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Treatment Efficacy of Targeted Therapies for Metastatic Renal Cell Carcinoma—A Review after Seven Years of Experience

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ABSTRACT

Renal cell carcinoma (RCC) is the 10th leading cause of deaths from cancer in the Western world. During the last two decades this type of malignancy was difficult to treat with limited treatment options using cytokines like interferon alpha (IFN) or interleukin-2 (IL-2). The development of targeted therapies that interfere with specific pathways of tumor angiogenesis and proliferation has profoundly changed this situation and improved the prognosis for patients diagnosed with metasatic renal cell carcinoma (mRCC) considerably. To date, seven targeted therapies have been approved for the first- and second-line treatment of metastatic renal cell carcinoma. In addition, recent data suggest that sequential treatment with these modern drugs is feasable and effective and leads to extended overall survival compared to historical data. As more progress is being made, the variety of therapeutic options makes it challenging in clinical practice to choose the best treatment option for the individual mRCC patient. This review revisits results from the pivotal trials of currently approved therapeutic agents (in chronological order of their approval) in context with latest results from current clinical trials.

Keywords: Kidney Cancer; Systemic Therapy; Review

1. Introduction

Renal cell carcinoma (RCC) is a malignancy whose global incidence has been steadily increasing over the past decades. One third of patients present with advanced stages of disease, and another third develop metastases in the follow-up. This leads to the high mortality-to-incidence ratio [1,2].

Until recently, the prognosis for most patients diagnosed with mRCC was poor. Because mRCC is widely resistant to chemotherapy, systemic treatment options were restricted to immune modulation with cytokines that resulted in rather low response rates combined with high toxicity. This situation changed with the approval of sorafenib and sunitinib, the first targeted therapies for the treatment of mRCC in 2006. To date, seven new drugs for the treatment of mRCC patients are available (**Table 1**). Since their introduction, targeted therapies prolonged significantly the median overall survival time of mRCC patients. They have established a promising new treatment paradigm by interfering with specific pathways of tumor angiogenesis and proliferation.

These agents typically exert their therapeutic effects either by inhibiting angiogenetic signalling cascades mediated by vascular endothelial growth factor receptors (VEGFR) or by blocking the mammalian target of rapamycin (mTOR), an important downstream switchboard of intracellular communication. The first group comprises the monoclonal antibody bevacizumab and the receptor tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, pazopanib and axitinib. The mTOR inhibitors temsirolimus and everolimus belong to the second group [3,4].

2. Approved Targeted Therapies

2.1. Sorafenib

In the prospective randomized phase 3 TARGET trial 903 patients who had previously been treated with cytokines were randomly assigned to receive either sorafenib

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Table 1. Approval trials mRCC.

	PFS (months)	OS (months)	Response rate
Sorafenib (*vs*. placebo)	5.5 *vs*. 2.8	17.8 *vs*. 14.3 (censored)	PR 10% *vs*. 2% DCR 62% *vs*. 37%
Sunitinib (*vs*. IFN-α)	11 *vs*. 5	26.4 *vs*. 21.8	ORR 47% *vs*. 12%
Bevacizumab + IFN-α (*vs*. placebo + IFN-α)	10.2 *vs*. 5.4	18.3 *vs*. 17.4 (CALGB) 23.3 *vs*. 21.3 (AVOREN)	ORR 31% *vs*. 13%
Temsirolimus (*vs*. TEM + IFN *vs*. TEM)	5.5 *vs*. 4.7. *vs*. 3.1	10.9 *vs*. 8.4 *vs*. 7.3	ORR 8.6% *vs*. 8.1% *vs*. 4.8%
Everolimus (*vs*. placebo 2:1)	4.0 *vs*. 1.9	mOS in Ev group not yet reached; 8.8 mo. in placebo group	PR 3% *vs*. 0%
Pazopanib (*vs*. placebo 2:1)	9.2 *vs*. 4.2	22.9 *vs*. 20.5	ORR 30% *vs*. 3%
Axitinib (*vs*. sorafenib open-label)	6.7 *vs*. 4.7	20.1 *vs*. 19.2	ORR 19% *vs*. 9%

