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ANTI-ANGIOGENIC AND TARGETED THERAPY IN RENAL CANCER:
Molecularly Targeted Therapy in Renal Cell Carcinoma: Sequential versus Combination-based Therapies

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Introduction

Metastatic clear cell renal cell carcinoma (mRCC) is a cancer with a complex molecular pathogenesis that has been exploited for drug development.[1] Inhibition of tumor angiogenesis, through targeting the VEGF pathway, has been an effective approach in mRCC.[2] Four VEGF pathway inhibitors, sunitinib, pazopanib, sorafenib, and bevacizumab, have been approved.[3-10] Blocking the mTOR pathway, which plays a role in tumor cell survival and proliferation, has also been an effective therapeutic approach and mTOR inhibitors currently approved for patients with RCC include, temsirolimus and everolimus.[11-13] All of these agents have improved survival endpoints (PFS or OS), however, complete responses are rare and patients still succumb to their cancer. In an effort to improve upon clinical outcomes, two trial design strategies are being explored: sequential therapy and combination therapy (Figure 1A, B). Select prospective data and a highlight of ongoing trials evaluating these methods will be presented in this review

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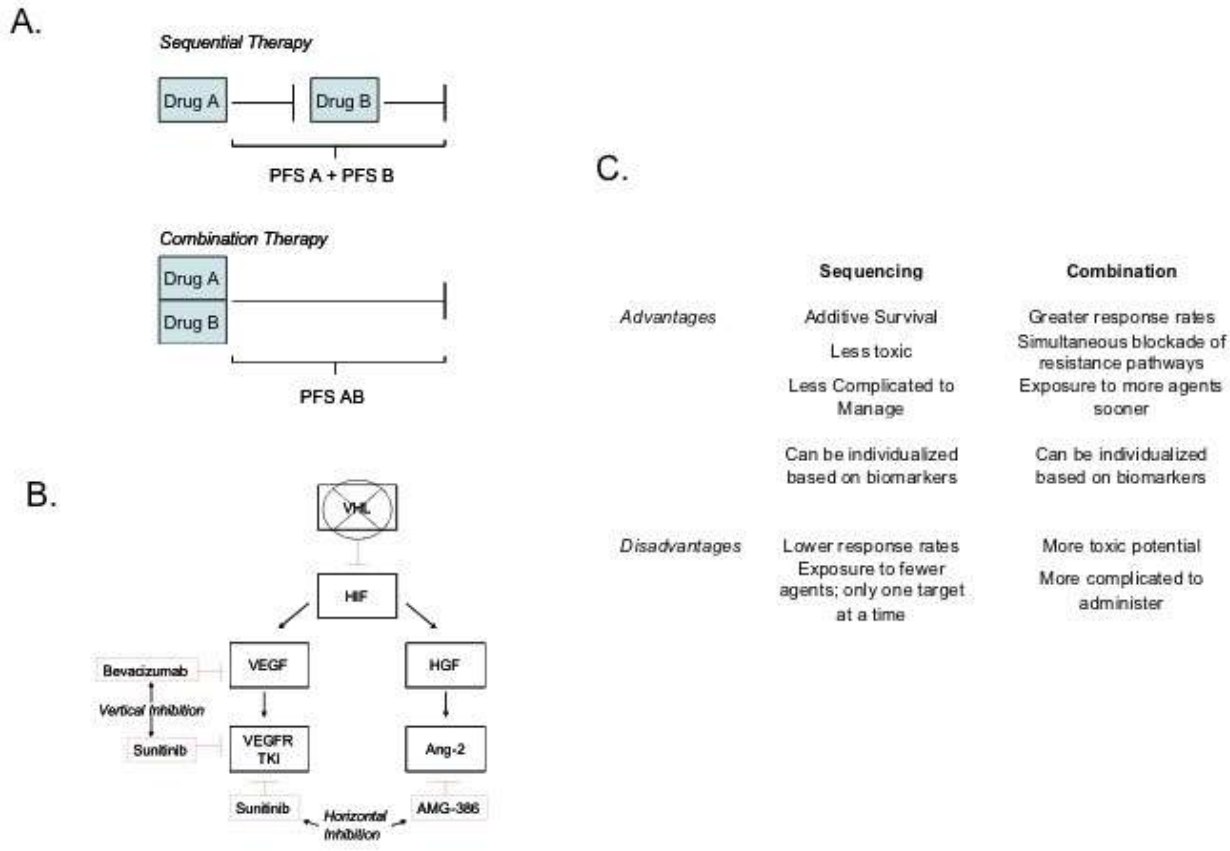
Figure 1



Clinical Trials Involving Sequential Use Targeted Agents

Multiple studies have been published evaluating the use of sequential targeted agents for the treatment of mRCC (Table 1). Given the available classes of agents, two approaches have been examined, sequential use of VEGF pathway inhibitors and sequential use of VEGF and mTOR inhibitors.

