMDC factors for the IPI-NIVO (log-rank $p < 0.0001$), IO-VEGF (log-rank $p = 0.01$), and VEGF-TT (log-rank $p < 0.0001$) cohorts. In an exploratory analysis, we did not find any interaction between the treatment cohort and IMDC prognostic categories.

ORRs in favorable-, intermediate-, and poor-risk groups were 41.3%, 40.6%, and 33.0% for those receiving IPI-NIVO; 60.3%, 56.8%, and 40.9% for IO-VEGF; and 39.3%, 33.5%, and 20.9% for VEGF-TT, respectively. ORR was significantly

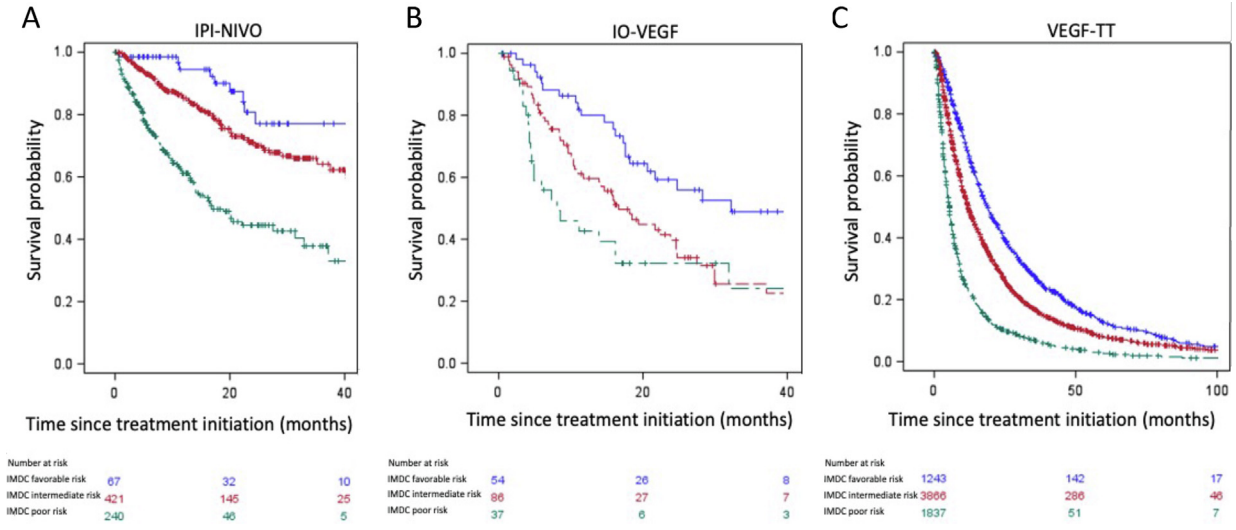

Fig. 1 – Kaplan-Meier curves for overall survival by IMDC favorable (blue), intermediate (red), and poor (black) risk for (A) IPI-NIVO (log-rank $p < 0.0001$), (B) IO-VEGF (log-rank $p = 0.0012$), and (C) VEGF-TT (log-rank $p < 0.0001$). IPI-NIVO is not indicated in favorable risk and must be interpreted with caution. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO-VEGF = immuno-oncology agent plus vascular endothelial growth factor targeted therapy; IPI-NIVO = ipilimumab plus nivolumab; VEGF-TT = vascular endothelial growth factor targeted therapy.

