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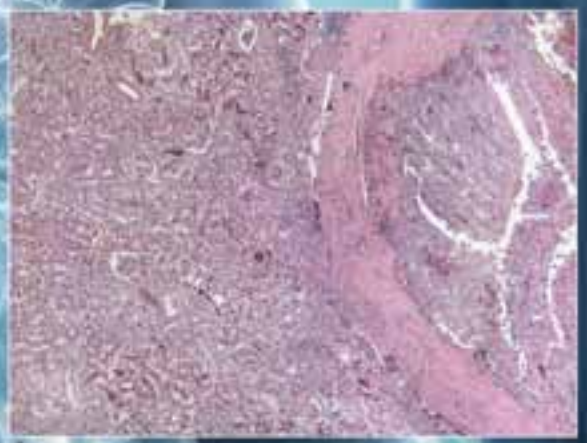
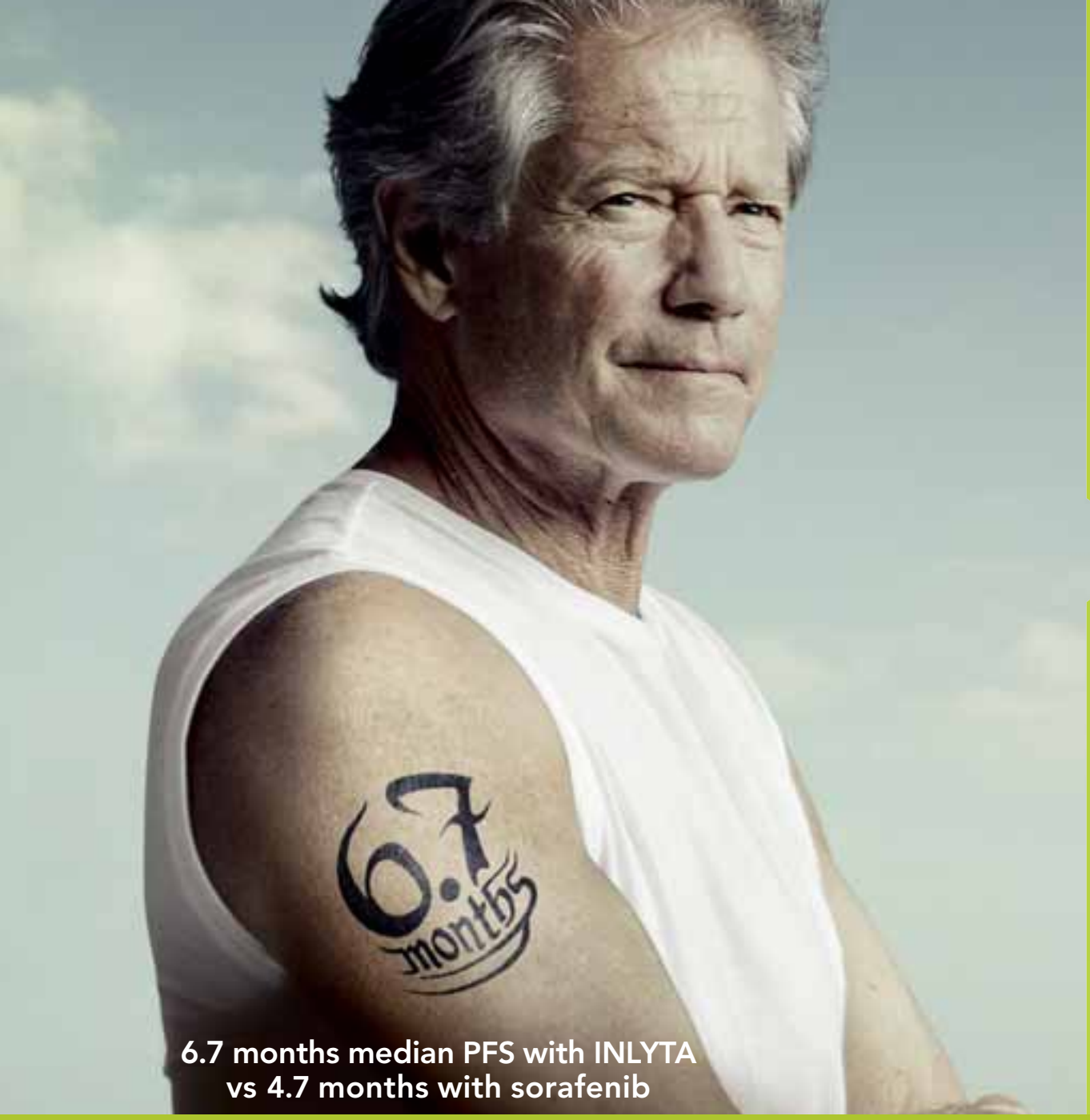
Meeting the Challenge of Positive Surgical Margins After NSS

Point-Counterpoint: Cytoreductive Nephrectomy in the Era of Targeted therapy

European RCC Meeting: Highlights and New Insights



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



6.7 months median PFS with INLYTA vs 4.7 months with sorafenib

INLYTA 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 those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

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.

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

Inlyta™
axitinib 1mg and 5mg tablets

for the treatment of advanced RCC after failure of one prior systemic therapy

What truly matters to you in 2nd-line mRCC?

EVIDENCE

In the phase 3, head-to-head study of exclusively 2nd-line patients with mRCC...

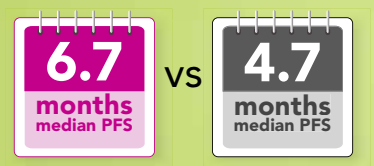
INLYTA was the 1st agent to demonstrate

SUPERIOR EFFICACY

to sorafenib

Primary endpoint: PFS

HR=0.67 (95% CI: 0.54, 0.81; *P*<.0001)



INLYTA (n=361) **sorafenib** (n=362)

95% CI: 6.3, 8.6 and 4.6, 5.6, respectively

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). Patients were randomized to either INLYTA (5 mg twice daily) or sorafenib (400 mg twice daily) with dose adjustments allowed in both groups. Primary endpoint was PFS. Secondary endpoints included ORR, OS, and safety and tolerability.[1,2]

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, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, weight decreased, vomiting, asthenia, and constipation.

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

The most common (≥20%) **lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine, decreased bicarbonate, hypocalcemia, decreased hemoglobin, decreased lymphocytes (absolute), increased ALP, hyperglycemia, increased lipase, increased amylase, increased ALT, and increased AST.

Please see brief summary on the following pages.

Inlyta™
axitinib 1mg and 5mg tablets

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 persistent 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 4/359 patients (1%) receiving INLYTA and 4/355 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.

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)		Sorafenib (N=355)	
	All Grades[b]	Grade 3/4	All Grades[b]	Grade 3/4
	%	%	%	%
Diarrhea	55	11	53	7
Hypertension	40	16	29	11
Fatigue	39	11	32	5
Decreased appetite	34	5	29	4
Nausea	32	3	22	1
Dysphonia	31	0	14	0
Palmar-plantar erythrodysesthesia syndrome	27	5	51	16
Weight decreased	25	2	21	1
Vomiting	24	3	17	1
Asthenia	21	5	14	3
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	3	12	3
Abdominal pain	14	2	11	1
Headache	14	1	11	0
Pain in extremity	13	1	14	1
Rash	13	<1	32	4
Proteinuria	11	3	7	2
Dysgeusia	11	0	8	0
Dry skin	10	0	11	0
Dyspepsia	10	0	2	0
Pruritus	7	0	12	0
Alopecia	4	0	32	0
Erythema	2	0	10	<1

[a]Percentages are treatment-emergent, all-causality events

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

Selected adverse reactions (all grades) that were reported in <10% of patients treated with INLYTA included dizziness (9%), upper abdominal pain (8%), myalgia (7%), dehydration (6%), epistaxis (6%), anemia (4%), hemorrhoids (4%), hematuria (3%), tinnitus (3%), lipase increased (3%), glossodynia (3%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), and transient ischemic attack (1%).

The following table presents the most common laboratory abnormalities reported in ≥10% patients who received INLYTA or sorafenib.

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

Laboratory Abnormality	N	INLYTA		N	Sorafenib	
		All Grades[a]	Grade 3/4		All Grades[a]	Grade 3/4
		%	%		%	%
Hematology						
Hemoglobin decreased	320	35	<1	316	52	4
Lymphocytes (absolute) decreased	317	33	3	309	36	4
Platelets decreased	312	15	<1	310	14	0
White blood cells decreased	320	11	0	315	16	<1
Chemistry						
Creatinine increased	336	55	0	318	41	<1
Bicarbonate decreased	314	44	<1	291	43	0
Hypocalcemia	336	39	1	319	59	2
ALP increased	336	30	1	319	34	1
Hyperglycemia	336	28	2	319	23	2
Lipase increased	338	27	5	319	46	15
Amylase increased	338	25	2	319	33	2
ALT increased	331	22	<1	313	22	2
AST increased	331	20	<1	311	25	1
Hypernatremia	338	17	1	319	13	1
Hypoalbuminemia	337	15	<1	319	18	1
Hyperkalemia	333	15	3	314	10	3
Hypoglycemia	336	11	<1	319	8	<1
Hyponatremia	338	13	4	319	11	2
Hypophosphatemia	336	13	2	318	49	16

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

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

Selected laboratory abnormalities (all grades) that were reported in <10% of patients treated with INLYTA included hemoglobin increased (above the upper limit of normal) (9% for INLYTA versus 1% for sorafenib) and hypercalcemia (6% for INLYTA versus 2% for sorafenib).

DRUG INTERACTIONS

In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 Inhibitors. Co-administration of ketoconazole, a strong inhibitor of CYP3A4/5, increased the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inhibitors should be avoided. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be coadministered, the INLYTA dose should be reduced *[see Dosage and Administration]*.

CYP3A4/5 Inducers. Co-administration of rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended *[see Dosage and Administration]*. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category D *[see Warnings and Precautions]*.

There are no adequate and well-controlled studies with INLYTA in pregnant women. INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Axitinib was teratogenic, embryotoxic and fetotoxic in mice at exposures lower than human exposures at the recommended starting dose. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

Oral axitinib administered twice daily to female mice prior to mating and through the first week of pregnancy caused an increase in post-implantation loss at all doses tested (≥15 mg/kg/dose, approximately 10 times the systemic exposure (AUC) in patients at the recommended starting dose). In an embryo-fetal developmental toxicity study, pregnant mice received oral doses of 0.15, 0.5 and 1.5 mg/kg/dose axitinib twice daily during the period of organogenesis. Embryo-fetal toxicities observed in the absence of maternal toxicity included malformation (cleft palate) at 1.5 mg/kg/dose (approximately 0.5 times the AUC in patients at the recommended starting dose) and variation in skeletal ossification at ≥0.5 mg/kg/dose (approximately 0.15 times the AUC in patients at the recommended starting dose).

Nursing Mothers. It is not known whether axitinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INLYTA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and efficacy of INLYTA in pediatric patients have not been studied.

Toxicities in bone and teeth were observed in immature mice and dogs administered oral axitinib twice daily for 1 month or longer. Effects in bone consisted of thickened growth plates in mice and dogs at ≥15 mg/kg/dose (approximately 6 and 15 times, respectively, the systemic exposure (AUC) in patients at the recommended starting dose). Abnormalities in growing incisor teeth (including dental caries, malocclusions and broken and/or missing teeth) were observed in mice administered oral axitinib twice daily at ≥5 mg/kg/dose (approximately 1.5 times the AUC in patients at the recommended starting dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatric Use. In a controlled clinical study with INLYTA for the treatment of patients with RCC, 123/359 patients (34%) treated with INLYTA were ≥65 years of age. Although greater sensitivity in some older individuals cannot be ruled out, no overall differences were observed in the safety and effectiveness of INLYTA between patients who were ≥65 years of age and younger.

No dosage adjustment is required in elderly patients.

Hepatic Impairment. In a dedicated hepatic impairment trial, compared to subjects with normal hepatic function, systemic exposure following a single dose of INLYTA was similar in subjects with baseline mild hepatic impairment (Child-Pugh class A) and higher in subjects with baseline moderate hepatic impairment (Child-Pugh class B).

No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). A starting dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B).

