Prognostic and Predictive Markers in Metastatic Renal Cell Carcinoma

Khattak, Muhammad A.; Bakr, Farrah; Krzystanek, Marcin; Szallasi, Zoltan Imre; Gerlinger, Marco; Santos, Claudio; Swanton, Charles; Pickering, Lisa M.; Gore, Martin E.; Larkin, James M.G.

Published in:
Journal of Clinical Oncology

Link to article, DOI:
[10.1200/JCO.2012.46.9353](https://doi.org/10.1200/JCO.2012.46.9353)

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Khattak, M. A., Bakr, F., Krzystanek, M., Szallasi, Z. I., Gerlinger, M., Santos, C., Swanton, C., Pickering, L. M., Gore, M. E., & Larkin, J. M. G. (2013). Prognostic and Predictive Markers in Metastatic Renal Cell Carcinoma. *Journal of Clinical Oncology*, 31(7), 20971-972. <https://doi.org/10.1200/JCO.2012.46.9353>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Prognostic and Predictive Markers in Metastatic Renal Cell Carcinoma

TO THE EDITOR: Significant progress in systemic therapy of metastatic renal cell carcinoma (mRCC) has been made over the last 5 years, with a plethora of targeted agents currently approved in different clinical settings. However, not all mRCC patients respond to treatment with these drugs and currently there are no validated biomarkers to predict clinical outcome. We therefore read with interest Armstrong et al's¹ report of the prognostic and predictive significance of baseline serum lactate dehydrogenase (LDH) in patients with intermediate- and poor risk mRCC treated in a first-line trial of the mammalian target of rapamycin (mTOR) inhibitor temsirolimus, interferon- α , or both in combination. As expected, in multivariate analysis, overall survival (OS) was significantly shorter in patients with LDH more than $1 \times$ the upper limit of normal (ULN) compared with patients with LDH $\leq 1 \times$ ULN at baseline. The importance of a high baseline LDH as a predictor of response to temsirolimus was also examined: in patients with LDH more than ULN, median OS with temsirolimus was 6.9 months versus 4.2 months with interferon- α (hazard ratio, 0.56; 95% CI, 0.38 to 0.81; $P = .002$). There was no difference in risk of death between temsirolimus and interferon- α treatment in patients with normal LDH. However, patients with an elevated LDH in this trial were more likely to be of poor risk by Motzer criteria and it is unlikely that interferon- α provided any benefit in this group² and, given the associated toxicity, it may even have been detrimental. Survival comparisons between temsirolimus and interferon- α should therefore be viewed with caution.

The prognostic impact of baseline LDH was evaluated in the RECORD-1 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily) trial of the mTOR inhibitor everolimus in mRCC refractory to anti-vascular endothelial growth factor (VEGF) therapy.³ High LDH was found to be prognostic for OS, but not progression free survival (PFS) in univariate analysis, but it was not included in the final model of multivariate analysis because of its nonlinear effect. High pretreatment LDH is however a prognostic marker for both PFS and OS in the first-line setting during treatment with the VEGF receptor tyrosine kinase inhibitor sunitinib and interferon- α in predominantly good or intermediate risk (93%) mRCC⁴ as well as for OS in the sunitinib-refractory setting during treatment with the VEGF receptor tyrosine kinase inhibitor axitinib.⁵ To examine further the relationship between prognosis and LDH during everolimus therapy, we evaluated all patients with mRCC from our institutional database treated with inhibitor everolimus ($n = 57$) after failure of prior anti-VEGF therapy. The majority of patients (78%) were of good or intermediate risk. We found a high baseline LDH to be prognostic for OS, similar to Armstrong et al's results¹; the median OS of patients with a normal LDH in our series was 8.6 months compared with 6.2 months for those with an LDH of more than ULN (hazard ratio, 1.71; 95% CI, 0.99 to 2.96; log-rank $P = .05$). We could not evaluate the predictive effect of baseline LDH owing to a lack of a comparator arm; the retrospective

nature and small single-institution sample size are limitations of this analysis.

Finally, hypertension is commonly associated with anti-VEGF therapy and appears to be a class effect. The incidence of all-grade hypertension ranges between 22% and 55% in various studies with these agents.⁶⁻¹⁰ Data suggest that hypertension secondary to treatment with sunitinib is associated with improvement in clinical outcomes (objective response rate, PFS, and OS)¹¹ and similar results have been observed with other anti-VEGF agents.^{12,13} mTOR inhibitors may also have antiangiogenic activity,¹⁴ and treatment-emergent hypertension has been observed as a consequence of treatment with non-VEGF therapy (eg, cytotoxic agents in non-small-lung cancer in which it has been found to be prognostic but not predictive of differential outcome).¹⁵ Therefore, it would be interesting to know from the data set reported by Armstrong et al¹ whether the development of hypertension correlated with survival on therapy or correlated with baseline LDH.