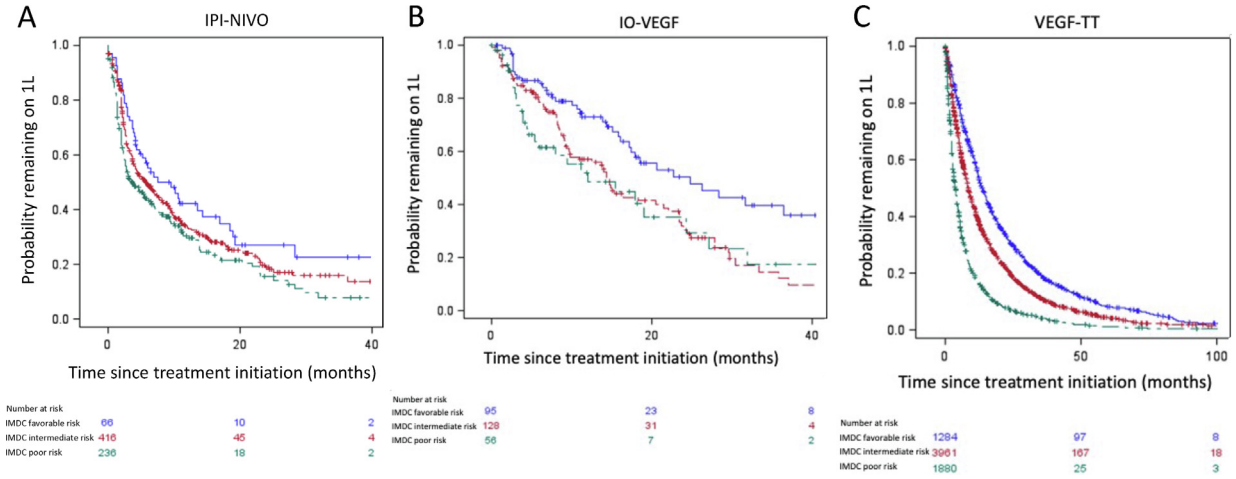

Fig. 2 – Kaplan-Meier curves for treatment duration by IMDC favorable (blue), intermediate (red), and poor (black) risk for (A) IPI-NIVO (log-rank $p = 0.0135$), (B) IO-VEGF (log-rank $p = 0.0058$), and (C) VEGF-TT (log-rank $p < 0.0001$). IPI-NIVO is not indicated in favorable risk and must be interpreted with caution. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO-VEGF = immuno-oncology agent plus vascular endothelial growth factor targeted therapy; IPI-NIVO = ipilimumab plus nivolumab; 1L = first line; VEGF-TT = vascular endothelial growth factor targeted therapy.

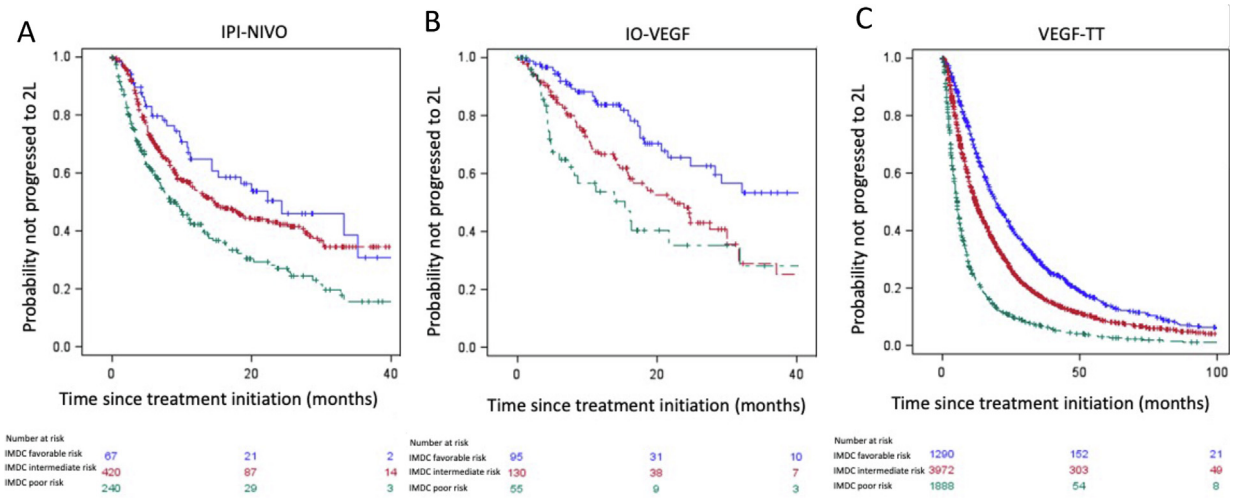

Fig. 3 – Kaplan-Meier curves for time to next treatment by IMDC favorable (blue), intermediate (red), and poor (black) risk for (A) IPI-NIVO (log-rank $p < 0.0001$), (B) IO-VEGF (log-rank $p = 0.0003$), and (C) VEGF-TT (log-rank $p < 0.0001$). IPI-NIVO is not indicated in favorable risk and must be interpreted with caution. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO-VEGF = immuno-oncology agent plus vascular endothelial growth factor targeted therapy; IPI-NIVO = ipilimumab plus nivolumab; 2L = second line; VEGF-TT = vascular endothelial growth factor targeted therapy.

