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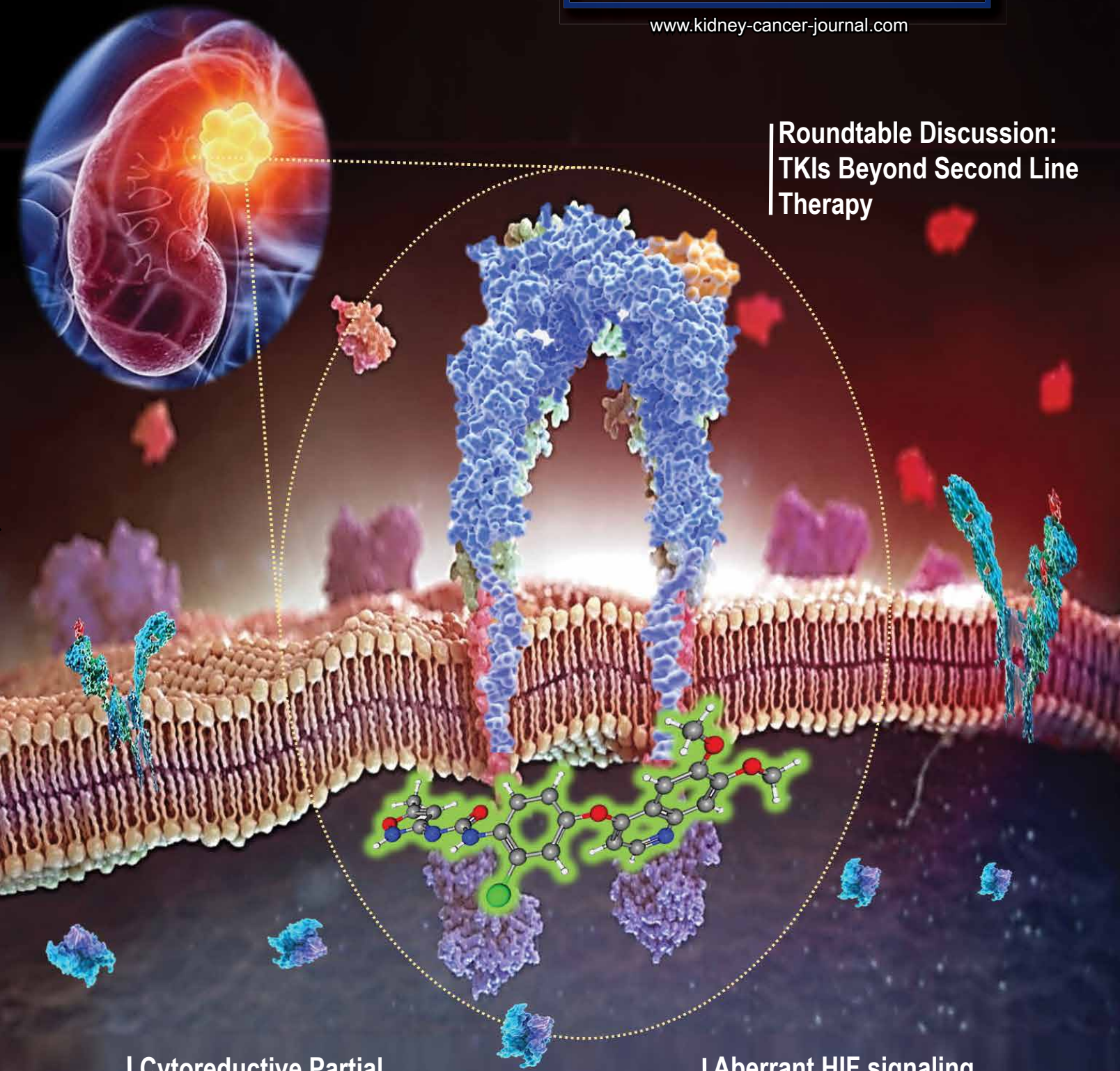

Roundtable Discussion: TKIs Beyond Second Line Therapy

Cytoreductive Partial Nephrectomy in Metastatic RCC setting

Aberrant HIF signaling orchestrates metabolic reprogramming

An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

ABOUT THE COVER
A graphical illustration of tivozanib molecule, a selective potent VEGFR TKI exerting its actions by selectively inhibiting the phosphorylation of vascular endothelial growth factor receptors: VEGFR-1, VEGFR-2 and VEGFR-3. Tivozanib suppresses tumor angiogenesis by being selectively inhibitory against VEGFRs in Renal Cell Carcinoma.

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KCJ CONTENTS

KCJ Editor's Memo

Novel Drug Combinations Gain Traction Across Therapeutic Landscape


Robert A Figlin, MD

More than a year since the COVID-19 crisis upended the face of health care in the United States, its impact on cancer clinical trials has continuously been seismic. Right now, it seems likely to be a while before we enroll newly designed studies and start gathering trial data at the rate they once were. While there is only a limited capacity for bringing in new trials or launching new therapies into clinical practice, the oncology community certainly moved quickly with a concerted effort to get the halted cancer trials back up and running. This year's ASCO Genitourinary Cancers Symposium sessions offered tantalizing preview of clinical breakthroughs and practice-changing research updates in GU cancers landscape despite the pandemic's impact on clinical trials space worldwide.

As highlighted in the recent *Kidney Cancer Journal* online edition, GU ASCO21 abstracts provided snapshots of the most important trends, foremost research and key strategies from latest clinical trials that impact the current standard of care in renal cancer. Certainly, looming on the horizon are the new IO/IO and IO/TKI combinations, which generated a lot of buzz at this year's ASCO in the renal cancer therapeutics space. Least to say, while targeted agents and immune monotherapies are still moving the needle to some extent, combination regimens comprised of IO/IO, IO/TKI, or other molecularly targeted agents are gaining momentum in evolving RCC landscape.

Let's have a quick snapshot of the latest data from the GU21 sessions. In the pivotal phase 3 CLEAR study (KEYNOTE-581), lenvatinib plus pembrolizumab demonstrated statistically significant and clinically meaningful improvements in progression-free survival, overall survival and objective response rate versus sunitinib, supporting the regimen as a potential first-line treatment for advanced RCC. Also, improvement in ORR and PFS, but not OS was observed for lenvatinib at 2 different starting doses in combination with everolimus vs sunitinib. Other related abstract presented quality of life outcome data from a phase II trial of lenvatinib plus everolimus in patients with RCC. Investigation by

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KCJ Editorial Advisory

KCJ Author Guidelines

Scope of Manuscripts

Kidney Cancer Journal considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to kidney cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of renal cell carcinoma.
- Clinical case studies.

Manuscript Submission

Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Robert A. Figlin, MD, at robert.figlin@cshs.org. Please provide in a word processing program. Images should be submitted electronically as well. All material reproduced from previously published, copyrighted material should contain a full credit line acknowledging the original source. The author is responsible for obtaining this permission.

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Manuscript Preparation

Length: Full-length manuscripts should not exceed 4000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally 4-5 figures and 2-3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a legend for all abbreviations. Manuscripts should not contain an abstract but an introduction is recommended.
Spacing: One space after periods. Manuscripts should be double spaced.

References

All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style. Example: Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest. 2001;119:818-823.

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TKIs Beyond Second-Line Therapy: New Perspectives in Renal Cell Carcinoma Therapeutics

Brian I. Rini, MD, FASCO[1], Thomas E. Hutson, DO, PharmD, FACP[2], Robert A. Figlin, MD, FACP[3]

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This roundtable discussion held on March 10, 2021 explores the potential role of current tyrosine kinase inhibitors (TKIs) in the therapeutic landscape of advanced renal cell carcinoma (aRCC). This discussion also integrates new concepts emerging from a phase-3 TIVO-3 trial which demonstrated a robust safety/tolerability portfolio of a novel drug tivozanib as third- or fourth-line therapy for patients with heavily pretreated aRCC while preserving the quality of life (QoL) of these patients.

Dr. Figlin: Welcome to the Kidney Cancer Journal webinar, focusing on exciting developments in renal cancer therapeutics. I am Robert A Figlin, Steven Spielberg Family Chair in Hematology-Oncology, at Cedars Sinai Medical Center in Los Angeles. I am going to moderate this session with my colleagues Drs. Brian Rini and Thomas Hutson. As many of you know, Brian is an Ingram Professor of Medicine and leads kidney cancer clinical research efforts at Vanderbilt-Ingram Cancer Center. Dr. Thomas Hutson, well known to all of you, is the director of the Urologic Oncology Program, and co-chair of the Urologic Cancer Research and Treatment Center at Baylor University, and Professor of Medicine at Texas A&M College.

This is an interesting time and we are going to focus on a novel drug tivozanib, which on March 10, was approved by the FDA for advanced or refractory kidney cancer, after second line therapies[1]. Let's start with Brian (Rini). Can you please talk about the tivozanib molecule and especially its potential role in targeting VEGF receptors?

Dr. Rini: In the family of TKIs, you have more selective agents like tivozanib and axitinib and you have multi-targeting agents - sorafenib and cabozantinib. The beauty of tivozanib is its selectivity and potency against the VEGFR targets and, as you all know that is integral to the biology of kidney cancer and fundamental to its very being. Which is why these VEGF inhibitors have precise activities[2]. Tivozanib was developed to be a potent and selective agent[2, 3] which I think probably is mostly reflected in its tolerability profile, so we do not see off-target toxicities with tivozanib, and you just tend to see on-target side effects like hypertension etc.

Dr. Figlin: Thomas (Hutson), I always like having you on the call because of your pharmacy background. In terms of pharmacology and pharmacodynamics, how should a practicing medical oncologist think about tivozanib when using and delivering it in a clinical setting?

Dr. Hutson: What is really striking about the tivozanib molecule is that at nanomolar concentration, it can inhibit VEGF receptors 1, 2, and 3, which are the putative receptors known to be important in kidney cancer pathogenesis[2] and equally, it does not inhibit the off-target receptors like c-Kit, which contribute to side effects. Pharmacodynamically it is very potent. Pharmacokinetically, tivozanib has a half-life of 99 hours so it is going to stay in the system for a longer period of time. Although tivozanib is similar to axitinib in terms of specificity, it has a longer half-life than axitinib. Some investigators believe that this long half-life may be advantageous. Certainly, the pharmacokinetic and pharmacodynamic profile of tivozanib allows for very small milligram dosing, and it is given for three weeks on and one week off allowing for continual suppression of VEGF receptor. Overall, this results in better tolerability and then the prolonged suppression of VEGF receptor[4].

Dr. Figlin: Yes, I think that is very insightful because when we are treating patients, we think about not only the target, but also we think about the half-life of the molecules to see if we need to hold or discontinue depending upon their toxicity profiles. So Brian, next take us through tivozanib's development, a little bit about TIVO-1[5] and more recently, TIVO-3 clinical trial[6] that ultimately has led to FDA approval. So help us understand the patient population, some of the results and dive into the outcomes that you think are important.

Dr. Rini: Sure, as we were discussing, tivozanib probably has one of the most interesting regulatory and development histories for an anti-cancer molecule. This is probably going back ten years, there was an initial phase-2 study published at the ASCO meeting[3, 4] and it came along at least in a 2nd wave of

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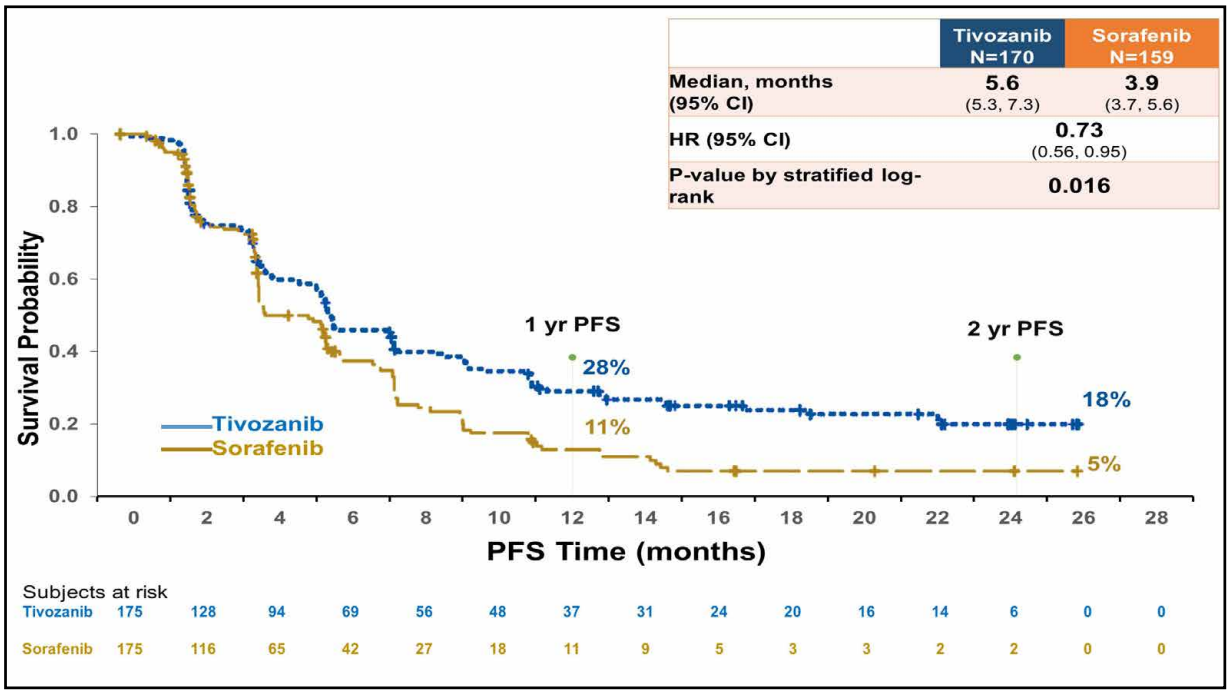
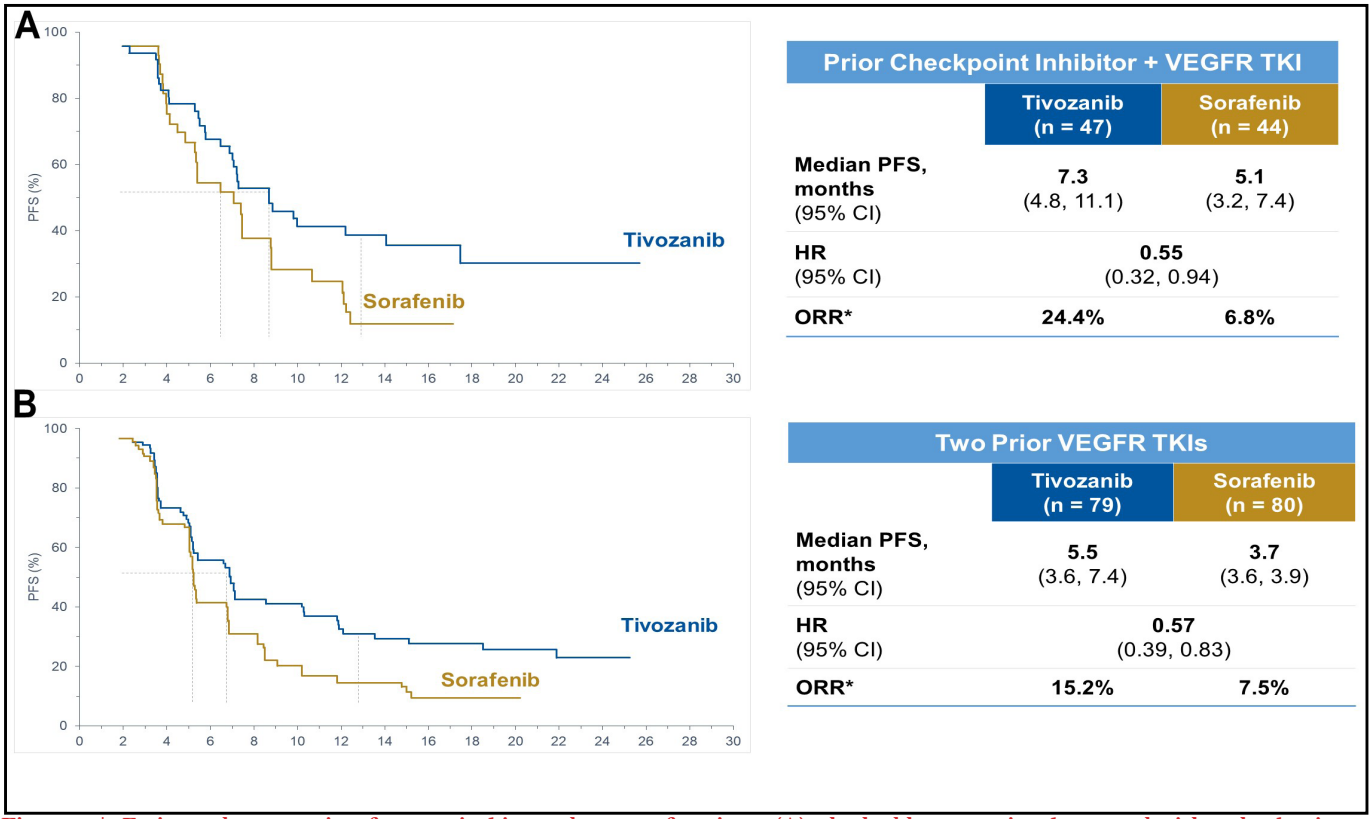


