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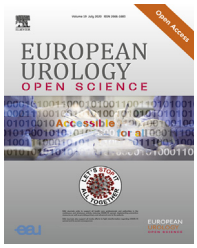

European Association of Urology

Opinion: Open Science

Management of Favorable-risk Advanced Renal Cell Carcinoma: Is Dual Therapy the Answer?

Dual therapy (immune checkpoint inhibitor [ICI]-ICI, ICI-tyrosine kinase inhibitor [TKI]) has changed the treatment landscape for patients with metastatic renal cell carcinoma (mRCC) [1–6]. While the overall survival (OS) benefits of dual therapy over sunitinib monotherapy have undoubtedly been proven for patients with International Metastatic RCC Database Consortium (IMDC) intermediate or poor risk, this benefit has not been demonstrated in the IMDC favorable-risk group [1–6]. In fact, not even progression-free survival (PFS) or complete response (CR) benefits were reported consistently across dual therapy in the IMDC favorable-risk group (Table 1) [1–6], although none of these trials was powered for subgroup analysis. Nevertheless, dual therapy (in particular pembrolizumab-axitinib [7,8], pembrolizumab-lenvatinib [8], avelumab-axitinib [8], and nivolumab-cabozantinib [7,8]) was incorporated in established guidelines as a potential first-line treatment option for IMDC favorable-risk patients. There are no roles for atezolizumab-bevacizumab [4] or nivolumab-ipilimumab [5] in the management of favorable-risk RCC, with the first trial failing to demonstrate an OS benefit across any RCC IMDC risk group and the second enrolling an IMDC favorable-risk group only for exploratory purposes [4]. While we agree with the overall recommendation to improve drug access, we are concerned about the potential risk of overtreatment if dual therapy is used as a straightforward intervention for this patient subgroup. Here, we address the urgent need to develop strategies to improve patient selection criteria for dual therapy in this subgroup.

To understand the utility of dual therapy in IMDC favorable-risk RCC, we must first understand the limitations of the IMDC risk model. In a way, trials evaluating dual therapy have been using the IMDC risk model as a predictive tool for dual therapy efficacy rather than its originally intended use as a prognostic tool in the TKI era. The IMDC model holds true in its ability to prognosticate the three groups of patients with advanced RCC; however, the same model is predictive of dual therapy efficacy only in the intermediate-risk/poor-risk group, and not the favorable-risk group. This suggests that the tumor biology of IMDC favorable-risk RCC is probably heterogeneous, which may not be captured in the clinical variables of the IMDC model. Besides the lack of predictive biomarkers for dual therapy and the absence of OS benefits, especially in the IMDC favorable-risk group, it would be even more important to rely on clinical judgment and the patient's own value for an acceptable risk-benefit balance.

For patients with IMDC favorable-risk disease who are symptomatic, systemic treatment is indicated. In the absence of ICI contraindications, dual therapy may be favored over sunitinib for two reasons. First, Checkmate-9ER [2] and Checkmate-214 [5] suggested that quality of life (QoL) and disease-related symptoms were better in the dual therapy arm than in the sunitinib arm, although this analysis was conducted in the intention-to-treat population rather than the favorable-risk group alone, but is still relevant for symptomatic patients. Keynote-426 also demonstrated that QoL at least did not worsen with dual therapy compared to a TKI alone [9]. Second, dual therapy did not have a negative impact on OS, even after treatment discontinuation because of toxicities [5]. This durable response may translate to longer treatment-free-survival, less financial toxicity, and less frequent clinic visits. Even without an OS benefit, dual therapy may provide other clinically meaningful benefits compared to sunitinib if patients require systemic treatment.

Conversely, most patients with IMDC favorable-risk disease are asymptomatic owing to the indolent tumor biology. Giving a dual therapy for PFS benefit would be irrelevant in this patient subgroup. In fact, assessing whether this subgroup requires immediate treatment is the most important clinical distinction. A previous observational phase 2 trial reported a median surveillance time of 22.2 mo without systemic therapy among 52 previously untreated patients with asymptomatic mRCC with zero or one IMDC adverse risk factors and two or fewer metastatic sites who were on active surveillance [10]. Some 86% of the patients were still able to receive systemic treatment on

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Table 1 – Summary of previous clinical trials evaluating first-line systemic treatment in advanced renal cell carcinoma

