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Radiation and RCC: Will New Data Crush the Myth of Radioresistance?

Plus: The Ultimate Guide to Sunitinib Dosing to Optimize VEGF Blockade, Efficacy & Tolerability

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

Now in Its 15th Year

INLYTA® (axitinib) is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

Important Safety Information

Hypertension including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in these patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

Inlyta.
axitinib

Continue the fight with INLYTA

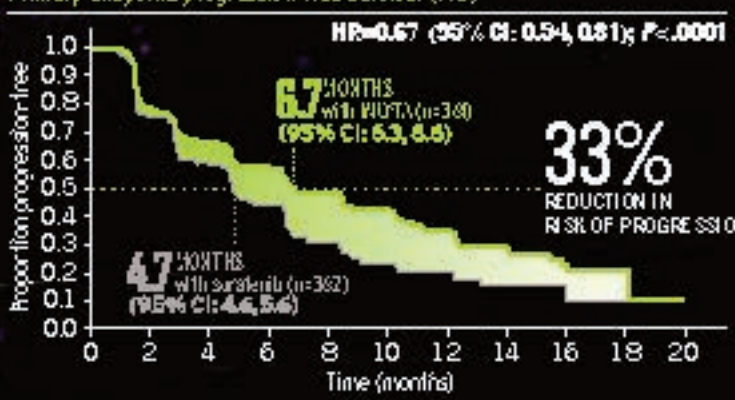
Proven efficacy with a distinct safety profile

The ONLY approved treatment option to demonstrate

Significant and superior PFS vs a VEGFR-TKI in a phase 3 trial for 2nd-line mRCC*

*Based on MEDLINE® literature review for phase 3 trials in mRCC as of November 2016.

Primary endpoint: progression-free survival (PFS)



Data are from a multicenter, open-label, phase 3 trial of 723 patients with mRCC after failure of 1st-line therapy (sunitinib-, temsirolimus-, bevacizumab-, or cytokine-containing regimen [84%, 8%, 8%, and 3.5% of patients in each of the treatment arms, respectively]). Patients were randomized 1:1 to either INLYTA 5 mg twice daily (n=361) or sorafenib 400 mg twice daily (n=362), with dose adjustments allowed in both groups. Primary endpoint was PFS. Secondary endpoints included objective response rate, overall survival, and safety and tolerability.[1]

A distinct safety profile

Over 4 years of clinical experience	49,000 patients treated worldwide†	7 clinical studies reported in a long-term safety analysis[2]

†IMS® MIDAS®, July 2016.

Monitor for **proteinuria** before initiation of and periodically throughout treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

Women of childbearing potential should be advised of potential hazard to the fetus and to avoid becoming **pregnant** while receiving INLYTA.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

The **most common (≥20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 47%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 38%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

Please see Brief Summary on the following pages.

November 2016

U.S. Pharmaceuticals

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939.
2. Rini BI, Escudier B, Hariharan S, et al. Long-term safety with axitinib in previously treated patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer*. 2015;13(6):540-547.

mRCC=metastatic renal cell carcinoma; TKI=tyrosine kinase inhibitor.

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION
Initial U.S. Approval: 2012
Brief Summary of Prescribing Information

INDICATIONS AND USAGE: INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosing. The recommended starting oral dose of INLYTA is 5 mg twice daily. Administer INLYTA doses approximately 12 hours apart with or without food. INLYTA should be swallowed whole with a glass of water.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose Modification Guidelines. Dose increase or reduction is recommended based on individual safety and tolerability.

Over the course of treatment, patients who tolerate INLYTA for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the INLYTA dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria.

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA therapy [see *Warnings and Precautions*]. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily.

__*Strong CYP3A4/5 Inhibitors:*__ The concomitant use of strong CYP3A4/5 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although INLYTA dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of INLYTA by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the INLYTA dose should be returned (after 3–5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

__*Hepatic Impairment:*__ No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the INLYTA starting dose should be reduced by approximately half in patients with baseline moderate hepatic impairment (Child-Pugh class B). The subsequent doses can be increased or decreased based on individual safety and tolerability. INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

DOSAGE FORMS AND STRENGTHS

1 mg tablets of INLYTA: red, film-coated, oval tablets, debossed with "Pfizer" on one side and "1 XNB" on the other side.

5 mg tablets of INLYTA: red, film-coated, triangular tablets, debossed with "Pfizer" on one side and "5 XNB" on the other side.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis. In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving INLYTA and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of INLYTA treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA. Hypertension was managed with standard antihypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib.

Blood pressure should be well-controlled prior to initiating INLYTA. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the INLYTA dose. Discontinue INLYTA if hypertension is severe and persists despite anti-hypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis. If INLYTA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Arterial Thromboembolic Events. In clinical trials, arterial thromboembolic events have been reported, including deaths. In a controlled clinical study with INLYTA for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 3/359 patients (1%) receiving INLYTA and 3/355 patients (1%) receiving sorafenib. Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib [see *Adverse Reactions*].
In clinical trials with INLYTA, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 17/715 patients (2%), with two deaths secondary to cerebrovascular accident.

Use INLYTA with caution in patients who are at risk for, or who have a history of, these events. INLYTA has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.

Venous Thromboembolic Events. In clinical trials, venous thromboembolic events have been reported, including deaths. In a controlled clinical study with INLYTA for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving INLYTA (including pulmonary embolism, deep vein thrombosis, retinal vein occlusion and retinal vein thrombosis) and 2/355 patients (1%) receiving sorafenib. Fatal pulmonary embolism was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, venous thromboembolic events were reported in 22/715 patients (3%) with two deaths secondary to pulmonary embolism.

Use INLYTA with caution in patients who are at risk for, or who have a history of, these events. INLYTA has not been studied in patients who had a venous thromboembolic event within the previous 6 months.

Hemorrhage. In a controlled clinical study with INLYTA for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving INLYTA and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 (1%) patients receiving INLYTA (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 (3%) patients receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving INLYTA (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.
INLYTA has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac Failure. In a controlled clinical study with INLYTA for the treatment of patients with RCC, cardiac failure was reported in 6/359 patients (2%) receiving INLYTA and 3/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal Perforation and Fistula Formation. In a controlled clinical study with INLYTA for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, gastrointestinal perforation was reported in 5/715 patients (1%), including one death. In addition to cases of gastrointestinal perforation, fistulas were reported in 4/715 patients (1%).
Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment with INLYTA.

Thyroid Dysfunction. In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving INLYTA and 25/232 patients (11%) receiving sorafenib.

Monitor thyroid function before initiation of, and periodically throughout, treatment with INLYTA. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.

Wound Healing Complications. No formal studies of the effect of INLYTA on wound healing have been conducted.

Stop treatment with INLYTA at least 24 hours prior to scheduled surgery. The decision to resume INLYTA therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible Posterior Leukoencephalopathy Syndrome. In a controlled clinical study with INLYTA for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. There were two additional reports of RPLS in other clinical trials with INLYTA.
RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. Discontinue INLYTA in patients developing RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

Proteinuria. In a controlled clinical study with INLYTA for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%) receiving INLYTA and 26/355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving INLYTA and 6/355 patients (2%) receiving sorafenib.

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with INLYTA is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt INLYTA treatment.

Elevation of Liver Enzymes. In a controlled clinical study with INLYTA for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the INLYTA arm and 2% of patients on the sorafenib arm.
Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with INLYTA.

Hepatic Impairment. The systemic exposure to axitinib was higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Pregnancy. INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women using INLYTA. In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose.
Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of INLYTA has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described reflect exposure to INLYTA in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib.

The following risks, including appropriate action to be taken, are discussed in greater detail in other sections of the label: hypertension, arterial thromboembolic events, venous thromboembolic events, hemorrhage, gastrointestinal perforation and fistula formation, thyroid dysfunction, wound healing complications, RPLS, proteinuria, elevation of liver enzymes, and fetal development.

Clinical Trials Experience. The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received INLYTA and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse reaction occurred in 199/359 patients (55%) receiving INLYTA and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse reaction occurred in 34/359 patients (9%) receiving INLYTA and 46/355 patients (13%) receiving sorafenib.

The most common (≥20%) adverse reactions observed following treatment with INLYTA were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

The following table presents adverse reactions reported in ≥10% patients who received INLYTA or sorafenib.

Adverse Reactions Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

Adverse Reaction[a]	INLYTA (N=359) All Grades[b]	INLYTA Grade 3/4	Sorafenib (N=355) All Grades[b]	Sorafenib Grade 3/4
	%	%	%	%
Diarrhea	55	11	[illegible]	7
Hypertension	[illegible]	16	29	11
Fatigue	[illegible]	11	[illegible]	5
Decreased appetite	[illegible]	5	29	[illegible]
Nausea	[illegible]	[illegible]	22	1
Dysphonia	[illegible]	0	[illegible]	0
Palmar-plantar erythrodysesthesia syndrome	27	5	51	16
Weight decreased	25	2	21	1
Vomiting	24	[illegible]	17	1
Asthenia	21	5	[illegible]	[illegible]
Constipation	20	1	20	1
Hypothyroidism	19	<1	8	0
Cough	15	1	17	1
Mucosal inflammation	15	1	12	1
Arthralgia	15	2	11	1
Stomatitis	15	1	12	<1
Dyspnea	15	[illegible]	12	[illegible]
Abdominal pain	[illegible]	2	11	1
Headache	[illegible]	1	11	0
Pain in extremity	[illegible]	1	[illegible]	1
Rash	[illegible]	<1	[illegible]	[illegible]
Proteinuria	11	[illegible]	7	2
Dysgeusia	11	0	8	0
Dry skin	10	0	11	0
Dyspepsia	10	0	2	0
Pruritus	7	0	12	0
Alopecia	[illegible]	0	[illegible]	0
Erythema	2	0	18	<1

[a]Percentages are treatment-emergent, all-causality events
[b]National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

[illegible]

[illegible]

Laboratory Abnormalities Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

Laboratory Abnormality	N	INLYTA All Grades[a]	INLYTA Grade 3/4	N	Sorafenib All Grades[a]	Sorafenib Grade 3/4
		%	%		%	%
Hematology						
Hemoglobin decreased	320	[illegible]	<1	310	[illegible]	[illegible]
Lymphocytes (absolute) decreased	[illegible]	[illegible]	3	[illegible]	[illegible]	[illegible]
Platelets decreased	[illegible]	[illegible]	<1	310	[illegible]	0
White blood cells decreased	320	11	0	[illegible]	16	<1
Chemistry						
Creatinine increased	[illegible]	[illegible]	0	[illegible]	[illegible]	<1
Bicarbonate decreased	[illegible]	[illegible]	<1	[illegible]	[illegible]	0
Hypocalcemia	[illegible]	[illegible]	1	[illegible]	[illegible]	2
ALP increased	[illegible]	[illegible]	1	[illegible]	[illegible]	1
Hyperglycemia	[illegible]	[illegible]	2	[illegible]	[illegible]	2
Lipase increased	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Amylase increased	[illegible]	[illegible]	2	[illegible]	[illegible]	2
ALT increased	[illegible]	22	<1	[illegible]	22	2
AST increased	[illegible]	20	<1	[illegible]	[illegible]	1
Hypernatremia	[illegible]	[illegible]	1	[illegible]	[illegible]	1
Hypoalbuminemia	[illegible]	[illegible]	<1	[illegible]	[illegible]	1
Hyperkalemia	[illegible]	[illegible]	3	[illegible]	10	3
Hypoglycemia	[illegible]	11	<1	[illegible]	[illegible]	<1
Hyponatremia	[illegible]	[illegible]	[illegible]	[illegible]	11	2
Hypophosphatemia	[illegible]	[illegible]	2	[illegible]	[illegible]	[illegible]

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase

[illegible]

DRUG INTERACTIONS

[illegible]

USE IN SPECIFIC POPULATIONS

[illegible]

OVERDOSAGE

[illegible]

NONCLINICAL TOXICOLOGY

[illegible]

PATIENT COUNSELING INFORMATION

[illegible]

[illegible] [illegible]

Editorial Mission
The purpose of Kidney Cancer Journal is to serve as a comprehensive resource of information for physicians regarding advances in the diagnosis and treatment of renal cell carcinoma. Content of the journal focuses on the impact of translational
research in oncology and urology and also provides a forum for cancer patient advocacy. Kidney Cancer Journal is circulated to medical oncologists, hematologist-oncologists, and urologists.