Figure 1 | Kaplan-Meier estimated progression-free survival in the intention-to-treat population. HR=hazard ratio, CI= confidence interval.

TKI development. TIVO-1 was a large phase-3 study in the frontline setting, involving previously untreated patients randomized to tivozanib vs sorafenib[5]. Tivozanib had its progression free survival (PFS) endpoint and response rate (RR) advantages and tivozanib was very potent as other TKIs in the frontline setting[5]. However, the problem with TIVO-1 was its one-way crossover design; when patients progressed on sorafenib, they crossed over and got tivozanib, which we now know is a very potent refractory agent. Whereas some patients who were initially randomized into tivozanib and did not cross over left to get a standard of care, which probably would not be a problem today but at the time and especially in the countries where it was conducted in parts of eastern Europe and Russia, there was no second line therapy so it became a trial of two drugs versus one; sorafenib + tivozanib versus tivozanib alone for many patients. Because of that, the survival hazard ratio was above one, which I believe really reflects that two drugs versus one drug phenomenon. But at the time, the FDA was not so convinced and certainly you can understand that they do not want to approve a drug that may adversely affect survival. Also, you can see how different regulators view data differently; the drug was approved in Europe years later, although it was not approved in the US[7]. TIVO-3 was eventually developed as a response by AVEO (clinicaltrials.gov, NCT02627963) to avoid this crossover problem[6]. So that is the reason why tivozanib was a bit unique in a refractory setting because you can no longer do frontline TKI versus frontline TKI. TIVO-3 trial showed PFS and ORR advantages in the later lines setting[6]. Some people have questioned the use of sorafenib as a control arm but that was entirely in response to TIVO-1 so as to recapitulate the study again in a different setting. We have seen that in other TKI trials on TKI versus TKI have shown about equivalent survival outcomes, reflection of all the active drugs that patients can get upon progression. So that is the very short version of a very long TIVO history.

Dr. Figlin: Thomas, your thoughts about quality of life (QoL) data associated with targeted effectiveness of VEGF inhibition and less off-target toxicity?

Dr. Hutson: We saw the unique characteristics of tivozanib play out during its development from the phase-2 randomized discontinuation trial and we saw an untargeted and minimal level of grade 1 or 2 toxicities that have been problematic with this generation of TKIs[4]. For instance, some side effects like hand-foot skin reaction, fatigue were much less with tivozanib. We did see an increase in some side effects especially hypertension and dysphonia as a result of its potent inhibition of VEGFR[4]. Later, based on the results from phase-3 TIVO-1 trial where I was a senior author, we hoped for approval of tivozanib but unfortunately it was not approved in the US. The most recent trial of tivozanib, TIVO-3, really allowed us to reconfirm and shed light on the benefits of tivozanib and its tolerability in a refractory patient population which may not respond or tolerate therapy well[6]. So, what we know from this trial is that patients who have had prior VEGF targeted therapy like axitinib or prior IO therapies seem to have benefit efficacy, as well as good tolerability[6]. In particular, there was no sign of any new side effects and the side effects looked fairly similar to TIVO-1 study. A recent real world trial was published after tivozanib was approved in 2017 in the EU[7]. In a real world data analysis, our colleague



Prior Checkpoint Inhibitor + VEGFR TKI	Tivozanib (n = 47)	Sorafenib (n = 44)
Median PFS, months (95% CI)	**7.3** (4.8, 11.1)	**5.1** (3.2, 7.4)
HR (95% CI)	**0.55** (0.32, 0.94)	
ORR*	**24.4%**	**6.8%**

Two Prior VEGFR TKIs	Tivozanib (n = 79)	Sorafenib (n = 80)
Median PFS, months (95% CI)	**5.5** (3.6, 7.4)	**3.7** (3.6, 3.9)
HR (95% CI)	**0.57** (0.39, 0.83)	
ORR*	**15.2%**	**7.5%**

Figure 2 | Estimated progression-free survival in a subgroup of patients (A) who had been previously treated with a checkpoint inhibitor and a TKI (B) who had been previously treated with two TKIs

Michael Staehler from the University of Munich, Germany, pulled together 23 patients between November, 2017 and October 2018, and treated patients both in the frontline setting as well as in second-line up to sixth line settings[8]. They were able to show what we had seen in the TIVO-1 and TIVO-3 trials that they were getting a median PFS of 14.9 months (95% CI 5.1–24.8). Median PFS was 30.3 months for first line patients versus 8.6 months (CI 5.1–12.2) (p=0.291) for later line which was again consistent with what we saw in Brian's report. The side effects observed in terms of QoL were very similar to TIVO-3; hypertension, diarrhea, fatigue and hoarseness with grade one or two severity[8].

Dr. Figlin: Brian, this seems like evidence of VEGF dependence in kidney cancer and TKI therapy continues to benefit patients after multiple prior line therapies, even in later settings. So how do you conceptualize using this data in your day in, day out practice when you start seeing these patients post multiple prior lines, but still have some evidence of that VEGF dependence?

Dr. Rini: Yes, I think your point is a good one, analogous to prostate cancer where it is still testosterone dependent through multiple lines of therapies, kidney cancers are dictated by VEGF through multiple lines of therapy. These patients in the third- or fourth- line settings had seen at least one VEGF therapy and perhaps some patients have seen two or more therapies. So you are absolutely right, the biology remains at least in part, although not in whole VEGF dependent that is why we see potent activity here. As you are aware, again, there is a debate - do you want to get more or less selective in your TKI use as you go into refractory setting? We could certainly argue that tivozanib is not necessarily a contemporary multi-targeting TKIs like cabozantinib or lenvatinib would be but, I think even more impressive when you have this level of potency with a very selective agent, because it specifically inhibits VEGF; not non-specific targets. So, again, to your point, there is a level of fundamental VEGF dependency here. To answer your question, as I move from an IO containing regimen upfront, I use a lot of IO-TKI to a refractory regimen which for me is usually a single agent TKI. My mindset has gone away from cure and is rather focused on disease control as I do not think TKIs cure patients as IO based therapy does. The tolerability profile of the agent has always been very important to me in the refractory setting. That is why I use a lot of axitinib in that setting[9] before I was using axitinib-pembrolizumab[10]. So I think the major advantage for tivozanib is not just activity because I think the activity is probably comparable to other TKIs but also its tolerability. As patients get pretty beat up in the third- and fourth- line settings, you are starting to question: Am I really helping this patient by giving them more therapy or am I hurting them more? I know this is something I face when patients are getting into third- or fourth- line setting so I am pretty careful about choosing agents with what I perceive the best tolerated profile. Because at least I am not harming the patient so I can use this agent very liberally in the third- or fourth- line setting or even if they fail to an IO- TKI regimen, I think tivozanib is perfectly appropriate in that setting.

Dr. Figlin: Thomas, your thoughts on the potential of TKI therapies in the later line therapeutics space as an experienced investigator?

Dr. Hutson: Yes, I agree with Brian. At a bit more granular level on the actual regimens we would choose IO-TKI in the community setting, especially axitinib based regimen, like axitinib-pembrolizumab is most utilized[10]. We are evaluating VEGF TKIs with IO therapies so you may have drugs combined to IO like cabozantinib or lenvatinib[12], but when we start moving into the second line setting after cabozantinib and into the third line space, we know that lenvatinib-everolimus is a very active regimen. In the refractory setting, we are looking for a therapy as Brian communicated that can accomplish the goal of stabilizing disease. We are not looking so much at that shrinkage of tumor with the disease control rate which is actually very impressive if I recall, and then a tolerability profile that makes tivozanib an ideal drug to choose in a third line after a cabozantinib or a fourth line. So, again, what we showed in TIVO-3 was that you could have exposure to axitinib, as you would have in first line combo with an IO-TKI, and then later tivozanib, and still get this level of activity. Prior to TIVO-3 , we really did not have a lot of therapies with phase-3 data. But, now we know things are going to change as we know what you pick first, dictates what you choose second, third and fourth line. For instance, if you get cabozantinib-nivolumab[13], that is going to change what you are going to get second as you are no longer going to get cabozantinib second, so have to think - could it be a tivozanib? axitinib, or could it be lenvatinib, everolumab? I think the data from TIVO-3 certainly makes tivozanib an ideal option in the later lines setting[6].

Dr. Figlin: We know, for example that there is clearly a dose-response effect to TKIs targeting VEGFR in clear cell RCC. I am just wondering out loud to the two of you, whether the real benefits of tivozanib are in part explained by its nanomolar IC_{50} so that you can get such inhibition at relatively low concentrations?

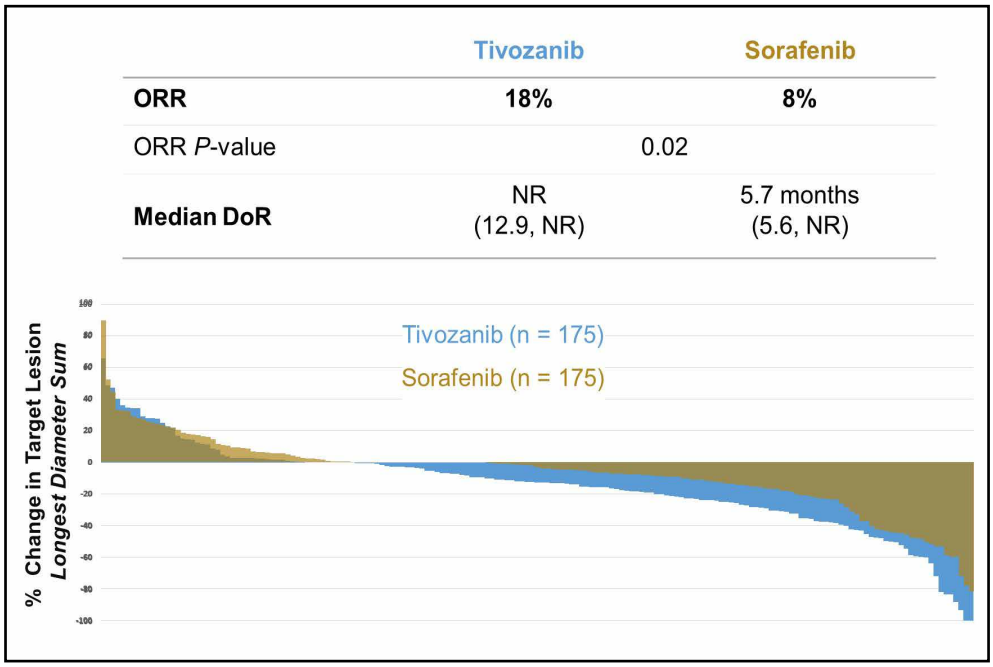


Figure 3 | Estimated overall survival rate and duration of response (DoR). HR=hazard ratio, CI= confidence interval.

Dr. Rini: Yes, I think so. I am a big believer in an optimal dosing of TKIs and I spent a lot of time thinking about it. You can achieve the benefits with optimal dosing that is appealing to you in a clinical community practice. So I think there is good pharmacokinetics and pharmacodynamics. You have the half-life issue which could be good or could be bad. We can sort of debate that, but obviously it is what it is. I think the long half-life of tivozanib does not hurt patients because it is so darn tolerable due to its optimal dosing advantage. I think some other multi-target TKI agents are much more toxic in my opinion as it takes a long time to get out of the system. Therefore I just do not think there is any major tolerability issue to any extent with tivozanib even in later line setting.

Dr. Figlin: So you do not think that there is any challenge in navigating the hypertension associated with tivozanib because of the long half-life in terms of controlling it once a person develops it?

Dr. Rini: I think in the early years we were all refreshing our memories about anti-hypertensives. But now it is been 15 or 20 years since we started dealing with with VEGF TKI associated hypertension or other side effects. So I feel my staff and I feel pretty comfortable managing hypertension. I can not think of a patient where I have permanently stopped for hypertension. As most people feel comfortable enough dealing with such issues, I do not think that is going to be a huge issue.

Dr. Figlin: For you Thomas?

Dr. Hutson: Absolutely the same, there is no pure or ideal VEGF inhibitor. So what we see with tivozanib is that it is active even at nanomolar concentration, the next off-target is so much higher. You are just never going to get off-target toxicity from tivozanib as you would have to take a bottle of the drug at one time to hit other off-targets. We get only on-target side effects which are manageable, so I think that is what makes tivozanib so advantageous and well tolerated.

Dr. Figlin: So just thinking out loud, now that we have FDA approval for tivozanib, and we have good toxicity profile, do you think it is an easily combinable drug for future design, I mean is it something that we should be thinking about in clinical trial design involving next generation IO-TKI at a nanomolar concentration?

