RENAL CELL CARCINOMA TREATMENT REGIMENS (Part 1 of 2)

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

General treatment notes:[1]

- Targeted therapy using tyrosine kinase inhibitors and anti-vascular endothelial growth factor antibodies is now widely used as first- and second-line treatments in renal cell carcinoma (RCC). To date, seven such agents have been approved by the FDA for the treatment of advanced RCC: axitinib, bevacizumab with or without interferon (IFN), everolimus, pazopanib, sorafinib, sunitinib, and temsirolimus.
- Prior to targeted therapies, systemic treatment options were limited to cytokine therapy, notably IL-2 and interferon-α-2A (IFN-α-2a).

First-line Therapy for Patients with Predominantly Clear Cell Histology[1]

Note: All recommendations are Category 2A unless otherwise indicated.

REGIMEN	DOSING
Sunitinib (Category 1)[2,3]	Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off.
Temsirolimus (Category 1: poor-prognosis patients; Category 2B: selected patients of other risk groups)[4,5]	Temsirolimus 25mg IV over 30–60 minutes once weekly until disease progression or unacceptable toxicity.
Bevacizumab + IFN-α (Category 1)[6-8]	Bevacizumab 10mg/kg IV every 2 weeks + IFN-α.
Pazopanib (Category 1)[9,10]	Pazopanib 800mg orally once daily without food.
High-dose IL-2 (for selected patients with excellent performance status and normal organ function)[11,12‡]	**Days 1–5 and 15–19:** IL-2 600,000 IU/kg IV every 8 hours (max 14 doses). Repeat cycle every 4 weeks for max 3 cycles.
Axitinib[13,14*]	Axitinib 5mg orally every 12 hours.
Sorafenib[15†]	Sorafenib 400mg orally twice daily without food.

Subsequent Therapy for Patients with Predominantly Clear Cell Carcinoma[1]

High-dose IL-2[11,12‡]	**Days 1–5 and 15–19:** IL-2 600,000 IU/kg IV every 8 hours (max 14 doses). Repeat cycle every 4 weeks for max 3 cycles.
After Tyrosine Kinase Inhibitor Therapy	
Axitinib (Category 1)[13,14*]	Axitinib 5mg orally every 12 hours.
Cabozantinib (Category 1)[16§]	Cabozantinib 60mg orally once daily without food until disease progression or unacceptable toxicity.
Nivolumab (Category 1)[17,18]	Nivolumab 3mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.
Everolimus (Category 1)[19,20]	Everolimus 10mg orally once daily with or without food.
Sorafenib[21-24]	Sorafenib 400mg orally twice daily without food.
Sunitinib[2,25,26]	Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off.
Pazopanib[9,10]	Pazopanib 800mg orally once daily without food.
Temsirolimus (Category 2B)[27,28]	Temsirolimus 25mg IV over 30-60 minutes weekly until disease progression or unacceptable toxicity.
Bevacizumab (Category 2B)[29]	Bevacizumab 10mg/kg IV every 2 weeks.
After Cytokine Therapy	
Axitinib (Category 1)[13,14*]	Axitinib 5mg orally every 12 hours.
Sorafenib (Category 1)[21-24]	Sorafenib 400mg orally twice daily without food.
Sunitinib (Category 1)[2,25,26]	Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off.
Pazopanib (Category 1)[9,10]	Pazopanib 800mg orally once daily without food.
Temsirolimus[27,28]	Temsirolimus 25mg IV over 30-60 minutes weekly until disease progression or unacceptable toxicity.
Bevacizumab[29]	Bevacizumab 10mg/kg IV every 2 weeks.

continued

RENAL CELL CARCINOMA TREATMENT REGIMENS (Part 2 of 2)

Systemic Therapy for Patients with Non-Clear Cell Histology[1]