VEGF inhibitor → VEGF inhibitor. Cross resistance between VEGF inhibitors appears uncommon. This has been shown in several retrospective studies, and validated in other prospective trials. A recently published study explored sorafenib therapy following prior front-line sunitinib.[14] This study showed continued benefit of VEGFR tyrosine kinase inhibition in this cohort (ORR, 9.6%, median TTP 16 weeks, OS 32 weeks). Another trial examining the use of sorafenib following either front-line bevacizumab or sunitinib, showed similar results (tumor shrinkage rate 38%, PFS 3.8 months).[15] Sunitinib also has been evaluated in the second-line setting following bevacizumab. In this phase II study, sixty-two patients were treated with second-line sunitinib therapy with a ORR of 23% and a PFS of 7.0 months.[16] Axitinib, a highly potent and selective VEGF inhibitor, has been explored following sorafenib failure. Sixty-two patients were treated in this manner and an ORR of 22.6%, PFS of 74%, and OS of 13.6 months were noted.[17] In summary, numerous trials have shown that sequential use of VEGF inhibitors can result in meaningful responses and continued clinical benefit.

Table 1. Trials of Molecularly Targeted Agents in Sequence or Combination

Sequencing or Combination	Authors/Trial Name	No.	Comparator Arm	Results or Primary Endpoint
Sequencing Trials				
Sorafenib->Axitinib	Rini, et al [17]	62	Single arm	ORR 22.6%, PFS 7.4 mos., OS 13.6 mos.
Sorafenib->Sunitinib	Zimmerman, et al [24]	22	Single arm	ORR 18%, PFS 4.8 mos.
Sunitinib->Sorafenib	DiLorenzo, et al [14]	52	Single arm	ORR 9.6%, TTP 16 wks, OS 32 wks
Sunitinib->ABT869(VEGF TKI)	Tannir, et al [25]	53	Single arm	ORR 18.1%, PFS 4.9 mos.
Bevacizumab->sunitinib	Rini, et al [16]	61	Single arm	ORR 23%, PFS 7 mos
Bevacizumab or sunitinib ->sorafenib	Shepard, et al [15]	31	Single arm	ORR 0%, PFS 3.8 mos.
VEGF TKI ->everolimus	Motzer, et al/ RECORD-1 study [12,13]	410	placebo	PFS 4.9 v. 1.9 mos.
VEGF inhibitor +/-mTOR i -> perifosine	Vogelzang, et al [26]	45	Single arm	ORR 9%, PFS 15 wks
Upcoming or Ongoing Sequencing Trials				
Sunitinib ->everolimus	RECORD-3 study	390	Everolimus->sunitinib	PFS, noninferiority
Sunitinib, bevacizumab, temsirolimus, or cytokine ->axitinib	Axis study	650	Sorafenib	PFS
Sunitinib->sorafenib	Switch study	540	Sorafenib->sunitinib	total PFS
Sunitinib->Temsirolimus	Torisel 404 study	480	Sunitinib->sorafenib	PFS
Combination Trials				
Bevacizumab + sorafenib	Sosman, et al [19]	47	Single arm	ORR 46%, TTP 11.2 mos.
Bevacizumab + temsirolimus	Merchan, et al [27]	35	single arm	ORR 16%
Bevacizumab + erlotinib	Hainsworth, et al [22]	59	Single arm	ORR 25%, PFS 11 mos.
Bevacizumab + erlotinib + imatinib	Hainsworth, et al [23]	88	Single arm	ORR 17%
Bevacizumab + everolimus	Hainsworth, et al [20]	80	Single arm	ORR 28%, PFS 8.1 mos.
Bevacizumab + temsirolimus	Escudier, et al [21]	88	Sunitinib	NPR at 48wks: 30.7%(BT), 40.5%(S), 65.9%(BI)
			Bevacizumab/ interferon	PFS: 8.2 mos (BT), 8.2 mos. (S), 16.8 mos. (BI)
Bevacizumab + sunitinib	Feldman, et al [18]	26	Single arm	ORR 52%
Bevacizumab + IL-2	Dandamudi, et al [28]	51	Single arm	ORR 28%, PFS 9 mos.
Upcoming or Ongoing Combination Trials				
Bevacizumab + sorafenib	BeST trial	360	bevacizumab	PFS
Bevacizumab + temsirolimus				
Temsirolimus + sorafenib				
Bevacizumab + temsirolimus	INTORACT trial	800	bevacizumab/interferon	ORR and Survival
AMG 386 + sorafenib	Amgen	150	Sorafenib	PFS
AMG 386 + sunitinib	Amgen	80	Phase II	Safety and tolerability
BNC105P + everolimus	Bionomics	152	everolimus	Phase I: MTD Phase II: 6-mo PFS

Table 1: Prospective studies evaluating sequencing and combination targeted therapies. Legend: BI, bevacizumab/interferon; BT, bevacizumab+temsirolimus; MTD, maximum tolerated dose; NPR, non-progression rate; ORR, overall response rate; OS, median overall survival; PFS, median progression-free survival; S, sunitinib; TTP, median time-to-progression.