Table 2 – Clinical outcomes for patients in favorable-, intermediate-, and poor-risk IMDC groups receiving IPI-NIVO, IO-VEGF, or VEGF-TT

IMDC risk (*n*)	IPI-NIVO (*n* = 728)			IO-VEGF (*n* = 282)			VEGF-TT (*n* = 7163)		
	Favorable[a] (67)	Intermediate (421)	Poor (240)	Favorable (95)	Intermediate (130)	Poor (57)	Favorable (1293)	Intermediate (3983)	Poor (1887)
12-mo OS (95% CI)	95% (89–100)	85% (81–89)	61% (54–68)	96% (92–100)	90% (84–96)	78% (66–90)	92% (90–94)	75% (74–76)	38% (36–40)
18-mo OS (95% CI)	90% (82–98)	78% (73–83)	50% (42–58)	93% (87–99)	83% (76–90)	74% (60–88)	84% (82–86)	64% (62–66)	28% (26–30)
TD (mo), median (95% CI)	9.6 (4.3–14.3)	5.7 (4.2–7.5)	3.7 (2.6–6.0)	24.8 (17.2–41.4)	14.3 (9.7–20.4)	12.0 (5.4–24.2)	13.7 (12.6–14.8)	8.4 (8.2–8.9)	3.8 (3.5–4.1)
TTNT (mo), median (95% CI)	24.3 (14.3–NE)	14.7 11.1–19.8	8.4 (6.8–11.2)	42.6 (24.8–53.5)	22.5 (15.9–30.0)	15.4 (6.0–31.9)	19.5 (18.2–21.2)	12.1 (11.6–12.7)	5.3 (5.0–5.6)

CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO-VEGF = immuno-oncology agent plus vascular endothelial growth factor targeted therapy; IPI-NIVO = ipilimumab plus nivolumab; NE = not estimable; OS = overall survival; TD = treatment duration; TTNT = time to next treatment; VEGF-TT = vascular endothelial growth factor targeted therapy.
[a] IPI-NIVO is not indicated in favorable risk and therefore must be interpreted with caution

Table 3 – Best overall response rates for patients in favorable-, intermediate-, and poor-risk IMDC groups receiving IPI-NIVO, IO-VEGF, or VEGF-TT

IMDC risk (*n*)	IPI-NIVO (*n* = 622)			IO-VEGF (*n* = 233)			VEGF-TT (*n* = 6137)		
	Favorable[a] (58)	Intermediate (367)	Poor (197)	Favorable (78)	Intermediate (111)	Poor (44)	Favorable (1156)	Intermediate (3452)	Poor (1529)
ORR	41.3% (24)	40.6% (149)	33.0% (65)	60.3% (47)	56.8% (63)	40.9% (18)	39.3% (458)	33.5% (1157)	20.9% (320)
CR	6.9% (4)	5.2% (19)	2.1% (4)	6.4% (5)	3.6% (4)	0.0% (0)	3.4% (40)	3.5% (121)	1.5% (23)
PR	34.5% (20)	35.4% (130)	31.0% (61)	53.9% (42)	53.2% (59)	40.9% (18)	35.9% (418)	30% (1036)	19.4% (297)
SD	43.1% (25)	33.2% (122)	32.5% (64)	32.1% (25)	34.2% (38)	31.8% (14)	46.0% (536)	42.5 (1466)	34.9% (533)
PD	15.5% (9)	26% (96)	34.5% (68)	7.7% (6)	9.0% (10)	27.3% (12)	14.6% (170)	24% (829)	44.2% (676)

CR = complete response; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO-VEGF = immuno-oncology agent plus vascular endothelial growth factor targeted therapy; IPI-NIVO = ipilimumab plus nivolumab; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; VEGF-TT = vascular endothelial growth factor targeted therapy.
[a] IPI-NIVO is not indicated in favorable risk and therefore must be interpreted with caution.

different between favorable-, intermediate-, and poor-risk groups for VEGF-TT ($p < 0.00001$). Although there are numerical differences in ORRs between the favorable-, intermediate-, and poor-risk groups for IPI-NIVO and IO-VEGF, there were no statistically significant differences (IPI-NIVO $p = 0.18$; IO-VEGF $p = 0.10$).

4. Discussion

This large, real-world cohort study of patients with mRCC demonstrates the utility of the IMDC prognostic model in stratifying real-world populations treated with contemporary IO combination therapies into favorable-, intermediate-, and poor-risk groups according to OS, TD, and TTNT. Furthermore, this study provides meaningful clinical benchmarks regarding the effectiveness of contemporary first-line therapies in a real-world setting.

The IMDC prognostic score was established during the era of VEGF-TT in mRCC to reflect a modern strategy for stratifying patients according to risk, and thereby facilitate risk-directed treatment decisions and development of clinical trials [1,2]. The field of mRCC treatment has expanded since the inception of the IMDC model to include combinations of IO agents and IO plus VEGF-TT. Clinical trials examining these novel strategies have relied on previously established risk schema such as the IMDC and Memorial Sloan Kettering Cancer Center (MSKCC) models; yet, validation of these models within the new treatment paradigm is essential to ensure continued reliability in this context. This study demonstrated that the IMDC prognostic model stratifies patients into statistically significant risk groups, reflecting continued utility in the setting of IO combination therapies with statistical and clinical significance for patients receiving IPI-NIVO, IO-VEGF, and VEGF-TT. A recent updated analysis of the CHECKMATE-214 clinical trial examined IMDC prognostic factors and included 1052 patients treated with either IPI-NIVO or sunitinib with a median follow-up of 67 mo. The CHECKMATE-214 update demonstrated hazard ratios for OS ranging from 1.1 for platelets higher than the ULN to 2.7 for corrected calcium higher than the ULN in the IPI-NIVO cohort [10]. The IMDC model remains a robust tool for prognostication in the era of IO combination therapies; however, incorporation of molecular and pathologic biomarkers in the future may further refine the prognostic ability of the IMDC model.