	Checkmate-214	Keynote-426	Javelin Renal 101	IMmotion151	Checkmate-9ER	CLEAR
Treatment arms [a]	I + N (*N* = 550; *n* = 125) vs S (*N* = 546; *n* = 124)	P + Ax (*N* = 432; *n* = 138) vs S (*N* = 429; *n* = 131)	Av + Ax (*N* = 442; *n* = 94) vs S (*N* = 444; *n* = 96)	At + B (*N* = 454; *n* = 89 [c]) vs S (*N* = 461; *n* = 90 [c])	N + C (*N* = 323, *n* = 74) vs S (*N* = 328, *n* = 72)	P + L (*N* = 355, *n* = 110) vs S (*N* = 357, *n* = 124)
Primary endpoint(s)	OS, PFS, and ORR in intermediate-risk/ poor-risk patients	OS and PFS	OS and PFS in PD-L1$^+$ patients	OS and PFS in P D-L1$^+$ patients	PFS	PFS
Median FU (mo)						
Initial analysis	5.2	12.8	9.9	15	18.1	26.6
Updated analysis	Minimum 4 yr	30.6	Minimum 13 mo	N/A	N/A	N/A
OS (HR, 95% CI)						
Initial analysis						
Overall	0.63 (0.44–0.89) [b]	0.53 (0.38–0.74)	0.82 (0.53–1.28)	0.84 (0.62–1.15)	0.60 (0.40–0.49)	0.66 (0.49–0.88)
Favorable risk	1.45 (0.51–4.12)	0.64 (0.24–1.68)	NR	NR	0.84 (0.35–1.97)	1.15 (0.55–2.40)
Updated analysis						
Overall	0.66 (0.55–0.80) [b]	0.68 (0.55–0.85)	0.83 (0.60–1.15)	N/A	N/A	N/A
Favorable risk	0.93 (0.62–1.40)	1.06 (0.60–1.86)	0.81 (0.34–1.96)	N/A	N/A	N/A
OS rate						
Favorable risk	65.1% vs 68.9% at 4 yr	85.3% vs 87.7% at 2 yr				
PFS (HR, 95% CI)						
Initial analysis						
Overall	0.82 (0.64–1.05)	0.69 (0.57–0.84)	0.61 (0.47–0.79)	0.74 (0.57–0.96)	0.51 (0.41–0.64)	0.39 (0.32–0.49)
Favorable risk	2.18 (1.29–3.68)	0.81 (0.52–1.24)	0.50 (0.26–0.97)	0.71 (0.39–1.29)	0.62 (0.38–1.01)	0.41 (0.28–0.62)
Updated analysis						
Overall	0.76 (0.63–0.91)	0.71 (0.60–0.84)	0.62 (0.49–0.78)	N/A	N/A	N/A
Favorable risk	1.84 (1.29–2.62)	0.79 (0.57–1.09)	0.63 (0.40–0.99)	N/A	N/A	N/A
ORR						
Initial analysis						
Overall	42% vs 27%	59% vs 36%	55% vs 26%	43% vs 35%	56% VS 27%	71% vs 36%
Favorable risk	29% vs 52%	NR	75% vs 33%	NR	NR	NR
Updated analysis						
Overall	39% vs 33%	60% vs 40%	56% vs 27%	N/A	N/A	N/A
Favorable risk	29% vs 54%	70% vs 50%	67% vs 40%	N/A	N/A	N/A
Complete response						
Initial analysis						
Overall	9% vs 1%	6% vs 2%	4% vs 2%	9% vs 4%	8% vs 5%	16% vs 10%
Favorable risk	11% vs 6%	NR	NR	NR	NR	NR
Updated analysis						
Overall	10% vs 2%	9% vs 3%	6% vs 2%	N/A	N/A	N/A
Favorable risk	12% vs 7%	11% vs 6%	NR	N/A	N/A	N/A
All-grade toxicity	93% vs 97%	96% vs 98%	100% vs 99%	91% vs 96%	97% vs 93%	100% vs 99%
Grade ≥3 toxicity	46% vs 63%	67% vs 62% (4 vs 6 deaths)	71% vs 72% (3 vs 1 deaths)	40% vs 54%	61% vs 51% (1 vs 2 deaths)	82% vs 72%
TRTD	22% vs 12%	7% vs 20%	8% vs 13%	5% vs 8%	3% vs 9%	37% vs 14%
QoL improvement	FKSI-19 favors I + N over S	No differences between P + A and S [d]	NR	NR	FKSI-19 favors N + C over S	NR

FU = follow-up; I = ipilimumab; Ni = nivolumab; P = pembrolizumab; Av = avelumab; At = atezolizumab; Ax = axitinib; B = bevacizumab; C = cabozantinib; L = lenvatinib; S = sunitinib; N/A = not applicable; NR = not recorded; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; TRTD = toxicity-related treatment discontinuation; QoL = quality of life; FKSI-19 = Functional Assessment of Cancer Therapy–Kidney Symptom Index.

