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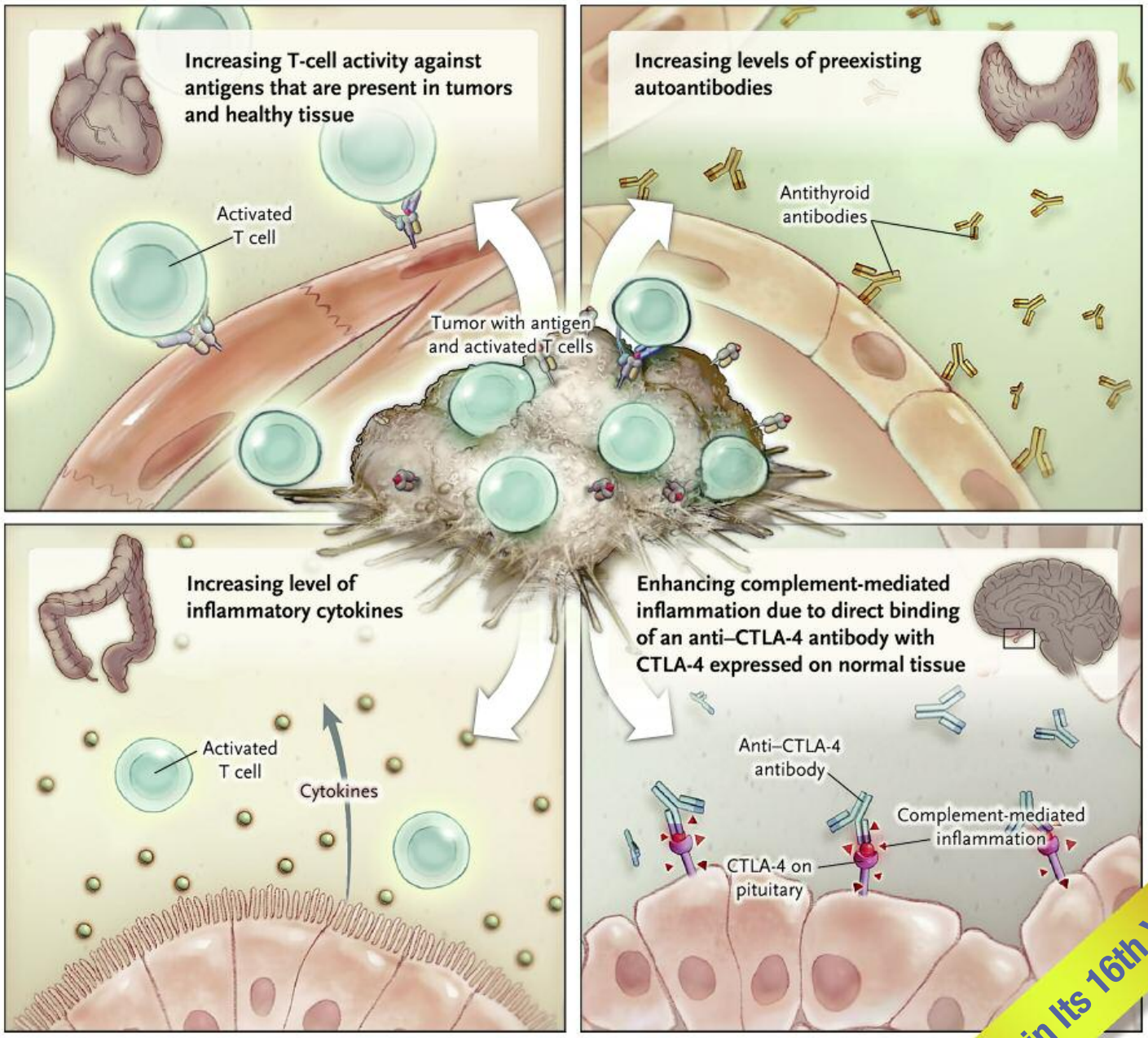
Checkpoint Inhibitors: Guidelines to Limit Immune-Related Adverse Effects

Controversies and Consensus on Initial Cytoreductive Nephrectomy vs Targeted Therapy

ASCO 2018: What's the Impact on Your Practice?



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

Now in Its 16th Year

After failure of a prior systemic advanced RCC therapy,

MAKE THE NEXT MOVE TO INLYTA® (axitinib)

Demonstrated efficacy • Safety and tolerability profile

EFFICACY MEASURES

From the AXIS trial: an open-label, phase 3 trial in metastatic RCC after failure of one prior systemic therapy (N=723)*

PROGRESSION-FREE SURVIVAL (PFS): PRIMARY ENDPOINT

6.7 months median PFS vs 4.7 months with sorafenib

(95% CI: 6.3, 8.6 and 4.6, 5.6, respectively; HR=0.67 [95% CI: 0.54, 0.81; *P*<.0001])

OBJECTIVE RESPONSE RATE (ORR): SECONDARY ENDPOINT

19.4% ORR vs 9.4% with sorafenib

(95% CI: 15.4, 23.9 and 6.6, 12.9, respectively; risk ratio: 2.06 [95% CI: 1.4, 3.0])

- The *P* value for the risk ratio is not included because it was not adjusted for multiple testing
- All responses were partial responses per RECIST criteria[1]

OVERALL SURVIVAL (OS): SECONDARY ENDPOINT

20.1 months median OS vs 19.2 months with sorafenib

(95% CI: 16.7, 23.4 and 17.5, 22.3, respectively; HR=0.97 [95% CI: 0.80, 1.17; the difference between the treatment arms was not statistically significant])

*From AXIS, a multicenter, open-label, phase 3 trial of 723 patients with metastatic RCC after failure of 1st-line therapy (sunitinib-, temsirolimus-, bevacizumab-, or cytokine-containing regimen [54%, 3%, 8%, and 35% of patients in each of the treatment arms, respectively]). Patients were randomized 1:1 to either INLYTA 5 mg twice daily (n=361) or sorafenib 400 mg twice daily (n=362), with dose adjustments allowed in both groups. Primary endpoint was PFS. Secondary endpoints included ORR, OS, and safety and tolerability.[1,2]

AEs=adverse events; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors.

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

TOLERABILITY CONSIDERATIONS

In the phase 3 AXIS trial*

91% of patients did not discontinue INLYTA due to AEs

- 9% of patients discontinued INLYTA (n=34/359) due to AEs vs 13% of patients with sorafenib (n=46/355)
  - —Overall, 61% of patients receiving INLYTA discontinued treatment vs 71% receiving sorafenib[1]
  - —In both study groups, the most common reasons for discontinuation included disease progression or relapse and AEs[1]
- Fewer patients receiving INLYTA had dose modifications or temporary delay of treatment due to AEs compared with patients receiving sorafenib (55% vs 62%, respectively)

MOST COMMON AEs

- The **most common (≥20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).
- The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).
- The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

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.

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.

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.

Please see Brief Summary of full Prescribing Information on the following pages.

Printed in USA/February 2018

Pfizer U.S. Pharmaceuticals

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.

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

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

Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment with INLYTA.

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

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

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

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

Reversible Posterior Leukoencephalopathy Syndrome. In a controlled clinical study with INLYTA for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. There were two additional reports of RPLS in other clinical trials with INLYTA.

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. Discontinue INLYTA in patients developing RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

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

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

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

Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with INLYTA.

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

Pregnancy. INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women using INLYTA. In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

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

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

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

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

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

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

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

Adverse Reaction[a]	INLYTA (N=359)		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 August 2014

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

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About the Cover
Possible mechanisms underlying immune-related adverse events, potentially related to use of checkpoint inhibitors, are depicted. These include increasing T-cell activity against antigens in tumors, elevated levels of preexisting autoantibodies, rising level of inflammatory cytokines, and enhanced inflammation due to binding of anti-CTLA-4 antibody with CTLA-4 on normal tissue. (Reprinted with permsission of *New England Journal of Medicine* and Michael A. Postow, MD).

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KCJ EDITOR'S MEMO

CARMENA Trial: Will It Reset the Paradigm on Initial Cytoreductive Nephrectomy in Targeted Therapy Era?


Robert A. Figlin, MD

"Location, location, location." Anyone in the market looking at real estate is likely to hear this mantra-like advice. But what if you had a patient with metastatic renal cell carcinoma (mRCC) staring at the prospect of initial cytoreductive nephrectomy or initial targeted therapy as options. As a medical oncologist or urologist evaluating this case in the targeted therapy era, you should be accustomed to following what might be another mantra—"selection, selection, selection." Yes, cytoreductive nephrectomy is the preferred standard in selected patients. And yet, targeted therapy may be the appropriate choice for other patients. In any case, the selection of patients plays a critical role in day-to-day patient care as well as in clinical trial design.

The Plenary Session at the 2018 meeting of the American Society of Clinical Oncology (ASCO) is likely to have a lasting and significant impact on the management of mRCC. For those of us who have closely followed the debate over the initial use of CN in the targeted therapy era, then "selection, selection, selection" of appropriate candidates for each modality should be the buzz words guiding the decision making process. But one can argue that this has always been true. Guidelines from the National Comprehensive Cancer Network (NCCN) and other groups have touted the importance of careful selection of patients undergoing nephrectomy on the basis of published risk models such as the Memorial Sloan-Kettering Cancer Center (MSKCC) paradigm. At the Plenary Session, there were four studies deemed to have the greatest potential impact on patient care out of the more than 5,800 abstracts featured as part of the 2018 ASCO Annual Meeting. One of these studies is the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogeniques) trial.

A comprehensive report on CN in the targeted therapy era is presented in this issue of the *Kidney Cancer Journal* by my esteemed colleague, Michael Blute, MD, who has analyzed virtually all of the current studies leading up to CARMENA. Like other presentations at ASCO over the years, the CARMENA trial is a striking phenomenon, debunking myths and in some cases shattering preconceptions of long standing standards of care. Is it pivotal? Probably. Can it markedly change the paradigm as a so-called

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Robert A. Figlin, MD, at robert.figlin@cshs.org. Please provide in a word processing program. Images should be submitted electronically as well.

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Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

Spacing: One space after periods. Manuscripts should be double spaced.

References

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

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Essential Peer-Reviewed Reading in Kidney Cancer

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

Comparing the relative importance of attributes of metastatic renal cell carcinoma treatments to patients and physicians in the United States: A Discrete-Choice Experiment. González JM, Doan J, Gebben DJ, et al. *Pharmacoeconomics*. 2018 Jun 5; doi: 10.1007/s40273-018-0640-7.

Summary: Patients with RCC and physicians who treat RCC completed an online discrete-choice experiment survey. In a series of 12 questions, respondents chose between two hypothetical treatments defined in terms of six attributes: progression-free survival (PFS), probability of living ≥3 years (PL3Y), skin reactions, severity of fatigue, mode of administration, and monthly co-payment. Treatment choices were analyzed using a random-parameters logit model to estimate relative preference weights for the attribute levels and relative attribute importance. Overall, 201 patients and 142 physicians completed the survey. For both patients and physicians, PL3Y was the attribute with the greatest and statistically significant conditional relative importance. Estimates of the conditional relative importance of PFS, skin reactions, and mode of administration for patients, and for PFS and mode of administration for physicians, were not statistically significant. The preferences for improvements in PFS were independent of the level of PL3Y for both patients and physicians. Conditional relative attribute importance varied by patient disease stage.

Conclusion: Patients and physicians indicated that PL3Y was the most important treatment attribute and was significantly more important than PFS. Importance rankings differed between physicians and patients and between all patients and those with advanced/metastatic disease.

Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. McDermott DF, Huseni MA, Atkins MB, et al. *Nat Med*. 2018 Jun; 24(6):749-757. doi: 10.1038/s41591-018-0053-3. Epub 2018 Jun 4.

Summary: Results are from IMmotion150, a randomized phase 2 study of atezolizumab (anti-PD-L1) alone or combined with bevacizumab versus sunitinib in 305 patients with treatment-naive metastatic renal cell carcinoma. Co-primary endpoints were progression-free survival (PFS) in intent-to-treat and PD-L1+ populations. Intent-to-treat PFS hazard ratios for atezolizumab+bevacizumab or atezolizumab monotherapy versus sunitinib were 1.0 (95% confidence interval (CI), 0.69-1.45) and 1.19 (95% CI, 0.82-1.71), respectively; PD-L1+ PFS hazard ratios were 0.64 (95% CI, 0.38-1.08) and 1.03 (95% CI, 0.63-1.67), respectively.

Conclusion: Exploratory biomarker analyses indicated that tumor mutation and neoantigen burden were not associated with PFS. Angiogenesis, T-effector/IFN-response, and myeloid inflammatory gene expression signatures were strongly and differentially associated with PFS within and across the treatments. These molecular profiles suggest that prediction of outcomes with anti-VEGF and immunotherapy may be possible and offer mechanistic insights into how blocking VEGF may overcome resistance to immune checkpoint blockade.

Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. Méjean A, Ravaud A, Thezenas S, et al. *N Engl J Med*. 2018 Jun 3; doi: 10.1056/NEJMoa1803675.

Summary: this study assessed the role of nephrectomy in patients with metastatic renal-cell carcinoma who were receiving targeted therapies. The phase 3 trial randomly assigned, in a 1:1 ratio, patients with confirmed metastatic clear-cell RCC at presentation who were suitable candidates for nephrectomy to undergo nephrectomy and then receive sunitinib (standard therapy) or to receive sunitinib alone. Randomization was stratified according to prognostic risk (intermediate or poor) in the Memorial Sloan Kettering Cancer Center prognostic model. Patients received sunitinib at a dose of 50 mg daily in cycles of 28 days on and 14 days off every 6 weeks. The primary end point was overall survival. A total of 450 patients were enrolled from September 2009 to September 2017. At this planned interim analysis, the median follow-up was 50.9 months, with 326 deaths observed. The results in the sunitinib-alone group were non-inferior to those in the nephrectomy-sunitinib group with regard to overall survival. The median overall survival was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy-sunitinib group. No significant differences in response rate or progression-free survival were observed. Adverse events were as anticipated in each group.

Conclusion: Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease.

Sunitinib in patients with metastatic renal cell carcinoma: Clinical Outcome According to International Metastatic Renal Cell Carcinoma Database Consortium Risk Group. Rini BI, Hutson TE, Figlin RA, et al. *Clin Geni-*

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

FDA approves nivolumab plus ipilimumab combination for intermediate or poor-risk advanced renal cell carcinoma

The Food and Drug Administration has granted approvals to nivolumab and ipilimumab (Opdivo and Yervoy) in combination for the treatment of intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC). Approvals were based on CheckMate 214 (NCT02231749), a randomized open-label trial. Patients with previously untreated advanced RCC received nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for 4 doses followed by nivolumab monotherapy (3 mg/kg) every 2 weeks, or sunitinib 50 mg daily for 4 weeks followed by 2 weeks off every cycle.

The trial demonstrated statistically significant improvements in overall survival (OS) and objective response rate (ORR) for patients receiving the combination (n=425) compared with those receiving sunitinib (n=422). Estimated median OS was not estimable in the combination arm compared with 25.9 months in the sunitinib arm (hazard ratio 0.63, 95% CI: 0.44, 0.89; $P<0.0001$). The ORR was 41.6% (95% CI: 36.9, 46.5) for the combination versus 26.5% (95% CI: 22.4, 31) in the sunitinib arm ($P<0.0001$). The recommended schedule and dose for this combination is nivolumab, 3 mg/kg, followed by ipilimumab, 1 mg/kg, on the same day every 3 weeks for 4 doses, then nivolumab, 240 mg, every 2 weeks or 480 mg every 4 weeks.

Peloton Therapeutics initiates phase 2 trial of oral HIF-2α inhibitor PT2977 for treatment of von Hippel-Lindau Disease-associated kidney cancer

Peloton Therapeutics, Inc., announced dosing of the first patient in a Phase 2 trial evaluating the efficacy and safety of lead investigational oncology agent, PT2977, to treat von Hippel-Lindau (VHL) disease-associated kidney cancer. PT2977 is a once-daily, oral inhibitor of HIF-2α, a transcription factor that has been implicated in the development and progression of RCC. The primary objective of the Phase 2 trial is to evaluate the efficacy of PT2977 for the treatment of VHL disease-associated renal tumors as measured by overall response rate. Secondary objectives include duration of response, time to response, progression free survival, and time to surgery for VHL disease-associated renal tumors. The trial will also evaluate the efficacy of PT2977 in other VHL disease-associated tumor types as well as the safety and pharmacokinetics of PT2977. Patients will be evaluated radiologically approximately every 12 weeks while continuing in the study.

Peloton's drug discovery and development efforts focus on identifying novel compounds capable of modulating complex protein-protein interactions that drive disease which have eluded conventional small molecule approaches. Peloton has the only clinical stage small-molecule inhibitors of HIF-2α, and PT2977 has demonstrated a favorable profile in a Phase 1 study in patients with advanced solid tumors including RCC. The study will enroll 50 patients at clinical trial centers across the United States and Europe. More information about the trial is available at www.clinicaltrials.gov, identifier NCT NCT03401788.

First patient enrolled in phase 1 trial of INCB01158, Keytruda combo for solid cancers

The first patient has been treated in a Phase 1 clinical trial evaluating a combination of INCB01158 (aka CB-1158) plus Keytruda (pembrolizumab) in patients with advanced solid tumors, including RCC. The trial is evaluating the safety and effectiveness of INCB01158, given alone or in combination with an anti-PD-1 immune checkpoint inhibitor like Keytruda. Developed by Calithera in collaboration with Incyte Corporation, INCB01158 is an immunotherapy that targets selectively the arginase enzyme.

Arginase is an enzyme produced in the tumor microenvironment by immunosuppressive cells, like myeloid-derived suppressor cells (MDSCs). Its activity depletes the amino acid arginine, which is essential for immune T-cells to proliferate and survive. Inhibiting arginase is thus expected to promote the T-cell expansion at the tumor site in cancers where arginase-secreting MDSCs are known to play an immunosuppressive role. These include renal cell cancer, breast cancer, lung cancer, and acute myeloid leukemia. Because INCB01158 increases the amount of T-cells within the tumors, researchers believe it might work in synergy with other immunotherapies that unleash T-cells' tumor-killing functions.

The Phase 1 trial (NCT02903914) is designed to assess the safety of INCB01158 and define a recommended dose to be used in planned Phase 2 studies, both as a monotherapy and in combination with immune checkpoint therapy. The study is being conducted in the U.S. and is expected to include 236 patients with advanced or metastatic solid tumors. Enrollment is ongoing.

Delayed mRCC targeted therapy does not worsen survival

SAN FRANCISCO—Delayed rather than early initiation of

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Optimizing Benefit and Limiting Immune-Related Adverse Effects Following Checkpoint Inhibitor Blockade

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As the population of patients treated with immune checkpoint blockade expands and with even more agents likely to be approved there is a growing need for guidelines on managing immune-related adverse effects. New recommendations from several national societies could not be more timely because these now commonplace therapies do not exhibit the typical side effects of cytotoxic or targeted agents. Clinicians find themselves facing daily challenges to manage immune-related adverse effects with appropriate strategies and to recognize subtle complications that could be overlooked or underestimated. This report highlights valuable resources and strategies to adopt the latest advisories on managing adverse events arising from immune checkpoint blockade.

As the footprint of immune checkpoint inhibitors (ICI) grows larger across the landscape of oncology, especially in renal cell carcinoma (RCC), this revolutionary change in therapy is undergoing even closer scrutiny in view of the speed with which these drugs have been adopted in clinical practice after approval by the FDA. The speed of approval, as noted in a recently published study[1], is one of the most important aspects of the ICI story, an aspect sometimes overlooked in view of the potential benefits conferred by these agents.

A recently published study showed that the majority of patients eligible for ICI received treatment within a few months of FDA approval, indicating an extremely rapid implementation timeline.[1] One of the long-standing concerns about the adoption of novel therapeutics is that they enter the market based on data from a selective group of patients established by particular clinical trial inclusion and exclusion criteria. For clinicians in the community this can pose a challenge treating the general population with key issues regarding lack of knowledge surrounding the full side effect profiles.[2,3] The good news for those who have or are considering adopting ICI is that there is a rapidly growing wealth of information on the adverse effects likely to be encountered as well as emerging effective consensus guidelines from leading medical oncology societies.

Another challenge from the findings is the need to reevaluate new and changing distributions of immune related adverse events (ir-AE), in particular with the use of recently approved combinations of immunotherapies in RCC treatment. Postow et al tackled ten essential questions practitioners will encounter as they consider the use of ICI in RCC.[4] The questions range from the most basic (Why do these ir-AE occur? Can we predict who will have ir-AE?), to a more nuanced consideration involving issues including whether it is safe to continue or restart ICI after patients experience an ir-AE. As the experience with ICI expands beyond the early studies establishing their clinical benefit, there is a growing awareness of an expanding range of issues. In view of all the new studies, we have reached an inflection point in the use of ICI in terms of managing the associated adverse effects so that we can move on to optimizing the benefit/risk ratio. In RCC, support for the use of ICI began several years ago with the report of phase 2 results on the safety of nivolumab in patients with metastatic RCC.[5]

The rationale for ICI begins with an understanding of mechanisms involved in the pathogenesis of RCC, mech-

Keywords: immune checkpoint blockade, immune-related adverse effects, checkpoint inhibitors, PD-1, CTLA-4, dermatologic, pulmonary, endocrine, management, corticosteroids.

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anisms that go beyond historically standard of care targeted therapeutics inhibiting such signaling as vascular endothelial growth factor (VEGF) or the mammalian target of rapamycin (mTOR) pathway. Multiple mechanisms evolve during tumorigenesis including systemic dysfunction in T cell signaling and exploitation of immune checkpoints.[6-11] These mechanisms help tumors evade specific immune responses despite the presentation of tumor antigens to the immune system.[12] Further elucidation of these immune evasive mechanisms in the host-tumor immune environment led to the development of novel antibodies directed against immune checkpoint proteins.[13,14]

Few agents have ushered in as much excitement as that seen with FDA approval of the novel human immunoglobulin G4 programmed death (PD-1) ICI that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2.[15] By blocking this negative regulator on T cells, the first drug approved in this class, nivolumab, ostensibly inhibits events that normally lead to downregulation of a cellular immune response. The important message from early phase clinical trials is that nivolumab can enhance T-cell function and thus, result in antitumor activity.[16] The pivotal study demonstrated benefits in progression-free survival, overall response rate and overall survival, supporting the use of nivolumab as monotherapy to restore T-cell immune activity in patients with RCC.[17]

Although the precise pathophysiology underlying immune-related adverse effects is still unknown, various hypotheses help delineate some potential mechanisms. These adverse events may be related to the role that ICI agents play in maintaining immunologic homeostasis. As this connection has been explored, a better understanding has emerged concerning the way in which unique checkpoint blocks down regulate immunity.[4] There are some clear-cut distinctions proposed. For example the checkpoint protein CTLA-4 is upregulated in the periphery during immune priming.[18] It is expected that varying ir-AE arising from PD-1 blockade vs CTLA-4 blockade might be related to timing or sight of action, for example, PD-1 blockade is generally believed to inhibit T cells at the site of the tumor.[19,20] Additionally, mice lacking PD-1 have variable autoimmunity including arthritis and cardiomyopathy.[21,22] The pathophysiology of ir-AE remains highly controversial and we are only beginning to understand why the effects of anti-CTLA-4 or anti-PD-1 blockade differ from one another in severity, timing, and preponderance of specific ir-AE. This review will focus on practical aspects and implications for managing ir-AE, particularly in the setting of expanding FDA approval of ICI in patients with RCC.

