Biomarkers for tyrosine kinase inhibitors in renal cell cancer

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Introduction

Renal cell carcinoma (RCC) is a common malignancy. In 2012, in the USA, there were 65,000 new cases and 13,500 disease-specific deaths. In the same year it was the 6th most common new cancer diagnosed (1). During the last 50 years, despite an increase in incidence, the mortality has fallen, a possible result of earlier detection and improvements in therapy (2).

Traditionally, renal cell cancer has proven refractory to cytotoxic therapies, and for many years immunotherapy was the standard of care, even though it was not particularly effective. Over the past decade, the molecular biology behind renal cancer development has been better understood and subsequently a number of targets have been identified for potential therapies (3).

Mutations in the tumour suppressor Von Hippel-Landau (VHL) gene are responsible for the majority of cases of sporadic clear cell renal cell carcinoma. VHL mutations result in aberrant binding of hypoxia-inducible factor 1 (HIF1) subunits which translocate to the cell nucleus and result in transcriptional activation of a number of factors necessary for angiogenesis, including the vascular endothelial growth factor (VEGF) (4). Efforts directed towards inhibiting neoplastic neoangiogenesis, via the VEGF or the mammalian target of rapamycin (mTOR) pathways (5), have yielded positive results with clinical benefit.

To date, four tyrosine kinase inhibitors (TKI’s) have been shown to benefit patients in phase III randomized controlled trials: sunitinib (6), sorafenib (7), pazopanib (8) and axitinib (9). Similarly, randomized data has also supported the use of the mTOR inhibitors temsirolimus (10) and everolimus (11). Despite these encouraging data, improvements in progression free survival (PFS) and overall survival (OS) have been measured in months, and not all patients have benefited uniformly.

Hence a need exists to develop robust biomarkers for renal cancer that will help direct therapy in patients destined to do either very well or poorly.

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (12). Biomarkers serve an important role in oncology. They can assist in diagnosis, screening, prognosticating and as measures of response to certain therapies (4,13). A prognostic biomarker is able to estimate the chance of disease recurrence or death, regardless of any intervention (14). Conversely, a predictive factor is one which assists in predicting the probability of a response to a certain therapy (4). Predictive markers can provide information about the effect of a particular treatment, or serve as a target of a particular intervention (14). Identifying predictive biomarkers can therefore identify patients most likely to benefit from certain treatments. This maximizes efficacy and minimizes unnecessary exposure of patients to toxic therapies for which they are destined to derive no benefit.

As the molecular understanding of the pathogenesis of renal cell carcinoma has grown, a number of potential predictive markers have become apparent. In this review, we describe the predictive factors related to each of the tyrosine kinase inhibitors that are presently available for the treatment of metastatic renal cell carcinoma. Due to space constraints, we will consider only molecular biomarkers.

Sunitinib

Sunitinib is an tyrosine kinase inhibitor targeting VEGF receptors-1, -2, -3, platelet-derived growth factors, KIT, FLT-3, colony-stimulating factor-1 receptor and RET (15). The pivotal phase III trial of treatment-naive patients
with metastatic RCC showed significant improvements in response rate, progression-free and overall survival (16) with similar results confirmed in an expanded-access trial of over 4,000 patients (17). However, not all patients respond to sunitinib and some develop significant toxicities resulting in dose delays, reductions or discontinuations. There is emerging evidence for the importance of maintaining sunitinib exposure in maximising efficacy (18), and therefore potential biomarkers are needed to identify patients who will most likely benefit or develop significant toxicities.

Single nucleotide polymorphisms (SNPs) have been investigated as potential biomarkers, particularly in angiogenesis and drug metabolising genes such as CYP3A4. In a prospective pharmacogenomic study of 101 patients with advanced clear cell RCC, Garcia-Donas and colleagues (19) reported two VEGFR3 missense polymorphisms (rs307826 and rs307821) that were associated with a reduced PFS with sunitinib use (HR 3.57 and 3.31 respectively). The authors also discovered that the CYP3A5*1 (rs776746) high metabolising allele was associated with increased dose reductions due to toxicity (HR 3.75). Several smaller studies have reported associations between genetic variants in VEGF and VEGFR2 (20), CYP3A4, NR113 and ABCB1 genes (21) and outcomes. A large prospective multinational trial, of which 75% of the 219 enrolled patients had metastatic renal cell carcinoma, identified variants in CYP1A1, ABCB1, ABCG2, NR113, VEGFR2 and FLT3 genes that were associated with toxicity from treatment with sunitinib (22). A retrospective study of 135 patients (65 who received sunitinib) examined the associations between four molecular markers (HIF-1α, CAIX, PTEN and p21) determined by immunohistochemistry and outcomes from treatment. CAIX overexpression was associated with more responses to newer targeted agents (64.7% versus 21.1%). High PTEN and low P21 expression were associated with an improved response to sunitinib (23).