Characteristic	Tivozanib (N=173)*		Sorafenib (N=170)*
Mean number of cycles initiated	**11.9**		**6.7**
AEs leading to dose reductions (%)	25	*P*=0.0147	39
AEs leading to dose interruption (%)	50	*P*=0.0164	64
ADRs leading to permanent discontinuation (%)	8		15
Treatment-related SAEs (%)	12		11
Treatment-related deaths (%)	0		0
Deaths within 30 days of tx (N)	15		13
Exposure adj deaths per month of tx	0.72%		1.11%

Figure 4 | Favorable tolerability profile of tivozanib compared to sorafenib in TIVO-3 as demonstrated by significantly fewer dose reductions, interruptions, and discontinuations due to AEs

Dr. Hutson: Yes, absolutely. We are looking for combinable therapies to add on the backbone of VEGF inhibitors. Since we know from the pathogenesis of clear cell renal carcinoma that VEGF is going to be an important target for us to continue to suppress, having a drug that has predictable side effects is going to be advantageous when we combine two. I think that is one of the advantages we have seen already in the marketplace with axitinib-pembrolizumab[10] that it is gotten such great uptake as physicians feel the drug is well tolerated and I think they are going to be equally pleased when the tivozanib-nivolumab[13] study continues to enroll and hopefully that will be a positive trial.

Dr. Figlin: You guys have been spectacular as I knew you would be, Brian and Tom. Why don't you speak to the community physician seeing the occasional clear cell RCC patient and kind of summarize for them, how they should be thinking about tivozanib and integrating it into their practice?

Dr. Rini: I would think about it as a very clean, potent and well tolerated VEGF inhibitor and would integrate it early in the refractory setting, which is where the data supports. We will investigate Thomas's point about other combos and triplets as well. You will be pleasantly surprised not just at its efficacy, which I think is impressive but also at its tolerability especially after being beat up with a frontline doublet, or a second line combo. So, tolerability is the calling card of this tivozanib agent and I think you and your staff are going to like that very much.

Dr. Figlin: Any special population data that we are aware of what happens in a brain metastatic patient? Is there any information from the TIVO-3 trial that helps us figure out exactly what kind of refractory patient might benefit?

Dr. Rini: The short answer is no, I do not think brain mets were allowed and I do not think we have looked at organ subsets yet. You know those analyses are always a bit flawed and I am not aware of any data that would support a subpopulation that is particularly enriched or not enriched.

Dr. Figlin: Thomas, speaking to the community practice what would be your take home lessons?

Dr. Hutson: Sure. For the community oncologist, I would also echo what Brian said that this would be one of the agents that you put in the tool box of therapies that you are going to choose from to give your patients. We now have the advantage or disadvantages of having multiple lines of therapy to choose from, knowing that patients never make it past the third or fourth line for most people. When treating a patient, it will be important to select the most active sequence of agents to make sure that patients are able to be exposed to the best therapies available. Having new therapies with data in later lines is crucial, therapies especially which provide disease control. So, tivozanib is going to be pushed over into that box of therapies we want to use. Unfortunately many patients do not make it past the fourth line of therapy and people need to realize this is the therapy they are going to want to have on their list of therapies to choose from.

Dr. Figlin: Well, Brian and Thomas, you have been spectacular as I expected you would be. This is a great summary of another novel agent that is going to have a potential role in treating our patients. Thank you and best regards.

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EDITOR'S MEMO *(continued from Page 2)*

Choueiri and colleagues was the first to report efficacy of combining the novel HIF-2alpha inhibitor plus cabozantinib (a VEGF TKI) in 118 patients with advanced clear-cell RCC. Belzutifan in combination with cabozantinib demonstrated promising antitumor activity and better tolerability in previously treated patients with metastatic ccRCC. CheckMate 9ER (NCT03141177), a phase III open-label trial has shown that nivolumab + cabozantinib demonstrated statistically significant HRQoL benefits and superior efficacy versus sunitinib. Also, nivolumab + cabozantinib demonstrated improved efficacy and prolonged survival vs sunitinib in previously untreated aRCC patients regardless of sarcomatoid status. In a phase II SWOG 1500 study by Pal and colleagues that put cabozantinib, crizotinib, or dacomitinib to the test, the small molecule inhibitor cabozantinib was found most effective in treating 180 patients with metastatic papillary RCC following progression. The exploratory analysis by Plimack and colleagues provide an update of phase III KEYNOTE-426 study which demonstrates that a significant proportion of patients in the pembrolizumab and axitinib arm were able to complete 2 years of pembrolizumab with ongoing clinical benefit. In previous reports of KEYNOTE-426, investigators showed that pembrolizumab plus axitinib prolonged OS and PFS vs sunitinib in patients with treatment-naive advanced RCC.

Emerging data from these trials will position such IO/IO or IO/TKI combination regimens as the new standards of care for patients with renal cell carcinoma. There were several useful additions to the repertoire of currently approved therapies, which should prompt further conversations. As oncologists gear up to gauge the potency of newly available combination regimens in a real-world perspective, significant challenges remain in regard to management of overlapping toxicities, while maintaining quality of life in patients. Ultimately, the rationale for optimal treatment selection for a given combination regimen depends on multi-factorial elements including safety/efficacy, tolerability, cancer progression, comorbidities, drugs cost etc.

This edition of *Kidney Cancer Journal* provides a stimulating roundtable discussion which I chaired, participated by expert panelists Drs. Brian I Rini and Thomas E. Hutson. This discussion shed light into the robust safety/tolerability portfolio of VEGF-TKIs especially tivozanib which could potentially carve out a space within the area of unmet need : third- or fourth-line therapy for heavily pretreated RCC population. The discussion also integrated new concepts emerging from the phase-3 TIVO-3 trial and analyze the potential impact of novel data. On the heels of the recent US FDA approval of tivozanib (Fotivda) in the relapsed/refractory RCC setting based on data from phase 3 TIVO-3 trial, tivozanib is now being investigated in combination with the PD-1 inhibitor nivolumab (Opdivo) in the phase 3 TiNivo-2 trial in patients with relapsed/refractory RCC. A case study by Russo's team in this edition describes the cytoreductive partial nephrectomy (cPN) approach in a patient with metastatic disease in the context of a small renal mass and pre-existing chronic kidney disease and discusses a framework for patient selection. A review article by Rathmell and colleagues summarizes how glycogen, lipid, and cholesterol metabolism which has long been recognized as a differentiating feature of ccRCC play key roles in ccRCC tumor growth. This review also provides key insights about therapeutic potential of targeting bioenergetic metabolism pathways.

Robert A. Figlin, MD, FACP
Editor-in-Chief

Cytoreductive Partial Nephrectomy: Framework for Patient Selection

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ABSTRACT

Cytoreductive nephrectomy in metastatic renal cell carcinoma has demonstrated a significant survival benefit in properly selected patients, however the role of cytoreductive partial nephrectomy in this setting and whether it undermines oncologic efficacy is not well defined. Indeed, cytoreduction coupled with nephron preservation to both optimize cancer control and abate the renal and cardiovascular morbidities of chronic kidney disease represents the preferred approach in patients with imperative indications for renal preservation. We present a case of a cytoreductive partial nephrectomy in a patient with metastatic disease in the context of a small renal mass and pre-existing chronic kidney disease and describe a framework for patient selection.

KEYWORDS: Cytoreductive Partial Nephrectomy • Radical Nephrectomy • Renal Cell Carcinoma • Patient Selection

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of adult malignancies and is the eighth leading cause of cancer in the United States[1]. Up to 30% of patients diagnosed with RCC present with synchronous metastases and recurrence is seen in 30% of patients after complete resection of the primary tumor[2,3]. Although the 5-year survival of early-stage RCC is 93%, patients presenting with metastatic disease have dismal 5-year survival rates of approximately 12%, and at least half of patients with RCC will eventually require systemic therapy[4]. Metastatic RCC (mRCC) can have an unpredictable and highly variable natural history which can range from indolent with years of small volume metastatic disease off treatment to rapid progression and death within months[5].

Distinct clinical variables, including performance status, serum hemoglobin, corrected calcium, and serum LDH can segregate patients into risk strata associated with overall survival[6]. Identifying patients likely to derive benefit from cytoreductive nephrectomy poses a significant clinical challenge. Careful selection of patients for cytoreductive operations based on these prognostic models is key with avoidance of poor risk and debilitated patients unlikely to benefit who are referred instead for upfront systemic therapies[7]. Cytoreductive radical nephrectomy (cRN) classically involves radical nephrectomy, yet metastatic disease has been reported in 0.5-8% of patients with small renal masses which usually are of high grade with renal sinus, perinephric fat, or branched renal vein extension (T3a)[8-10]. Two published prospective active surveillance series report metastatic rates of tumors <4cm ranging from 0-1.1%[11,12]. In such patients, the role of cytoreductive partial nephrectomy (cPN) and whether it undermines oncologic efficacy is ill-defined. We herein describe cPN in a patient with mRCC, a small renal mass, and pre-existing chronic kidney disease (CKD) and discuss the contemporary experience with cPN.

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Case Presentation

A 57-year-old male initially presented with a one-month history of an enlarging, painless right chest wall mass. His medical and surgical history is significant for hyperlipidemia and diverticulitis for which he previously underwent a sigmoid resection. His family history is remarkable for maternal aunts with non-small cell lung cancer, ovarian cancer, a maternal grandfather with bladder cancer, and a father who died of metastatic prostate cancer. He endorses a 7.5 pack-year smoking history but is not a current smoker.

Work-up of the right chest wall mass included a CT chest which demonstrated an expansile destructive right rib lesion measuring 5.8 x 4.1 x 6.5 cm and a non-specific 3mm pulmonary nodule (Figure 1). A CT-guided biopsy of the chest wall mass was most consistent with clear cell RCC (Figure 3). Subsequent CT of his abdomen demonstrated a 3.9 x 4.2 x 4.0 cm heterogenous exophytic right renal mass (Figure 2). The patient denied gross hematuria, unintentional weight loss, constitutional symptoms, and pain. His physical exam was remarkable for a palpably firm right chest wall mass, and lab data revealed normal serum hemoglobin, absolute

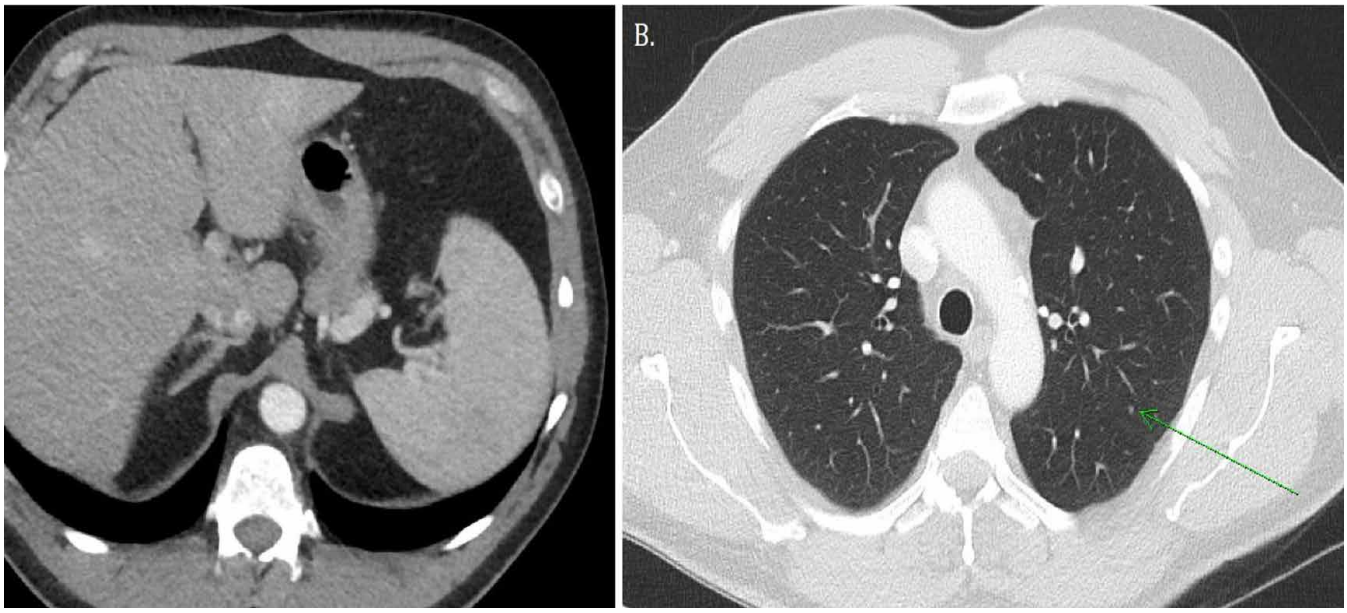

Figure 1 | (A) CT chest demonstrating an expansile destructive right rib lesion measuring 5.8 x 4.1 x 6.5 cm and (B) non-specific 3 mm pulmonary nodule.

neutrophil count, platelets, and calcium. With his excellent performance status and normal lab results he was assigned to the intermediate risk group as per the International Metastatic RCC Database Consortium (IMDC) prognostic model[13]. Notably, he had mild baseline chronic kidney disease with a serum creatinine of 1.5 and an estimated glomerular filtration rate was 48.2 ml/min/1.78 m^2.

He was taken to the operating room for thoracoscopy, chest wall mass resection, and cPN. Thoracoscopy revealed an approximately 6cm oval, lobulated soft tissue mass involving the lateral portion of the right ninth rib, and a small nodule in the right lower lobe superior segment. A right lower lobe wedge resection and right chest wall resection, including partial ninth rib and adjacent intercostal tissue, was performed without complication. The chest wall was reconstructed with the use of surgical mesh and a chest tube was placed. The right renal mass was approached via a separate 8 cm mini-flank incision and a cPN was successfully performed using a completely off clamp (no ischemia) approach. Total estimated blood loss for the combined resections was 300cc. The patient had an uneventful hospital course and was discharged on day 4 with a serum creatinine at baseline of 1.5. He has made a near complete recovery and at 6 weeks is being reassessed by the medical oncology team for either careful interval follow-up or the initiation of systemic therapy depending on an upcoming extent of disease evaluation.

Histopathologic examination of the partial nephrectomy specimen revealed a 5.5 cm clear cell RCC with negative surgical margins, Fuhrman Grade 3. Metastatic RCC was present in the right lower lobe wedge (0.25cm) as well as the chest wall resection (7.4cm) which involved bone, skeletal muscle, and fibroadipose tissue (Figure 4). All surgical margins were negative, and a pathologic stage of pT1bNxM1 was assigned.

Discussion

Partial nephrectomy is a standard of care approach in select patients with localized renal tumors and provides the same local tumor control compared to radical nephrectomy while at the same time preserving renal function and preventing or delaying cardiovascular ill-effects of CKD[14,15]. However, a paucity of data exists regarding partial nephrectomy in the metastatic setting. As recently developed systemic therapies have extended life expectancies in patients with metastatic disease[16], surgical approaches need to consider baseline renal function, avoidance of development of concomitant serious medical renal disease which carries its own distinct potential for cardiovascular morbidity and mortality, and improve patient's ability to tolerate additional therapies. The surgical approach in this case was driven by two salient features, namely, his pre-existing CKD and the exophytic position of his small renal mass. Assuming that each renal unit in this patient contributes half to his overall renal function, a radical nephrectomy would potentiate his renal impairment to stage IV CKD (GFR 15-29) per the CKD-EPI creatinine equation[17].