or placebo [5,6]. Overall survival (OS) was the primary endpoint of the TARGET study. When a pre-planned analysis of OS revealed a 28% reduction in the risk of death among patients receiving sorafenib, patients from the placebo group were allowed to cross over to the sorafenib group to benefit from active treatment. When post-cross-over survival data of placebo patients were censored, sorafenib demonstrated a significant improvement in OS (17.8 vs. 14.3 months; HR 0.78; p = 0.0287). Progression-free survival (PFS) was prolonged by sorafenib to 5.5 months compared with 2.8 months in the placebo group. Based on these data, sorafenib has been approved for the treatment of patients who are not suited for or have progressed on a cytokine-based therapy. Large expanded access trials with 2.504 patients in North America and 1.159 patients in Europe have confirmed the efficacy and tolerability of sorafenib in first- and second-line-settings in daily routine treatment with a median PFS of 8.1 and 6.6 months, respectively [7,8].

2.2. Sunitinib

Sunitinib received its approval as a first-line therapy for mRCC after a phase 3 study with 750 patients who were randomized into two groups: one treated with sunitinib and the other with IFN-α [9]. PFS was defined as the primary endpoint. It was significantly longer in the sunitinib group (11 vs. 5 months; HR 0.42; p < 0.001). Overall survival in the approval study was longer in the sunitinib group than in the IFN-α group (26.4 vs. 21.8 months; p = 0.051), although statistically insignificant. Significance was reached, however, when the confounding effects of cross-over and poststudy cancer treatment were censored (28.1 vs. 14.1 months; p = 0.003) [10]. A large expanded access trial with 4.564 patients in 52 countries has confirmed the results of the approval study for sunitinib in terms of efficacy and tolerability with a median PFS of 9.4 and OS of 18.7 months, respectively [11].

2.3. Bevacizumab plus Interferon

In combination with IFN-α, bevacizumab was clinically tested in two phase 3 trials. Their primary endpoint was overall survival. Both trials did not meet the predefined criteria for its statistical significance, although OS data of 23.3 and 18.3 months for the combination therapy were reported. However, both trials successfully demonstrated a significant extension of PFS, which led to the approval of bevacizumab plus IFN-α for the first-line treatment of mRCC in 2009. The AVOREN trial randomized 649 first-line patients to receive IFN-α and bevacizumab or IFN-α and placebo. PFS increased to 10.2 months for the combination therapy versus 5.4 months for IFN-α (HR 0.63; p = 0.0001) [12,13]. The similarly designed CALGB study randomized 732 patients to receive either the combination or IFN-α alone. PFS was significantly longer in patients receiving the combination therapy (8.5 vs. 5.2 months; p < 0.001; HR 0.71) [14,15].

2.4. Temsirolimus

In 2009, the intravenously applied mTOR inhibitor temsirolimus has been approved for the first-line treatment of mRCC patients with a poor prognosis based on the results of the phase 3 trial ARCC. This trial randomized 626 previously untreated mRCC patients with a poor risk (MSKCC score, modified by Hudes) to receive temsirolimus, IFN-α, or a combination of temsirolimus and IFN-α. The primary endpoint was OS, which was significantly longer in the temsirolimus group compared with the IFN-α group (10.9 vs. 7.3 months; HR 0.73; p = 0.008). Median OS in the combination group did not differ significantly from the IFN-α group (8.4 vs. 7.3 months; HR 0.96; p = 0.70). Median PFS times in the ARCC study reached 5.5, 4.7 and 3.1 months in patients receiving temsirolimus, the combination therapy, or IFN-α alone [16].

2.5. Everolimus

The orally administered mTOR inhibitor Everolimus has been approved in 2010 for the second- or third-line therapy of mRCC patients after failure of TKIs. The approval is based on the results of the phase 3 RECORD-1 trial. 416 patients with mRCC who had progressed on sunitinib, sorafenib, or both, were randomized in a two to one ratio to receive either everolimus or placebo. The primary endpoint was PFS. The trial was halted early after the second interim analysis had shown a significant difference between the two groups: Median PFS in the everolimus group was 4.9 months vs. 1.9 months in the placebo group (HR 0.33; $p < 0.001$). OS did not differ significantly between the two groups (14.8 vs. 14.4 months; HR 0.87; $p = 0.16$) [17,18].