[a] *N* = overall population; *n* = favorable-risk group.

[b] Only in intermediate-risk/poor-risk patients.

[c] Memorial Sloan-Kettering Cancer Center risk stratification.

[d] Assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS), EORTC Core Quality of Life (QLQ-C30), EuroQol Group-5 Dimensions-3 Levels (EQ-5D-3 L), and Visual Analog Scale (VAS) questionnaires.

disease progression and achieved median OS of 38.6 mo (95% confidence interval 30.1–not reached) after progression [11]. Real-world evidence suggested that 57% (493/863) of patients who were on active surveillance never required systemic therapy and were still alive at ≥1 yr [11]. Therefore, the sequential approach of active surveillance followed by dual therapy on progression may be the optimal option for patients who value the potential of delaying, or at times avoiding, treatment.

Nevertheless, there are two groups of asymptomatic patients with IMDC favorable-risk RCC who may derive clinically meaningful benefits from dual therapy. First, dual therapy may be an option for those who wish for a "potential cure", providing they are young and have few comorbidities interfering with life expectancy. Checkmate-214 [5] and Keynote-426 [1] demonstrated a 5% absolute CR benefit favoring dual therapy over sunitinib in the IMDC favorable-risk group. CR was associated with prolonged survival outcomes compared to non-CR in 6-mo landmark survival analyses regardless of IMDC risk groups or treatment arms [1,9]. The 30-mo OS in Keynote-426 approaching 94–100% [1] and 3-yr OS in Checkmate-214

of 97–100% [12], depending on the treatment arm, highlight the potential of CR leading to a "potential cure". However, it is important to balance this potential benefit against patient age and comorbidities, especially given that the potential survival benefit with dual therapy may not be apparent until at least 54 mo, when the Kaplan-Meier curve had started to cross over to favoring dual therapy over sunitinib in Checkmate-214 [12]. Overall, dual therapy may be an option for asymptomatic patients with IMDC favorable-risk RCC with reasonable life expectancy who wish for a potential cure.

Second, dual therapy may be an option for asymptomatic patients with IMDC favorable-risk RCC with sarcomatoid features. Current evidence suggests that patients with favorable-risk disease have a more angiogenic milieu, which may partly explain why a TKI may be the main driving factor in attaining a survival benefit. However, certain tumor histologies or gene expression levels may feature a more inflammatory milieu, even in the favorable-risk group. Sarcomatoid features have been associated with lower prevalence of *PBRM1* mutations, frequent *CDKN2A/B* alterations, and elevated PD-L1 expression, all of which were associated with increased cell-cycle activity, anabolic metabolism, and low angiogenesis [13]. This suggested that tumor biology in the IMDC favorable-risk group may be heterogeneous in itself, indicating that there may be a subset of favorable-risk tumors with biology having a more inflammatory milieu rather than an angiogenic milieu, whereby dual therapy would be more important than sunitinib monotherapy.

Overall, we believe there is a role for dual therapy in the IMDC favorable-risk group despite the lack of definite OS benefit thus far. A meta-analysis may be required to further evaluate the role of dual therapy in the IMDC favorable-risk group, although it is likely that longer follow-up duration rather than increasing sample size would be required to truly evaluate the OS benefit of dual therapy in this subgroup owing to its favorable survival outcomes regardless of treatment options. In the absence of available predictive biomarkers, careful patient selection and shared patient-physician discussion are important to minimize the risk of overtreatment while maximizing the personalized clinically meaningful benefit.

Conflicts of interest: Adi Kartolo and Francisco E. Vera-Badillo have nothing to disclose. Giuseppe Procopio has received personal fees from AstraZeneca, Bayer, BMS, Janssen, Ipsen, Merck, MSD, Novartis, and Pfizer outside the submitted work.

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