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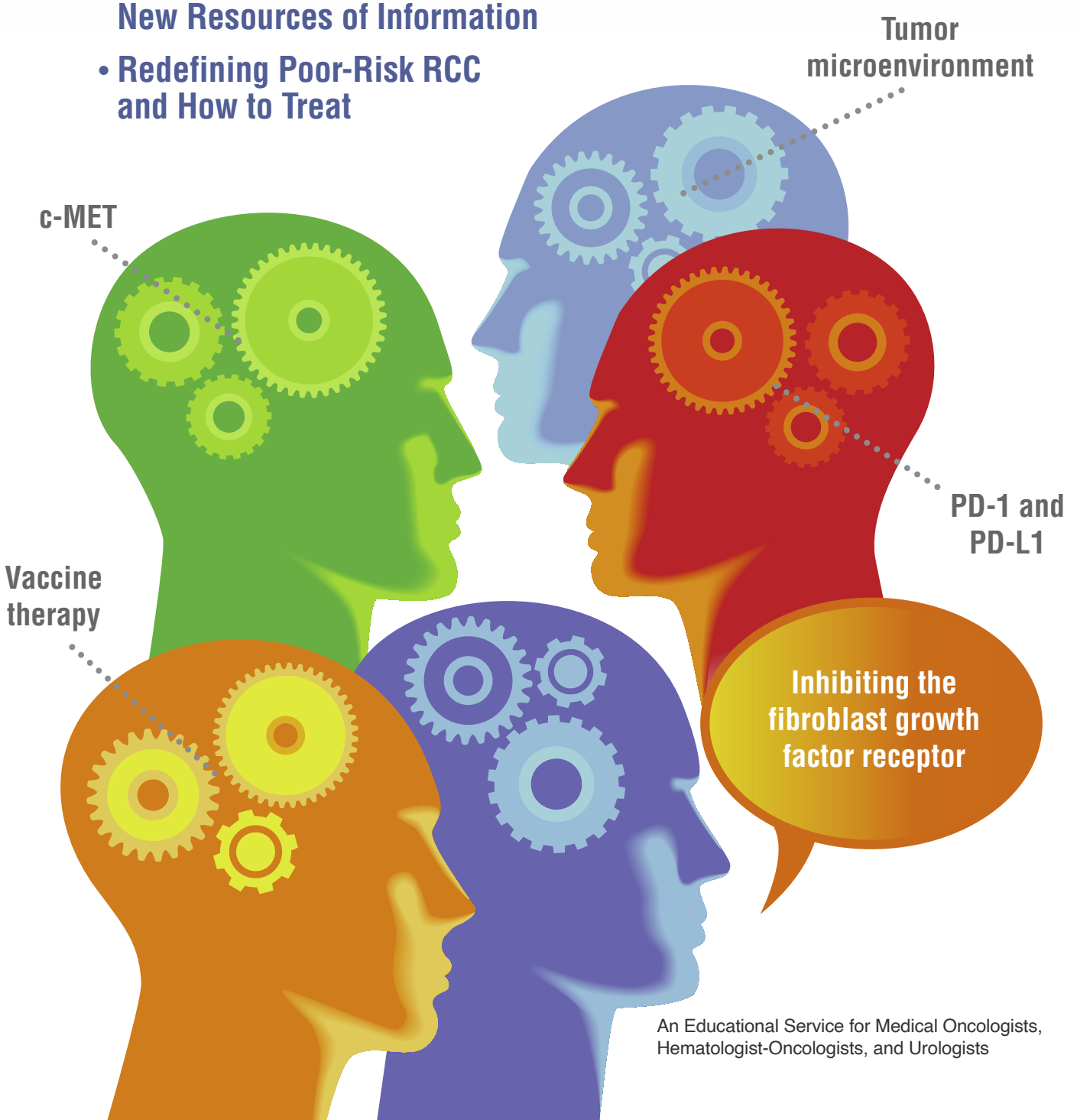
- **ASCO 2013: A Meeting of the Minds Explores Controversies, Consensus in RCC**
- **Medical Intelligence: Trends in Trials, New Resources of Information**
- **Redefining Poor-Risk RCC and How to Treat**



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

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

WHAT'S NEXT

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

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

Proven experience[1]

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

3x antitumor effect[1-3]

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

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

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

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

Important Safety Information

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

Noninfectious Pneumonitis:

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

Infections:

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

Continued on next page

Important Safety Information (cont)

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

Oral Ulceration:

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

Renal Failure:

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

Laboratory Tests and Monitoring:

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

Drug-Drug Interactions:

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

Hepatic Impairment:

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

Vaccinations:

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

Embryo-Fetal Toxicity:

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

Adverse Reactions:

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

Laboratory Abnormalities:

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

Please see Brief Summary of Prescribing Information on adjacent pages.

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

NOVARTIS ONCOLOGY

AFINITOR® (everolimus) tablets

2.5mg | 5mg | 7.5mg | 10mg

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

Noninfectious Pneumonitis

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

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

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

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

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

Infections

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

Oral Ulceration

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

Renal Failure

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

Laboratory Tests and Monitoring

Renal Function

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

Blood Glucose and Lipids

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

Hematologic Parameters

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

Drug-drug Interactions

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

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

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

Hepatic Impairment

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

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

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

Vaccinations

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

Embryo-fetal Toxicity

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

6 ADVERSE REACTIONS

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

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

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

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

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

CTCAE Version 3.0
[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.
[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).
[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

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

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

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

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

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

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

Psychiatric disorders: Insomnia (9%)

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

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

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

Renal and urinary disorders: Renal failure (3%)

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

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

Hematologic disorders: Hemorrhage (3%)

Key observed laboratory abnormalities are presented in Table 7.

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

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

CTCAE Version 3.0
[a] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

7 DRUG INTERACTIONS

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

Agents That May Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

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

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

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

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

Agents That May Decrease Everolimus Blood Concentrations

CYP3A4 Inducers

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

Drugs That May Have Their Plasma Concentrations Altered by Everolimus

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

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

Nursing Mothers

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

Pediatric Use

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

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

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

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

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

Geriatric Use

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

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

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

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

Renal Impairment

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

Hepatic Impairment

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

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

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

10 OVERDOSAGE

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

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

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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.

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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.

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

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

References

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

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

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About the Cover
This illustration suggests an exchange of current concepts in treatment presented at the 2013 meeting of the American Society of Clinical Oncology. The concepts relate to various pathways that need to be inhibited to achieve improved outcomes in renal cell carcinoma. Copyright © VLADGRIN, BigStock.