VEGF inhibitor → mTOR inhibitor.

The benefit of using mTOR inhibitors following VEGFR TKIs has also been demonstrated. In the randomized phase III RECORD-1 trial, 410 mRCC patients who had failed at least one prior VEGF TKI were randomized to everolimus or placebo. Everolimus demonstrated a superior PFS compared to placebo (4.9 v. 1.9 months).[12] The findings from this trial led to the approval of everolimus for patients with mRCC who have failed prior VEGFRTKI therapy. Although inhibition of the mTOR pathway in patients who have progressed on VEGFR TKIs is a reasonable approach, the optimal sequencing approach, VEGF inhibitor → VEGF inhibitor or VEGF inhibitor → mTOR inhibitor, currently remains to be seen.

Ongoing or Upcoming Sequencing Trials.
There are several ongoing trials which are focusing on the question of sequencing of targeted agents in mRCC (Table 1). The RECORD3 trial is a randomized, open-label, multicenter phase II trial that will evaluate the efficacy of everolimus followed by sunitinib compared to sunitinib followed by everolimus in treatment naive mRCC patients. Another study, known as the AXIS trial, will compare axitinib versus sorafenib for patients with mRCC who have received either sunitinib, bevacizumab (plus interferon), temsirolimus, or cytokine therapy in the front-line setting. In a trial evaluating the optimal sequencing of sunitinib and sorafenib, the SWITCH trial will randomize patients with treatment naive mRCC to sorafenib followed by sunitinib compared with sunitinib followed by sorafenib. Finally, the TORISEL 404 is comparing second-line sorafenib compared to second-line temsirolimus in patients with mRCC who have progressed on first-line sunitinib. The results of these studies will help to further delineate the optimal sequencing of targeted agents for patients with mRCC.

Clinical Trials involving Combination Targeted Therapies
Unlike the sequencing approach, the goal of combination therapy is to provide an additive or synergistic anti tumor effects including enhanced tumor shrinkage or a more durable response. Several studies have been performed evaluating combination regimens for patients with mRCC patients (Table 1). Although several trials have shown promising clinical activity, this has often been offset by increased toxicity or low clinical activity.

Vertical Inhibition.
Efforts to target the same pathway at two different points have focused on the VEGF pathway, which appears to be the most critical, targetable pathway in RCC to date. A phase I study of bevacizumab and sunitinib was recently reported. In this study 26 patients were treated, with an ORR of 52% which is higher than that expected with either agent alone.[18] The combination resulted in an increased frequency of grade 3 or 4 hypertension, proteinuria and thrombocytopenia. Many patients (48%) had to come off of the trial due to adverse events and several patients developed microangiopathic hemolytic anemia or reversible posterior leukoencephalopathy syndrome. A similar phase I trial combining bevacizumab and sorafenib (nG) demonstrated an ORR of 46% and a median time to progression of 11.8 months.[19] Of note, in order for the combination to be tolerable, lower doses of both agents were required.Although the combination of VEGF inhibitors has provided some of the highest response rates seen in studies, the accumulation of toxicity outweighs the benefit.

Horizontal Inhibition.
Horizontal inhibition has the potential advantage of combining agents with non-overlapping toxicities with a goal of an additive or synergistic effect. This method has been employed in several prospective studies (Table). Two phase II studies evaluating the combination of VEGF inhibition and mTOR inhibitors have recently been reported. In one study, 80 patients with metastatic RCC were treated with a combination of bevacizumab and everolimus.[20] The ORR was 28% and median PFS of 8.1 months, similar to findings seen with bevacizumab alone. Grade 3 and 4 toxicities were higher than would be anticipated with each agent alone. The phase II TORAVA study compared the combination bevacizumab/temsirolimus (BT, n=88) versus sunitinib (S, n=42) versus bevacizumab/interferon (BI, n=40).[21] The primary endpoint was non-progression rate (NPR) at 48 weeks. Results from this trial showed no benefit from the bevacizumab/temsirolimus combination compared to the other arms (NPR at 48 wks: BT: 30.7%, S: 40.5%, BI: 65.9%), but did show increased grade 3 or 4 toxicities (BT: 38.5%, S: 14.3%, BI: 27.5%). The BT combination arm was associated with three deaths compared to none on the comparator arms. Other attempts at horizontal inhibition have been made including bevacizumab combinations with other agents such as epidermal growth factor receptor inhibitors or c-kit/pdgfR inhibitors.[22,23] These studies have failed to show clinical benefit over expected outcomes with bevacizumab alone.