REGIMEN	DOSING
Temsirolimus (Category 1: poor-prognosis patients; Category 2A: selected patients of other risk groups)[27,28]	Temsirolimus 25mg IV over 30–60 minutes weekly until disease progression or unacceptable toxicity.
Sorafenib[21-24]	Sorafenib 400mg orally twice daily without food.
Sunitinib[2,25,26]	Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off.
Pazopanib[9,10]	Pazopanib 800mg orally once daily without food.
Axitinib[13,14]*	Axitinib 5mg orally every 12 hours.
Everolimus[19,20]	Everolimus 10mg orally once daily with or without food.
Bevacizumab[29]	Bevacizumab 10mg/kg IV every 2 weeks.
Erlotinib[30]¶	Erlotinib 150mg orally once daily without food.

* May increase to 7mg every 12 hours after 2 weeks based on criteria; may increase to 10mg every 12 hours after 2 weeks based on criteria.

† Patients who progressed were dose-escalated to 600 mg twice daily.

‡ Treatments divided into 60-day courses, with each IV treatment course consisting of 2 cycles of therapy, separated by approximately 7–10 days of rest with no other therapy during the remainder of the 60 days.

§ Cabozantinib has not yet been approved by the FDA in RCC, but it received breakthrough designation for this indication in August 2015. The NCCN recommendation is based on data from phase III trials, which suggest that eligible patients should preferentially receive cabozantinib over everolimus.

¶ Erlotinib is used off-label for RCC. The NCCN guidelines include it as an optional first-line therapy for patients with relapsed or medically unresectable stage IV non-clear cell carcinoma.

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology™. Kidney. v 2.2016. Available at: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed January 2, 2016.
2. Sutent [package insert]. New York, NY: Pfizer Labs; 2015.
3. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol*. 2009;10:757–763.
4. Torisel [package insert]. Philadelphia, PA: Wyeth; 2015.
5. Hudes G, Carducci M, Tomczak P, et al; Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356:2271–2281.
6. Avastin [package insert]. San Francisco, CA: Genentech; 2015.
7. Escudier B, Pluzanska A, Koralewski P, et al; AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*. 2007;370:2103–2111.
8. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol*. 2010;28:2137–2143.
9. Votrient [package insert]. Research Triangle Park, NC: GSK; 2014.
10. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061–1068.
11. Proleukin [package insert]. San Diego, CA: Prometheus Laboratories; 2015.
12. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23:133–141.
13. Inlyta [package insert]. New York, NY: Pfizer Inc; 2014.
14. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomized phase 3 trial. *Lancet*. 2011;378:1931–1939.
15. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27(8):1280–1289.
16. Choueiri TK, Escudier B, Powles T, et al; METEOR Investigators. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1814–1823.
17. Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803–1813.
18. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.
19. Afinitor [package insert]. East Hanover, NJ: Novartis; 2015.
20. Motzer RJ, Escudier B, Oudard S, et al; RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372:449–456.
21. Nexavar [package insert]. Wayne, NJ: Bayer HealthCare; 2015.
22. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear cell renal-cell carcinoma. *N Engl J Med*. 2007;356:125–134.
23. Di Lorenzo G, Carteni G, Autorino R, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. *J Clin Oncol*. 2009;27:4469–4474.
24. Garcia JA, Hutson TE, Elson P, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. *Cancer*. 2010;116:5383–5390.
25. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24:16–24.
26. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA*. 2006;295:2516–2524.
27. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol*. 2004;22:909–918.
28. Hutson TE, Escudier B, Esteban E, et al. Temsirolimus vs Sorafenib as Second Line Therapy in Metastatic Renal Cell Carcinoma: Results from the INTORSECT Trial [abstract]. *Ann Oncol*. 2012;23:Abstract: LBA22.
29. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody,for metastatic renal cancer. *N Engl J Med*. 2003;349:427–434.
30. Gordon MS, Hussey M, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. *J Clin Oncol*. 2009;27:5788–5793.

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