# Targeted therapy for metastatic renal cell carcinoma: Current treatment and future directions

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## ABSTRACT

Renal cell carcinoma (RCC) is the most common renal tumor and accounts for 3% of all adult cancers. The treatment of metastatic renal cell carcinoma (mRCC) has recently evolved from being a predominantly cytokine-based treatment to the use of targeted agents, which include Sorafenib, Sunitinib, Bevacizumab, Temsirolimus, Everolimus, Pazopanib, Axitinib, and most recently Tivozanib. Despite these advances mRCC remains a major health problem. Additional studies are needed to optimize the use of these agents in both advanced and early stage disease, either in combination or sequentially. In addition the development of biomarkers should be a priority in order to guide rational tailored development of emerging agents. This literature review was conducted using PubMed, Medline, and Cochrane databases for articles published until January 2013. Abstracts from relevant meeting of the American Society of Clinical Oncology and the European society of medical oncology were also included.

**Key words:** Mammalian target of rapamycin, renal cell carcinoma, targeted therapy, tyrosine-kinase inhibitor, vascular endothelial growth factor, von Hippel-Lindau

## INTRODUCTION

Renal cell carcinoma (RCC) is responsible for about 2-3% of all malignant diseases in adult.[1] As RCCs are generally resistant to chemo and radiotherapy, cytokine therapies were the standard of care despite limited clinical efficacy and significant toxicity.[2] However, a better understanding of the pathogenesis and tumor biology of sporadic RCC had led to the approval of 7 drug regimens by regulatory authorities in the United States and Europe: 4 oral multi-targeted tyrosine-kinase inhibitors (Sorafenib, Sunitinib, Pazopanib, and Axitinib), 2 inhibitors of the mammalian target of rapamycin (Temsirolimus and Everolimus), and 1 monoclonal antibody against the vascular endothelial growth factor (Bevacizumab).[3] Despite these advancements in treatment modalities, there are many limitations and durable complete responses remain elusive.

The objectives of this article are to review the clinical evidence supporting the benefits of these agents, to summarize the treatment guidelines, and to identify their limitations. Furthermore, future research directions with these targeted therapies are discussed.

## EPIDEMIOLOGY OF RCC

RCC is the most common renal tumor and accounts for 3% of all adult cancers.[1] The American Cancer Society estimated 64,77O new cases and 13,570 deaths from renal cancer in the united states in 2012.[4] The incidence and mortality of renal malignancies have been on the rise worldwide over the past years, particularly in the Western world. The reason for this increase is still unknown. Approximately 90% of renal tumors are RCC and 75% of these are clear cell tumors.[5] Papillary renal cell carcinoma is the second most common (15%); the Chromophobe and the Bellini duct histological subtype are less common. There is a 1.5:1 predominance in men over women, with peak incidence occurring between 60 and 70 years old. Identified etiological

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factors are mainly related to lifestyle: Smoking, obesity, and hypertension.[6,7] Several hereditary types of RCC also exist with VHL disease as the most common, it predisposes to clear cell carcinoma and other proliferative vascular lesions. The outcome of patients with mRCC is poor and factors influencing prognosis can be classified into anatomical, histological, clinical, and molecular.[8]

# MOLECULAR MECHANISMS UNDERLYING THE RENAL TUMORIGENESIS

The understanding of the biology behind mRCC has converged with the development of new drugs that target downstream effectors of VHL and HIF which have a central role in tumor angiogenesis and progression. Patients with VHL syndrome have an aberrant VHL allele on chromosome 3p25 which predisposes them to disease if the second allele is mutated. The majority of non-hereditary ccRCCs also exhibit VHL aberrations. Consequently, in patients with aberrant VHL, the alpha-subunits of HIF are accumulated freely without degradation even under normal oxygen conditions and leads to the transcription of a wide repertoire of genes, including VEGF, PDGF, and TGF. The HIFα are also regulated at the translational level by growth factors through the PI3K-AKT-mTOR signal transduction pathway.[9] Thus the elucidation of the VHL/HIF pathway has led to the successful evaluation and regulatory approval of agents targeting the VEGF and mTOR axes.