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KCJ EDITOR'S MEMO

Turn on Your GPS: Here's a Road Map to the Next Decade


Robert A. Figlin, MD

It was my privilege recently to serve as Guest Editor of an issue of *The Cancer Journal* and its coverage of how developments in renal cell carcinoma (RCC) suggest the shape of translational research in the near future and beyond. In this issue of *The Cancer Journal* (Volume. 19, Number 4: July/August 2013) a distinguished group of investigators provided a road map for the next decade of development that will continue to raise the bar for improved outcomes for this population.

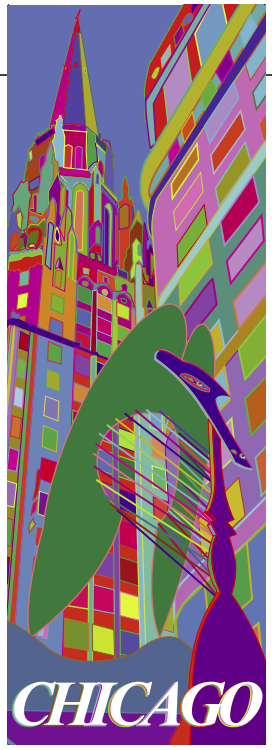
The publication of their work came at a particularly appropriate time, following closely the 2013 meeting of the American Society of Clinical Oncology (ASCO). Given the pace of research and the rapid evolution of treatment approaches, one of our biggest challenges—aside from managing this difficult disease itself—is keeping track of the factors impinging on our evaluation of patients, including alternative pathways of angiogenesis that are being investigated, new genetic abnormalities, including the significance of PBMR1 and BAP1 mutations and a broad spectrum of other issues.

Recent evidence, for example, suggests that epigenetic modifications and alterations in genes and their regulation are important in RCC. Another area of great excitement concerns our understanding of program death receptors, their ligands, the interplay of cytotoxic T lymphocytes, and novel therapeutic approaches. At ASCO attendees learned of the early promising results of programmed death-1 (PD-1) and PD-L1inhibitors in RCC. And one of the most dynamic directions is the future role of vaccine therapy; trials are in place using peptide pulsed vaccines or personalized immunotherapy generated through RNA-loaded dendritic cells both combined with sunitinib to both inhibit the vascular endothelial growth receptor and the tumor microenvironment to achieve sustained remissions.

As clinicians seek to gauge the impact of these analyses on their practice, the 2013 ASCO meeting and the publication of this "road map" for the next decade affords a rare opportunity, much like a snapshot of where we are now and where it appears things are headed. I suggest "appears" because the field of RCC research is much like a moving target. Just when we think we have it clearly in our sights, the landscape changes rapidly and new developments cast our strategies and perspectives in a different light. Consider, for example, the recent rejection by the FDA of the new tyrosine kinase inhibitor, tivozanib, one of the leading candidates for treatment that had been building momentum until Phase 3 data unexpectedly led to its demise in RCC. Although this was a disappointment, new trial data involving other agents suggest we are still on the threshold of possibly another era, this one involving personalized immunotherapy.

As I noted in my Guest Editor's message in *The Cancer Journal*: "The future of kidney cancer therapeutics will be shepherded by the translation of many of these observations and others to the clinic. It will continue to require an innovative collaborative effort by academia, industry and patients who are challenged by this disease." Building on the foundation of the last decade, we look toward the next decade during which new approaches will further extend the benefits of innovative treatment options for patients and their families.

Robert A. Figlin, MD
Editor-in-Chief



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Survey of the Literature: Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research. The articles in this section were selected from a recent issue of The Cancer Journal, *which focused on current insights on renal cell carcinoma.*

A new age for vaccine therapy in renal cell carcinoma. Pal SK, Hu A, Figlin RA. *Cancer J*. 2013 Jul-Aug;19(4):365-70.
Summary: Over the past several years, the dominant paradigm in drug development for metastatic renal cell carcinoma (mRCC) has been to more selectively and potently target moieties such as the vascular endothelial growth factor receptor. The effectiveness of this strategy appears to be nearing a plateau, however, underscoring the need for novel approaches. Vaccine-based therapies represent one such approach. Several distinct vaccines are currently being examined in mRCC, each using a distinct mechanism of action. For instance, the autologous dendritic cell vaccine AGS-003 uses patient-specific antigens derived from primary tumor tissue. In contrast, the poxvirus vaccine TG4010 produces an antigenic response to MUC1, a cell surface glycoprotein that reduces cell-cell interactions and thereby precludes contact inhibition. Other vaccines elicit a response to a broader spectrum of antigens—for instance, the vaccine IMA901 is based on 9 tumor-associated peptides identified from a novel biotechnology platform combining mass spectroscopy, microarray analysis of RNA expression, and immunogenicity assays.
Conclusion: The current status of vaccine-based therapies for mRCC is described in detail. Furthermore, challenges to clinical implementation (eg, cost, optimal pairing with targeted agents, appropriate sequencing) are presented.

Modification of the tumor microenvironment as a novel target of renal cell carcinoma therapeutics. Finke JH, Rayman PA, Ko JS, et al. *Cancer J*.2013;19:353-364.
Summary: To move forward with immunotherapy, it is important to understand how the tumor microenvironment generates systemic immunosuppression in patients with renal cell carcinoma (RCC) as well as in patients with other types of solid tumors. Even though antigen discovery in RCC has lagged behind melanoma, recent clinical trials have finally authenticated that RCC is susceptible to vaccine-based therapy. Furthermore, judicious coadministration of cytokines and chemotherapy can potentiate therapeutic responses to vaccine in RCC and prolong survival, as has already proved possible for melanoma. Although high-dose interleukin 2 immunotherapy has been superseded as first-line therapy for RCC by promiscuous receptor tyrosine kinase inhibitors (rTKIs) such as sunitinib, sunitinib itself is a potent immunoadjunct in animal tumor models. A reasonable therapeutic goal is to unite antiangiogenic strategies with immunotherapy as first-line therapy for RCC. This strategy is equally appropriate for testing in all solid tumors in which the microenvironment generates immunosuppression. A common element of RCC and pancreatic, colon, breast, and other solid tumors is large numbers of circulating myeloid-derived suppressor cells (MDSCs), and because MDSCs elicit regulatory T cells rather than vice versa, gaining control over MDSCs is an important initial step in any immunotherapy. Although rTKIs like sunitinib have a remarkable capacity to deplete MDSCs and restore normal T-cell function in peripheral body compartments such as the bloodstream and the spleen, such rTKIs are effective only against MDSCs, which are engaged in phospho-STAT3-dependent programming (pSTAT3+). Unfortunately, rTKI-resistant pSTAT3- MDSCs are especially apt to arise within the tumor microenvironment itself, necessitating strategies that do not rely exclusively on STAT3 disruption. The most utilitarian strategy to gain control of both pSTAT3+ and pSTAT3- MDSCs may be to exploit the natural differentiation pathway, which permits MDSCs to mature into tumoricidal macrophages (TM1) via such stimuli as Toll-like receptor agonists, interferon , and CD40 ligation.
Conclusion: Overall, this review highlights the mechanisms of immune suppression used by the different regulatory cell types operative in RCC as well as other tumors. It also describes the different therapeutic strategies to overcome the suppressive nature of the tumor microenvironment.

