Volume 9, Number 2 2011

Kidney Cancer JOURNAL

Official Journal of The Kidney Cancer Association

ASCO 2011 Highlights & Abstracts

Chemotherapy for CNS Metastases in RCC

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

In the treatment of advanced RCC

When prognostic risk is high —let evidence chart the course

Important Safety Information

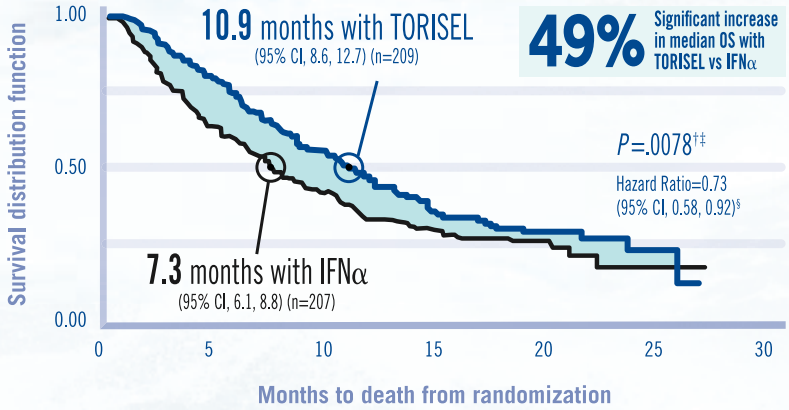
- TORISEL is contraindicated in patients with bilirubin >1.5 x ULN and should be used with caution when treating patients with mild hepatic impairment (bilirubin >1 - 1.5 x ULN **or** AST >ULN but bilirubin ≤ULN). If TORISEL must be given to patients with mild hepatic impairment, reduce the dose of TORISEL to 15 mg/week. In a phase 1 study, the overall frequency of ≥grade 3 adverse reactions and deaths, including deaths due to progressive disease, was greater in patients with baseline bilirubin >1.5 x ULN.
- Hypersensitivity/infusion reactions, including flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity and anaphylaxis, may occur very early in the first infusion or with subsequent infusions. Pretreat with an H_1 antihistamine. TORISEL infusion should be interrupted in patients with infusion reactions and appropriate therapy given.
- Serum glucose, serum cholesterol, and triglycerides should be tested before and during TORISEL treatment.
  - TORISEL is likely to result in hyperglycemia and hyperlipemia. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy and/or lipid-lowering agents, respectively.
- TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections.
- Cases of interstitial lung disease, some resulting in death, have occurred. Some patients were asymptomatic or had minimal symptoms. Patients should undergo baseline radiography prior to TORISEL therapy and periodically thereafter, even in the absence of clinical respiratory symptoms. Follow patients closely and, if clinically significant respiratory symptoms develop, consider withholding TORISEL until recovery of symptoms and radiographic improvement of pneumonitis findings. Some patients required TORISEL discontinuation and/or treatment with corticosteroids and/or antibiotics.
- Cases of fatal bowel perforation occurred with TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen.
- Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL.
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period.
- Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.
- Live vaccinations and close contact with those who received live vaccines should be avoided.
- TORISEL may cause fetal harm. Patients and their partners should be advised to avoid pregnancy throughout treatment and for 3 months after TORISEL therapy has stopped.
- Elderly patients may be more likely to experience certain adverse reactions, including diarrhea, edema, and pneumonia.

Powerful 1st-line evidence—TORISEL significantly extended overall survival in poor-risk patients

TORISEL® (temsirolimus) injection

Powerful evidence

Median overall survival (OS)* results—TORISEL vs IFNα[1]



Results from a phase 3, multicenter, 3-arm, randomized, open-label study conducted in 626 previously untreated patients with advanced RCC.[1] Patients received TORISEL (25 mg IV weekly) or IFNα (maximum 18 MU SubC 3 times weekly).[2]

- Studied 1st-line in patients with ≥3 of 6 preselected prognostic risk factors[1‖]
- Median duration of treatment was 17 weeks (range 1 - 126 weeks) for the TORISEL arm and 8 weeks (range 1 - 124 weeks) for the IFNα arm[1]

TORISEL has a Category 1 NCCN recommendation *specific* to poor-risk patients as 1st-line treatment in advanced RCC.[3]

TORISEL is indicated for the treatment of advanced renal cell carcinoma.[1]

- The most common (incidence ≥30%) adverse reactions observed with TORISEL are: rash (47%), asthenia (51%), mucositis (41%), nausea (37%), edema (35%), and anorexia (32%). The most common laboratory abnormalities (incidence ≥30%) are anemia (94%), hyperglycemia (89%), hyperlipemia (87%), hypertriglyceridemia (83%), elevated alkaline phosphatase (68%), elevated serum creatinine (57%), lymphopenia (53%), hypophosphatemia (49%), thrombocytopenia (40%), elevated AST (38%), and leukopenia (32%).
- Most common grades 3/4 adverse events and laboratory abnormalities included asthenia (11%), dyspnea (9%), hemoglobin decreased (20%), lymphocytes decreased (16%), glucose increased (16%), phosphorus decreased (18%), and triglycerides increased (44%).
- Pleural effusion, hemodynamically significant pericardial effusions requiring intervention, convulsions, rhabdomyolysis, Stevens-Johnson Syndrome, complex regional pain syndrome and extravasations have been reported during postmarketing use.
- Strong inducers of CYP3A4/5 (eg, dexamethasone, rifampin) and strong inhibitors of CYP3A4 (eg, ketoconazole, atazanavir) may decrease and increase concentrations of the major metabolite of TORISEL, respectively. If alternatives cannot be used, dose modifications of TORISEL are recommended.
- Avoid St. John's Wort which may decrease TORISEL plasma concentrations, and grapefruit juice which may increase plasma concentrations of the major metabolite of TORISEL.
- The combination of TORISEL and sunitinib resulted in dose-limiting toxicity (Grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization).

Please see the brief summary of the full Prescribing Information on the next page.

RCC=renal cell carcinoma. IFNα=interferon alpha. CI=confidence interval. NCCN=National Comprehensive Cancer Network.
*Time from randomization to death.
† A comparison is considered statistically significant if the *P*-value is <.0159 (O'Brien-Fleming boundary at 446 deaths).
‡ Based on log-rank test stratified by prior nephrectomy and region.
§ Based on Cox proportional hazard model stratified by prior nephrectomy and region.
‖ Prognostic risk factors included: <1 year from time of initial RCC diagnosis to randomization, Karnofsky Performance Status of 60 or 70, hemoglobin <lower limit of normal, corrected calcium >10 mg/dL, lactate dehydrogenase >1.5 x upper limit of normal, >1 metastatic organ site.

References: 1. TORISEL® Kit (temsirolimus) Prescribing Information. June 2011. **2.** Data on file, Pfizer Inc. **3.** National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: kidney cancer. V.2.2011.

TRS00330/290053

July 2011

Pfizer Oncology

TORISEL® Kit

[tor-a<sel]
(temsirolimus) injection

℞ **only**

FOR INTRAVENOUS ADMINISTRATION

Brief Summary of Prescribing Information

This product's label may have been revised after this insert was used in production. See package insert for full Prescribing Information. For further product information and current package insert, please visit www.wyeth.com or call our Medical Communications Department toll-free at 1-800-934-5556.

INDICATIONS AND USAGE

TORISEL is indicated for the treatment of advanced renal cell carcinoma.

CONTRAINDICATIONS

TORISEL is contraindicated in patients with bilirubin >1.5 x ULN.

WARNINGS AND PRECAUTIONS

Hepatic Impairment: The safety and pharmacokinetics of TORISEL were evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment. Patients with baseline bilirubin >1.5 x ULN experienced greater toxicity than patients with baseline bilirubin ≤1.5 x ULN when treated with TORISEL. The overall frequency of ≥grade 3 adverse reactions and deaths, including deaths due to progressive disease, were greater in patients with baseline bilirubin >1.5 x ULN. TORISEL is contraindicated in patients with bilirubin >1.5 x ULN due to increased risk of death.

Use caution when treating patients with mild hepatic impairment. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. If TORISEL must be given in patients with mild hepatic impairment (bilirubin >1 - 1.5 x ULN **or** AST >ULN but bilirubin ≤ULN), reduce the dose of TORISEL to 15 mg/week (see **USE IN SPECIFIC POPULATIONS, Hepatic Impairment**).

Hypersensitivity Reactions: Hypersensitivity/infusion reactions, including but not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored throughout the infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered.

TORISEL should be used with caution in persons with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any other component (including the excipients) of TORISEL.

An H_1 antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. TORISEL should be used with caution in patients with known hypersensitivity to an antihistamine, or patients who cannot receive an antihistamine for other medical reasons.

If a patient develops a hypersensitivity reaction during the TORISEL infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H_1-receptor antagonist (such as diphenhydramine), if not previously administered, and/or an H_2-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the TORISEL infusion. The infusion may then be resumed at a slower rate (up to 60 minutes).

A benefit-risk assessment should be done prior to the continuation of temsirolimus therapy in patients with severe or life-threatening reactions.

Hyperglycemia/Glucose Intolerance: The use of TORISEL is likely to result in increases in serum glucose. In the phase 3 trial, 89% of patients receiving TORISEL had at least one elevated serum glucose while on treatment, and 26% of patients reported hyperglycemia as an adverse event. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy. Serum glucose should be tested before and during treatment with TORISEL. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

Infections: The use of TORISEL may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections (see **ADVERSE REACTIONS**).

Interstitial Lung Disease: Cases of interstitial lung disease, some resulting in death, occurred in patients who received TORISEL. Some patients were asymptomatic, or had minimal symptoms, with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of TORISEL and/or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms.

It is recommended that patients undergo baseline radiographic assessment by lung computed tomography scan or chest radiograph prior to the initiation of TORISEL therapy. Follow such assessments periodically, even in the absence of clinical respiratory symptoms.

It is recommended that patients be followed closely for occurrence of clinical respiratory symptoms. If clinically significant respiratory symptoms develop, consider withholding TORISEL administration until after recovery of symptoms and improvement of radiographic findings related to pneumonitis. Empiric treatment with corticosteroids and/or antibiotics may be considered.

Hyperlipemia: The use of TORISEL is likely to result in increases in serum triglycerides and cholesterol. In the phase 3 trial, 87% of patients receiving TORISEL had at least one elevated serum cholesterol value and 83% had at least one elevated serum triglyceride value. This may require initiation, or increase in the dose, of lipid-lowering agents. Serum cholesterol and triglycerides should be tested before and during treatment with TORISEL.

Bowel Perforation: Cases of fatal bowel perforation occurred in patients who received TORISEL. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen. Patients should be advised to report promptly any new or worsening abdominal pain or blood in their stools.

Renal Failure: Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received TORISEL. Some of these cases were not responsive to dialysis.

Wound Healing Complications: Use of TORISEL has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of TORISEL in the perioperative period.

Intracerebral Hemorrhage: Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving TORISEL.

Co-administration with Inducers or Inhibitors of CYP3A Metabolism:

Agents Inducing CYP3A Metabolism: Strong inducers of CYP3A4/5 such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampicin may decrease exposure of the active metabolite, sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease TORISEL plasma concentrations unpredictably. Patients receiving TORISEL should not take St. John's Wort concomitantly.

Agents Inhibiting CYP3A Metabolism: Strong CYP3A4 inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin may increase blood concentrations of the active metabolite sirolimus. If alternative treatments cannot be administered, a dose adjustment should be considered.

Concomitant use of TORISEL with sunitinib:

The combination of TORISEL and sunitinib resulted in dose-limiting toxicity. Dose-limiting toxicities (Grade 3/4 erythematous maculopapular rash, and gout/cellulitis requiring hospitalization) were observed in two out of three patients treated in the first cohort of a phase 1 study at doses of TORISEL 15 mg IV per week and sunitinib 25 mg oral per day (Days 1-28 followed by a 2-week rest).

Vaccinations: The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with TORISEL. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

Pregnancy:

Pregnancy Category D: There are no adequate and well-controlled studies of TORISEL in pregnant women. However, based on its mechanism of action, TORISEL may cause fetal harm when administered to a pregnant woman. Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after TORISEL therapy has stopped.

Men should be counseled regarding the effects of TORISEL on the fetus and sperm prior to starting treatment. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of TORISEL.

Elderly Patients: Based on the results of a phase 3 study, elderly patients may be more likely to experience certain adverse reactions, including diarrhea, edema, and pneumonia.

Monitoring Laboratory Tests: In the randomized, phase 3 trial, complete blood counts (CBCs) were checked weekly, and chemistry panels were checked every two weeks. Laboratory monitoring for patients receiving TORISEL may need to be performed more or less frequently at the physician's discretion.

ADVERSE REACTIONS

The following serious adverse reactions have been associated with TORISEL in clinical trials and are discussed in greater detail in other sections of the label (see **WARNINGS AND PRECAUTIONS**).

Hypersensitivity/Infusion Reactions, Hyperglycemia/Glucose Intolerance, Interstitial Lung Disease, Hyperlipemia, Bowel Perforation, Renal Failure

The most common (≥30%) adverse reactions observed with TORISEL are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common (≥30%) laboratory abnormalities observed with TORISEL are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

In the Phase 3 randomized, open-label study of interferon alfa (IFN-α) alone, TORISEL alone, and TORISEL and IFN-α, a total of 616 patients were treated. Two hundred patients received IFN-α weekly, 208 received TORISEL 25 mg weekly, and 208 patients received a combination of TORISEL and IFN-α weekly.

Treatment with the combination of TORISEL 15 mg and IFN-α was associated with an increased incidence of multiple adverse reactions and did not result in a significant increase in overall survival when compared with IFN-α alone.

Table 1 shows the percentage of patients experiencing treatment emergent adverse reactions. Reactions reported in at least 10% of patients who received TORISEL 25 mg alone or IFN-α alone are listed. Table 2 shows the percentage of patients experiencing selected laboratory abnormalities. Data for the same adverse reactions and laboratory abnormalities in the IFN-α alone arm are shown for comparison.