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About the Cover
Artist's depiction of a targeted radiation beam destroying a malignant tumor. Definitive, high-dose-per-fraction stereotactic radiation is having a sharp impact as an option for a growing population of kidney cancer patients. (Copyright ©, Science Source)

KCJ TABLE OF CONTENTS

KCJ GUEST EDITOR'S MEMO

Connecting More Dots in Kidney Cancer: Updates on Radiation Therapy, Optimal Dosing Schedules for VEGF Blockade


Bernard J. Escudier, MD

It has always been the aim of the *Kidney Cancer Journal* to cover the broadest spectrum of topics related to all aspects of managing renal cell carcinoma (RCC). When I was asked to serve as Guest Editor, I knew that this issue of the journal would be no exception. The assortment of articles attests to how our field is rapidly evolving—whether it is new information emerging from the 2017 meeting of the European Society of Medical Oncology (ESMO) or updates from our authors on changing standards in clinical practice or new results from the bench with translational impact.

This year's ESMO scientific sessions presented some pivotal information on key issues with potential translational impact, including the combination of immunotherapy and targeted therapy, and the sequence of sunitinib and nephrectomy. These findings, notably an update on the Checkmate 214 trial and the SURTIME trial, are reviewed in this issue of the *Kidney Cancer Journal* on Pages 65 and 82, in addition to other results from ESMO.

If you follow the medical literature as closely as I do, you may be surprised at how the latest studies have not only more pointedly addressed long-standing controversies in RCC but go further—approaching a consensus that tends to debunk some of the myths surrounding practice standards. A case in point—our content on the safety and efficacy of stereotactic body radiation therapy (SBRT) for RCC, both primary and metastatic.

In terms of our knowledge about and application of this technique, we are light years away from the 1950s when a Swedish neurosurgeon first described single-dose ablative radiotherapy delivered to brain lesions. The revolutionary development concerns the way this principle has been extrapolated to the stereotactic delivery of severely hypofractionated treatments to body targets, including kidney, either primary or metastatic, cranial and extracranial. And yet, the myth has lingered that such application in RCC is limited by perceived radioresistance to conventional fractionation. If this is still your perception (a misconception, I might add) then review the article by Raquib Hannan, MD, on how such resistance can be overcome in many clinical settings, thus sparing many patients from nephrectomy, especially those who are poor surgical candidates.

One of the areas that has long been a focus of my research is the optimal dosing schedule for sunitinib and efforts to

(continued on page 80)

Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

The *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.

Contact information

List all authors, including mailing address, titles and affiliations, phone, fax, and email. Please note corresponding author.

Peer Review and Editing

Manuscripts will be peer reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style. Authors whose manuscripts are not initially accepted may have the opportunity to revise the manuscript based on recommendations from peer reviewers and at the discretion of the Editor-in-Chief.

Conflict of Interest

Kidney Cancer Journal policy requires that authors reveal to the Editor-in-Chief any relationships that they believe could be construed as resulting in an actual, potential, or apparent conflict of interest with regard to the manuscript submitted for review. Authors must disclose this information in the covering letter accompanying their submission.

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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Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Guest Editor, Bernard J. Escudier, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. **Motzer RJ, Haas NB, Donskov, et al. *J Clin Oncol*. 2017 Sep 13; JCO2017735324. doi: 10.1200/JCO.2017.73.5324.**

Summary: This phase III trial evaluated the efficacy and safety of pazopanib versus placebo in patients with locally advanced renal cell carcinoma (RCC) at high risk for relapse after nephrectomy. A total of 1,538 patients with resected pT2 (high grade) or ≥ pT3, including N1, clear cell RCC were randomly assigned to pazopanib or placebo for 1 year; 403 patients received a starting dose of 800 mg or placebo. To address toxicity attrition, the 800-mg starting dose was lowered to 600 mg, and the primary end point analysis was changed to disease-free survival (DFS) for pazopanib 600 mg versus placebo (n = 1,135). Primary analysis was performed after 350 DFS events in the intent-to- treat (ITT) pazopanib 600 mg group (ITT600mg), and DFS follow-up analysis was performed 12 months later. Secondary end point analyses included DFS with ITT pazopanib 800 mg (ITT800mg) and safety. The primary analysis results of DFS ITT600mg favored pazopanib but did not show a significant improvement over placebo (P = .165). The secondary analysis of DFS in ITT800mg (n = 403) yielded an HR of 0.69. Follow-up analysis in ITT600mg yielded an HR of 0.94 (95% CI, 0.77 to 1.14). Increased ALT and AST were common adverse events leading to treatment discontinuation in the pazopanib 600 mg (ALT, 16%; AST, 5%) and 800 mg (ALT, 18%; AST, 7%) groups.

Conclusion: The results of the primary DFS analysis of pazopanib 600 mg showed no benefit over placebo in the adjuvant setting.

Long-Term Response to Sunitinib Treatment in Metastatic Renal Cell Carcinoma: A Pooled Analysis of Clinical Trials. **Tannir NM, Figlin RA, Gore ME, et al. *EClin Genitourin Cancer*. 2017 Jun 20. S1558-7673(17)30171-4.**

Summary: We characterized clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib who were long-term responders (LTRs), defined as patients having progression-free survival (PFS) > 18 months. A retrospective analysis of data from 5714 patients with mRCC treated with sunitinib in 8 phase II/III clinical trials and the expanded access program. Duration on-study and objective response rate (ORR) were compared between LTRs and patients with PFS ≤ 18 months ("others"). PFS and overall survival (OS) were summarized using Kaplan-Meier methodology. Overall, 898 (15.7%) patients achieved a long-term response and 4816 (84.3%) patients did not achieve long-term response. The median (range) duration on-study was 28.6 (16.8-70.7) months in LTRs and 5.5 (0-68.8) months in others. ORR was 51% in LTRs versus 14% in others (P < .0001). Median PFS in LTRs was 32.11 months and median OS was not reached. LTRs had higher percentage of early tumor shrinkage ≥ 10% at the first scan (67.1% vs. 51.2%; P = .0018) and greater median maximum on-study tumor shrinkage from baseline (-56.9 vs. -27.1; P < .0001) versus others.

Conclusion: White race, Eastern Cooperative Oncology Group performance status 0, time from diagnosis to treatment ≥ 1 year, clear cell histology, no liver metastasis, lactate dehydrogenase ≤ 1.5 upper limit of normal (ULN), corrected calcium ≤ 10 mg/dL, hemoglobin greater than the lower limit of normal, platelets less than or equal to ULN, body mass index ≥ 25 kg/m2, and low neutrophil-to-lymphocyte ratio were associated with LTR. A subset of patients with mRCC treated with sunitinib achieved long-term response. LTRs had improved ORR, PFS, and OS.

Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer. **Choueiri TK, Plimack E, Arkenau HT, et al. *J Clin Oncol*. 2017 Sep 10;35(26):2993-3001. doi: 10.1200/JCO.2017.72.2967**

Summary: Patients with advanced papillary renal cell carcinoma (PRCC) have limited therapeutic options. PRCC may involve activation of the MET pathway, for example, through gene amplification or mutations. Savolitinib (AZD6094, HMPL-504, volitinib) is a highly selective MET tyrosine kinase inhibitor. We report results of a single-arm, multicenter, phase II study evaluating the safety and efficacy of savolitinib in patients with PRCC according to MET status. Patients and Methods Patients with histologically confirmed locally advanced or metastatic PRCC were enrolled and received savolitinib 600 mg orally once daily. MET-driven PRCC was defined as any of the following: chromosome 7 copy gain, focal MET or HGF gene amplification, or MET kinase domain mutations. Efficacy was assessed according to MET status. Safety, toxicity, and patient-reported health-related quality-of-life outcomes were assessed in all patients. Results Of 109 patients treated, PRCC was MET driven in 44 (40%) and MET independent in 46 (42%); MET status was unknown in 19 (17%). MET-driven PRCC was strongly associated with

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Newsworthy, late-breaking information from Web-based sources, professional societies, and government agencies

KCJ Medical Intelligence: ESMO Highlights

CABOSUN Update Affirms PFS Advantage With Cabozantinib Over Sunitinib in Advanced RCC

MADRID—-Patients with untreated advanced renal cell carcinoma (RCC) lived significantly longer without disease progression when they received the multikinase inhibitor cabozantinib (Cabometyx) as initial therapy versus sunitinib (Sutent), according to results of an independent review of the randomized CABOSUN trial reported at the 2017 European Society of Medical Oncology (ESMO) Congress.

Results showed that cabozantinib-treated patients had a median progression-free survival (PFS) of 8.6 months compared with 5.3 months for patients treated initially with sunitinib. The difference represented a 52% reduction in the hazard for progression or death.The independent review of the data confirmed the primary analysis of the CABOSUN randomized trial, which showed a median PFS of 8.2 months with cabozantinib and 5.6 months with sunitinib by investigator assessment (HR, 0.66; 95% CI, 46%-95%; 1-sided $P = 0.012$).

"Cabozantinib treatment resulted in clinically meaningful and statistically significant prolongation of progression-free survival per independent review compared with sunitinib as initial targeted therapy in patients with advanced RCC," Toni Choueiri, MD, director of the Kidney Cancer Center at Dana-Farber Cancer Institute, and collaborators concluded in a poster presentation. An updated review of overall survival (OS) showed a numerical advantage in favor of cabozantinib, but the difference did not achieve statistical significance, which was consistent with the initial investigator review of survival. The CABOSUN trial involved 157 poor- and intermediate-risk patients with advanced RCC, a subgroup of patients with worse prognosis and survival compared with patients who advanced RCC and favorable risk characteristics. Intermediate-risk patients accounted for 81% of the study population.

The patient population had a median age of about 63. Key clinical features included bone metastases in about 36% of patients, prior nephrectomy in 75%, and 3 or more metastatic sites in about 35%. The most common sites of metastasis were lung (70%), lymph nodes (55%), and bone (38%). Patients were randomized 1:1 to receive oral cabozantinib at 60 mg once daily (n = 79) or oral sunitinib at 50 mg daily for 4 weeks on/2 weeks off (n = 78). Treatment was administered until disease progression or intolerable toxicity.

CABOSUN had a primary endpoint of PFS as assessed by trial investigators. A key secondary endpoint was assessment of PFS by an independent review committee. The review was conducted by means of retrospective blinded review of radiographic images.

The independent review of PFS confirmed the primary analysis, and the 3.3-month absolute difference in favor of cabozantinib remained statistically significant, consistent with the primary analysis (HR, 0.48; 95% CI, 0.31-0.74; $P = 0.0008$). A subgroup analysis favored cabozantinib for all prespecified patient groups, including intermediate or poor risk, presence or absence of bone metastases, and positive or negative MET status. The updated survival analysis occurred after a median follow-up of 30.8 months and showed a median OS of 26.6 months in the cabozantinib arm versus 21.2 months in the sunitinib arm. The difference represented a 20% reduction in the hazard ratio in favor of cabozantinib—a difference that did not achieve statistical significance (HR, 0.80; 95% CI, 0.53-1.21; $P = 0.29$).

Twice as many patients had objective responses with cabozantinib compared with sunitinib (20% vs 9%). In the cabozantinib group, 16 patients had confirmed partial responses and 43 had stable disease, resulting in a disease control rate (DCR) of 75%. That compared with 7 partial responses, stable disease in 30 patients, and a DCR of 47% in the sunitinib arm. The original report of investigator-assessed outcomes showed DCRs of 78% and 54% for cabozantinib and sunitinib, respectively.