At baseline, CKD is more prevalent in the RCC patient, with 26% of patients having GFRs <60 despite normal serum creatinine.18 CKD has been found to be an independent risk factor for the development of kidney cancer[19]. The benefit of partial nephrectomy in the management of the small renal mass was brought to light in a 2006 study from our institution; the incidence of new-onset CKD in patients with normal serum creatinine and two functioning kidneys who underwent nephron sparing surgery and radical nephrectomy for small renal masses was found to be 17% and 69%, respectively for a eGFR of a 60.18 The effect was

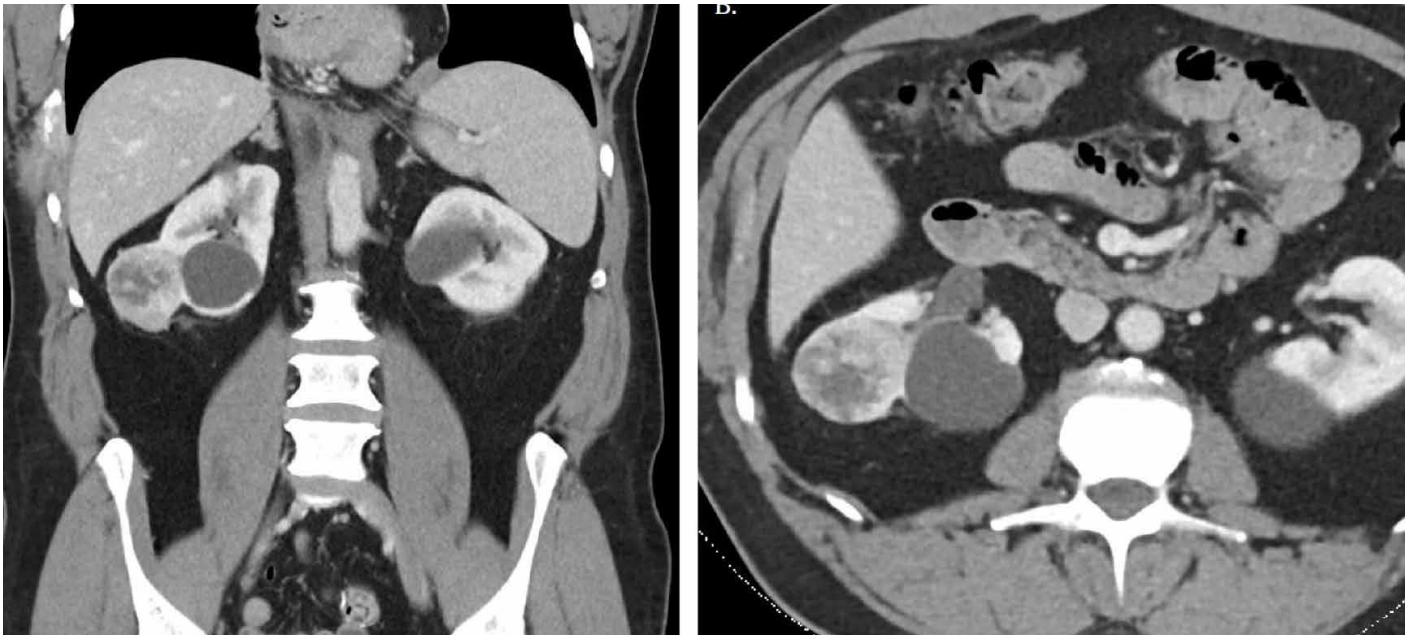

Figure 2 | CT abdomen and pelvis demonstrating a 3.9 x 4.2 x 4.0cm heterogenous enhancing mass in the right kidney and bilateral renal cysts in the (A) coronal and (B) axial plane.

more remarkable at a GFR cutoff of 45 (2.9% vs. 35.9% respectively for PN VS. RN respectively).

Tumor size is an important predictor of survival in the localized setting, however limited data is available regarding the role of tumor size as a predictor of survival in the metastatic setting. In a report from our center, the impact of tumor size on survival in patients with mRCC at diagnosis who underwent CN was assessed[20]. Our cohort was comprised of 304 patients; 21 patients with tumors < 4 cm (8 patients underwent cPN; 13 patients underwent cRN), with an IMDC validation cohort (n=778). Extent of metastatic disease sites was directly related to primary tumor size. Smaller tumors were found to have fewer metastatic sites, a finding that was specific to tumors of clear cell histology. A significant difference in overall survival was observed when using a 4 cm size cutoff to distinguish small vs. large masses, and a subgroup analysis stratified patient into clear cell and non-clear cell histology, demonstrating that tumor size was a significant prognostic factor only in patients with clear cell RCC.

In 2006 and in 2007, two papers reported cause-specific survival data in metastatic RCC patients treated with cPN. In the first report from the Mayo Clinic, patients undergoing cPN (n=16) did not demonstrate inferior cancer-specific survival rates compared to those

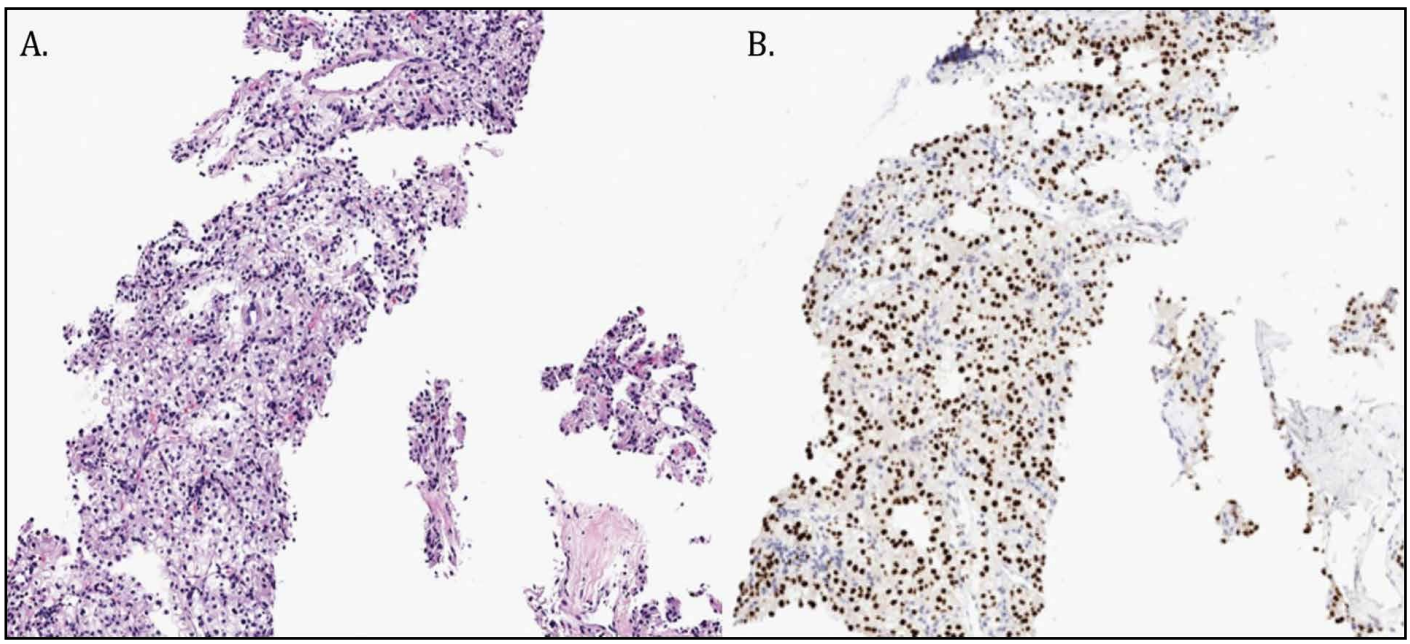

Figure 3 | (A) Chest wall biopsy showing metastatic deposit of clear cell renal cell carcinoma. (B) Diffuse PAX8 expression within the tumor.

undergoing cRN (n=404)[21]. Although early and late complications were higher with cPN, there were no differences in complications in M1 pts undergoing cPN compared to a matched cohort of non-metastatic patients undergoing partial nephrectomy. One critical confounder in this study was that 87.5% of the patients in the cPN group underwent complete resection of all metastatic disease (like our patient did) compared to only 22.5% in the cRN group. The second paper from the University of Montreal Health Center included larger patient numbers (cRN: 732 patients; cPN: 45 patients), and detected a 1.5-fold, albeit statistically nonsignificant, increase in cancer-specific mortality for cRN cases (p=0.2), confirming the non-inferiority cPN described in the previous study[22]. Given the multi-institutional nature of the study, differences in surgical and adjuvant treatments could have affected the results of this study.

The first retrospective study to demonstrate a survival benefit with cPN was published in 2013 from Roswell Park Cancer Center, which included 2,880 patients who underwent cRN and 70 patients who underwent cPN from the Surveillance, Epidemiology, and End Results (SEER) database[23]. Patients undergoing cPN were 0.54 times less likely to die and 0.49 times less likely to die of RCC than those who underwent cRN (95% CI 0.3–0.73, p<0.001 and 95% CI 0.35–0.69, p<0.001; respectively). The largest single institution study of cPN from MD Anderson Cancer Center reported in 2014 identified the indications for and outcomes of cPN with particular attention paid to cPN subgroups[24]. A total of 33 patients were included; 8 patients had bilateral synchronous tumors, 20 patients had metachronous contralateral tumors, and 5 patients had unilateral renal tumors. Although all patients had metastatic disease before PN, not all had metastatic disease at the original diagnosis; 17 (52%) presented with M1 disease, and 16 (49%) developed metastases after original diagnosis but before cPN. Twelve patients (36%) experienced 17 early postoperative complications within 3 months after surgery, ranging from Clavien grade 1 to 4a (the commonest complications including urine leak (n=5), acute kidney injury (n=2), and wound infection (n=2)). Patients who underwent cPN for a metachronous contralateral renal mass and a renal mass < 4cm had the best overall survival (61 and 42 months, respectively). A significant difference was observed in median overall survival in patients presenting with M1 vs. M0 disease[27]; vs. 63 months, respectively (p=0.003). These findings suggest that metastasis at original diagnosis and the timing of presentation of the index lesion have an important role in survival.

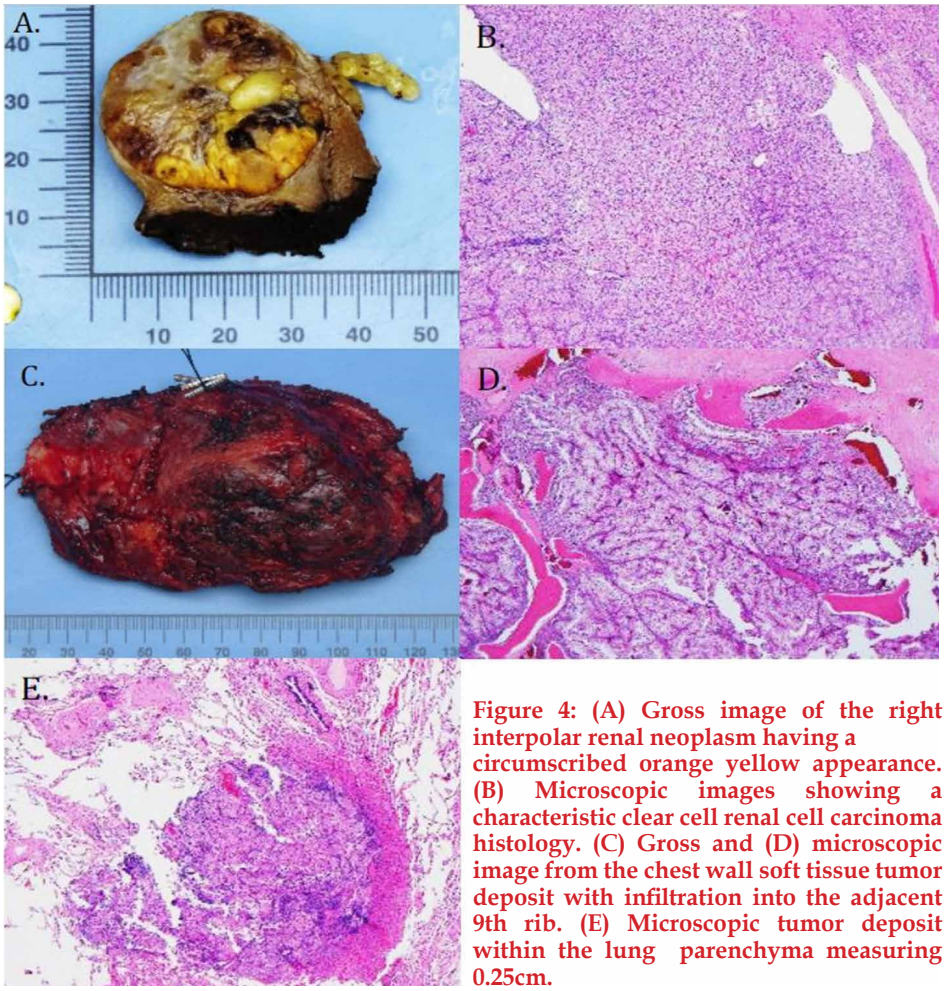

Figure 4: (A) Gross image of the right interpolar renal neoplasm having a circumscribed orange yellow appearance. (B) Microscopic images showing a characteristic clear cell renal cell carcinoma histology. (C) Gross and (D) microscopic image from the chest wall soft tissue tumor deposit with infiltration into the adjacent 9th rib. (E) Microscopic tumor deposit within the lung parenchyma measuring 0.25cm.

The most recent addition to the literature was a report from the National Cancer Database (NCDB) which examined the trends in usage of cPN and effect on overall survival in 10,144 patients with mRCC (9,764 patients undergoing cRN, 381 patients undergoing cPN)[25]. Rates of cPN increased over the 2006-2013 study period, from 1.8% to 4.3%. Survival curves were constructed for a matched cohort, and overall survival was significantly improved in patients undergoing cPN compared to cRN, with a 1-year overall survival of 67% and 76% in the cRN and cPN cohorts, respectively. When stratified by tumor size, cPN conferred a survival advantage only in patients with tumors <4 cm, and in a multivariate analysis, cPN was found to be independently associated with improved overall survival (HR = 0.81; 95% CI: 0.71–0.93; p=0.002). As with all registry-based analyses, these data are limited by lack of important prognostic variables used in risk stratification, the extent of metastatic burden, and the systemic therapies received.

Our institutional practice is to recommend nephron sparing approaches when technically feasible. In this case the indication for cPN

must be considered imperative given the patient's pre-existing CKD. In the cytoreductive setting, consideration for cPN is given to patients with pre-existing CKD, and is prioritized in patients with an anatomically or functionally solitary kidney and those with bilateral renal masses. Careful preoperative assessment of tumor complexity is critical, and patient counseling should include the potential for post-operative complications including bleeding events and urinary fistulae (greater in the partial compared to radical nephrectomy), understanding that such events could potentially delay the start of systemic therapy and/or enrollment onto a clinical trial. In patients in whom renal preservation is non-imperative (i.e. small renal mass with a normal contralateral kidney and no pre-existing CKD), cPN may be performed when technically feasible.