Several plasma markers have been investigated for their role in predicting clinical outcomes, including those involved in angiogenesis such as VEGF and VEGF-related proteins, placental growth proteins, SDF-1, sVCAM-1 (24-28) and cytokines (29). Rini and colleagues [2008] reported the value of baseline sVEGFR-3 and sVEGF3, PDGF and SDF-1 between therapy leads to modulation of circulating proteins involved in angiogenesis such as VEGF and VEGF-C as potential biomarkers of PFS and RR (28). Several small prospective studies have shown that sunitinib therapy leads to modulation of circulating proteins involved in VEGF signaling. In these studies, significant changes in VEGF, sVEGFR-2, sVEGF3, PDGF and SDF-1 between baseline and either day 14 or 28 led to associations with RR, PFS and OS (24,26). TNF-alpha and MMP-9 were identified as potential biomarkers of sunitinib activity in a study of 31 patients. Five candidate cytokines (TNF-alpha, MMP-9, ICAM-1, BDNF and SDF-1) were evaluated and elevated levels of TNF-alpha and MMP-9 were associated with reduced PFS and OS (29).

Emerging evidence suggests that circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs) may be promising as potential biomarkers with sunitinib treatment. Several studies have examined the dynamics of CECs with sunitinib treatment, and suggested significant CEC increases during treatment represent the targeting of immature tumour vessels (30) and are associated with improved PFS (31). Conversely, Farace and colleagues [2011] found no association between baseline changes in CECs and PFS or OS (24). The role of CEPs are unclear, however studies have shown an increased recruitment of these cells and haematopoietic progenitor cells into the neangiogenic perivasculature, playing an important role in events necessary for tumour invasion and metastasis (24). Although promising, the reliability and sensitivity of measurements of CECs and CEPs using flow cytometry remains an issue and may limit its use in the research setting and application in clinical practice.

**Sorafenib**

Sorafenib is a tyrosine kinase inhibitor targeting serine/threonine kinase Raf-1 (Wilhelm et al., 2004) and VEGFR, platelet-derived growth factor receptor receptor β (PDGFR-β), c-KIT, RET, and FLT-3 (32,33). Sorafenib is able to directly affect tumor cell proliferation as well as angiogenesis (34).

A randomized Phase II study of sorafenib with or without interferon alfa-2b (35) showed no particular benefit of the combination, though it is likely the study was underpowered, as only 80 patients were randomized. Nevertheless, increased pAkt predicted for poorer progression-free survival and overall survival.

In the pivotal Phase III treatment approaches in renal cancer evaluation (TARGET) trial, 903 previously treated RCC patients were randomly assigned to sorafenib or placebo. In the final analysis reported by Escudier et al. (7), OS was not different between patients in the sorafenib or placebo arm, though when post cross-over effects were excluded, OS did continue to favour sorafenib (HR 0.78, P=0.029). In that study, baseline VEGF levels were prognostic for both PFS and OS. In a further subset
biomarker analysis of that study, a number of biological markers were found to be prognostic for survival: VEGF, carbonic anhydrase IX (CAIX), tissue inhibitor of metalloproteinase 1 (TIMP-1), and Ras p21 levels. Of these, only TIMP-1 was found to be independently prognostic in multivariate models (36). However, VHL mutational status was not related to sorafenib benefit.