INLYTA has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

Renal Impairment. No dedicated renal impairment trial for axitinib has been conducted. Based on the population pharmacokinetic analyses, no significant difference in axitinib clearance was observed in patients with pre-existing mild to severe renal impairment (15 mL/min ≤creatinine clearance [CLcr] <89 mL/min). No starting dose adjustment is needed for patients with pre-existing mild to severe renal impairment. Caution should be used in patients with end-stage renal disease (CLcr <15 mL/min).

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

In a controlled clinical study with INLYTA for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with INLYTA, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

In cases of suspected overdose, INLYTA should be withheld and supportive care instituted.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility. Carcinogenicity studies have not been conducted with axitinib.

Axitinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human lymphocyte chromosome aberration assay. Axitinib was genotoxic in the *in vivo* mouse bone marrow micronucleus assay.

INLYTA has the potential to impair reproductive function and fertility in humans. In repeat-dose toxicology studies, findings in the male reproductive tract were observed in the testes/epididymis (decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, reduced sperm density and count) at ≥15 mg/kg/dose administered orally twice daily in mice (approximately 7 times the systemic exposure (AUC) in patients at the recommended starting dose) and ≥1.5 mg/kg/dose administered orally twice daily in dogs (approximately 0.1 times the AUC in patients at the recommended starting dose). Findings in the female reproductive tract in mice and dogs included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at ≥5 mg/kg/dose (approximately 1.5 or 0.3 times the AUC in patients at the recommended starting dose compared to mice and dogs, respectively).

In a fertility study in mice, axitinib did not affect mating or fertility rate when administered orally twice daily to males at any dose tested up to 50 mg/kg/dose following at least 70 days of administration (approximately 57 times the AUC in patients at the recommended starting dose). In female mice, reduced fertility and embryonic viability were observed at all doses tested (≥15 mg/kg/dose administered orally twice daily) following at least 15 days of treatment with axitinib (approximately 10 times the AUC in patients at the recommended starting dose).

PATIENT COUNSELING INFORMATION

Reversible Posterior Leukoencephalopathy Syndrome. Advise patients to inform their doctor if they have worsening of neurological function consistent with RPLS (headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances).

Pregnancy. Advise patients that INLYTA may cause birth defects or fetal loss and that they should not become pregnant during treatment with INLYTA. Both male and female patients should be counseled to use effective birth control during treatment with INLYTA. Female patients should also be advised against breast-feeding while receiving INLYTA.

Concomitant Medications. Advise patients to inform their doctor of all concomitant medications, vitamins, or dietary and herbal supplements.

Rx only

Issued: September 2013

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.** Data on file. Pfizer Inc, New York, NY.

mRCC=metastatic renal cell carcinoma; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

About the Cover
Computer-generated figure with kidney cancer is paired with micrograph of renal cell carcinoma (inset). Normal cells are to the left and malignant cells are at the right of the micrograph. (Copyright, Science Photo and Science Source)

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KCJ EDITOR'S MEMO

Finding the Needle in a Haystack: Navigating Oncology Websites for News You Can Use


Robert A. Figlin, MD

An overwhelming number of websites, many providing a portal to information on kidney cancer, confront us as professionals to integrate this non peer reviewed information into our patient support and interactions. Navigating this vast cyberspace for information of true value, relevance, and practical merit represents a daunting challenge for anyone seeking to understand its true benefit to the patient experience; and frequently the information is derived from sources lacking scientific validation or confirmation in rigorous clinical trials. For the many unsolicited emails vying for your attention, perhaps a few will be worthwhile.

By now we all have our favorite "go-to" websites for trusted information, but it is worthwhile or at least intriguing to explore a few other online resources that may not be within your frame of reference. If you have not explored some of the following websites, you may want to investigate whether they provide some helpful information. Although they are not all targeted to kidney cancer, they may provide portals to information about the disease or other data of interest to you as a clinician. In some cases, the information on these websites explores the business side or entrepreneurial issues of health care, offering a glimpse of drugs in the pipeline and trends within pharma beginning to emerge but with potential implications for patient care.

- ***OncologyEducation.com*** is a comprehensive resource providing evidence-based educational content exclusively developed and authored by a leading international faculty of oncology physicians. All content focuses on presenting timely, unbiased information for the oncology community, including oncologists and other related specialists, physicians, nurses, pharmacists, students, residents and researchers. OncologyEducation.com resources are updated regularly and include more than 4,000 pages of original, expert-reviewed content on recent advances in literature and clinical trials, conference updates and presentations, and disease-specific information, all of which are delivered through integrated online and mobile platforms.
- ***kidneycancer.org*** is intended primarily as a resource for patients and medical professionals and the information presented is periodically reviewed by the Kidney Cancer Association's medical and scientific advisors. News about clinical trials, patient advocacy issues, legislative awareness, and other sources of information for professionals also can be accessed on this website.
- ***obroncology.com*** (*Oncology Business Review*) is the most comprehensive digital platform for oncology focused news and information. This website aggregates,

(continued on inside back cover)

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 rfiglin@coh.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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Survey of the Literature: Essential Peer-Reviewed Reading in Kidney Cancer

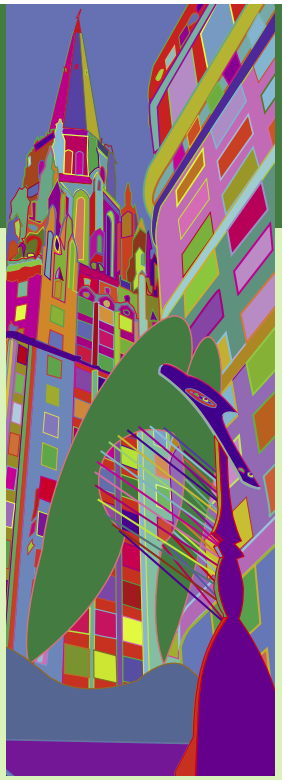
The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Chromosome 3p loss of heterozygosity is associated with a unique metabolic network in clear cell renal carcinoma. Gatto F, Nookaew I, Nielsen J. *Proc Natl Acad Sci USA*. 2014;111:E866-E875.
Summary: Several common oncogenic pathways have been implicated in the emergence of renowned metabolic features in cancer, which in turn are deemed essential for cancer proliferation and survival. However, the extent to which different cancers coordinate their metabolism to meet these requirements is largely unexplored. This study showed that even in the heterogeneity of metabolic regulation a distinct signature encompassed most cancers. On the other hand, clear cell renal cell carcinoma (ccRCC) strongly deviated in terms of metabolic gene expression changes, showing widespread down-regulation. The authors observed a metabolic shift that associates differential regulation of enzymes in one-carbon metabolism with high tumor stage and poor clinical outcome. A significant yet limited set of metabolic genes that explained the partial divergence of ccRCC metabolism correlated with loss of von Hippel-Lindau tumor suppressor (VHL) and a potential activation of signal transducer and activator of transcription 1. Further network-dependent analyses revealed unique defects in nucleotide, one-carbon, and glycerophospholipid metabolism at the transcript and protein level, which contrasts findings in other tumors. Notably, this behavior is recapitulated by recurrent loss of heterozygosity in multiple metabolic genes adjacent to VHL.
Conclusion: This study shows how loss of heterozygosity, hallmarked by VHL deletion in ccRCC, may uniquely shape tumor metabolism.

Anti-VEGF therapy in mRCC: differences between Asian and non-Asian patients. Wang Y, Choueiri TK, Lee JL, et al. *Br J Cancer.* 2014; Feb 18. doi: 10.1038/bjc.2014.28. [Epub ahead of print]
Summary: Several reports suggest that vascular endothelial growth factor (VEGF)-targeted therapy in metastatic renal cell carcinoma (mRCC) may be more toxic in Asian vs non-Asian populations. Comparative efficacy of these agents with respect to ethnicity is not well characterised. A multicenter, retrospective, cohort study using Asian and non-Asian centers collected data on ethnicity, dose reductions and outcomes using the
International mRCC Database Consortium. This study included 1024 (464 Asian, 560 non-Asian) patients with a 29.4 months median follow-up. The percentage of dose modifications/reductions between non-Asians and Asians was similar (55% vs 61% *P*=0.1197). When adjusted for risk groups, there was no difference in overall or progression-free survival between non-Asians and Asians. Patients with dose reductions due to toxicity had longer treatment durations and overall survival than those who did not in both non-Asian (10.6 vs 5.0 months, *P*<0.0001; 22.6 vs 16.1 months, *P*=0.0016, respectively) and Asian populations (8.9 vs 5.4 months, *P*=0.0028; 28.0 vs 18.7 months, *P*=0.0069, respectively).
Conclusion: Adjusting for risk groups, there appears to be no difference in outcome between Asian vs non-Asian patients with mRCC treated with VEGF-targeted therapy. Judicious dose reductions may allow for better outcomes in both populations due to longer treatment durations, but direct comparisons are needed.

Surgical outcomes in the management of isolated nodal recurrences: a multicenter international retrospective cohort. Russell CM, Espiritu PN, Kassouf W, et al. *J Urol*.2014; Feb 13. pii: S0022-5347(14)00261-4. doi: 10.1016/j.juro. 2014. 02.010.[Epub ahead of print]
Summary: Results are from a multicenter international cohort representing the largest surgical experience in the management of isolated retroperitoneal nodal recurrences of renal cell carcinoma (RCC), a unique subset of locoregional disease, yet to be described in detail. Patients with isolated nodal recurrence of $pT_{any}N+M0$ disease following nephrectomy were identified through retrospective chart review at three independent institutions. Progression free survival (PFS), estimated using the Kaplan-Meier method, was utilized to compare survival outcomes between primary $T(1-2)N_{(any)}M0$ and $T3N_{(any)}M0$ tumors, as well as clear cell and non-clear cell histology RCC's. A total of 22 patients met inclusion criteria. Median time to local post-nephrectomy recurrence was 31.5 months (IQR 12.9-43.3). Following resection of isolated nodal recurrence, 10 patients (46%) developed a secondary recurrence at a median of 11.2 months (IQR 8.1-18.4), and of those 2 (9%) succumbed to their disease. Overall median PFS was 12.7 months, and was 24.8 months in $T(1-2)N_{(any)}M0$ tumors, 9.9 months in $T3N_{(any)}M0$ tumors, 13.4 months in clear cell RCC's, and 17.6 months in non-clear cell RCC's.
Conclusion: Surgical resection represents the best curative option for patients presenting with isolated retroperitoneal lymph node recurrence of RCC, and a durable PFS following surgery is attainable in many patients regardless of histology or clinical TNM staging. In addition, the cohort demonstrated a lower RCC related mortality rate than previously reported series of local metastasis. As such, all patients free of precluding comorbidities should be considered for complete surgical resection by an experienced genitourinary surgeon.

Molecular Biomarkers in Advanced Renal Cell Carcinoma. Maroto P, Rini B. *Clin Cancer Res*. 2014 Feb 13;[Epub ahead of print]
Summary: The availability of agents directly targeting tumorigenic and angiogenic pathways has significantly improved the outcomes of patients with advanced renal cell carcinoma (RCC) in recent years. However, all patients eventually become resistant and a substantial percentage experience immediate disease progression with first-line targeted therapy.
(continued on page 30)



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Meeting the Challenge of Positive Surgical Margins After Nephron-Sparing Surgery

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It is not the "dilemma" some authors called it only a few years ago, but the management of positive surgical margins following partial nephrectomy is still a worrisome, challenging, and controversial situation. Despite a debate on a wide range of issues, a consensus on appropriate management strategies seems to be emerging; the latest reports highlight important considerations with implications for vigilant followup and counseling of patients with regard to possible recurrence of tumor as the use of robotic partial nephrectomy expands rapidly for some lesions previously targeted by a radical procedure.

It may be tempting to call radical nephrectomy somewhat of a dinosaur among oncologic treatments, especially for single renal tumors, because it is hardly the dominant force it once was. And yet, when a surgical technique has remained the standard of therapy for more than 50 years, clinical practice does not change swiftly but evolves slowly over time. This was the case about 10 years ago when radical nephrectomy was still entrenched as the treatment of choice for even relatively small renal tumors. Within the last decade, however, numerous reports have ushered in a new era, major advances in nephron-sparing surgery, and a dramatically different paradigm in the surgical approach for relatively small tumors, to such an extent that partial nephrectomy (PN) is now considered the standard of care for these small renal cortical tumors.[1-4] These recent reports have established the oncological efficacy of PN with the added benefit of preserving long-term renal function and minimizing the risk of chronic kidney disease.[5] Although PN has been a harbinger of a new rationale, it has also ushered in a myriad of questions, not easily resolved yet persistently addressed, about its role in the treatment paradigm.