# AGENTS RECOMMENDED IN CURRENT TREATMENT REGIMENS

### VEGF ligand-directed therapy: Bevacizumab (+IFN-α)
Bevacizumab is an anti-VEGF monoclonal antibody which binds and neutralizes the circulating VEGF. Two trials contributed to bevacizumab and IFN-α combination's approval in first line setting. In AVOREN trial, PFS with bevacizumab plus IFN was 10.2 months versus 5.4 months in the placebo and IFN-α arm ($P = 0.001$).[10] In CALGB trial, PFS was 8.5 months with bevacizumab plus IFN versus 5.2 months with IFN-α alone ($P < 0.0001$).[11] Interim analysis of both trials showed a significantly longer PFS with the combination of bevacizumab and IFN-α compared with placebo and IFN-α, or IFN-α alone; but without statistically significant OS. This may be partly due to confounding because in AVOREN, patients were allowed to crossover to the double treatment group. Furthermore, the majority of patients who discontinued the trial received subsequent treatment. In CALGB 90206, although the crossover was not allowed, the post-trial analysis revealed that most patients in the IFN-α only arm received subsequent treatment.[12,13]

## VEGFR tyrosine kinase inhibitors
### Sunitinib
Sunitinib is an oral multikinase inhibitor that blocks VEGFR-1, 2, and 3, PDGFR-B and related RTKs. A pivotal phase III randomized controlled trial comparing first-line sunitinib with IFN, enrolled 750 patients, 94% of whom were favorable or intermediate risk MSKCC prognostic criteria. This trial demonstrated a statistically significant advantage in favor of sunitinib for ORR (39 versus 8%; $P < 0.000001$) and PFS which was the primary endpoint (11 months versus 5 months, $P < 0.001$).[14] The median OS of the sunitinib and IFN groups was 26.4 months and 21.8 months, respectively, which was of borderline statistical significance ($P = 0.051$); an analysis that accounted for crossover effects revealed significantly prolonged OS with sunitinib, compared with IFN-α (26.4 months versus 20.0 months, $P = 0.036$). Further analysis revealed that patients who did not receive treatment after the closing of the trial had doubled the median OS in the sunitinib group, compared with IFN-α (28.1 months versus 14.1 months, $P = 0.003$).[15] Because of these results, sunitinib has become a standard of care for the first-line treatment of mRCC.

### Sorafenib
Sorafenib is a dual-specificity multikinase inhibitor targeting signaling by VEGFRs, PDGFRs and raf, a member downstream of ras. Sorafenib was the first targeted agent to receive approval by the FDA shortly before sunitinib in December 2005. TARGET was a randomized, double-blind, phase III study of sorafenib treatment in patients who were refractory to cytokine therapy.[16] The Initial analysis of PFS was significantly prolonged with sorafenib in comparison with placebo (5.5 months versus 2.8 months, $P < 0.001$), regardless of MSKCC risk score, age, prior treatment or presence of metastases. Therefore, patients in the placebo group were allowed to cross over to the sorafenib arm. At the final analysis, median OS was 17.8 months with sorafenib and 15.2 months with placebo, but this did not reach statistical significance. However, in an analysis that accounted for crossover effects, median OS was significantly longer in the sorafenib group compared to placebo (17.8 month versus 14.3 months, $P = 0.0287$).

The common toxicities experienced with sorafenib are similar to sunitinib except that the hand-foot syndrome may be more pronounced and cardiotoxicity and fatigue appears to occur less frequently. Giving its acceptable safety profile, sorafenib is preconized for selected patients at risk of cardiac toxicity as well as older patients with reduced organ function.

### Pazopanib
Pazopanib is an oral angiogenesis inhibitor that has a higher selectivity and has a remarkable VEGFR-2 inhibitory

potential. A randomized, double-blind, placebo-controlled phase III trial assessed monotherapy with pazopanib in treatment-naïve patients, or patients who had been pretreated with cytokine therapy,[17] the median PFS in the entire cohort was 9.2 for the pazopanib-treated patients versus 4.2 months in the control group (*P* < 0.0000001). An interim analysis of OS revealed medians of 21.1 months and 18.7 months, respectively, (not statistically significant) but it should be noted that 48% of placebo patients crossed over to receive Pazopanib after progression which would dilute the OS effect. This superiority of PFS was sufficient for regulatory approval by the FDA in 2009. Recently the results of The COMPARZ trial which aimed to provide a direct comparison of sunitinib and pazopanib, indicated that the two drugs were similarly effective with a median PFS slightly more than 10 months for both. However, QOL questionnaires favoredpazopanib (Votrient) because of its safety profile.[18]