**Pazopanib**

Pazopanib is an oral tyrosine kinase inhibitor that received FDA approval in 2009 for the treatment of metastatic renal cell carcinoma. It binds to VEGF receptor-1, -2 and -3, platelet derived growth factor (PDGF) receptor -α and -β and c-kit receptors (37). In a phase III study published in 2010, 435 patients with metastatic renal cell carcinoma, half of who had previously received cytokine treatment, were randomised to placebo or pazopanib. The pazopanib arm was associated with a superior progression free survival (9.2 vs. 4.2 months, P<0.0001) and a better overall response rate 30% vs. 3% (P<0.0001) (8).

Xu and colleagues (38) tested their hypothesis that genetic polymorphisms are associated with differing clinical responses to pazopanib. 27 polymorphisms, known to affect angiogenesis, metabolism or the mode of action of pazopanib were identified and retrospectively tested in 397 patients previously enrolled in pazopanib vs. placebo clinical trials. Polymorphisms in interleukin 8 (IL-8) and HIF1A were associated with a significantly poorer progression free survival compared to the wild type form (27 vs. 48 weeks, P=0.01 and 20 vs. 44 weeks, P=0.03 respectively). Inferior response rates were noted in patients expressing variant HIFA, NR1I2 and all three subsets of the VEGF gene. Similar associations between PFS and variant IL-8 and HIF1A were not seen in those patients treated with placebo, and hence these polymorphisms were considered to be predictive biomarkers.

These findings have biological merit; IL-8 is up regulated in murine models exposed to another TKI, sunitinib, and provides an alternative pathway to angiogenesis and drug resistance (39). Variant forms of HIF1A are known to provide endothelial cells with a greater capacity for angiogenesis (40), and ability to overcome the antineoplastic activity of pazopanib.

Recently, Tran et al. (41) examined the predictive and prognostic utility of circulating cytokine and angiogenic factors (CAF's) in patients with metastatic renal cell carcinoma treated with pazopanib. A small number of biomarkers were selected and then determined in stored serum from patients involved in the earlier pazopanib phase II and III clinical trials. Using a systematic process, these biomarkers were tested in the phase II study, and then validated in the larger phase III trial. Although high concentrations of IL-6, IL-8 and osteopontin were prognostic, only IL-6 demonstrated greater benefit relative to placebo. In the placebo arm, an elevated level of IL-6 above the median (relative to below the median) was associated with a statistically superior PFS of 9.9 vs. 24 months (P<0.0001). Although a difference also existed in the pazopanib group, it was no longer statistically significant (33 vs. 42 months, P=0.445). The authors concluded that high levels of IL-6 were predictive of PFS benefit with pazopanib. Similar results were not noted for overall survival, a likely consequence of the high level of cross over in the original phase III trial.

Aiming to validate these findings, Liu et al. (42) retrospectively re-tested a selection of biomarkers from patients in the original phase III trial and again found IL-6 to be predictive of an improved PFS in patients treated with pazopanib. IL-6 has been described as an independent predictor of poorer survival in metastatic renal cancer as early as 2004 (43) and has also been implicated in the paraneoplastic manifestations of the disease, including fever, weight loss and anaemia (44).

In a retrospective study presented in an abstract form in 2008, low levels of serumVEGF-2 correlated with response rate in patients with metastatic renal cell cancer treated with pazopanib (45). In a separate pre-clinical study, a nuclear medicine tracer linked the VEGF receptor was shown to provide evidence for early tumour regression in murine models treated with pazopanib (46). Such a tracer may allow for an immediate assessment of anti-tumour efficacy and provide much more timely information than standard radiological evaluation. The lack of a placebo control in these two studies make it difficult to conclude that these biomarkers are indeed predictive for outcome.

**Temsirolimus and everolimus**

The mammalian target of rapamycin (mTOR) pathway has become a successful target for two new FDA approved agents in renal cancer, Temsirolimus and Everolimus. Two Phase III trials have established a benefit of these agents either used first line in poor risk patients or following treatment with a tyrosine kinase inhibitor (10,47).

The advanced renal cell carcinoma (ACRR) trial
randomized treatment-naive patients to temsirolimus, interferon-α (IFN) or a combination. Patients receiving temsirolimus alone experienced a progression free survival and overall survival benefit compared to IFN-α or the combination arm (10). Tumour samples in this study were assessed using immunohistochemistry for a range of potential molecular markers including HIF1α, HIF2α, phosphorylated Akt (pAkt) and phosphatase and tensin homolog (PTEN). In the single treatment arms, data was assessed in only 50% of patients for HIF1α and PTEN and not at all for pAKT and HIF2α. Neither baseline PTEN nor HIF1α levels were found to be of predictive value (48). In an explanation for this, the authors cited a number of logistical issues (poor tissue availability and an inability of immunohistochemistry to detect subtle biomarker quantities), which made this type of analysis difficult to perform.