Spectrum of Therapy and Epidemiology of Immune Related Adverse Events

Since 2011, beginning with the approval of the CTLA-4 antibody ipilimumab in melanoma, there has been an influx into the market of drugs targeting both pathways including the PD-1/PD-L1 inhibitors: nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab as well as the CTLA-4 inhibitor ipilimumab. There are many more in development.[23] The incidence of any grade ir-AE in clinical trials is reportedly as low as 15% to as high as 90%, and toxicities range from mild requiring treatment with topical cream to severe enough that drug discontinuation and the initiation of systemic immunosuppressive medications occur 10–55% of the time.[24,25]

The reason for this huge variability may be due to the lack of agreed upon uniform definitions as to what constitutes a particular ir-AE, although recently there have been attempts to standardize grading and criteria for ir-AE.[26-28] Possible underreporting of toxicities within clinical trials may also lead to heterogeneity in the reported incidence of these adverse events.[29] While the spectrum and rate of various ir-AE is different between PD-1/PD-L1 inhibitors and CTLA4 inhibitors, trials are increasingly investigating the potential of using these drugs in combination, which has been shown to be more toxic than targeting either pathway alone.[30,31] While there are many combination regimens being tested in mRCC, the combination of two uniquely targeting immunotherapy agents or combination of an anti-VEGF agent with an immunotherapy agent have recently been reported.[31-33] Results from the CheckMate 214 trial showed that overall survival and objective response rates were significantly higher with the combination of nivolumab and ipilimumab vs sunitinib (risk of death was 37% lower with nivolumab and ipilimumab and objective response rate was 42% vs 27%). CheckMate214 also provided a detailed analysis of the safety profile of this combination (nivolumab and ipilimumab), now part of the first-line treatment algorithm in intermediate- and poor-risk patients with previously untreated RCC.[31] The safety profile of nivolumab plus ipilimumab was consistent with that in previous studies in multiple tumor types, including advanced RCC with a lower incidence of grade 3 and 4 treatment-related adverse events than observed with suniti= nib. The frequencies of treatment-related gastrointestinal, skin, and hepatic adverse events were lower than those seen in a trial involving patients with melanoma, in which a higher dose of ipilimumab (3 mg per kilogram) and a lower dose of nivolumab (1 mg per kilogram) were used.[34] Patients in CheckMate214 reported better health-related quality of life, as measured by the FKSI-19, with nivolumab plus ipilimumab than with sunitinib. Dose delays, treatment with glucocorticoids, and prompt diagnostic workup to rule out noninflammatory causes were used to manage toxic effects according to management algorithms developed for immuno-oncology treatment-related adverse events.[27] Therefore, recognizing and treating ir-AE promptly is of paramount importance.

Mapping Immune Related Adverse Events by Organ System Involvement

New guidelines have been issued by groups like the European Society of Medical Oncology (ESMO), the Ameri-

Table 1. Routine Pre-treatment Screening

History
Detailed questioning for autoimmune, infectious disease, endocrine and organ-specific disease history
History of base line bowel habit (frequency of bowel movements, usual stool consistency)
Blood tests
Complete blood count (CBC)
Assessment of renal function and acid balance (creatinine, creatinine clearance, BUN, CO2)
Liver function tests (total bilirubin, AST, ALT, Alkaline phosphatase, LDH)
Electrolytes (Na, Cl, K, Phos, Mg, Ca)
Endocrine: TSH, free T4, 8am cortisol (optional), 8am ACTH (optional)
Total CK, Troponin I or T, brain naturetic peptide (optional)
Blood glucose and hemoglobin A1C (optional)
Infectious disease screen: HBsAg, HBsAb, HBcAb, HCAb, CMV, HIV antibody, HIV antigen (p24)a
Fasting lipid profile
Dermatologic examination
Full skin and mucosal exam, taking note of the extent and type of lesions present
Pulmonary tests
Baseline oxygen saturation on room air and during ambulation
Pulmonary function testing with DLCO
Cardiac tests
ECG, echocardiography for baseline ejection fraction (optional)

Recommendations for anticipatory management based on SITC guidelines.[26] Testing should be applied based on available testing and clinical judgement. Abbreviations: BUN, blood urea nitrogen; CO2, carbon dioxide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Na, sodium; Cl, choloride; K, potassium; Phos, phosphorus; Mg, magnesium; Ca, calcium; TSH, thyroid stimulating hormone; T4, free thyroxine; ACTH, adrenal corticotrophic hormone; CK, creatine kinase; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HCAb, hepatitis C antibody; CMV, cytomegalovirus; HIV, human immunodeficiency virus; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram

can Society of Clinical Oncology (ASCO), and the Society for Immunotherapy of Cancer (SITC).[26-28] Each of these groups addresses the importance of managing the most common toxicities based on organ system involvement. The majority of ir-AE are in the range from mild to moderate, but treatment-related deaths have been known to occur in up to 2% of patients. Skin, gut, endocrine, lung, and musculoskeletal AE are relatively common, whereas cardiovascular, hematologic, renal, neurologic, and ophthalmologic AE occur much less frequently.[26]

Immune related adverse events can be characterized by the following:

- Compared to cytotoxic chemotherapy, ir-AE may have a delayed onset and prolonged duration.
- Inflammation of target tissue, characterized by an influx of immune cells, granuloma formation, or fibrosis.
- A detailed summary of pre-treatment evaluation and diagnostic tests to consider in all patients prior to initiating checkpoint inhibitor therapy is indicated in **Table 1**.[26]

Immune-related Skin Toxicity

The spectrum of dermatologic reactions to immune checkpoint blockade is fully described in clinical practice guidelines from ESMO.[28] Skin AE are the most frequent ir-AE (43%-45% with ipilimumab, and 34% with nivolumab and pembrolizumab) and usually develop within the first few weeks after initiation of treatment. The good news is that serious reactions are rare and generally grade 1 reactions do not require dose reductions or treatment discontinuation. ICI is most commonly associated with a maculopapular rash, pruritus, psoriasis, and vitiligo with the latter seen more commonly in melanoma than RCC.[35] An example is shown in the **Figure**. One statistic suggests combination ICI therapy is more likely to show significantly elevated rates of AE vs monotherapy, with rash reported in 40% of patients receiving nivolumab and ipilimumab vs 24% on ipilimumab alone or 15% on single- nivolumab or pembrolizumab. Although pruritus is commonly seen with both categories of checkpoint inhibitors (anti-PD-1 and anti-CTLA-4), it only reaches grade 3 or 4 in fewer than 2.5% of patients.[36]

The ESMO guidelines divide skin reactions histopathologically into four groups:

1. Inflammatory skin disorders involving acute, subacute, or chronic inflammation, associated with epidermal changes.
2. Immunobullous skin lesions, similar to dermatitis herpetiformis or bullous pemphigoid.
3. Keratinocyte alteration.

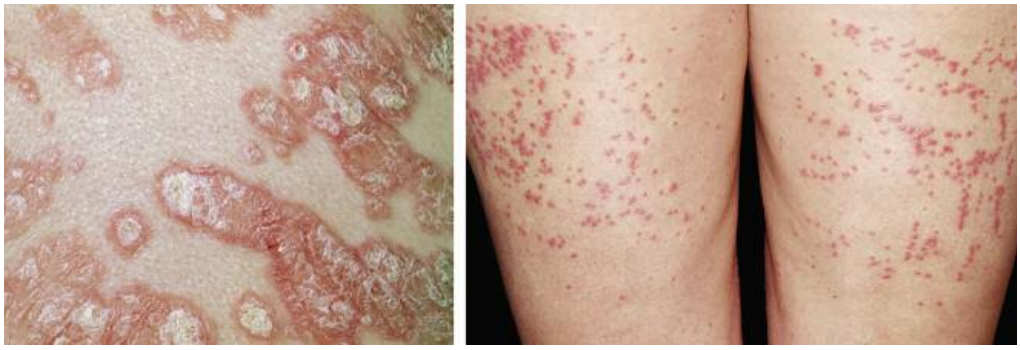

Figure. Example of inflammatory skin manifestations of ICI reactions. Psoriatic reaction, left; dermatitis, right.

4. Immune-reaction mediated by alteration of melanocytes, as in vitiligo

Endocrine-related Adverse Effects on the Rise With Immunotherapy

The introduction of ICI has resulted in an increase in both transient hyperthyroidism and the more commonly observed hypothyroidism.[28] Hyperthyroidism tends to be transient and may precede hypothyroidism. While still unclear, it is thought that the pathogenesis of thyroid disorders is mediated by T cells and not B cell autoimmunity. The incidence of thyroid dysfunction requiring thyroid hormone replacement in a study of 51 patients was 21% compared with 8% in patients who did not develop thyroid dysfunction.[37]

Reviewing data with respect to each type of checkpoint blockade, Haanen et al[27] suggest that thyroid dysfunction is most common upon treatment with anti- PD-1/PD-L1 or combination of anti-CTLA4 and agents blocking the PD-1/PD-L1 axis. Regardless of tumor type, thyroid dysfunction rates vary from 5% to 10% with either anti-PD-1 (pembrolizumab or nivolumab) or anti-PD-L1 therapy (atezolizumab). A sharp impact on thyroid dysfunction has been noted with combination therapy. The incidence with combination of nivolumab and ipilimumab, for example, rises markedly to 20%; however, the events are rarely higher than grade 2. Routine blood tests (TSH and FT4) are most likely to reveal thyroid dysfunction and should be done before every infusion of therapy, at least once a month when 2 weekly infusions are administered.

Another sometimes overlooked endocrine side effect of these medications is immunotherapy-induced hypophysitis. Inflammation of the pituitary gland can contribute to hypothyroidism as indicated above, but also disordered expression of cortisol, ACTH, LH, FSH, and prolactin. Routine screening of thyroid function tests has become the norm, along with serial measurement of ACTH and serum cortisol.[38]

> "It is critical to remember that occasional severe adverse events can be triggered upon-treatment with these agents (checkpoint inhibitors) that can produce fatal consequences. Particularly as we advance these drugs into the adjuvant and neoadjuvant settings, it is critical to consider the potential consequences."

Highlighting Less Common Immune Related Adverse Events: Pulmonary, Cardiac and GI Toxicity

It is critical to remember that occasional severe adverse events can be triggered upon treatment with these agents that can produce fatal consequences. Particularly as we advance these drugs into the adjuvant and neoadjuvant settings, it is critical to consider the potential consequences. While any of the events reported above can lead to fatality, these less common events have a greater potential to become severe and irreversible rapidly.