*Axitinib*
Axitinib is a small molecule multi-target TKI approved by the FDA in January 2012 as second line therapy for the treatment of mRCC after sunitinib or sorafenib failure. Previously, in the phase III AXIS trial the value and safety of Axitinib in second line was confirmed in 723 mRCC patients. An overall ORR of 19% and PFS of 6.7 months were achieved and they were significantly longer compared to sorafenib (PFS: 4, 7 months, ORR: 11% by investigator assessment).[19] We must note however that the trial was non-blinded and that patients without hypertension and with high tolerance in the axitinib group were allowed to increase their doses, whereas those in the sorafenib group were not. Concerning the OS of the axitinib and sorafenib it was 20.1 months and 19.2 months, respectively, which was not statistically significant (*P* = 0.3744).

As the long median PFS noted for axitinib after cytokine failure (12.1 versus 6.5 months) Bex and his colleagues proposed the use of axitinib in treatment-naïve mRCC.[20]

*Tivozanib*
Tivozanib is an oral, once-daily, selective inhibitor of the VEGF receptors 1, 2, and 3. In TIVO-1 trial, tivozanib demonstrated a statistically significant improvement in PFS of 11.9 months compared to 9.1 months for sorafenib in the overall study population (*P* = 0.042). Furthermore, Tivozanib demonstrated a significant improvement in PFS in the pre-specified subpopulation of patients who were treatment-naïve (12.7 versus 9.1 months *P* = 0,037). This study demonstrated that a more potent, selective VEGFR inhibitor with a long half-life achieved superior efficacy combined with decreased off-target toxicity. The results of TIVO-1 were presented at the ASCO 2012 Annual Meeting, and new safety analyses from TIVO-1 were recently presented at the ESMO 2012 Congress.

## Mammalian target of rapamycin inhibitors
*Temsirolimus*
Temsirolimus is the only drug recommended as category 1 therapy for RCC patients with poor prognosis. It was assessed in the Global Advanced Renal-Cell Carcinoma trial that compared Temsirolimus or Temsirolimus plus IFN-α with IFN-α alone in patients with mRCC and poor prognosis with OS as a primary endpoint. Temsirolimus alone compared with IFN-α alone significantly prolonged OS (10.9 months versus 7.3 months, *P* = 0.008) regardless of tumor histology or patient age, but in combination therapy OS was not prolonged.[21] The median PFS interval was 3.8 months with Temsirolimusmonotherapy, 1.9 months with IFN-α monotherapy, and 3.7 months with the combination of both. ORR was 8.6% versus 4.8% versus 8.1%, respectively.

This agent is the only one to show prolonged OS, in a phase III trial. This could be explained by the fact that such poor-prognosis patients did not receive subsequent active therapy upon progression and thus an OS benefit was able to be shown.

*Everolimus*
Everolimus is an orally administered mTOR inhibitor that was approved by the FDA in 2009 for the treatment of mRCC in patients who had failed treatment with sorafenib or sunitinib. The RECORD-1 trial, a randomized, double-blind, placebo-controlled phase III trial demonstrated longer median PFS with Everolimus than with placebo (4.0 months versus 1.9 months, *P* < 0.0001), this was significantly prolonged regardless of age, sex, MSKCC risk score, or previous treatment. The study was subsequently unblinded and all patients in the placebo group were then offered Everolimus therapy. The final analysis confirmed the significant statistical improvement in the PFS in favor of Everolimus.[22] Median OS was 14.8 months with Everolimus versus 14.4 months with placebo (*P* = 0.162), and 80% of patients in the placebo arm crossed over to Everolimus. Correcting for crossover, survival was 1.9 times longer [95% confidence interval (CI) 0.5-8.5] with Everolimus. The most recent records of this study showed a PFS of 5.42 months of the Everolimus-treated patients who received only one VEGFTKI treatment previously and 3.78 months in patients who received two prior VEGFR-TKI treatments.

# FUTURE TREATMENT STRATEGIES

## Sequence of targeted therapy
Sequential therapy has the potential to change mRCC into a chronic disease that can be managed for a long term through the administration of targeted agents in sequence, but the best strategy of sequencing targeted therapies remains a matter of debate.