Conclusions

The role of partial nephrectomy in mRCC is currently supported by retrospective series which suggest the non-inferiority of cPN compared to cRN. Indeed, the framework for patient selection for cPN should prioritize those in whom renal preservation is imperative to prevent the further progression of CKD and its associated potential for cardiovascular morbidity and mortality and obviate the potential for end stage renal disease and dialysis. Partial nephrectomy in both the localized and metastatic settings demonstrate higher surgical complication rates compared to radical nephrectomy, and such risks, particularly for non-imperative indications, must be weighed against the benefits of nephron sparing approaches in properly selected patients.

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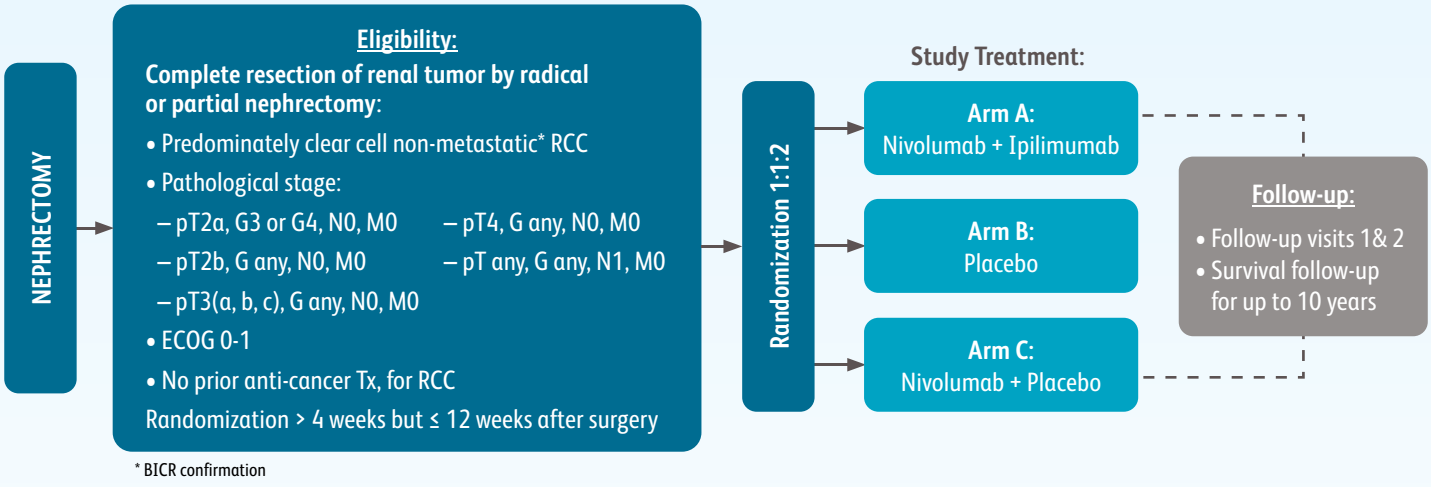
CHECKMATE 914 Study Design



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Reference: Data on file. Clinical protocol CA209-914. Princeton, NJ: Bristol-Myers Squibb Company, 2020.

RCC
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It's Clear as Day: HIF Signaling is Driving Force of the Clear Cell Morphology

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ABSTRACT

Clear cell renal carcinoma (ccRCC) is the most common form of kidney cancer with few therapeutic options in its advanced stages. ccRCC has genetic predisposition linked to the von Hippel Lindau gene. The product of this gene is responsible for proteasomal degradation of the hypoxia induced factors, which when stabilized activate hundreds of pathways, some of which promote tumor growth via angiogenesis, and upregulating glycogen and lipid biosynthesis. The "clear cell" morphology exhibits a large, translucent cytoplasm attributed to excessive glycogen and lipid deposition. Biochemical analyses have demonstrated that these lipid depots in ccRCC are enriched with high concentrations of high-density lipoprotein cholesterol, which is known to play an integral role in membrane rigidity and drug resistance. Glycogen synthesis serves as an energy source for tumoral growth, and lipid and cholesterol buildup within tumors has been linked to the formation of new cell membranes for cellular growth. In this review we will summarize how glycogen, lipid, and cholesterol metabolism play key roles in ccRCC tumor growth and the therapeutic potential of targeting these pathways.

KEYWORDS: • Hypoxia • Glycogen • Lipids • Cholesterol • Metabolism • ccRCC • Clear Cell Renal Cell Carcinoma •

INTRODUCTION

Clear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer, accounting for 70-75% of all kidney cancers, which affects males twice as often as females[1]. Current therapies include tyrosine kinase inhibitors (TKI) targeting factors involved in angiogenesis, which is essential for ccRCC tumor growth[2, 3], immunotherapies, targeting checkpoints regulating T cell activation[4], and the combination of both[5]. Identifying strategies to enhance the efficacy of current therapeutics, or to achieve durable disease control with reduced toxicity, has become the focus of current investigations.

ccRCC is linked to genetic factors that control cell metabolism, which makes it a ripe target for studying the oncologic metabolic shift known as the Warburg effect[5] as a potential therapeutic angle. The Warburg effect describes a dependence on aerobic glycolysis and lactic acid fermentation, while the tricarboxylic acid (TCA) cycle is downregulated even in the presence of oxygen. Studies have shown an increase in glucose uptake and aerobic glycolysis[6–9]. Fewer TCA intermediates were present in ccRCC, further confirming a shift towards aerobic glycolysis and indicating that pyruvate dehydrogenase is less active in ccRCC[6, 10]. This discovery also demonstrates that ATP production is dependent on aerobic glycolysis rather than oxidative phosphorylation[6, 10]. Within the TCA cycle, fumarate and malate levels were lower than normal tissues, while succinate, isocitrate, and citrate were higher, indicating a dependence on reductive carboxylation through citrate[8, 9]. This upregulation of reductive carboxylation was shown to be the route for fatty acid synthesis in ccRCC[11–13]. Given that a Warburg shift is a complex matter with many intermediates, this discovery in ccRCC provides multiple targets for therapeutic interventions; currently glutaminase inhibitors are being examined as target to prevent the formation of citrate, and therefore prevent reductive carboxylation in ccRCC[13].

These genetic predispositions in ccRCC are linked to chromosome 3 translocations, deletions, and mutations that effect the von Hippel Lindau (VHL) gene and its expression. This molecule is well known as a major effector of the hypoxia response, as the key negative regulator of the hypoxia inducible factors (HIF), a potent family of transcription factors and their downstream transcriptional targets such as vascular endothelial growth factor (VEGF)[14–16]. HIFs interact with the product of VHL (pVHL) through oxygen dependent domains that are targeted prolylhydroxylation enzymes[15, 17–19]. Under normal oxygen conditions, pVHL forms a ubiquitin ligase complex that recognizes hydroxylated proline residues and binds to the alpha subunit of HIF, leading to its polyubiquitination and degradation[16]. In hypoxic conditions HIF-α is not recognized by pVHL, allowing it to dimerize with HIF-ß. This dimer is an essential transcriptional regulator of hundreds of genes and signaling cascades that promote hypoxic adaptation[16], such as the activation of vascular endothelial growth factor receptor (VEGFR) signaling[20]. The HIF

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transcriptional network activates many enzymes and proteins integral to key metabolic pathways whose enhanced activity promotes tumor growth when pVHL is absent[21, 22].

The alpha subunit of HIF is present in two main forms—HIF-1α and HIF-2α. These both have different functions in the cell and presentation in ccRCC, and this distinction is critical for discussions of metabolism. Although both HIF factors are targets of pVHL, HIF-1α is not always present in ccRCC, and VHL-mutated tumors can be classified as expressing both HIF-1 and HIF-2 (HIH2), or HIF-2 only (H2)[23]. The downregulation of HIF-1α is one feature that drives more aggressive disease states[16] and suggests that HIF-1α has tumor suppressor functionality in ccRCC. While HIF-1α expression and activity cannot completely counteract the oncogenic effects of HIF-2α, its presence can decrease the severity of the prognosis16. When stabilized, HIF-1α, as a transcription factor, has potent effects on genes involved in activating aerobic glycolysis[24,25]. HIF-2α is expressed in all VHL-/- ccRCC and its elimination in these cells prevents tumor growth. The role of HIF-2α inhibition is to block HIF-2α transcription and therefore inhibit its downstream targets, such as VEGF, as well[26]. Studies have shown decreased tumor formation in xenograft models when HIF-2α is inhibited and pVHL is absent[27–29]. An effective mechanism of inhibition has been identified as inhibiting translation of HIF-2α by targeting the binding of its iron responsive element (IRE)[27, 30–32]. This study showed that hypoxia increases HIF concentration via a 5′-UTR IRE that binds to iron responsive protein 1 (IRP1), and when exogenous iron is added, translation of HIF proteins increases[30, 33]. Additionally, a recent study showed via proximity ligation assays that an inhibitor of HIF-2α, PT2385, decreased HIF-2α complexes in ccRCC biopsies analyzed before and during treatment[34]. In this study, they measured efficacy based on three factors: (1) the concentration of a downstream target of HIF-2α, erythropoietin (EPO), (2) the dissociation of HIF-2 complexes, and (3) the amount of gene expression. They found significantly decreased levels of EPO in 90% of patients after two weeks, showing the HIF inhibition was effective[34]. Using fluorescently conjugated antibodies for HIF-2α and HIF-1β, they were able to detect proximity via florescence microscopy to show a significant decrease in HIF-2α complexes during drug treatment as compared to pretreatment observations in two of three patient samples, and via RNA-seq analysis they found that 277 genes were downregulated by the inhibitor in those same two patients[34]. Complex dissociation and gene expression were found to be correlated to one another, indicating that downregulation of HIF-2α dependent genes may be necessary for antitumor activity[34]. Since this inhibitor was shown to have high variability, it was later improved to PT2977 and is now known as MK6482. The improvements were made with the goal of improving pharmacokinetic stability by decreasing binding to serum proteins, increasing the binding affinity for the HIF-2α binding pocket, and lowering the susceptibility of glucuronidation to a key hydroxyl group[26, 35–37]. A phase I trial with MK6482 concluded that 67% of patients had reduced target-lesion size with manageable anemia being the most common adverse event, and hypoxia being the only adverse event that caused patient discontinuation/dosage reduction[26, 38, 39]. A phase II trial used a cohort of patients with VHL-associated, nonmetastatic ccRCC; 87% of the cohort had decreased tumor size[26, 40]. A phase III trial is currently being conducted to compare the efficacy of MK6482 versus everolimus[26, 41]. The mechanism of resistance to HIF-2α inhibitors has been identified as either mutations that prevent drug binding or mutations that increase HIF stabilization[26, 34, 42], but newer HIF-2α inhibitors have the potential to overcome these mutation barriers by using a combinatorial

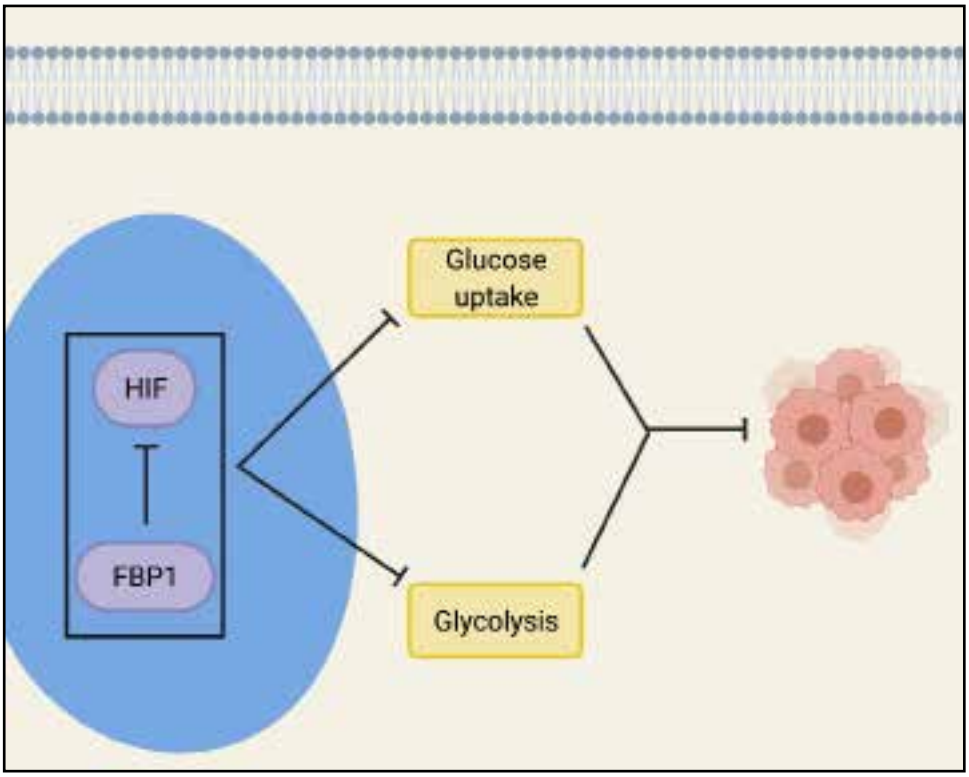

Figure 1 | FBP1 inhibits glucose uptake and glycolysis via HIF interaction. The rate-limiting gluconeogenic enzyme FBP1 can translocate to the nucleus, where it directly binds to the HIF inhibitory domain and negates HIF transcriptional activity. Consequentially, FBP1-mediated HIF inhibition impedes glucose uptake and glycolytic activity resulting in reduced ccRCC growth.

approach, targeting factors that are implicated when resistance occurs[26, 43–47]. Inhibitors of HIF-2α show great clinical promise alongside other targets in ccRCC.

Another target with approved therapies for RCC treatment is the mammalian target of rapamycin (mTOR). This classical metabolism regulator is a serine/threonine kinase that functions as a nutrient sensor by responding to environmental conditions, such as changes to oxygen levels, metabolite abundance, amino acids and growth factors[48]. Rapamycin (sirolimus), and rapamycin analogs everolimus and temsirolimus, block mTOR activity by forming a gain-of-function complex with FK506-binding-protein (FKBP12)[12–14]. This complex acts as an allosteric inhibitor of mTOR complex 1 to accomplish this inhibitory effect[48, 51]. In addition to regulating metabolic responses, this factor acts upstream of VEGFR to further promote angiogenesis. In vitro experiments have shown that inhibition of mTOR prevents angiogenesis and tumor growth as well as decreasing lipogenesis[48]. We will continue to discuss specific targets within glycogen metabolism, lipid metabolism, and cholesterol metabolism for the remainder of this review.