Immune checkpoint inhibitors as novel targets for renal cell carcinoma therapeutics. Bailey A, McDermott DF. *Cancer J*.2013;19:348-352.
Summary: Monoclonal antibodies targeting programmed death 1, programmed death ligand 1, and cytotoxic T-lymphocyte antigen 4 pathways are currently in development for metastatic renal cell carcinoma. By inhibiting these immune regulatory pathways, these agents improve the immune response to cancer with the goal of creating durable responses. Although still early in development, several agents have been studied in phases I and II setting for metastatic renal cell carcinoma, with 1 drug in phase III testing (nivolumab). The unique toxicity profile of this class of therapy presents challenges to the treating clinician.
Conclusion: Ongoing clinical trials hope to define patients who will benefit based on predictive biomarkers. Immune checkpoint inhibitors may play a key role in the future of management of solid tumors including kidney cancer.

PBRM1 and BAP1 as Novel Targets for Renal Cell Carcinoma. Brugarolas J. *Cancer J*. 2013;19:324-33
Summary: Technological advances in genome sequencing have led to the identification of novel driver genes mutated in renal cancer. Hitherto, one gene was known to be frequently mutated in renal cell carcinoma of clear cell type (ccRCC), the von Hippel-Lindau (VHL) gene. VHL was identified by positional cloning as the gene responsible for a familial syndrome with renal cancer predisposition, von Hippel-Lindau. Subsequently, VHL was found to be inactivated in approximately 90% of sporadic ccRCC. The discovery of VHL, together with the elucidation of its function, transformed the treatment of ccRCC leading to the introduction of 5 new drugs into the

(continued on page 58)

Immunotherapy Steals the Show at a Meeting Designed to "Build Bridges" Toward a Cure

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Like meetings before it, the 2013 Scientific Sessions of the American Society of Clinical Oncology (ASCO) raised hopes worldwide for new benchmarks in renal cell carcinoma RCC) or at least some glimmer of dramatic changes in diagnosis and management. Regardless of expectations—and this year the expectations were not dauntingly high to begin with—attendees looked for new directions and perspectives, a hopeful sign of yet another banner year in the treatment of kidney cancer. It comes as no surprise that this did not happen this year. The 2013 meeting essentially ran true to the form of the last few years—not groundbreaking, to be sure, but nonetheless establishing a clear course for the next year and a solid indication of what might be expected from ASCO 2014. The overall theme of the ASCO 2013 meeting was "Building Bridges to Cure Cancer," and this title seemed to accurately characterize the RCC agenda.

There are some closely watched themes that emerged at 2013 ASCO and other trends that grew stronger, pointing toward perhaps another new era in therapy, this one arising from immunotherapeutic approaches rather than the targeted treatments characterizing the last 8 years. Immunotherapy for RCC was the strongest trend to emerge from the sessions, but the trials are still not mature and the data are more tantalizing at this stage than confirmatory. In still other news, more information surfaced on targeted therapies, their limitations, optimal sequencing approaches and whether VEGF inhibition can be augmented with the use of an agent to target fibroblast growth factor. In brief, these were the major themes to emerge from the sessions:

Immunotherapy. Two studies featured by ASCO highlighted a new immunotherapy that is under study in kidney cancer and melanoma—an engineered, programmed death-L1 (PD-L1) targeted antibody. PD-L1 is a protein frequently overexpressed on the surface of cancer cells that acts as a disguise, allowing cancer cells to hide from the immune system. When the new immunotherapeutic agent attaches to the PD-L1 protein, the cancer can no longer hide from the patient's immune system, allowing the body's T-cells to fight the cancer. A phase 1 study of the PD-L1 targeted antibody MPDL3280A reports tumor shrinkage in 21% of patients with advanced melanoma and lung, kidney, colorectal, and stomach cancer. Therapy responses are still ongoing for 26 out of 29 patients who have been on the study between 3-15 months.

Nivolumab. The second of these studies examined another immunotherapy, nivolumab, which produced durable survival and responses in a subset of heavily pretreated mRCC patients, with an acceptable safety profile, even after long term continuous dosing.

RECORD-3: Sunitinib vs Everolimus. One of the most closely watched studies is RECORD-3, and it confirmed the standard of care of sunitinib as first-line compared with an mTOR inhibitor. The postmortem analysis from this trial suggests that VEGF-targeted therapy remains the standard of care in metastatic RCC. Moving forward, it will be important to identify tumors addicted to mTOR pathway signaling, as that might help predict longer time to progression on mTOR inhibitors.

Inhibiting the FGFR. Although it was not powered for a full comparison between nintedanib and sunitinib, a Phase 2 study suggested that nintedanib might be a useful alternative to sunitinib to avoid the adverse effects that prevent about 20% of sunitinib-treated patients from continuing on this TKI. The findings suggest that nintedanib may be effective as an inhibitor of the fibroblast growth factor receptor (FGFR) when this pathway is involved in RCC.

Pazopanib prior to nephrectomy. A Phase II Study Investigating Upfront Pazopanib In Metastatic Renal Cancer Renal Cancer, referred to as the PANTHER study, was important in demonstrating that nephrectomy after upfront pazopanib can be performed safely in mRCC and obtains control of disease in the majority of patients. This approach could potentially allow for shrinkage of primary tumors prior to surgery and upfront control of metastatic disease, while giving physicians important information about an individual patient's disease responsiveness to targeted therapy prior to nephrectomy.

Motzer RJ, Barrios CH, Kim TM, et al. Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC).

Background: Sequential SUN (tyrosine kinase inhibitor, TKI) until progression of disease (PD) followed by EVE (mTOR inhibitor) is standard therapy for patients with mRCC. This open-label, multicenter, phase II trial compared 1st-line EVE to 1st-line SUN (NCT00903175). Sequential EVE SUN was also compared with standard SUN EVE.