In one hand, RECORD-1 was the first study to investigate sequential targeted therapy in mRCC.[22] In this study, patients who had failed an earlier anti-VEGF therapy (71% had received sunitinib previously) were treated with either everolimus or placebo. The median PFS was 4.9 months versus 1.9 months for those treated with everolimus or the placebo, respectively (HR = 0.33; *P* < 0.01). Furthermore the improvement in PFS was higher for patients who received only one VEGF-TKI previously than two prior VEGFR-TKI treatments (PFS = 5.42 versus 3.78 months, respectively) indicating a potential benefit of an early change of mode of action by switching from VEGFr-targeted therapy to mTOR inhibition.

In the other hand, INTORSECT trial was the first study to compare VEGFI (Sorafenib) to an mTORI (Temsirolimus) in patients with mRCC who failed prior therapy with Sunitinib.[23] Median PFS with Temsirolimus (Torisel) was 4.28 months compared to 3.91 months for Sorafenib (Nexavar). The researchers concluded that Torisel does not improve survival over Nexavar in the second-line setting and suggest that VEGFI may be a better option than mTORI for patients whose disease progresses after treatment with Sutent.

In addition, the results of the AXIS study confirmed that sequential TKIs are also thought to be effective. However, the median PFS was lower in post-sunitinib than in the total patient population for both axitinib (4.8 months) and sorafenib (3.4 months). So this shorter median PFS observed is suggestive of at least partial cross-resistance with sequential VEGF-targeted therapy.

A better understanding of the mechanism underlying treatment resistance will help optimize the treatment strategy. Results from two ongoing trials are urgently needed: SWITCH Study and RECORD 3 study that comparing different sequence options with sorafenib/sunitinib and Everolimus/sunitinib, respectively.

In third line setting, no therapies are approved. Recently, several studies evaluating the efficacy of a second VEGFR-TKI, following a VEGFR-TKI and mTOR inhibitor treatment sequence, have been reported with encouraging results.[24,25] In addition, a small prospective study showed that third and fourth-line treatment with mTOR inhibitors are feasible and could lead to increase in survival after failure on TKI therapy.[26]

## Combination therapy

A potential way to increase therapeutic efficacy is to combine agents that block different steps in the same or different cellular signaling pathways. "Vertical blockade" refers to targeting the same pathway at two or more steps, for example, the inhibition of VEGF by bevacizumab in combination with a VEGFR-TKI. The hope is to overcome the resistance that may develop through feedback mechanisms. An alternative approach, "horizontal blockade", refers to the inhibition of target molecules in different pathways. Bevacizumab appears to be the most versatile agent in combination, perhaps because it has a single well-defined target. Although mTORI are target specific, the mTOR protein is central to a large number of cellular processes, and this may explain the difficulty of combining mTORI with either immunotherapy or multitargeted kinase inhibitors. Rational combinations of active agents continue to be evaluated [Table 1]. They are generally associated with high financial cost and risk of increased toxicity due to additive and overlapping side-effect profiles.

In the INTORACT trial which compared Temsirolimus (Torisel) plus Bevacizumab (Avastin) with interferon plus Avastin as first-line treatment in mRCC.[27] Median PFS was 9.1 months versus 9.3 months and OS was 25.8 months versus 25.5 months in the Torisel and the interferon group, respectively. The researchers concluded that Torisel plus Avastin is not superior to interferon plus Avastin in the first-line treatment of patients with mRCC.

Additionally, The RECORD II trial, demonstrated recently that the combination of everolimus with bevacizumab is not superior to bevacizumab plus IFN-$\alpha$.[28] Currently, combinations of targeted therapy remain experimental and they should only be employed in the context of a clinical trial because the results of published trials.

