EDITORIALS

Renal-Cell Cancer — Targeting an Immune Checkpoint or Multiple Kinases

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Therapy for advanced renal-cell cancer has evolved considerably in the past decade, with new agents greeted like "buried treasure," although these agents come with substantial costs to both patients and the health system. Before 2005, the widely used systemic agents were cytokines — interferon alfa and interleukin-2, which yielded modest efficacy and substantial toxicity. Nevertheless, underlining the immunogenic nature of renal-cell cancer, durable complete responses occur in some patients who receive interleukin-2; these patients are mostly cured.[1] After 2005, angiogenesis and mammalian target of rapamycin (mTOR) pathway inhibitors displaced cytokine therapy.[2,3] Although the most effective sequence of therapies is not known, most patients with advanced renal-cell cancer receive a vascular endothelial growth factor (VEGF)–receptor (VEGFR) kinase inhibitor up front; at disease progression, options include another type of angiogenesis-targeted therapy or "switching the mechanism of action" to an mTOR inhibitor (e.g., everolimus). For everolimus, the benchmark median progression-free survival is 4.9 months and the median overall survival is 14.8 months; these values are based on a placebo-controlled trial involving patients whose disease progressed during angiogenesis-targeted therapy.[4] In previously treated patients, therapy with sorafenib (a VEGFR inhibitor) resulted in better overall survival than did therapy with temsirolimus (an mTOR inhibitor),[5] whereas axitinib proved superior to sorafenib with regard to progression-free survival[6] (Table 1).

Two newer agents — nivolumab, an immunotherapeutic agent that inhibits the T-cell checkpoint regulator programmed death 1 (PD-1),[10,11] and cabozantinib, a multikinase inhibitor targeting VEGFR, MET, RET, and AXL[9,12] — now join the list of active therapies. In two trials now published in the *Journal*, patients whose disease progressed during VEGFR-targeted therapy were randomly assigned to receive the new agent or everolimus. In the nivolumab trial (CheckMate 025),[10] the primary end point was overall survival; in the cabozantinib trial (METEOR),[9] it was progression-free survival.

The benefit from these agents, as compared with everolimus, is unequivocal. With nivolumab, there was a clinically relevant reduction in the risk of death (27%), a higher tumor response rate (25% vs. 5%), and a lower incidence of high-grade treatment-related adverse events (19% vs. 37%). With cabozantinib, there was a 42% reduction in the risk of progression or death, a higher response rate (21% vs. 5%), and a similar incidence of high-grade adverse events (68% vs. 58%). These results — in particular, the data on overall survival from the nivolumab trial — establish new efficacy benchmarks for this patient context (Table 1).

Yet for all the success reported here, many questions remain. Complete remissions, the first step to a cure with "old-fashioned" immunotherapy with interleukin-2, remained disappointingly elusive in these studies. For cabozantinib, the rate was 0%; for patients with a partial tumor response, long-term durability of the response was rare. In the case of nivolumab, the complete remission rate was 1%. Although it is possible that complete remission with nivolumab may be unnecessary to achieve a long-term benefit, the lack of profound responses begs for selection or combination approaches that expand the benefit spectrum. The activity of nivolumab is somewhat analogous to that of interleukin-2,

Table 1. Comparison of End Points from Recent Phase 3 Trials Involving Previously Treated Advanced Renal-Cell Cancer.*