One of the more alarming complications arising from checkpoint inhibitor therapy is pneumonitis. The incidence of pneumonitis is approximately 5%, with grade 3, 4, or 5 reactions occurring less than 2% of the time.[39] Physicians should have an index of suspicion especially with PD-1 blockade, where according to one report the median time from drug initiation to the development of pneumonitis was 2.6 months; however, symptoms were seen as soon as 2 weeks or as late as 11.5 months after starting therapy and may occur even later.[23] In the case of pneumonitis, there have been some clear-cut differences in the frequency of this AE with the use of single vs combination therapy where the combination raises the incidence up to 3x more all- grade and grade >3 events.[34]

Although cardiac toxicity is relatively rare, adverse effects with PD-L1 and CTLA-4 blockade have been increasingly recognized in the last few years as a potentially fatal complication.[40] Despite being uncommon, reports have emerged on a wide variety of toxicities, particularly since the use of checkpoint blockade has grown. Among the complications noted are asymptomatic cardiomyopathy, symptomatic heart failure, pericarditis, myocarditis, tachyarrhythmias, and bradyarrhyth- mias.[41] A major concern raised by many is that markers of cardiac dysfunction such as left ventricular ejection fraction or cardiac cell death (troponin-I, CK-MB) are not routinely checked in patients on immunotherapy and thus more likely that cardiac toxicity associated with these medications may be underestimated.[42]

As is the case with cardiac toxicity, gastrointestinal adverse effects are classified among the more uncommon complications. Diarrhea has been one of the more frequently reported adverse events, and is more likely to be seen with the CTLA-4 inhibitors. Of greater concern is that diarrhea may be a symptom of severe bowel inflammation and as an immune related AE if not properly identified as such improper diagnosis and treatment can be

Table 2. General guidance for corticosteroid management of immune-related adverse events

Grade 1	Corticosteroids not usually indicated, monitor and continue immunotherapy
Grade 2	Hold immunotherapy oral prednisone 0.5-1 mg/kg/day -or - methylprednisolone 0.5-1 mg/kg/day IV If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day Once improved to ≤grade 1 AE, start 4–6 week steroid taper • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids
Grade 3	Hold immunotherapy Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) Escalate immunosuppression every 2-3 days if no improvement Once improved to ≤grade 1 AE, start 4–6 week steroid taper
Grade 4	Hold immunotherapy Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) If no improvement in 2–3 days, add additional/alternative immunosuppressent, e.g. infliximab If symptoms do not improve in 4-6 weeks, discontinue immunotherapy
General	Add PCP prophylaxis if > 3 weeks of immunosuppression expected (>30 mg prednisone/day or equivalent) Provide supportive care as needed Start proton pump inhibitor for GI prophylaxis Supplement calcium and vitamin D to prevent osteoporosis if steroid use is chronic

catastrophic. A report by Wang et al, suggests that the rising use of checkpoint inhibitors means that immune-related colitis is increasingly encountered.[43] These authors identified 34 studies in a meta-analysis totaling 8863 patients. The overall incidence during ipilimumab monotherapy was 9.1% for all-grade colitis, 6.8% for severe colitis, and 7.9% for severe diarrhea. The incidence was lowest during PD-1/PD-L1 inhibitor monotherapy with 1.3% for all-grade colitis, 0.9% for severe colitis and 1.2% for severe diarrhea. Combination ipilimumab and nivolumab resulted in the highest incidences of all-grade colitis (13.6%), severe colitis (9.4%) and severe diarrhea (9.2%) among ICI regimens. Among melanoma, NSCLC, and RCC patients, incidences of colitis and diarrhea with PD-1/PD-L1 inhibitor monotherapy did not significantly differ. Severe colitis incidence was similar with ipilimumab monotherapy at 3 mg/kg and 10 mg/kg (7.1% vs 5.1%, respectively), but significantly higher for severe diarrhea with 10mg/kg (11.5% vs 5.2%).

Management Guidelines

Three major medical groups have published comprehensive guidelines to the management of toxicities related to immune checkpoint blockade.[26-28] Working groups within ESMO, SITC, and ASCO have formulated recommendations to standardize management of ir-AE. There is considerable overlap of these consensus guidelines, and some general principles of management can be identified as each group addresses a myriad of issues arising from the increased use of checkpoint inhibitors. The SITC working group offered some overall perspectives that suggest a framework for management:

- Effective management depends on early recognition and prompt intervention with a break in therapy or necessary immune suppression with appropriate immunomodulatory strategies depending on the severity of toxicity.
- A multi-disciplinary team is among the advisories to include specialists such as endocrinology, cardiology, dermatology, etc should be involved early, and hospitalization may be necessary in grade 3 adverse effects that do not respond to therapy or serious (more than grade 4).
- Patient education emerges as a key component prior to the initiation of immunotherapy.
- Short term adverse events related to use of moderate to high-dose corticosteroids should be expected and discussed with patients. Patients receiving long-term or high-dose corticosteroids are at risk for diabetes and osteoporosis and should receive vitamin D and calcium supplementation.

As delineated in **Table 2**, the management of ir-AE relies heavily on corticosteroids and other immunomodulatory agents.[26] In general a graded approach to steroid management should be applied, and occasional severe toxicities may require the application of additionally potential anti-inflammatories more widely used in rheumatology. The most widely studied of these is the use of anti-tumor necrosis factor (TNF) agents for treatment of severe colitis. Strategies to administer these agents are determined based on the grade of immune-related AE. Use of prophylactic antibiotics is still controversial to reduce the risk of opportunistic infections. In any case, corticos-

teroids should be used on an individualized basis, depending on medical history, co-morbidities, underlying disease status, type and number of adverse events and ability to tolerate corticosteroids. Keeping in mind that depending on severity of ir-AE a prolonged taper of corticosteroids may be required, which should be factored into decisions to delay or withhold treatment. In general, immune therapy should be held until steroids are nearing a physiologic level, both to avoid recurrence of symptoms, and to apply the agents in a physiologic setting where they can be effective. The SITC guidelines contain specific recommendations for each AE and should be consulted for specific management strategies.[26]

Conclusion

The treatment algorithm for advanced RCC has undergone dramatic changes with the introduction of immune checkpoint blockade, thus mandating more attention to the risk of adverse effects related to the expanding use of immune checkpoint inhibitors. Comprehensive guidelines from several international groups represent a benchmark in how these ir-AE can be managed. Involvement by a multi-disciplinary team of specialists is one of the cornerstones of management highlighted by each set of guidelines. One of the gaps in our understanding remains the need for more information on the pathophysiology of these untoward effects. As future studies unravel more details on this issue, clinicians may obtain more clues on how to prevent and minimize adverse reactions to a therapy that has revolutionized RCC care.

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Conflict of Interest

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ASCO 2018: Highlights From the Meeting Through the Lens of a Key Opinion Leader

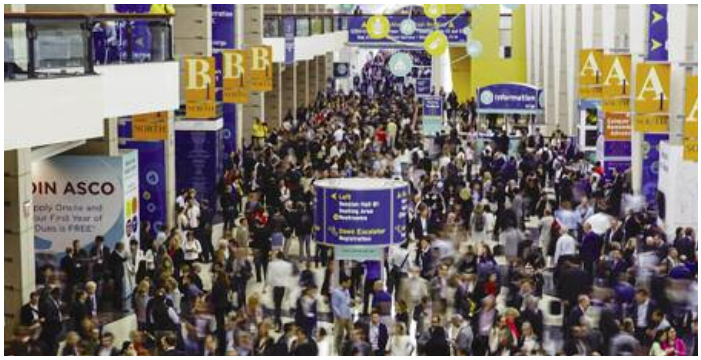
In this wide ranging interview, Nicholas J. Vogelzang, MD, FASCO, FACP, shares insights, perspectives, and real-world observations from his practice following the 2018 Scientific Sessions of the American Society of Clinical Oncology. Dr Vogelzang serves as Vice Chair of the SWOG GU Committee and is Associate Director, Genitourinary Research Program, US Oncology Research, Comprehensive Cancer Centers of Nevada, in Las Vegas. He recently was recognized as one of 21 physicians for their outstanding contributions to quality care and inducted as a Giant in Cancer Care by OncLive.

Q. What impression were you left with after the 2018 ASCO meeting? Was there anything with significant translational impact?

Dr Vogelzang: I did not find any breakthroughs at this year's meeting, nothing that I could describe as "practice changing." With regard to CARMENA, one of the trials discussed during the Plenary Session, the data did not change my practice. I've always recommended a neoadjuvant TKI (tyrosine kinase inhibitor) for the last 10 years because of some traumatic experiences early on when everyone was recommending upfront nephrectomy regardless of risk factor stratification or selection considerations. In some cases, patients died before they could receive systemic therapies. I don't recommend nephrectomy upfront unless the tumor is really small or there is minimal metastatic burden.

Q. There has been a lot of controversy surrounding this issue. There are physicians, for example, especially at academic centers like the Massachusetts General Hospital, who say that cytoreductive nephrectomy has been largely underused in the targeted therapy era and that strategies should be reconsidered. What is your opinion of these observations?

Dr Vogelzang: I think that physicians at these centers, particularly urologists, do not see the kind of kidney cancer patients whom most of us in community practice see. The problem often arising for community oncologists is that patients are sick when they come to us; they are symptomatic and should not have their kidney removed initially. It's obvious that when you have clinical experience under your belt, the TKIs work extremely quickly to reduce pain and bleeding.



Q. Can you provide a real-world experience where this was the case?

Dr Vogelzang: Yes. A prisoner was brought to my office recently and he came in with a palpable mass and in severe pain. He had been shuttled around from one doctor to another and had undergone a biopsy but no treatment. When he walked into my office he was in shackles. After examining him, I told him, "You need to start a TKI right now." So I went to my samples and selected Votrient, which I had available at the time. Within two days his pain was gone, his mass was smaller, evidence that the TKI was working extremely quickly. Unfortunately, the patient died because he could not find a surgeon who would operate on him because it was inoperable. The point of this case, however, is the rapidity with which TKIs reduce inflammation, the pain, and reduce peritumoral infiltrates. It is really remarkable.

Q. So to sum up the controversy on initial cytoreductive nephrectomy in the targeted therapy era, is there anything recent in the literature that can serve as a guide, aside from society or working group guidelines?

Dr Vogelzang: Yes there is. I would refer our readers to an Editorial in the *New England Journal of Medicine* by Motzer and Russo (June 3, 2018 DOI: 10.1056/ NEJMe1806331). It reflects my views and is an excellent analysis and interpretation of the results from the CARMENA trial. It emphasizes the need to appropriately select patients for either modality.

Q. How would you frame the current discussion about the treatment algorithm for RCC after the ASCO meeting? What are some of the pitfalls in selecting various strategies?

Dr Vogelzang: Based on the ASCO meeting, the treatment paradigm is not changing yet. The biggest problem is that insurance companies are still not reimbursing for the ipinivo (ipilimumab and nivolumab) combination and we have no definitive data on frontline IO agents (nivolumab or pembrolizumab) given as monotherapy. The phase 2 data on pembrolizumab frontline were very encouraging. I participated in that study and I had very good results with it. So that is an encouraging step forward because we now have upfront information on this agent. We don't have upfront nivolumab data. We have very strong upfront ipilimumab/nivolumab but a lot of us are unable to use it because of insurance issues.

Q. There was considerable speculation at ASCO about the need for using a checkpoint inhibitor as the comparator arm vs combination regimens with checkpoint inhibition. Would you agree that there is a need for such study?

Dr Vogelzang: Yes, that would be very helpful. Let's look at the landscape of therapy: we have 2 combos (nivo/ipi and atezolizumab/bevacizu-mab) that are superior to sunitinib. We have a 3rd com-bo (avelumab/axitinib) that has been compared to sunitunib but not yet reported. We have five IO agents (nivolu-mab, pembrolizumab, atezolizumab, durvalumab and avel- umab) and at least three TKIs that will template well with them. These TKIs are axitinib, lenvatinib, and cabozantinib. Cabozantinib seems to be the most difficult to give in combination with an IO. Lenvatinib is also a bit tough to administer with an IO because of adverse effects, namely hypertension and significant diarrhea. Axitinib seems clinically easiest to combine but these are my own subjective opinions.