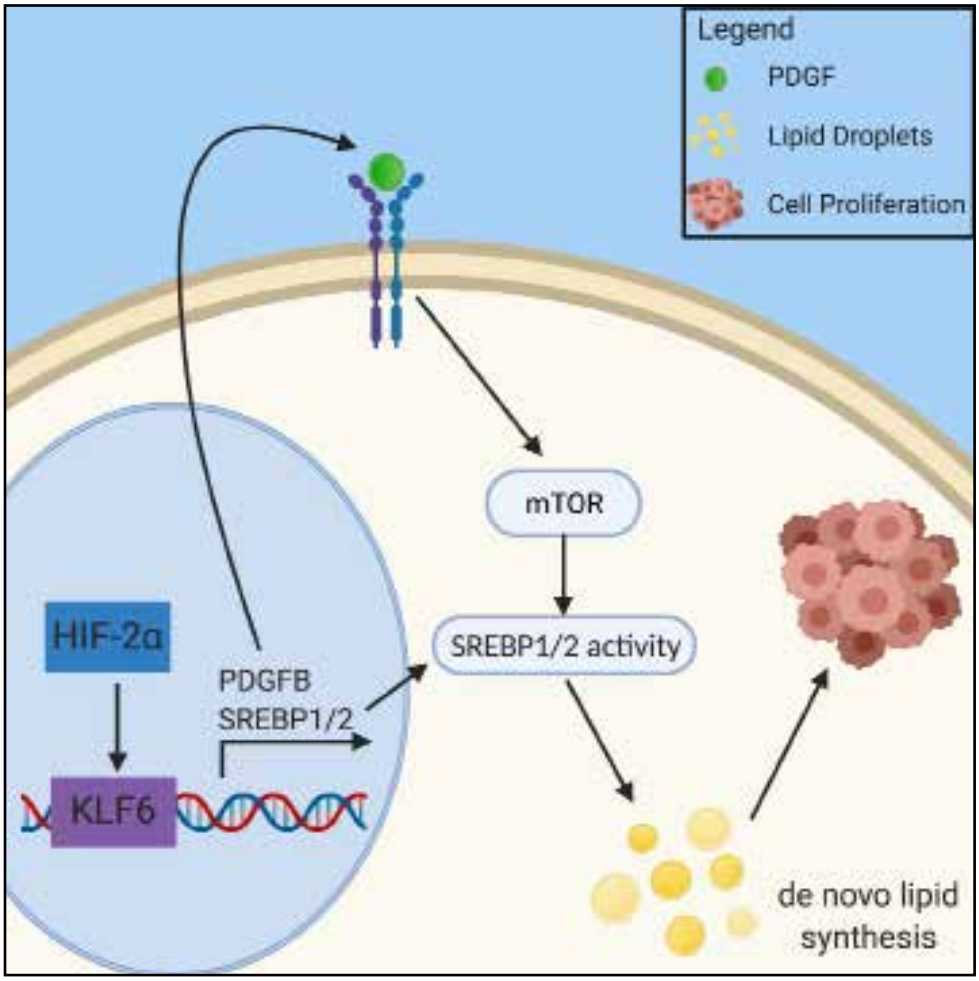

Figure 2 | Super enhancer activation by HIF-2α promotes KLF6-mediated transcription driving mTOR signaling and de novo lipid and cholesterol biosynthesis. The gene encoding the transcription factor KLF6 exists within a robust super enhancer which contains HIF-2α binding sites. When bound by HIF-2α, the super enhancer is activated, driving the expression of KLF6 resulting in upregulated transcription of its target genes PDGFB, SREBP1, and SREBP2. PDGFB signaling activates the mTOR pathway, which also promotes the activity of SREBP1 and SREBP2. Collectively, HIF-2α-mediated activation of KLF6 via the super enhancer potentiates de novo lipid and cholesterol biosynthesis supporting ccRCC tumorigenesis.

Glycogen Metabolism

ccRCC is classified by highly regulated lipid and glycogen metabolisms and increased deposits in the cell for both[52]. In general, activation of glycolysis and inactivation of the TCA cycle is associated with ccRCC and explains the energy supply for the tumor[53]. Furthermore, there is evidence that oxidative phosphorylation is inhibited in ccRCC, which further supports that the energy supply of these tumors is dependent on glycolysis[53]. Specifically, high concentrations of glycolytic enzymes, which are supported by a hypoxic microenvironment, and low concentrations of TCA cycle intermediates are found in these tumor cells[52]. In ccRCC cells, lactate is also upregulated, in part due to transcriptional activation of Lactate Dehydrogenase (LDH), further suggesting that the cells function on aerobic glycolysis[52, 54].

Although these trends are seen across the spectrum of ccRCC tumors, quantitatively, glycogen and lipid deposits are tumor grade dependent, with glycogen and lipid accumulation more prevalent in lower grade tumors[54]. These features have been linked to prognostic algorithms, such as the transcriptional ccA and ccB signature[55, 56]. Further investigations into the metabolic shifts associated with stage progression are being described with increasing frequency, most recently with the Cancer Genome Atlas index paper on ccRCC[5, 7] and dedicated metabolomic profiling[9]. Finally, failure of antitumor therapies has also been linked to the expression of glycolytic and hypoxia factors and presumed upregulation of compensatory signaling pathways[52].

Glycolysis and glycogen synthesis are regulated by several factors in the cell. As discussed previously, mTOR promotes tumor growth and angiogenesis in ccRCC. One way mTOR accomplishes this is by activating glycolysis and glycogen synthesis, providing an energy source for the tumors. A recent study showed that the phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mTOR signaling axis is associated with the progression of ccRCC[57]. Human ccRCC cell lines CAKI-1 and RCC4 were treated with NVP/MEZ2[35], a dual inhibitor of both PI3K and mTOR, and showed decreased phosphorylation of AKT protein and mTOR. By effectively

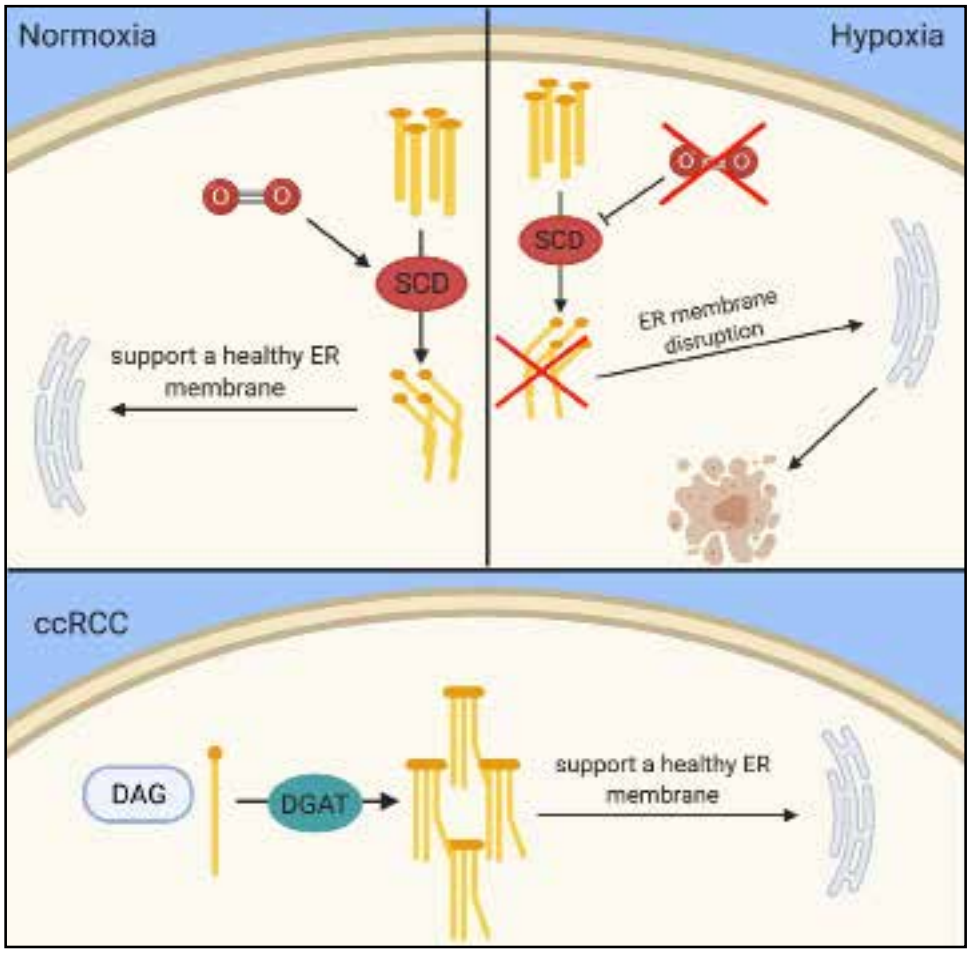

Figure 3 | Hypoxia promotes the accumulation of saturated fatty acids. Stearoyl-CoA desaturase (SCD) is an oxygen-dependent enzyme localized in the endoplasmic reticulum that catalyzes the incorporation of a double-bond into stearate, producing the monounsaturated fatty acid oleate. Under hypoxic conditions, the enzyme is rendered inactive leading to an accumulation of saturated fatty acids which disrupt the ER membrane and induce an apoptotic cascade. ccRCCs utilize HIF signaling to mobilize triglycerides via diglyceride acyltransferase (DGAT) activity into lipid droplets and evade lipotoxicity induced cell death.

blocking AKT and mTOR activation, the researchers observed significant inhibition of glycolysis and glycogen synthesis, removing the energy source and decreasing tumoral growth[57]. As a tyrosine kinase that orchestrates a robust signaling cascade regulating many biosynthetic processes, PI3K has long been an integral target for TKI treatments[58].

Another key regulator of glucose metabolism is glycogen synthase 1 (GYS1)[59]. Glycogen synthase is a major regulator of glycogen catabolism which, when active, promotes the synthesis of glycogen. A recent study showed that GYS1 is significantly overexpressed in ccRCC tumors and was mostly found in the cytoplasm, which is where glycogen synthesis occurs. This overexpression was then correlated to poor overall survival in the clinical setting[59]. Additionally, this study showed in a western blot that p65 expression increased when GYS1 was overexpressed via, indicating that GYS1 interacts with the canonical NF-κB pathway. Glycogen synthase is inactivated in the body by glucagon and epinephrine, so finding treatments that mimic these effects in tumor cells and treating in combination with inhibitors of glycolysis, could be an area for further investigation.

In addition to factors that promote the expression and activity of glycolytic enzymes for energy generation, several cellular modifications have been observed which suggest the regulation of this bioenergetic pathway is tightly controlled. Fructose-1,6-bisphosphatase 1 (FBP1) is a rate-limiting gluconeogenic enzyme that plays a large role in glucose metabolism and inhibits HIF proteins in the nucleus[54, 60]. FBP1 opposes ccRCC by inhibiting glycolysis and cell proliferation in cells[52, 60]. Inhibition of FBP1 increases glucose uptake and, therefore, allows tumor growth to progress. Evidence supported by cellular fractionation and immunofluorescent staining suggests that FBP1 suppresses HIF proteins in the nucleus, and showed that an interaction between FBP1 and HIF proteins is necessary for an effect on glucose metabolism[60]. This was further proven by using a nuclear-excluded form of FBP1 which failed to inhibit the HIF proteins in the cell, showing that the effects of FBP1 inhibition originate in the nucleus[60]. Overall, the FBP1 activity in the cell that affects the growth and development of tumors, works by regulating HIF from the nucleus. The inhibition of FBP1 promotes glycolytic functions, thereby enhancing the Warburg effect, while simultaneously failing to suppress nuclear HIF function, both of which is associated with poor prognosis in ccRCC (Figure 1).

Lipid Metabolism

In ccRCC, lipid metabolism is an important factor for tumor cell growth because it provides the membrane structures for the newly formed tumor cells. Specifically, lipid droplet buildup serves as fuel for membrane synthesis for these tumor cells[24–26]. This process of lipid droplet buildup occurs through increased lipogenesis via reductive carboxylation in parallel with the inhibition of beta-oxidation[11–13, 61]. Evidence shows that increased lipid storage in ccRCC cells is associated with increased tumorigenesis, and there is a correlation between lipid metabolism and ccRCC risk score[62, 63]. A recent study looked into the effects of VHL status on lipid catabolism versus lipid uptake. By staining with Oil red O to assess changes to the presence of lipid droplets, Du *et al.* observed a decrease in lipid droplets in cells where VHL was reconstituted, suggesting that the presence of pVHL impacts either lipid uptake/synthesis or promotes lipid catabolism[62]. In an effort to interrogate the effect on lipid uptake, this study

tracked the uptake of BODIPY fluorescent fatty acid dyes and concluded that lipid uptake occurred independently from VHL status[62]. Therefore, lipid deposition is VHL-mediated while lipid uptake occurs independently of VHL, indicating that de novo lipid synthesis is the major contributor to lipid droplet formation in VHL-/- ccRCC[62]. Several factors in the cell regulate this process and are currently being studied as points of therapeutic intervention.

One regulator of interest is Kruppel life factor 6 (KLF6). KLF6 is a zinc finger family transcription factor that was shown to have effects on lipid metabolism[64] and has been implicated as a tumor promoting factor in ccRCC via its effects on cell proliferation and high levels of expression. The gene encoding this transcription factor was found to be located within a locus containing one of the strongest super enhancers. Additionally, this association was linked to enhanced KLF6 expression when comparing ccRCC samples to adjacent normal tissue, as well as to other solid tumors lacking this super enhancer. The Cancer Genome Atlas data of ccRCC showed a correlation between HIF-2α expression and KLF6 expression; this study investigated this interaction through VHL reintroduction experiments[64]. The reintroduction of VHL caused a decrease in mRNA expression of KLF6 and, using ChIP-seq, they showed that VHL introduction caused a decrease in activity in the region where the super enhancer is located64. Additionally, the ChIP-seq data show that HIF-2α was bound at this same region[64]. This indicates that HIF-2α is an activator of this super enhancer, so when HIF-2α is present, it binds to the super enhancer and there is robust transcription of KLF6. To expand on their findings, the researchers next assessed the impact of altering KLF6 expression in ccRCC. Pathway analysis was performed on RNA-seq data collected from cells depleted of KLF6 and revealed a significant downregulation of lipid and cholesterol metabolism pathways[64]. Specifically, they identified sterol regulatory element binding protein 1 and 2 (SREBP1 and SREBP2), master transcriptional regulators of lipid signaling, were downregulated in response to KLF6 suppression. These findings were validated with qPCR experiments, where it was observed that SREBP1, SREBP2, and several of their downstream targets were downregulated in response to KLF6 inhibition. Importantly, these results translated further into an overall decrease in intracellular cholesterol and lipids when KLF6 is depleted. These studies elegantly display the critical role HIF-2α plays in regulating KLF6, an essential piece of lipid and cholesterol metabolism in ccRCC.

mTOR signaling through mTORC1 also regulates SREBP1 and SREBP2. Investigations into the interaction between mTORC1 and KLF6 revealed that KLF6 both directly interacts with SREBP1 and SREBP2, and promotes mTOR signaling by enhancing platelet-derived growth factor subunit B (PDGFB); both of these factors contribute to an increase in lipid metabolism and anabolic signaling, resulting in increased tumor growth[64] (Figure 2). SREBP acts by inducing the production of enzymes involved in cholesterol and lipid synthesis, including the rate-limiting enzyme of cholesterol synthesis, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR)[65–67]. A recent study showed that the gene TRC8 represses the translation of these key transcription factors, therefore inhibiting lipid and cholesterol synthesis, which makes it a target for future investigation[65].