2.6. Pazopanib

The TKI Pazopanib was evaluated in a phase 3 trial with 435 mRCC patients who were previously untreated or had failed on a cytokine based therapy. These patients were randomized in a two to one ratio to receive either pazopanib or placebo. PFS was defined as the primary endpoint. It was significantly longer in the pazopanib group (9.2 vs. 4.2 months; HR 0.46; $p < 0.0001$). The objective response rate was 30% with pazopanib in comparison to 3% with placebo. OS did not differ significantly between the two groups (22.9 vs. 20.5 months; HR 0.91; $p = 0.224$) [19,20].

Based on these results, pazopanib has been approved in 2010 under the condition that its efficacy and safety be tested in direct comparison to sunitinib. This comparison in the COMPARZ trial whose results were presented at the ESMO 2012 (see 3.1.2.) supported the positive opinion on Pazopanib [21].

2.7. Axitinib

Axitinib is a TKI proven in second-line therapy of mRCC in direct comparison to sorafenib. In the open-label phase 3 trial AXIS 723 patients who had progressed on first-line therapy with sunitinib, bevacizumab plus IFN-α, temsirolimus, or cytokines were randomized to receive axitinib or sorafenib. PFS was defined as the primary endpoint. It was significantly longer for axitinib (6.7 vs. 4.7 months; HR 0.665; $p < 0.0001$) [22]. Median OS did not significantly differ between the axitinib arm and the sorafenib arm of the trial (20.1 vs. 19.2 months; HR 0.969; $p = 0.3744$) [23,24]. Based on the results of the AXIS trial, axitinib achieved market authorization for second-line therapy of mRCC in 2012.

3. Current Prospective Trials

Eight studies and subgroup analyses have been recently published regarding the field of first-line and second-line treatment in mRCC (**Tables 2** and **3**). The purpose of most of these studies was to define the optimal sequential treatment with the new drugs.

Table 2. First-line therapy mRCC.

	Drugs tested	ORR (%)	PFS (months)	OS (months)
EFFECT Phase II (n = 292)	Sunitinib (4/2) *vs*. Sunitinib (cont.)	32.2 *vs*. 28.1	8.5 *vs*. 7.0	23.1 *vs*. 23.5
COMPARZ Phase III (n = 1110)	Pazopanib *vs*. Sunitinib	31 *vs*. 25	8.4 *vs*. 9.5	28.4 *vs*. 29.3
AMG 386 Phase II (n = 152)	Sorafenib + AMG 386 (10 mg) *vs*. Sorafenib + AMG 386 (3 mg) *vs*. Sorafenib + Placebo	38 *vs*. 37 *vs*. 25	9.0 *vs*. 8.5 *vs*. 9.0	n.p.
TIVO-1 Phase III (n = 517)	Tivozanib *vs*. Sorafenib	33 *vs*. 23	11.9 *vs*. 9.1	28.8 *vs*. 29.3
NCT00920186 Phase III (n = 288)	Axitinib *vs*. Sorafenib	32.3 *vs*. 14.6	10.1 *vs*. 6.5	n.p.
INTORACT Phase III (n = 791)	Bevacizumab + IFN-α *vs*. Bevacizumab + Temsirolimus	28 *vs*. 27	9.3 *vs*. 9.1	25.5 *vs*. 25.8

n.p.: not published.

Table 3. Data sequential therapy.