Q. What are your thoughts on first-line options at this point? Once again, how does your real-world experience line up with the data being presented?

Dr Vogelzang: We have participated in the phase 2 of pembrolizumab and lenvatinib, so this combination is a contender for first line. There were quality-of-life data presented at ASCO 2018 for atezolizumab and bevacizumab that were quite promising based on a presentation by Bernard Escudier. That should be considered as a first-line therapy whether or not the patient has undergone a nephrectomy. In addition there is the avelumab/axitinib combination, and then there is nivolumab and cabozantinib. We have seen promising results reported in the JAVELIN Renal 100 Study for avelumab plus axitinib. The safety profile of the combination avelumab plus axitinib in treatment-naive patients with advanced RCC seems to be manageable and consistent with that of each drug alone, and the preliminary data on antitumor activity are encouraging. This was reported by Toni Choueiri and his team in the *Lancet Oncology*. (Vol. 19:451–460; April 2018) A phase 3 trial is assessing avelumab and axitinib compared with sunitinib monotherapy.

Q. Is there a consensus on which of these combinations seems to have the inside track for first line therapy?

Dr Vogelzang: These are all established regimens now and it's very difficult to know which of them is best. When I am forced to, for one reason or another, I usually decide to use nivolumab and axitinib or nivolumab and cabozantinib. I do that because nivolumab is currently the only IO that is covered by insurance.

Q. Then to what extent are you using the ipi-nivo regimen?

Dr Vogelzang: So far I've only treated 2 patients because ipi-nivo is expensive, not covered by most 3rd parties and only recently was put on the NCCN compendium. Over-

all, the IO and TKI combinations have lived up to my expectations. As the experience has accumulated, we are all fairly convinced than an IO in combination—either IO-IO, IO-bevacizumab, or an IO-TKI is frontline, acceptable, and better.

Q. Is it safe to say there is little room now for monotherapy? That's a big change compared to two years ago.

Dr Vogelzang: Yes, two years ago, it was Sutent and Votrient for first line. But in the immunotherapy era, Votrient could not be combined, Sutent probably cannot be combined and as a result, they are now scrambling to find a place in second or third line therapy, with some exceptions.

Q. And what might those exceptions be?

Dr Vogelzang: The one that comes to mind is the situation I mentioned previously with the prisoner who came in with pain. In his case I did not want to wait for the IO-TKI combination to be approved. I needed to put out the fire right now. A TKI is still very appropriate upfront. In another case, I had a patient in severe respiratory distress from metastatic disease. I started him on axitinib as monotherapy and when he stabilized, I added nivolumab. Now he is out of danger but has grade 2 hypertension and diarrhea. This case underscores the limitations in some patients of using combinations.

Q. As we move further into the era of combinatorial therapy, do you envision the possibility that a much more clearly delineated treatment algorithm will emerge or will it continue to be appropriate choices, sometimes empirically determined, from a broad spectrum of regimens?

Dr Vogelzang: I do not foresee any clear-cut algorithm. The NCCN guidelines, for example, have always directed us to a potpourri of choices and that is not going to change. Each one of us sees a different spectrum of disease and each one of us sees a different level of acuity in each patient who walks in the door. My rationale is to get the ball rolling, so to speak, and put people on a TKI with a sample I have available. Once I have initiated therapy, I know their tumors will be slowing down. Then I will apply for reimbursement for nivolumab or ipi-nivo. The only drug I can apply for with success is nivolumab. Pembrolizumab is not indicated for monotherapy, nor is atezolizumab or avelumab. The only monotherapy is nivolumab among these agents. And I would add that a clinician who treats renal cell is generally pretty happy with nivolumab—achieving long term CRs and drug-free intervals. I've got about 20 patients who are in CR or off the drug.

Q. With ASCO 2018 behind us, what is at the top of your list as far as unresolved issues you would like to see addressed at future meetings?

Dr Vogelzang: I'd like to see some toxicity comparisons among the various combinations. Many of my colleagues say that the ipi-nivo regimen is much easier than most of us have been led to believe. And the reason for this is that the ipilimumab dose has been reduced from 3 mg/kg to 1 mg/kg in combination with nivolumab. Secondly, it's only four doses and nivolumab is then every four weeks. It may be that the ipi-nivo combination is the least toxic of all of these regimens. And yet, I would like to see proof of that.

Q. Have you seen any superiority among the combos in terms of complete responses?

Dr Vogelzang: I don't think any of the five combination regimens will be superior for CR. Reasonably, we will see CR differing—ranging from 5% to 20% in all of the combinations and the differences are likely just due to patient selection. Basically, all five of the combinations are quite effective, but we have to sort out their toxicities and we have to decide which one we can afford. If ipi-nivo is the best combination, it is also the most expensive and that is not a good thing. Unfortunately, none of the TKIs are going off patent in the near future so they remain expensive as well. KCJ

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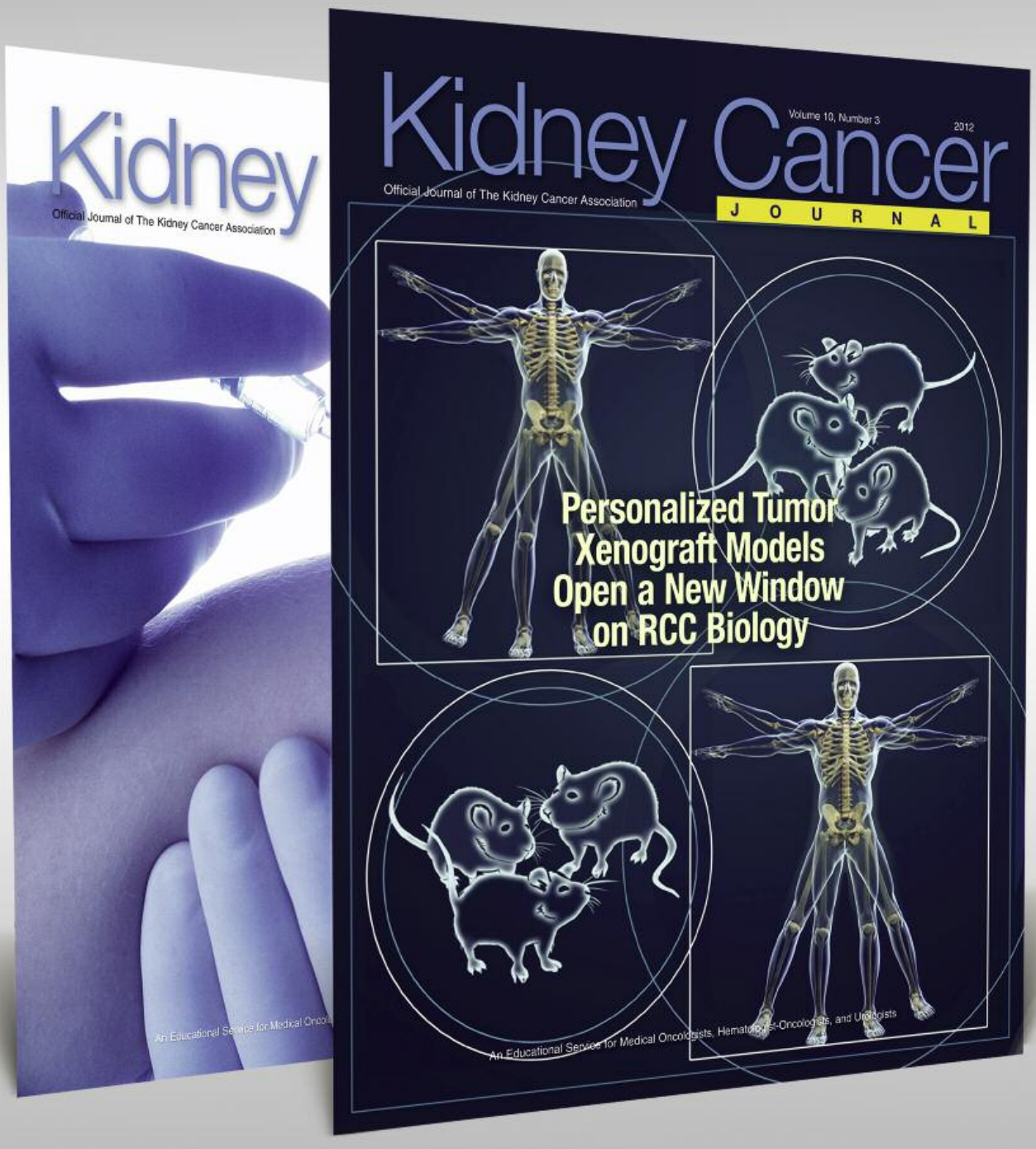

Controversies and Consensus Surrounding Initial Cytoreductive Nephrectomy vs Targeted Therapy: What Is the Optimal Approach?

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Few topics have generated as much controversy and debate as determining the optimal approach for cytoreductive nephrectomy in the targeted therapy era. Although the paradigm has been a moving target, with many reports taking opposing viewpoints, new population-based studies are closing in on a consensus. The debate is not going away soon, but clear guidelines are emerging.

Compared to the era of cytokine therapy, when the benefits of initial cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma (mRCC) were well established, the advent of targeted therapy has not only ushered in a new treatment paradigm, it has created a conundrum surrounding the role of CN, its timing, and related survival benefits. Here is the conundrum: In the targeted therapy era, recent reports have indicated declining utilization rates of CN; and yet, the most up-to-date guidelines from the National Comprehensive Cancer Network support the role of CN with targeted therapy (TT) in the appropriate clinical setting.[1]

Questions and quandaries about CN have been around for a long time so this is nothing new. However, as Molina et al posted in an analysis in the *Journal of Clinical Oncology,*[2] the current trajectory and confusion about the role of CN is alarming when one considers differences in overall survival between patients who did and did not undergo such surgery. For clinicians in the 1990s, a debate raged about the benefit of CN for patients who were subsequently treated with cytokine therapies, such as interleukin-2 or interferon-alfa (IFN-alpha-2a). But the debate was virtually laid to rest when two randomized trials comparing CN plus IFN-alpha-2a vs IFN-alpha-2a alone demonstrated a significant improvement in survival of patients with mRCC, thereby offering compelling evidence that CN should be the new standard in this setting. In the cytokine era, urologists and oncologists would evaluate every patient who presented with mRCC to determine whether they were an appropriate surgical candidate for CN before systemic therapy.

Why is that not true today, despite the evidence? For example, consider survival data for 13,000 patients from the National Cancer Data Base (NCDB)[3] that showed a median survival of 17.1 months for patients who underwent CN compared with 7.7 months for patients who did not. These results are markedly similar to what was found in the pivotal study by Flanigan et al[4] at the tail end of the cytokine era when median survival differences were compared for patients randomly assigned to receive CN.

CN Questioned in Era of Targeted Therapy

As phase 2 and phase 3 studies of targeted therapies (such as sunitinib and pazopanib, and sorafenib) suggested translational impact and radically changed the treatment paradigm, the success of these efforts began to undermine the rationale for upfront CN. Questions about the conventional wisdom of going to CN initially arose, namely:

- Does CN extend survival in the era of VEGF-targeted therapies?
- Should CN be performed before or after targeted therapy?

The era of targeted therapies has brought with it a wide range of other questions as well, and although these are beyond the scope of this paper, they reflect a more nuanced approach to the management of mRCC, including strategies that evaluate far more closely than was the case in the cytokine era various risk factors and a basis for stratification (favorable to intermediate to poor risk) that influences clinical decision making. As is the case with the rationale for using different approaches of targeted therapy, a somewhat similar line of thinking can be applied to the use of CN. And many recent reports highlight the extent to which these risk factors should be considered in delineating the role of CN.