Keywords: kidney; nephrectomy; robotics; carcinoma, renal cell; positive surgical margins; nephron-sparing surgery; partial nephrectomy

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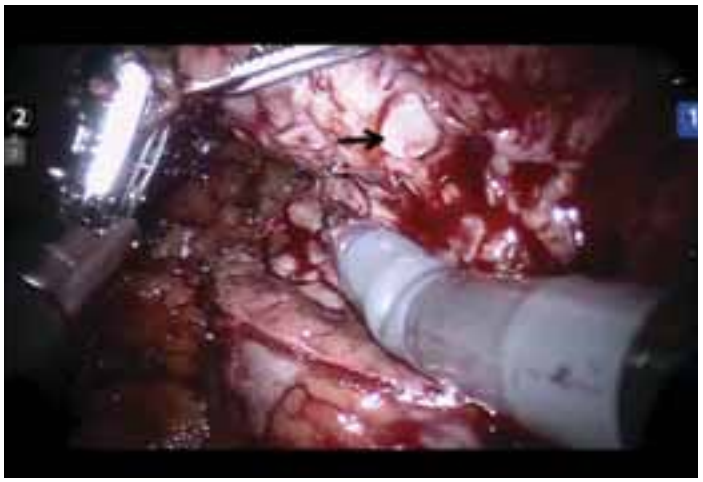
As the experience with PN grew, emerging data further suggested that PN could be safely offered to appropriately selected patients with larger tumors, 4 to 7 cm in size, without a significant increase in postoperative morbidity or compromise of long-term disease-free survival.[6,7] Of available options for nephron-sparing surgery PN is the most widely practiced and has proved to be as safe and efficient as radical nephrectomy.[8] It is also the only approach that provides definite tumor excision.[9] Despite these advantages, there is controversy surrounding the use of PN. As in any other oncologic surgery, the surrogate of complete tumor resection during PN remains a negative surgical margin. The risk of an incomplete tumor excision, leaving a positive surgical margin, remains one of the dilemmas associated with the use of nephron-sparing surgery, according to some authors. The standard surgical technique of PN involves removal of the tumor with an additional rim of negative renal parenchyma. The rationale is that by excising a wide margin of normal parenchyma, we ensure the preserved portion of the kidney will be clear of malignancy.

However, what is the optimal margin required for oncological safety? Some authors, for example, suggest that a tumor-free margin, regardless of size, is sufficient to achieve complete local excision.[10,11] On the other hand, if tumor is detected by pathology studies at the inked margin, theoretically this would constitute an incomplete cancer removal; the implication from this finding would be a potential increased risk of local or distant recurrence. Nephron-sparing surgery is associated with a risk of an incomplete tumor excision. The debate over the significance of a positive surgical margin—and how to manage it—has been the focus of numerous reports seeking to clarify options and provide a consensus. A positive surgical margin is defined as extension of tumor to the inked surface of the resected specimen, which suggests a possible incomplete excision of the neoplasm. Earlier studies warned of a higher recurrence rate when PSMs were found in cases of tumors with high malignant potential; subsequent re-



During partial nephrectomy, a suspicious area is seen on the cut edge highly concerning for a gross positive margin (arrow).

ports tended to contradict those results, and as larger series emerged, investigators stated that PSMs have negligible or no impact on tumor recurrence or metastasis.[12]

Enucleation: Is It a Valid Option for Conservative Therapy?

As recent studies further delineate appropriate strategies for the excision of tumor with PN, controversy still surrounds what standard should be used with regard to the width of healthy tissue that should be excised with the lesion to ensure negative margins. For example, some authors have demonstrated that negative surgical margins (NSMs) can be achieved while reducing the safety margin to 5 mm.[13,14] Subsequently, guidelines emerged from groups like the European Association of Urology recommending the presence of a minimal tumor-free surrounding margin of healthy renal parenchyma to be taken.[15] When these guidelines emerged, several studies explored the advantages of simple enucleation instead of traditional PN.[16-18]

SE consists of incision of the renal parenchyma within a few millimeters of the tumor, and blunt dissection of a plane between the capsule of the tumor and the healthy renal tissue without the inclusion in the removed tissue of any visible normal renal parenchyma.[19] In what is reportedly the first multicenter, comparative study, Minervini et al examined oncologic outcomes after standard PN and simple enucleation. Despite some reports showing excellent long-term oncologic results with enucleation, there is still a widespread belief among urologists that enucleation is unsafe with a high risk of incomplete tumor excision, especially for larger lesions.[20]

In their report,[19] retrospectively analyzing results in 982 patients who underwent standard PN and 537 who had SE, local recurrence, cancer specific survival and progression-free survival were the endpoints. The results confirmed that the two procedures produced similar oncologic outcomes in terms of PFS and CSS estimates: 5 and 10-year PFS estimates were 88.9% and 82% after standard PN, and 91.4% and 90.8% after enucleation. The 5 and 10-year CSS estimates were 93.9% and 91.6% after PN, and 94.3% and 93.2% after enucleation. Minervini et al also found a lower rate of PSMs in patients undergoing SE: 0.2% vs 3.4% for those undergoing PN.

An intriguing finding from this study was evidence that patients who underwent SE for Fuhrman grade 4 disease showed significantly worse cancer-specific survival (CSS) compared to those undergoing PN. The multivariate analysis of this study confirmed that age at diagnosis and pathological primary tumor stage are the most important predictors influencing PFS and CSS, regardless of the surgical technique used to perform nephron-sparing surgery. Despite these results, there is still controversy about whether enucleation should be considered equivalent to PN. For tumors less than 4 cm, enucleation appears to provide negative margins equivalent but skeptics remain concerned about whether this option should be extensively used. Most surgeons would advocate against enucleation for tumors that are not well circumscribed on imaging.

Prevalence and Impact of Positive Surgical Margins on Recurrence

Risk factor assessment is an all-important issue to evaluate in determining the impact of PSMs on recurrence and survival. It has been suggested that tumor size may be a risk factor and the centrality of the tumor has been found to be an increased risk factor; the indication and location of the tumor have also been found to be an independent risk factor for recurrence, according to Ani et al,[21] whose study had an intermediate-term followup of 7.9 years after PN. On final pathology, 10.7% of the 664 patients had PSMs, a prevalence greater than what is generally reported; only stage and fat invasion were significantly associated with PSMs. Tumor size was not a significant factor. Although PSMs were fairly prevalent—a conclusion not generally reached by most studies—they appeared to have little to no impact on 5-year survival rates.

> "Nephron-sparing surgery is associated with a risk of an incomplete tumor excision. The debate over the significance of a positive surgical margin—and how to manage it—has been the focus of numerous reports seeking to clarify options and provide a consensus."

The paper by Ani et al is important because few studies have examined the predictors of PSMs. Their results showed that pathological stage T1b and fat invasion were significantly associated with PSM. Pathological stages T2 and T3 were not significant, but that was probably due to low statistical power. Their study also did not find an association between surgeon volume and PSMs with similar rates of PSMs despite the difference in number of cases. Ani et al acknowledge that long-term followup to assess the implications of PSMs are still lacking, but data appear to suggest no difference in recurrence rate

(continued on page 17)

After failure of first-line VEGFR-TKIs sunitinib or sorafenib in aRCC, **look to**

WHAT'S NEXT

AFINITOR® (everolimus) Tablets is the first and only oral mTOR inhibitor indicated for the treatment of adults with aRCC after failure of treatment with sunitinib or sorafenib

Abbreviations: aRCC, advanced renal cell carcinoma; BSC, best supportive care; mTOR, mammalian target of rapamycin; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

Proven experience[1]

- AFINITOR is now approved in 5 indications, with experience in aRCC
- A safety profile based on data in 274 patients with aRCC

3x antitumor effect[1-3]

- AFINITOR inhibits angiogenesis, growth and proliferation, and metabolism in in vitro and/or in vivo studies

More than 2x median PFS[1,4*]

- AFINITOR (n=277): 4.9 months (95% CI, 4.0-5.5); placebo (n=139): 1.9 months (95% CI, 1.8-1.9) (HR=0.33; 95% CI, 0.25-0.43; log-rank *P*<0.0001)

*In the RECORD-1 trial, AFINITOR + BSC (n=277) extended PFS vs placebo + BSC (n=139) after progression on sunitinib or sorafenib (4.9 months [95% CI, 4.0-5.5] vs 1.9 months [95% CI, 1.8-1.9]; log-rank *P*<0.0001).[1,4]

Important Safety Information

AFINITOR is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.

Noninfectious Pneumonitis:

- Noninfectious pneumonitis was reported in up to 19% of patients treated with AFINITOR. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 noninfectious pneumonitis was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed
- If symptoms are moderate, patients should be managed with dose interruption until symptoms improve
- The use of corticosteroids may be indicated. For grade 4 cases, discontinue AFINITOR. Corticosteroids may be indicated until symptoms resolve
- For grade 3 cases, interrupt AFINITOR until resolution to grade ≤1
- AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered, depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of AFINITOR
- The development of pneumonitis has been reported even at a reduced dose

Infections:

- AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections (including those with opportunistic pathogens). Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections, including reactivation of hepatitis B virus, have occurred
- Some of these infections have been severe (eg, leading to respiratory or hepatic failure) or fatal
- Physicians and patients should be aware of the increased risk of infection with AFINITOR
- Treatment of preexisting invasive fungal infections should be completed prior to starting treatment
- Be vigilant for signs and symptoms of infection and institute appropriate treatment promptly; interruption or discontinuation of AFINITOR should be considered

Continued on next page

Important Safety Information (cont)

- Discontinue AFINITOR® (everolimus) Tablets if invasive systemic fungal infection is diagnosed and institute appropriate antifungal treatment

Oral Ulceration:

- Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44% to 86% across the clinical trial experience. Grade 3/4 stomatitis was reported in 4% to 9% of patients
- In such cases, topical treatments are recommended, but alcohol-, peroxide-, iodine-, or thyme-containing mouthwashes should be avoided
- Antifungal agents should not be used unless fungal infection has been diagnosed

Renal Failure:

- Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR

Laboratory Tests and Monitoring:

- Elevations of serum creatinine, proteinuria, glucose, lipids, and triglycerides, and reductions of hemoglobin, lymphocytes, neutrophils, and platelets, have been reported
- Renal function (including measurement of blood urea nitrogen, urinary protein, or serum creatinine), blood glucose, lipids, and hematologic parameters should be evaluated prior to treatment and periodically thereafter
- When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR

Drug-Drug Interactions:

- Avoid coadministration with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole)
- Use caution and reduce the AFINITOR dose to 2.5 mg daily if coadministration with a moderate CYP3A4 and/or PgP inhibitor is required (eg, amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem)
- Avoid coadministration with strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital); however, if coadministration is required, increase the AFINITOR dose from 10 mg daily up to 20 mg daily, using 5-mg increments

Hepatic Impairment:

- Exposure of everolimus was increased in patients with hepatic impairment. For patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk
- For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended

Vaccinations:

- The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR

Embryo-Fetal Toxicity:

- Fetal harm can occur if AFINITOR is administered to a pregnant woman. Women of childbearing potential should be advised to use a highly effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment

Adverse Reactions:

- The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%)
- The most common grade 3/4 adverse reactions (incidence ≥5%) were infections (10%), dyspnea (7%), stomatitis (5%), and fatigue (5%). Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm

Laboratory Abnormalities:

- The most common laboratory abnormalities (incidence ≥50%, all grades) were: decreased hemoglobin (92%) and lymphocytes (51%); and increased cholesterol (77%), triglycerides (73%), glucose (57%), and creatinine (50%)
- The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were: decreased hemoglobin (13%), lymphocytes (18%), and phosphate (6%), and increased glucose (16%)

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. AFINITOR [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2012. **2.** Yuan R, Kay A, Berg W, Lebwohl D. Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. *J Hematol Oncol*. 2009;2:45. **3.** Dancey JE. Inhibitors of the mammalian target of rapamycin. *Expert Opin Investig Drugs*. 2005;14:313-328. **4.** Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer*. 2010;116(18):4256-4265.