The study establishes real-world clinical benchmarks that can aid in clinician counseling. In the IPI-NIVO cohort, 18-mo OS values are 90%, 78%, and 50% for favorable, intermediate, and poor IMDC risk patients, respectively. IPI-NIVO did not gain regulatory approval in the favorable-risk setting; therefore, OS must be interpreted with caution in the favorable-risk group. The IO-VEGF cohort demonstrated 18-mo OS of 83%, 78%, and 74% for favorable, intermediate, and poor IMDC risk groups, respectively. A VEGF-TT cohort was examined for historical context and demonstrated 18-mo OS of 84%, 64%, and 28% for favorable, intermediate, and poor IMDC risk, respectively. OS at 18 mo was chosen as the primary endpoint because that was the furthest time point that was representative of both the IPI-NIVO and the IO-VEGF cohort based on the length of follow-up. Additional follow-up is required to characterize the tails of the survival curves beyond 18 mo. ORRs observed in the real-world IPI-NIVO and IO-VEGF cohorts were similar to those observed in the phase III clinical trials evaluating their efficacy; however, lower CR rates were noted [3–8].

Clinical trial enrollment tends to produce highly selected cohorts; however, the population examined in this retrospective study is reflective of real-world treatment outcomes, including patients with non–clear cell histology, and are more generalizable to patients encountered in routine clinical practice. Additionally, this study has not yet reached the same length of follow-up as the clinical trials that established the efficacy of these combination treatments. Future real-world comparisons of IPI-NIVO and IO-VEGF effectiveness are necessary to guide selection of first-line therapy; however, longer follow-up is required to characterize the tails of these curves and the patients with durable responses to ensure that such a comparison adequately represents the true benefit of each treatment. Therefore, we intentionally did not statistically compare treatments at this time.

Baseline prognostic characteristics of IPI-NIVO and IO-VEGF were compared with those of VEGF-TT for each risk group to determine whether there were differences between the populations receiving contemporary IO combination therapies and those receiving the historical standard VEGF-TT. Baseline characteristics for the IPI-NIVO and VEGF-TT cohorts were similar apart from fewer nephrectomies ($p < 0.00001$ in each risk group) and a greater proportion of pathology with sarcomatoid features ($p < 0.001$ in each risk group) in the IPI-NIVO group. The IO-VEGF cohort also had a greater proportion of pathology with sarcomatoid features than the VEGF-TT cohort in the intermediate-risk group only ($p = 0.004$); however, there was no statistical difference in the proportion of nephrectomies. Nephrectomies included both cytoreductive nephrectomy (CN) and curative intent nephrectomy. One explanation for the discrepancy between the IPI-NIVO and VEGF-TT cohorts could be changing practices. The CARMENA trial demonstrated noninferiority of sunitinib alone compared with sunitinib plus upfront CN in MSKCC intermediate- and poor-risk disease [11]. Therefore, in current practice, fewer patients who require systemic therapy undergo upfront CN, and deferred CN is reserved for patients with response to systemic therapy. Another explanation is that IPI-NIVO is indicated for patients with intermediate- and poor-risk disease. Thus, other poorer-risk characteristics may be associated with this cohort explaining fewer nephrectomies and more sarcomatoid features, which is associated with poorer prognosis [12].

A strength of this study is that it is the largest multicenter real-world patient sample to the authors' knowledge. IO combination and VEGF-TT regimens were limited to those approved for clinical use, and a heterogeneous population was examined, including those with nonclear histology, to reflect modern clinical practice.

The weaknesses of this study include that it is retrospective and thus there may be a selection bias and missing data. Consecutive patient samples were used to limit this, however. The follow-up has not reached the same maturity

as the phase III clinical trials because most patients started their therapy after the clinical trials were reported. Additionally, we used physician assessment of the best overall response, which, although prone to a bias, is generalizable to clinical practice.

5. Conclusions

The IMDC prognostic model continues to risk stratify patients treated with contemporary first-line IO combination therapies. These findings provide real-world survival and response benchmarks for contemporary first-line mRCC treatments, and may be useful for patient counseling and future trial development.

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