CheckMate-214: Nivolumab + Ipilimumab vs Sunitinib in First-LineTreatment for Advanced or Metastatic RCC

MADRID—Combined immunotherapy with nivolumab plus ipilimumab resulted in a greater objective response rate (ORR) and prolonged progression-free survival (PFS) compared to sunitinib in intermediate- and poor-risk patients with previously untreated advanced or metastatic renal cell carcinoma (RCC). These results came from the CheckMate-214 study presented at ESMO 2017. Greater benefit was observed in these patients, especially those with higher levels of PD-L1 expression at baseline; however, ORR and PFS were improved with sunitinib in patients with favorable risk, advanced or metastatic disease.

Bernard Escudier, MD Institut Gustave Roussy, Villejuif, France presented the results of the phase III, randomised, open-label CheckMate-214 study evaluating the combination of nivolumab and ipilimumab compared to sunitinib in patients with previously untreated advanced or metastatic RCC. The 550 patients in the combination arm were treated with nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks for 4 doses, followed by nivolumab at 3 mg/kg every 2 weeks and 546 patients received sunitinib at 50 mg once daily for 4 weeks and 2 weeks off in 6-week cycles. After approximately 17.5 months of follow-up, CheckMate-214 met the co-primary endpoint of ORR in

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Optimizing Sunitinib Dosing: Balancing Efficacy and Tolerability

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In what might be described as "real-world" data meeting clinical trial results, guidelines for the optimal use of sunitinib reflect the manner in which clinical practice has kept pace with and even supplanted some of the evidence-driven recommendations. More specifically, there has been a move from the 4-weeks-on / 2-weeks-off towards the 2-weeks-on / 1-week-off schedule. New studies, albeit mostly retrospective or single-arm prospective, provide key insights as to how exposure to the drug can be maximized while solving the riddle of adverse effects that often stand in the way of treatment compliance.

If there is a textbook example of how oncologists modify the indicated dosing of oral anticancer drugs to coincide with what is happening in "real-world" clinical practice, then look no further than how the rules are changing for the scheduling of sunitinib in metastatic renal cell carcinoma (mRCC). And yet, there is still significant controversy surrounding the optimal approach to the use of sunitinib. The most commonly used sunitinib dosing regimens are the traditional 50 mg by mouth 4-weeks-on / 2-weeks-off (4/2) and the alternative schedule of 50 mg by mouth 2-weeks-on / 1-week-off (2/1). Until we obtain further prospective data from head-to-head trials of the safety and efficacy of these two widely used strategies, the conundrum will remain: what is the sunitinib dosing schedule that delivers the optimal benefit-risk balance for patients with mRCC?

Despite the growing evidence from numerous trials addressing sunitinib dosing, one of the most intriguing aspects of the analyses and meta-analyses is that real-world experience from many centers around the globe has emerged as a driving force frequently determining, or at least influencing, the dosing choice.[1-3] However, to accept a strategy as the standard of care we need to examine a number of questions before reaching a consensus, before a truly evidenced based approach is validated. Recent reports are elucidating much of this needed information and they point toward a time when we will be able to more accurately predict which patients are most likely to benefit from a specific dosing strategy while ensuring that more patients are started on the optimal dose of sunitinib.

The use of sunitinib in the first-line setting is being challenged in numerous Phase III studies testing other tyrosine kinase inhibitors (TKIs), the combination of immune checkpoint inhibitors with TKIs, or the combination of two immune checkpoint inhibitors.[4,5] It remains to be seen what the impact of these studies will be on first-line choices, and how the use of the 4/2 and 2/1 schedules of sunitinib will have relative merit. It is indeed important to delineate the optimal schedule for sunitinib before designing a fair comparison of this drug with newer agents.

Pharmacokinetics and Antitumor Activity of Sunitinib

Initial preclinical and clinical data elucidated the pharmacokinetics and pharmacodynamics of sunitinib in patients with advanced malignancies, and ultimately determined the recommended dose and tolerability that served as the basis for sunitinib's approval. In their report more than 10 years ago, Faivre et al[6] delineated the profile of sunitinib, a novel at that time, oral, multitargeted TKI with antitumor and antiangiogenic activities. Earlier reports identified the drug as a potent inhibitor of Vascular Endothelial Growth Factor Receptors -1 and -2 (VEGFR-1 and VEGFR-2), fetal liver tyrosine kinase receptor 3 (FLT3), KIT, Platelet Derived Growth Factor receptors α

Keywords: sunitinib, dosing schedules, pharmacokinetics, RESTORE trial, RAINBOW trial, dose modification, VEGF blockade, adverse effects.

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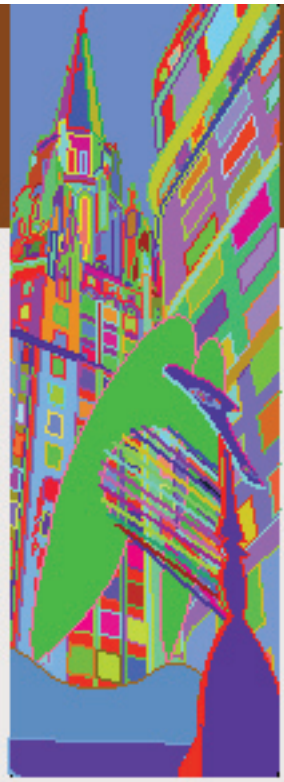

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and β (PDGFRα and PDGFRβ). *In vitro* data showed that sunitinib was metabolized by cytochrome CYP3A4, thus forming a major pharmacologically active metabolite, SU12662.[7] Subsequent pharmacokinetic studies in animal models extended this line of evidence: target plasma concentrations of sunitinib plus SU12662 ranging from 50-100 ng/mL successfully inhibited the phosphorylation of PDGFR and VEGFR-2.[7] These earlier studies led to the Phase I dose-escalation trial that determined the recommended dose, tolerability, basic pharmacokinetics and antitumor effects of sunitinib when given orally daily for a 4-week on, 2-week off schedule (4/2) in patients with advanced malignancies.[6] The recommended dose of 50mg/day led to the desired plasma concentration of 50-100 ng/mL, the maximum plasma concentration occurred ~5 hours after administration, and half-life ranged from 41 to 86 hours. This 50 mg 4/2 schedule became the standard that was used in the subsequent pivotal phase III trial that led to the FDA approval of sunitinib.[8]

Alternative Sunitinib Schedules: Improving Outcomes and Increasing Tolerability

Higher exposure to sunitinib results in improved overall response rate, progression-free survival and overall survival.[9] Thus, maintaining drug adherence and maximizing drug exposure can result in improved outcomes. The main obstacle, however, is treatment-related adverse effects (AEs) such as fatigue, hypertension, hand-foot syndrome, and diarrhea. Numerous completed and ongoing trials are exploring whether alternative sunitinib doses and schedules provide a better balance between efficacy and tolerability than the traditional 50 mg 4/2 schedule.[10] AEs generally tend to increase throughout the active drug period of each treatment cycle, and improve during the "week-off" period.[11] Indeed, patients on the 4/2 schedule report the lowest quality of life scores after the 4 weeks on treatment, and the highest scores following the 2-week break.[12]

Continuous daily administration of sunitinib at a lower dose is not preferred after a randomized prospective phase II trial showed that sunitinib 37.5 mg daily continuously with no "weeks off" does not provide any safety benefit and may produce slightly worse outcomes compared with the standard 50 mg 4/2 schedule.[12] Phase II data in patients with gastrointestinal stromal tumors have shown no difference in morning vs evening administration of sunitinib.[13] On the other hand, preclinical data suggest that pulsatile high dose sunitinib at doses of 200 mg once weekly or higher may produce a potent direct antitumor effect,[14] and this approach is now studied in a phase I trial (NCT02058901 at clinicaltrials.gov). Furthermore, given the data suggesting that patients who develop less toxicity to sunitinib can have inferior disease response,[15,16] it is possible that the cause of disease progression in at least some patients on the 50 mg 4/2 (or 2/1) regimens is underdosing. This hypothesis is being tested in a phase II trial of sunitinib dose escalation up to 75 mg 2/1 (NCT01499121 at clinicaltrials.gov).

Comparisons Between the 4/2 and 2/1 Schedules

The theoretical advantages of the 2/1 schedule vs 4/2 include the shorter duration of both the "on treatment" and "treatment break" periods while maintaining the same overall dose exposure over each 6-week period.[17] Population pharmacokinetic and phamacodynamic modeling predicted that the 2/1 regimen produces comparable efficacy to 4/2 with a less severe toxicity profile.[17] Sunitinib plus SU12662 reach steady-state concentrations and optimally suppress vascular perfusion within 14 days, while additional days of therapy do not produce substantial changes in pharmacokinetics.[10] Furthermore, longer treatment break durations provide more time for both tumor and vascular endothelial cells to recover and proliferate.[10] These considerations, along with the potentially more favorable toxicity profile and emerging efficacy data, have prompted clinicians to often favor the 2/1 over the FDA-recommended 4/2 schedule.[1]

A number of single center retrospective studies have suggested a favorable toxicity profile for the 2/1 schedule.[15, 18-21] These data were further corroborated by the RAINBOW analysis, a large multicenter, retrospective analysis of 3 separate patient groups: one group was switched to the 2/1 schedule after developing significant AEs with the 4/2 format; the second group used the 2/1 schedule from the beginning; the third group served as a 4/2 control.[22] Switching from 4/2 to 2/1 reduced the overall incidence of grade 3-4 AEs from 45.7% to 8.2%.[22] These AEs, including fatigue, hypertension, hand-foot syndrome, and thrombocytopenia, are the greatest deterrent to the continued use of the 4/2 regimen both in clinical trials and in real-world practice.[2,8,23] As expected, patients who switched to the 2/1 regimen achieved a long treatment duration, at least in part explained by the lower incidence of unmanageable toxicities.[22] There was also evidence of increased efficacy in the 4/2-to-2/1 group compared with the 4/2 control.[22] However, this finding may have been influenced by selection bias.[24] Despite such limitations, the RAINBOW analysis showed that a switch from 4/2 to 2/1 can ameliorate the toxicity of sunitinib. It would be reasonable to speculate that such an improved safety profile may translate into a survival benefit, as it allows higher and more prolonged drug exposure. A retrospective analysis of patients from 2 hospitals in China corroborated the results of the RAINBOW analysis by finding that switching from 4/2 to 2/1 reduces toxicity. Of note, however, median progression-free survival (PFS) was significantly longer for patients who were initiated on 2/1 compared with those that started on 4/2 and then switched to 2/1.[25] A retrospective review of the 'real-world' experience with 2/1 in four Australian cancer centers showed that almost 1/3 of patients starting on 50 mg 2/1 required subsequent dose reductions but very few (6%) discontinued sunitinib due to toxicity, and there were no treatment-related deaths or grade 4 toxicities.[3]

The RESTORE trial was the first multicenter, randomized, phase II trial comparing 4/2 with 2/1 in mRCC, and used 6-month failure-free survival (FFS) rate as the primary endpoint.[26] It found that the 6-month FFS rates