Table 1—Adverse Reactions Reported in at Least 10% of Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial

	TORISEL 25 mg n=208		IFN-α n=200	
Adverse Reaction	**All Grades* n (%)**	**Grades 3&4* n (%)**	**All Grades* n (%)**	**Grades 3&4* n (%)**
Any	208 (100)	139 (67)	199 (100)	155 (78)
General disorders				
Asthenia	106 (51)	23 (11)	127 (64)	52 (26)
Edema[a]	73 (35)	7 (3)	21 (11)	1 (1)
Pain	59 (28)	10 (5)	31 (16)	4 (2)
Pyrexia	50 (24)	1 (1)	99 (50)	7 (4)
Weight Loss	39 (19)	3 (1)	50 (25)	4 (2)
Headache	31 (15)	1 (1)	30 (15)	0 (0)
Chest Pain	34 (16)	2 (1)	18 (9)	2 (1)
Chills	17 (8)	1 (1)	59 (30)	3 (2)
Gastrointestinal disorders				
Mucositis[b]	86 (41)	6 (3)	19 (10)	0 (0)
Anorexia	66 (32)	6 (3)	87 (44)	8 (4)
Nausea	77 (37)	5 (2)	82 (41)	9 (5)
Diarrhea	56 (27)	3 (1)	40 (20)	4 (2)
Abdominal Pain	44 (21)	9 (4)	34 (17)	3 (2)
Constipation	42 (20)	0 (0)	36 (18)	1 (1)
Vomiting	40 (19)	4 (2)	57 (29)	5 (3)
Infections				
Infections[c]	42 (20)	6 (3)	19 (10)	4 (2)
Urinary tract infection[d]	31 (15)	3 (1)	24 (12)	3 (2)
Pharyngitis	25 (12)	0 (0)	3 (2)	0 (0)
Rhinitis	20 (10)	0 (0)	4 (2)	0 (0)
Musculoskeletal and connective tissue disorders				
Back Pain	41 (20)	6 (3)	28 (14)	7 (4)
Arthralgia	37 (18)	2 (1)	29 (15)	2 (1)
Myalgia	16 (8)	1 (1)	29 (15)	2 (1)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	58 (28)	18 (9)	48 (24)	11 (6)
Cough	53 (26)	2 (1)	29 (15)	0 (0)
Epistaxis	25 (12)	0 (0)	7 (4)	0 (0)
Skin and subcutaneous tissue disorders				
Rash[e]	97 (47)	10 (5)	14 (7)	0 (0)
Pruritus	40 (19)	1 (1)	16 (8)	0 (0)
Nail Disorder	28 (14)	0 (0)	1 (1)	0 (0)
Dry Skin	22 (11)	1 (1)	14 (7)	0 (0)
Acne	21 (10)	0 (0)	2 (1)	0 (0)
Nervous system disorders				
Dysgeusia[f]	41 (20)	0 (0)	17 (9)	0 (0)
Insomnia	24 (12)	1 (1)	30 (15)	0 (0)
Depression	9 (4)	0 (0)	27 (14)	4 (2)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.

[a] Includes edema, facial edema, and peripheral edema

[b] Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis

[c] Includes infections not otherwise specified (NOS) and the following infections that occurred infrequently as distinct entities: abscess, bronchitis, cellulitis, herpes simplex, and herpes zoster

[d] Includes cystitis, dysuria, hematuria, urinary frequency, and urinary tract infection

[e] Includes eczema, exfoliative dermatitis, maculopapular rash, pruritic rash, pustular rash, rash (NOS), and vesiculobullous rash

[f] Includes taste loss and taste perversion

The following selected adverse reactions were reported less frequently (<10%).

Gastrointestinal Disorders – Fatal bowel perforation occurred in 1 patient (1%).

Eye Disorders – Conjunctivitis (including lacrimation disorder) occurred in 15 patients (7%).

Immune System – Allergic/Hypersensitivity reactions occurred in 18 patients (9%).

Angioneurotic edema-type reactions (including delayed reactions occurring two months following initiation of therapy) have been observed in some patients who received TORISEL and ACE inhibitors concomitantly.

Infections – Pneumonia occurred in 17 patients (8%); upper respiratory tract infection occurred in 14 patients (7%).

General Disorders and Administration Site Conditions – Impaired wound healing occurred in 3 patients (1%).

Respiratory, Thoracic and Mediastinal Disorders – Interstitial lung disease occurred in 5 patients (2%), including rare fatalities.

Vascular – Hypertension occurred in 14 patients (7%); venous thromboembolism (including deep vein thrombosis and pulmonary embolus [including fatal outcomes]) occurred in 5 patients (2%); thrombophlebitis occurred in 2 patients (1%).

Table 2—Incidence of Selected Laboratory Abnormalities in Patients Who Received 25 mg IV TORISEL or IFN-α in the Randomized Trial

	TORISEL 25 mg n=208		IFN-α n=200	
Laboratory Abnormality	**All Grades* n (%)**	**Grades 3&4* n (%)**	**All Grades* n (%)**	**Grades 3&4* n (%)**
Any	208 (100)	162 (78)	195 (98)	144 (72)
Hematology				
Hemoglobin Decreased	195 (94)	41 (20)	180 (90)	43 (22)
Lymphocytes Decreased**	110 (53)	33 (16)	106 (53)	48 (24)
Neutrophils Decreased**	39 (19)	10 (5)	58 (29)	19 (10)
Platelets Decreased	84 (40)	3 (1)	51 (26)	0 (0)
Leukocytes Decreased	67 (32)	1 (1)	93 (47)	11 (6)
Chemistry				
Alkaline Phosphatase Increased	141 (68)	7 (3)	111 (56)	13 (7)
AST Increased	79 (38)	5 (2)	103 (52)	14 (7)
Creatinine Increased	119 (57)	7 (3)	97 (49)	2 (1)
Glucose Increased	186 (89)	33 (16)	128 (64)	6 (3)
Phosphorus Decreased	102 (49)	38 (18)	61 (31)	17 (9)
Total Bilirubin Increased	16 (8)	2 (1)	25 (13)	4 (2)
Total Cholesterol Increased	181 (87)	5 (2)	95 (48)	2 (1)
Triglycerides Increased	173 (83)	92 (44)	144 (72)	69 (35)
Potassium Decreased	43 (21)	11 (5)	15 (8)	0 (0)

* NCI CTC version 3.0

** Grade 1 toxicity may be under-reported for lymphocytes and neutrophils.

Post-marketing and Other Clinical Experience:

The following adverse reactions have been identified during post approval use of TORISEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to readily estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been observed in patients receiving temsirolimus: pleural effusion, hemodynamically significant pericardial effusions requiring intervention, convulsions, rhabdomyolysis, Stevens-Johnson Syndrome, and complex regional pain syndrome (reflex sympathetic dystrophy).

There are also postmarketing reports of temsirolimus extravasations resulting in swelling, pain, warmth, and erythema.

DRUG INTERACTIONS

Agents Inducing CYP3A Metabolism:

Co-administration of TORISEL with rifampin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus C_{max} (maximum concentration) and AUC (area under the concentration versus the time curve) after intravenous administration, but decreased sirolimus C_{max} by 65% and AUC by 56% compared to TORISEL treatment alone. If alternative treatment cannot be administered, a dose adjustment should be considered (see **Dosage and Administration** in full Prescribing Information).

Agents Inhibiting CYP3A Metabolism:

Co-administration of TORISEL with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus C_{max} or AUC; however, sirolimus AUC increased 3.1-fold, and C_{max} increased 2.2-fold compared to TORISEL alone. If alternative treatment cannot be administered, a dose adjustment should be considered. (see **Dosage and Administration** in full Prescribing Information).

Interactions with Drugs Metabolized by CYP2D6:

The concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of TORISEL was co-administered. No clinically significant effect is anticipated when temsirolimus is co-administered with agents that are metabolized by CYP2D6 or CYP3A4.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D (see **WARNINGS AND PRECAUTIONS, Pregnancy**).

Nursing Mothers: It is not known whether TORISEL is excreted into human milk, and due to the potential for tumorigenicity shown for sirolimus (active metabolite of TORISEL) in animal studies, a decision should be made whether to discontinue nursing or discontinue TORISEL, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of TORISEL in pediatric patients have not been established.

Geriatric Use: Clinical studies of TORISEL did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

Renal Impairment: No clinical studies were conducted with TORISEL in patients with decreased renal function. Less than 5% of total radioactivity was excreted in the urine following a 25 mg intravenous dose of [^{14}C]-labeled temsirolimus in healthy subjects. Renal impairment is not expected to markedly influence drug exposure, and no dosage adjustment of TORISEL is recommended in patients with renal impairment.

TORISEL has not been studied in patients undergoing hemodialysis.

Hepatic Impairment: TORISEL was evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment as defined by AST and bilirubin levels and patients with liver transplant (Table 3).

Table 3—Adverse Reactions in Patients With Advanced Malignancies Plus Normal or Impaired Hepatic Function

Hepatic Function*	TORISEL Dose Range	Adverse Reactions Grade ≥ 3** n (%)	Death*** n (%)
Normal (n=25)	25 – 175	20 (80.0)	2 (8.0)
Mild (n=39)	10 – 25	32 (82.1)	5 (12.8)
Moderate (n=20)	10 – 25	19 (95.0)	8 (40.0)
Severe (n=24)	7.5 – 15	23 (95.8)	13 (54.2)
Liver Transplant (n=2)	10	1 (50.0)	0 (0)

* Hepatic Function Groups: normal = bilirubin and AST ≤ULN; mild = bilirubin >1 - 1.5 x ULN **or** AST >ULN but bilirubin ≤ULN; moderate = bilirubin >1.5 - 3 x ULN; severe = bilirubin >3 x ULN; liver transplant = any bilirubin and AST.

** Common Terminology Criteria for Adverse Events, version 3.0, including all causality.

***Includes deaths due to progressive disease and adverse reactions.

Because there is a need for dosage adjustment based upon hepatic function, assessment of AST and bilirubin levels is recommended before initiation of TORISEL and periodically thereafter (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Hepatic Impairment**).

Drug-Transport Systems - P-glycoprotein:

Temsirolimus is a substrate of the efflux transporter P-glycoprotein (Pgp) in vitro. If TORISEL is administered with drugs that inhibit Pgp, increased concentrations of temsirolimus are likely and caution should be exercised.

In vitro, temsirolimus inhibited human Pgp (IC50 value of 2μM). If TORISEL is administered with drugs that are substrates of Pgp, increased concentrations of the substrate drug are likely and caution should be exercised.

OVERDOSAGE

There is no specific treatment for TORISEL intravenous overdose. TORISEL has been administered to patients with cancer in phase 1 and 2 trials with repeated intravenous doses as high as 220 mg/m^2. The risk of several serious adverse events, including thrombosis, bowel perforation, interstitial lung disease (ILD), seizure, and psychosis, is increased with doses of TORISEL greater than 25 mg.

This brief summary is based on TORISEL Prescribing Information LAB-0461-1.0, revised 06/11.

Distributed by Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., Philadelphia, PA 19101.

About the Cover
Conceptual rendering suggests how targeted therapies for renal cell carcinoma could reshape strategies in the future. (Copyright Photo Researchers)

KCJ TABLE OF CONTENTS

KCJ GUEST EDITOR'S MEMO

ASCO 2011 Serves as a Time Capsule to View the Future


Robert A. Figlin, MD

Wikepedia defines a time capsule as "a historic cache of goods and/or information, usually intended as a method of communication with future people and to help future archaeologists, anthropologists, and/or historians. Time capsules are sometimes created and buried during celebrations such as a World's Fair, a cornerstone laying for a building, or at other events. Intentional time capsules are placed with a purpose and are usually intended to be opened or accessed at a particular future date."

The 2011 American Society of Clinical Oncology (ASCO) Scientific Sessions might be described as a time capsule—aimed at the not-too-distant-future when clinicians can look back at the presentations from the meeting as a harbinger of new therapeutic strategies, laying the groundwork for the reinvention of the treatment algorithm in renal cell carcinoma (RCC). It could be an intriguing exercise to take this year's Scientific Sessions, and, as the definition suggests, view the data against future developments. Although ASCO 2011 was not exciting in terms of offering "groundbreaking" information, we can still glean important messages.

Within the time capsule are some nuggets of new results from ongoing clinical trials that involved targeted therapies in phase 3 trials, especially those targeting all 3 vascular endothelial growth factor (VEGF) receptors. We do not know how all of the information will sort itself out at future meetings of ASCO, but one thing is certain, change is in the air again and there are promising signs that we will see some significant gains in progression-free survival and an improved adverse effect profile with agents such as axitinib and tivozanib, touted as "cleaner" tyrosine kinase inhibitors because of their improved adverse effect profiles.

Axitinib made the biggest splash at ASCO but tivozanib is not far behind in its lifecycle. Axitinib is now on a fairly fast track at the FDA and it may not be long before we indeed realize some revisions of the decision tree in RCC. Nevertheless, the challenges remain awesome and the new drugs may ultimately fail because we still need to address other pathways in addition to those involving tyrosine kinase. However, as a researcher—and clinician—I am encouraged by the progress made in disrupting angiogenesis and in enhanced approaches to combine and sequence targeted agents. Although the progress is incremental, perhaps related studies—such as those involving biomarkers—can help improve our selection of patients for various modalities. Identifying relevant biomarkers is generally considered the highest research priority in kidney cancer, according to one of our authors, Thomas E. Hutson, DO, PharmD, in his report on ASCO highlights in this issue of the journal.

Six new agents and 3 classes of drugs have been approved over the last 5 years. Hopefully, the expanded access trials, providing the largest prospective "real world experience" using targeted therapy in metastatic RCC patients, will yield data on which to base clinical decisions. Although this year's ASCO fell short of delivering that caliber of information, the time capsule alluded to earlier offers tantalizing results of new directions in therapy.

Robert A. Figlin, MD
Editor-in-Chief

Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

All material reproduced from previously published, copyrighted material should contain a full credit line acknowledging the original source. The author is responsible for obtaining this permission.

Contact information

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

Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

Copyright

Chemotherapy for Central Nervous System Metastases in Renal Cancer: A Review

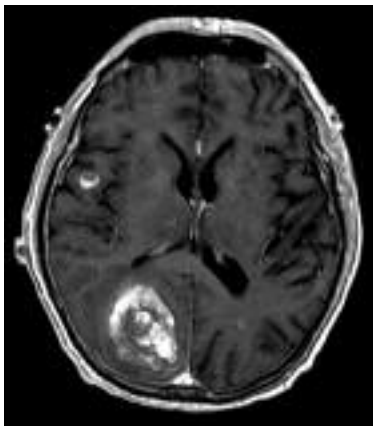
Tiffany Chen, MD
University of Washington-Seattle,
Department of Internal Medicine
Seattle, Washington

Edwin Posadas, MD
Samuel Oschin Comprehensive Cancer Institute,
Cedars-Sinai Medical Center
Los Angeles, California

Rimas V. Lukas, MD
University of Chicago,
Department of Neurology
Chicago, Illinois

Approximately 2% to 11% of patients with renal cell cancer (RCC) will initially present with or develop brain metastases (BM).[1,2] BM are typically considered late events in the natural history of metastatic disease. As with other solid tumors, they portend poor prognosis with historical data estimating a median survival of 4 to 7 months, though this may reflect a lack of sensitivity of traditional imaging.[3] It is less clear whether BM themselves drive mortality in RCC or are merely a manifestation of late stage disease in patients with declining performance status.[4] It is difficult to make broad generalizations about the clinical course of patients with metastatic RCC (mRCC), as some patients may have a relatively indolent course compared with others.[5] With the progress in vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) directed therapies, the contemporary understanding of natural history has changed tremendously.[6]

Systemic therapy focused on solid tumor BM typically plays a role only after surgery and/or radiation therapy (RT) have been exhausted. Some patients with BM from solid tumors will benefit from chemotherapy either by an objective radiological response and/or an improved functional status even after the BM has recurred/progressed after localized therapy.[7] Typically, patients with BM are excluded from clinical trials for systemic treatment.