Methods: Patients with mRCC (clear or non-clear cell) naive to prior systemic therapy were randomized 1:1 to either 1st-line EVE 10 mg/day or SUN 50 mg/day (4 weeks on, 2 weeks off) until PD. Patients then crossed over and continued on the alternate drug until PD. Primary objective was to assess PFS noninferiority of 1st-line EVE to 1st-line SUN; defined as an observed hazard ratio $(HR)_{1st\ EVE/SUN} \leq 1.1$. Overall survival (OS), combined 1st-line and 2nd-line PFS, and safety were secondary end points.

Results: From10/09 to 6/11, 471 patients enrolled (EVE SUN, n = 238; SUN EVE, n = 233). Median age was 62 years, 85.4% had clear-cell RCC, and MSKCC favorable/intermediate/poor risk was 30/56/14%. Median follow-up was 22.7 months. A total of 53.7% of patients who discontinued 1st-line EVE entered into 2nd-line SUN and 51.6% of patients who discontinued 1st-line SUN entered into 2nd-line EVE. Median PFS (95% CI) was 7.9 (5.6-8.2) months for 1st-line EVE and 10.7 (8.2-11.5) months for 1st-line SUN. $HR_{1st\ EVE/1st\ SUN}$ (95% CI) was 1.43 (1.15-1.77). Median OS (95% CI) was 22.4 (19.7-NA) months for EVE SUN and 32.0 (20.5-NA) months for SUN EVE; $HR_{EVE\text{-}SUN/SUN\text{-}EVE}$ (95% CI) was 1.24 (0.94-1.64). A trend in favor of SUN EVE for OS was observed, but will need to be confirmed with final OS analysis. Additional efficacy results for secondary end points are forthcoming. Common treatment-emergent adverse events for 1st-line EVE vs SUN, respectively, were stomatitis (53% vs 57%), fatigue (45% vs 51%), and diarrhea (38% vs 57%).

Conclusions: Noninferiority of PFS for 1st-line EVE compared with SUN was not achieved in this randomized phase II trial of mRCC patients. The treatment paradigm remains SUN EVE since the sequence achieved optimal clinical benefit.

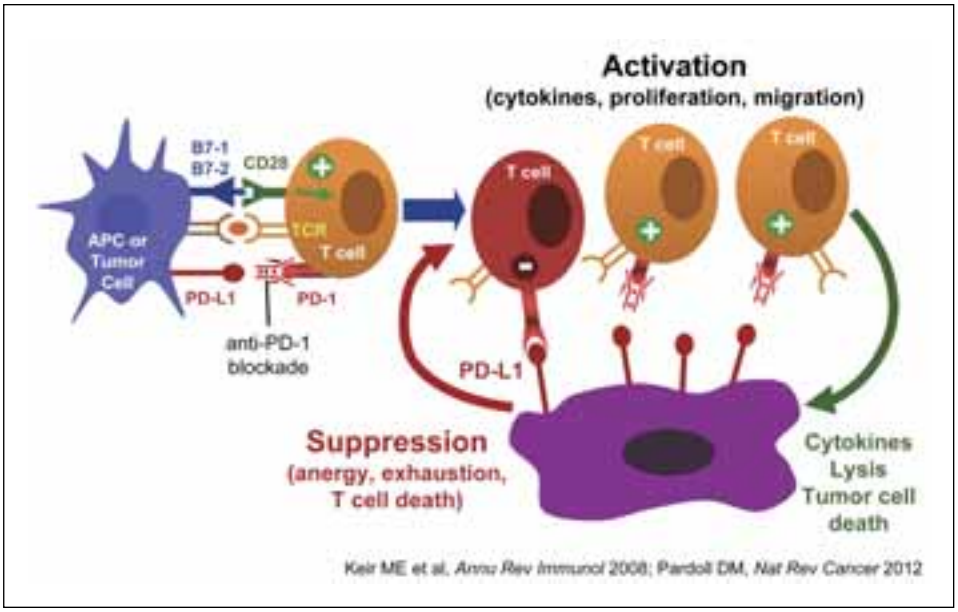
Comment: Because fewer than half of the patients actually proceeded from the first to the second line therapy, whether it was everolimus or sunitinib, the sequencing aspect of this studyis difficult to interpret.. The findings do imply that everolimus is inferior to sunitinib in the first line setting and thus, providing further evidence in support of the current stand of care of first-line TKIs.

Topalian SL, Sznol M, Brahmer JR, et al. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with advanced solid tumors: Survival and long-term safety in a phase I trial.

Background: Blockade of programmed death-1 (PD-1), a co-inhibitory receptor expressed by activated T cells, can overcome immune resistance and mediate tumor regression (Topalian et al., *NEJM* 2012). Here we present long-term safety and efficacy outcomes from a phase I study of nivolumab, a PD-1 blocking mAb, in patients (pts) with advanced solid tumors.

Methods: Pts enrolled between 2008-2012 received nivolumab (0.1–10 mg/kg IV Q2W) during dose escalation and/or cohort expansion. Tumors were assessed by RECIST 1.0 after each 4-dose cycle. Pts received ≤12 cycles until unacceptable toxicity, confirmed progression, or CR.

Results: 304 pts with non-small cell lung cancer (NSCLC, n=127, squamous and nonsquamous), melanoma (MEL, n=107), renal cell (RCC, n=34), colorectal (n=19) or prostate cancer (n=17) were treated. Durable ORs (CR/PR) were observed in MEL, NSCLC and RCC (Table); in 54 responders with ≥1 yr follow-up, 28 lasted ≥1 yr. Median OS in these heavily pretreated pts (47% with 3-5 prior systemic therapies) compared favorably with expected outcomes as of July 2012. Drug-related AEs (any grade) occurred in 72% (220/304) and G3/G4 AEs in 15% (45/304) of pts. Drug-related pneumonitis occurred in 3% (10/304), including G3/G4 in 1% (3/304), resulting in 3 deaths early in the trial, which led to increased clinical monitoring and an emphasis on management algorithms. Nivolumab-related pneumonitis characteristics and management will be summarized. Updated survival and safety data from Feb 2013 (≥1 yr follow-up all pts)will



In this schematic, the PD-1 pathway is illustrated, suggesting how PD-1 blockade can improve the immune response and provide a new treatment strategy.

be presented, including OS at 3 yr.

Conclusions: Nivolumab pro-duced sustained survival with a manageable long-term safe-ty profile in advanced MEL, NSCLC and RCC, supporting its ongoing clinical development in controlled phase III trials with survival endpoints.

Comment: Tumor cells express PD-L1, which in turn binds to the T-cell receptors PD-1 and B7.1. As long as there's PD-L1 on the surface of tumor cells, the T cell PD-1 recognizes it as "self" and therefore does not attack it, according to Roy S. Herbst, MD, PhD, a key investigator discussing immunotherapy at ASCO 2013.As soon as that PD-L1 is inactivated—in this case by blocking it with an antibody—the tumor becomes visible to the immune system, , making it for T celldestruction.