NOVARTIS ONCOLOGY

AFINITOR® (everolimus) tablets

2.5mg | 5mg | 7.5mg | 10mg

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

Brief Summary of Prescribing Information. See full prescribing information for complete product information

1 INDICATIONS AND USAGE

AFINITOR® is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.

4 CONTRAINDICATIONS

AFINITOR is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

Noninfectious Pneumonitis

Noninfectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Noninfectious pneumonitis was reported in up to 19% of patients treated with AFINITOR in clinical trials. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 noninfectious pneumonitis was up to 4.0% and up to 0.2%, respectively *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered *[see Table 1 in Dosage and Administration (2.2) in the full prescribing information]*.

For cases of grade 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. For cases of grade 3 non-infectious pneumonitis interrupt AFINITOR until resolution to less than or equal to grade 1. AFINITOR may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances *[see Table 1 in Dosage and Administration (2.2) in the full prescribing information]*. If toxicity recurs at grade 3, consider discontinuation of AFINITOR. The development of pneumonitis has been reported even at a reduced dose.

Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR, be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44-86% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4-9% of patients *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. In such cases, topical treatments are recommended, but alcohol-, peroxide-, iodine-, or thyme-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions]*.

Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR *[see Laboratory Tests and Monitoring]*.

Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematologic Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4 inhibitors should be avoided *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4 and/or PgP inhibitor *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions]*.

Hepatic Impairment

Exposure to everolimus was increased in patients with hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]*.

For patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR Tablets or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5) in the full prescribing information]*.

Vaccinations

During AFINITOR treatment, avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

Embryo-fetal Toxicity

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to use a highly effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations]*.

6 ADVERSE REACTIONS

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 6 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 6: Adverse Reactions Reported in at least 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations[b]	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (d)		**141**			**60**	

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[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key observed laboratory abnormalities are presented in Table 7.

Table 7: Key Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

[a] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Agents That May Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4 should not be used *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4 and/or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions]*.

Agents That May Decrease Everolimus Blood Concentrations

CYP3A4 Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4 inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2, 2.5) in the full prescribing information]*.

Drugs That May Have Their Plasma Concentrations Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (sensitive CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$.

Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

Coadministration of everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

8 USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D *[see Warnings and Precautions]*.

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use a highly effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses ≥ 0.1 mg/kg (0.6 mg/m^2) with resulting exposures of approximately 4% of the exposure ($AUC_{0\text{-}24h}$) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m^2), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Pediatric use of AFINITOR Tablets and AFINITOR DISPERZ is recommended for patients 1 year of age and older with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The safety and effectiveness of AFINITOR Tablets and AFINITOR DISPERZ have not been established in pediatric patients with renal angiomyolipoma with TSC in the absence of SEGA.

The effectiveness of AFINITOR in pediatric patients with SEGA was demonstrated in two clinical trials based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume *[see Clinical Studies (14.5) in the full prescribing information]*. Improvement in disease-related symptoms and overall survival in pediatric patients with SEGA has not been demonstrated. The long term effects of AFINITOR on growth and pubertal development are unknown.

Study 1 was a randomized, double-blind, multicenter trial comparing AFINITOR (n=78) to placebo (n=39) in pediatric and adult patients. The median age was 9.5 years (range 0.8 to 26 years). At the time of randomization, a total of 20 patients were < 3 years of age, 54 patients were 3 to < 12 years of age, 27 patients were 12 to < 18 years of age, and 16 patients were ≥ 18 years of age. The overall nature, type, and frequency of adverse reactions across the age groups evaluated were similar, with the exception of a higher per patient incidence of infectious serious adverse events in patients < 3 years of age. A total of 6 of 13 patients (46%) < 3 years of age had at least one serious adverse event due to infection, compared to 2 of 7 patients (29%) treated with placebo. No patient in any age group discontinued AFINITOR due to infection *[see Adverse Reactions (6.5) in the full prescribing information]*. Subgroup analyses showed reduction in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Study 2 was an open-label, single-arm, single-center trial of AFINITOR (N=28) in patients aged ≥ 3 years; median age was 11 years (range 3 to 34 years). A total of 16 patients were 3 to < 12 years, 6 patients were 12 to < 18 years, and 6 patients were ≥ 18 years. The frequency of adverse reactions across the age groups was generally similar *[see Adverse Reactions (6.5) in the full prescribing information]*. Subgroup analyses showed reductions in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Everolimus clearance normalized to body surface area was higher in pediatric patients than in adults with SEGA *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 5 to 15 ng/mL are the same for adult and pediatric patients with SEGA *[see Dosage and Administration (2.3, 2.4) in the full prescribing information]*.

Geriatric Use

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 and over. No overall differences in effectiveness were observed between elderly and younger subjects. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age *[see Warnings and Precautions]*.

In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger subjects. In the randomized advanced RCC study, 41% of AFINITOR treated patients were ≥ 65 years of age, while 7% were 75 and over. In the randomized advanced PNET study, 30% of AFINITOR-treated patients were ≥ 65 years of age, while 7% were 75 and over.

Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3) in the full prescribing information]*.

Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) in the full prescribing information]*.

For patients with SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50%. For patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed. Subsequent dosing should be based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5) in the full prescribing information]*.

10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

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between PSMs and negative margins. Since most patients in their study were managed expectantly, Ani et al suggest that a PSM may not necessitate salvage radical nephrectomy or re-resection. Consequently, the authors suggest that surveillance may be a reasonable approach, avoiding potential morbidity associated with re-resection and completion nephrectomy.

A comprehensive overview of the incidence and significance of PSMs with recommendations on how to avoid and treat PSMs after nephron-sparing surgery provides additional insights. In contrast to Ani et al, Marszalek et al[12] call PSM a rare event after PN—ranging from 0.7 to 4% after laparoscopic PN and 3.9-5.7% after robot-assisted PN. Their paper addressed a broad spectrum of concerns and controversies, including whether PSM is a risk factor for recurrence. Results, they say, are comparable in most series: PSMs increase the risk of disease recurrence, especially in patients with tumors of high malignant potential, but the influence on survival is limited.

Avoiding a Positive Surgical Margin

(continued on page 18)

A Road Map to Positive Surgical Margins

In these brief comments, ***Mohamad E. Allaf, MD****, offers personal perspectives based on clinical experience and a review of recent literature with respect to current strategies and observations on the use of partial nephrectomy and the management of positive surgical margins.*

On enucleation: "With enucleation, the tumor is removed with the pseudocapsule surrounding it and no additional safety margin. Enucleation appears to be safe for tumors 4cm or less that are well encapsulated. However, there are some authors who still argue against enucleation and suggest it is more likely to leave a positive margin. This argument contends that by using this technique surgeons risk violating the tumor and leaving cancer behind. I do not advocate enucleation for large infiltrating tumors."

On partial nephrectomy: "It is underutilized as a treatment option for small tumors because technically it is a difficult operation and requires extensive experience. Recently, we demonstrated that robotic technology has increased the utilization of partial nephrectomy in our region. The bottom line is that in expert hands, a positive margin is rare following partial nephrectomy."

Gross vs microscopic findings: "A dilemma arises when the surgeon removes a tumor and on gross examination it looks good. But a pathologist may call a few days later to inform them of a microscopic positive margin. What do you do? It creates a lot of anxiety for both the urologist and the patient. Clearly patient and tumor characteristics will determine the next step."

Current study on PSM: "In our study, we looked at patients with a positive margin and their recurrence rate was higher than those who had a negative margin. This is a finding that is different than the prevailing wisdom. The question we are asked is 'Why is the conclusion of your paper different from the conclusion of other papers?' We don't know for sure, but our study represents a contemporary analysis of patients undergoing partial nephrectomy by a very experienced group of surgeons. We in no way are recommending automatic nephrectomy for these patients, but our study emphasizes the need to be cautious and that margins do matter during partial nephrectomy. In most circumstance, we would still recommend surveillance for these patients."

Why the higher recurrence rate? "This is conjecture, but the biology of renal tumors with time may have changed to a more aggressive phenotype or alternatively we are choosing partial nephrectomy for more aggressive tumors that are more likely to recur. In the past, partial nephrectomy was exclusively performed for so-called simple, small exophytic tumors. As we became more experienced with PN, increasingly we are operating on more complex tumors, larger and deeper in the kidney. These cancers tend to be more aggressive and potentially different from those in earlier reports. Our study had a significant number of patients with high grade 3 or 4 tumors."

Up-staging of tumors: "As we tackle the larger tumors towards the middle of the kidney, what seemingly looks like a T1 lesion can become a T3a tumor when you remove it. We have even seen tumors invading segmental renal veins while performing partial nephrectomy. When faced with a positive margin, it is important to assess the size of the margin and grade of the tumor. You then balance this information with the patient's kidney function and ability to tolerate potential reoperation." KCJ

Among the risk factors for the occurrence of a PSM are impaired intraoperative visibility, poor orientation and rather small but deeply infiltrating tumors. No difference was observed in PSM rate in a recent analysis comparing PN with and without hilar clamping.[22] Intraoperative ultrasound can be valuable in correctly defining tumor extent; there are also investigational augmented navigation systems to superimpose virtually created and real-time images to facilitate identification of tumor and adjacent structures, all of which may increase the precision of PN in the future, although the impact on the rate of PSMs remains to be clarified.

Management of Positive Surgical Margins

The argument against radical nephrectomy for a PSM is its deleterious effect on functioning renal tissue, the same argument used against its use in many smaller tumors. Patients should be counseled on all available options—radical nephrectomy, repeat PN, energy ablation, and observation. The nephrectomy specimen after PN will only contain tumor remnants in 6.9% to 15% of cases.[23,24] Although repeat PN is often favored because it preserves renal function, it is technically demanding; as with radical nephrectomy, viable tumor will rarely be found in resected tissue. Marszalek et al[12] recommend possible repeat PN with tumors presenting aggressive or high-grade features, including the aforementioned Fuhrman grade 4. Radiofrequency ablation may be minimally invasive but retrieval of tissue for histological evaluation is not possible. Thus, these authors favor watchful waiting as the most reasonable strategy because in most cases it will spare the patient needless repeat surgery while allowing for early salvage treatment during the period of surveillance.

The Natural History of PSMs and Predictors of Cancer Recurrence

As the experience with NSS grew, recurrence rates after PN have been found to be <5%, equivalent to those of radical nephrectomy. Yet, much still needs to be known about the natural course of PSM by comparing PSM and negative surgical margin tumors. Bensalah et al[25] identified 111 patients with a PSM who were compared with 664 negative surgical margin patients. Imperative indications accounted for 39% (43 of the 111) of the cases. Some 91% of the patients who had recurrences and 83% of the patients who died after a mean followup of 37months belonged to the group with imperative surgical indications. The analysis showed that the two variables that could predict recurrence were the indication and tumor location (central vs peripheric). Imperative tumors are of larger diameter, higher stage, and higher grade than their elective counterparts. In this study, as in others, PSM status did not appear to influence cancer-specific survival.

Robotic Partial Nephrectomy:

Controversy on Tumor Up-Staging

With the widespread adoption of robotic technology, the use of PN has expanded to complex, small renal masses. This advance means more tumors with occult adverse pathological features are now detected, including those with renal fat or venous invasion. Yet another controversy has emerged in this context—and there is a lack of clarity in the urological literature regarding the oncological adequacy of PN for these small up-staged tumors. The up-staging of tumors may leave surgeons with questions about patients found to have pT3a RCC at PN. Would these patients have been better served, for example, if they had undergone a radical nephrectomy.

A paper by Gorin et al[26] addressed some key issues related to a decision to excise with PN a larger tumor toward the center of the kidney. Thus, what seemingly appears to be a T1a lesion can be up-staged to a T3a upon removal. The authors aimed to (1) evaluate the early oncological end point of recurrence-free survival in cases upstaged in this manner and (2) identify preoperative factors associated with pathological tumor up-staging.

"With the widespread adoption of robotic technology, the use of PN has expanded to complex, small renal masses. This advance means more tumors with occult adverse pathological features are now detected, including those with renal fat or venous invasion."