MRI brain, T1-post contrast, axial cut image. Scan demonstrates a large hemmorhagic right parieto-occipital region metastasis as well as smaller metastases in the right temporal lobe and left occipital region.

Most RCC-BM patients die from extracerebral disease rather than BM-related complications.[4] In turn, therapy that addresses systemic as well as central nervous system (CNS) disease will play a growing role in the treatment of RCC-BM. Patients with RCC-BM are a heterogeneous population, and by evaluating specific prognostic factors, one can identify those more likely to have prolonged survival comparable to the general mRCC population.[8,9] Improvement of functional status with systemic therapy may be of greater value in patients with longer predicted survival. Predictive biomarkers for response to therapy have yet not been established.

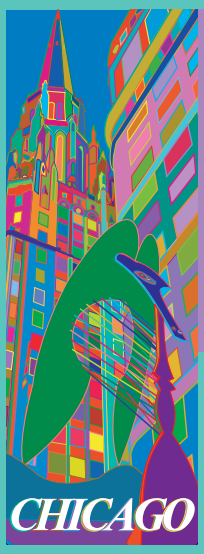
Systemic therapies currently approved for mRCC are cytokines (interleukin-2 [IL-2], interferon-α [IFN-α]), VEGF receptor (VEGFR)-active tyrosine kinase inhibitors (TKI) (sorafenib, sunitinib, pazopanib), an anti-VEGF antibody (bevacizumab), and mTOR inhibitors (temsirolimus, everolimus). Unique considerations must be taken into account when choosing an agent for patients with BM.

Drug Concentration

Drug delivery into the CNS is limited by the blood-brain barrier, which prohibits passage of most molecules larger than 180 Daltons and those that are not lipophilic. Agents crossing the blood-brain barrier are potentially

Keywords: Renal cancer; brain metastases; leptomeningeal metastases; chemotherapy; central nervous system.
Acknowledgement—Grant support received from the Ben & Catherine Ivy Foundation (R.V.L.).

Address for reprints and correspondence: Rimas V. Lukas, MD, 5841 South Maryland Ave., MC 2030, Chicago, IL 60637; 773-834-9026, 773-702-7485 (fax); email: rlukas@neurology.bsd.uchicago.edu.



Register Now for the 10th International Kidney Cancer Symposium

October 14-15, 2011

Swissôtel Chicago

Learning Objectives:

- Evaluate the growing body of knowledge regarding clinical, molecular, genetic, and biologic characteristics of renal cell carcinoma
- Discuss options for operative and non-operative management of localized and metastatic renal cell carcinoma
- Evaluate novel imaging modalities to improve detection of primary tumors and evaluate metastatic disease
- Define research directions of novel agents and combinations and standard of care therapy for metastatic renal cell carcinoma

Scientific Program Committee

William P. Bro
Chief Executive Officer
Kidney Cancer Association

Jorge A. Garcia, M.D., FACP
Taussig Cancer Institute
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, OH

Bradley C. Leibovich, M.D.
Mayo Clinic
Rochester, MN

David F. McDermott, M.D.
Beth Israel Deaconess Medical Center/
Dana-Farber/Harvard Cancer Center
Boston, MA

Kidney Cancer Association®
KidneyCancer.com

In joint sponsorship with

Cleveland Clinic

This activity has been approved for *AMA PRA Category 1 Credit™*

www.kidneycancersymposium.com

Table 1. Molecular weight and lipophilicity of targeted agents

Molecule	Molecular weight (g/mol)	Lipophilicity (XLogP3-AA)[a]
Sunitinib	398	2.6
Sorafenib	465	4.1
Pazopanib	474	3.1
Temsirolimus	1030	5.6
Everolimus	958	5.9

[a]Computation of octanol-water partition coefficient.

Table 2. Interactions between targeted therapies and the CYP450 system

Targeted therapy	CYP metabolism
Sunitinib	CYP3A4
Sorafenib	CYP3A4
Pazopanib	CYP3A4, CYP2C8, CYP1A2
Temsirolimus	CYP3A4
Everolimus	CYP3A4, CYP2C8

subject to efflux by ATP-binding cassette (ABC) transporters such as P-glycoprotein (P-gp/ABCB1) and breast cancer resistance protein (ABCG2).[10] For many agents, there is limited or no published data on CNS concentrations in humans and their use is based on assumptions that they can reach adequate concentrations in BM (**Table 1**).

Another concern in attaining adequate drug concentrations in BM patients is the interactions between systemic chemotherapies and antiepileptic drugs (**Table 2**). About 10% of RCC-BM patients initially present with seizures.[8] Many antiepileptic drugs affect the metabolism of chemotherapies by inducing/inhibiting the cytochrome P450 (CYP) system. A more complete list of contemporary antiepileptic drugs and their effects on CYP has been published previously.[11]

Sunitinib

Sunitinib (Sutent, SU11248) is a multitargeted TKI active on VEGFR-1, -2, platelet derived growth factor-α (PDGF-α), PDGF-β, c-Kit, and FMS-like tyrosine kinase 3 (Flt-3). It possesses both antiangiogenic and antitumor proliferative activity and is approved as first line treatment in mRCC.[12]

There are no reported data regarding CNS concentrations of sunitinib in humans. In animal models, sunitinib penetrates the CNS to a much lesser extent than other tissues. In mice, a single dose of sunitinib showed rapid CNS penetration with a concentration 7-fold greater in the brain than plasma. This effect was more modest upon repeat dosing in primates, which resulted in brain concentrations only 1- to 3-fold higher than plasma, which is lower than the accumulation in other tissues.[13]

In vitro studies demonstrated that sunitinib had moderate efflux via ABCB1 and minimal transport by ABCG2. Interestingly, sunitinib also inhibits multiple ABC transporters and prevents efflux of known substrates.[14,15] This should be considered when combining sunitinib with other agents that are substrates for ABC transporters. The rational pairing of agents may lead to more effective concentrations of drug in the CNS and variable patterns of toxicity.[16]

In addition to anecdotal reports of RCC-BM regression after sunitinib treatment, a prospective expanded-access trial included patients with RCC-BM and provided further support for the safety and efficacy of sunitinib in RCC-BM.[17-22] The expanded-access trial enrolled 321 (7%) RCC-BM patients with predominantly clear cell histology (92%) and extracerebral metastases (98%). Previous treatments included nephrectomy (88%) and systemic therapy with either antiangiogenic agents (12%) and/or cytokines (74%). No data regarding CNS RT were reported. Sunitinib was administered at 50 mg daily on a 4-week on/2-week off schedule. One-fourth of the patients required dose reductions.[22]

The incidence of adverse events and dose modifications in RCC-BM was comparable to both the overall expanded-access trial and phase 3 trial populations. As with all antiangiogenic agents, there has been concern about the increased risk of intracranial hemorrhage. A single grade 1/2 intracranial hemorrhage was reported in the RCC-BM subgroup.[22]

Response rates were available for 213 (66%) of the RCC-BM patients. One(<1%) patient had a complete response, 25 (12%) had partial response, 111(52%) had stable disease for at least 3 months. Radiographic response in the CNS of patients treated with antiangiogenic agents may reflect the effects of these agents on blood-brain barrier permeability and may not truly correlate with effect on tumor volume. However, progression-free survival and overall survival for patients with BM were 5.6 and 9.2 months respectively, and were not affected by prior cytokine therapy. These are favorable results compared with historical data that estimated an overall survival of 4 to 6 months for patients with RCC-BM. This may in part be due to more aggressive screening for CNS disease following the advancement of clinical studies in RCC. In this study, progression-free survival (10.9 months) and overall survival (18.4 months) were much longer in mRCC patients without BM.[22]

A review of BM incidence in RCC patients treated with sunitinib noted no difference in incidence compared with historical controls.[17] This implies that sunitinib may not have a role in preventing the development of RCC-BM, but no prospective studies validate this.

Sorafenib

Sorafenib (Nexavar, BAY 43-906) is another multitargeted TKI against VEGFR-1, -2, -3, platelet derived growth

factor receptor-α (PDGFR-α), Flt-3, c-Kit, RET receptor, and Raf with both antiangiogenic and antiproliferative activity. It was the first approved TKI for mRCC; data showed activity following cytokine or other TKI therapy.[23]

As with sunitinib, there are no reported data on CNS concentrations of sorafenib in humans. In mice, sorafenib modestly penetrated the CNS with parenchymal brain accumulation at 6 hours after a single dose of approximately 5 times the serum concentration.[24] Notably, brain penetration with sunitinib was 10-fold greater than with sorafenib in mice (31% vs 3%).[24] In primates, cerebrospinal fluid concentrations were low (0.02%) compared with total plasma drug exposure.[25] CNS penetration by sorafenib is restricted by P-gp and to a greater degree ABCG2.[24] In turn, active blockade of these transporters could be explored as a means for increasing CNS concentrations of sorafenib. To date, we are not aware of a study that examines the effect of sorafenib and sunitinib coadministration on brain penetration of either drug.

There is evidence for the safety and efficacy of sorafenib in RCC-BM patients. Similar to sunitinib, a prospective expanded-access trial provided sorafenib to 2504 RCC patients, of which 70 (2.8%) had BM. Regarding the RCC-BM patients specifically, nearly all had extra-cerebral metastases (99%). Previous treatments included nephrectomy (79%), RT (81%), and systemic therapies (49%) with either cytokines, bevacizumab, and/or thalidomide. The incidence and severity of adverse events in RCC-BM were similar to those in sorafenib's phase 3 trial. There were no intracranial hemorrhages in the RCC-BM patients. However, dose reduction and interruptions occurred in a number of the expanded-access trial patients compared with patients in the phase 3 trial.[26]

Data for overall best response were available for 50 (71%) RCC-BM patients. Compared with sunitinib's expanded-access trial, few RCC-BM patients in the sorafenib expanded-access trial had an objective response; 2 (4%) patients showed partial response and there were no complete responses. However, 34 (68%) had stable disease for at least 8 weeks. RCC-BM patients have a poor prognosis, limited treatment options, and may have an impaired quality of life. Approximately 80% to 98% of patients with RCC-BM are symptomatic.[26] In turn, although case reports of sorafenib have resulted in objective response in both brain and cerebrospinal fluid metastases, stable disease may prove to be a more realistic but still worthwhile end point in this patient population.[6,27,28]

Pazopanib

Pazopanib, a second generation multitargeted TKI against VEGFR-1, -2, -3, PDGFR-α, β, and c-Kit is approved as a first-line agent for mRCC.[29] To our knowledge there have been no reports of pazopanib brain concentration. Evidence of objective response in glioblastoma with pazopanib suggests CNS activity.[30] It is uncertain if these responses are a result of a stabilized leaky blood-brain barrier via VEGF inhibition or if it is a direct antitumor effect. Nevertheless, reduction of vasogenic edema alone, regardless of antitumor effects, may have clinical benefits.[31] We are not aware of any studies that have evaluated the safety or efficacy of pazopanib in RCC-BM.

Bevacizumab

Bevacizumab is a monoclonal antibody that inhibits angiogenesis by binding VEGF, thereby preventing interaction with receptors. Because of activity on the luminal side of the blood-brain barrier, penetration into the CNS is not required to exert its effects. In combination with IFN-α, it is approved as first-line therapy for mRCC.[32]

Although phase 3 studies excluded RCC-BM patients, retrospective analysis of data from the AVOREN trial identified patients that either had occult BM at baseline or developed BM during the trial. Twenty-three (3.6%) patients were found to have BM; 10 received bevacizumab. No bevacizumab-treated RCC-BM patients developed intracranial hemorrhage; 1 bevacizumab-naive RCC-BM patient died from intracranial hemorrhage. Although patients in this review are not representative of the general RCC-BM population, who may initially have larger or symptomatic BM that would have excluded them from the trial, bevacizumab is likely relatively safe in RCC-BM patients.[33]

Data regarding the efficacy of bevacizumab in RCC-BM is limited to a handful of patients in retrospective analyses. An analysis of data from 114 RCC patients who received targeted agents, found that 2 (2%) RCC-BM patients treated with bevacizumab monotherapy as first line treatment after resection or RT had stable disease that progressed 8.7 to 21.6 months after initiation of bevacizumab.[4] Another analysis of data from 144 RCC patients treated with antiangiogenic agents (sunitinib, sorafenib, or bevacizumab) identified 4 (3%) RCC-BM patients treated with bevacizumab monotherapy or in combination with IFN-α who did not achieve objective response. No data about stable disease/progressive disease (PD) was reported. In comparison, RCC-BM patients who received sunitinib or sorafenib achieved objective response in 20% (2 of 10) and 16% (1 of 6) respectively.[34]

mTOR Inhibitors

Everolimus (Affinitor, RAD001) and temsirolimus (Torisel) affect cell division, metabolism, and angiogenesis. Both are FDA approved for mRCC. Everolimus has demonstrated activity after failure on VEGFR-directed TKI, and temsirolimus showed activity in patients with poorer prognosis by Motzer criteria and those with non–clear cell histologies. Although phase 3 trials for both agents allowed treated or neurologically stable RCC-BM, neither reported BM subgroup analyses. In the everolimus trial, 29 (15%) patients had BM.[35] BM prevalence was not reported in the temsirolimus trial.[36]

In regards to temsirolimus CNS penetration, tumor

and blood concentrations of temsirolimus and its major active metabolite, sirolimus, were measured 2.7 to 5.6 hours after a single infusion of temsirolimus in 6 patients with recurrent glioma. The average tumor-to-whole blood ratio for temsirolimus and sirolimus was 1.43 and 0.84 respectively. Concentrations of these agents in glioma may not, however, be comparable to concentrations in RCC-BM.[37]

Everolimus has modest but significant brain tissue penetration in rodents. After a single oral dose of everolimus, the 24-hour AUC_{brain} to $AUC_{whole\ blood}$ concentration was 0.02 in mice. Despite this low relative concentration, brain tissue concentrations still reached predetermined therapeutic levels for treating glioblastoma cell lines. In rats, everolimus demonstrated dose-dependent rapid uptake into the brain, followed by slow efflux and metabolism. Accordingly, it also exhibited accumulation in the brain with a brain-to-whole blood ratio of 20 when measured 24 hours after once-per-day oral dosing for 14 days.[38]

Regarding efficacy, retrospective analysis of 114 mRCC patients identified one RCC-BM patient treated with stereotactic radiosurgery and temsirolimus who achieved stable disease.[4] This result may exclusively arise from the stereotactic radiosurgery. To our knowledge, there are no other studies or case reports that provide data about the safety or efficacy of either mTOR inhibitor in RCC-BM patients.

Immunotherapy

Immunotherapy with IFN-α and/or high dose IL-2 was the mainstay of treatment for mRCC before the introduction of VEGFR or mTOR-directed therapy. However, high dose IL-2 monotherapy is still approved as first-line treatment for patients with mRCC. Both IL-2 and IFN-α have also been used as second-line treatment.