Table. Ongoing trials of alternative sunitinib regimens

Trial identifier	Trial Title	Phase	Control group	Alternative sunitinib schedule	Tumor Type	Primary Endpoint	Results/Current status
NCT02060370	A Phase II Study of Alternative Sunitinib Scheduling in Patients With Metastatic Renal Cell Carcinoma (mRCC)	II	None (single-arm trial)	50 mg 2/1	Metastatic renal cell carcinoma	Rate of Toxicity defined as percentage of patients who experience one or more ≥grade 3 fatigue, hand-foot syndrome, or diarrhea that are possibly, probably, or definitely related to study therapy	Completed accrual. Preliminary data analysis* showed that the 2/1 schedule did not result in a lower rate of toxicity compared with historical data from the 4/2 schedule
NCT02689167	Open Label, Randomized Multi-centre Phase II Study to Assess the Efficacy and Tolerability of Sunitinib by Dose Administration Regimen (Dose Modification or Dose Interruptions) in Patients With Advanced or Metastatic Renal Cell Carcinoma (SURF trial)	II	Start at 50 mg 4/2. When a dose adjustment of sunitinib is required switch to 37.5 mg 4/2	Start at 50 mg 4/2. When a dose adjustment of sunitinib is required switch to 50 mg 2/1.	Metastatic renal cell carcinoma	Median duration of treatment calculated from sunitinib initiation.	Ongoing study.
NCT02398552	A Randomized Phase II Trial of Sunitinib Four-weeks on/Two-weeks Off Versus Two-weeks on/One-week Off as First Line Therapy in Metastatic Renal Cell Carcinoma.	II	50 mg 4/2	50 mg 2/1	Metastatic renal cell carcinoma	Progression-free survival	Ongoing study.
NCT01499121	A Phase II, Multi-Centre, Study of the Efficacy and Safety of Sunitinib Given on an Individualized Schedule as First-Line Therapy for Metastatic Renal Cell Cancer	II	None (single-arm trial)	Sunitinib is started at 50 mg /day for 4 weeks. If there is at least grade 2 toxicity then stay on 50 mg with the number of days on sunitinib individualized to goal ≤ grade-2 toxicity. Dose can be reduced to 37.5 mg and then to 25 mg if 50 mg or 37.5 mg respectively cannot be tolerated for at least 7 days. If no grade ≥2 toxicity on 50 mg / day for 4 weeks then dose escalate to 62.5 mg 2/1 and up to 75 mg 2/1.	Metastatic renal cell carcinoma	Progression-free survival	Completed accrual. Preliminary data analysis** that this individualized dosing strategy is feasible and safe. The null hypothesis of PFS 8.5 months was rejected at $p < 0.001$.
NCT02058901	A Phase I Study of High-dose, Intermittent Sunitinib in Patients With Solid Tumors.	I	None (single-arm trial)	Initial dose of sunitinib 200 mg once weekly which can be escalated by 100 mg increments until the maximum tolerated dose is reached	Locally advanced or metastatic solid malignanies	Determine the maximum tolerated dose (MTD), safety and tolerability	Ongoing study.
ISRCTN06473203	A randomized multi-stage, phase II/III trial of standard first-line therapy (sunitinib or pazopanib) comparing temporary cessation with allowing continuation in the treat= ment of locally advanced and/or metastatic renal cancer (STAR trial)	II/III	Sunitinib 50 mg 4/2 or pazopanib 800 mg daily conventional continuation strategy	Sunitinib 50 mg 4/2 or pazopanib 800 mg daily drug-free interval strategy	Locally advanced or metastatic renal cell carcinoma	Stage A: Recruitment rate/ month Stage B: Time to Strategy Failure Stage C/Overall: 2 year OS and averaged quality adjusted life years (over recruitment and follow-up)	Ongoing study.

*http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.6_suppl.533
** http://meetinglibrary.asco.org/record/144696/abstract

were higher in the 2/1 (63%) vs the 4/2 group (44%). In addition, patients in the 2/1 group achieved an objective response rate (ORR) of 47% with a median time to progression (TTP) of 12.1 months compared with ORR 36% and median TTP 10.1 months in the 4/2 group. Furthermore, AEs such as fatigue and neutropenia were more common in the 4/2 group.[26] Due to its open-label design, it is possible that some patients in the 4/2 group may have crossed-over to 2/1 if they were aware of the potentially better tolerability of this schedule. FFS is a composite outcome that can be difficult to interpret since the published results do not specify how many failures were due to disease progression, treatment toxicity, patient refusal, or death. Furthermore, the small sample size hindered the detection of differences in more established outcomes such as PFS and overall survival (OS). Nevertheless, the RESTORE trial added to the growing number of data showing that the 2/1 schedule can reduce toxicity without a substantial compromise in efficacy.

The abundance of mainly retrospective information published on alternative dosing schedules for sunitinib may leave the clinician without a consensus. Despite the doubts cast on the traditional 4/2 schedule, it still has the highest level of evidence and is used in most clinical trial protocols. It is therefore still deeply rooted in many practices and at least some skepticism surrounds the decision to switch to the 2/1 schedule despite the clear trend in this direction. A group of European experts recently critically reviewed[27] the data of the RESTORE trial[26] and of three retrospective published studies[18,19,22] comparing 4/2 with 2/1. Although their analysis supported the large consensus that the 2/1 schedule improves tolerability compared with 4/2, the low level of evidence regarding the comparative efficacy of 2/1 vs 4/2 precluded the authors from endorsing the use of 2/1 in all patients with mRCC. They thus suggested a strategy incorporating both schedules, echoing the RAINBOW ana-lysis: all patients should be started on 4/2 but then be switched to 2/1 if they develop dose-limiting toxicities during weeks 3-4 of the 4/2 cycle. This reasonable recommendation, favoring a switch in schedules instead of a dose-reduction, will need to be readdressed as higher level data are published comparing 4/2 with 2/1. The best test will be a randomized clinical trial comparing the safety, tolerability, and efficacy of switching from 4/2 to 2/1 vs dose-reducing but maintaining the 4/2 schedule in patients who develop AEs. Such a phase II trial is currently underway (NCT02689167 at clinicaltrials.gov).

"Despite the growing evidence from numerous trials addressing sunitinib dosing, one of the most intriguing aspects of the analyses and meta-analyses is that 'real world' experience from many centers around the globe has emerged as a driving force frequently determining, or at least influencing, the dosing choice."

Withholding and Re-initiating Sunitinib: The 'Stop and Go' Strategy

One of the strategies receiving attention is called the 'stop and go' approach, so called because sunitinib is 'stopped' when a prespecified response endpoint has been reached and only reinitiated upon predefined disease progression.[28] Initial retrospective data in small cohorts indicated that disease control can be achieved by the reintroduction of sunitinib in cases where the drug was held after a complete response.[29] A phase II single-arm study conducted at the Cleveland Clinic tested the efficacy of 'stop-and-go' sunitinib in 20 patients. Sunitinib was initially dosed at the standard 50mg 4/2 schedule for 4 cycles (24 weeks total) and then the treatment was held if there was a ≥ 10% reduction in tumor burden. The patients were closely monitored and sunitinib was restarted if there was a ≥ 10% increase in tumor burden. Treatment would then be held again if there was a ≥ 10% reduction in tumor burden. This intermittent dosing scheme was followed until there was disease progression or unacceptable toxicity.[30] The major limitations of this trial include its small size, lack of comparator arm, and use of feasibility as the primary endpoint, defined as the proportion of eligible patients who underwent the 'stop and go' strategy on trial. Thus, this small trial was not designed to test whether the 'stop-and-go' approach produced better efficacy or lower toxicity compared with the standard 4/2 approach. Nevertheless, its results indicated that the 'stop-and-go' strategy is feasible, tolerable, and low-cost as patients can spend prolonged time periods off therapy without major compromises in clinical efficacy.[30] A variation of this approach is currently being tested in the randomized multi-stage phase II/III STAR trial (ISRCTN06473203) which is investigating whether temporary discontinuation of first-line sunitinib or pazopanib is non-inferior compared with conventional dosing in terms of 2-year overall survival (OS) and quality adjusted life year (QALY).[31]

Future Directions: Ongoing Trials Search for the Elusive Prospective Data

While the 2/1 schedule is gaining more traction in the 'real-world' a number of ongoing trials, listed in the **Table**, are seeking the prospective evidence to guide optimal sunitinib dosing. At the same time, however, upcoming results from studies of novel drug regimens may completely change the treatment landscape of mRCC within the next 1-2 years, and substantially reduce the role of sunitinib as a first-line agent. Nevertheless, sunitinib will still be used as a salvage regimen or as part of combination strategies, and these decisions should be guided by data on how to best balance efficacy and tolerability.

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Stereotactic Ablative Radiation for RCC: Novel Paradigms Emerge as the Myth of Radioresistance Fades

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Are we at an inflection point for the use of radiotherapy in renal cell carcinoma? Perhaps. Definitive, high-dose-per-fraction stereotactic radiation is having a sharp impact as an option for a growing population of patients. A review of the emerging data calls for guidelines for its use as an alternative to invasive approaches.

A new consensus is emerging for the treatment of a broad spectrum of renal cell tumors at multiple stages, including primary renal cell carcinoma (RCC), locally advanced RCC, central nervous system (CNS) RCC metastases, and extra cranial oligo-metastases. It is part of a significant evolution in thinking emphasizing the use of stereotactic ablative radiotherapy (SAbR) to deliver high ablative doses of radiation focally to the tumor to achieve local control in cases previously thought to be a radioresistant histology. SAbR is an emerging treatment that delivers a very high and ablative dose of radiation very precisely to any site within the body. SAbR has been implemented successfully in the definitive management of several cancers including primary lung and prostate,[1-4] and is currently under investigation in many other sites including breast, pancreas and liver.[5-9] SAbR has also been successfully implemented for the local control of metastatic lesions in multiple sites.[5,10-12]

Several lines of evidence have converged in recent years to largely debunk the long-held belief that radiotherapy is not well suited to the paradigm of treatment in kidney cancer. First, for early stage RCC (T1a) as the standard of care has shifted away from radical nephrectomy and toward more nephron-sparing approaches, the goals of treatment have also pivoted toward less invasive ablative treatments such as radiofrequency ablation or cryo-ablation. However, these modalities are also invasive, have attendant risks and limited to treatment on selective tumor locations within the kidney.[1]

RCC has traditionally been considered a radioresistant tumor.[13] This conclusion was based entirely on a **single** study that examined the radiosensitivity of multiple human cancer cell lines *in vitro*[14] and examined **one** human RCC cell line, which happened to be the most radioresistant among all tested cell lines when conventional low dose per fraction radiation was used. Since then, multiple *in vitro* and *in vivo* studies have demonstrated that RCC is indeed radiosensitive, particularly at higher doses per fraction such as are used for SAbR.[15,16] Clinical experience mimics this conclusion with SABR showing efficacy ranges of 90-100% and 82-95% for RCC CNS and extra-CNS metastases respectively.[17-23]

Nomenclature is not always the same in the literature. Different terminology is often used to refer to SAbR. In some cases, it has been referred to as "stereotactic radiosurgery" or stereotactic body radiotherapy (SBRT). The significant advantage of SAbR is its ability to deliver high-dose radiotherapy to the tumor while minimizing dose to adjacent normal tissues.[24] In their review of SAbR with respect to local control and toxicity outcomes, Siva et al[25] delineate the reasons for the technique's effectiveness. The very large hypofractionated doses used in SAbR can be given safely because:

1) The treated volumes are small with tight margins (**Figure 1**) and
2) The technique employs a large number of beams (8 or more) which individually contribute small dose along their path but together result in a much larger dose where they intersect and are summed at the locus of the cancer (**Figure 2**).

The utilization of volumetric modulated arc (VMAT) therapy, where the gantry delivering radiation rotates continuously around the tumor to deliver radiation and

Keywords: Stereotactic ablative radiation, renal cell carcinoma, SBRT, primary RCC, metastatic, CNS metastases, oligometastases, spine.

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essentially utilizes an infinite number of beams, further reduces the fraction of doses in in the path of radiation, intensifying it to the tumor. With even more advancement of technology such as image guided radiation and appropriate tumor motion assessment and management, it is now possible to precisely target even a moving tumor in the kidney that exhibits respiratory motion with pinpoint accuracy. As the experience grows with SAbR in various RCC settings—not just primary but metastatic as well—we need benchmark data regarding changes in size and rate of growth. There is now growing evidence supporting the use of this technique as it becomes more widely adapted clinically and its potential therapeutic benefit is realized.