A database of robotic PN cases performed at 5 academic centers served as the basis for an analysis of outcomes following surgery for a solitary cT1 renal mass. At final pathological evaluation, 855 tumors were found to be RCC, of which 4.8% were upstaged to pT3a. The 24-month recurrence-free survival estimates for pT1-2 and pT3a tumors were 99.2% and 91.8% (P=0.003). Analysis indicated that a high vs low R.E.N.A.L (radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior and location relative to polar lines) nephrometry score was associated with tumor upstaging. Increasing tumor diameter and hilar location were also associated with up-staging. Reviewing these and other findings from the literature Gorin et al conclude there is still a lack of clarity on the efficacy of PN for pT3a tumors. The preoperative risk of tumor up-staging needs to be considered when deciding between treatment approaches since imaging alone has low sensitivity for detecting tumor extension outside the renal parenchyma.

A Multi-Institutional Analysis Warns of Increased Risk for Recurrence With PSMs

Addressing many of the controversies and concepts of previous reports, one of the latest papers examining the oncologic outcomes of robot-assisted PN introduced some provocative findings. Although Khalifeh et al[9] concur with earlier reports that PSMs at robot-assisted PN remain rare with a disease progression rate comparable to these previously published results, they conclude that PSMs are an independent factor that significantly increases the risk of recurrence and metastasis. This view challenges current practice in regard to PSMs and contradicts prevailing wisdom in some respects.

Khalifeh analyzed followup data from 5 institutions; a total of 943 robot-assisted PNs were completed. There were 21 patients (2.2%) who had PSMs on final pathological assessment. PSMs had higher recurrence and metastasis rates (P<0.001). There was a statistically significant difference in recurrence-free and metastasis-free survival between patients with positive and negative surgical margins.

There are a number of implications from this study, including:

- Further resection from the PN bed or proceeding to radical nephrectomy should be considered if there is suspicion of tumor violation or PSMs intraoperatively.
- Since most postoperatively noted PSMs do not present with cancer recurrence, a period of watchful waiting and patient counseling is essential.
- Any increased risk of disease progression may warrant more aggressive followup therapy.

Although not specifically addressed by this study, Khalifeh et al highlight issues raised by previous studies that focused on tumor molecular biology and such factors as the histopathology of the peritumor pseudocapsule, with special attention on the potential relationship of these factors to oncologic outcomes. As the experience with PN grows, it appears that more complex and larger tumors are being excised in locations deeper within the kidney. With the removal of these more complex lesions, the database of patients is enriched with more aggressive cancers that are potentially different than those studied in the earlier reports. As patient populations treated with PN show higher grade tumors, perhaps we need to revisit the concepts applied to PSMs based on an earlier subset of patients. There is a clear need to establish guidelines on when and how to follow, and when to intervene in patients with PSMs.[27]

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RCC Experts Meet in Paris to Discuss Optimizing Practice to Improve Outcomes

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Paris served as the gathering site for a number of renal cell carcinoma (RCC) experts who met there to discuss "optimizing clinical practice to improve patient outcomes." Attendees enjoyed talks from leaders in the field on topics ranging from the evolution of anti-angiogenic targeted therapies to the search for illusive biomarkers to guide treatment. Real-world data and the challenges of designing effective trials were also major topics addressed.

The Continuing Evolution of Targeting Angiogenesis

The interactive conference began with a talk from Yihai Cao of the Karolinska Institutet, a renowned researcher, with over 40 years of experience in investigating angiogenesis. Cao's address first focused on a historical perspective, reviewing decades of progress in the under- standing of how tumors autonomously create new blood vessels and the development of antiangiogenic agents. He concluded his presentation noting challenges and potential opportunities for the future. Specifically, he discussed the rebound effect of rapid disease progression noted after the discontinuation of VEGF-targeted tyrosine kinase inhibitors (TKIs), and the challenge of maintaining therapy to prevent this effect. [1] He also introduced the concept of implantable drug chips, that one day may automatically deliver precise combinations of antineoplastic drugs to patients via a system that could be wirelessly controlled and allow for minute adjustments and personalized combinations of therapies. Similar technology has already been used in humans during research trials to deliver human parathyroid hormone to women with osteoporosis. [2]

Recent Data and Beyond

Cora Sternberg of the San Camillo Forlanini Hospital in Rome, a distinguished leader in the field of genitourinary medical oncology, reviewed what has been achieved in the management of metastatic renal cell carcinoma over the last decade and discussed latest efforts to develop targeted therapies. She addressed the complex issues surrounding the TIVO-1 study, in which the novel TKI tivozanib did not show a significant difference in overall survival (OS) when compared with sorafenib in patients with renal cell carcinoma who received up to one prior line of therapy excluding targeted agents. [3] The study's ability to identify a difference in OS was limited by its one-sided cross-over design, and resulted in a discrepancy between the Progression Free Survival (PFS) favoring tivozanib , but no difference in OS. Based on this study, the FDA's Oncologic Drugs Advisory Committee voted in May 2013, 13-to-1 against recommending approval of tivozanib for renal cell carcinoma.

Results of the AGILE 1046 study were discussed, in which front-line axitinib failed to meet its primary endpoint of demonstrating a longer median progression-free survival (PFS) than sorafenib. Many consider the study to have been overly ambitious in its endpoint targets, being designed as a one-sided superiority trial that sought a 78% improvement in PFS to achieve statistical significance. [4] The design allowed researchers to conduct a study with a relatively small number of patients (n=288), but may have been underpowered to fully assess the superiority of the study drug. A breakout session devoted to pitfalls in trial design suggested that adaptive trial design might help overcome the challenges faced in the TIVO-1 and AGILE studies. Adaptive design allows for dynamic evolution of trial design during the study itself, as long as adaptation parameters are pre-specified in the protocol. [5]

Sternberg went on to discuss the GOLD study, which showed no difference in outcomes between the novel combination FGFR/VEGF inhibitor dovitinib and the FDA-approved VEGF-targeted TKI sorafenib, and then reviewed major current trials, including the METEOR trial (combination c-MET/VEGF inhibitor carbozantinib vs everolimus). Anti-PD-1 therapy is being investigated in several studies. The PD-1 inhibitor nivolumab is being compared to everolimus in the ongoing CheckMate 025 study and a study investigating pazopanib in combination with PD-1 blockade is also in development.

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Table 1. The spectrum of clinical research, with expanded access programs representing some characteristics of both real-world studies and randomized clinical trails.

Randomized Clinical Trials	Expanded Access Programs	Real-world Studies
• Prospective • Interventional • Blinded/open-label		• Retrospective (usually) • Observational • Medical records • Insurance claims database • Patient surveys • Registries

Table 2. Real-world insight: First-line treatment efficacy in community and academic practice

Retrospective mRCC registry involving 325 mRCC patients at Duke University Medical Center and 11 US community-based oncology practices (January 2007 to May 2001)[1]

	Sunitinib	
Setting	**Real-world N=188[1]**	**RCT, N=375[2]**
First-line PFS, median months (95% CI)	8.97 (7.5-10.5)	11.0 (10.0-12.0)
Patient characteristics		
Average age, years	63.7	62.0
Sex, % male	66	71
Performance status, % Composite: Not impaired; impaired ECOG:); 1: ≥2*	 88; 12 —	 — 62; 38; 0
Prior nephrectomy, %	70	91

1. Harrison MR, et al. *Clin Genitourin Cancer*. 2013 July 12.
2. Motzer RJ, et al. *N Eng J Med*. 2007; 356:115-124.

Real World Data Complements Randomized Trials

Marc Matrana, representing the Genitourinary Medical Oncology Department at MD Anderson Cancer as well as Ochsner Medical Center in New Orleans, Louisiana spoke on the role of real-world data in supplementing prospective clinical trial results. While real world experience can certainly never be directly comparable to the robust findings of prospective clinical trials, these types of studies do have certain advantages that can complement data from prospective trials (**Tables 1** and **2**). First, this data tends to be generalizable. These studies have wide inclusion criteria which allows for the study of patients with multiple comorbidities, advanced age, and poor performance status. Likewise, ethnic minorities, may be underrepresented in prospective trials, but are better represented in real world data. Taken together, these wider inclusion criteria create a more representative sample that better characterizes the heterogeneous makeup of real life patients with metastatic RCC. Also, real world studies include patients with poor adherence to therapy, a lack of close monitoring, and those that are treated with liberal dose adjustments and off label use of therapies, providing a more realistic picture that may be more reflective of true clinical practice.

Matrana reviewed several real world studies in metastatic renal cell carcinoma patients. The first, a retrospective registry study conducted by Duke University Medical Center, pulled together data from Duke data sets as well as 11 US community-based oncology practices.[6] The study, which included 325 patients with metastatic renal cell carcinoma who received various targeted therapies in the first line setting. The study for example found a median PFS of nearly 9 months in patients on front-line sunitinib compared to 11 months in the randomized control trials of the drug. [7] The largest difference in the patient populations studied compared to the clinical trial, was that 12% of the population studies in the real world trial had a impaired performance status, as compared to know patients with a PFS of 2 or greater in the clinical trial. Also a higher number of patients in the clinical trial underwent prior nephrectomy (91 vs 70%).

The speaker also reviewed his findings of outcomes using first-line pazopanib to treat patients with clear cell metastatic RCC at M.D. Anderson Cancer Center in Houston. He reviewed records of 88 consecutive, unselected clear-cell mRCC patients treated with first-line pazopanib, 23% of which had a impaired performance status. The MD Anderson group found a median PFS of 13.7 months (**Figure 1**) and 31% response rate.[8] A similar study was conducted by Victoria Galvis and colleagues at The Christie Hospital in the UK.[9] This groups reviewed charts of 104 patients with metastatic RCC treated with front-line pazopanib, 29% of which had an impaired PS. The Christie group found a median PFS of 13.0 months in this population. Both studies found that adverse events (**Figure 2**) were mild-to-moderate and manageable. The internal validity between these two independent studies was remarkable, and further confirmed that reproducibility of well-designed and well-executed real-world retrospective studies.

Certainly, though, like all studies, retrospective real-world studies do have pitfalls and challenges. Re-staging studies are typically not performed as frequently, or at during strict pre-defined disease assessment schedules as in randomized controlled trials and this can lead to an overestimation of PFS. [10] This can be at partially addressed by excluding patients from analysis who lack regular follow-up and imaging. Retrospective studies also tend to under-report adverse events, as surveillance is less vigilant as compared to randomized controlled trials.[11] This is especially true for more minor adverse events that may not be reported by the patients or recorded in the record by the physician. Finally, patients in real-world settings often have a higher incidence of treatment and dosing modifications than in strict, protocol-driven trials, which may be a challenge, but also an opportunity for researchers to study drugs in a setting that more precisely mimics real clinical scenarios.