	Sequences tested	ORR (%)	PFS (months)	OS (months)
AXIS Phase III (n = 723)	Sunitinib→Sorafenib *vs.* Sunitinib→Axitinib		3.4 *vs.* 4.8	16.5 *vs.* 15.2
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	IFN-α→Sorafenib *vs.* IFN-α→Axitinib		6.5 *vs.* 12.1	27.8 *vs.* 29.4
INTORSECT Phase III (n = 512)	Sunitinib→Sorafenib *vs.* Sunitinib→Temsirolimus	8 *vs.* 8	3.91 *vs.* 4.28	16.64 *vs.* 12.27

3.1. First-Line Therapies

3.1.1. EFFECT

The approved dosing schedule of sunitinib calls for four weeks on treatment (50 mg per day) followed by two weeks off treatment. A continuous daily dosing of 37.5 mg sunitinib has shown antitumor activity, too. In the phase 2 EFFECT trial, 292 previously untreated mRCC patients were randomized to receive sunitinib in one of both schedules in order to compare their safety and efficacy. Time to tumor progression (TTP) was defined as the primary endpoint. While there was a trend towards an inferior TTP and PFS (estimated as a sensitivity analysis for TTP) with continuous dosing, both parameters did not differ significantly between the treatment groups. Median PFS reached 8.5 months on schedule 4 weeks on/2 weeks off compared with 7.0 months on continuous dosing (HR 0.77; p = 0.070). Kaplan Meier estimates of OS suggested a slight yet insignificant advantage for continuous dosing (23.1 vs. 23.5 months; HR 1.09; p = 0.615). In their conclusion, the study investigators recommend to adhere to the approved sunitinib dose and schedule [25].

3.1.2. COMPARZ

The open-label phase 3 COMPARZ was a head-to-head analysis between pazopanib and sunitinib in first-line treatment of mRCC. 1110 patients were randomized to receive pazopanib on a continuous schedule or sunitinib on the 4 weeks on/2 weeks off schedule. PFS as the primary endpoint showed no statistical significant superiority for either of the two treatments (8.4 months for pazopanib vs. 9.5 months for sunitinib). An interim analysis revealed a median OS of 28.4 months in the pazopanib group compared with 29.3 months in the sunitinib group (HR 0.908; p = 0.275). Both treatments elicited similar objective response rates with 31% and 25%, respectively. In conclusion, COMPARZ has proven the non-inferiority of pazopanib's efficacy compared with sunitinib [21].

3.1.3. AMG 386

AMG 386 is an investigational biological drug, a peptibody, whose antitumor activity was tested in a double-blind phase 2 trial in comparison with sorafenib. 152 previously untreated patients were randomized to receive sorafenib daily plus AMG 386 at 10 mg/kg (group A), or sorafenib plus AMG 386 at 3 mg/kg (group B), or sorafenib plus placebo (group C) once weekly. Median PFS did not differ significantly between the three groups and reached 9.0, 8.5 and 9.0 months, respectively. The objective response rate was 38%, 37%, and 25%, respectively [26].

3.1.4. TIVO-1

Tivozanib is an investigational TKI that has been evaluated in direct comparison to sorafenib as a first-line treatment for mRCC. In the phase 3 TIVO-1 trial 517 patients were randomized to receive either tivozanib or sorafenib. First results demonstrate a significant longer PFS in the tivozanib group (11.9 vs. 9.1 months; HR 0.797; p = 0.042). In treatment-naïve patients (70% of total study population) median PFS in the tivozanib group reached 12.7 months versus 9.1 months in the sorafenib group (HR 0.756; p = 0.037). The objective response rate for tivozanib was 33% compared with 23% for sorafenib (p = 0.014) [27]. While median PFS differed considerably in patients with an ECOG 0 performance status (14.8 months in the tivozanib versus 9.1 months in the sorafenib group; HR 0.617; p = 0.004), it was almost equal in ECOG 1 patients (9.1 vs. 9.0 months; HR 0.920; p = 0.588). A similar observation emerged from a subgroup analysis according to the MSKCC score. For patients with a favorable risk, median PFS was 16.7 versus 10.7 months (HR 0.590; p = 0.018), while it reached 9.4 versus 7.4 months (HR 0.786; p = 0.076) for intermediate risk patients [28]. Median OS data showed no significant difference between both arms (29.3 vs. 28.8 months; HR 1.25; p = 0.105) [29].