HIF proteins promote lipid metabolism via a variety of mechanisms. HIF proteins promote dietary lipid uptake, interact with the gene PLIN2 to promote lipid storage, and interacts the gene encoding carnitine palmitoyl transferase 1 (CPT1A) to promote lipid droplet formation. Lipid droplet formation was shown to be HIF protein dependent; cells that were double knockdown for HIF-1α and HIF-2α had a significant decrease in lipid droplet formation[62]. Additionally, this study showed that HIF-1α and HIF-2α bind specifically to a CPT1A promoter via ChIP analysis with HIF-1α and HIF-2α antibodies in 12 regions identified as HIF response elements[62]. A recent study showed that dietary lipid uptake leading to increased lipid in the kidneys being driven by HIF-1α signaling in human ccRCC[12]. The gene PLIN2 was found to be over expressed in ccRCC and suggests an interaction with HIF-2α allows for heightened lipid storage. The mechanism by which this occurs is through stabilization of the endoplasmic reticulum (ER). The interaction between PLIN2 and HIF-2α is required to maintain ER homeostasis and prevents cell death under stressful conditions68. This is a possible explanation for drug resistance; when the ER is targeted by therapeutic interventions, this interaction could be preventing apoptosis. Another study further analyze the HIF dependence of lipid droplet formation by focusing on the interaction between HIF proteins and the gene encoding CPT1A, which is a major regulator of lipid synthesis. When CPT1A was in low concentrations, it has shown increased lipid storage associated with tumorigenesis. It was discovered that HIF-1α and HIF-2α directly bind with CPT1A to inhibit its function and therefore increase lipid droplet formation[62].

Another enzyme intimately involved in lipid metabolism is hydroxyacyl-CoA dehydrogenase alpha subunit (HADHA). The role of HADHA in regulating lipid droplet formation has been examined in several models of ccRCC, including the ccRCC cell line 786-O. In this cell line, OmicsNet and STRING analysis revealed an abundance of enzymes involved in lipid metabolism, including HADHA and acetyl-CoA acetyltransferase 2 (ACAT2), exist in a network. Additionally, several direct protein-protein interactions were identified in this network, including a link between HADHA and ACAT2, which allows them to interact with substrates in a coordinated manner[69, 70]. HADHA was shown to activate ACAT2, an enzyme directly involved in lipid breakdown, so at low HADHA levels, there are low levels of lipid breakdown causing lipid stores to be maintained, which is associated with ccRCC tumor cell proliferation[69]. In a separate study, it was confirmed that there is downregulation of both HADHA and ACAT2 in ccRCC patient tissues and that this

downregulation of HADHA expression in ccRCC tumors was associated with better patient survival[70]. The goal in studying lipid metabolism of ccRCC is to identify opportunities to intervene therapeutically inhibiting the rapid proliferation and expansion of cells present in the tumor, as well as impeding formation of new cells. KLF6, PLIN2, HIF-2α, HADHA, ACAT, and CPT1A are only a few of the lipid regulators that have been identified for discussion in this review, but the findings linked to these mediators suggest avenues that effect lipid droplet buildup could be attractive targets for metabolic factors incorporated into ccRCC prognosis and treatment.

Cholesterol Metabolism

The clear cell phenotype is characterized by lipid buildup, but recent studies have shown that high-density lipoprotein (HDL) cholesterol is accumulated in the highest levels within ccRCC tissues. HDL-cholesterol is also seen in higher amount in ccRCC tumoral cells compared the surrounding non-malignant kidney tissues[71–73]. The deregulation of cholesterol compounds with the accumulation of other lipids to stabilize the membrane of the tumoral cells and increases tumorigenesis when it cannot be regulated properly. In multiple studies, cholesterol synthesis did not appear to be affected, which suggests that the cholesterol buildup seen within the cells is due to exogenous cholesterol influx and endogenous cholesterol efflux[71, 74]. Cholesterol was also discovered to play a role in promoting metastasis of ccRCC[75]. Hypoxia effects fatty acid saturation via the oxygen dependent enzyme stearoyl-CoA desaturase (SCD). SCD under hypoxic conditions is inhibited, which leads to a buildup of fatty acid precursors in the cell[76]. This leads to disruption of the endoplasmic reticulum and induces apoptosis[76–78] (Figure 3).

A recent study demonstrated how cholesterol buildup in tumoral cells is due to the uptake of cholesterol rather than synthesis[71]. The cholesterol synthesis rate limiting enzyme HMGCR was inhibited in tumors containing higher levels of cholesterol, suggesting that cholesterol de novo synthesis is unlikely to be occurring in the tumor cell. Furthermore, they showed that the receptor for HDL-cholesterol, scavenger receptor B1 (SR-B1), which is usually in very low concentrations in the cell, had elevated levels in tumors containing high levels of cholesterol[71].

Another study explored the difference in predicted treatment efficacy by targeting the transcription factor receptor, liver X receptor (LXR) with an agonist versus an inverse agonist. The agonist used was LXR623 and the inverse agonist was SR9243. Both inhibited cell proliferation and induced apoptosis, but by different mechanisms. LXR623 killed tumor cells by promoting cholesterol efflux and inhibiting cholesterol influx. SR9243 upregulated the HMOX2 gene which reduced the angiogenic potential and proliferation, and it also caused a decrease in intracellular triglycerides. Neither affected the cholesterol synthesis pathway[74]. This makes these therapeutic targets attractive for future consideration because the synthesis of cholesterol is the main mechanism of cholesterol accumulation in normal cells. Since there is little to no new synthesis of cholesterol in ccRCC tumoral cells, but rather change in how much cholesterol is moving into the cell, the cholesterol receptors can be targets for therapeutic intervention with a potential window of specificity for tumor cells in this case.

Although high cholesterol levels are common to all ccRCC tumors, cholesterol levels in the body have also been associated with outcome in the case of ccRCC. High HDL-cholesterol levels were correlated with better outcomes and can act as a similar predictor in other forms of cancer as well[79]. The mechanism by which this is achieved is believed to be that the higher HDL-cholesterol in the body, the less uptake of low-density lipoproteins (LDL) by tumor cells which would suggest that there is less lipid support for tumor growth[75], although additional work is needed to understand this association more fully. Statins, which are clinically used to lower LDL levels in patients, have been considered as a possible therapeutic target. A recent study showed that treatment with statins in VHL-deficient ccRCC elicited promising early findings and suggested that the observed lethality is HIF dependent, highlighting statins as promising therapeutic tools[80].

Future Directions

Further analysis is needed for current treatments that can augment the current armamentarium for ccRCC. An area for growth in the research of therapeutic treatments is in targeting the metabolic dependencies, such as glycolysis, lipid, and cholesterol metabolism pathways, that discriminate ccRCC cells from normal tissues, or that reveal cellular adaptations associated with disease progression.

In order to control glycogen metabolism in a favorable manner, promoting glycogen breakdown while simultaneously preventing glucose metabolism and glycogen synthesis is the goal. Glucagon is a natural substance in the body that accomplishes this by activating glycogen phosphorylase through the activity of protein kinase A. Finding a molecular target that can mimic this pathway specifically in ccRCC could be a direction worth pursuing. It is worth noting, glycogen breakdown to glucose-1-phosphate feeds into glycolysis which could fuel growth, so another approach could involve a combination of nutrient restriction and current frontline therapies that impede cell growth and metabolism. There are no current studies that have examined the effects of dietary restrictions on ccRCC patients, but a correlation between BMI and the presence or absence of a VHL mutation in ccRCC patients has been observed[81].

In considering lipid and cholesterol metabolism for therapeutic development, it is known how the inhibition of SCD leads to cholesterol accumulation, but there have been no further studies completed to show the relationship between VHL mutations and cholesterol synthesis. Secondly, while statins look to be a promising target and have shown to inhibit the proliferation of VHL-deficient ccRCC in vitro and in vivo, further analysis needs to

be done on the efficacy, mode of action, and safety of these treatments. Also, since dietary lipid intake was shown to effect lipid buildup in the kidneys, further investigation should be conducted to determine outcomes when cholesterol treatments are compounded with dietary and host factors.

There is minimal literature in ccRCC investigating the role of acetate metabolism, an important branch of acetyl-CoA production and a key contributor to lipogenesis. Therefore, acetate metabolism and the enzyme acetate-dependent acetyl-CoA synthetase 2 (ACSS2) could be a potential therapeutic target. While this has not been explored in ccRCC, researchers have demonstrated in other tissues that inhibition of ACSS2 leads to the inhibition of lipid metabolism, changes to histone acetylation, and reduced tumor growth[82]. ACSS2 is required for acetate uptake and ACSS2 deficient mice were shown to have decreased liver tumor formation[83]. Nuclear ACSS2 synthesizes acetyl-CoA for histone acetylation, which activates lysozyme biogenesis[84] Interestingly, it has been shown that acetyl-CoA derived from ACSS2 is required for the acetylation of HIF-2α and results in optimal signaling[85]. These factors make ACSS2 an enzyme of interest for further investigation.

In summary, bioenergetic metabolism has long been recognized as a differentiating feature of ccRCC, and as we gain insights into these pathways and methods to intervene. Future work to incorporate these strategies in combination or in sequence with existing therapies will be a major opportunity to impact this metabolically driven disease.

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Essential Peer-Reviewed Reading

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Recent eUpdate to the ESMO Clinical Practice Guidelines on renal cell carcinoma on cabozantinib and nivolumab for first-line clear cell renal cancer: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Powles T, on behalf of theESMO Guidelines Committee. DOI:https://doi.org/10.1016/j.annonc.2020.11.016

Summary: This eUpdate outlines updated treatment recommendations for first-line ccRCC. The changes are based on recent data for the combination of cabozantinib and nivolumab. This is based on data from the CheckMate 9ER study, which is one of a number of practice-changing studies comparing PD-1 inhibitors plus VEGF TKIs vs sunitinib in the front-line setting. Results showed that the study met the primary endpoint of PFS, with a median of 16.6 months for the combination vs 8.3 months for sunitinib ($P < 0.0001$). There was also a significant overall survival advantage for cabozantinib and nivolumab at interim analysis (18.1 months median follow-up) [hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.40-0.89; $P < 0.001$]. Reponses rates also significantly favoured the combination (56% versus 27% and HR 0.51, 95% CI 0.41-0.64, respectively). No new adverse event (AE) signals were identified and AE profiles were in line with expectation.

Results of a multicenter, phase 2 study of nivolumab and ipilimumab for patients with advanced rare genitourinary malignancies. McGregor et al. J Immunother Cancer. 2021; 127(6), 840-849.

Results: Fifty-five patients were enrolled at 6 institutions between April 2018 and July 2019 in 3 cohorts: BUTCVH (n = 19), adrenal tumors (n = 18), and other tumors (n = 18). The median follow-up was 9.9 months (range, 1 to 21 months). Twenty-eight patients (51%) received 4 doses of nivolumab and ipilimumab; 25 patients received nivolumab maintenance for a median of 4 cycles (range, 1-18 cycles). The ORR for the entire study was 16% (80% confidence interval, 10%-25%); the ORR in the BUTCVH cohort, including 2 complete responses, was 37%, and it was 6% in the other 2 cohorts. Twenty-two patients (40%) developed treatment-related grade 3 or higher toxicities; 24% (n = 13) required high-dose steroids (≥40 mg of prednisone or the equivalent). Grade 5 events occurred in 3 patients; 1 death was treatment related.

Conclusions: Nivolumab and ipilimumab resulted in objective responses in a subset of patients with rare genitourinary malignancies, especially those with BUTCVH. An additional cohort exploring their activity in genitourinary tumors with neuroendocrine differentiation is ongoing.

Efficacy and Safety of Atezolizumab Plus Bevacizumab Following Disease Progression on Atezolizumab or Sunitinib Monotherapy in Patients with Metastatic Renal Cell Carcinoma in IMmotion150: A Randomized Phase 2 Clinical Trial. Powles T et al. Eur Urol. 2021. S0302-2838(21)00003-8.

Abstract: Objective: To evaluate the efficacy and safety of atezolizumab + bevacizumab following disease progression on atezolizumab or sunitinib monotherapy in patients with mRCC.

Results: Fifty-nine patients in the atezolizumab arm and 78 in the sunitinib arm were eligible, and 103 initiated second-line atezolizumab + bevacizumab (atezolizumab arm, n = 44; sunitinib arm, n = 59). ORR (95% confidence interval [CI]) was 27% (19-37%). The median PFS (95% CI) from the start of second line was 8.7 (5.6-13.7) mo. The median event follow-up duration was 19.4 (12.9-21.9) mo among the 25 patients without a PFS event. Eighty-six (83%) patients had treatment-related adverse events; 31 of 103 (30%) had grade 3/4 events. Limitations were the small sample size and selection for progressors.

Conclusions: The atezolizumab + bevacizumab combination had activity and was tolerable in patients with progression on atezolizumab or sunitinib. Further studies are needed to investigate sequencing strategies in mRCC.

Combination antiangiogenic tyrosine kinase inhibition and anti-PD1 immunotherapy in metastatic renal cell carcinoma: A retrospective analysis of safety, tolerance, and clinical outcomes

Methods: We conducted a retrospective analysis of mRCC patients who received combination TKI-IO post-first-line therapy between November 2015 and January 2019 at MD Anderson Cancer Center and Duke Cancer Institute. Chart review detailed patient characteristics, treatments, toxicity, and survival. Independent radiologists, blinded to clinical data, assessed best radiographic response using RECIST v1.1.

Results: We identified 48 mRCC patients for inclusion: median age 65 years, 75.0% clear cell histology, 68.8% IMDC intermediate risk, and median two prior systemic therapies. TKI-IO combinations included nivolumab-cabozantinib (N +C; 24 patients), nivolumab-pazopanib (N+P; 13), nivolumab-axitinib (6), nivolumab-lenvatinib (2), and nivolumab-ipilimumab-cabozantinib (3). The median progression-free survival was 11.6 months and the median overall survival was not reached. Response data were available in 45 patients: complete response (CR; n = 3, 6.7%), partial response (PR; 20, 44.4%), stable disease (SD; 19, 42.2%), and progressive disease (3, 6.7%). Overall response rate was 51% and disease control rate (CR+PR+SD) was 93%. Only one patient had a grade ≥3 adverse event.

Conclusion: To our knowledge, this is the first case series reporting off-label use of combination TKI-IO for mRCC. TKI-IO combinations, particularly N+P and N+C, are well tolerated and efficacious. Although further prospective research is essential, slow disease progression on IO or TKI monotherapy may be safely controlled with addition of either TKI or IO.

Outcomes of Patients with Metastatic Renal Cell Carcinoma Treated with Targeted Therapy After Immuno-oncology Checkpoint Inhibitors. Graham J. Eur Urol Oncol. 2021; 4(1), 102-111.