Drake CG, McDermott DF, Sznol M, et al. Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up.

Background: Programmed death-1 (PD-1) is an immune checkpoint receptor that negatively regulates T-cell activation. PD-L1, a PD-1 ligand, has been associated with poor prognosis in mRCC pts. In a phase I study of nivolumab, a PD-1 receptor blocking antibody, in pts with previously treated mRCC and other solid tumors, an MTD was not reached at 10 mg/kg IV Q2WK. Cohorts of mRCC pts were expanded at the 1 and 10 mg/kg dose levels.

Methods: Pts received nivolumab for ≤12 cycles (4 doses/cycle) until unacceptable toxicity, progression, or complete response. We report overall survival (OS), updated response data, and long-term safety for the mRCC cohorts from a data analysis in July 2012.

Results: 34 pts with mRCC were treated at 1 mg/kg (n=18) or 10 mg/kg (n=16). 44% of pts had received ≥3 prior therapies (74% prior antiangiogenic therapy; 59% prior immunotherapy). Median OS across doses has not yet been reached. Median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥1 year. The incidence of grade 3-4 related adverse events for the RCC cohort was 21% and included hypophosphatemia (6%) and respiratory disorders (6%), with no con- firmed-drug related deaths or grade 3 pneumonitis. Treatment discontinuation due to drug-related AEs occurred in 18/304 (6%) of patients in the overall treated population.

Conclusions: Nivolumab produced durable survival and responses in a subset of heavily pretreated mRCC pts, with an acceptable safety profile, even after long term continuous dosing. Overall survival appears promising for this population of pts. These findings provide the basis for an ongoing randomized phase III trial of nivolumab in mRCC (NCT01668784). Follow-up data through a February 2013 cutoff is being collected

Comment: PD-L1/PD-1 interaction can also be blocked by targeted PD-1, the mechanism of action of nivolumab. Data from this study are expected to be more mature for 2014 ASCO and this may be one of the most closely watched studies next year.

Eisen T, Shparyk Y, Jones R, et al. Phase II efficacy and safety study of nintedanib versus sunitinib in previously untreated renal cell carcinoma (RCC) patients.

Background: Sunitinib (S) is established as a standard first-line therapy for patients (pts) with advanced RCC. However, treatment can be limited by the occurrence of drug-related adverse events (AEs). This Phase II study assessed the efficacy and safety of nintedanib (N) – a potent, triple angiokinase inhibitor of VEGFR-1–3, PDGFR-_/_, and FGFR-1–3, as well as RET and Flt3 – vs S in previously untreated pts with RCC.

Methods: Ninety-nine eligible pts (96 of whom were treated) with advanced, unresectable/recurrent clear cell RCC, an ECOG performance status of 0–1, and no prior systemic therapy were randomized 2:1 to receive N 200 mg twice daily (n_64; given in 4-week cycles) or S 50 mg once daily(n_32; 4 weeks on, 2 weeks off schedule). Treatment continued until disease progression or unacceptable drug-related AEs. Primary endpoints were progression-free survival at 9 months (PFS-9) and, in N-treated pts only, QTc interval change (baseline to day 15). Secondary end-

Tracking the Trends Likely to Emerge at ASCO 2014: A Preview of Translational Research That Could Be Presented

Speculating on what the agenda will look like in kidney cancer for the 2014 meeting of ASCO is much like taking aim at a moving target, but some trends are already in place and they can be expected to re-emerge in the months ahead and next year as topics are selected and an agenda finalized. Although key clinical trials are still enrolling and other studies are still engaged in completing Phase 2 and Phase 3 of their protocols, this year's meeting highlights some directions likely to be followed in 2014. Among them, we predict:

- Immunotherapy will continue to maintain a large share of the focus in renal cell carcinoma (RCC). Further exploration of efforts to inhibit PD-L1 and PD-1 signaling are likely to produce new results with potential implications for treatment, not likely by ASCO's next meeting but possibly within 2 years. These agents are still undergoing Phase 3 study and interim results are expected by the middle of 2014.
- The vaccine trials, including the Phase 3 stage of AGS-003 by Argos Therapeutics, are likely to produce more robust data with more definitive signs of when such treatments could become available. There are hopeful signs that this "personalized" approach to immunotherapy will signal a dramatically new direction for management. Trial enrollment in the AGS-003 trial is now complete.
- New findings should emerge from the GOLD study reporting on dovinitinib vs sorafenib, which may lead to the first drug registered for metastatic RCC in the 3rd line. The GOLD (**G**lobal **O**ncologic **L**earnings for **D**ovitinib) Trials are a series of global initiatives led by Novartis that encompass a broad range of malignancies, such as renal cell carcinoma (RCC), breast cancer, gastric cancer, hepatocellular carcinoma (HCC), multiple myeloma, and urothelial cancer. The Gold trial for RCC is a 500+ subject trial of dovitinib versus sorafenib in third-line therapy following progression after VEGF-targeted plus mTOR inhibitor therapy. Dovitinib (TKI258), is an inhibitor of FGFR1, FGFR2, and FGFR3.
- Findings from the closely watched METEOR trial should be anticipated. METEOR is a phase 3 pivotal trial comparing cabozantinib to everolimus in patients with metastatic renal cell carcinoma (mRCC) who have experienced disease progression following treatment with at least one prior VEGFR tyrosine kinase inhibitor (TKI). The primary endpoint for the trial is progression-free survival. The cabozantinib data to date in RCC patients previously treated with VEGFR-TKIs showed encouraging anti-tumor activity, and provide a sound rationale for the design of the METEOR phase 3 study comparing cabozantinib to everolimus in this indication. Preclinical results with cabozantinib revealed VEGF, KIT and MET inhibition in a variety of solid tumors such as thyroid, ovarian, renal, lung, liver and prostate cancers.

METEOR is an open-label trial of cabozantinib in patients with mRCC that is being conducted at up to 200 sites in up to 26 countries. The trial is expected to enroll 650 patients with clear cell RCC who have received and progressed on at least one VEGFR-TKI. Patient enrollment will be weighted toward Western Europe, North America, and Australia, and patients will be stratified based on the number of prior VEGFR-TKI therapies received and commonly applied RCC risk criteria developed by Motzer et al. Patients will be randomized 1:1 to receive 60 mg of cabozantinib daily or 10 mg of everolimus daily. No crossover is allowed between the study arms.

Although these advances in therapy are encouraging, clinicians still need biomarkers that will help guide their choices to optimize the use of targeted agents and potentially usher in an area of truly personalized therapy for mRCC. There are no biomarkers that are used in directing standard management today.