Optimizing Treatment

Tom Powles of St Bartholomew's Hospital, London gave

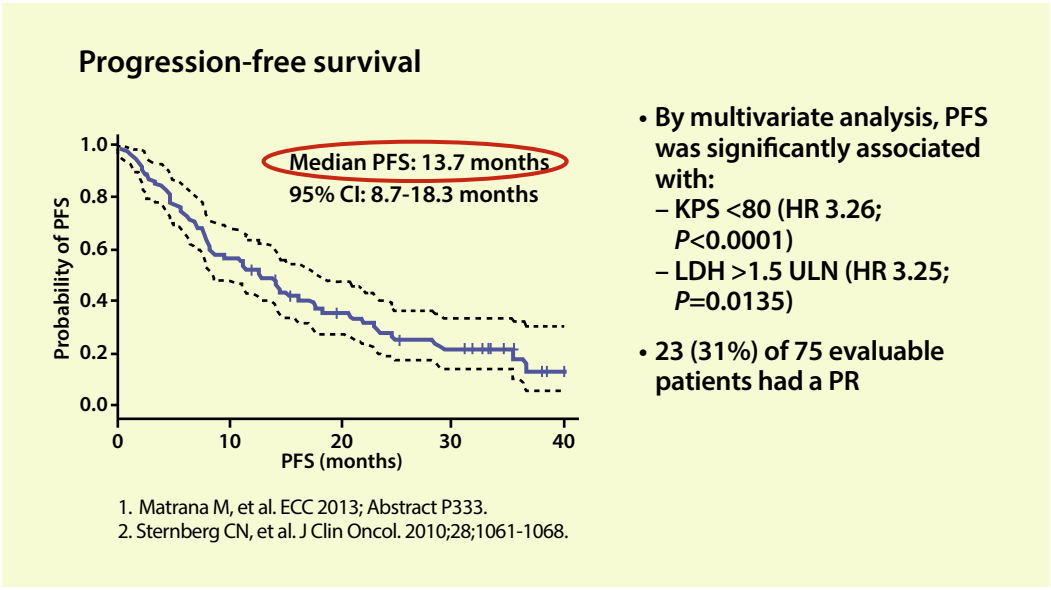


Figure 1. Progression-free survival of unselected real-world metastatic renal cell carcinoma patients treated with first line pazopanib at MD Anderson Cancer Center, Houston, Texas (n=88).

two excellent presentations on optimizing the clinical treatment of metastatic RCC. He challenged current clinical study tools, questioning whether the common toxicity criteria used to measure adverse events in clinical trials accurately reflects patients' experiences. For example, Powles noted that a single episode of moderate diarrhea is often tabulated as equivalent to an entire year of mild diarrhea. He further went on to question the appropriateness of RECIST criteria to accurately measure response in the age of targeted therapies, a concern voiced by many over the last few years. Many have suggested that functional imaging, such as PET scan, or a novel response criteria may provide a more accurate measurement of progression, but neither of these approaches have yet been proven by research. [12]

Prognostic factors in RCC were also discussed. Conditional survival, which accounts for time since treatment initiation, is a prediction measure that alters the prognosis of patients with metastatic RCC on the basis of therapy duration. Research suggests that patients who respond well to targeted therapies tend to have better outcomes regardless of their baseline risk stratification. [13]

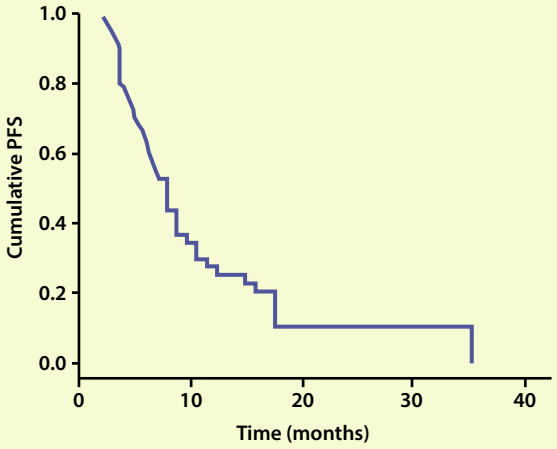
Powles reviewed current efforts to identify biomarkers to guide RCC management, focusing on interesting genes that may provide greater insight into RCC biology on an individual patient level. Recent studies have identified several genes of interest in clear cell RCC that may be useful as clinical biomarkers. These include histone/chromatin regulators such as SETD2, KDM6A, KDM5C, BAP1 and PBRM1. Polybromo-1 (PBRM1) for example, is the second most frequently mutated gene in clear cell RCC after VHL, and recent studies suggest that functional inactivation of PBRM1 in the setting of pVHL loss-of-function may represent a key event in the development of tumors with particularly aggressive behavior. [14]

Finally, Powles introduced a new tool that may soon guide treatment decisions in metastatic RCC. ReCATT, the Renal Cancer Appropriateness-based Treat Tool, is an online system being developed by GlaxoSmithKline, one of the Paris meeting's sponsors, which takes into account guidelines and expert opinion as applied to specific clinical scenarios. The tool is expected to go live in the near future, and will allow clinicians the opportunity to insert clinical data into an online system and receive guidance on treatment selection.

Multidisciplinary Teams Can Make a Difference

Simon Chowdry and Michael Flynn of Guy's Hospital in London discussed multidisciplinary care in the management of RCC. Although there is little formal evidence to support a multi-disciplinary approach, Chowdry and Flynn have found that using a diverse team of providers and support personnel to treat cancer patients results in improved outcomes, better patient satisfaction, and greater patient access; furthermore, it also leads to increased job satisfaction for providers. Challenges to this approach include overcoming a lack of administrative support, as well as the challenge of transitioning away from traditional hierarchical job boundaries towards true team synergy.

Flynn, an oncology nurse, gave his perspective noting that as a nurse on a multi-disciplinary oncology clinic team he is able to serve as a point of contact for patients, assisting them in accessing services and assessing their understanding of their disease. Pharmacists on the team provide real-time advice to prescribers and patients, evaluate potential drug-drug interactions, and educate patients about their medications. The multi-disciplinary oncology teams at Guy's Hospital have been strengthened by the institution of a comprehensive patient questionnaires which assesses physical, pycho-social, family, financial, spiritual, and emotional well being. They have also created structured patient education and regimen-specific consent forms for patients, thereby standardizing communication and patient education. Finally, Chowdry and Flynn noted that by pre-rounding on each patient before clinic begins each day, their multi-disciplinary team is able to work together to create an individualized plan for each patient, and by establishing a 24-hour emergency contact system for patients, they are able to extend contact between patients and providers beyond the clinic and avoid some emergency room visits.



Patient group		Median PFS, months
All patients, N=104		13
MSKCC, %		
Favorable	19	29
Intermediate	63	12
Poor	18	6

1. Galvis V, et al. ECC 2013; Abstract P317.

Figure 2. Progression-free survival of unselected real-world metastatic renal cell carcinoma patients treated with pazopanib in the front line setting (or after cytokine failure) at The Christie Hospital, UK (n=104).

Conclusions

The treatment of metastatic renal cell carcinoma has evolved rapidly over the last decade, bringing basic science discoveries about angiogenesis from the lab to the clinic, where these breakthroughs are benefiting more patients than ever. The results of recent clinical trials have exposed our own shortcomings when it comes to clever trial design, and we are challenged to design better, leaner, more dynamic trials, which can more precisely define true clinical efficacy of new and emerging agents. Beyond the boundaries of randomized control trials, real world data has been shown to be reliable and reproducible in mRCC, complementing prospective data by providing an often more inclusive and realistic view of complex, heterogeneous patient populations. It is clear that optimizing clinical outcomes requires us to challenge the tools we use to guide our research efforts, such as toxicity measurements and response criteria, while searching for new tools—such as illusive biomarkers—to guide clinical management. Finally, we must never forget that the patient is always central to our work, and by developing better models of patient care delivery, such as multidisciplinary team clinics, we may be able to achieve better outcomes through improved human interaction.

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Point-Counterpoint: Cytoreductive Nephrectomy Remains a Surgery In Search of a Consensus, But Perhaps Not for Long

As recently as a month ago at the ASCO GU Cancer Symposium one of the topics explored was the use of cytoreductive nephrectomy (CN) in the era of targeted therapy. For a few years now, this has been a controversy high on the agenda of scientific sessions. The following Point-Counterpoint discussion reviews the data for a question still unresolved but awaiting more data from trials that could provide important insight. Since the approval of targeted therapies for RCC, the use of CN needs to be further delineated because most patients enrolled in clinical trials leading to the approval of these agents already had their kidneys removed. Because of the yet unproven advantage of CN in the context of targeted therapies, there is still some debate about whether it should represent the standard of care for patients with metastatic kidney cancer.

The Pro Position:
Assessing Current Data in Support of Cytoreductive Nephrectomy and Selection Criteria

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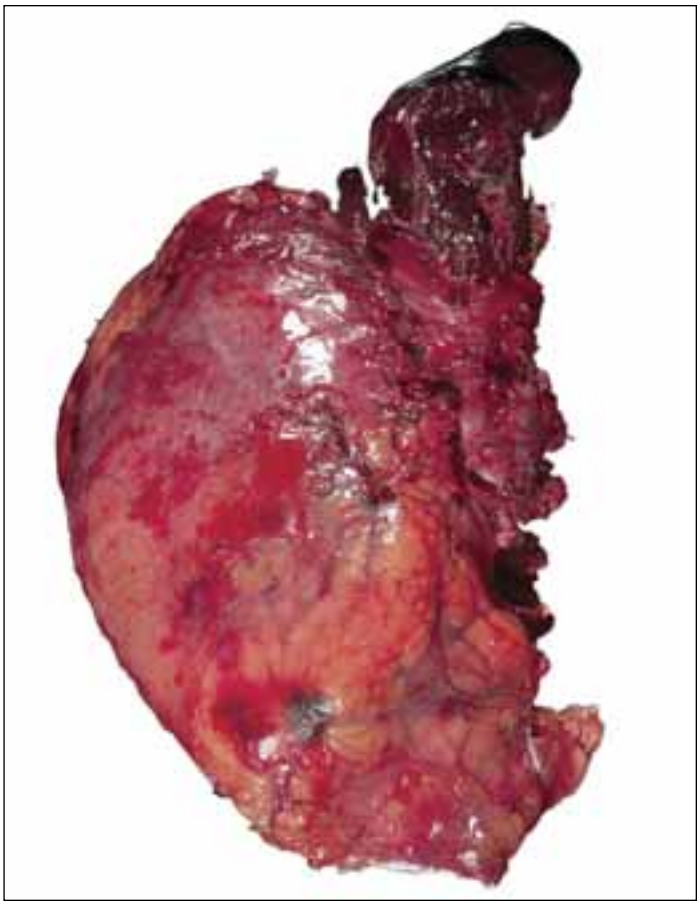
The rationale for cytoreductive nephrectomy has historically included potential benefits such as palliation of symptoms, eradication of paraneoplastic processes, debulking of disease burden, eliminating ongoing source of metastatic spread, as well as removal of immunosuppressive factors present in the primary tumor which, albeit rarely, can foster spontaneous regression of metastatic disease. Opponents cite the concern of disease progression in the postoperative recovery period, the possibility that complications will preclude therapy, and the lack of data demonstrating benefit in the targeted therapy era. This review will assess the current data in support of cytoreductive nephrectomy and discuss selection criteria for surgery in the setting of metastatic disease.

Two parallel randomized trials published in 2001 established the modern paradigm for the use of cytoreductive nephrectomy in the management of metastatic renal cell carcinoma (mRCC) by demonstrating a survival benefit to surgical resection in these patients. Specifically, the Southwest Oncology Group (SWOG) 8949[1] and the European Organization for Research and Treatment of Cancer (EORTC) 30947[2] studies utilized similar protocols to prospectively determine the incremental beneficial impact of cytoreduction in addition to systemic therapy for patients with mRCC.

Eligible patients had mRCC with the primary tumor *in situ* and good performance status. Patients were randomized to treatment with interferon alpha alone versus cytoreductive nephrectomy followed by interferon alpha. Both studies provided level I evidence that cytoreduction improved survival by 3 months and 10 months in the nephrectomy arms compared with the non-surgical arms of the SWOG and EORTC trials, respectively. Moreover, when results of these studies were combined, a significant survival difference of 13.6 months versus 7.8 months was reported for the surgery arm and the no surgery arm, respectively.[3] Thus, the use of cytoreductive nephrectomy in the cytokine era became the standard of care for appropriately selected patients.

The subsequent approval of multiple targeted therapy agents for the treatment of mRCC has provided reason to reconsider the practice of cytoreduction. Notably, one important distinction with newer therapeutic options is the observation that primary tumor response occasionally occurs with tyrosine kinase inhibitors whereas this was the rare exception with cytokine therapy.[4-6] As such, an ongoing European clinical trial is assessing the role of cytoreduction in a non-inferiority trial comparing sunitinib alone to cytoreductive nephrectomy followed by sunitinib. However, until the results of this trial (CARMENA) are available, we must review the currently available retrospective data, especially as it relates to standards from level I evidence in the cytokine era, to determine current best practice. Indeed, it is important to point out that the majority of available data regarding the efficacy of targeted therapies in mRCC has been from patients who have undergone prior nephrectomy.

Choueiri et al[7] reported a series of 314 mRCC patients treated with various targeted therapy agents, with a portion of patients having cytoreductive nephrectomy. There were significant differences between the cohorts having surgery (n=201) and those that did not have surgery (n=113), with more adverse prognostic factors in the non-surgical group. Nevertheless, the median survival was significantly better among patients who had undergone cytoreductive surgery than those who did not



A right kidney with IVC thrombus that was extending into the right atrium.