3.1.5. NCT 00920186

In a first-line comparison between axitinib and sorafenib, 288 previously untreated mRCC patients were randomized at a 2:1 ratio to receive either of the two drugs. Median PFS was 10.1 months in the axitinib versus 6.5 months in the sorafenib group (stratified HR 0.77; 1-sided p = 0.038). In contrast, in ECOG 1 patients, both treatments yielded a similar PFS of 6.5 and 6.4 months, respectively. Overall, the study did not reach its primary endpoint, which had called for a hazard ratio of under 0.56 and a 1-sided p of 0.025 [30].

3.1.6. INTORACT

The phase 3 trial INTORACT compared bevacizumab plus interferon with bevacizumab plus temsirolimus as a first-line treatment for mRCC. 791 patients, predominantly with clear cell histology, were randomized to receive one of the two combination therapies. No superiority for the combination with temsirolimus could be demonstrated. Patients receiving bevacizumab plus IFN-α showed a median progression-survival time of 9.3 months, a median OS time of 25.5 months, and an objective response rate of 28% compared with 9.1 months, 25.8 months, and 27% in the group that received the combination with temsirolimus [31].

3.2. Sequential Therapies

None of the new drugs available is able to completely block all angiogenic or proliferative signalling pathways.

Ultimately, tumor cells will adapt to this incomplete inhibition and develop resistance. Yet because there is no absolute cross-resistance between TKIs such as sorafenib and sunitinib, as retrospective studies suggest, sequential therapies have the potential to prolong the life of mRCC patients. This assumption is confirmed by data from current prospective trials.

3.2.1. AXIS

The AXIS trial compared axitinib and sorafenib in a second-line setting. Stratification of the overall study population by prior first-line treatment allowed for subgroup analyses of different therapeutic sequences. In fact, AXIS was the first prospective phase 3 trial proving a benefit for TKI-TKI treatment sequences. Second-line PFS in patients with a previous sunitinib regimen was longer in the axitinib than in the sorafenib group (4.8 vs. 3.4 months; HR 0.741; $p = 0.0107$). Yet second-line median OS was shorter for patients treated with a sunitinib-axitinib sequence than for those receiving sorafenib after sunitinib, although with no statistical significance (15.2 vs. 16.5 months; HR 0.997; $p = 0.4902$). The objective response rate in the second line treatment was 19% in the axitinib and in 9% the sorafenib arm. The patients treated with cytokines prior to TKI showed the longest PFS (12.1 months for axitinib; and 6.5 months for sorafenib; HR 0.464; $p < 0.0001$) [22]. Their median OS reached 29.4 months in the axitinib and 27.8 months in the sorafenib group (HR 0.813; $p = 0.1435$). While axitinib's efficacy was superior to sorafenib as a second-line treatment in most subgroups, sorafenib patients with an intermediate prognosis according to the MSKCC risk score had a clear advantage in OS (23.9 vs. 18.8 months) [23,24].

3.2.2. INTORSECT

The INTORSECT trial was another second phase 3 trial prospectively proving the efficacy of sequential TKI therapies. Its primary objective was to compare safety and efficacy of temsirolimus and sorafenib in a second-line setting for mRCC patients after failure on prior sunitinib. 512 patients were randomized to receive either temsirolimus or sorafenib. Patients in both groups experienced a prolongation of their PFS time, slightly longer yet with no statistical significance in the temsirolimus group (4.28 vs. 3.91 months; HR 0.87; $p = 0.193$). The OS, however, was significantly shorter in the temsirolimus than in the sorafenib group (12.27 vs. 16.64 months; HR: 1.31; $p = 0.014$) [32].

4. Comment

Sorafenib and sunitinib have been the first targeted therapies for the treatment of mRCC, and their safety and efficacy has extensively been evaluated and confirmed since their approval by the FDA in December 2005 and January 2006, respectively. While sunitinib was initially regarded as the standard systemic therapy for treatment-naïve mRCC patients, sorafenib was also approved as a first-line treatment only for those patients who do not tolerate a cytokine-based therapy. It is noteworthy that both the TIVO-1 and the AMG 386 trial reported a much longer median PFS for first-line Sorafenib treatment (9.1 and 9.0 months, respectively) compared to the presented data from Escudier *et al*. with PFS of 5.7 months [33]. Sorafenib appears to exert its optimal efficacy in patients with an intermediate prognosis and/or limited performance status [23,24,28,30]. Sunitinib, on the other hand, showed a shorter PFS in the EFFECT and the COMPARZ trials than in the phase III approval trial (8.5 and 9.5 months, respectively, vs. 11 months) [9,21,25]. The longest median PFS reported to date in treatment-naïve mRCC patients has been reached with 12.7 months in the TIVO-1 trial by tivozanib in direct comparison to sorafenib [27].