Keywords: cytoreductive nephrectomy, initial, targeted therapy, CARMENA trial, SURTIME, IMDC risk criteria, NCCN guidelines, TKI.

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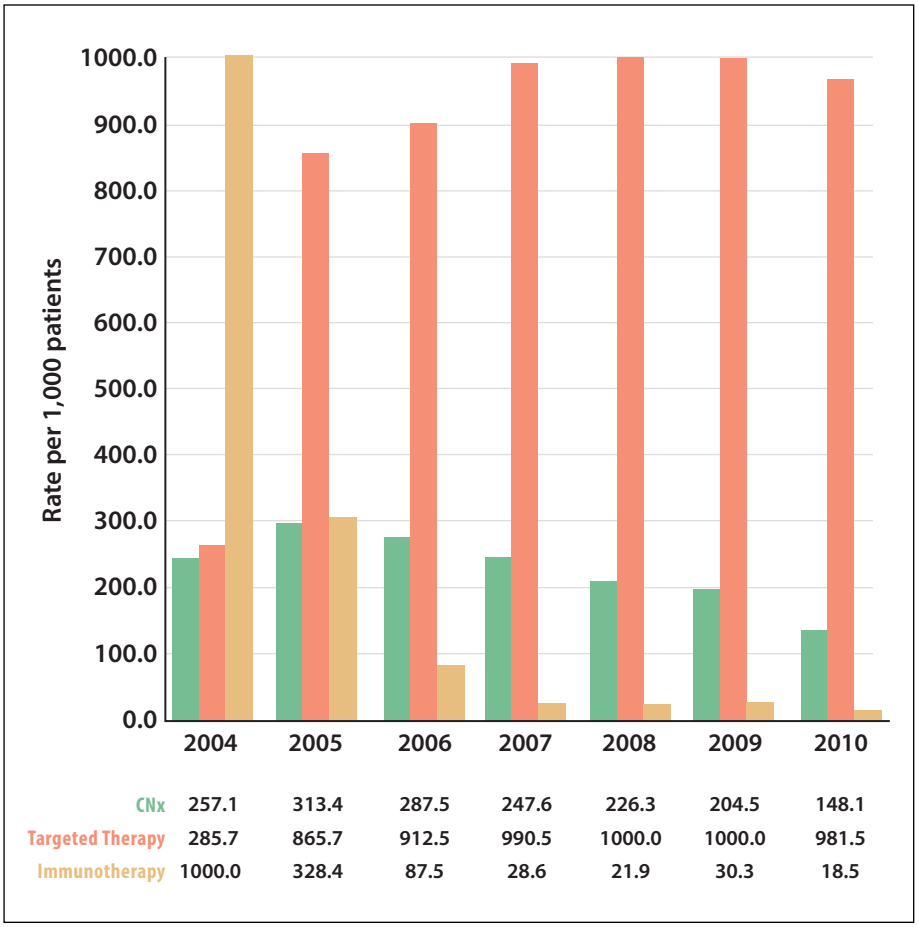

Figure 1. Trend use of cytoreductive nephrectomies. The annual number of cytoreductive nephrectomies (CNx) decreased between 2005 and 2010 by about 50%. This decline began when the use of targeted cancer therapies nearly tripled from 2004 to 2005.

There are hopeful signs, however, that new studies will more definitively address all of these issues. Two prospective randomized trials, the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA)[5] and the European Organisation for Research and Treatment of Cancer's Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer (SURTIME)[6] were designed to examine these issues. Still, the conundrum endures: there has been a decline observed in the number of CNs over the last 10 years, (**Figure 1**) a decline coinciding with the use of effective systemic medical therapy.[7-9] This is a decline that has occurred despite retro- spective reports showing that CN improves outcomes, including a meta-analysis concluding that CN reduces the risk of death in mRCC by more than 50%.[10-15]

In view of this confusing picture, and while we await results from studies like CARMENA and SURTIME, there are reports not only evaluating contemporary utilization rates of CN but examining the survival benefit of CN compared with non-CN patients treated with targeted therapy, and proposing risk stratification criteria to be followed. In their analysis of these risk factors, a new calculus has emerged to more clearly understand the benefits of CN in the targeted therapy era. Several conclusions can be made regarding use of CN in this context:

- Guidelines suggest that upfront CN should be considered in all patients with good to intermediate prognosis.
- Patients with rapidly progressing mRCC based on IMDC risk factor stratification (25% to 30%) are difficult to identify and yet, this is the group that should receive upfront targeted therapy or immunotherapy. There are ongoing efforts to identify these patients.
- The magnitude of benefit with CN in the targeted therapy era appears to be three times greater than what was observed in the cytokine era.
- As more therapies become available, PFS is likely to improve, and although total cures are not achievable, controlling the primary tumor in the retroperitoneum will become more important.

Beyond these key conclusions, the narrative on the use of CN has become more nuanced, especially with regard to a myriad of considerations related to risk factor stratification and the timing of CN. Recent reports highlight how thinking has evolved, helping to pave the way for new data hopefully to be obtained by studies like CARMENA and SURTIME. One of the important considerations in sorting through the nuances affecting clinical decision making is how various prognostic models have changed in the era of targeted therapy. Many of the existing models, such as the MSKCC and IMDC scoring systems were created for treatment of mRCC with cytokines.[16]

The most widely used scoring system is from MSKCC. Adverse prognostic factors in this model are:

- Interval from diagnosis to treatment of <1 year.
- Karnofsky performance status (KPS) of <80%.
- Serum lactate dehydrogenase levels >1.5 times the upper limit of normal.
- Corrected serum calcium >10 mg/dL.
- Serum hemoglobin less than the lower limit of normal.
- Previous radiotherapy.
- >1 metastatic site.

The adverse prognostic factors for OS in the IMDC model include:

- Anemia, thrombocytosis, neutrophilia.
- KPS <80%
- <1 year from diagnosis to first-line targeted therapy

Drilling Down into the CARMENA Trial: Let's Reassess Its Methodology and Preserve the 'Window of Opportunity' for Cytoreductive Nephrectomy

An analysis by Michael L. Blute, Sr., MD

The development of targeted, non-surgical cancer therapies has led some physicians to question cytoreductive nephrectomy—surgery to remove the primary tumor—as the standard of care for metastatic renal cell carcinoma patients. Since the advent of targeted cancer therapies in the mid-2000s, there has been a 50% reduction in the number of cytoreductive nephrectomies. A review of the NCCDB showed that currently only three out of ten patients with metastatic kidney cancer undergo cytoreductive nephrectomy.

Improved systemic effectiveness and markedly increased tolerability compared to cytokine therapy has resulted in targeted therapy as front line therapy; however, it clouds the role of cytoreductive nephrectomy in patients with metastasis. The standard of care has shifted away from cytoreductive nephrectomy in the absence of level 1 evidence for its cancer survival benefit in the targeted therapy era. Abandoning cytoreductive nephrectomy as a standard of care should be viewed with concern.

Even with the advent of new agents, studies continue to suggest that a combination of surgery and targeted therapy produces the best outcome for patients. Two preliminary reports in 2011[1,2] suggested a benefit from cytoreductive nephrectomy before the initiation of targeted therapy. The first report showed that median survival was 21.6 months for patients undergoing cytoreductive nephrectomy and targeted therapy (sunitinib or sorafenib), vs. 13.9 months for patients undergoing targeted therapy alone. However, the differences were not statistically significant due to small sample size. The second report, with larger sample size, showed that median survival was 19.8 months for the group undergoing cytoreductive nephrectomy combined with targeted therapy and 9.4 months for patients treated with targeted therapy (sunitinib, sorafenib, or bevacizumab) alone.

Although targeted therapies are effective (**Figure 2**) and usually well-tolerated by patients, they are not a cure. Another concern is that many tumors eventually develop resistance to targeted therapies. Theoretically, surgically removing the primary tumor reduces the tumor burden, diminishes the primary tumor's suppression of the immune system and can delay disease progression by removing growth promoters and angiogenic factors. If you treat with targeted therapy alone and the disease progresses, you may put patients out of the window of opportunity where the surgery has a great impact. The major concern is to identify patients who will not benefit with cytoreductive nephrectomy as up to 17-20% of patients with metastatic disease will rapidly progress. Improved understanding of risk factors, surgical indication and overall health of patients will improve patient selection. Ultimately, molecular signals may help personalize options for these patients.

Sunitinib Alone or After Nephrectomy in Metastatic Renal-Cell Carcinoma?

The results of the 450-patient CARMENA Trial were reported by Méjean et al.[3] This trial demonstrates that sunitinib alone was not inferior to the addition of surgery in patients who present with stage IV disease. This was an intention to treat analysis wherein not all patients received the assigned treat-

Patients who received CN have also been reported to have better IMDC prognostic profiles for OS; patients with <4 IMDC prognostic factors were found likely to benefit from CN.[17] A number have found significantly longer OS associated with previous CN.[18-22] Despite these results, a countervailing trend has emerged in the literature with regard to the probability that CN will be performed in the targeted therapy era. Psutka et al filled in some gaps in the literature by analyzing trends in national practice patterns in their study regarding the uptake of targeted therapies and their impact on CN rates at a time when these associations were poorly described. One of the areas sparsely covered concerns the use of different targeted therapies in conjunction with CN among younger, pre-Medicare-aged patients. This is the group that could benefit the most from multimodal treatment .[17]

Characterizing trends observed between 2004 to 2010, when the annual rate of targeted therapy utilization increased markedly from 10% to 98.2%, Psutka et al found a considerable decline in the utilization of CN. Among the key findings:

- Lower rates of CN were observed in women.
- Increasing age was inversely related to receipt of CN, even among the cohort of younger patients.

Intuitively, the authors suggest that physicians perceive targeted therapy as less morbid than CN and thus are less likely to recommend surgery. Despite retrospective data on the relative safety of performing CN after neoadjuvant targeted therapy, more study is needed to generate compelling data in this regard for the targeted therapy era. Nevertheless, there already are data from the clinical trials that led to the approval of the targeted agents.

The benefit of these therapies was demonstrated in patients who, overwhelmingly, had undergone prior CN.[7] Subsequently, and much further into the experience with targeted therapies, observational data from two large European studies suggest that CN is independently associated with improved survival in mRCC patients undergoing treatment with targeted therapy—and this was after an adjustment for prognostic factors.[12,23] Delineating strategies to include the use of established drugs and po-

ment and accrual was slow over an 8-year interval but nonetheless, there was statistically significant improvement in overall clinical benefit in patients who did not undergo nephrectomy. This is the second of two highly anticipated randomize controlled trials of timing of cytoreductive nephrectomy (CN) in the targeted therapy (TT) era.[4] Both study trials failed to achieve original estimated enrollment. This is mainly due to patient non-compliance to randomization.[5]

These randomized control trials have proven to be in contrast to large data sets that seem to demonstrate an overall survival benefit to multimodal therapy. For instance, in a recent national cancer data base study of over 15,000 patients., more patients completed multimodal therapy with initial CN and achieved significantly improved overall survival compared with patients who had initial TT.[6] However, patients who underwent initial targeted therapy and subsequent cytoreductive nephrectomy appeared to have comparable overall survival outcomes. The current CARMENA trial is remarkable for inclusion of the highest risk groups, i.e. 55% Memorial Sloan Kettering (MSK) intermediate risk and 44% MSK poor risk. In addition, 70% of the nephrectomy/sunitinib group was tumor stage T-3 or T-4 vs 51% of the sunitinib alone group. In addition, 30% of the nephrectomy/sunitinib group had cN+ designation versus only 19% of the sunitinib alone group. MSKCC poor risk grouping, clinical T3 or 4 disease and evidence of lymphadenopathy are all identified as poor selection factors for patients to undergo CN.