The brain is considered an "immunologically privileged site." The therapies listed above may have both direct effect on the CNS by modulating CNS endothelial functioning as well as a systemic effect on the immune cells, which traffic in the CNS.[39]

IL-2 has often been avoided in BM because of the potential risk of peritumoral edema that can lead to exacerbation of CNS symptoms. This is in contrast to antiangiogenic agents that decrease cerebral edema and therefore potentially improve CNS symptoms.[31] However, there is evidence to suggest that IL-2 is tolerable in BM.[40] An analysis of 64 patients with BM (61 melanoma, 3 RCC) found that grade 3/4 toxicities from IL-2 were similar in patients with and without BM. However, a trend for patients with BM to stop treatment because of greater disorientation (23%, $P = .029$) and depressed level of consciousness (11%, $P = .031$) was noted. Selection bias of BM patients that were either effectively treated with localized therapy or with small lesions and minimal edema may limit the generalizability of this study.

There are data to suggest that immunotherapy may play a role in RCC-BM. Samlowski and colleagues[3] retrospectively reviewed 32 patients with RCC-BM who received stereotactic radiosurgery. They analyzed 19 (59%) patients additionally treated with immunotherapy (IL-2, IFN-α, or both). Immunotherapy given at any point in a patient's disease was not associated with a prolonged median overall survival (6.1 months for patients who had received immunotherapy compared with 7.3 months for patients who had not received immunotherapy). However, immunotherapy given poststereotactic radiosurgery was associated with a significantly prolonged median overall survival of 17.1 months compared with 5.2 months for patients who either never had immunotherapy or received it before stereotactic radiosurgery ($P < .0007$). Although this may be secondary to selection of healthier patients for systemic treatment after stereotactic radiosurgery, the survival benefit for immunotherapy after stereotactic radiosurgery remained statistically significant after multivariate Cox regression analysis adjusted for known risk factors.[3]

Another study retrospectively reviewed 1855 patients with RCC from a single institution and identified 138 (7.4%) patients with BM. Baseline characteristics of the RCC-BM patients included: 93% with clear cell histology, 95% with extracerebral metastases, 68% with solitary BM, and 95% who had received local treatment with either stereotactic radiosurgery (35%), surgery (16%), or whole brain radiation therapy (12%), or various combinations of the modalities listed above. A total of 18 RCC-BM patients with good performance status were administered IL-2 after localized treatment. Three (16.6%) patients achieved partial response. There were no complete responses, and stable disease/PD rates were not specified.[41]

One small prospective study of 5 RCC-BM patients and Karnofsky performance status of 50 or less evaluated treatment with a single-agent IFN-α. One had no change in neurological symptoms or tumor size by CT. The other 4 progressed clinically and radiographically. All 5 patients in this poor prognostic category died within 1 to 4 months of diagnosis of BM.[42] There is an anecdote in the literature of a large, symptomatic RCC-BM resolving with IFN-α monotherapy over the course of 6 months.[43]

Sequential Therapy With Sunitinib and Sorafenib

Although targeted therapy has improved the treatment of mRCC, most patients eventually develop PD. Nonrandomized studies have demonstrated that sequential therapy with sunitinib and sorafenib provides some clinical benefit without evidence of cross resistance.[44]

Although many of these studies did not explicitly exclude RCC-BM patients, only one to our knowledge provides RCC-BM specific data. A retrospective study analyzed results from 71 patients who received sunitinib after failure on sorafenib or bevacizumab.[45] Of the 6 (8%) patients with BM, 1 (17%) had an objective re-

Table 3. Summary of tumor response by RECIST criteria, progression-free survival, and overall-survival with systemic treatment in patients with RCC-BM

			Efficacy		
Study	**n**	**Systemic treatment**	**RECIST criteria**	**PFS (mo)[c]**	**OS (mo)[c]**
Prospective, single arm[22]	213	Sunitinib	1 (<1%)…...CR 25 (12%)….PR 111 (52%)...SD ≥ 3 mo	Median 5.6 (5.2-6.1)	Median 9.2 (7.8-10.9)
Prospective single arm[26]	70	Sorafenib	0……...CR 2 (4%)…….PR 34 (68%)….SD ≥8 wk	N/A	N/A
Retrospective[45]	6	Sunitinib (after failure on bevacizumab or sorafenib)	1 (17%)…..OR[a] 5 (83%)…..SD or PD	Median 3.6 (1.7-5.73)	Median 12.5 (8.9-NR)
Retrospective[34]	11 8 4	Sunitinib Sorafenib Bevacizumab	2 (18%)…...PR[b] 2 (25%)…...PR[b] 0……...PR[b]	N/A N/A N/A	N/A N/A N/A
Retrospective[4]	2 1	Bevacizumab Temsirolimus	2 (100%)….SD 1 (100%)….SD	21.6; 8.7 N/A	46.9; 36.9 6
Retrospective[41]	18	IL-2	3 (17%)….. PR 15 (83%)… SD or PD	N/A	N/A
Retrospective[3]	19	Immunotherapy (IFN-α, IL-2, or both)	n/a	N/A	Median X 6.1[d] (4.5-∞)
Prospective single arm[42]	5	IFN-α	4 (80%) progressed clinically and by head CT 1 (20%) no change clinically or by head CT	N/A	1-4[d]

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NR, not reached; PFS, progression free survival; OS, overall survival.
[a]Objective response (OR) was not specified as CR or PR.
[b]No patients achieved CR; no data about SD.
[c]Time from start of systemic treatment.
[d]Time from diagnosis of brain metastasis

sponse; the remaining patients exhibited stable disease/PD. Median progression-free survival for RCC-BM was 3.62 months compared with 6.53 months for patients without BM, which is similar to findings in previous studies. Median overall survival for RCC-BM was 12.47 months. These findings raise the hope that in a small percentage of RCC-BM patients, failure on one agent does not preclude potential benefit on the CNS with subsequent agents.

Conclusions

Morbidity and mortality from RCC-BM is clinically significant and treatment options are limited. Surgery and RT are the initial modalities used in addressing CNS disease from RCC. Systemic chemotherapy is developing a growing role in the treatment of progressive CNS metastases. CNS pharmacokinetic data in humans for the FDA-approved agents for RCC is lacking. We have reviewed the preclinical data and have attempted to parcel out clinical data on efficacy in the CNS from larger more inclusive studies (**Table 3**).

While no agent has demonstrated superiority over others in the treatment of RCC-BM, all agents have demonstrated at least a limited degree of clinical and/or radiographic improvement in a select number of patients. For patients with progressive RCC-BM, systemic chemotherapy options should be considered.

References

1. Saitoh H. Distant metastases from renal carcinoma. *Cancer.* 1988;48:1487-1491.
2. Muacevic A, Siebels M, Tonn JC, et al. Treatment of brain metastases in renal cell carcinoma: radiotherapy, radiosurgery, or surgery? *World J Urol*. 2005;23:180-184.
3. Samlowski WE, Majer M, Boucher KM, et al. Multidisciplinary treatment of brain metastases derived from clear cell renal cancer incorporating stereotactic radiosurgery. *Cancer*. 2008;113: 2539-2548.
4. Vogl UM, Bojic M, Lamm W, et al. Extracerebral metastases deter-

mine the outcome of patients with brain metastases from renal cell carcinoma. *BMC Cancer.* 2010;10:480.
5. Gleave ME, Elhilali M, Fradet Y, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. *New Engl J Med*. 1998;338:1265-1271.
6. Larkin J, Gore M. Is advanced renal cell carcinoma becoming a chronic disease? *Lancet*. 2010;376:574-575.
7. Ammirati M, Cobbs CS, Linskey ME, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96:85-96.
8. Culine S, Bekradda M, Kramar A, et al. Prognostic factors for survival in patients with brain metastases from renal cell carcinoma. *Cancer.* 1998;83:2548-2553.
9. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4259 patients. *Int J Radiat Oncol Biol Phys*. 2010;77:655-661.
10. Muldoon LL, Soussain C, Jahnke K, et al. Chemotherapy delivery issues in central nervous system malignancy: a reality check. *J Clin Oncol*. 2007;25:2295-2305.
11. Lukas RV, Chmura S, Nicholas MK. Management of central nervous system metastases from renal cancer. *Emerg Cancer Therap*. 2011;2:157-168.
12. Motzker RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alpha in metastatic renal cell carcinoma. *New Engl J Med*. 2007;356: 115-24.
13. Haznedar J, Patyna S, Bello CL, et al. Single and multiple dose disposition kinetics of sunitinib malate, a multitargeted receptor tyrosine kinase inhibitor: comparative plasma kinetics in non-clinical species. *Cancer Chemother Pharmacol*. 2009;64:691-706.
14. Hu S, Chen Z, Franke R, et al. Interaction of the multikinase inhibitors sorafenib and sunitinib with solute carriers and ATP-binding cassette transporters. *Clin Cancer Res*. 2009;15:6062-69.
15. Shukla S, Robey RW, Bates SE, et al. Sunitinib (Sutent, SU11248), a small-molecule receptor tyrosine kinase inhibitor, blocks function of the ATP-binding cassette (ABC) transporters p-glycoprotein (ABCB1) and ABCG2. *Drug Metab Dispos*. 2009;37:359-365.
16. Feldman DR, Baum MS, Ginsberg MS, et al. Phase 1 trial of bevacizumab plus escalated doses of sunitinib in patients with metastatic renal cell carcinoma. *Genitourinary Cancer.* 2009;27:1432-1439.
17. Helgason HH, Mallo HA, Droogendijk H, et al. Brain metastases in patients with renal cell cancer new targeted treatment. *J Clin Oncol*. 2008;26:152-154.
18. Medioni J, Cojocarasu O, Belcaceres JL, et al. Complete cerebral response with sunitinib for metastatic renal cell carcinoma. *Ann Oncol*. 2007;18:1282-1283.
19. Thibault F, Billemont B, Rixe O. Regression of brain metastases of renal cell carcinoma with antiangiogenic therapy. *J Neurooncol*. 2008; 86:243-244.
20. Zeng H, Li X, Yao J, et al. Multifocal brain metastases in clear cell renal cell carcinoma with complete response to sunitinib. *Urol Int*. 2009;83:482-485.
21. Dalhaung A, Haukland E, Nieder C. Leptomeningeal carcinomatosis from renal cell cancer: treatment attempt with radiation and sunitinib. *World J Surg Oncol*. 2010;8:36.
22. Gore ME, Hariharan S, Porta C, et al. Sunitinib in metastatic renal carcinoma patients with brain metastases. *Cancer.* 2011;117:501-509.
23. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cell cancer global evaluation trial. *J Clin Oncol*. 2009;27:3312-3318.
24. Lagas JS, van Waterschoot RA, Sparidans RW, et al. Breast cancer resistance protein and p-glycoprotein limit sorafenib brain accumulation. *Molec Cancer Ther.* 2010;9:319-326.
25. Kim A, McCully C, Cruz R, et al. The plasma and cerebrospinal fluid pharmacokinetics of sorafenib after intravenous administration in non-human primates. *Invest New Drugs*. 2010; doi:10.1007/s10637-010-9585-1; [Epub ahead of print].
26. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer.* 2010;116:1272-1279.
27. Valcamonico F, Ferrari V, Amoroso V, et al. Long lasting successful cerebral response with sorafenib in advanced renal cell carcinoma. *J Neurooncol*. 2009;91:47-50.
28. Ranze O, Hoffman E, Distelrath A, et al. Renal cell cancer presented with leptomeningeal carcinomatosis effectively treated with sorafenib. *Onkologie.* 2007;30:450-451.
29. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061-1068.
30. Iwamoto FM, Lamborn KR, Robins IH, et al. Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study 06-02). *Neuro Oncol*. 2010;12:855-861.
31. Vredenburgh JJ, Cloughesy T, Samant M, et al. Corticosteroid use in patients with glioblastoma at first or second relapse treated with bevacizumab in the BRAIN study. *Oncologist*. 2010;15:1329-1334.
32. Escudier B, Bellmut J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alpha-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol*. 2010; 28:2144-2150.
33. Besse B, Lasserre SF, Compton P, et al. Bevacizumab safety in patients with central nervous system metastases. *Clin Cancer Res*. 2010; 16:269-278.
34. Choueiri TK, Duh MS, Clement J, et al. Angiogenesis inhibitor therapies for metastatic renal cell carcinoma: effectiveness, safety and treatment patterns in clinical practice-based on medical chart review. *BJU Int*. 2009;105:1247-1254.
35. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer.* 2010;116:4256-4265.
36. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alpha, or both for advanced renal cell carcinoma. *New Engl J Med*. 2007;456:2271-2281.
37. Kuhn JG, Chang SM, Wen PY, et al. Pharmacokinetic and tumor distribution characteristics of temsirolimus in patients with recurrent malignant glioma. *Clin Cancer Res*. 2007;13:7401-7406.
38. O'Reilly T, McSheehy P, Kawai R, et al. Comparative pharmacokinetics of RAD001 (everolimus) in normal and tumor-bearing rodents. *Cancer Chemother Pharmacol*. 2010;54:625-639.
39. Nicholas MK, Lukas R. Immunologic privilege and the brain. In: Arnason BG, ed. *NeuroImmune Biology: The Brain and Host Defense, Vol. 9*. London, UK: Elsevier; 2010: 169-181.
40. Guirgis LM, Yang JC, White DE, et al. Safety and efficacy of high dose IL-2 therapy in patients with brain metastasis. *J Immunother.* 2002; 25:82-87.
41. Shuch B, LaRochelle JC, Klatte T, et al. Brain metastasis from renal cell carcinoma: presentation, recurrence, and survival. *Cancer.* 2008; 113;1641-1648.
42. Yamanaka K, Gohji K, Hara I, et al. Clinical study of renal cell carcinoma with brain metastasis. *Int J Urol.* 1998;5:124-128.
43. Murata JI, Sawamura Y, Terasaka S, et al. Complete response of a large brain metastasis of renal cell cancer to interferon-alpha: case report. *Surg Neurol.* 1999;51:289-291.
44. Kirchner H, Strumberg D, Bahl A, et al. Patient based strategy for systemic treatment of metastatic renal cell carcinoma. *Expert Rev Anticancer Ther.* 2010;10:585-596.
45. Elfiky AA, Cho DC, McDermott DF, et al. Predictors of response to sequential sunitinib and the impact of prior VEGF-targeted drug washout in patients with metastatic clear cell renal carcinoma. *Urol Oncol*. 2010; doi:10.1016/j.urolonc.2010.01.008; [Epub ahead of print]. KCJ

Recapping Highlights of ASCO 2011 and Exploring Its Potential Impact

Thomas E. Hutson, DO, PharmD
Director of Genitourinary Oncology
for Texas Oncology
Baylor University Medical Center
Sammons Cancer Center
Dallas, Texas
Co-Chair of GU Research
for US Oncology
Dallas, Texas

Stu Chapman
Executive Editor
Kidney Cancer Journal
New York, New York

Although this year's meeting of the American Society of Clinical Oncology (ASCO) could hardly be considered "groundbreaking" for treatment of kidney cancer, new data—presented in abstracts, posters, and key oral sessions—eventually will prove to be significant as we look toward a revised paradigm in therapy offering prolonged progression-free survival (PFS), improved adverse-effect profiles, and a better understanding of how to use targeted therapy, not only in combination but in more effective sequences. In that sense, the 2011 ASCO Scientific Sessions helped lay the groundwork for future meetings when data emerging from phase 3 trials might indeed be considered the "groundbreaking" results clinicians hope for to guide therapeutic choices.