Although these advances in therapy are encouraging, clinicians still need biomarkers that will help guide their choices to optimize the use of targeted agents and potentially usher in an area of truly personalized therapy for mRCC. There are no biomarkers that are used in directing standard management today. Unlike other malignancies, such as lung cancer, a tumor-specific biomarker has not been identified to predict outcome to either VEGF-targeted therapies, such as sunitinib and pazopanib, or to mTOR inhibitor agents (ie, temsirolimus and everolimus). Likewise, soluble proteins detected in blood, including VEGF and VEGF-receptor, have not been shown to predict RCC treatment.

It remains disappointing that development of reliable biomarkers lags behind therapeutic advances. Ironically, one of the areas where biomarker identification seemed to look promising was in the use of tivozanib, a TKI that initially showed huge promise in RCC but whose later results were not as impressive. Tivozanib was shot down by an FDA committee prior to the submission of Phase 3 results. It is unlikely that this drug will surface again as a potential agent in RCC, but perhaps new biomarkers will help guide treatment choices for other targeted therapies. Hopefully, ASCO 2014 will reveal progress in this critical area. KCJ

points included PFS, objective response rate (ORR; RECIST 1.1), overall survival (OS), time to progression (TTP), time to treatment failure (TTF), and AEs.

Results: Baseline characteristics were balanced between the arms. PFS-9 was not statistically significantly different between N- and S-treated pts(43 vs 45%; p_0.85). There were also no statistically significant differences between N and S with regard to PFS (median: 8.44 vs 8.38 mo; hazard ratio: 1.16; 95% CI: 0.71–1.89; p_0.56), confirmed ORR (18.8 vs 31.3%; p_0.19), OS (median: 20.37 vs 21.22 mo; p_0.63), TTP (median: 8.48 vs 8.54 mo; p_0.52), and TTF (median: 8.41 vs 8.36 mo; p_0.46). Grade _3 AEs occurred in 47% of N-treated pts and 56% of S-treated pts. Common AEs (all grades; N vs S) included diarrhea (61 vs 50%), nausea (38 vs 34%), fatigue (both 25%), and vomiting (16 vs 22%). Dermatologic AEs (8 vs 47%) were less frequent with N than S. There was no increase from baseline in QTc _60 ms on days 1 or 15 in N-treated pts, and there was no relationship between N exposure and QT interval change.

Conclusions: N demonstrated similar efficacy to S and had a manageable safety profile, including a lower incidence of dermatologic AEs vs S. In addition, N was not associated with QT prolongation.

Comment: Nintedanib is TKI which targets VEGFR, PDGFR, and uniquely FGF. It is hypothesized that targeting FGF may help to combat resistance to TKIs (elevated levels of FGF have been linked to disease pro- gression on sunitinib in mRCC patients). This early study suggests that nintedanib preformed similarly to the sunitinib in the front-line setting. In patients FGF signaling is a prominent mechanism of progression, and agents such as this may potentially have an important role to play. Phase 3 studies are anticipated and will be required to change the standard of care.

Powles T, Sarwar N, Stockdale A, et al. Pazopanib prior to planned nephrectomy in metastatic clear cell renal cancer: A clinical and biomarker study.

Background: The safety and efficacy of upfront pazopanib, prior to nephrectomy in metastatic clear cell renal cancer (mRCC), has not been prospectively evaluated. The toxicity profile of pazopanib potentially makes it an attractive agent in this setting.

Methods: A single arm phase II study (2009-016675-29) evaluated 12-14 weeks of pazopanib prior to planned nephrectomy in 102 untreated patients with mRCC. Patients had MSKCC intermediate (n=80) and poor risk disease (n=22). The Primary endpoint of the trial was to achieve at least a 75% clinical benefit rate (absence of disease progression) with pazopanib at the time of surgery. Sequential tissue was used for biomarker analysis (exploratory endpoint). Tissue from a previous sunitinib trials with a similar design was included for comparative purposes.

Results: Overall 81% of patients obtained clinical benefit prior to surgery. The partial response rate of the primary tumor was 14% by RECIST v1.1. The median reduction in the size of the primary tumor was 14% (range 33% to - 41%). No patients became inoperable due to local progression of disease. A nephrectomy was performed in 66% of patients. The two commonest reasons for not having surgery were patient choice (9%) and progression of disease (16%). There were 2 (3%) post operative surgical death. Delayed wound healing occurred in 5%. Progression during the treatment free interval for surgery was 26%. Median PFS has not been reached. Results from biomarker analysis of sequential tissue revealed therapy resulted in a significant decrease in CD31 (-49%), PDL-1 (-31%) and pS6K (-26%), while FGF-2 (+147%), MET (+34%) and Ki-67 expression increased with therapy. Increased ki-67 and CD31 correlated with a poor outcome.

Conclusions: Nephrectomy after upfront pazopanib can be performed safely in mRCC and obtains control of disease in the majority of patients. Biomarker analysis shows dynamic changes, some of which are prognostically significant.

Comment: As noted above, treating mRCC with targeted therapy prior to cytoreductive nephrectomy could potentially allow for shrinkage of primary tumors and upfront control of metastatic disease prior to surgery, while also providing information about an individual patient's disease responsiveness to targeted therapy before surgery

Currently, the treatment algorithm agreed upon by most centers for patients with mRCC that is not fully resectable, is to consider cytokine therapy (such as high-dose IL-2) for highly selected patients with an excellent performance status and few-to-no co-morbidities, to treat patients with poor-risk mRCC with temsirolimus, and to consider an upfront cytoreductive nephrectomy in patients with asymptomatic disease and relatively low burden of distant metastatic disease. Usually, all other patients are treated with frontline VEGF-targeted TKIs (sunitinib, sorafenib, or pazopanib). At progression, patients are typically switched to another targeted therapy, often alternating a sequence of VEGF-targeted TKIs and mTOR inhibitors. Data from this year's ASCO meeting provides further evidence in support of this current standard of care of first-line TKIs for most mRCC patients and suggests that treating with a TKI prior to cytoreductive nephrectomy is an acceptable strategy. KCJ

Reexamining the Latest Prognostic Indicators, Stratification and Treatment Approaches in Poor-Risk Renal Cell Carcinoma

In this interview with the Kidney Cancer Journal, *Daniel J. George, MD, discusses a wide range of considerations in the diagnosis and management of patients classified with poor-risk prognosis renal cell carcinoma (RCC). He reviewed current guidelines on the criteria used in determining prognosis and appropriate treatment options.*

Dr George is Director, GU Oncology, Duke Cancer Institute, Durham, North Carolina. His clinical interests include new drug development in prostate and kidney cancer, angiogenesis and targeted therapy, and molecular and radiographic surrogate markers for biologic activity of tumors.