According to the MD Anderson Cancer Center, low albumin, high lactate dehydrogenase, tumor stage-clinical T3 or T4, nodal stage cN+, symptoms at presentation, and liver metastasis aide in identifying patients that will profit the most from cytoreductive nephrectomy.[7] Specifically, patients with three or fewer adverse prognostic factors based on each of these stratifications are likely to draw greater benefit from cytoreductive nephrectomy. The indication for surgical treatment in metastatic renal cell cancer remains a difficult decision. The potential for survival benefit must be measured against the morbidity of an aggressive surgical procedure. It is clear that metastatic risk group stratification is important and close attention to adverse prognostic findings would seem to mean that patients with poor risk features should not receive initial cytoreductive nephrectomy. Patients with excellent performance and low volume metastasis remain candidates for CN followed by surveillance, TT or judicious consideration for metastasectomy.

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sition the role of CN within the framework of a stepwise approach, Choueiri and Motzer[24] presented an algorithm in their paper on the use of systemic therapy. Published in 2017 this report touts the advantages offered by combinatorial strategies, including the use of immunotherapy combinations. Nevertheless, the algorithm favors consideration of CN as the initial step in management.

Other recent papers have more directly addressed the utilization of CN as they evaluated utilization rates and examined the survival benefit of CN compared with non-CN patients treated with targeted therapy. Using the National Cancer Data Base to identify patients with mRCC treated in the targeted therapy era, Hanna et al[3] unpacked data from information gathered on 15,390 patients. Highlights from their results:

- As might be expected, patients who were younger, privately insured, treated at an academic center, and had a lower tumor stage and cN0 disease were more likely to undergo CN.
- CN use was stable between 2006 and 2012; performance was relatively seldom in approximately 3 of 10 patients with mRCC treated with targeted therapy.
- Significantly, the median OS of CN vs non-CN patients was 17.1 vs 7.7 months.
- In an adjustment analysis to consider other covariates, CN patients had a lower risk of any death (hazard ratio, 0.45, $P<.001$).

Lower Rate of CN Is Worrisome

In parsing their data, and observing some distinctions between their results and other papers, Hanna et al[3] suggest some disturbing trends in utilization of CN. One observation was that the overall rate of CN observed in their study (approximately 30%) was lower than the overall rate reported from centers of excellence (approximately 58% to 85%). If one extrapolates the data further, there is additional reason for concern, especially because the NCDB data are based on a sample of patients treated by cancer-accredited programs with a minimum threshold of 100 cases per year. The worrisome aspect, the authors suggest, is due to the disparity in rates that may be inferred from the academic setting to what is being utilized in the general population. It may be that the underuse of CN in the community setting may be even greater than

we suspect. The study also alludes to but does not directly address the issue of timing of CN in the targeted therapy era (See the report in this section on the results from CARMENA presented at the 2018 ASCO sessions). In the study by Hanna et al,[3] patients who underwent CN after targeted therapy had better OS compared with those who underwent CN before targeted therapy. However, these results with regard to timing should be regarded cautiously because there were limited data on how clinicians opted to administer targeted therapy—before or after CN.

Still another issue addressed by Hanna et al is of overriding importance—namely, the impact of risk stratification criteria. As they report, careful patient selection remains critical in determining if patients will benefit from CN:

- Patients with poor survival outcomes or those with rapidly progressing disease are less likely to benefit from CN. This confirms a much earlier report in 2011 by Choueiri et al[25] who found that patients with poor risk features (according to the IMDC criteria) did not benefit from CN.
- The National Comprehensive Cancer Network (NCCN) has formalized guidelines on the likelihood of CN benefit. Those likely to benefit include patients with lung-only metastases, good prognostic features, and good performance status.

Timing: Initial CN or Deferred? What Is the Optimal Sequence?

The debate over the optimal sequence of CN has continued unremittingly in the last few years, and results emerging in 2018, however, have begun to more clearly delineate at least some aspects of the discussion as efforts remain underway to produce a consensus. Results from the 2017 European Society of Medical Oncology[26] and two reports in 2018[27,28] contribute substantially to an improved understanding regarding the benefits of CN.

Treating primary tumors by administering targeted therapy with sunitinib prior to cytoreductive nephrectomy (CN) did not improve the progression-free rate at 28 weeks over a sequence of immediate CN followed by sunitinib in patients with synchronous metastatic renal cell carcinoma (mRCC), according to findings presented by Axel Bex, MD, Surgical Oncology-Urology, The Netherlands Cancer Institute in Amsterdam, Netherlands and colleagues.[26] They investigated whether the outcome after sequential cytoreductive nephrectomy (CN) followed by targeted therapy with sunitinib could be improved with the opposite sequence. They randomized 99 patients with mRCC to immediate CN followed by sunitinib (n=50) versus three cycles of sunitinib followed by CN plus sunitinib (n=49). The study (EORTC 30073 SURTIME NCT01099423) included patients with histologically confirmed clear-cell subtype, and a resectable asymptomatic primary tumor plus 3 or fewer surgical risk factors. Due to poor accrual (and that is a fundamental flow in this study), it was decided to report the progression-free rate (PFR) at week 28 as the primary endpoint, which required 98 patients, instead of median progression-free survival, which required 380 events to detect a 3-month increase.

At a median follow-up of 3.3 years, 46 of 50 patients underwent CN in the immediate CN arm and 40 of these patients had received post-CN sunitinib. In the deferred CN arm, 48 of 49 patients had been treated with sunitinib prior to CN; of these patients, 40 underwent CN and 26 also received post-CN sunitinib. No significant difference between the treatment sequence was observed in PFR, which was 42.0% (95% confidence interval [CI] 28.2, 56.8) versus 42.9% (95% CI 28.8, 57.8) in the immediate and deferred arms, respectively ($P > 0.99$)

One of the conundrums to emerge in the targeted therapy era is our lack of level 1 evidence for CN. The evidence has been equivocal and the need for consensus has become imperative. While one study compared the sequence of CN and targeted therapy among patients who received both therapies,[3] in clinical practice not all patients undergoing initial CN will receive subsequent targeted therapy; and not all patients undergoing targeted therapy will undergo subsequent CN.[28] Other variations on this theme have also been observed, further suggesting how practice patterns can diverge. In retrospective studies, for example, approximately one-third of patients did not receive targeted therapy after initial CN, according to the analysis by Bindhi et al. To what extent is targeted therapy administered in a timely fashion? Several reports indicate that approximately 40% received targeted therapy in a timely manner (defined as within 60 days of CN). If this picture seems confusing as to consistency of approaches, then consider that in single-arm trials, 30-40% of patients initially treated with a tyrosine kinase inhibitor prior to planned CN actually underwent sub- sequent surgery.

> "Although more level 1 evidence for the use of initial CN in the era of targeted therapy is still needed, a consensus is taking shape from large analyses of population-based data. Initial CN is underutilized, particularly in non-academic centers where this underuse contributes to inferior survival among patients who present with mRCC."

For proponents of initial CN followed by targeted therapy, two current studies offer supporting if not compelling evidence. A population-based cohort in patients over age 665 from the Surveillance, Epidemiology, and End Results registries served as the starting point for an analysis by Macleod et al.[27] Strategies were categorized by initial treatment and linked with Medicare claims from 2006 to 2011. Results were accrued from 537 patients' 190 had initial CN followed by targeted therapy and 347 had initial targeted therapy. Median OS in the initial CN group was 17.4 months compared with 9.2 months for initial targeted therapy.[31]

The second study to focus on similar questions identified patients in the NCDB diagnosed from 2006-2013

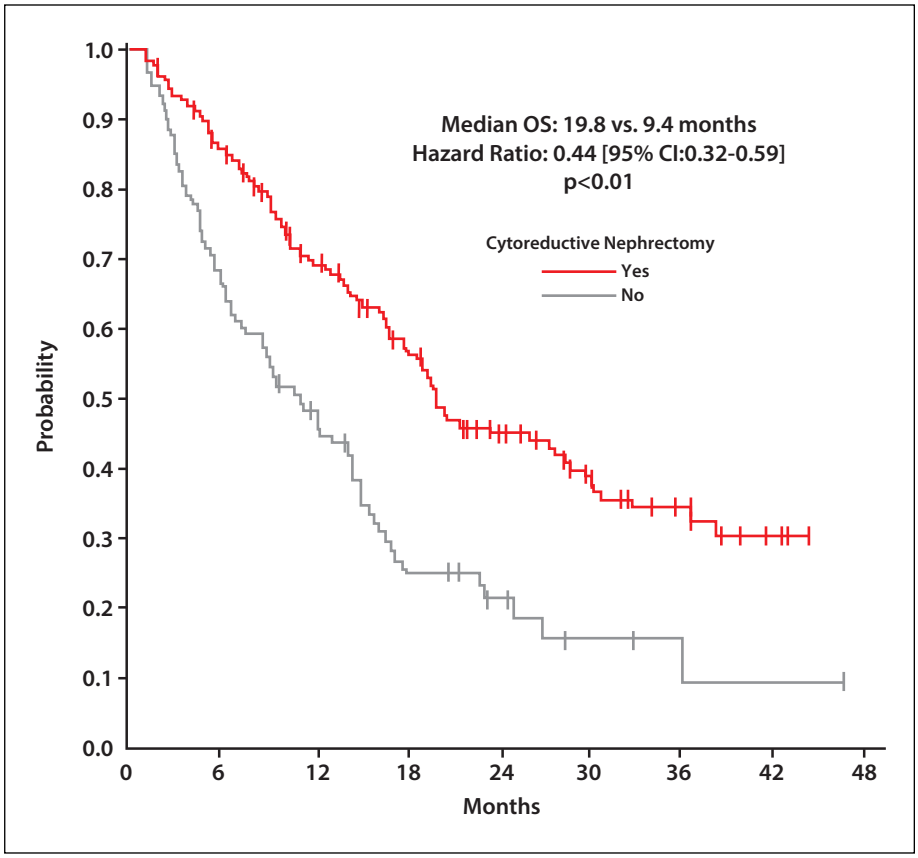

Figure 2. Overall survival of patients who did or did not receive cytoreductive nephrectomy in patients receiving TK1 Therapy ERA. This graph depicts overall survival from initiation of VEGF (Vascular endothelial growth factor) targeted therapy for 314 patients who did or did not receive cytoreductive nephrectomy. The median survival for those who received CN was 19.8 months compared to 9.4 months for those who did not receive CN.

with kidney cancer.[28] The report by Bindhi et al had OS as its primary outcomes with secondary outcomes that included receipt of targeted therapy after initial CN, and CN after initial targeted therapy, with death prior to receipt of the second treatment as a competing risk. The data base included 15,068 patients; 6,7731 underwent initial CN and 8,337 underwent targeted therapy. The key results:

- At 6 months after initial CN, 48% received targeted therapy; 15.3% had died after receiving initial CN prior to receiving targeted therapy.
- At 6 months after initial targeted therapy, 4.7% underwent CN, with 44.9% having died after initial targeted therapy prior to moving on to CN.
- Initial CN was associated with improved OS compared to initial targeted therapy (median 16.5 months vs 9.2 months, *P*<0.001).