(19.8 months versus 9.4 months median survival). Even when the authors adjusted for known prognostic factors in multivariable analysis, the survival benefit to cytoreduction remained, with an adjusted hazard ratio of 0.68 (95% CI 0.46 – 0.99, $P = 0.040$) relative to no surgery. Of note, the benefit in patients with poor risk disease was minimal. These investigators also observed that cytoreduction was associated with improved overall response rates and time to treatment failure. Likewise, Warren et al[8] reported a retrospective population-based study of mRCC patients treated in Alberta. In a group of 134 patients treated with sorafenib or sunitinib they similarly observed that survival was improved in patients who had undergone cytoreductive nephrectomy. In this study, cytoreductive nephrectomy was an independent predictor of improved survival (hazard ratio relative to no nephrectomy of 0.38, 95% CI, 0.19 – 0.74 p – 0.005).

Retrospective reviews examining the role of cytoreduction will always be critiqued by the inherent selection bias present outside of a randomized trial setting. Clearly, selection criteria are critical for predicting favorable results with cytoreduction. The above mentioned studies demonstrate that patients who are selected for cytoreductive benefit from surgery. On the contrary, Kutikov et al[9] reported that 30% of their 141patients selected for cytoreductive nephrectomy never received systemic therapy postoperatively, with the most common reason for lack of further therapy being rapid progression of systemic cancer in the postoperative period. It is clear from the cytokine era data that nephrectomy alone has minimal impact on survival. In a response to the SWOG study[1], Pantuck et al reported that nephrectomy alone for mRCC resulted in a median survival of 7.2 months verus a median survival of 6 months in patients having no therapy.[10] These data suggests that the extension of life from surgery alone is approximately equal to the convalescence from surgery. Until effective biomarkers and clinical trial data are available to guide optimal selection of patients for surgery, other criteria must be utilized to select appropriate candidates who will benefit from surgery and subsequent therapy.

Assessing Tumor Burden and Timing of Cytoreduction

Kassouf et al found that patients having cytoreductive nephrectomy for non-clear cell histology had inferior survival relative to those having cytoreduction for clear cell mRCC.[11] Alternatively, a SEER based study revealed that cytoreductive nephrectomy benefited all histologic subtypes they were able to assess and found improved survival with non-clear cell disease.[12] Data regarding localized renal cell carcinoma indicates that papillary and chromophobe RCC have improved survival relative to clear cell.[13] However, current systemic therapy options are tailored for clear cell disease and have limited efficacy in other histologic subtypes. Until robust systemic therapy for non-clear cell RCC is available, the use of cytoreduction in these patients must be highly individualized and should probably be reserved for those with a small burden of metastatic disease, preferable those with resectable metastatic deposits.

In fact, tumor burden is an important factor to consider when evaluating a patient for cytoreduction in the setting of mRCC, as multiple studies have suggested that cytoreductive nephrectomy should be reserved for patients who will have the majority of the disease removed by surgery. The ratio of the amount of disease removed to residual after surgery is debatable. However, two studies of patients treated with cytoreduction in the cytokine era indicated that 50% or 75% of tumor removed surgically was associated with better outcome.[14,15] A recent study of targeted therapy era patients indicated that the greater the fraction of disease removed, the better the outcome. [16] Perhaps the ultimate cytoreduction is surgical elimination of all disease including primary tumor and metastatic lesions. Aggressive metastasectomy has been applied to limited numbers of highly selected patients in small series.[17,18] Nevertheless, survival in these patients is impressive, with median survival of 5 years in completely resected patients without subsequent systemic therapy. Many urologic surgeons consider not only the bulk of residual disease expected after nephrectomy but the location of the disease. High volume metastases in a location that may threaten the patient with even minimal progression in the postoperative period should caution early cytoreduction. In such a setting, preoperative therapy with delayed surgical resection in the setting of favorable tumor response may be most appropriate.

The timing of cytoreduction relative to institution of systemic therapy will be assessed in another European prospective clinical trial. That is, the EORTC SURTIME trial will randomize patients to upfront surgery followed by sunitinib versus suni-

tinib for 3 cycles followed by surgery and then more sunitinib. While we wait for these results, cytoreductive surgery after upfront systemic therapy has been shown to be safe from relatively small institutional series to date. Chapin et al reported that delayed cytoreduction (n=70) after systemic therapy did not result in a difference in complication rates relative to a group of patients treated with immediate cytoreduction (n=103).[19] If tumor burden is a concern in a patient who would otherwise be a good surgical candidate for cytoreduction, upfront therapy with surgery offered in the setting of a robust response is a reasonable and preferred alternative to initial surgical intervention.[20] In fact, Rini et al published a small series of advanced RCC patients who were considered to be unresectable at diagnosis and found that 45% of patients were able to have a nephrectomy after a median of 4 cycles of sunitinib.[21]

Most providers utilize the Motzer[22] or Heng[23] criteria to stratify patients, and those with mRCC who have poor risk disease are not considered as candidates for surgical cytoreduction due to inferior survival. Recently, Culp et al reviewed the outcomes of 676 patients with mRCC to identify preoperative predictors of outcome.[24] Seven risk factors were identified: albumin level, LDH level, symptoms due to a metastatic site, presence of liver metastasis, retroperitoneal adenopathy, supradiaphragmatic adenopathy, and clinical stage ≥ T3. Patients with 4 or more risk factors did not appear to benefit from cytoreductive therapy. However, application of this study in clinical practice should not preclude the possibility of delayed cytoreduction in patients with more than 3 risk factors who are shown to have a robust response to systemic therapy.

In conclusion, level I evidence supports the role of cytoreduction in patients treated with immunotherapy. Further, we are embarking on new therapeutic approaches to manipulate the immune system after novel investigations regarding the immunosuppressive environment present within the primary tumor.[25-27] As we look forward to the results of two clinical trials investigating the role of surgery and timing of surgery in the management of mRCC, we must currently combine results from previous randomized trials in conjunction with contemporary retrospective data to appropriately select patients for cytoreductive nephrectomy. Future therapies and trial results may strengthen or diminish the case for primary tumor resection. In the interim, the majority of available, albeit retrospective, data from patients treated in the targeted therapy era supports the use of cytoreduction as beneficial in extending survival. The ideal candidate has a good performance status, the majority of the disease resectable, and absence of features predictive for rapid decline. In less than ideal candidates, cytoreduction should remain in the thoughts of the multidisciplinary team with consideration for surgery after a trial of systemic therapy.

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The Con Position:
Cautious Approach Advised Until Compelling Evidence for Cytoreductive Nephrectomy Emerges from Pivotal Trials

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In 2001, two randomized phase 3 trials consolidated the role of cytoreductive nephrectomy in the treatment of patients with metastatic renal cell carcinoma. Flanigan et al[1] (SWOG 8949) randomized 246 patients and demonstrated a 3-month survival benefit for patients treated by cytoreductive nephrectomy and interferon alpha 2b, as compared to those treated with interferon alpha 2b only (11.1 vs 8.1 months, respectively). Similarly, Mickisch et al[2] (EORTC 30947) randomized 85 patients and showed a 10-month survival benefit for patients treated by cytoreductive nephrectomy and interferon alpha 2b, versus interferon alpha 2b alone (17 vs 7 months, respectively).

While these 2 studies showed a benefit for the combination of surgery and immunotherapy, it is important to note some nuances of the methods and results that are often understated. For example, in the EORTC trial, out of the 42 patients assigned to surgery and immunotherapy, only 29 completed the treatment (1 was not eligible, 4 did not have surgery, and 8 did not have immunotherapy). In the SWOG trial, more than 25% of patients did not have measurable disease at baseline, but they were included in the trial as patients with metastatic RCC. In addition, clinical and pathologic T stage, clinical and pathologic N stage, primary tumor histology, primary tumor grade, laboratory values, and metastatic burden were not reported in these trials. These trials were limited to patients with ECOG or WHO performance status of 0 or 1. In the ECOG study, two thirds of patients had lung-only metastases, which by itself is considered to be a favorable prognostic factor, when compared to other metastatic sites.

> "For patients with metastatic RCC, the question is generally not if, but when, to perform cytoreductive nephrectomy. Until the SURTIME and CARMENA trials are completed, it is advisable to continue performing cytoreductive nephrectomy in younger patients with clear cell histology, good performance status, limited metastatic burden, with 3 or less MDACC risk factors, and preferably in high-volume centers."

In the SWOG trial, patients with ECOG performance status of 1 had much worse prognosis compared to those patients with ECOG of 0, regardless of randomization arm. Median survival was 11.7 months in patients with ECOG PS 0 but was 4.8 months in those with ECOG PS 1 treated with Interferon only, and median survival was 17.4 months in patients with ECOG PS 0 but was 6.9 months in those with ECOG PS 1 treated with combination therapy.

Several factors have been studied over the years, and were shown to be associated with outcomes in patients undergoing cytoreductive nephrectomy, and will be discussed in this review.

Cytoreductive Nephrectomy and Age

Using a cohort of patients who underwent cytoreductive nephrectomy, Kader et al[3] compared 24 patients older than 75 years with 380 patients younger than 75 years of age. Perioperative mortality was higher in elderly patients compared to younger ones (5, or 21% versus 4, or 1%, respectively), although the performance status, tumor histology, stage, grade and size were not different. Similarly, Sun et al[4] used the National Inpatient Sample (NIS) database to study the morbidity of cytoreductive nephrectomy in elderly patients (defined as 75 years of age or older). Perioperative mortality was 4.8% in elderly patients, while it was 1.9% in younger counterparts. In addition, elderly patients were more likely to have postoperative complications (27.8 versus 22.8%), receive blood transfusions (29.8 versus 21.5%), and experience hospital stays of 8 days or more (45 versus 32%).

Cytoreductive Nephrectomy and Hospital Factors

Trinh et al[5] used the NIS database to evaluate more than 16,000 patients with metastatic RCC who underwent cytoreductive nephrectomy, and aimed to study the failure to rescue rates (defined as death in patients who had a postoperative complication after cytoreductive nephrectomy) and contributing factors. The overall failure to rescue rate was 5% in this study, and was noted to be higher in older patients, patients with more comorbidities, and patients treated in smaller hospitals. In addition, patients who experienced cardiac, respiratory, vascular or infectious complications were more likely to have deaths related to complications.

Cytoreductive Nephrectomy in the Targeted Therapy Era

Tsao et al[6] used the National Cancer Data Base (NCDB) to study over 47,000 patients with metastatic RCC, and stratified the patients to those treated in the pre-TKI era (defined as years 2000-2005) and in the TKI era (defined as years 2005-2008). The authors noted a 3% increase in the rate of cytoreductive nephrectomies between 2000 and 2005, coinciding with the publication of the 2 phase III trials presented earlier in this review, with a subsequent decline of 3% per year in the rate of surgeries performed, this time coinciding with the introduction of targeted therapies in the management of patients with metastatic RCC. Interestingly, the authors noted that patients

who were Caucasian, had private insurance and/or were treated at teaching institutions were more likely to undergo cytoreductive nephrectomy, compared to black or Hispanic patients, patients with Medicare/Medicaid/no insurance, or patients treated in community hospitals. It is noteworthy to mention that the authors could not really ascertain who received targeted therapy, immunotherapy or no therapy based on the available data, and the date cutoff used was more of a timeline when targeted therapy was FDA approved. The authors performed a similar study using the SEER database, and compared patients treated between 2001 and 2005 (pre-TKI era) with those treated between 2006 and 2008 (TKI era), and found that the use of cytoreductive nephrectomy was stable in the pre-TKI era (in 50% of patients with metastatic RCC), while it decreased to 38% in the TKI era in 2008. In addition, they confirmed their prior findings that older patients and minorities were less likely to undergo cytoreductive nephrectomy.

Cytoreductive Nephrectomy in Non-clear cell Histologies

In a single-institutional study, Kassouf et al[7] compared the outcomes of cytoreductive nephrectomy in 514 patients with clear cell RCC with 92 with non-clear cell histology and noted that survival was worse in patients with non-clear cell histology (9.7 versus 20.3 months). On the other hand, Aizer et al[8] noted that cytoreductive nephrectomy provided a survival benefit in patients with non-clear cell histology in a SEER population. However, limitations related to SEER are important to note in this context: laboratory values, comorbidities, performance status, and metastatic disease burden are not present in SEER and cannot be accounted for in their study.