Cho et al. assessed baseline levels of carbonic anhydrase IX (CAIX), phosphorylated S6 (pS6), pAkt and PTEN in tumour specimens from 20 patients receiving temsirolimus in a phase II trial. Patients with increased expression of pS6 were more likely to have a clinical response. Although a similar trend was found for pAkt, this did not reach statistical significance (49). These biomarkers deserve further study to establish if they are of predictive value in patients receiving treatment with an mTOR inhibitor.

Lactate dehydrogenase (LDH) has prognostic significance in RCC. Elevated levels of LDH are associated with reduced OS, and as such are widely incorporated into prognostic models (50-52). Retrospective analysis of the ARCC trial found that pretreatment LDH levels (>1× upper limit of normal (ULN)) were associated with an adjusted hazard ratio (HR) for death of 2.81 (P<0.001). For patients with an elevated LDH (>1× ULN), OS was improved in the patients receiving temsirolimus compared to IFNα with a HR for death of 0.56 (P=0.002) with no difference found in patients with a low LDH (53).

Axitinib

Axitinib is an oral tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptors (VEGF) 1, 2 and 3 (54). It binds with increased affinity to VEGF-2, thereby differentiating it from other TKIs (55). In addition to activity in renal cell cancer, Axitinib has demonstrated efficacy in thyroid, breast, non-small-cell lung cancer cancer (56-58). The phase III AXIS trial randomized 723 previously treated patients to either Axitinib or Sorafenib (9). Axitinib was associated with a PFS benefit of 6.7 vs. 4.7 months (P<0.0001) and was subsequently approved by the FDA in early 2012. The role of Axitinib as a second line therapeutic option however, is not clearly defined given the positive results of everolimus also in the second line setting (47).

Given its relatively recent history, there are comparatively few published studies regarding predictive molecular biomarkers for axitinib. In a phase I study conducted by Mukohara et al. (59), 12 patients were administered Axitinib in escalating doses. Axitinib exposure correlated inversely with the concentration of soluble growth factor receptor 2 (s-VEGFR2), This observation appeared to be a function of drug concentration and was not predictive of efficacy. The association between s-VEGF2 and Axitinib was further explored in a phase I study conducted by Tomita et al. (60). A PFS benefit existed for those patients with s-VEGF-2 concentrations below the median (13 vs. 9 months, P=0.01). Although these results were interesting, this trial was not placebo controlled, and therefore could not conclusively prove that s-VEGF2 is a predictive marker.