In conclusion, the results of the study by Armstrong et al¹ are encouraging and indicate progress toward predicting the clinical outcome of mRCC patients treated with a targeted agent. However, further corroboration of these findings is needed to establish their relevance for clinical practice.

Muhammad A. Khattak and Farrah Bakr

Royal Marsden National Health Service Foundation Trust, London, United Kingdom

Marcin Krzystanek

Technical University of Denmark, Lyngby, Denmark

Zoltan Szallasi

Technical University of Denmark, Lyngby, Denmark; Harvard Medical School, Boston, MA

Marco Gerlinger, Claudio Santos, and Charles Swanton

Cancer Research UK, London Research Institute, London, United Kingdom

Lisa M. Pickering, Martin E. Gore, and James M.G. Larkin

Royal Marsden National Health Service Foundation Trust, London, United Kingdom

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory**

Role: Lisa M. Pickering, Pfizer (C), Novartis (C), Astellas (C); Martin E. Gore, Roche (C), Pfizer (C), Bristol-Myers Squibb (C), Novartis (C), GlaxoSmithKline (C), Aveo (C); James M.G. Larkin, Pfizer (C), Novartis (C), Bristol-Myers Squibb (C), Roche (C), Aveo (C) **Stock Ownership:** None **Honoraria:** Lisa M. Pickering, Pfizer, GlaxoSmithKline, Novartis; Martin E. Gore, Pfizer, GlaxoSmithKline, Novartis, Bristol-Myers

Squibb, Roche, Aveo; James M.G. Larkin, Pfizer, Roche, Bristol-Myers Squibb, Novartis **Research Funding:** Charles Swanton, Bayer, Novartis; Marco Gerlinger, Bayer, Novartis; Lisa M. Pickering, Pfizer; James M.G. Larkin, Pfizer, Bayer, Novartis **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

1. Armstrong AJ, George DJ, Halabi S: Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin. *J Clin Oncol* 30:3402-3407, 2012
2. Negrier S, Perol D, Ravaud A, et al: Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: Results of a randomized controlled trial. *Cancer* 110:2468-2477, 2007
3. Motzer RJ, Escudier B, Oudard S, et al: Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. *Cancer* 116:4256-4265, 2010
4. Patil S, Figlin RA, Hutson TE, et al: Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. *Ann Oncol* 22:295-300, 2011
5. Motzer R, Escudier B, Tomczak P, et al: Axitinib versus sorafenib for advanced renal cell carcinoma: Phase III overall survival results and analysis of prognostic factors. European Society of Medical Oncology Congress, Vienna, Austria, September 28-October 2, 2012 (abstr 793)
6. Humphreys BD, Atkins MB: Rapid development of hypertension by sorafenib: Toxicity or target? *Clin Cancer Res* 15:5947-5949, 2009
7. Rixe O, Bukowski RM, Michaelson MD, et al: Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: A phase II study. *Lancet Oncol* 8:975-984, 2007
8. Wu S, Chen JJ, Kudelka A, et al: Incidence and risk of hypertension with sorafenib in patients with cancer: A systematic review and meta-analysis. *Lancet Oncol* 9:117-123, 2008
9. Zhu X, Stergiopoulos K, Wu S: Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: Systematic review and meta-analysis. *Acta Oncol* 48:9-17, 2009
10. Zhu X, Wu S, Dahut WL, et al: Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: Systematic review and meta-analysis. *Am J Kidney Dis* 49:186-193, 2007
11. Rini BI, Cohen DP, Lu DR, et al: Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 103:763-773, 2011
12. Bhargava P, Esteves B, Al-Adhami M, et al: Effect of hypertension, nephrectomy, and prior treatment on the efficacy of tivozanib (AV-951) in a phase II randomized discontinuation trial (RDT) in patients with renal cell carcinoma (RCC). Genitourinary Cancers Symposium, San Francisco, CA, March 5-7, 2010 (abstr 342)
13. Rixe O, Dutcher J, Motzer R, et al: Diastolic blood pressure (dbP) and pharmacokinetics (PK) as predictors of axitinib efficacy in metastatic renal cell cancer (mRCC). *J Clin Oncol* 27:245s, 2009 (abstr 5045)
14. Lane HA, Wood JM, McSheehy PM, et al: mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. *Clin Cancer Res* 15:1612-1622, 2009
15. Goodwin R, Ding K, Seymour L, et al: Treatment-emergent hypertension and outcomes in patients with advanced non-small-cell lung cancer receiving chemotherapy with or without the vascular endothelial growth factor receptor inhibitor cediranib: NCIC Clinical Trials Group Study BR24. *Ann Oncol* 21:2220-2226, 2010

DOI: 10.1200/JCO.2012.46.9353; published online ahead of print at www.jco.org on January 7, 2013