Cytoreductive Nephrectomy in Patients with Advanced T Stage Disease

Kassouf et al[9] reported on a single-institutional experience with cytoreductive nephrectomy in 23 patients with stage T4 RCC. In this selected group, outcomes were quite dismal, with overall and disease-specific survival of 6.8 months. Twenty-one percent of patients could not receive postoperative systemic therapy due to progression of disease. However, palliation was achieved in 5 of 7 patients with local symptoms related to the presence of the tumor.

Cytoreductive Nephrectomy and Tumor Burden

Several studies have shown that cytoreductive nephrectomy is mainly beneficial if the bulk of the tumor burden is present in the affected kidney and is removed at time of surgery. Robertson et al[10] recommended cytoreductive nephrectomy if the renal tumor burden is larger than that of metastatic sites. Fallick et al[11] noted benefit for patients with tumor burden of 75% or more removed at time of cytoreductive nephrectomy. Pierorazio et al[12] reported benefit for patients with more than 90% of burden removed. More recently, Barbastefano et al[13] showed worse outcomes for patients with less than 90% of tumor burden removed at time of surgery.

Cytoreductive Nephrectomy and Selection Factors

Using the MSKCC[14] and Heng[15] criteria, patients who fall into the poor-risk category have been shown to have poor survival, and therefore, are indirectly not considered as candidates for cytoreductive nephrectomy.

Culp et al[16] used a large retrospective cohort to preoperatively identify patients who do not benefit from cytoreductive nephrectomy. They compared 566 patients who underwent cytoreductive nephrectomy with 110 patients who only received medical therapy (without surgery), and identified seven risk factors that were indicators of poor prognosis. These included a low serum albumin, a high serum lactate dehydrogenase, clinical stage T3 or T4, symptoms at presentation caused by a metastatic site, presence of liver metastasis, and radiographic evidence of retroperitoneal or supradiaphragmatic adenopathy at the time of cytoreductive nephrectomy. Patients who had 4 or more of these preoperative risk factors present had comparable survival with those patients who received medical therapy alone without cytoreductive nephrectomy, and those patients with only 3 risk factors or less had improved survival. Therefore, the authors recommended that only patients with 3 risk factors or less be considered for cytoreductive nephrectomy.

Presurgical therapy has been used as a litmus test to try to identify patients who progress while on therapy, and who are unlikely to benefit from cytoreductive nephrectomy. Jonasch et al[17] used bevacizumab (with or without erlotinib) in 52 patients with metastatic RCC with the primary tumor in place. Fifty patients were evaluable and 6 patients did not undergo cytoreductive nephrectomy due to progression of disease while on therapy.

Cytoreductive Nephrectomy and Ongoing Clinical Trials

Given that the only level I evidence in support of cytoreductive nephrectomy stems from the immunotherapy era in 2001, it is clear we need newer data to investigate the use of cytoreductive nephrectomy in the targeted therapy era. Two current trials are currently underway to that effect. The SURTIME trial (EORTC 30073) is planning to randomize 458 patients to either sunitinib (3 cycles) followed by cytoreductive nephrectomy followed by sunitinib *or* cytoreductive nephrectomy followed by sunitinib, with progression-free survival as primary outcome. Patients are not eligible if they fall in the poor-risk MSKCC group or have four or more risk factors as described by Culp et al.*16* On the other hand, the CARMENA trial will be similar in design to the 2 phase III trials published in the immunotherapy era, in that patients will be randomized to received sunitinib only *or* undergo cytoreductive nephrectomy followed by sunitinib, with a primary endpoint of overall survival (non-inferiority design), and an estimated accrual of 576 patients.

Conclusions

For patients with metastatic RCC, the question is generally not if, but when, to perform cytoreductive nephrectomy. Until the SURTIME and CARMENA trials are completed, it is advisable to continue performing cytoreductive nephrectomy in younger patients with clear cell histology, good performance status,

limited metastatic burden, with 3 or less MDACC risk factors, and preferably in high-volume centers. Patients who fall in other categories should not be automatically denied surgery, but their cases should be individually assessed for potential surgical therapy.

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In addition, patients have variable clinical benefit and/or tolerance to different agents, including drugs within the same class. Thus, the choice of therapy for an individual patient remains empiric at present. Upon this landscape, several molecular biomarkers have been investigated with the purpose of guiding therapy. This review discusses prognostic biomarkers correlating with the outcome of patients independent of therapy, and predictive biomarkers of treatment response, including circulating biomarkers (such as vascular endothelial growth factor [VEGF] and VEGF-related proteins, cytokine and angiogenic factors, and lactate dehydrogenase), and tissue-based biomarkers (such as single nucleotide polymorphisms).
Conclusion: Many potential prognostic and predictive molecular biomarkers have now been identified in RCC, although none has yet entered into clinical practice, and all require prospective validation in appropriately designed randomized studies. In the near future, however, validated biomarkers may become integral to management strategies in RCC, enabling tailored treatment for individual patients to improve clinical outcomes.

Renal cell carcinoma in patients with end-stage renal disease has favorable overall prognosis. Shrewsberry AB, Osunkoya AO, Jiang, et al. *Clin Transplant.* 2014;28:211-216.
Summary: Patients with end-stage renal disease (ESRD) demonstrate a greater risk for renal cell carcinoma (RCC) than the general population. This study compared pathological and clinical outcomes in patients with RCC with and without ESRD. Patients with ESRD who underwent nephrectomy and were found to have RCC since 1999 were identified. The control group was composed of patients from the general population with RCC. The primary outcome was risk of cancer recurrence. The study included 338 RCC patients: 84 with ESRD and 243 without ESRD. In the ESRD group, mean tumor size was smaller, there was decreased prevalence of advanced T category (>3) , and the average Karakiewicz nomogram score was lower. ESRD was associated with decreased tumor recurrence and clear cell pathology. No patients with ESRD had metastatic disease. There was no difference in overall or cancer-specific mortality between the ESRD and control groups.
Conclusion: Patients with ESRD who develop RCC have a better prognosis compared to RCC in patients without ESRD, which is likely secondary to favorable histopathologic phenotype as well as the likelihood of early diagnosis. Thus, the delay between nephrectomy and renal transplantation may not be necessary, especially in patients with asymptomatic, low grade tumors.

Randomized controlled trial of expressive writing for patients with renal cell carcinoma. Spelman A, Wood C, Matin SF, et al. *J Clin Oncol.* 2014;32:663-670.
Summary: This randomized controlled trial examined the quality-of-life benefits of an expressive writing (EW) intervention for patients with renal cell carcinoma (RCC) and identified a potential underlying mechanism of intervention efficacy. Patients (N = 277) with stage I to IV RCC were randomly assigned to write about their deepest thoughts and feelings regarding their cancer (EW) or about neutral topics (neutral writing [NW]) on four separate occasions. Patients completed the Center for Epidemiologic Studies Depression Scale (CES-D), MD Anderson Symptom Inventory (MDASI), Brief Fatigue Inventory (BFI), Pittsburgh Sleep Quality Index (PSQI), Medical Outcomes Study Short Form-36 (SF-36), and Impact of Event Scale (IES) at baseline and 1, 4, and 10 months after the intervention. The mean age of participants (28% stage IV; 41% female) was 58 years. Multilevel modeling analyses, using a Bonferroni-corrected $\alpha = .021$ for six outcomes adjusted for the correlation among outcomes, revealed that, relative to the NW group, patients in the EW group reported significantly lower MDASI scores ($P = .003$) and higher physical component summary scores on the SF-36 ($P = .019$) at 10 months after the intervention. Mediation analyses revealed that significant group differences for MDASI scores at 10 months were mediated by lower IES scores at 1 month after the intervention in the EW group ($P = .042$). No significant group differences were observed in the BFI, CES-D, PSQI, and mental component summary of the SF-36.
Conclusion: Expressive writing, in which patients explore their deepest thoughts about their cancer, may reduce cancer-related symptoms and improve physical functioning in patients with RCC. Evidence suggests that this effect may occur through short-term improvements in cognitive pro-

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- ***KidneyCancerHome Page at cancer.gov*** This is the NCI's gateway for information about kidney cancer. Access is also available to information about clinical trials on the website.
- ***kidney-cancer-journal.com*** is the website for *Kidney Cancer Journal*, enabling you to access all content in the current issue for free and review past issues.

Please let us know if you regularly spend time on other websites of possible interest to medical oncologists and urologists, especially those with a focus on renal cell carcinoma.

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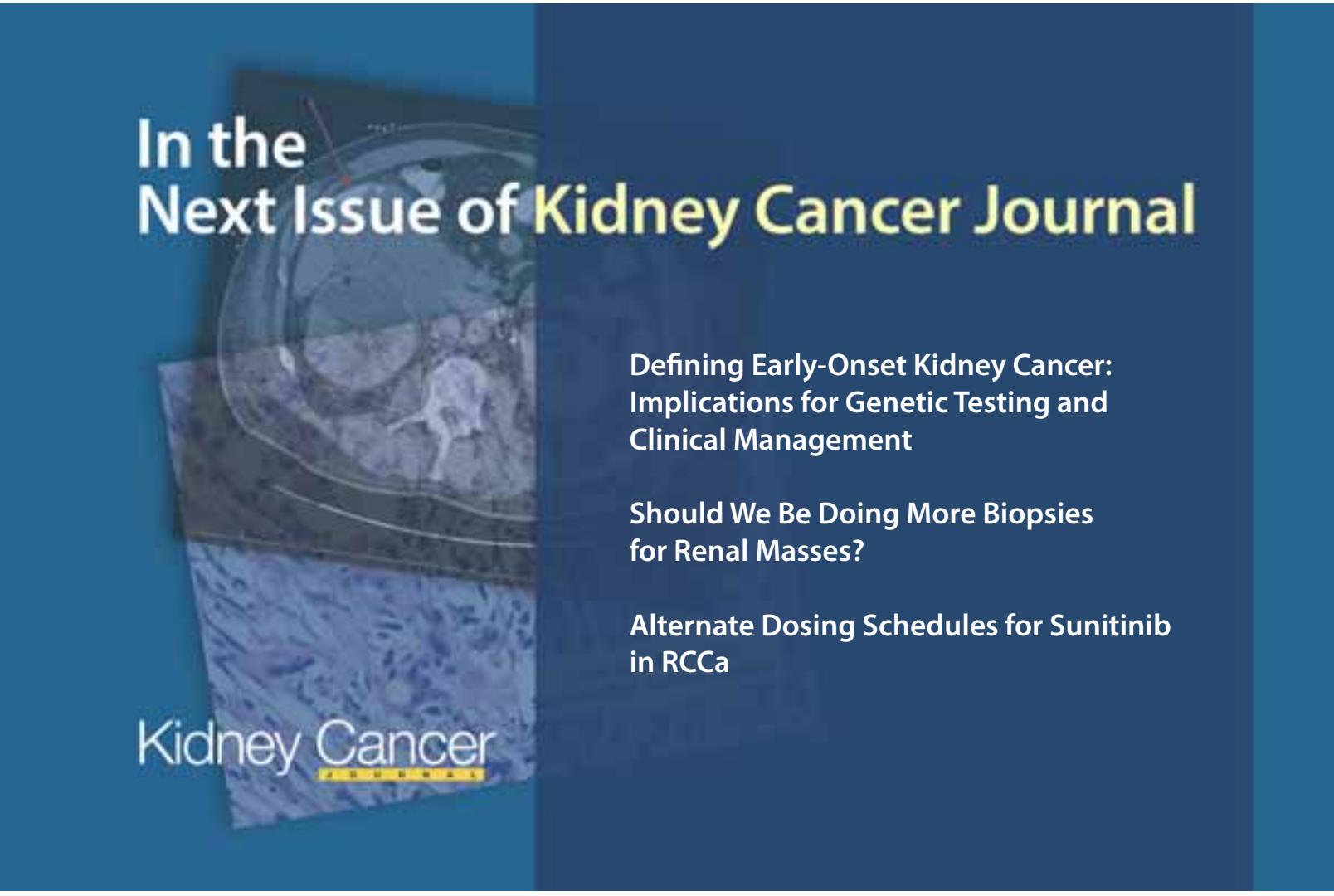

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