Conclusions

At the present time there is no prospectively validated predictive or prognostic biomarker to help guide treatment selection decisions for which patients might most benefit from therapy with one tyrosine kinase inhibitor over another. While there are several candidate markers that deserve further investigation, there needs to be an increased focus on incorporation of biomarker assessment into large prospective clinical trials if we are to understand the clinical significance of these biomarkers. Even so, the collection of biomarker samples based on convenience leads to difficulty in interpretation of results. Ideally, the best biomarkers should be defined upfront and clinical trials of therapy designed around them in order to build on their utility.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012.
CA Cancer J Clin 2012;62:10-29.
2. Pantuck AJ, Zisman A, Beldegrun AS. The changing natural history of renal cell carcinoma. J Urol 2001;166:1611-23.
3. Brugarolas J. Renal-cell carcinoma--molecular pathways and therapies. N Engl J Med 2007;356:185-7.
4. Vickers MM, Heng DY. Prognostic and predictive biomarkers in renal cell carcinoma. Target Oncol 2010;5:85-94.
5. Atkins MB. Management of advanced renal cancer. Kidney Int 2005;67:2069-82.
6. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.
7. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for advanced renal cell cancer. N Engl J Med 2007;356:2271-81.
8. 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;28:1061-8.
9. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011;378:1931-9.
10. Hudes G, Carducci M, Tomczak P, et al. Sunitinib for metastatic renal-cell carcinoma. J Clin Oncol 2007;25:1271-83.
11. Motzer RJ, Escudier B, Oudard S, et al. Sunitinib versus interferon alfa in patients with metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer 2010;116:4256-65.
12. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95.
13. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem 2008;54:e11-79.
14. Oldenhuis CN, Oosting SF, Gietema JA, et al. Prognostic versus predictive value of biomarkers in oncology. Eur J Cancer 2008;44:946-53.
15. Garcia-Donas J, Esteban E, Leandro-Garcia LJ, et al. Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. Lancet Oncol 2011;12:1143-50.
16. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584-90.
17. Gore ME, Szczyzik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009;10:757-63.
18. Houk BE, Bello CL, Poland B, et al. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. Cancer Chemother Pharmacol 2010;66:357-71.
19. Garcia-Donas J, Esteban E, Leandro-García LJ, et al. Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. Lancet Oncol 2011;12:1143-50.
20. Kim JJ, Vaziri SA, Rini BI, et al. Association of VEGF and VEGFR2 single nucleotide polymorphisms with hypertension and clinical outcome in metastatic clear cell renal cell carcinoma patients treated with sunitinib. Cancer 2012;118:1946-54.
21. van der Veldt AA, Eechoute K, Gelderblom H, et al. Genetic polymorphisms associated with a prolonged progression-free survival in patients with metastatic renal cell cancer treated with sunitinib. Clin Cancer Res 2011;17:620-9.
22. van Erp NP, Eechoute K, van der Veldt AA, et al. Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J Clin Oncol 2009;27:4406-12.
23. Muriel López C, Esteban E, Astudillo A, et al. Predictive factors for response to treatment in patients with advanced renal cell carcinoma. Invest New Drugs 2012;30:2443-9.
24. Farace F, Gross-Goupil M, Tournay E, et al. Levels of circulating CD45(dim)CD34(+)VEGFR2(+) progenitor cells correlate with outcome in metastatic renal cell carcinoma patients treated with tyrosine kinase inhibitors. Br J Cancer 2011;104:1144-50.
25. Porta C, Paglino C, De Amici M, et al. Predictive value of baseline serum vascular endothelial growth factor and neutrophil gelatinase-associated lipocalin in advanced kidney cancer patients receiving sunitinib. Kidney Int 2010;77:809-15.
26. Deprimo SE, Bello CL, Smeraglia J, et al. Circulating protein biomarkers of pharmacodynamic activity of sunitinib in patients with metastatic renal cell carcinoma: modulation of VEGF and VEGF-related proteins. J Transl Med 2007;5:32.
27. Kontovinis LF, Papazisis KT, Touplikioti P, et al. Sunitinib treatment for patients with clear-cell metastatic renal cell carcinoma: clinical outcomes and plasma angiogenesis markers. BMC Cancer 2009;9:82.

28. Rini BI, Michaelson MD, Rosenberg JE, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. J Clin Oncol 2008;26:3743-8.

29. Perez-Gracia JL, Prior C, Guillén-Grima F, et al. Identification of TNF-alpha and MMP-9 as potential baseline predictive serum markers of sunitinib activity in patients with renal cell carcinoma using a human cytokine array. Br J Cancer 2009;101:1876-83.

30. Vroeling L, van der Veldt AA, de Haas RR, et al. Increased numbers of small circulating endothelial cells in renal cell cancer patients treated with sunitinib. Angiogenesis 2009;12:69-79.

31. Gruenwald V, Beutel G, Schuch-Jantsch S, et al. Circulating endothelial cells are an early predictor in renal cell carcinoma for tumor response to sunitinib. BMC Cancer 2010;10:695.

32. Wilhelm S, Carter C, Lynch M, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 2006;5:835-44.

33. Carlomagno F, Anaganti S, Guida T, et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst 2006;98:326-34.

34. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099-109.

35. Jonasch E, Corn P, Pagliaro LC, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low-dose interferon alfa in patients with advanced renal cell carcinoma: clinical and biomarker analysis. Cancer 2010;116:57-65.

36. Peña C, Lathia C, Shan M, et al. Biomarkers predicting outcome in patients with advanced renal cell carcinoma: Results from sorafenib phase III Treatment Approaches in Renal Cancer Global Evaluation Trial. Clin Cancer Res 2010;16:4853-63.