## Adjuvant therapy

The aim of adjuvant therapy is to eliminate non-detectable residual disease, which is the source of tumor recurrence. To date all clinical trials regarding adjuvant immunotherapy in RCC have been essentially negative but with the advent of the new targeted drugs, interest in adjuvant therapy of RCC has been renewed.[29] Currently, several randomized, phase III trials are evaluating the impact of VEGF pathway

| Table 1: The combination systemic therapy for advanced RCC | | |
|---|---|---|
| **Trial** | **Phase** | **Design** |
| Best | II | Bevacizumab versus bevacizumab+temsirolimus versus bevacizumab+sorafenib versus sorafenib+temsirolimus |
| TORAVA | II | Bevacizumab+IFN-$\alpha$ versus bevacizumab+temsirolimus versus sunitinib |
| INTORACT | III | Bevacizumab+IFN-$\alpha$ versus bevacizumab+temsirolimus |
| RECORD-2 | II | Bevacizumab+IFN-$\alpha$ versus bevacizumab+everolimus |
| CALGB | III | Bevacizumab+everolimus versus everolimus |
| CONCERT | II | Sorafenib versus sorafenib+IFN-$\alpha$ |

IFN: Interferon, CALGB: the Cancer and Leukemia Group B, RCC: Renal cell carcinoma

antagonists on PFS, OS and safety/tolerability in the adjuvant setting [Table 2].

The results of these trials are eagerly awaited to determine the role of targeted therapy in the adjuvant setting.

### Neoadjuvant therapy

The theoretical advantages of administering systemic therapy before surgery are many and include assessment of primary tumor response, tumor downstaging, and decreasing circulating tumor cells. Early reports suggest that neoadjuvant-targeted therapy can only downstage or improve the resectability of the primary tumor or associated lesions in 20-25% of patients.[30]

The current paradigm of debulking nephrectomy in metastatic disease is based on data generated in the era of cytokine therapy, but is commonly used as a prelude to targeted therapy. Two studies are designed to clarify these critical issues: The SURTIME study (NCT01099423) from the EORTC is a phase III trial that randomized 458 subjects to sunitinib followed by nephrectomy or nephrectomy followed by sunitinib with PFS as the primary endpoint. The second study, CARMENA (NCT00930033), is a randomized phase III trial comparing sunitinib therapy alone versus cytoreductive nephrectomy followed by sunitinib therapy.

Although studies have demonstrated the general tolerability of targeted agents, there is still limited data on the safety of surgical resection following treatment with these agents, and several reports have shown increased perioperative complications after treatment.[31]

## THE MECHANISMS OF RESISTANCE TO TARGETED THERAPY IN MRCC

Unfortunately, most patients with mRCC inevitably develop resistance to targeted agents after a median of 5-11 months of treatment. That's highlighted the need to better understand mechanisms underlying this drug resistance to improve patient outcomes further. Two general modes have been proposed:

| Table 2: The ongoing trials in adjuvant renal cell cancer | | |
|---|---|---|
| **Trial** | **Population** | **Design** |
| ASSURE | High-risk | 1 year of sunitinib versus sorafenib for 1 year versus placebo for 1 year |
| SORCE | High or intermediate risk | Placebo for 3 years versus sorafenib for 1 year combined with placebo for 2 years versussorafenib for 3 years |
| S-TRAC | High risk | Sunitinib versus placebo for 12 months |
| EVEREST | Intermediate, high-risk or very high-risk | Everolimus versus placebo for 1 year |
| PROTECT | High risk | Pazopanib for 1 year versus placebo |

Intrinsic resistance (pre-existing): In patients who fail to show any degree of response to VEGF-targeted therapies. This indifference may be due to myeloid cells because, in a preclinical study, no responsive tumors were associated with an increase in infiltrating CD11b + GR1 + myeloid cells, which expressed several pro-angiogenic factors. Another mechanism was described and concern, the pre-existence of pro-angiogenic signals which compensate for the inhibition of VEGF signaling and allow angiogenesis to continue.[32]

Evasive resistance (adaptive): Concern patients who progressed after initial clinical benefit with targeted therapy, it can be accomplished by mutation, epigenetic reprogramming, or remodeling of the stromal microenvironment that can reestablish the functional capability, permitting renewed tumor growth and clinical relapse.[33] Potential mechanisms of this resistance involve the upregulation of alternative pro-angiogenic factors and/or downregulation of angiostatic.

Several strategies have been tested to manage the drug resistance including: Adjusting the dose of the drug, combination therapy or switching to an alternative agent. Moreover alternative pathways are currently under investigation particularly targeting of RAF, MEK, and the PI3K/AKT pathway.

## BIOMARKERS IN METASTATIC RENAL CELL CARCINOMA

RCC is not one disease but comprises a spectrum of subtypes based on different molecular drivers and host genetic backgrounds.[34] At the present time there is no prospectively validated predictive biomarker but their development should be a priority in order to guide treatment selection decisions. Table 3 resume the potentially predictive molecular biomarkers reported in the literature.