Objective: To describe treatment sequence and assess clinical effectiveness of targeted therapy for mRCC patients who received prior IO therapy. Design: A retrospective, longitudinal cohort study using data from eight international cancer centers was conducted. Patients with mRCC were ≥18 yr old, received IO therapy in any line, and initiated targeted therapy following IO therapy discontinuation. Patients were treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) or mammalian target of rapamycin inhibitors (mTORIs). Outcomes were time to treatment discontinuation (TTD), overall survival (OS), and objective response rate (ORR). Crude and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard models.

Results: Among 314 patients, 276 (87.9%) and 38 (12.1%) were treated with VEGFR-TKI and mTORI therapy, respectively. The most common tyrosine kinase inhibitor treatments were axitinib, cabozantinib, and sunitinib following IO therapy. In adjusted models, patients treated with VEGFR-TKI versus mTORI therapy had lower hazard of TTD after IO treatment (aHR = 0.46; 95% CI: 0.30–0.71; $p < 0.01$). One-year OS probability (65% vs 47%, $p < 0.01$) and proportion of ORR (29.8% vs 3.6%, $p < 0.01$) were significantly greater for patients treated with VEGFR-TKIs versus those treated with mTORIs.

Conclusions: Targeted therapy has clinical activity following IO treatment. Patients who received VEGFR-TKIs versus mTORIs following IO therapy had improved clinical outcomes. These findings may help inform treatment guidelines and clinical practice for patients post-IO therapy.

Real-world evidence of cabozantinib in patients with metastatic renal cell carcinoma: Results from the CABOREAL Early Access Program. Albiges L. Eur J Cancer . 2021 Jan;142:102-111.

Patients and methods: This multicentre (n = 26), observational, retrospective study enrolled patients with mRCC who had received ≥1 dose of cabozantinib. Overall survival (OS) was estimated using the Ka-

plan-Meier method; subgroups were compared using the log-rank test. A multiple Cox regression model assessed predictive factors of OS after cabozantinib initiation.

Results: Four hundred and ten recruited patients started treatment between September 2016 and February 2018: the Eastern Cooperative Oncology Group Performance Status ≥2, 39.3%; poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk, 31.7%; 0-1, 2 and ≥3 previous treatment lines, 25.3%, 33.4% and 41.2%, respectively; bone metastases, 55.9%; brain metastases, 16.8%. Median (min-max) follow-up was 14.4 (0-30) months. Overall, 57.0% of patients had a dose reduction, 15.6% an alternative dose schedule. The median average daily dose was 40.0 mg. Median (quartile [Q]1-Q3) treatment duration was 7.6 (0.1-29.1) months, median OS was 14.4 months, and the 12-month OS rate was 56.5% (95% confidence interval: 51.5-61.2). Most patients (54.4%) received subsequent treatment. Predictive factors associated with longer OS were body mass index ≥25 kg/m2 (p = 0.0021), prior nephrectomy (p = 0.0109), favourable or intermediate IMDC risk (p < 0.0001) and cabozantinib initiation at 60 mg/day (p = 0.0486).

Conclusion: In the largest real-world study to date, cabozantinib was effective in unselected, heavily pretreated patients with mRCC. Initiation at 60 mg/day was associated with improved outcomes. CLINICALTRIALS: NCT03744585.

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. Motzer R et al. N Engl J Med. 2021 Feb 13. doi: 10.1056/NEJMoa2035716.

Results: A total of 1069 patients were randomly assigned to receive lenvatinib plus pembrolizumab (355 patients), lenvatinib plus everolimus (357), or sunitinib (357). Progression-free survival was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 vs. 9.2 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.32 to 0.49; P<0.001) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 vs. 9.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.80; P<0.001). Overall survival was longer with lenvatinib plus pembrolizumab than with sunitinib (hazard ratio for death, 0.66; 95% CI, 0.49 to 0.88; P = 0.005) but was not longer with lenvatinib plus everolimus than with sunitinib (hazard ratio, 1.15; 95% CI, 0.88 to 1.50; P = 0.30). Grade 3 or higher adverse events emerged or worsened during treatment in 82.4% of the patients who received lenvatinib plus pembrolizumab, 83.1% of those who received lenvatinib plus everolimus, and 71.8% of those who received sunitinib. Grade 3 or higher adverse events occurring in at least 10% of the patients in any group included hypertension, diarrhea, and elevated lipase levels.

Conclusions: Lenvatinib plus pembrolizumab was associated with significantly longer progression-free survival and overall survival than sunitinib. CLEAR ClinicalTrials.gov number, NCT02811861.

Open-Label, Single-Arm, Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Non-Clear Cell Renal Cell Carcinoma. McDermott D et al. J Clin Oncol. 2021; 39(9):1029-1039.

Results: Among enrolled patients (N = 165), 71.5% had confirmed papillary, 12.7% had chromophobe, and 15.8% had unclassified RCC histology. Most patients (67.9%) had intermediate or poor International Metastatic RCC Database Consortium risk status and tumors with programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥ 1 (61.8%). The median time from enrollment to database cutoff was 31.5 months (range, 22.7-38.8). In all patients, the ORR was 26.7%. The median duration of response was 29.0 months; 59.7% of responses lasted ≥ 12 months. The ORR by CPS ≥ 1 and CPS < 1 status was 35.3% and 12.1%, respectively. The ORR by histology was 28.8% for papillary, 9.5% for chromophobe, and 30.8% for unclassified. Overall, the median progression-free survival was 4.2 months (95% CI, 2.9 to 5.6); the 24-month rate was 18.6%. The median overall survival was 28.9 months (95% CI, 24.3 months to not reached); the 24-month rate was 58.4%. Overall, 69.7% of patients reported treatment-related adverse events, most commonly pruritus (20.0%) and hypothyroidism (14.5%). Two deaths were treatment related (pneumonitis and cardiac arrest).

Conclusion: First-line pembrolizumab monotherapy showed promising antitumor activity in nccRCC. The safety profile was similar to that observed in other tumor types.

KCJ MEDICAL INTELLIGENCE

Newsworthy, Late-breaking Information From Web-based Sources, Professional Societies, and Government Agencies

FDA Approves Tivozanib as First Therapy for a Relapsed/Refractory Advanced RCC Subgroup

The first therapy for adults with relapsed or refractory advanced renal cell carcinoma who have received two or more prior systemic therapies has been granted approval by the FDA. This US FDA approval was granted based on the data from the phase 2 TIVO-3 clinical trial (NCT02627963). TIVO-3 is a controlled, multicenter, open-label, phase III trial of 350 patients with highly refractory metastatic RCC who had failed ≥2 prior regimens, including VEGF TKI treatment.

Lead investigator Dr. Brian Rini of this trial (NCT02627963) along with other senior investigator Dr. Thomas Hutson discussed the TIVO-3 outcomes and prospect of tivozanib for combinatorial therapy with other IO agents (See Page 4: *Roundtable Discussion* in this issue).

Results that the hazard ratio for overall survival (OS) with tivozanib versus sorafenib was 0.97 (95% CI, 0.75-1.24; P =.78). The median OS in the tivozanib arm was 16.4 months (95% CI, 13.4-22.2) and 19.2 months in the sorafenib arm (95% CI, 15.0-24.2). The study included a subgroup of patients who received previous checkpoint inhibitor and VEGF inhibitor therapy, and in this population, the HR for death was 0.55 and was 0.57 for those who received 2 prior checkpoint or VEGF inhibitors. In terms of response, tivozanib led to an 18% (95% CI: 12%-24%) overall response rate compared with 8% (95% CI: 4%-13%) in the sorafenib arm. Tivozanib appeared to have a favorable safety profile during the study. Treatment-related adverse events (TRAEs) were observed in 84% compared with 94% of the sorafenib arm. Serious TRAEs were observed in 11% of the patients who received tivozanib compared with 10% of those treated with sorafenib.

Reference: 1. Rini BI, Pal SK, Escudier BJ, Atkins MB, Hutson TE, Porta C, Verzoni E, Needle MN, McDermott DF. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol. 2020 Jan;21(1):95-104. PMID: 31810797.

FDA approves nivolumab/cabozantinib combo for frontline kidney cancer

On January 22, 2021, the Food and Drug Administration approved the combination of nivolumab (Opdivo, Bristol-Myers Squibb Co.) and cabozantinib (Cabometyx, Exelixis) as first-line treatment for patients with advanced renal cell carcinoma (RCC). The approval of nivolumab/cabozantinib combination regimen is based on findings from the phase 3 CheckMate-9ER trial (NCT03141177). Results indicated that the combination reduced the risk of disease progression or death by 49% versus sunitinib (Sutent) in treatment-naïve patients with advanced RCC, with a median progression-free survival of 16.6 months versus 8.3 months, respectively (HR, 0.51; P <.0001). The objective response rate (ORR) was also doubled with nivolumab/cabozantinib in this setting compared with sunitinib, at 55.7% versus 27.1%, respectively (P <.0001). In the combination arm, the complete response (CR) rate was 8.0%, the partial response (PR) rate was 47.7%, and the stable disease (SD) rate was 32.2%. Additionally, 5.6% of patients had progressive disease (PD) and 6.5% were not evaluable or not assessed. In the sunitinib arm, the CR, PR, and SD rates were 4.6%, 22.6%, and 42.1%, respectively.

Regarding safety, the incidence of the most common, any-grade and high-grade treatment-related adverse events (TRAEs) were similar in both arms. The overall rate of serious AEs was similar between the 2 groups; however, liver toxicity was more common with cabozantinib/nivolumab. Nineteen percent of patients on the combination required corticosteroids due to immune-related AEs, 4% of whom needed corticosteroids for at least 30 days.

Reference: Choueiri TK, Powles T, Burotto M, et al. Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial. Ann Oncol. 2020;31(4). Abstract 696O.

FDA Grants Belzutifan Priority Review for VHL-Associated RCC.

The novel, selective HIF-2 alpha inhibitor belzutifan was granted a priority review by the FDA for the treatment of patients with VHL–associated RCC who do not require immediate surgery. The primary end point of the study is ORR in VHL disease–associated RCC tumors and secondary end points include DOR, TTR, PFS, and time to surgery (TTS) in VHL disease–associated RCC tumors as well as ORR, DOR, TTR, PFS, and TTS in non-RCC tumors. This open-label phase 2 Study-004 trial (NCT03401788) supported the NDA, showing a significant response rate of 36.1% (95% CI, 24.2%-49.4%) in patients with VHL disease–associated RCC treated with belzutifan.

Treatment-related adverse events (TRAEs) were observed in 96.7% of patients, most of which were grade 1 or 2 in severity; no grade 4 or 5 TRAEs were reported. The most common TRAEs were anemia in 83.6%, which was considered an on-target toxicity; fatigue in 49.2%; and dizziness in 21.3%. Grade 3 TRAEs, primarily fatigue and anemia, were reported in 9.8% of patients. Belzutifan is also being investigated in phase 3 trials as a monotherapy and in combination regimens in patients with RCC.

Reference: Jonasch E, Donskov F, Iliopoulos O, et al. Phase II study of the oral HIF-2alpha inhibitor MK-6482 for Von Hippel-Lindau disease–associated renal cell carcinoma. J Clin Oncol. 2020;38(suppl 15):5003. doi:10.1200/JCO.2020.38.15_suppl.5003.

Nivolumab Plus Ipilimumab Sparks Hope for Patients With RCC and Sarcomatoid Features.

Nivolumab plus ipilimumab combination therapy has improved survival and response rates compared with sunitinib, in patients with advanced renal cell carcinoma with sarcomatoid histology, including those with intermediate and poor-risk features.

The post hoc, phase 3 CheckMate 214 clinical trial evaluated the efficacy of nivolumab (Opdivo) plus ipilimumab (Yervoy) versus sunitinib (Sutent) in patients with sRCC. 139 patients had sRCC and intermediate/poor-risk disease and 6 had favorable-risk disease from 1,096 included in the study. The study found that led to unprecedented long-term survival, response, and complete response when compared with sunitinib. Based on the results, investigators support the use of nivolumab plus ipilimumab as frontline treatment of patients with sRCC. PFS, on the other hand, was significantly longer with nivolumab plus ipilimumab at 26.5 months (95% CI, 8.4 to NE) compared with the 5.1 months (95% CI, 4.0-6.9) seen with sunitinib (HR, 0.54; 95% CI, 0.3-0.9; P = .0093). The median OS however was not reached with nivolumab plus ipilimumab (95% CI, 25.2 months–not estimable [NE]) versus 14.2 months (95% CI, 9.3-22.9) vs sunitinib (HR, 0.45; 95% CI, 0.3-0.7; P = .0004). Patients who received nivolumab with ipilimumab also achieved a higher ORR of 60.8% (95% CI, 49%-72%) compared with 23.1% (95% CI, 14%-35%) in the sunitinib arm (P < .0001). The complete response rate in the combination arm was 18.9% compared with only 3.1% in the control arm. "I believe patients with clear cell RCC, who have sarcomatoid features in the tumor should be, in my opinion, nivolumab and ipilimumab if you're doing that for treatment in first line setting, I think the data we have from Checkmate-214 support this recommendation as the preferred first-line therapy for these patients" said Nizar Tannir, lead author of this trial.

Reference: Tannir NM, Signoretti S, Choueri TK, et al. Efficacy and safety of nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. Clin Can Res. Published Online January 2021. Accessed February 3, 2021. https://bit.ly/36W2gSr.

Researchers unravel how kidney tumors' microenvironments change in response to immunotherapy.

By using single-cell RNA sequencing, researchers from Dana-Farber Cancer Institute and the Broad Institute of MIT and Harvard investigated how kidney tumors' microenvironments change in response to immunotherapy. Researchers discovered that in advanced stage disease these CD8+ T cells were "exhausted," and not able to carry out their usual function. "These companion studies shed important new light on the biology of advanced kidney tumors and their surrounding environments. With this increased understanding, researchers will be able to identify new potential drug treatment targets and, overall, expand the number of patients who can receive effective treatment." said Catherine J. Wu, MD, professor of medicine at Harvard Medical School. “A patient’s immune system plays a critical role in controlling both the progression of cancer and the response to immune therapies,” adds Toni K. Choueiri, MD, co-senior author of this paper.

In other study, researchers performed single-cell RNA and T cell receptor sequencing on 164,722 individual cells from tumor and adjacent non-tumor tissue. They also discovered more anti-inflammatory or "M2-like" macrophages, a type of white blood cell that suppresses the immune system, in advanced stage disease. CD8+ T cells and macrophages were playing off each other and caught in an "immune dysfunction circuit," said co-lead author David A. Braun, MD, PhD, an oncologist at Dana-Farber. "There may be immune evasion mechanisms outside of PD-1/PD-L1 that play an important role in response or resistance,” said Kevin Bi, computational biologist at Dana-Farber and co-lead author on the paper. Study found that immune dysfunction circuit is associated with a worse prognosis in external cohorts and identifies potentially targetable immune inhibitory pathways in ccRCC.

Reference: Bi, K., et al. (2021) Tumor and immune reprogramming during immunotherapy in advanced renal cell carcinoma. Cancer Cell. doi.org/10.1016/j.ccell.2021.02.015.

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