37. Ward JE, Stadler WM. Pazopanib in renal cell carcinoma. Clin Cancer Res 2010;16:5923-7.

38. Xu CF, Bing NX, Ball HA, et al. Pazopanib efficacy in renal cell carcinoma: evidence for predictive genetic markers in angiogenesis-related and exposure-related genes. J Clin Oncol 2011;29:2557-64.

39. Huang D, Ding Y, Zhou M, et al. Interleukin-8 mediates resistance to antiangiogenic agent sunitinib in renal cell carcinoma. Cancer Res 2010;70:1063-71.

40. Tanimoto K, Yoshiga K, Eguchi H, et al. Hypoxia-inducible factor-1alpha polymorphisms associated with enhanced transactivation capacity, implying clinical significance. Carcinogenesis 2003;24:1779-83.

41. Tran HT, Liu Y, Zurita AJ, et al. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. Lancet Oncol 2012;13:827-37.

42. Liu Y, Tran HT, Lin Y, et al. Plasma cytokine and angiogenic factors (CAFs) predictive of clinical benefit and prognosis in patients (Pts) with advanced or metastatic renal cell cancer (mRCC) treated in phase III trials of pazopanib (PAZO). J Clin Oncol 2012;29:abstr 334.

43. Negrer S, Perol D, Menetrier-Caux C, et al. Interleukin-6, interleukin-10, and vascular endothelial growth factor in metastatic renal cell carcinoma: prognostic value of interleukin-6—from the Groupe Francais d’Immunotherapie. J Clin Oncol 2004;22:2371-8.

44. Blay JY, Rossi JF, Wijdenes J, et al. Role of interleukin-6 in the paraneoplastic inflammatory syndrome associated with renal-cell carcinoma. Int J Cancer 1997;72:424-30.

45. Hutson TE, Davis ID, Machiels JH, et al. Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor. J Clin Oncol 2008;26:abstr 5046.

46. Blankenberg FG, Levashova Z, Sarkar SK, et al. Noninvasive assessment of tumor VEGF receptors in response to treatment with pazopanib: a molecular imaging study. Transl Oncol 2010;3:56-64.

47. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.

48. Figlin RA, de Souza P, McDermott D, et al. Analysis of PTEN and HIF-1alpha and correlation with efficacy in patients with advanced renal cell carcinoma treated with temsirolimus versus interferon-alpha. Cancer 2009;115:3651-60.

49. Cho D, Signoretti S, Dabora S, et al. Potential histologic and molecular predictors of response to temsirolimus in patients with advanced renal cell carcinoma. Clin Genitourin Cancer 2007;5:379-85.

50. Manola J, Royston P, Elson P, et al. Prognostic model for survival in patients with metastatic renal cell carcinoma: results from the international kidney cancer working group. Clin Cancer Res 2011;17:5443-50.

51. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors
for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004;22:454-63.
52. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530-40.
53. 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 2012;30:3402-7.
54. Hu-Lowe DD, Zou HY, Grazzini ML, et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res 2008;14:7272-83.
55. Carmichael C, Lau C, Josephson DY, et al. Comprehensive overview of axitinib development in solid malignancies: focus on metastatic renal cell carcinoma. Clin Adv Hematol Oncol 2012;10:307-14.
56. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol 2008;26:4708-13.
57. Rugo HS, Stopeck AT, Joy AA, et al. Randomized, placebo-controlled, double-blind, phase II study of axitinib plus docetaxel versus docetaxel plus placebo in patients with metastatic breast cancer. J Clin Oncol 2011;29:2459-65.
58. Schiller JH, Larson T, Ou SH, et al. Efficacy and safety of axitinib in patients with advanced non-small-cell lung cancer: results from a phase II study. J Clin Oncol 2009;27:3836-41.
59. Mukohara T, Nakajima H, Mukai H, et al. Effect of axitinib (AG-013736) on fatigue, thyroid-stimulating hormone, and biomarkers: a phase I study in Japanese patients. Cancer Sci 2010;101:963-8.
60. Tomita Y, Uemura H, Fujimoto H, et al. Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: a phase II study in Japanese patients with cytokine-refractory metastatic renal cell carcinoma. Eur J Cancer 2011;47:2592-602.

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