The extended PFS upon treatment with the new TKIs is certainly a breakthrough in the management of mRCC. Even if it is probably true, though, that PFS can be regarded as a surrogate marker for OS, it is questionable whether a linear correlation between both parameters exists [34]. With the exception of sorafenib, all phase 3 trials for the currently approved TKIs did define PFS as their primary endpoint. This shortened the time to registration and avoided the risk of missing OS as the primary endpoint—like Sorafenib initially did in its pioneering TARGET trial. Because it turned out in the interim analysis that the disease was controlled significantly by sorafenib, patients from the placebo group were allowed to cross over to the verum group. This crossover of 48% confounded the trial data and subsequently made it impossible to determine a statistically significant advantage in OS for sorafenib on an intention-to-treat basis. The phase III trial ARCC with the mTOR inhibitor temsirolimus was the only mRCC approval study so far that succeeded in meeting OS as the primary endpoint without censoring data [16].

It is remarkable that the head-to-head comparison of temsirolimus and sorafenib in a second-line setting revealed a significant longer OS in the sorafenib group [32].

Crossover effects are not the only confounding source for the correct determination of OS; post-study tumor treatments also play an important role in this respect. In case of the approval study for sunitinib it was possible to analyze the subgroups of patients with no post-study cancer treatment separately and thus to calculate a significant OS compared with the IFN-α group (28.1 vs. 14.1 months) [10]. Similar OS data were presented in the interim analysis of the COMPARZ trial with sunitinib in

a first-line setting is estimated to reach 29.3 months compared with 28.4 months for Pazopanib [21]. Also in the AXIS trial comparing axitinib and sorafenib as second-line therapies in patients previously treated with cytokines the OS was 29.4 and 27.8 months, respectively [22].

Sequential therapies with the new drugs may permit mRCC patients to survive even longer, but the optimal sequence is still unknown. In several retrospective studies the question of optimal TKI sequencing was investigated [35-40]. In a study with 90 patients at four French academic centers Sablin *et al*. reported a significant difference in OS between the Sor-Sun and the Sun-Sor group of patients (135 vs. 82 weeks; HR 0.49; $p = 0.04$) [35]. In a meta-analysis of Sablin's and 21 further studies Stenner *et al*. conclude that the Sor-Sun sequence translates into a longer overall PFS than the Sun-Sor sequence [38]. Calvani supposes that the higher affinity of sunitinib for certain receptor kinases may lead to an overcome of drug resistance emerging after initial first-line treatment [37]. In first-line treatment this potency might induce an aggressive tumor phenotype and make first-line sunitinib an independent predictor of inferior OS in sequential therapies. Yet subgroup analyses of the RECORD-1 study send mixed messages in this regard: The group who received sorafenib prior to everolimus as only previous TKI experienced a longer PFS than the one who received sunitinib (5.9 and 3.9 months, respectively). With a HR of 1.97 it was discussed that sunitinib pretreatment could be a negative prognostic factor for OS ($p < 0.001$) [18].

5. Conclusion

In spite of these data the optimal sequence of targeted therapies remains unclear. As the European Association of Urology emphasizes in its current guidelines on renal cell carcinoma, no recommendations in this regard can be given yet, although it suggests levels of evidence for each targeted therapy. Second-line options after prior TKI are axitinib, sorafenib and everolimus. The only mentioned third-line therapy is everolimus [41]. Further randomized trials are needed to evaluate sequential therapies for mRCC, especially those in which alternative sequences are evaluated in a head-to-head comparison. The results of the currently ongoing prospective SWITCH study that randomizes 355 treatment-naïve patients to receive a sequence of sorafenib followed by sunitinib or vice versa are expected to shed a clearer light on what is the optimal TKI-TKI sequence [42].

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