Among the brightest spots at this year's meeting:

- Results for a new tyrosine kinase inhibitor (TKI), axitinib, now being considered by the FDA based on phase 3 data presented at ASCO. Data from the pivotal phase 3 AXIS 1032 trial, showed that patients with previously treated advanced RCC, axitinib significantly extended PFS, with a median PFS of 6.7 months, compared with 4.7 months for patients who were treated with sorafenib. In addition, PFS was significantly longer in axitinib-treated patients compared with patients who were treated with sorafenib, regardless of prior therapy with Sutent® (sunitinib malate) or cytokines.[1]
- Phase 2 results for another new TKI, tivozanib, were also encouraging. In patients with clear-cell RCC who had undergone nephrectomy and had not received prior therapy with a vascular endothelial growth factor (VEGF) inhibitor, tivozanib demonstrated the greatest efficacy, with PFS of 14.8 months and an overall response rate (ORR) of 36%.[2]
- Two trials that explored the use of combination therapy also yielded favorable and noteworthy results.[3,4] One of these trials involved the use of the mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, combined with bevacizumab. The other trial produced promising results in clear-cell RCC with the use of bevacizumab and low-dose interferon.
- The ongoing search for a biomarker with predictive value received a boost from a study, which suggests the potential value of *c-MET* as a single-nucleotide polymorphism (SNP). An oral presentation reviewed the first study to implicate germline variations in the *c-MET* gene with cancer recurrence in patients with localized renal cell carcinoma (RCC).[5]

The Next Generation of Targeted Therapy: ASCO's Focus on Axitinib

Most of the attention in kidney cancer, however, was focused on axitinib and the possibility that it could be approved by the end of the year or soon after as an additional therapeutic option for patients with advanced RCC. The new data, from the first head-to-head phase 3 study that compared active targeted therapies in advanced RCC (axitinib vs sorafenib), showed clinically meaningful improvement in PFS with axitinib while accompanied by generally manageable tolerability, an important consideration for these patients.

Axitinib is an oral, potent, and selective inhibitor of VEGF receptors 1, 2, and 3. The randomized, open-label, phase 3 trial compared the efficacy and safety of axitinib with sorafenib as second-line therapy for metastatic RCC. Eligible patients had clear-cell metastatic RCC; measurable, RECIST-defined PD after 1 earlier trial of first-line systemic therapy with a sunitinib-, bevacizumab-, temsirolimus-, or cytokine-based regimen; and Eastern Cooperative Oncology Group performance status (PS) of 0 or 1. Patients were stratified by PS and prior therapy, then randomized 1:1 to axitinib, administered at a starting dose of 5 mg bid, titrated to 7 mg bid and then to 10 mg bid as tolerated, or sorafenib 400 mg bid. The primary endpoint was PFS per blinded, independent radiographic review.

A total of 723 patients were randomized to either axitinib (n = 361) or sorafenib (n = 362). Baseline patient characteristics included median age of 61; 72% male; 76% white; and 55% PS 0. Prior therapy included 54% sunitinib-, 35% cytokine-, 8% bevacizumab-, and 3%

temsirolimus-based regimens. Median PFS was 6.7 months for axitinib compared with 4.7 months for sorafenib, ($P < .0001$). PFS favored axitinib in both the prior cytokine subgroup (12.1 vs 6.5 months; $P < .0001$) and the prior sunitinib subgroup (4.8 vs 3.4 months; $P = .0107$). Objective response rates were 19.4% for axitinib vs 9.4% for sorafenib ($P = .0001$).

Common adverse effects were more frequent with axitinib compared with sorafenib and included hypertension (40% vs 29%, all grades), fatigue (39% vs 32%), dysphonia (31% vs 14%), and hypothyroidism (19% vs 8%). The more frequent adverse effects with sorafenib included hand-foot syndrome (27% vs 51%), rash (13% vs 32%), alopecia (4% vs 32%), and anemia (4% vs 12%). Rini and colleagues[1] concluded that axitinib should be considered the reference standard for second-line treatment in metastatic RCC.

Tivozanib Phase 2 Data Look Promising

Although axitinib is further along on its path toward possible approval, tivozanib is another potent and selective small molecule TKI of VEGFR-1, -2, and -3. In the final analysis of phase 2 results, patients with advanced RCC (all histologies) and no prior VEGF-targeted therapy were enrolled. All received 16 weeks of open-label tivozanib 1.5 mg daily. Patients were then stratified: those with ≥25% tumor shrinkage continued in the tivozanib group, those with ≥25% tumor increase were discontinued, and patients with <25% tumor change from baseline (SD) were randomized to 12 weeks of double-blind tivozanib or placebo; randomized patients were unblinded at the time of PD or at the end of the double-blind phase, and those on placebo were allowed to restart tivozanib.

Of the 272 patients who were enrolled in the study, 83% had clear-cell RCC, 73% had undergone nephrectomy, and 46% had received prior therapy. In the overall study population, 84% of the patients demonstrated partial response (PR) or SD by week 16. In the overall population, the ORR was 30%, disease control rate (DCR) was 85% and median PFS 11.7 mo. The greatest efficacy was seen in patients with clear-cell histology who had undergone a nephrectomy; they had an ORR of 36%, DCR of 88% and median PFS of 14.8 months. Hypertension (45%) and dysphonia (22%) were the most common drug-related adverse effects of any grade. There was a low incidence of drug-related diarrhea (12%), asthenia (10%), fatigue (8%), dyspnea (6%), cough (5%), anorexia (5%), stomatitis (4%), hand-foot syndrome (4%) and proteinuria (3%). Grade 3/4 adverse effects were infrequent; the most common grade 3/4 adverse effect was hypertension, reported in 12% of the patients.

Tivozanib showed promising efficacy and acceptable safety and tolerability as a selective VEGFR TKI for patients with advanced or metastatic RCC. In the overall study population, the median PFS, DCR, and ORR were 11.7 months, 85%, and 30%, respectively. In patients with clear-cell RCC who had undergone nephrectomy, tivozanib demonstrated the greatest efficacy, with PFS of 14.8 months and ORR of 36%. The safety profile was acceptable with a low incidence of off-target toxicities, such as hand-foot syndrome and proteinuria. Based on these results, tivozanib is being evaluated in nephrectomized patients with advance clear-cell RCC in the global phase 3 TIVO-1.

Combination Therapy: Temsirolimus and Bevacizumab

Findings from studies of combination therapy suggest strategies to maximize the use of the mTOR inhibitor temsirolimus and the anti-VEGF agent bevacizumab. In the first trial to prospectively assess the safety and efficacy of bevacizumab with low-dose interferon (IFN) (3 MIU) in patients with metastatic RCC, showed a PFS of 15.6 months compared with the 10.5 months reported in the earlier AVOREN study that used a higher dose of IFN. The ORR was 22% in BEVLiN. (BEVLiN is the prospective study of the safety and efficacy of first-line bevacizumab [BEV] plus low-dose interferon-2α (IFN) in patients with metastatic RCC.)

The incidence of any grade and grade ≥3 specific IFN-associated adverse effects in BEVLiN were lower than in an AVOREN subgroup. Thus, the incidence of IFN-associated adverse effects appears to be decreased with low-dose IFN + BEV without compromising PFS in BEVLiN, compared with a historical control subgroup in AVOREN (15.6 vs 10.5 months, respectively).

Final results of the phase 2 study of temsirolimus combined with bevacizumab in RCC patients previously treated with a VEGFR TKI also showed promise as an effective strategy. Patients with measurable Stage IV RCC with a component of clear/conventional cell type, performance status 0-2, and good organ function were eligible. The phase 2 dose was intravenour (IV) temsirolimus 25 mg weekly and bevacizumab 10 mg/kg every 2 weeks repeated in 4 week cycles. The primary objective was to assess the proportion of patients who were progression-free 6 months after study entry. Secondary objectives were the assessment of response rates and toxicity. Forty patients were evaluable for response assessment and 45 evaluable for toxicity. Most common (>5%) grade 3-4 adverse effects (n = 45) included fatigue (17.8%), hypertriglyceridemia (11.1%), stomatitis (8.9%), proteinuria (8.9%), abdominal pain (6.7%), and anemia (6.7%).

The best responses were: PR 9 (23%); SD 25 (63%); PD 6 (14%). The 6-month progression-free rate was 40% (16/40 pts); median time to progression was 7 months; median overall survival was 20.6 (11.5-23.7) months.

The authors concluded that the combination at the recommended phase 2 doses is feasible and active in receptor tyrosine kinase inhibitor (RTKI) treated RCC patients. The 6-month progression-free rate (40%) met the efficacy endpoint and warrants confirmatory studies for clinical activity.

The feasibility, tolerability, and efficacy of multiple

combinations of currently available therapies are being tested in the Eastern Oncology BeST trial. This 4-arm study randomly assigns patients to bevacizumab 10 mg/kg IV every 2 weeks, bevacizumab 10 mg/kg IV every 2 weeks plus temsirolimus 25 mg IV weekly, bebacizumab 5 mg/kg IV every 2 weeks plus sorafenib 200 mg orally twice daily, or sorafenib 200 mg orally twice daily and temsirolimus 25 mg IV weekly. This study was recently closed to accrual and data analysis is ongoing.[6]

Sequencing of agents may hold slightly less intellectual appeal than combination therapy, but it is a more accurate reflection of current medical practice and ultimately may provide more benefit.[6] It is not currently possible to clearly state that sequential therapy is superior to combination therapy. But it is currently preferred because of its better tolerability, and the absence of any convincing data that combination therapy provides any superiority from a response, PFS, or overall survival perspective.[6] This is why results from the BeST trial and other trials will be important.

The Next Frontier: *c-MET* as a Predictive Biomarker

Do genetic polymorphisms predict risk of recurrence in patients with localized RCC? This was the question addressed during an oral session led by Anthony Choueiri, MD, from the Dana-Farber Harvard Cancer Center, Boston. Gene polymorphisms in critical signaling pathways may affect recurrence in patients with localized RCC. To explore this issue, germline DNA was extracted from 403 patients of European-American ancestry enrolled in a prospective protocol with full baseline and follow-up clinical data. Using the Sequenom iPLEX Gold platform, genotyping was performed for select genes involved in RCC pathogenesis, angiogenesis, metabolism, and immune regulation, including *VHL, HIF-1, HIF-2, VEGF, VEGFR-2, c-MET, CAIX, mTOR, PI3K, CTLA4, PD1,* and *B7H1*.

The primary endpoint was recurrence free survival (RFS), defined as time from surgery to recurrence or death. Cox proportional hazards model was used to evaluate and identify SNPs associated with RFS. A multivariate model adjusted for clinical factors which predict recurrence. The false discovery rate (pFDR) was used to control for the number of tests performed. After a median follow-up of 43 months, clinical factors associated with RFS included clinical stage ($P < .001$), Fuhrman nuclear grade ($P < .001$) performance status ($P < .001$), tumor size ($P < .001$), and histology ($P = .003$).

A SNP in *c-MET* gene was found to be highly predictive of RFS. The prognostic features of this SNP remained significant after adjusting for clinical factors ($P = .02$ for the additive model, and $P = .01$ for the dominant model). Patients with 1 or 2 copies of the risk allele (heterozygotes and homozygotes for the rare allele, respectively) have an adjusted HR of 1.82 (95% CI, 1.14-2.91; $P = .01$) for shorter RFS compared with homozygotes for the common allele. This is the first study to implicate germline variations in the *c-MET* gene with cancer recurrence in patients with localized RCC. Validation of these findings in an independent population is planned.

New Directions, Perspectives, From Bench to Bedside

If there is a "take-home message" from ASCO 2011 it might be that we are on the threshold of some exciting developments, with some phase 3 clinical trials almost ready to mature and yield highly important data likely to have an impact on our treatment algorithm. The 2 new TKIs, Pfizer's axitinib and AVEO's tivozanib, are the candidates to watch because of their improved efficacy, "cleaner" adverse effect profile, and mechanism of inhibiting all 3 VEGF receptors. There are expectations that several new trials in progress will also produce results that will redefine how these and already approved agents should be used in the second- and third-line setting. ASCO 2012 could shape up as one of those "groundbreaking" meetings with potential revisions of the algorithm. Additional data are also expected from the head-to-head comparison of sunitinib versus pazopanib.

The overriding issue, however, remains whether research is on the verge of significant gains in overall survival. This remains to be seen and so far no combination or sequence of agents has been able to get over this hurdle. The problem with TKIs is that ultimately these drugs fail and patients require additional therapies to address the problem of resistance. It is doubtful that the new agents, albeit promising, will resolve this issue. Because they are more potent, the response rates will improve and ASCO 2012 will probably shed new results in this respect. The best that we can expect is a small and incremental benefit. New targeted therapies, addressing other pathways, are needed. The drugs in use and in phase 3 trials more effectively target the VEGF pathway, but until a better understanding of resistance emerges, significant gains in overall survival will largely remain an elusive goal.

References

1. Rini BI, Escudier B, Tomczak P, et al. *J Clin Oncol*. 2011;29(suppl): Abstract 4503.
2. Nosov D, Bhargava WB, Strahs AL, et al. Final analysis of the phase II discontinuation trial (RDT) of tivozanib (AV-951) versus placebo in patients with renal cell carcinoma. *J Clin Oncol*. 2011;29;(suppl): Abstract 4550.
3. Melichar B, Bracarda S, Matveev V, et al. BEVLiN: prospective study of the safety and efficacy of first-line bevacizumab (BEV) plus low-dose interferon- 2a (IFN) in patients (pts) with metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2011;29;(suppl): Abstract 4546.
4. Merchan JR, Pitot HC, Qin R, et al. Final phase II safety and efficacy results of study MC0452: Phase I/II trial of CCI 779 and bevacizumab in advanced renal cell carcinoma. *J Clin Oncol*. 2011;29(suppl): Abstract 4548.
5. Schutz Fabio AB, Gray KP, Pomerantz MM, et al. Do genetic polymorphisms predict risk of recurrence in patients with localized renal cell carcinoma? Results from a cohort study. Presented at the 2011 ASCO Annual Meeting. June 3-7, 2011: Chicago, IL.
6. Jonasch E, Hutson TE, Harshman LC, et al. Advanced renal cell carcinoma: overview of drug therapy for the practicing physician. *Educational Book: Genitourinary Cancer; ASCO*. 2011:145-151. KCJ

Genitourinary Cancer Abstracts

Presented at the ASCO Annual Meeting, June 3-7, 2011, Chicago, Illinois

Teh BT, Varela I, Tarpey P, et al. Identification of mutations of the SWI/SNF complex gene PBRM1 by exome: sequencing in renal carcinoma. *J Clin Oncol*. 2011;29(suppl): Abstract 4571.