Ongoing or Upcoming Combination Trials.
There are a variety of trials which are ongoing with some further exploring the VEGF/mTOR combination (e.g. BeST trial, Intoract trial) while others are evaluating new combinations (Table 1). AMG-386 is a unique agent which inhibits angiopoetin, which is an important pro-angiogenic molecule and a potential escape pathway during VEGF inhibition. AMG-386 is being studied in two different front-line combination trials for patients with RCC (paired with sunitinib or sorafenib). Another unique agent, BNC-105P, is a vascular disrupting agent, which is currently being combined with everolimus in a phase I/II trial for patients who have progressed on prior VEGFR tyrosine kinase inhibitors. At present, it remains to be seen if these novel combinations will produce more meaningful effects than sequential use; however, the benefit of a combination approach will require careful consideration of any additive toxicity impact the regimen produces.

Conclusion
The management of patients with RCC has changed dramatically with the introduction of six active molecularly targeted agents. Current approaches to improve survival endpoints include the serial use of agents or combination approaches. Both methods can potentially curtail escape mechanisms within the tumor and thus further extend anti-tumor effect. Although each approach has its potential advantages and disadvantages, it is unclear which is optimal. (Figure 1C)

At present, the combination of VEGF and mTOR inhibitors appears to compromise tolerability with no additional clinical benefit. The greatest improvement in response rate appears to be in trials which have implemented vertical inhibition of the VEGF pathway; however, this application also has the most toxic profile. For a combination approach to be reasonable, it will need to have a significantly longer PFS than the serial use of the two agents and be tolerable. Clinical trials are underway which will evaluate different sequencing and combination approaches which will hopefully shed light on the best management and further advance survival endpoints for patients.

The future of RCC patient management remains promising; however, as more active agents are identified their optimal application remains an ever growing challenge. It is imperative to identify and incorporate robust molecular biomarkers which will enable individualization of therapy for patients with RCC. With proper identification of patients for unique combinations or serial use of molecularly-targeted agents, greater strides forward in advancing survival outcomes will hopefully be made.

Discussion
Dr. Stadler: Are we doing any trials that really look at adding an agent at the time of progression?
Dr. Hutson: Not that I am aware of.
Dr. Atkins: Companies are reluctant. I think part of it is you need to have a combination that is tolerated first before you can feel comfortable adding an agent at progression. And, if it is a tolerable combination, why not just start it to begin with and compare it to the single agent?

Dr. George: A fundamental question that I do not think that we have addressed is whether continued VEGF pathway inhibition is important in this disease.
Dr. Atkins: Well, that is why that CALGB trial of everolimus with or without bevacizumab in VEGFR TKI resistant patients is so important. It will start before the end of the year.
Dr. George: Let me just ask one thing because this seems like a tremendous amount of work. You look at all the different randomized combination studies, thousands of patients, and are we going to learn anything from any of these using PFS as our only endpoint?
Dr. Hutson: I am worried that we are not going to learn much. I fear that we will enroll thousands of patients, and spend millions of dollars, but at the end of the day these PFS values are not going to be so dramatically different that we are going to conclude anything.
Dr. George: We control the patients. So should we be enrolling patients to these kinds of studies? Or should we say look, we need to do something different that actually addresses a key clinical or scientific question? That actually advances the field? Dr. Atkins: I think we will learn some things, but not what the pharmaceutical companies want. If we have the tumors, we can learn from the RECORD-3 trial whether different populations respond to TOR inhibitions than to VEGF pathway inhibitors, because it is the only head-to-head first-line comparison of these two strategies. The clinical endpoints may be irrelevant to that question. We may also learn with axitinib versus sorafenib or tivozanib versus sorafenib, to what extent hitting the VEGF pathway harder first-line influences the impact of subsequent therapies. This appeared to be the case in the RECORD -1 study, where everolimus appeared to be less effective in patients who had received prior sunitinib than those who had received prior sorafenib. Also what happens when we start giving therapies that hit other targets in the second line setting? Does the degree of VEGFR inhibition in the front line make a difference? But these are all ancillary questions that need to be looked at in the context of those trials, not the primary aims of those trials, so we will need to be vigilant and persuasive to ensure that they get addressed and not swept under the rug, if the trial does not achieve its primary objective.
Dr. Stadler: Unfortunately, most of these trials are not powered for any of those secondary endpoints, so I worry that they are not likely to provide definitive answers.

References

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