Trial and Treatment Group	Discontinuation for Adverse Events	Dose Reduction	Toxic Effects		Response Rate		Progression-free Survival			Overall Survival		
			Grade 3 or 4	Grade 5 or Death	Complete	Overall	Median Survival	Hazard Ratio (95% CI)	P Value	Median Survival	Hazard Ratio (95% CI)	P Value
	%	%	%		%		*mo*			*mo*		
RECORD-1[7]												
Best supportive care	1.4	1	NR	0	0	0	1.9			14.4		
Everolimus	13	7	NR	1.4	0	1.8	4.9	0.33 (0.25–0.43)	0.001	14.8	0.87 (0.65–1.15)	0.162
INTORSECT[5]												
Sorafenib	2.8	33	61†	8	<1	8	3.9			16.6		
Temsirolimus	0	16	62†	8	0	8	4.3	0.87 (0.71–1.07)	0.19	12.3	1.31 (1.05–1.63)	0.01
AXIS[6,8]												
Sorafenib	8	52	NR	0.6	0	9	4.7			19.2		
Axitinib	4	31	NR	0	0	19	6.7	0.665 (0.544–0.812)	<0.0001	20.1	0.97 (0.8–1.17)	0.37
METEOR[9]												
Everolimus	10	25	58†	8	0	5	3.8			NC		
Cabozantinib	9	60	68†	7	0	21	7.4	0.58 (0.45–0.75)	<0.001	NC	0.67 (0.51–0.89)	0.005‡
CheckMate 025[10]												
Everolimus	13	26	37§	0.5	<1	5	4.4			19.6		
Nivolumab	8	0¶	19§	0	1	25	4.6	0.88 (0.75–1.03)	0.11	25.0	0.73 (0.57–0.93)	0.002

* CI denotes confidence interval, NC not calculated (end point not reached), and NR not reported.
† Value reflects all cases of grade 3 or 4 toxic effects.
‡ The result was nonsignificant at the time of analysis.
§ Value reflects cases of treatment-related grade 3 or 4 toxic effects.
¶ Dose reduction was not permitted.

to which a fixed proportion of patients (20 to 25%) have a response. Patients who have a response may represent a prevalent "immune-responsive" subset of patients who benefit from either cytokines or checkpoint inhibitors. Actionable immunologic drivers of renal-cell cancer response are not clear. In other tumors, PD-1 ligand 1 (PD-L1) expression, in tumor cells or infiltrating immune cells, is associated with benefit from PD-1 or PD-L1 inhibitors. Unfortunately, PD-L1 expression in renal-cell cancer tissue did not delineate the patients who were more likely to benefit. Alternative immunologic signatures, such as the number of immunogenic mutations, may be associated with efficacy and survival, but they require prospective validation.[13] In addition, the most effective duration of therapy with nivolumab and whether the therapy should continue beyond progression remains unknown. For cabozantinib, it is uncertain whether the inhibition of MET, RET, or AXL drives clinical activity or whether the benefit is simply due to a VEGFR-inhibitory effect.[12]

What does the addition of nivolumab and cabozantinib to the therapeutic armamentarium for previously treated advanced renal-cell cancer mean for the practicing clinician? Given the overall survival advantage it confers and its relatively good side-effect profile, nivolumab is the choice for patients who have disease progression while they are receiving VEGF-targeted therapy (Table 1). Cabozantinib is a salvage treatment for patients whose tumors progress during VEGF therapy; however, without a significant overall survival benefit and with significant side effects necessitating dose reduction in 60% or more of patients, it will not precede nivolumab in the therapeutic sequence. Cabozantinib will compete with other VEGFR inhibitors as third-line or later therapy.[5,6,8] Trials comparing cabozantinib with other VEGF-targeted therapies are much needed; a randomized phase 2 trial of sunitinib versus cabozantinib will provide this, albeit in the context of first-line therapy (ClinicalTrials.gov number, NCT01835158).

Finally, there is the practical question of whether these new therapies provide sufficient value in resource-constrained health care environments. New cancer treatments are typically marketed at a price that most patients cannot afford without insurance. In the United States, federally funded programs cover approximately 50% of patients with advanced renal-cell cancer. We are obligated to ensure that medicines provide maximal therapeutic benefit with the fewest side effects and smallest fiscal burden. Currently, Medicare is unable to negotiate for the best terms across its entire patient base; this represents a contrivance of free-market economics that is in no one's best interest. Effective treatments will work only if they are accessible to the patients they are designed to help. Buried treasure and value must coexist.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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