Background: The genetics of renal cancer is dominated by inactivation of the *VHL* tumor suppressor gene in clear cell carcinoma (ccRCC), the commonest histological subtype.

Methods: A recent large-scale screen of ~3500 genes by PCR-based exon re-sequencing identified several new cancer genes in ccRCC including *UTX (KDM6A)*, *JARID1C (KDM5C)*, and *SETD2*. These genes encode enzymes that demethylate (*UTX, JARID1C*) or methylate (*SETD2*) key lysine residues of histone H3.

Results: Modification of the methylation state of these lysine residues of histone H3 regulates chromatin structure and is implicated in transcriptional control. However, together these mutations are present in fewer than 15% of ccRCC, suggesting the existence of additional, currently unidentified cancer genes. Here, we have sequenced the protein coding exome in a series of primary ccRCC and report the identification of the SWI/SNF chromatin remodeling complex gene *PBRM1* as a second major ccRCC cancer gene, with truncating mutations in 41% (92/227) of cases.

Conclusions: These data further elucidate the somatic genetic architecture of ccRCC and emphasize the marked contribution of aberrant chromatin biology.

Kroeger N, Klatte T, Birkhaeuser FD, et al. The effect of tobacco exposure in renal call carcinoma (RCC) overall and cancer-specific survival. *J Clin Oncol*. 2011;29(suppl): Abstract 4578.

Background: Tobacco use is a leading cause of premature death in the United States, yet few studies have investigated the effect of tobacco exposure on RCC outcomes. We retrospectively studied the impact of smoking history on clinicopathological factors, survival outcomes, and p53 expression status in a large cohort of RCC patients.

Methods: 802 patients with ccRCC treated at UCLA formed the study cohort. Patients were divided into 2 groups, never smokers (457 patients) and patients with a positive tobacco exposure history (345 patients). The Kaplan Meier method and log rank test were used to evaluate survival outcomes. Cox models were constructed to evaluate independent risk factors. Immunohistochemistry (IHC) differences in p53 expression were correlated with smoking status.

Results: Patients who were current smokers presented more commonly with pulmonary (P <.0001) and cardiac medical comorbidities (P = .014), and with a worse performance status (P = .031) than nonsmokers. Smoking was significantly associated with tumor multifocality (P = .022), higher pT stages (P = .037), increased risk of lymph node metastases (P = .031) especially bulky N2 disease (P = .009), presence of distant metastases (P < .0001), especially lung metastases (P < .0001). Both overall survival (OS) 62.37 months vs 43.64 months (P =.001) and cancer specific survival (CSS) 87.43 months vs 56.57 months (P =.005) were significantly worse in the group of patients with a smoking history. In multivariate Cox models the number of pack years was retained as an independent predictor of CSS and OS in nonmetastatic patients. Mutated p53 was detected in 70.8% of current and 53.0% of nonsmokers, respectively (P = .017), and mean expression was significantly higher in current versus nonsmokers (P = .012).

Conclusions: In RCC patients, a history of smoking was associated with worse pathologic features and survival outcomes, and with increased risk of having mutated p53. Further investigation of the genetic and molecular mechanisms associated with decreased CSS in RCC patients with a smoking history are indicated.

Eto M, Kamba T, Miyake H, et al. An analysis of STAT3 polymorphism on outcomes of interferon-α treatment in patiens with metastatic renal cell carcinoma. *J Clin Oncol*. 2011;29(suppl): Abstract 4590.

Background: We previously reported that single nucleotide polymorphisms (SNPs) in the signal transducer and activator 3 (*STAT3*) gene were most significantly associated with better response to interferon (IFN)-α in patients with metastatic renal cell carcinoma (mRCC) in our retrospective analysis (*J Clin Oncol*. 2007;25:2785). Japan Immunotherapy SNPs-Study Group for Kidney Cancer (JISG-KC) conducted this trial to prospectively confirm the results.

Methods: In this multicenter, prospective study, patients with histologically confirmed RCC that was metastatic, measurable disease, age > 20 years, with an ECOG PS 0-1, and adequate organ function received 3 dosages of 5 million U per week of IFN-α treatment. The primary endpoint of the study was to evaluate the correlation between the antitumor effects of IFN-α and SNP allele frequencies of STAT3-2. The secondary endpoint

was to evaluate the correlation between the antitumor effects of IFN-α and SNP allele frequencies of STAT3-0, SOCS3-1, IL4R-34, PTGS1-3, PTGS1-4, PTGS1-5, PTGS2-12, IRF2-67, ICSBP-38, and TAP2-5 (*J Clin Oncol*. 2007; 25:2785). The association between response to IFN-α and genetic polymorphism was analyzed using the logistic model. All patients consented to provide blood samples that would be used for SNPs analysis.

Results: Two hundreds four eligible patients were enrolled between December 2006 and October 2009. All patients had prior nephrectomy, and 88.7% had ECOG PS 0. Ninety-four percent of patients had clear cell RCC, and 5% had papillary RCC. At the time of this analysis the central review assessed response rate was 13.7% (28/204) (7 CR, 21 PR). The CR rate of 3.4% (7/204) was more than we expected. Response (CR, PR) to IFN-α was not associated with any of the 11 SNPs examined. However, when we assessed patients with CR, PR, and SD more than 24 weeks as those with clinical benefits and reevaluated the correlation to the 11 SNPs, the significant association between STAT3-2 and clinical benefits of IFN-α (P = .039) was observed. Namely, C/C genotype of STAT3-2 was significantly associated with clinical benefits of IFN-α.

Conclusions: This is the first prospective study demonstrating that STAT3 polymorphism can predict clinical benefits of IFN-α in patients with mRCC.

Seidel C, Fenner M, Reuter CW, Ganser A, Gruenwald V. Progression-free survival (PFS) of first-line VEGF-targeted therapy as a prognostic parameter for overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2011;29(suppl): Abstract 4591.

Background: Recent scoring systems for mRCC include laboratory markers, clinical course, and performance status, without considering the response to systemic therapy. We therefore describe the validity of the PFS during first line VEGF-targeted therapy as an independent prognostic marker for the overall survival (OS) in mRCC.

Methods: Medical records of 119 patients treated with first-line VEGF targeted therapy were retrieved and analyzed retrospectively. Ninety one patients received sunitinib; 16 patients, sorafenib; 8 patients, axitinib, and 4 patients, bevacizumab combined with either interferon-α or everolimus. The median OS and PFS were determined from start of first line VEGF-targeted therapy. Response to treatment was assessed according to response evaluation criteria in solid tumors (RECIST) 1.0. Log-rang test, Kaplan-Meier-, and Cox-regression analysis were employed to predict OS or PFS.

Results: Best response to first-line therapy consisted of stable disease in 46, partial remission in 18, complete remission in 6 and progressive disease in 25 patients. In 24 patients, best response was not evaluated. The median PFS of first-line therapy was 8.1 months (range: 3.9-18.0) and was associated with a median OS of 22.7 months (range: 0.8-46.8). On univariate analysis, a PFS above 6 months (P < .0001), second line treatment (P = .018), absence of osseous lesions (P = .012), less than 3 metastatic organ sites (P = .011), a good MSKCC score (P = .011), clear cell histology (P = .04), ECOG 0 (P = .01), and achievement of complete response were associated with a prolonged OS. On multivariate analyses patients with a PFS above 6 months (95% CI 0.145-0.438; HR 0.252), good MSKCC score (95% CI 0.072-0.530; HR 0.195), and patients receiving second-line treatment (95% CI 0.156-.674; HR 0.324) were identified as independent prognostic factors. The median OS in patients. with a PFS ≤6 or >6 months was 12 or 33 months, respectively.

Conclusions: Our analyses describe first-line PFS as an independent prognostic parameter in mRCC, suggesting that VEGF-responsiveness may play a key role for patients. Prognosis and may serve as a selection criterion for subsequent therapy.

Ambring AE, Stierner UK, Oden AS, Bjorholt IN. Sorafenib and sunitinib in renal cell cancer: a study based on register data. *J Clin Oncol*. 2011;29(suppl): Abstract 4600.

Background: There is limited data on the use of sorafenib (SO) and sunitinib (SU) in clinical practice in the treatment of advanced renal cell cancer (RCC). It has been suggested that the sequence by which the drugs are given is important for the outcome. Register data could add valuable real-life evidence to previous clinical trial data on these drugs.

Methods: Sweden has a long tradition of keeping registers, eg, Swedish Cancer Registry since 1958, Cause of Death Register 1961, and Register on Prescribed Pharmaceuticals (RPP) 2005. All Swedish citizens have a unique personal identification number and retrospective studies can be conducted by linking information from several registers. Individuals with RCC and prescribed SO and/or SU were extracted from the RPP. The date of first purchase was captured from the RPP and duration of treatment was studied. Analysis was carried out on the actual observed data on duration of treatment for first-line/monotherapy. For sequential therapy time on treatment and time to death were analyzed without making the assumption that patients survived first-line therapy, ie, the risk to stop or to die during first-line/monotherapy was accounted for.

Results: We found 123 patients starting with SO and 261 patients with SU. Median time on therapy was 148 days for SO and 138 for SU. Forty-three of these patients were treated with SO+SU and 54 with SU+SO in sequence. The influence of the duration of the first-line therapy on the risk of discontinuing second-line treatment was significantly different for SO compared to SU (P = .0096). For death, a corresponding difference was assessed (P = .0278). Small differences were seen for the calculated median duration, 252 vs 234 days for combined endpoint and 398 vs 347 days for death (excluding time between treatments) but for the proportions of

patients remaining without endpoint at 1.5 years, larger differences were seen. All differences were in favor of those starting with SO.

Conclusions: In clinical practice in Sweden, treatment duration of SO and SU is similar when given as first-line treatment or monotherapy. The order in which treatment is given in sequential therapy is important and the results indicate that SO as first-line treatment is a favorable choice.

Grünwald V, Karakiewicz PI, Bavbek SE. et al. Final results of the international expanded-access program of everolimus in patients with advanced renal cell carcinoma who progress after prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy. *J Clin Oncol*. 2011;29(suppl): Abstract 4601.

Background: The phase 3 RECORD-1 trial established everolimus as the only agent proven to benefit patients with metastatic renal cell carcinoma (mRCC) after failure of initial VEGFr-TKI therapy. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, more than doubled median progression-free survival compared with placebo, from 1.9 months to 4.9 months. The REACT (RAD001 Expanded Access Clinical Trial in RCC) study was initiated in order to address an unmet medical need and provide everolimus in advance of regulatory approval and commercial availability to patients with mRCC after failure of initial VEGFr-TKI therapy.

Methods: REACT was an open-label, international, expanded-access clinical trial (Clinicaltrials.gov: NCT00655252). Eligible patients had measurable or nonmeasurable mRCC of any histology, were intolerant of, or progressed while on, VEGFr-TKI therapy, had a Karnofsky performance score ≥70%, and had adequate bone marrow, hepatic, and renal function. Patients received everolimus 10 mg/day orally, with dose and schedule modifications allowed for toxicity. The primary objective of REACT was to evaluate the long-term safety of everolimus in patients with mRCC, as determined by the overall incidence of grade 3/4 and serious adverse events (AEs). Tumor response to everolimus was also assessed according to RECIST.

Results: A total of 1367 patients from 34 countries were enrolled. Safety findings and tumor responses were consistent with those observed in RECORD-1. The most commonly reported grade 3/4 AEs were anemia (13.4%), fatigue (6.7%), and dyspnea (6.4%), and the most frequent serious AEs were dyspnea (5.0%), pneumonia (4.7%), and anemia (4.1%). Median dose intensity was 10.0 mg/day; relative dose intensity ranged from 0.90 to 1.10 in 68.9% of patients.

Conclusions: REACT evaluated the safety and tolerability of everolimus in a broader patient population than the controlled trial RECORD-1. Everolimus was well tolerated, with no new safety issues identified and infrequent dose reductions/interruptions in the majority of patients.

Stein AM, Carter A, Hollaender N. Motzer RJ, Sarr C. Quantifying the effect of everolimus on both tumor growth and new metastases in metastatic renal cell carcinoma (RCC): a dynamic tumor model of the RECORD-1 phase 3 trial. *J Clin Oncol*. 2011;29 (suppl): Abstract 4602.

Background: The randomized, placebo-controlled phase 3 trial RECORD-1 (NCT00410124) established mammalian target of rapamycin (mTOR) inhibitor everolimus as an effective therapy for prolonging progression-free survival (PFS) in patients with advanced RCC who had progressed after sunitinib or sorafenib. The 10-mg daily everolimus dose administered in RECORD-1 was based on phase 1 studies correlating this regimen with constant and near-complete inhibition of mTOR pathway signaling. Dose reduction to 5 mg daily was allowed for toxicity. We developed a mathematical model of tumor growth in RECORD-1 to evaluate the effect of these 2 everolimus doses on growth of target lesions, nontarget lesions, and new metastases.

Methods: Tumor growth in all patients with a baseline tumor measurement (n = 407) was described using nonlinear mixed effects modeling. Local radiological data were collected over time on the sum of largest target lesion diameters (SLD), progression status of nontarget lesions, and appearance of new lesions. By fitting a mathematical model for tumor growth to each patient, the impact of everolimus dose on all 3 lesion types was investigated.

Results: Everolimus slowed growth of all 3 lesion types versus placebo ($P < .0001$). For target lesions, a 10-mg dose had a larger effect than a 5-mg dose ($P < .0001$). No discernible difference between doses was seen for nontarget and new lesions. The model predicts that after 1 year of continuous dosing, the change in SLD of target lesions in the average patient would be 142.1% ± 98.3% on placebo, 22.4% ± 17.2% for a 5-mg dose, and –15.7% ± 11.5% for a 10-mg dose.

Conclusions: We developed a dynamic tumor model linking everolimus dosing history with overall tumor time course for each patient from RECORD-1. These tumor growth biomarkers are closer to the primary clinical endpoint (PFS) than measures of mTOR pathway inhibition, and thus may provide better predictions of trial success. Our analysis demonstrates a significant drug effect on target, nontarget, and new lesions. Furthermore, an everolimus daily dose of 10 mg is more efficacious than 5 mg in reducing growth of target lesions in metastatic RCC.

Hutson TE, Bukowski RM, Rini BI. et al. A pooled analysis of the efficacy and safety of sunitinib in elderly patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2011;29(suppl): Abstract 4604.

Background: Sunitinib is approved multinationally for mRCC treatment (Tx), with demonstrated activity and tolerability in both the first- and second-line Tx settings. Here, we report a retrospective analysis of the efficacy

and safety of sunitinib as a function of age in patients with mRCC from 6 clinical trials.