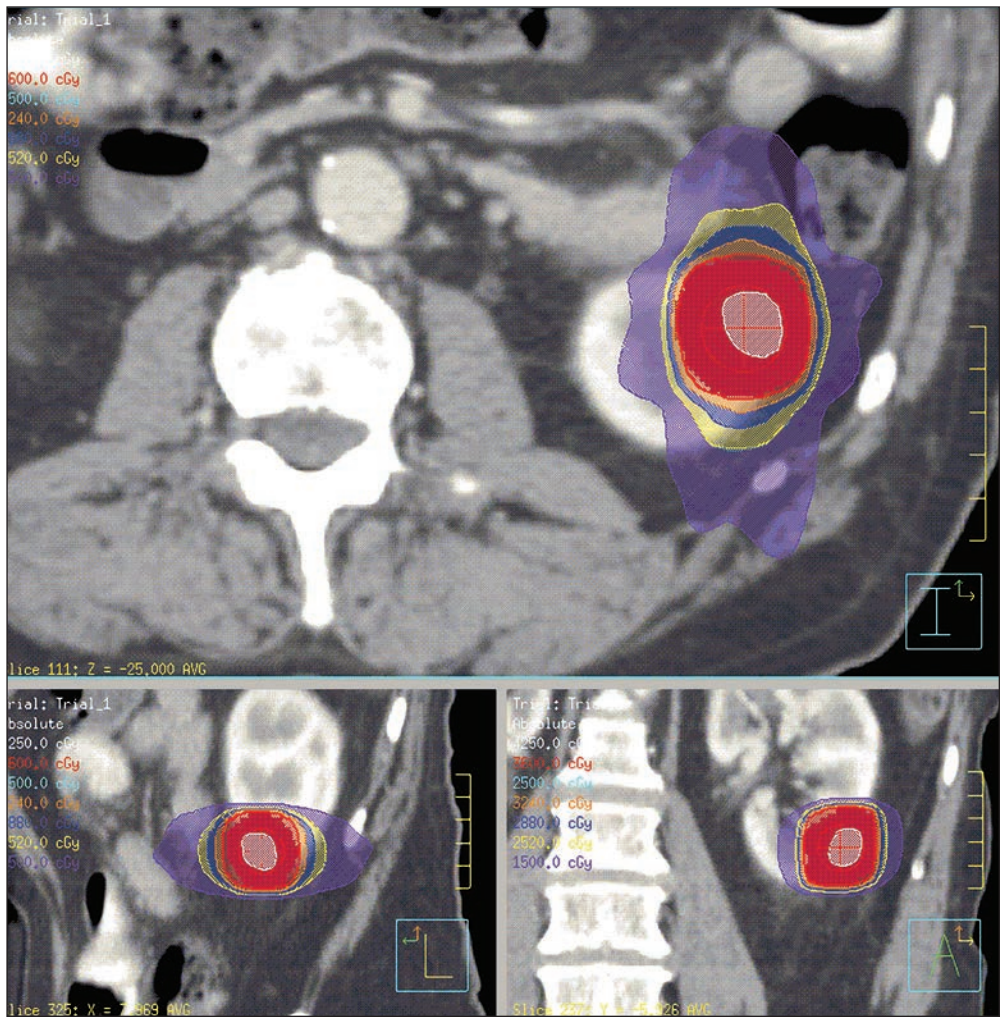


Figure 1. SAbR of a left lower pole kidney tumor. The isodose plan in three planes showing conformal dose distribution and adequate sparing of nearby bowel.

Primary Renal Tumors: Effect of SAbR on Growth Kinetics

From the histological evidence gathered in case reports to a meta-analysis on the use of SAbR in the treatment of primary renal tumors, there are numerous papers documenting favorable responses. Based on a review of recent literature, these trends have emerged:

- A systematic review[5] reported a weighted rate of local control for the treatment of RCC with SAbR in 126 patients to be 93.9%.
- Reported toxicities after SAbR appear to be tolerable with severe toxicity of 3.8% and a weighted rate of minor toxicity of 21.4%.
- SAbR has been reported to provide local control with preservation of adequate renal function in solitary kidneys and in patients with preexisting chronic kidney disease.[26]
- The consensus of preliminary results supports a role of SAbR as an alternative treatment option for patients with primary RCC and comorbidities that exclude total or partial nephrectomy.[27]

Even in the setting of surgical candidacy, it makes sense to consider SAbR since in the rare event that the tumor progresses after SAbR, partial or radical nephrectomy may still be a possibility. Formation of scar tissue in the radiated field has been the concern for surgeons in performing surgery after radiation. However, with SAbR delivering extremely focused doses of radiation, the extent of scar tissue will be limited to regions immediately surrounding the tumor which may keep even the partial nephrectomy options option. Data are clearly lacking in these clinical settings.

The trends of SAbR treatment for primary RCC were delineated by Sun et al in their report on the effect of SAbR on the growth kinetics and enhancement pattern of primary renal tumors. Even though this is a retrospective study, the majority of the patients included in this study are from the phase I dose escalation study that escalated doses of 7Gy in 3 fractions all the way to 16Gy in 3 fractions designed by McBride et. al and first reported in the 2013 ASTRO conference.[28] In their retrospective study of SAbR over a 5-year period involving 41 renal tumors from 40 patients they found that the mean pretreatment tumor growth rate of 0.68 cm/y decreased to -0.37 cm/y post treatment (P<0.0001), and the mean tumor volume growth rate of 21.2 cm^3/per year before treatment decreased to -5.35 cm3/y after treatment (P=0.002). Local control defined as less than 5 mm of growth—was achieved in 38 of 41 tumors. Interestingly, the three failures in this study were already reported in the 2013 ab-

stract to be on the 7Gy and 9Gy x3 dose fractionations and no failures were observed when >10Gy in three fractions were used.

Authors made an intriguing observation in this study. They noticed that even in the setting of good local control, SAbR did not have an impact on the enhancement of the residual mass. Physicians treating renal tumors with ablative technique are reassured when enhancement is lost since the technique inherently disrupts the treated tissue leading to loss of tumor vasculature and lack of contrast dye uptake. However, SAbR primarily kills tumor cells by DNA damage leading to mitotic catastrophe or a loss of their proliferative ability with minimal damage to the vasculature. As a result, it is not surprising that local control is seen in the setting of continued contrast enhancement.

Despite these promising results, there are unresolved issues concerning the tolerability of escalating doses of SAbR for primary treatment of localized RCC in poor surgical candidates.[29] For example, the dose regimens used in earlier studies from 2005 to 2007 ranged from 16-48 Gy in 3-5 fractions but no consensus emerged regarding the optimal dose regimen for RCC.[30] The phase 1 dose-escalation study by Ponsky et al offers insights as it explores data on achieving the maximum tolerated dose for SAbR. It highlights concerns with the delivery of ablative doses of radiation. These concerns are related to tumor motion with respiration and the close proximity to various organs at risk, including the small bowel.

Ponsky et al used a robotic radiosurgery system with tumor tracking capability to deliver the radiation requiring a smaller margin around the gross tumor volume (GTV) to create a target planning volume (PTV). This enabled the authors to treat a smaller amount of ipsilateral normal kidney and other organs at risk. A stepwise dose escalation regimen was followed and 48 Gy in 4 fractions was reached without causing dose-limiting toxicity. One patient experienced an acute and late grade 4 duodenal ulcer. Interestingly, while none of the 15 evaluable patients developed progression at a median follow up of 13.67 months, 7 of the 11 tumors biopsied post-SAbR showed "viable" tumor. The efficacy of radiation (or chemotherapy for that matter) in controlling tumor cells *in vitro* comes from cell survival curves from clonogenic assays where after a certain dose of radiation the tumor cell's ability to form colonies are measured and reported as surviving fraction. In reality, the surviving fraction is not reporting on whether the cells are alive or dead, they are merely reporting on whether the cells are able to divide and form colonies. In essence, a cancer cell that has lost its ability to divide, is perhaps not a cancer anymore.

In the context of no progression, a "viable" reading from H&E staining on a biopsy that did not perform any tests of proliferation is certainly inconclusive and the authors address this in the discussion and agrees to add proliferative indices in the future patients. Therefore, while the dose escalation design and primary endpoint of this study is robust, the secondary endpoint of local control

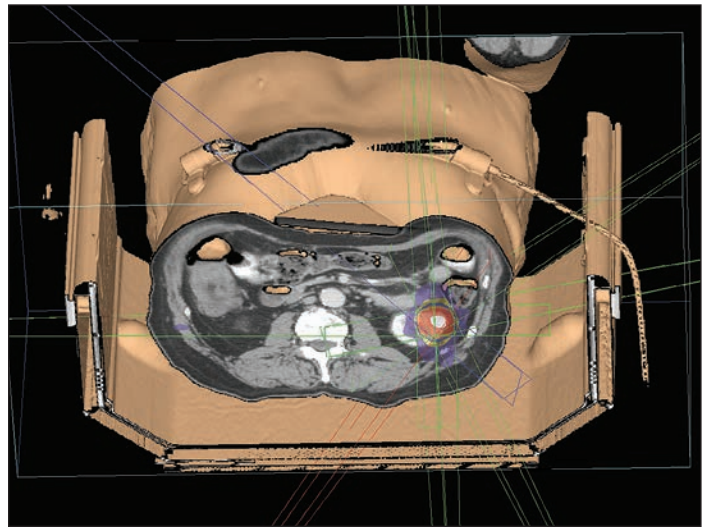
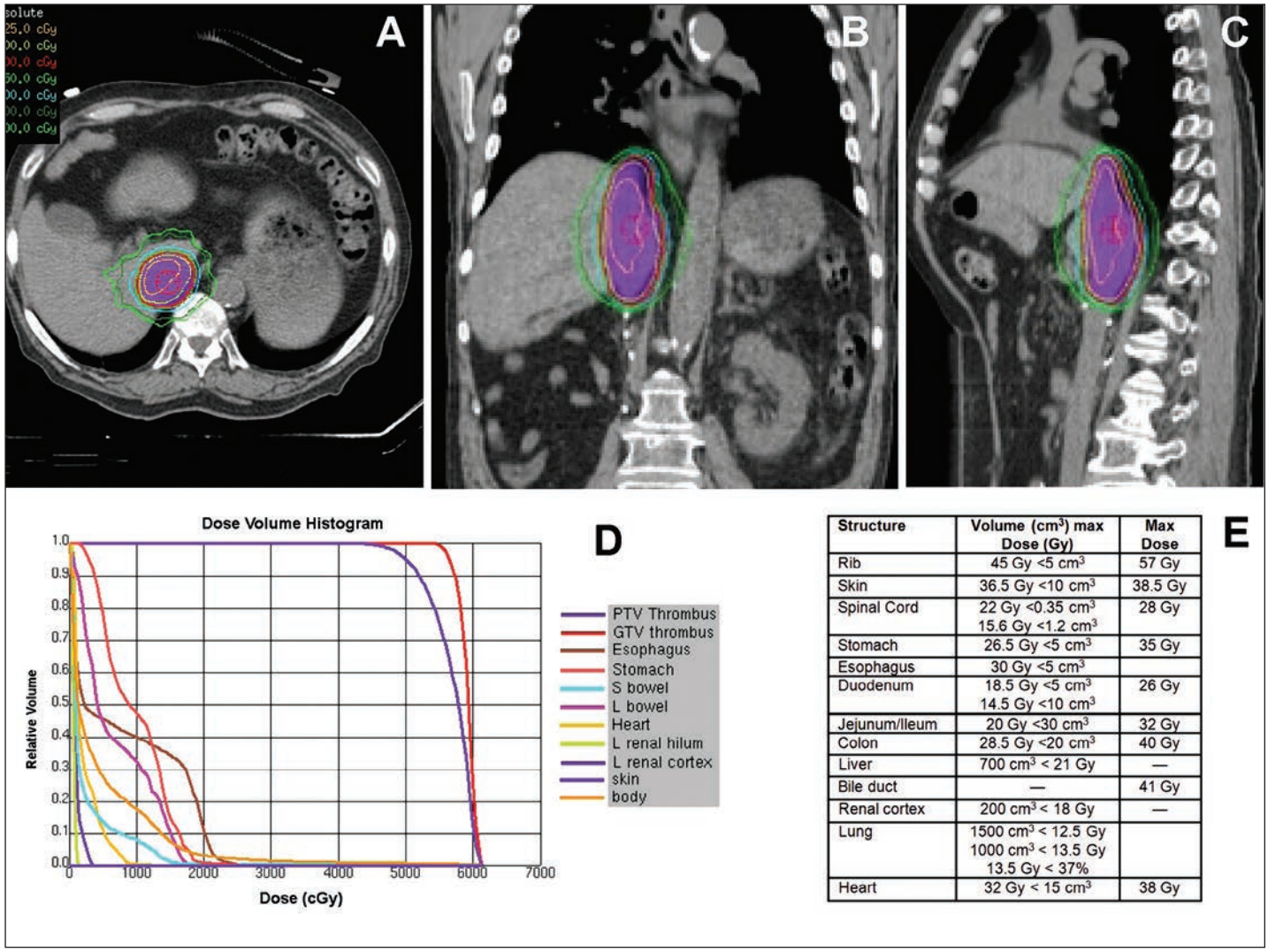


Figure 2. SAbR setup and beam arraignment for kidney lesion. The setup for SAbR abdominal treatment includes a vacuum bag for accurate reproducibility and a body frame that allows the stereotaxy. Multiple beams in non-coplanar arrangements are typically used to produce the focal dose distribution.

definition (loss of enhancement and biopsy) is flawed. As a result, with the goal of further improving local control, the investigators are enrolling patients for a starting dose of 48 Gy in 3 fractions. If the acute toxicity is acceptable, then the next 4 patients will be escalated to 54 Gy in 3 fractions. And then, if a dose limit has not been reached at that point, the last group of 4 patients will be treated to 60 Gy in 3 fractions. Based on all the other reported doses and local control rates for primary and metastatic RCC, one might argue that a dose escalation to this extent is likely unnecessary. Nonetheless, the reported study remains to be an important and the first prospective dose escalation study on SAbR for primary RCC.