KCJ: What constitutes a poor-prognosis patient?

Dr George: We have studied this disease for the last 30 years from the perspective of prognostic factors and there is a wide variation across the spectrum. There have been now probably between 5 to 10 factors that have been shown to have prognostic significance. What's important is they have independent prognostic significance so that no one factor describes the whole prognosis of the patient. We need to look at this in terms of multiple factors because they each add some perspective in terms of how that patient ultimately is likely to do. The most common and critical one is performance status—their functional status, ability to perform normal tasks of living each day, dressing, making and fixing meals. Patients who have a good performance status are unimpeded by their disease. Patients who have more and more symptoms have a worse performance status and worse outcome.

KCJ: What about clinical factors?

> "What we desperately want to know is what's driving that aggressive biology that's leading to the poor prognosis. And if we can identify markers that are not only indicators but are actual biologically relevant drivers of that aggressive to how to treat that cancer."

Dr George: An important clinical factor is the status of their primary tumor, whether the primary tumor is still in the body or not. The reason that is important is because patients who are diagnosed with metastases from the start have a worse prognosis. Many of those patients are unable to undergo surgery to remove the primary tumor. But for patients who have good performance status, many can undergo surgery to remove the primary tumor and gain clinical benefit from that. So having that primary tumor out whether they were originally diagnosed with localized disease and later recurred or whether because they presented with metastatic disease but had a good performance status and were able to undergo surgery and have that primary tumor taken out — in either case, having that tumor taken out is a good prognostic factor.

KCJ: What other factors need to be considered?

Dr George: The other factors are laboratory factors—values like low hemoglobin, elevated calcium levels or an elevated level in a protein called LDH—lactose dehydrogenase, kind of an inflammatory factor. More recent models have also suggested that high platelet counts or high white cell counts are also important.

KCJ: Are these known as the MSKCC prognostic criteria?

Dr George: These are the MSKCC criteria, the Cleveland Clinic criteria and most recently the Heng criteria. All three have a lot of overlap but are slightly different in one or two factors. But the basic factors (functional status, having the primary tumor out and some of those laboratory values) are pretty consistent across the board.

NEW ONCOLOGY INFORMATION!

Launching this Fall...

The GIST Cancer Journal

The Official Journal of The Life Raft Group

For the first time, a new, peer-reviewed medical journal offering comprehensive and exclusive coverage of Gastrointestinal Stromal Tumors (GIST)

- The official medical journal of The Life Raft Group, the only GIST advocacy organization dedicated to research, patient support, and worldwide educational inititatives
- Published quarterly
- Distributed to medical oncologists, select gastroenterologists, and additional healthcare providers directly involved in GIST
- Editor-in-Chief: Leading research scientist Jonathan C. Trent, MD, PhD, University of Miami
- Presenting essential clinical information on GIST-related issues and new research findings with translational impact
- Expert opinion on diagnostic and treatment trends
- Accessible this fall on www.thegistcancerjournal.org

The Life Raft GROUP

KCJ: Does the model from Cleveland Clinic in some way modify the MSKCC criteria for poor prognosis?

Dr George: They are all slightly different. The Cleveland Clinic criteria include patients who have 3 or more organ sites of disease. That was not found in the MSKCC database. One set of criteria is not better than the other. I look at all of these factors, the ones that are consistent in all 3 panels—those are the ones I put the most emphasis on—things like anemia, the presence of the primary tumor, and the performance status.

KCJ: Are there biomarkers or gene expression profiles that help to define poor risk?

Dr George: This is absolutely where we need to go in the future because not only will biomarkers and gene expression profiles and other molecular characteristics help us understand the prognosis of these poor-risk patients but it is also going to give us a clue on how to treat them. What we desperately want to know is what's driving that aggressive biology that's leading to the poor prognosis. And if we can identify markers that are not only indicators but are actual biologically relevant drivers of that aggressive biology then we've really got a clue to how to treat that cancer.

"Importantly, mTOR inhibitors like temsirolimus and everolimus are very specific - they do not block any other protein in the body. It is a remarkable biologic feat that temsirolimus is so specific in its function and yet can improve the survival for patients with an aggressive, and in many cases, widespread disease. This tells us that the mTOR biology is a driver of that aggressive poor-risk cancer."

KCJ: What is the role of the mTOR pathway in this population?

Dr George: It's really interesting because a lot has been made about blocking the growth of new blood vessels and angiogenesis in kidney cancer. But what has also emerged as an important mechanism in the last 7-10 years of research is that kidney cancer, especially aggressive kidney cancer, has a self-proliferative or growth pattern to it that allows it to grow and spread. That biology is driven through the mTOR protein. Blocking that mTOR pathway with agents like temsirolimus has led to true clinical benefit in patients; specifically in the case of temsirolimus in patients with the poor prognosis, mTOR inhibition significantly improves overall survival. Importantly, mTOR inhibitors like temsirolimus and everolimus are very specific - they do not block any other protein in the body. It is a remarkable biologic feat that temsirolimus is so specific in its function and yet can improve the survival for patients with an aggressive, and in many cases, widespread disease. This tells us that the mTOR biology is a driver of that aggressive poor-risk cancer.

KCJ: What are the endpoints for these poor-risk patients?

Dr George: The number 1 endpoint for patients who have poor risk disease is to prolong their survival as much as possible. This is a disease that is progressing, that is causing symptoms such as weight loss, loss of appetite, pain, fatigue, weakness, as well as in organ systems, such as shortness of breath or other organ dysfunction. For us to be able to control that disease, stop that progression, is critical. What goes along with that in many cases is a quality of life improvement because there are patients who are symptomatic. Treatment that can freeze or stall that cancer progression will likely result in improvement of quality of life and ultimately, a longer survival. In kidney cancer patients with poor risk disease treated with temsirolimus, we see a high rate of disease control, see an improvement in some cases of patient symptoms, and we see a significant improvement in overall survival.

KCJ: How would you characterize current guidelines for poor prognosis in the era of targeted therapy? In recent years there has not been a significant change in the algorithm. How would you say guidelines for therapy are beginning to change?