Methods: Analyses included pooled data from 1059 patients who received single-agent sunitinib on the approved 50 mg/d 4-weeks-on/2-weeks-off schedule (n = 689; 65%) or at 37.5 mg continuous once-daily dosing (n = 370; 35%), in both the first- (n=783; 74%) and second-line (n = 276; 26%) Tx settings. Median progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan-Meier method and compared between patients <70 vs ≥70 years of age by log-rank test. Adverse event (AE) rates were also compared.

Results: Of 1059 patients, 857 (81%) were younger than 70 years and 202 (19%) were 70 years or older, with median ages of 57 and 73 years, respectively; 73% and 59% were male, but otherwise baseline characteristics were similar. Median PFS was similar in both groups (9.0 vs 10.9 months; HR, 0.85; 95% CI, 0.70-1.02; *P* = .0830), as was median OS (23.3 vs 23.7 months; HR, 0.94; 95% CI, 0.76-1.15; *P* = .5441). In addition, efficacy was similar by age regardless of Tx setting. In first-line patients <70 vs ≥70 years, median PFS and OS were 9.9 months (95% CI, 8.3-10.7) vs 11.0 months (95% CI, 9.0-14.7) and 23.5 months (95% CI, 21.1-27.6) vs 25.5 months (95% CI, 21.6-38.4); in second-line patients, median PFS and OS were 8.1 months (95% CI, 7.8-8.7) vs 8.4 months (95% CI, 6.3-14.2) and 20.1 months (95% CI, 16.2–25.0) vs 15.8 months (95% CI, 13.7-23.9). Most Tx-emergent AEs occurred at similar rates in both age groups; however, some AEs were significantly less common in patients aged <70 vs ≥70 years, including fatigue (59% vs 69%), decreased appetite/weight (29% vs 53%), cough (20% vs 29%), peripheral edema (17% vs 27%), anemia (17% vs 25%), and thrombocytopenia (16% vs 25%; all P<0.05). Hand–foot syndrome was more common in younger patients (32% vs 24%; *P* < .05).

Conclusions: In patients with mRCC, the efficacy of sunitinib was comparable in the elderly population, deriving similar benefit as younger patients regardless of Tx setting. The AE profiles were also similar, although some AEs were more common in elderly patients.

Gore ME, Jones RJ, Ravaud A, et al. Efficacy and safety of intrapatient dose escalation of sorafenib as first-line treatment for metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2011;29(suppl): Abstract 4609.

Background: Previous data of intrapatient dose-escalated sorafenib in mRCC suggest that doses up to 800 mg bid were manageable with enhanced activity in terms of PFS and responses compared to the standard dose of 400 mg bid. This phase 2 study was conducted to investigate these earlier findings.

Methods: Main eligibility criteria were metastatic and/or unresectable clear cell RCC; at least one measurable lesion, ECOG PS 0/1, MSKCC score good or intermediate, no prior systemic anticancer therapy. Patients (patients) were to receive sorafenib 400 mg bid for 4 weeks, then 600 mg bid for 4 weeks, and 800 mg bid from month 3 to 6+, with response evaluated at 6 months. The primary endpoint was response rate (best overall response) within the first 6 months of treatment (≥4 months of treatment at the highest tolerated dose for all patients).

Results: Of the 83 enrolled patients (65% male) who received at least 1 dose of sorafenib (safety population); 16 withdrew due to grade 1/2 toxicities and 67 had at least 1 postbaseline assessment (ITT population). Dose escalation per protocol was tolerated by 18 patients; all achieved clinical benefit (9-PR; 9-SD). The other 49 patients had dose escalations and reductions as tolerated throughout the study. Results for the ITT population and subgroups taking 400, 600, or 800 mg bid for the longest time while on study are shown (**Table**). Median age in the 400, 600, and 800 mg bid groups was 64.5, 58.5, and 57 years, respectively; other baseline characteristics were comparable. No clinically relevant differences in the severity or frequency of adverse effects were seen across the 3 groups.

	400 mg bid (n = 25)	600 mg bid (n = 12)	800 mg bid (n = 20)	ITT population (n = 67)*
Partial response n (%)	1 (4)	2 (16.7)	7 (35)	12 (17.9)
Stable disease n (%)	15 (60)	10 (83.3)	13 (65)	46 (68.7)
Clinical benefit (PR+SD) n (%)	16 (64)	12 (100)	20 (100)	58 (86.6)
Median PFS mo (95% CI)	3.7 (1.8-9.5)	7.4 (6.3-12)	8.5 (5.6-14.9)	7.4 (6.3-9.7)
PFS rate at 12 months %	18.7	33.3	46.4	35.9

*The dose for the longest time on treatment was 200 mg/day for 3 pts and 400 mg/day for 7 pts.

Conclusions: In the majority of patients dose escalation per protocol was not feasible. Patients in whom the sorafenib dose could be escalated above 400 mg bid appeared to have greater clinical benefit.

Porta C, Escudier B, Hutson TE, et al. Karnofsky performance status (KPS) and tumor response in the RECORD-1 phase 3 trial of everolimus in patients with advanced renal cell carcinoma (RCC). *J Clin Oncol*. 2011;29(suppl): Abstract 4610.

Background: In the RECORD-1 phase 3 trial of patients with metastatic RCC who failed initial sunitinib or sorafenib, everolimus reduced tumor burden in 47% of patients (vs 10% on placebo). Notably, everolimus also prolonged the time to KPS deterioration (≥10%) (5.78 vs 3.84 months). This retrospective analysis of RECORD-1 further explores the relationship between KPS deterioration and response (as measured by best percent change in tumor size, best overall response, and progression-free survival [PFS]).

Methods: Eligible patients had baseline KPS ≥70% and measurable mRCC that progressed on initial suni-

tinib or sorafenib. Patients received everolimus 10 mg/day (n = 277) or placebo (n = 139) plus best supportive care. Tumor response was assessed centrally according to RECIST. KPS was determined at baseline, day 1 of each 28-day cycle, and at end of study treatment.

Results: Mean baseline KPS for all patients was 88%. At study end, everolimus-treated patients showed less deterioration in KPS than placebo-treated patients (mean KPS = –8.08 vs –13.09; *P* = .025). Patients in either arm who achieved a partial response (PR, n = 5) or stable disease (SD, n = 229) had less deterioration of KPS than patients with progressive disease (PD, n = 131): mean KPS = –2.00, –7.03, –14.50, respectively; *P* = .002 for SD vs PD. In everolimus-treated patients, however, the change in KPS was not correlated with best percent change in tumor size (Pearson correlation coefficient, 0.050; *P* = .489), suggesting that even patients with minimal or no reduction in tumor burden may derive KPS benefit from everolimus. In the subgroup of patients with no deterioration in KPS at the end of study treatment (KPS ≥0), everolimus significantly prolonged PFS vs placebo (4.90 vs 3.48 months, HR = 0.44, *P* < .001).

Conclusions: In RECORD-1, everolimus delayed and reduced the degree of KPS deterioration versus placebo. Furthermore, in patients with stable KPS, everolimus was associated with improved PFS over placebo. These results provide further evidence of the efficacy and tolerability of everolimus in patients with mRCC who fail initial sunitinib or sorafenib.

van der Veldt AA, Eechoute K, Oosting S, et al. Single-nucleotide polymorphisms (SNPs) in the endothelial nitric oxide synthase (NOS3) and vascular endothelial growth factor (VEGF) and its relationship to sunitinib-induced hypertension. *J Clin Oncol*. 2011;29 (suppl): Abstract 4611.

Background: Hypertension is a common adverse effect in patients treated with sunitinib and is likely associated with inhibition of the VEGF/VEGF receptor(R)-2 pathway. SNPs in *VEGF-A*, *VEGFR-2*, but also in *NOS3* and *endothelin-1* (*EDN1*) have been mentioned as possible candidates associated with a higher risk on development of hypertension.

Methods: A retrospective multicenter study was performed in 255 patients with advanced renal cell cancer and gastrointestinal stromal tumor treated with sunitinib 50 mg/day in a 4 weeks on 2 weeks off or 37.5 mg/day continuous schedule. Office systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at baseline and on days 14 and 28 of the first treatment cycle. Hypertension was graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE). Seven SNPs in genes encoding for *VEGF-A* (rs2010963, rs833061, rs3025039, rs699947), *VEGFR-2* (rs1870377), *EDN1* (rs5370) and *NOS3* (rs2070744) were selected. SNPs were univariately tested against hypertension grades according to CTCAE.

Results: During the first treatment cycle, sunitinib induced a mean increase of 13 ± 23 mmHg and 10 ± 12 mmHg in SBP and DBP (t-test, *P* < .001), respectively. According to CTCAE, 36.5 % of patients developed hypertension. Among these patients, 10.6%, 12.9%, and 12.9% had hypertension grade 1, 2, and 3, respectively. Development of grade 3 hypertension was associated with 2 copies of the C-allele in *VEGF-A* (rs833061; Chi-square, *P* = .048), 2 copies of the A-allele in *VEGF-A* (rs699947; *P* = .053), and a C-allele in *NOS3* (rs2070744; *P* = .051).

Conclusions: SNPs in genes of *NOS3* and *VEGF-A* are associated with the development of severe hypertension in patients treated with sunitinib. In particular, the association between the NOS3 pathway and hypertension induced by an inhibitor of the VEGF/VEGFR-2 pathway is a new finding. Hence, SNPs in *VEGF-A* and *NOS3* genes may identify patients predisposed to develop hypertension on sunitinib treatment.

Molina AM, Jia X, Ginsberg MS, et al. Long-term response to sunitinib for metastatic renal cell carcinoma (mRCC) patients treated on clinical trials at Memorial Sloan-Kettering Cancer Center. *J Clin Oncol*. 2011;29(suppl): Abstract 4615.

Background: Sunitinib has significant activity in patients with mRCC. We report long-term responders, defined as patients achieving ongoing complete response (CR) or remaining progression-free for >18 months on sunitinib.

Methods: 186 patients were treated with sunitinib alone or in combination on 9 clinical trials; all had >2 years of follow-up from sunitinib start to analysis. Median progression-free survival (PFS) was 11 months (95% CI 8-14); median OS was 27 months (95% CI 21-35). Thirty four long-term responders were identified.

Results: Characteristics for the 34 and the entire cohort of 186 were examined (**Table**). Best response for

	All (N = 186)	Long-term responders (n = 34)	Univariate logistic analysis (yes vs no)	
			Odds ratio (95%CI)	*P* value
Sites of disease*				
Bone	50 (27%)	5 (15%)	0.41 (0.15, 1.12)	0.08
Lung	130 (70%)	18 (53%)	0.39 (0.18, 0.84)	0.02
Liver	40 (22%)	4 (12%)	0.43 (0.14, 1.29)	0.13
>2 metastatic sites*	139 (75%)	22 (65%)	0.53 (0.24, 1.19)	0.12
Prior treatment	73 (39%)	16 (47%)	1.48 (0.70, 3.14)	0.30
Clear cell histology	164 (88%)	31 (91%)	1.48 (0.41, 5.30)	0.55
MSKCC risk group				
Favorable	91 (49%)	22 (65%)	2.21 (1.02, 4.78)	0.05
Intermediate/poor	95 (51%)	12 (35%)		

*1 patient missing.

the 38 patients was CR in 1, partial response in 26, and stable disease in 7 patients. Average duration of sunitinib therapy was 30 months (range 18.1-73.9 months) and 3 patients remain on therapy. Following 18 months progression-free on sunitinib, long-term responders had an additional median PFS of 25 months (95% CI, 9-51 mos). Univariate logistic regression analysis identified bone metastasis (P = .08), lung metastasis (P = .02), and intermediate/poor risk groups (P = .05) as adverse prognostic factors for long-term response (**Table**).

Conclusions: Sunitinib achieved long-term response in a subset of patients with mRCC. Lack of bone or lung metastases and good MSKCC risk may predict long-term response.

Huang P, Carducci MA, Eisenberger MA, et al. The association of pretreatment (pre-Tx) neutrophil to lymphocyte ratio (NLR) with outcome of sunitinib Tx in patients (patients) with metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2011;29(suppl): Abstract 4621.

Background: Sunitinib is a standard Tx for mRCC. The NLR, an index of systemic inflammation, is associated with recurrence of non–mRCC and poor prognosis in several types of cancer. We set out to assess the association between pre-Tx NLR and outcome of sunitinib Tx in patients with mRCC.

Methods: We performed a retrospective study of an unselected cohort of patients with mRCC, who were treated with 50 mg of oral sunitinib in cycles of 4 weeks followed by 2 weeks of rest. We analyzed the pre-Tx NLR (calculated by dividing the neutrophil count value by the number of lymphocytes) and potential factors associated with outcome such as age, past nephrectomy, RCC histology (clear cell vs non clear cell), time from diagnosis to Tx, ≥ 2 or more metastatic sites, ECOG performance status, anemia, corrected calcium >10 mg/dL, platelets count, prior cytokines/targeted Tx, sunitinib induced hypertension, percent of patients who had dose reduction/Tx interruption, and mean dose/cycle. Progression-free survival (PFS) and overall survival (OS) were determined by the Kaplan-Meier method. Multivariate analyses using Cox Regression model were performed to determine their independent effect. A survival tree analysis was used to find the best NLR cut-off value.

Results: Between 2004-2011, 133 patients with mRCC were treated with sunitinib. Excluded from the analysis were patients without available data on pre-Tx NLR, those with baseline comorbidity such as CLL, and recent (≤1 month) health event (infection, surgery) or Tx (steroids, radiation, cytokines) known to be associated with a change of blood counts. The analysis included 109 patients; 57 (53%) had an elevated NLR (>3) at baseline. Factors associated with PFS were NLR ≤ 3 (HR 0.38, P = .009, median PFS 4 vs 15 months in patients with baseline NLR >3 vs ≤ 3), past nephrectomy (HR 0.38, P = .049), and non–clear cell histology (HR 1.5, P = .0260). NLR ≤ 3 was associated with OS (HR 0.3, P = .007, median 14 months vs not reached with a median follow-up of 35 months).

Conclusions: In patients with mRCC treated with sunitinib, pre-Tx NLR may predict PFS and OS. Whether this is specific to sunitinib or generalizable to other TKIs is not known.

Fisher RA, Pender A, Thillai K, et al. Observation prior to systemic therapy in patients with metastatic renal cell carcinoma in the kinase inhibitor era. *J Clin Oncol*. 2011;29(suppl): Abstract 4630.

Background: Patients with metastatic renal cell carcinoma (mRCC) are heterogenous, with significant variation in clinical course. The use of vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR) kinase inhibitors has dramatically changed the prognosis for these patients. However, these treatments are noncurative, necessitating chronic therapy. There is a cohort of patients with indolent disease in whom the initiation of systemic therapy is often deferred. It is inferred that the planned deferment of systemic therapy does not negatively impact on clinical benefit, but there is a lack of published data in the "kinase inhibitor era" to support this contention.

Methods: This was a retrospective study. Patients with mRCC treated with sunitinib who had a planned period of observation before the initiation of systemic therapy because of asymptomatic or slowly progressive disease were analysed. The primary objective was to determine the progression-free survival (PFS) of patients on deferred first-line systemic therapy.