The finding that initial CN was associated with an improved OS can best be explained by the greater likelihood that patients will receive multimodal therapy. Regardless of which initial strategy was adopted, both were associated with delays in receipt or non-receipt of the second therapy. This finding points toward the need for a greater effort to ensure the delivery of multimodal therapy to these patients[28] The paper by Bindhi et al is particularly important in view of the failure of SURTIME to deliver what was expected: a trial evaluating the sequencing of CN and targeted therapy that closed prematurely due to poor accrual. SURTIME, however, did demonstrate no difference in PFS between the two approaches at 28 weeks. Underscoring the importance of careful patient selection in deciding initial treatment for mRCC, Bindhi et al point to earlier studies which found no benefit to CN in patients with poor-risk disease or poor performance status. If initial targeted therapy is to be pursued, then its rationale needs to be closely examined. This rationale should include assessing the biological responsiveness of the cancer to systemic treatment and using treatment response to assist with patient selection for subsequent CN. The authors describe such assessment as a "litmus test".

Conclusion

Although more level 1 evidence for the use of initial CN in the era of targeted therapy is still needed, a consensus is taking shape from large analyses of population-based data. Initial CN is underutilized, particularly in non-academic centers where this underuse contributes to inferior survival among patients who present with mRCC. It is important for medical oncologists and urologists to seriously consider CN for every patient who presents with mRCC. The choice of an appropriate option should be in accordance with guidelines established by the NCCN and should reflect careful evaluation of risk stratification. Patients with favorable to intermediate risk constitute the group with the greatest likelihood of benefiting from initial CN.

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tourin Cancer. 2018 May 4; pii: S1558-7673(18)30136-8. doi: 10.1016/j.clgc.2018.04.005.
Summary: This analysis reported benchmarks for clinical outcomes on the basis of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups for patients treated with sunitinib for mRCC in a first-line setting. A retrospective analysis was performed on data from sunitinib-treated patients (n = 375) in the pivotal phase III trial of sunitinib versus interferon- as first-line treatment for mRCC. Objective response rates (ORRs) were determined from independently reviewed radiologic assessments. Median PFS (95% confidence interval [CI]) was 14.1 (13.4-17.1), 10.7 (10.5-12.5), 2.4 (1.1-4.7), and 10.6 (8.1-10.9) months in sunitinib-treated patients in the IMDC favorable (n = 134), intermediate (n = 205), poor (n = 34), and intermediate + poor (n = 239) risk groups, respectively. Median OS (95% CI) was 23.0 (19.8-27.8), 5.1 (4.3-9.9), and 20.3 (16.8-23.0) months in sunitinib-treated patients in IMDC intermediate, poor, and intermediate + poor risk groups, respectively, and was not reached in the favorable risk group (>50% of patients were alive at data cutoff). ORRs were 53.0%, 33.7%, 11.8%, and 30.5% in sunitinib-treated patients in IMDC favorable, intermediate, poor, and intermediate + poor risk groups, respectively.
Conclusion: This retrospective analysis showed differences in patient outcomes for PFS, OS, and ORR on the basis of IMDC prognostic risk group assignment for patients with mRCC.

Phase 1 trials of anti-ENPP3 antibody drug conjugates in advanced refractory renal cell carcinomas. Thompson JA, Motzer RJ, Molina AM, et al. *Clin Cancer Res*. 2018 May 30; pii: clincanres.0481.2018. doi: 10.1158/1078-0432.CCR-18-0481.
Summary: The study determined the safety, pharmacokinetics, and recommended phase 2 dose of an antibody drug conjugate (ADC) targeting ectonucleotide phosphodiesterases-pyrophosphatase 3 (ENPP3) conjugated to monomethyl auristatin F (MMAF) in subjects with advanced RCC. Two phase 1 studies were conducted sequentially with 2 ADCs considered equivalent, hybridoma derived AGS-16M8F and Chinese Hamster Ovary derived AGS-16C3F. AGS-16M8F was administered intravenously every 3 weeks at 5 dose levels ranging from 0.6 to 4.8 mg/kg until unacceptable toxicity or progression. The study was terminated before reaching the maximum tolerated dose (MTD). A second study with AGS-16C3F started with the AGS-16M8F bridging dose of 4.8 mg/kg given every 3 weeks. The AGS-16M8F study (n=26) closed before reaching the MTD. The median duration of treatment was 12 weeks. One subject had durable partial remission (PR) (83 weeks) and 1 subject had prolonged stable disease (48 weeks). In the AGS-16C3F study (n=34), the protocol defined MTD as 3.6 mg/kg but this was not tolerated in multiple doses. Reversible keratopathy was dose limiting and required multiple dose de-escalations. The 1.8 mg/kg dose was determined to be safe and was associated with clinically relevant signs of antitumor response. Three of 13 subjects at 1.8 mg/kg had durable PRs (range 100-143 weeks). Eight (8) subjects at 2.7 mg/kg and 1.8 mg/kg had disease control after 37 weeks (37.5 - 141 weeks).
Conclusion: AGS-16C3F was tolerated and had durable antitumor activity at 1.8 mg/kg every 3 weeks.

Radium-223 dichloride in combination with vascular endothelial growth factor-targeting therapy in advanced renal cell carcinoma with bone metastases. McKay RR, Bossé D, Gray KP, et al. *Clin Cancer Res*. 2018 May 30; pii: clincanres.3577.2017. doi: 10.1158/1078-0432.CCR-17-3577.
Summary: This study investigated the biologic activity of radium-223 with vascular endothelial growth factor (VEGF)-targeted therapy in patients with advanced RCC and bone metastases. Fifteen treatment-naïve patients (n=15) received pazopanib 800 mg orally once-daily and 15 previously-treated patients received sorafenib 400 mg orally twice-daily. Radium-223 55 kilobecquerel/kg was administered concurrently every four weeks for up to 6 infusions in both cohorts. The primary endpoint was decline in bone turnover markers (Procollagen I Intact N-Terminal, N-telopeptide, C-telopeptide, osteocalcin and bone-specific alkaline phosphatase) compared to baseline. Secondary endpoints included safety, rate of symptomatic-skeletal event (SSE) and time to first SSE, objective response rate, change in analgesic use and quality of life. Exploratory analysis of tumor genomic alterations was performed. Of the 30 patients enrolled, 83% had IMDC intermediate- or poor-risk disease, 33% had liver metastases and 83% had a history of SSE prior to enrolment. No dose-limiting toxicity was observed. All bone turnover markers significantly declined from baseline at week 8 and 16. Forty percent of patients experienced treatment-related grade ≥3 adverse events. Response rates were 15% and 18% per RECIST v1.1 and bone response was 50% and 30% per MD Anderson criteria, in the pazopanib and sorafenib cohort, respectively. Median SSE-free interval was 5.8 months and not reached, respectively. Analgesic use remained stable over the study time.
Conclusion: Radium-223 combined with VEGF-targeted therapy is biologically active and safe. Randomized-controlled trials are needed to define the role of radium-223 in advanced RCC with skeletal metastases. KCJ

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targeted therapy (TT) following cytoreductive nephrectomy for metastatic renal cell carcinoma (mRCC) is not associated with worse survival, according to findings presented at the American Urological Association 2018 annual meeting. In a retrospective observational study that included 2716 patients with mRCC treated with both cytoreductive nephrectomy and TT, Solomon Woldu, MD, of the University of Texas Southwestern Medical Center in Dallas, and colleagues found that the risk of death among patients with moderately delayed, delayed, and late TT did not differ significantly from patients who had early TT. The investigators defined TT delivered within 2 months of mRCC diagnosis as early (1255 patients, 46.2%). They considered TT delivered in 2 to 4 months, 4 to 6 months, and more than 6 months to be moderately delayed (1072 patients, 39.5%), delayed 284 patients, 10.5%), and late (105 patients, 3.9%), respectively. The median time from mRCC diagnosis to initiation of TT was 2.1 months.

The investigators acknowledged that their study is limited by the study design and potential selection bias, but noted that the findings are consistent with the idea that, among carefully selected patients, initial observation might not compromise outcomes.

Partial vs radical nephrectomy lowers elderly patient mortality risk

SAN FRANCISCO—Compared with radical nephrectomy (RN), partial nephrectomy (PN) for small renal tumors in elderly patients is associated with a lower risk of cancer-specific and other-cause mortality, researchers reported at the American Urological Association 2018 annual meeting.

Using 2004–2014 data from the Surveillance, Epidemiology and End Results (SEER) registry, Michele Marchioni, MD, of SS Annunziata Hospital "G.D'Annunzio" University of Chieti, Chieti, Italy, and colleagues identified 4541 surgically treated patients aged 75 years or older who had non-metastatic pT1a renal cell carcinoma. After they matched 1 RN to 1 PN patient by propensity score, the investigators had a study cohort of 2826 patients.

In multivariate analysis, PN was associated with a sig-"nificant 36% and 33% decreased risk of cancer-specific and other-cause mortality, respectively. The investigators found no difference in 30-day mortality risk. The authors concluded that PN should be given strong consideration in the treatment of small renal tumors, even for elderly patients.

Global kidney cancer drugs market forecast for 2017-2025

DUBLIN—The global kidney cancer drug market was valued at US$ 3,302.3 million in 2016, and is expected to reach US$ 6,441.9 million by 2025, expanding at 8.1% from 2017 to 2025, according to data from ResearchAndMarkets.com

The incidence of renal cell cancer is observed highest in Northern America and Europe. Almost 59% of kidney cancer cases are observed in developed countries. Thus, rising incidence of kidney cancer and entry of novel drug treatments are the key factors contributing to the growth of the kidney cancer drug market. Sutent dominates the global kidney cancer/renal cell carcinoma drugs market. North America dominates the global kidney cancer drugs market followed by Europe.

Rise in incidence of renal cancer, increasing geriatric population and novel drug treatment are key drivers for the growth of the kidney cancer drug market in North America. Asia Pacific is the fastest growing regional market for kidney cancer drugs with the highest compound annual growth rate in the forecast period. Improvements in diagnostic technology, a rise in aged population and low cost production of drugs are some of the key factors contributing to the growth of the market in the Asia Pacific region. KCJ

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landmark trial? Not so fast, and here's why.

Let's not rush to judgement on this issue. In his enthusiasm to usher in the results of this trial, the lead author of CARMENA, Arnaud Mejean, MD, a urologist at the Department of Urology, Hôpital Européen Georges-Pompidou - Paris Descartes University in Paris, said: ."Our study is the first to question the need for surgery in the era of targeted therapies and clearly shows that surgery for certain people with kidney cancer should no longer be the standard of care." The pitfall lies in the propensity to extrapolate the results to a segment of the patient population for which CN may still be the standard of care, and this needs to be emphasized. These pitfalls are expertly described in an Editorial in a June issue of the *New England Journal of Medicine (*Motzer RJ, Russo P. Cytoreductive nephrectomy—patient selection is key. *N Engl J Med*. DOI: 10.1056/NEJMe1806331).

As Motzer and Russo point out, interpretation of the results is complicated for a number of reasons. Although CARMENA is pivotal and will soon be followed by other reports addressing the same questions, Motzer and Russo drill down into its data and methodology and enable us to question assumptions some observers have made and clarify its implications. One caveat: a slow and incomplete enrollment over 8 years at 79 centers in Europe raises the possibility that many centers saw few patients with stage IV disease. Or, when surgeons saw patients with intermediate-risk disease who were likely to benefit from combination therapy, they were unwilling for them to undergo randomization and instead treated them outside the trial.

The Editorial delves into other considerations possibly confounding the results, all of which serve to call us back to fundamental standards of care, namely, not to abandon nephrectomy but instead carefully select patients undergoing nephrectomy on the basis of published and well recognized risk models.

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