Corroborative evidence of safety and efficacy for SAbR appeared in a European study by Staehler et al[31] who reported on renal tumors treated with single fraction radiosurgery. This study demonstrated the short-term benefits of the technique in 40 patients who had an indication for nephrectomy and subsequent hemodilation. The phase 2 study devised an aggressive treatment approach delivering 25Gy in a single fraction with fiducial placement and respiratory motion tracking using the CyberKnife system. The study overcame the challenges seen with conventional radiation: even when lesions were close to or in the ureter, a measure that is not possible with ablative techniques, the authors achieved complete tumor control without functional impairment. A high dose of radiation could be applied precisely with 1 mm accuracy to the renal tumor, thus avoiding collateral damage to surrounding healthy tissue. The disadvantage of this set-up is the dependency on fiducial placement which is a (minimally) invasive procedure. Utilizing image guidance technology, it is now possible to administer the same dose without the need for fiducials making SAbR completely non-invasive.



Structure	Volume (cm^3) max Dose (Gy)	Max Dose
Rib	45 Gy <5 cm^3	57 Gy
Skin	36.5 Gy <10 cm^3	38.5 Gy
Spinal Cord	22 Gy <0.35 cm^3 15.6 Gy <1.2 cm^3	28 Gy
Stomach	26.5 Gy <5 cm^3	35 Gy
Esophagus	30 Gy <5 cm^3	
Duodenum	18.5 Gy <5 cm^3 14.5 Gy <10 cm^3	26 Gy
Jejunum/Ileum	20 Gy <30 cm^3	32 Gy
Colon	28.5 Gy <20 cm^3	40 Gy
Liver	700 cm^3 < 21 Gy	—
Bile duct	—	41 Gy
Renal cortex	200 cm^3 < 18 Gy	—
Lung	1500 cm^3 < 12.5 Gy 1000 cm^3 < 13.5 Gy 13.5 Gy < 37%	
Heart	32 Gy < 15 cm^3	38 Gy

E

Figure 3. SAbR plan for IVC tumor thrombus. (A-C) Representative axial, sagittal, and coronal images of the SAbR treatment plan with isodose lines showing dose distribution and coverage of the IVC-TT. (D) Radiation dose volume histogram from SAbR plan of 50 Gy in 5 fractions showing optimized doses to critical organs as well as target volume (PTV). (E) Radiation dose constraints used for treatment planning.

With a 98% local tumor control rate after a median followup of 28 months, according to this report, SAbR seems to be more effective and certainly less invasive than thermal ablation. There was a measurable size reduction in 38 lesions, including complete remission in 19 while the renal function remained stable. The authors can only speculate on what their results might look like when patients are followed for the long term. However, even if renal function were to fail after a longer followup, the patients still would have experienced a prolonged period free from hemodialysis.

Ongoing Trials Seek to Extend Findings

Two ongoing trials are recruiting patients to continue investigations into the use of SAbR. One is being conducted at the University of Texas Southwestern Medical Center where patients with enlarging (>4mm growth within the past year) early renal cancers will undergo treatment of SAbR of 36Gy in 3 or 40Gy in 5 fractions. The primary endpoint of this single arm phase II trial is local control at 1 year which will be evaluated with radiographic scans and a tumor biopsy one year after treatment carefully evaluating the proliferative capability of baseline compared to post-treatment bi-opsy to confirm tumor nonviability. The estimated study completion date is December of 2018. The Clinical Trials.gov identifier is NCT021 41919.[32]

A second ongoing study, also phase II single arm, TROG 15.03 FASTRACKII,[33] is being conduced in Australia, has an accrual target of 70 patients and is scheduled for completion in September of 2021. All participants will be assessed at regular intervals post treatment in order to estimate the activity and efficacy of the technique, tolerability, survival, distant failure rate, and change of renal function after SAbR. SAbR dose fractionation in this study depends on tumor size: fraction schedule 1: 26Gy in 1

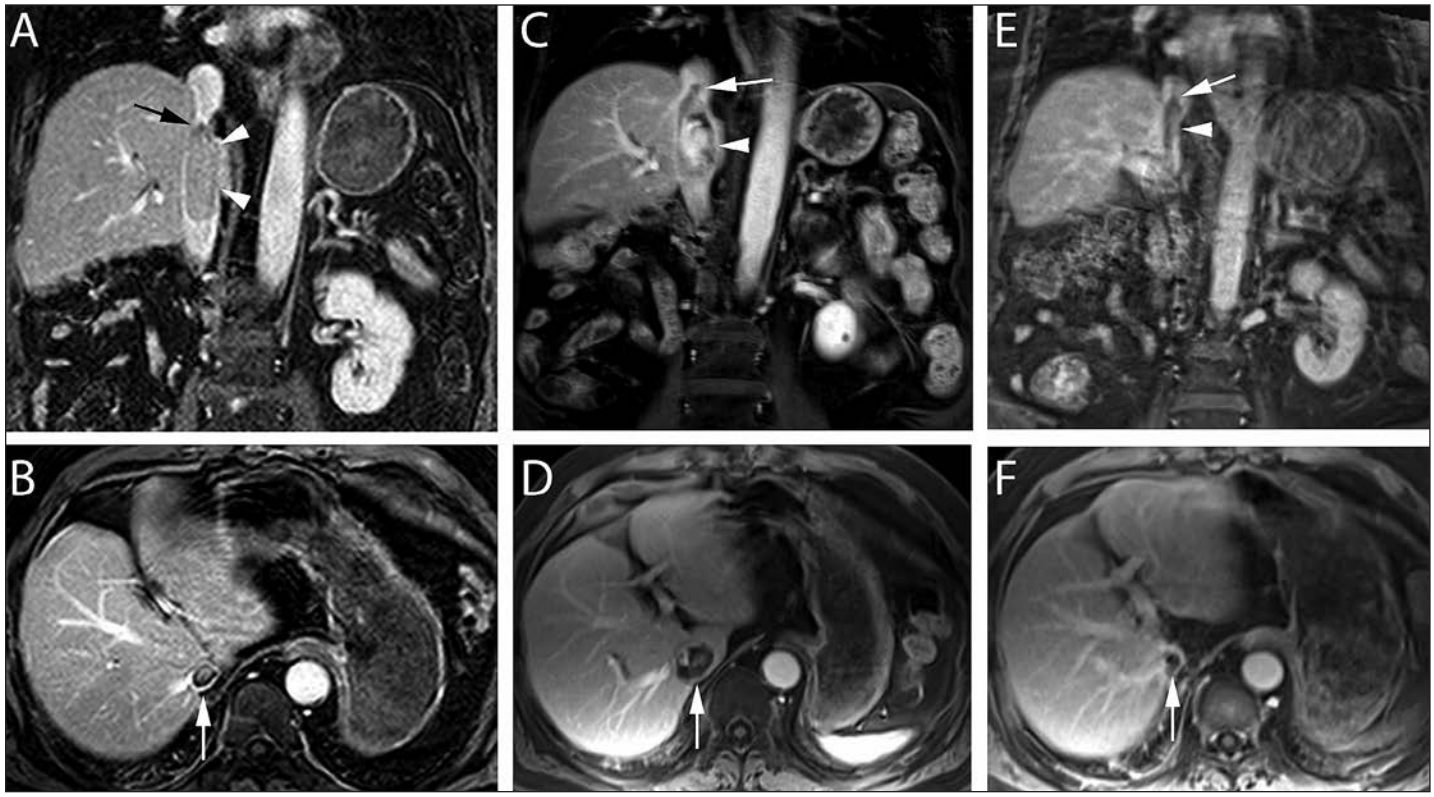


Figure 4. MRI of IVC Tumor Thrombus in clear cell RCC before and after SAbR. Coronal (top) and axial (bottom) contrast enhanced MR images at different time points during the course of treatment. After nephrectomy and thrombectomy, the patient had an intraluminal recurrence of tumor thrombus, which was adherent to the IVC wall (arrowheads, A). The superior extent of the thrombus is inferior to the diaphragm (Level III; arrow, A). Note the size of the thrombus at the level of the right hepatic vein (arrow, B). After systemic targeted therapy (C) there was obvious disease progression with thrombus extending superior to the diaphragm (level IV, arrow) and increased enhancement (arrowhead, C). Note marked increased in transverse diameter (arrow, D). Two years after SABR therapy there is persistent thrombus extending above the diaphragm (arrow, E) although exhibiting clear decrease in enhancement (arrowhead, E) and marked reduction in transverse diameter (arrow, F).

fraction, for tumors of less than or equal to 4cm in size; fraction schedule 2: 42Gy in 3 fractions, for tumors of greater than 4cm in size (i.e. 14Gy per fraction, given in 3 fractions over a maximum of 3 weeks, each fraction given on non-consecutive days).

SAbR in Locally Advanced RCC: A Bench to Bedside Case Report

The application of SAbR may find a role in a subset of kidney cancer patients—those who present with inferior vena cava (IVC) tumor thrombus (IVC-TT) and comprise up to 10% of RCC patients. Surgery is the only treatment with proven efficacy for this setting, but such resection is difficult, and mortality and morbidity is high. Until recently, the difficulty with surgery has left clinicians with no treatment options for recurrent or unresectable RCC IVC-TT which left untreated can lead to Budd-Chiari syndrome.

Our experience[34] treating 2 RCC patients with Level IV IVC-TT, one with recurrent disease and the other unresectable—with SAbR —suggests how this modality may have utility in this difficult-to-treat setting. Our case report followed two elderly (75 years old and 83 years old) male patients both of whom had been refractory to systemic therapy. One received 50 Gy in 5 fractions and at 2 years of followup is doing well with a significant decrease in the enhancement and size of the IVC-TT. (**Figures 3**, **4**) The second patient survived 18 months post SAbR. None of the patients that underwent SAbR to IVC-TT experienced any treatment-related toxicity. The survival of 18 months and 24 months for these patients is comparable to the reported median survival of 20 months in similar groups of patients who underwent surgical resection.[20]

Despite the high surgical mortality (10%) and morbidity (up to 30%), majority of the patients return with systemic metastasis perhaps from the tumor emboli shed from the IVC-TT itself.[35] Therefore, an intriguing hypothesis raised by our study is whether SAbR could have further application in the neoadjuvant setting and whether it might lower the likelihood of systemic metastases by making the tumor emboli non-viable. A safety lead-in phase 2 clinical trial is addressing this issue where level II or higher IVC-TT is being radiated to 40Gy in 5 treatments immediately prior to surgery and looking at relapse-free survival at one year as the primary outcome measure. The target enrollment is 30 patients and the estimated completion date is December of 2018 for this trial with a ClinicalTrials.gov identifier of NCT02 473536.[36]

SAbR for CNS RCC Metastases

Gamma knife surgery (GKS) for metastatic brain tumors from RCC has a long history since stereotaxis initially was invented and designed for intracranial lesions, beginning with the first report published more than 20 years ago. Recent studies, however, are not only building on the previous track record of successful results but elucidating additional benefits that may accrue from such radiosurgery, including improved tumor reduction and long-term survival. These reports are exploring some of the underappreciated nuances of GKS in this setting.