Results: Records of 251 patients treated with sunitinib between 2005 and 2010 were reviewed; 64 patients who met the criteria were identified. The median age at diagnosis was 56 years and 75% were male; 80% had clear cell mRCC. All patients but 1 had a favorable or intermediate prognosis (Heng). The median time from diagnosis of metastases to starting treatment was 14.7 months (95% CI 10.4-16.3). Initial systemic therapy was interferon for 28% of patients and sunitinib for 65% of patients. Interferon patients had a median PFS of 6.3 months (95% CI 3.3-9.9), and sunitinib patients had a median PFS of 4.3 months (95% CI 3.6-7.3). Patients who received a VEGFR kinase inhibitor as second-line therapy after interferon had a median PFS of 7 months (95% CI 4.3-12.5). The median overall survival for all patients was 35 months (95% CI 26-42.3).

Conclusions: In this cohort of patients with indolent favorable or intermediate prognosis mRCC, systemic treatment was deferred by a median of over 1 year but the efficacy of delayed sunitinib treatment was less than expected. Further study is required to define the group of patients for whom delayed systemic therapy is optimal.

Blagoev KB, Wilkerson J, Stein WD, Motzer RJ, Bates SE, Fojo AT. Effect of sunitinib (SU) administration on posttreatment survival in patients with metastatic renal cell carcinoma (mRCC) treated on the upfront randomized phase 3 trial of sunitinib or interferon α(IFN). *J Clin Oncol*. 2011;29(suppl): Abstract 4634.

Background: Drugs targeting VEGFR are approved for, or under investigation in, cancer treatment. Animal experiments suggest such therapies may accelerate metastases (Ebos et al. *Cancer Cell*. 2009). We sought to address whether treatment with a VEGFR agent might accelerate tumor growth after its discontinuation.

Methods: We compared the time on treatment (TOT), posttreatment survival (PTS), overall survival (OS), and tumor growth rate constants (g) of patients with mRCC randomized to either SU or IFN. We used linear regression models to evaluate associations between these measures.

Results: Although reported response rate and progression free survival were better in the SU arm (Motzer et al. *New Engl J Med*. 2006), patients randomized to IFN had a longer PTS than patients randomized to SU (median: 29.1 v 18.7 wks, $P = .006$). While acquisition of a growth-retarding immune response following IFN cannot be excluded, ≈ 60% of IFN patients eventually received SU or another VEGFR agent and this may have caused the longer PTS following IFN. That randomization to SU was not detrimental is supported by the observation that longer TOT did not reduce PTS (slope of regression line = –0.054, 95% CI –0.189-0.048) indicating increased SU exposure does not adversely impact PTS. Furthermore, tumor response defined as the minimum sum of the longest diameters (LD) divided by initial sum of LD, and thus analyzed as a continuous variable, modestly correlated with TOT (Rsq = 0.28, $P < .001$), but not at all with PTS ($R_{sq} = 0.027$, $P = .02$). Similarly, the g calculated while patients received on-study treatment was correlated with TOT ($R_{sq} = .68$; $P < .0001$) and OS ($R_{sq} = 0.40$; $P < .0001$) but not PTS ($R_{sq} = 0.008$; $P = .27$).

Conclusions: Neither the duration of SU treatment nor its antitumor activity, reflected in tumor response and g, had an effect on PTS. Thus, SU reduces tumor growth while administered, improves OS, and appears unlikely to alter tumor biology after treatment discontinuation. Concerns arising from animal models do not appear to apply to patients receiving SU.

Saroha S, Uzzo R, Hudes GR, Plimack ER, Ruth K, Al-Saleem TI. The prognostic significance of prenephrectomy absolute lymphocyte count in clear cell renal cell carcinoma. *J Clin Oncol*. 2011;29(suppl): Abstract 4641.

Background: We hypothesized that a low peripheral blood absolute lymphocyte count (ALC), a likely index of poor systemic immunity, may be associated with aggressive features and inferior outcome in clear cell renal cell carcinoma (RCC).

Methods: We retrospectively analyzed preoperative blood cell counts in patients undergoing primary surgical resection for clear cell RCC at Fox Chase Cancer Center between 1994 and 2009. The patients from year 2009 were excluded from analysis of overall survival (OS) due to a short follow-up. ALC values as a continuous variable and at a level below 1300/µl (below reference range in our laboratory) were correlated with tumor grade, pathologic tumor stage (pT), presence of distant metastases and a collaborative tumor-node-metastasis (TNM) stage. We used the Kaplan-Meier product-limit method to estimate the OS by low ALC status. Differences in the survival curves were assessed using the log rank test. We also performed Cox proportional hazards regression for inferences about the relationship of survival time with low ALC adjusting for age (<60 yrs vs 60+ yrs at surgery) and TNM stage as covariates.

Results: 516 patients were eligible for analysis (32% female; median age = 60 years, range 25-89 years); 138 (27%) patients had ALC <1300/µL; 430 patients were included for analysis of OS (median follow-up 33.5 months). As a continuous variable, low ALC was associated with higher nuclear grade ($P = .0044$), higher pT ($P = .0088$), presence of distant metastases ($P < .0001$), and higher TNM stage ($P < .0001$). Similarly, ALC at a level below 1300/µL was associated with high grade ($P = .0127$), high pT (0.027), distant metastases ($P < .0001$), and high TNM stage ($P < .0001$). Low ALC was also associated with significantly worse OS ($P < .0001$). The association with OS was independent of TNM stage and patient's age in multivariable analysis ($P = .018$).

Conclusions: Here we demonstrate for the first time that a low peripheral blood ALC is associated with higher nuclear grade, pathologic stage, presence of metastases and inferior overall survival in clear cell RCC patients.

Casper J, Goebel D, Gruenwald V, et al. Efficacy and safety of sunitinib in patients with metastatic renal cell carcinoma on hemodialysis. *J Clin Oncol*. 2011;29(suppl): Abstract 4646.

Background: Sunitinib treatment is currently a standard of care for the treatment of metastatic renal cell carcinoma. Patients (patients) on hemodialysis however were excluded from studies and only a few cases of patients on hemodialysis have been reported.

Methods: We have performed a retrospective study by contacting over 100 hemodialysis institutions in Germany. Twenty eight patients had been treated between November 2006 and July 2010. Twenty one patients, with a median age of 64 years (range 47-82) and a median ECOG of 1 (range 0-2) were evaluable: 16 patients had an intermediate risk, 2 patients a low risk, and 3 patients a poor risk according to MKSCC criteria. Sunitinib doses were 25 mg (3 patients), 37.5 mg (8 patients), and 50 mg (9 patients) in the 4 week treatment and 2 weeks off schedule. One patient received 50 mg continuously. In median, 9 courses were given (range 1–18).

Results: The estimated median progression-free survival of this cohort was 15 months (95% CI 11-19) with a median overall survival of 29 months (95% CI 12-47). One of 21 patients (5%) reached complete remission, 10 patients (47%) had a partial remission, 5 patients (24%) had stable disease, 3 patients (14%) had progressive disease, and 2 patients (10%) were not evaluable because of insufficient data. Most adverse effects were comparable to those commonly reported. However, nausea (4 patients, 19%), vomiting (3 patients, 14%), hypertension (4 patients, 19%), and cardiac failure (2 patients, 10%) may have had a higher incidence. In 5 out of 10 patients receiving 50 mg sunitinib, dose reductions were performed. Therapy was discontinued due to adverse effects in 7 of 21 patients (4 of 8 with 37.5 mg, 3 of 10 with 50 mg sunitinib) without prior dose reduction.

Conclusions: Therapy with sunitinib in patients on hemodialysis is feasible and well tolerated. Hypertension, nausea, and vomiting as well as cardiac failure may be more frequent. Dose adjustments may be necessary more frequently. Despite this, response rates as well as progression-free and overall survival compare well with patients with normal kidney function.

Reeves JA, Spigel DR, Daniel DB, Friedman EK, Burris HA, Hainsworth JD. Pazopanib in patients with metastatic renal cell carcinoma previously treated with sunitinib or bevacizumab: a Sarah Cannon Research Institute phase 3 trial. *J Clin Oncol*. 2011;29 (suppl): Abstract 4659.

Background: Pazopanib, a multitargeted inhibitor of VEGFR, PDGFR, and c-KIT, is an active first-line agent in the treatment of advanced renal cell carcinoma (RCC). The efficacy of pazopanib in patients who have progressed on other antiangiogenesis agents, particularly sunitinib, is unclear.

Methods: Patients with metastatic clear-cell RCC who had progressed on or were intolerant of first-line single-agent sunitinib or bevacizumab were eligible. Additional criteria: ECOG PS 0 or 1; measurable disease (RECIST); previous nephrectomy unless clinically inappropriate; no active CNS metastases; adequate bone marrow, kidney, liver function; no risk factors for antiangiogenesis agents; informed consent. All patients received pazopanib 800 mg PO daily. Response was assessed every 8 weeks until disease progression.

Results: 44 patients have been treated with pazopanib (previous sunitinib: 32; previous bevacizumab: 12). Additional patient characteristics: male/female, 77%/ 23%; Motzer risk low/intermediate/high, 25%/ 43%/ 32%; previous nephrectomy, 93%. The median duration of treatment was 24 weeks (range 0-52 weeks). After a median follow-up of 9 months, efficacy is as follows (**Table**): 37 patients remain alive and 13 are continuing treatment. Toxicity with pazopanib was similar to previous reports: frequent grade 3/4 toxicity included fatigue (14%), hypertension (11%), proteinuria (11%). Three patients discontinued treatment due to toxicity and 13 required dose reductions.

	All (N = 44)	Previous sunitinib (n = 32)	Previous bevacizumab (n = 12)
ORR	9 (20%)	5 (16%)	4 (33%)
Disease control rate (CR+PR+SD)	31 (77%)	21 (66%)	10 (83%)
Median PFS, mo.	9.23 (95% CI: 5.42, NA)	12.06 (95% CI: 6.14, NA)	8.05 (95% CI: 2.76, 11.93)

Conclusions: Pazopanib is active and well tolerated following treatment with either sunitinib or bevacizumab.

Crepel M, Escudier BJ, Machiels JH, et al. Comparison of 2 major prognostic models for patients with metastatic renal cell carcinoma treated in the contemporary era of targeted therapies. *J Clin Oncol*. 2011;29(suppl): Abstract 4660.

Background: The 2 most popular prognostic systems for patients with metastatic renal cell carcinoma (mRCC) are MSKCC and French Group of Immunotherapy (FGI) models. Both systems have initially been established by using cohorts of patients treated with cytokines. No direct comparison of these 2 models has been published so far in the modern era of targeted therapies. Our goal was to compare their effectiveness in predicting overall survival (OS) in mRCC patients treated with antiangiogenic drugs.

Methods: Based on an international cohort of 965 mRCC patients from 18 tertiary care centers treated with systemic treatment, we assessed OS in univariate Cox regression according to both prognostic models stratification. Then, variables of each model were compared in multivariate Cox regression. Area under the curve (AUC) of both models was also calculated.

Results: Median OS for the entire population was 31.8 months. Both systems were able to distinguish 3 groups with statistically significantly different survivals. Median OS in good, intermediate, and poor prognostic group were 45.9, 23.5, 13.5 months and 50.9, 33.4, 13.5 months in MSKCC and FGI models, respectively. In multivariate Cox regression analysis, 3 out of the 5 variables of MSKCC model achieved independent prognostic value: hemoglobin level (HR = 1.79, P = .001), LDH elevation (HR = 4.3; P = .001), and performance status (HR = 1.71; P = .006). Similarly, 3 out of the 5 variables of the FGI model achieved independent prognostic status: hemoglobin level (HR = 1.74; P = .04); number of metastasis (HR = 2.2; P = .008), and performance status (HR = 2.12; P = .006). AUC of MSKCC and FGI models were 0.57 and 0.65, respectively. When focusing on 369 patients who received sunitinib as first-line treatment, AUC of MSKCC and FGI models were 0.66 and 0.75, respectively.

Conclusions: MSKCC and FGI are both effective prognostic models in predicting OS in mRCC patients

treated in the contemporary period. However, based on our data, the FGI model seems to exhibit better predictive accuracy than the MSKCC model. The prognostic role of the FGI model should be therefore revisited in the era of targeted therapies.

Finelli A, Horgan AM, Evans A, et al. Preoperative sorafenib (SOR) and cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2011;29(suppl): Abstract 4668.

Background: CN for mRCC in the targeted therapy era is being studied in randomized trials. Pre-op treatment may improve patient selection for CN and allows for correlative studies. We report our completed phase 2 trial with pre-op SOR and CN.

Methods: Patients with biopsy confirmed clear cell mRCC, suitable for CN, were eligible. Oral SOR (400 mg PO BID), with dose reductions, was given for 12 weeks pre-op, with the option to restart post-CN until progression. The primary aim was to determine the relationship between pathological response (pR) and time to progression (RECIST). Feasibility, tolerability, response, and paired tissue and radiological correlates were secondary endpoints.

Results: 19 men (mean age 57, range 40 - 73) enrolled (June 2007 through September 2010). 17/19 patients (89%) had stable disease following pre-op Sor, 13 had an overall decrease in disease burden (mean decrease 17%, range 1%-62%); 1 patient had partial response (PR); 1 had early progression and did not have CN. Of 18 patients who had CN, there was 1 post-op death, unrelated to protocol. 12 patients continued SOR post-op with ongoing benefit. With median follow-up of 44 weeks (15-178), median time to progression was 44 weeks (7-170). Six patients have died. Increased fibrosis was the only notable intraoperative finding. Median post-op stay was 6 days (4-23). Although significant necrosis was seen after SOR, pathology review noted no morphologic differences in viable tumor pre- and post-SOR; 1 patient with PR had near complete pR. Tumors from the first 15 patients, as well as 8 metastases and 5 invasive areas were used for a tissue microarray. Anti-VEGFR1-2, PDGFRα/β and other antibodies were studied. Differences in expression between tumors, metastases, and invasive areas were not significant. There was a significant (r = 0.968; P = .005) positive correlation between PDGFR and VEGFR2 levels. Expression was higher in patients with the greatest response by RECIST (P = .006 and 0.036 for VEGFR2 and PDGFRβ, respectively).

Conclusions: Pre-op therapy with SOR in mRCC was well-tolerated, resulted in >70% patients having tumor size reductions and did not impact tolerability to CN. Preliminary correlative studies suggest a relationship between radiologic response and certain receptor subtype expression, warranting further review. KCJ

In the next issue of *Kidney Cancer Journal:*

New Findings on the Relationship between Smoking and Renal Cell Carcinoma

Keep tabs on this and other trends in the literature with the *Kidney Cancer Journal*, now in its 9th year of publication as the most authoritative source of information on renal cell carcinoma for physicians and oncology nurses.

Kidney Cancer
JOURNAL

160 Cabrini Blvd., Suite 95
New York, NY 10033

PRSRT STD
US POSTAGE
PAID
Utica, NY
Permit No. 566