## AGENTS UNDER INVESTIGATION

Besides the above-described drugs, a number of trials are currently enroute to confirm or reject potential new alternative angiogenic, immunotherapeutic, and cell-signaling strategies that hold promise for more effectively treating mRCC.

### Emerging strategies for angiogenesis inhibition

The FGFR is proving to play a key role especially as applies to resistance to VEGFR-targeted therapies. Dovitinib demonstrated inhibition of VEGFR and FGFRs and was suggested to be a feasible alternative for heavily pre-treated mRCC patients.[35] An ongoing phase

## Table 3: Reported potentially predictive molecular biomarkers in RCC

| Therapeutic agent | Biomarkers and predictive findings | Author |
|---|---|---|
| Sunitinib | VHL gene deletion is a predictive biomarker of response | Choueri *et al.* 2008 |
| | CAIX overexpression, high PTEN and low P21 expression were associated with improved RR | Muriel *et al.* 2012 |
| | Modulation of circulating proteins involved in VEGF signaling led to associations with RR, PFS, and OS | Farace F *et al.* 2011 Deprimo SE *et al.* 2007 |
| Sorafenib | Baseline VEGF levels were prognostic for PFS and OS | Escudier B *et al.* 2009 |
| Pazopanib | High levels of IL-6 were predictive of PFS benefit | Tram HT *et al.* 2012 Liu Y *et al.* 2012 |
| Temsirolimus | PTEN and HIF1-a were not of predictive value | Figlin RA *et al.* 2009 |
| | Increased expression of pS6 was associated with response | Cho D *et al.* 2007 |
| | High serum LDH predicts for OS benefit | Amstrong AJ *et al.* 2012 |

VHL: Van hippel-lindau, CAIX: Carbonic anhydrase IX, PTEN: Phosphatase and tensin homolog, VEGF: Vascular endothelial growth factor, PFS: Progression free survival, HIF: Hypoxia inducible factor, OS: Overall survival, LDH: Lactate deshydrogenase, RCC: Renal cell cancer

III trial (NCT01223027) is in progress but still without any preliminary results. Other orally administered multi-kinase inhibitors currently in evaluation include Regorafenib (BAY 73-4506), a multi-kinase inhibitor tested in a phase II trial administered for previously untreated patients (NCT00664326), and Linifanib which is administered after the failure of a previous TKI therapy. AMG 386 inhibits angiogenesis by sequestering angiopoietin-1 and -2, and preventing their interaction with the Tie2 receptor on endothelial cells. There are two ongoing studies on combination with sunitinib or sorafenib.

### Strategies for PI3K-Akt survival signaling inhibition

Upregulation of the phosphatidylinositol-3-kinase (PI3K) pathway is associated with poor prognosis in patients with mRCC. The serine/threonine kinase Akt lies at a critical signaling node downstream of PI3K and is important in promoting cell survival. There is an ongoing phase II trial of MK-2206 (a novel allosteric Akt inhibitor) or Everolimus in mRCC after prior anti-VEGF therapy.[36]

### Emerging immunotherapeutic strategies: Programmed death-1 inhibition

PD-1 is an inhibitory receptor expressed on activated T cells. There are two known ligands for PD1: B7-H1/PD-L1, the predominant mediator of PD-1-dependent immunosuppression, and B7-DC/PD-L2. Previously, PD-1 has been suggested as a prognostic marker in RCC. A phase II study evaluating two doses of MDX-1106 (antiPD-1) was recently presented and was shown to be safe and yielded responses including durable benefit.[37]

## CONCLUSIONS

The treatment of mRCC continues to be a major challenge for uro-oncologists. The rapid growth in therapeutic options, largely targeting the VHL/HIF pathway, has brought much needed improvements in OS and PFS, although durable complete responses remain elusive. The limitations of these strategies have highlighted the need to better understand drug resistance, at the same time the development of alternative treatment paradigms are currently under investigation: Sequential and combination targeted therapies in advanced disease as are adjuvant and neo-adjuvant approaches around nephrectomy. In addition predictive biomarkers should be a priority in early preclinical and clinical development in order to guide rational tailored development of emerging agents.

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