To what extent is GSK effective for growth control of metastatic tumors and what effect can it have on peritumoral edema control? This question was addressed in a retrospective report by Shuto et al studying 280 metastatic brain tumors—80 from RCC and others involving breast and lung. In addition, the authors included 11 patients with metastatic brain tumors from RCC who had direct surgery. After compiling the data, Shuto et al[17] present a treatment algorithm with a recommended strategy depending on tumor size, toleration of general anesthesia, presence of symptomatic peritumoral edema, and number of tumors.

"The application of SAbR is currently the standard of care for CNS and spine metastases from RCC where surgery is difficult and morbid. Additional indications currently under investigation include SAbR for oligometastatic and oligo-progressive mRCC and neo-adjuvant treatment for IVC tumor thrombus."

The retrospective findings suggested a tumor growth control rate of 84.3%. The key findings: The primary site (renal or not renal) and the delivered marginal dose (25 Gy or more) were significantly correlated with control of peritumoral edema; although peritumoral edema was extensive, it disappeared within 1-3 months. All tumors treated with direct surgery were 2 cm in maximum diameter.

Significant total tumor volume reduction at an early treatment seems to result in long-term survival, according to Kim et al, who proposed prognostic factors worth considering in determining outcomes. The median survival time for 46 patients in a study spanning 12 years was 18 months in the good response group, significantly longer than that observed in the poor response group (9 months. P=0.025). After treatment, local tumor control was achieved in 84.7% of the 85 tumors assessed.

Classification in the "good-response" group was the only independent prognostic factor for longer survival. Although the study did not specifically address the effect of total tumor volume reduction on quality of life, the authors suggest that such reduction can lead to improved neurologic symptoms and patients may be better able to undergo systemic therapy.

Spine Radiosurgery: Emerging Issues, Guidelines

Spine radiosurgery is an effective tool in managing patients with RCC. Although RT has little role in the treatment of primary disease, SRS does play an important role in the treatment of patients with spinal metastases, particularly those who received prior RT or instrumentation according to Taunk et al.[37] It is known from multiple series that spine SRS for RCC has extremely high rates of durable local control and palliation. However, it demands high quality control, precision guidance, and careful patient selection in multi-modality consultations to be safely and effectively implemented.

SAbR requires several special techniques to deliver ablative RT safely and effectively, including (1) use of multiple conformal beams with intensity-modulation, (2) accuracy within millimeters, (3) image guidance with each treatment, and (4) custom immobilization. Multiple beams allow for shaping of highly conformal dose, particularly sparing the spinal cord, which is usually within millimeters of the target volume. Custom immobilization requires comfortable, reproducible patient positioning while securely immobilizing the shoulders, neck, abdomen, or pelvis, as needed. Image guidance uses daily on-board imaging, ideally with pretreatment cone-beam CT.[38]

Between 2004 and 2010, MSKCC treated 105 RCC metastases (59 spine lesions) with single-dose SRS or hypofractionated SRS. The overall 3-year actuarial local progression-free survival rate was 44%. In patients with disease treated in a single fraction and with a dose of 24 Gy or greater, the 3-year local progression-free survival rate was 88%. In contrast, patients receiving hypofractionated treatment in 3 or 5 fractions had a 3-year local control rate of 17%. Treatment delivered in a single fraction and with a dose of 24 Gy or greater significantly improved local control in multivariate analysis.[20]

The authors' practice is to recommend SRS alone in patients with oligometastatic disease and mechanically stable spines. Operating in the NOMS (Neurologic, Oncologic, Mechanical instability, and Systemic disease) clinical framework, patients with spine lesions are assessed in a multidisciplinary clinic at MSKCC by a radiation oncologist, spine neurosurgeon, and neurointerventional radiologist. Careful patient selection is critical to identify those who may benefit the most from treatment, including patients for whom prior radiation treatment failed. Indicated procedures are performed for stabilization using implanted hardware or kyphoplasty before radiation. Patients with RCC who present with high-grade spinal cord compression often require surgical decompression and stabilization to separate the tumor from the spinal cord and facilitate delivery of SRS while remaining within spinal cord tolerance.

Stereotactic Radiotherapy for Extra-CNS Oligometastases

Although the evidence is relatively sparse compared to other treatment settings, data are growing and suggest compelling results for the use of SAbR in RCC extracranial

metastases. Theoretical basis for this approach comes from the surgical metastasectomy data that showed overall survival benefit for oligo-metastatic RCC patients when all site of metastases were resected.[39] SAbR offers a non-invasive technique for metastasectomy that can be applied to multiple sites of metastases throughout the body. The earlier reports on extracranial applications highlight how patient selection may be a key factor in whether SAbR is successful.

Svedman et al,[40] for example, suggest that SAbR can be considered as an option to surgery when there are a limited number of metastases, as local treatment in RCC with an indolent presentation or as a method of reducing tumor burden prior to medical treatment. One of the intriguing suggestions from this study is whether high-dose radiotherapy triggers regression of untreated metastases. Support for this hypothesis comes from other authors who speculate that this effect could be due to radiation induced immune response.[41] From the same institution, the report from Wersäll et al[23] also explored the extent to which certain patients may benefit more than others from SAbR, thus highlighting how patient selection could be used to greater advantage. For example, retrospective results in 58 patients in this Swedish study indicated that patients with one to three metastases and patients with inoperable primary tumors or local recurrence benefited more from this treatment than those with four or more metastases. The majority of patients were treated for metastases in the lungs.

In a detailed analysis of our institutional experience for treatment of extracranial mRCC,[24] we provide guidelines with dosimetric data and new insights on clinical factors affecting local control. Until recently, little has been known definitively about these factors. In the largest published experience of 175 metastatic lesions from 84 patients, we observed no failures when SAbR regimens of 24 Gy, 12 Gy, or 8 Gy in 1, 3, or 5 fractions were used with at least 95% PTV coverage. Overall local control rates were 91.2% at a one year. The most critical factors affecting local control of mRCC were adequate radiation dose and appropriate target coverage. Late toxicities were low and less than 3% were high grade. Interestingly, previous use of >1 systemic therapy came out to be an independent predictor of local failure in multi-variate analysis suggesting that higher radiation doses may be required to achieve the same local control in these patients.

In one of the subgroups analyzed in this retrospective study are patients that are showing progression on limited sites of disease on systemic therapy that received SAbR to delay the switching of systemic therapy or essentially to extend the progression free survival (PFS) of the ongoing systemic therapy. The benefits of treating oligo-progressive RCC metastases with SAbR could be many folds: 1) owing to the tumor genetic heterogeneity between primary and metastatic sites as described elegantly by Gerlinger et al.[42] It is possible that a majority of metastases in a patient are responding and only 1-2 sites are progressing. Therefore, SAbR allows continuation of a therapy that is otherwise effective and being tolerated by the patient. 2) By allowing effective continuation of the current therapy, SAbR may be preserving more lines of systemic therapy for a patient thereby possibly extending survival (OS). In a case report published by the same institution. Straka et. al. demonstrated extending the PFS of sunitinib from 14 months to 22 months by the use of SAbR for oligo-progressive disease.[43]

While the reported local control of SAbR for RCC is high, the question remains as to who truly benefits from the local control. It may be intuitive to treat oligo-metastatic RCC patients with SAbR either with a curative intent in the setting of metachronous metastasis or with the intent of preserving quality of live by delaying the initiation of systemic therapy. However, the most important question is whether by delaying systemic therapy, is the OS is being compromised? Data is lacking in this arena as to the effect of SAbR in PFS and OS, a few intriguing ongoing clinical trials are expected to provide insight to these settings. In one of these clinical trials begin conducted at UT Southwestern, oligo-metastatic RCC patients are being randomized to receive SAbR or standard of care systemic therapy in a phase II randomized trial. The accrual goal is 18 patients in each arm. The primary endpoint is the PFS on first line systemic therapy and essentially the study is measuring how long SAbR is able to extend the PFS on first line therapy. In addition to comparing OS, an important secondary endpoint is quality of life which is expected to be better in the SAbR arm that delayed the initiation of systemic therapy. The ClinicalTrials.gov. identifier is NCT02956798.

A second clinical trial being conducted at multiple locations in Canada by Georg Bjernason is evaluating how well SAbR can destroy kidney cancer metastases no longer controlled by sunitinib. Only oligo-progressive patients on sunitinib with up to 5 sits of progression will be enrolled. The primary endpoint is local control while the secondary endpoint is PFS. This study will seek an enrollment of 68 patients with an estimated completion date of December 2019.[44] The ClinicalTrials.gov. identifier is NCT020195766.

Conclusion

SAbR is becoming a more widely accepted modality for the treatment of a broad spectrum of renal tumors, including primary RCC, CNS RCC metastases, and extra-CNS oligometastases. It may also have potential application as neoadjuvant therapy. Renal tumors consistently show a very high (>85%) rate of local control in these settings after treatment with SAbR. The pivotal factor in optimizing the effectiveness of SAbR is appropriate dose selection. While additional clinical trials and longer-term follow ups are required to establish guidelines on the optimal dose in controlling RCC, the focus now is on how and when to integrate an effective local control modality such as SAbR with the growing armament of approved systemic agents for RCC. Treatment of oligo-progressive RCC metastasis may be a strategy to improve PFS of sys-

temic agents for RCC. The now well-known immune modulatory and antigen presenting properties of SAbR, which has not been elaborated and is beyond the scope of this review, may synergize with the approved and upcoming immunotherapies for RCC. While much is known about the local control, the impact of SAbR on PFS and eventually on extending patient survival is not known yet and careful design of prospective trials is clearly needed in this setting. With greater application of SAbR, the focus needs to be maintained on careful patient selection for the technique to be safely and effectively implemented and outcomes optimized, including long-term survival.

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EDITOR'S MEMO

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prolong exposure to the drug while limiting the adverse effects that often stand in the way of continuing with the 4 weeks on and 2 weeks off strategy. So here, too, an intriguing and significant
evolution in the standard of care is taking place with regards to the relative merits of the 4/2 dosing schedule vs the 2/1 schedule. The particularly interesting aspect of this evolution is the apparent initiative on the part of many of our colleagues in community practice to stay ahead of the curve or integrate novel approaches that enable them to prolong exposure to sunitinib or at least mitigate the impact of adverse effects through various drug-free interval strategies.

There are skeptics, however, who may ask whether it is appropriate to expend more resources prospectively testing (data we need to verify appropriate dosing schedules) a new schedule of an older targeted agent in lieu of the excitement over the latest generation of immune-oncologics in RCC. There are two reasons for continuing to investigate VEGF blockade in this context. First, not all RCCs respond to immunotherapy, as Lauren C. Harshman, MD reminds us in an Editorial in the *Journal of Clinical Oncology* (2017;35(16) 1755-1757. This is true of even the modern and more tolerable PD-1 pathway antibodies. Also, VEGF-pathway blockade remains the backbone of many ongoing, first-line PD-1 combination studies. These considerations remain essential in view of the new agents recently approved and the implications for the treatment paradigm. The article in this issue by Pavlos Msaouel, MD, and Nizar Tannir, MD, not only delineates these issues but suggests state-of-the-art thinking on tailoring sunitinib schedules to achieve maximum benefit.

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Guest Editor

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response; there were eight confirmed partial responders with MET-driven disease (18%), but none with MET-independent disease ($P = .002$). Median progression-free survival for patients with MET-driven and MET-independent PRCC was 6.2 months and 1.4 months, respectively (hazard ratio, 0.33; 95% CI, 0.20 to 0.52; log-rank $P < .001$). The most frequent adverse events associated with savolitinib were nausea, fatigue, vomiting, and peripheral edema.
Conclusion: These data show activity and tolerability of savolitinib in the subgroup of patients with MET-driven PRCC. Furthermore, molecular characterization of MET status was more predictive of response to savolitinib than a classification based on pathology. These findings justify investigating savolitinib in MET-driven PRCC.

Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study. Hammers HJ, Plimack ER, Infante JR, et al. *J Clin Oncol*. 2017 Jul 5;JCO20167219 85. doi: 10.1200.
Summary: Combination treatment with immune checkpoint inhibitors has shown enhanced antitumor activity compared with monotherapy in tumor types such as melanoma. The open-label, parallel-cohort, dose-escalation, phase I CheckMate 016 study evaluated the efficacy and safety of nivolumab plus ipilimumab in combination, and nivolumab plus a tyrosine kinase inhibitor in metastatic renal cell carcinoma (mRCC). Safety and efficacy results from the nivolumab plus ipilimumab arms of the study are presented. Patients with mRCC received intravenous nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), or nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3) every 3 weeks for four doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks until progression or toxicity. End points included safety (primary), objective response rate, and overall survival (OS). All patients in the N3I3 arm (n = 6) were censored at the time of analysis as a result of dose-limiting toxicity or other reasons. Forty-seven patients were treated in both the N3I1 and the N1I3 arm, and baseline patient characteristics were balanced between arms. Grade 3 to 4 treatment-related adverse events were reported in 38.3% and 61.7% of the patients in the N3I1 and N1I3 arms, respectively. At a median follow-up of 22.3 months, the confirmed objective response rate was 40.4% in both arms, with ongoing responses in 42.1% and 36.8% of patients in the N3I1 and N1I3 arms, respectively. The 2-year OS was 67.3% and 69.6% in the N3I1 and N1I3 arms, respectively.
Conclusion: Nivolumab plus ipilimumab therapy demonstrated manageable safety, notable antitumor activity, and durable responses with promising OS in patients with mRCC.

Correlation of c-MET Expression with PD-L1 Expression in Metastatic Clear Cell Renal Cell Carcinoma Treated by Sunitinib First-Line Therapy. Kammerer-Jacquet SF, Medane S, Bensalah K, et al. *Target Oncol*. 2017 Aug; 12(4):487-494.
Summary: Cabozantinib, an anti-angiogenic tyrosine kinase inhibitor that targets c-MET, provided interesting results in metastatic ccRCC treatment. To understand better the role of c-MET in ccRCC, we assessed its status in a population of patients with metastatic ccRCC. For this purpose, tumor samples were analyzed for c-MET expression by immunohistochemistry (IHC), for c-MET copy number alterations by fluorescence in situ hybridization (FISH), and for c-MET mutations by next generation sequencing (NGS) in a retrospective cohort of 90 primary ccRCC of patients with metastases treated by first-line sunitinib. The expression of c-MET was correlated with pathological, immunohistochemical (VEGFA, CAIX, PD-L1), clinical, and molecular criteria (VHL status) by univariate and multivariate analyses and to clinical outcome using Kaplan-Meier curves compared by log-rank test. Of ccRCC, 31.1% had low c-MET expression (absent to weak intensity by IHC) versus 68.9% with high expression (moderate to strong intensity). High expression of c-MET was associated with a gain in FISH analysis ($P = 0.0284$) without amplification. No mutations were detected in NGS. Moreover, high c-MET expression was associated with lymph node metastases ($P = 0.004$), sarcomatoid component ($P = 0.029$), VEGFA ($P = 0.037$), and PD-L1 ($P = 0.001$) overexpression, the only factor that remained independently associated ($P < 0.001$) after logistic regression. No difference was observed in clinical outcomes.
Conclusion: This study is the first to analyze c-MET status in metastatic ccRCC. The high expression of c-MET in the majority of ccRCC and its independent association with PD-L1 expression, may suggest a potential benefit from combining c-MET inhibitors and targeted immunotherapy.

New Insights into Adjuvant Renal Cell Carcinoma Treatment with Vascular Endothelial Growth Factor Inhibitors: What Have We Learned So Far? Escudier B, Staehler M. *Eur Urol*. 2017 Sep 7; pii: S0302-2838(17) 30713-3. doi: 10.1016
Summary: Adjuvant treatment of renal cell carcinoma with vascular endothelial growth factor inhibitors is feasible and effective with careful patient selection and standard dosing levels. □

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intermediate/poor risk patients, which was 41.6% for the nivolumab/ipilimumab combination compared to 26.5% for sunitinib ($P < 0.0001$) with 9.4% of patients receiving combination therapy achieving complete response (CR) compared to1.2% of patients on sunitinib. There was an improvement in median PFS with the combination in this cohort; median PFS was 11.6 months for the nivolumab and ipilimumab combination versus 8.4 months with sunitinib, hazard ratio [HR] 0.82 ($P = 0.03$).

The efficacy outcomes differed according to the levels of PD-L1 expression and IMDC risk group. Both the ORR per independent committee and PFS significantly favored nivolumab plus ipilimumab over sunitinib in intermediate/poor risk patients having baseline PD-L1 expression ≥1% where the ORR was 58% versus 25%, and median PFS was 22.8 (95% CI 9.4, NR) months versus 5.9 (95% CI 4.4, 7,1) months, respectively, HR 0.48 (95% CI 0.28, 0.82; $P = 0.0003$). The investigators found that baseline tumor PD-L1 expression was lower in the cohort of patients at favorable risk where 11% of patients on combination had PD-L1 levels ≥1% versus12% of patients on sunitinib compared to 26% versus 29% of patients at intermediate or poor risk in the respective treatment arms.

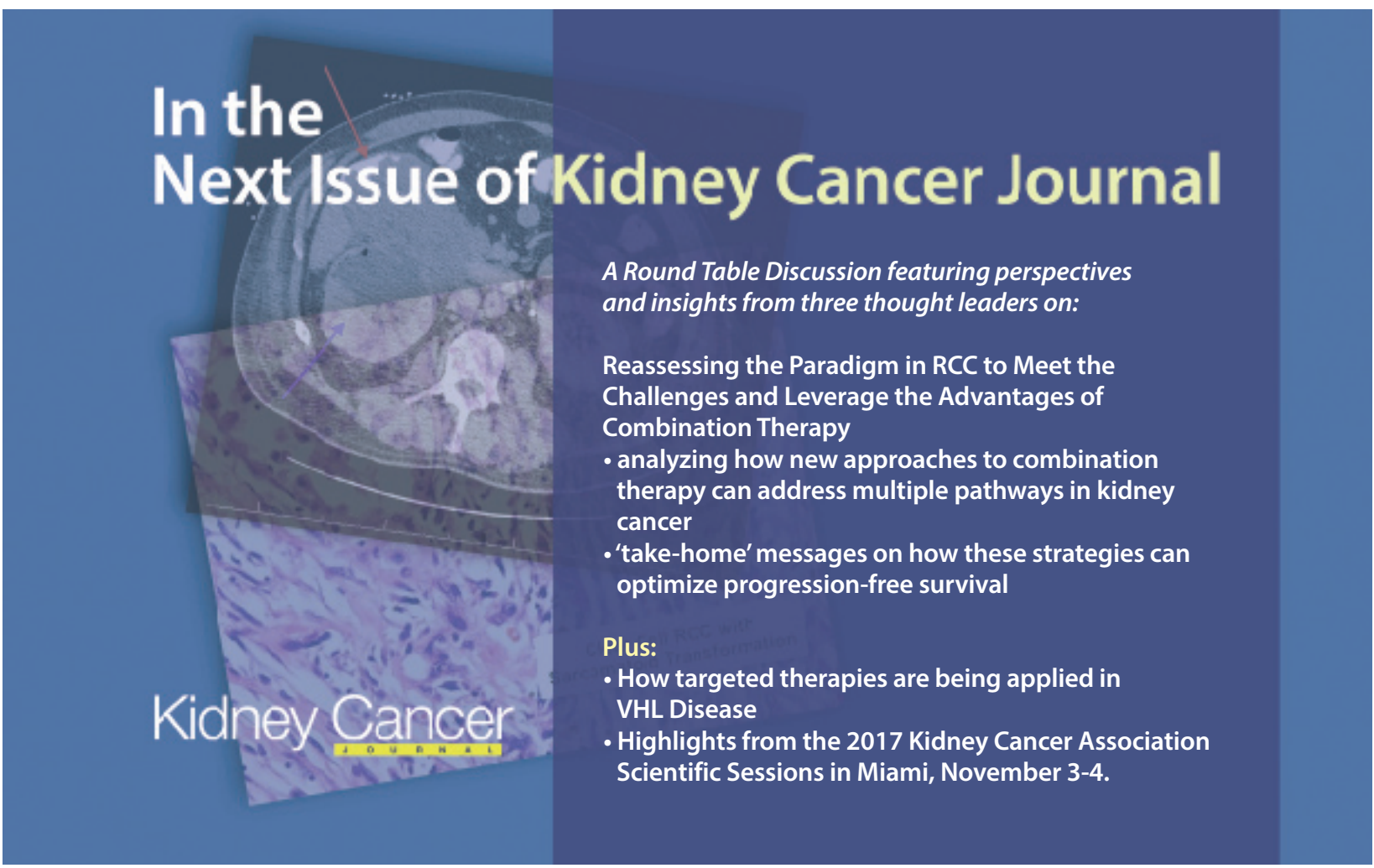
In patients at favorable risk, both the ORR and PFS were higher with sunitinib over combination; in this cohort, ORR was 29% with nivolumab/ipilimumab versus 52% with sunitinib ($P = 0.0002$) and median PFS was 15.3 (95% CI 9.7, 20.3) months versus 25.1 (95% CI 20.9, NR) months, respectively, HR 2.17 (95% CI 1.46, 3.22; $p < 0.0001$). In the overall composite of patients at any risk, no significant difference between treatments was demonstrated in ORR ($P = 0.0191$) or PFS ($P = 0.819$). Any grade drug-related adverse events (AEs) occurred in 509 (93%) of patients in the nivolumab/ipilimumab cohort and in 521 (97%) of patients receiving sunitinib. With the combination, 54% of patients had a grade 3 to 4 AE, and with sunitinib 63% of patients had a grade 3 to 5 AE.

Progression-free Rate Unaffected by Sequence of Cytoreductive Nephrectomy and Sunitinib in Patients with Synchronous mRCC

MADRID—Treating primary tumors by administering targeted therapy with sunitinib prior to cytoreductive nephrectomy (CN) did not improve the progression-free rate at 28 weeks over a sequence of immediate CN followed by sunitinib in patients with synchronous metastatic renal cell carcinoma (mRCC), according to findings from a randomized trial presented at ESMO 2017.

Axel Bex, Surgical Oncology-Urology, The Netherlands Cancer Institute in Amsterdam, Netherlands and colleagues investigated whether the outcome after sequential cytoreductive nephrectomy (CN) followed by targeted therapy with sunitinib could be improved with the opposite sequence. They randomized 99 patients with mRCC to immediate CN followed by sunitinib (n=50) versus three cycles of sunitinib followed by CN plus sunitinib (n=49). The study (EORTC 30073 SURTIME NCT01099423) included patients with histologically confirmed clear-cell subtype, and a resectable asymptomatic primary tumor plus 3 or fewer surgical risk factors.

After 5.7 years the study included 99 patients from 19 institutions. The immediate CN arm had 50 patients and the deferred CN arm had 49 patients. The majority of patients were male in both arms with a median age of 60 compared to 58 years, and MSKCC intermediate risk was reported for 86% versus 87.7% of patients, respectively. In the respective arms, WHO performance status (PS) was 0 and 1 in 72% and 28% versus 63.3 % and 36.7%; 86% versus 93.9% of patients had ≥ 2 measurable metastatic sites and the mean (standard deviation) size of the primary tumor was 93.1 (37.8) mm versus 96.8 (31.3) mm. Patients in each arm derived different benefit from each sequence. At a median follow-up of 3.3 years, 46 of 50 patients underwent CN in the immediate CN arm and 40 of these patients had received post-CN sunitinib. In the deferred CN arm, 48 of 49 patients had been treated with sunitinib prior to CN; of these patients, 40 underwent CN and 26 also received post-CN sunitinib.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