Dr George: This population of patients who have this aggressive disease need to be treated upfront with an mTOR inhibitor. Our guidelines recognize that and if you look at our guidelines we have Level 1 evidence for temsirolimus. The guidelines will say, for untreated or what they may call first line metastatic kidney cancer patients. The guidelines will list a number of Level 1 evidence treatment options. But only one of these in all the guidelines is based specifically on poor-risk patients. And that's the temsirolimus indication. So it is really unique in kidney cancer both in the guidelines and in its label specifically for patients who have features of this poor-risk, aggressive phenotype. This is important for a lot of clinicians who do not treat kidney cancer every week or every day. They may not be using a lot of these prognostic models. And there may be a tendency to say, "I treat all of my patients with drug A or drug B because that's what's indicated for most of them. It is important to recognize and is almost like the difference between high-grade or low-grade lymphomas.

KCJ: What would you say to the community oncologist who asks, why temsirolimus and not everolimus?

Dr George: Because that's where the evidence is. One thing that oncologists will follow more than anything is clinical evidence. That's why we put so much emphasis in our guidelines on randomized, controlled trials that have Level 1 evidence for a treatment and that has only been done with temsirolimus. There are differences between these drugs and the reality is temsirolimus is given as an IV drug once weekly. For a patient with a poor performance status, having an IV treatment and not having

to deal with the oral medication, the symptoms that go along with taking an oral medication, particularly if they have decreased appetite, if they're having GI symptoms and whatnot, there are advantages to administering that medication intravenously. There could be differences in oral absorption, there could be differences in GI tract toxicities, and the compliance here could be critical for these patients who are already tenuous to begin with. In addition, temsirolimus is given intravenously so it will have a peak exposure level that will then be cleared over time from the blood stream and the body. This is different from a daily oral medication that may reach a steady state level of exposure. These differences could lead to potentially a different side effect profile. We don't see in general as much pneumonitis with an agent like temsirolimus compared to other drugs in kidney cancer studies and that may be due to the route of administration. In summary, there are differences between these drugs in terms of route of administration, patient populations studied and most importantly in terms of data demonstrating survival benefit. It's this last point that oncologists will follow and are the basis for our guideline recommendations.

"For patients, prognosis is an ongoing assessment. Not a one time evaluation. So as we treat patients, the symptoms from the treatments as well as the disease can factor into their overall functional status and overall prognosis."

KCJ: There has been a focus on the FLIPPER trial and the possible use of pazopanib as a first line drug in RCC. Is anybody looking at pazopanib in poor-risk patients?

Dr George: The reality is we have not seen yet compelling randomized controlled data for VEGF inhibitors such as pazopanib against agents like temsirolimus in the poor risk population. If we can get to the point of using predictive factors for response to VEGF inhibitors like pazopanib, then we can figure out the subset of poor risk patients that will benefit from that strategy. The reality is agents like pazopanib and sunitinib have not been extensively studied in this poor risk population and my concern is the tolerability. If we're not able to give full doses of these drugs because these patients are already symptomatic from this disease, constitutionally impaired—we're going to be undermanaging these patients with drugs that have been dosed and developed for patients who are better off than this population. With temsirolimus I know that 90% of the patients get temsiro- limus and were able to tolerate full dose even in that poor performance status.

KCJ: What about the issue of "conditional survival"? An article in *Lancet Oncology* (Harshman LC, et al, 2012; 13:927-935) on prognostic measures assessed the use of conditional survival—a measure that accounts for elapsed time since treatment initiation—for prognostication in patients with mRCC treated with first-line VEGF-targeted therapies. An article in Lancet Oncology (Harshman LC, et al, 2012;13:927-935) on prognostic measures assessed the use of conditional survival—a measure that accounts for elapsed time since treatment initiation—for prognostication in patients with mRCC treated with first-line VEGF-targeted therapies. Are there any implications for the poor risk-group in this concept?

Dr George: For patients, prognosis is an ongoing assessment. Not a one time evaluation. So as we treat patients, the symptoms from the treatments as well as the disease can factor into their overall functional status and overall prognosis. The study in *Lancet Oncology* is trying to take out the time it took from diagnosis until treatment. So they are looking at the survival from the time of treatment onward. This is what all of our clinical trial data are based on. Our survival data for patients on a clinical trial are not necessarily from the time of diagnosis. It's from the time of enrollment onto that study until death. So that is what they are referring to as the conditional survival. That's what we saw in the ARCCs study demonstrating an improved survival for patients treated with temsirolimus vs interferon. With some of our prognostic models, many of those are derived from the time of diagnosis or the time of diagnosis of metastatic disease to death. Not necessarily tied to the timing of a specific treatment. So it is a relevant distinction in that when we're thinking of starting a therapy on somebody, we're really thinking about it in terms of conditional survival. When we're seeing anybody for the first time and diagnosing them with metastatic disease we're really thinking about prognostic models in terms of prognosis independent of treatment.

KCJ: Is there anything else you would like to add?

Dr George: The only other thing I would say that is critical for people to recognize is that many of these patients who have poor-risk kidney cancer are not going to make it to clinical trials. They're not going to make it to academic centers. They may not necessarily have the drive or ambition because of how they are feeling. We encourage physicians to treat them quickly and definitively with temsirolimus and to recognize that by treating them on a weekly basis you're going to be able to follow them closely over the first month and assess how these patients are tolerating and maybe benefiting from that therapy. It's an important assessment to make. These are patients who historically would go straight to hospice. Even though it is not curative therapy, it is therapy that can make a big difference. Median survivals were over 10 months for patients treated with temsirolimus vs 7 months for patients with interferon; a very significant hazard ratio and significant improvement there. Community physicians should not be afraid to treat these patients with aggressive kidney cancer before referring them to an academic center. KCJ

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

Kidney Cancer Association to Hold Annual Scientific Symposium in October

CHICAGO—The 12th International Kidney Cancer symposium will be held October 25-26, bringing together key individuals and representatives from leading laboratories and centers working with renal cell carcinoma. Sponsored by the Kidney Cancer Association, the scientific sessions provide a forum for the exchange of ideas and information that will continue to frame directions for future research and treatment. The meeting will be held at the Raddison Blu Acqua Hotel in Chicago.

Objectives for this CME event:

- Discuss options for operative and minimally invasive management of localized and metastatic renal cell carcinoma
- Evaluate the growing body of knowledge regarding clinical, molecular, genetic, and biologic characteristics of renal cell carcinoma
- Discuss the molecular genetics and biology of renal cancers and assess the effects of targeted therapy for this tumor
- Define research directions of novel agents and combinations and standard of care therapy for metastatic renal cell carcinoma
- Project future surgical and medical directions and research in non metastatic and metastatic disease.

This meeting is directed to medical oncologists, urologists, and scientists involved in the clinical and research aspects of renal cell carcinoma. The activity has been approved for AMA PRA Category 1 Credit™.

A New Medical Journal, Targeting GIST, Launching This Fall

WAYNE, NJ—A new medical journal, specifically focused on gastrointestinal stromal tumors (GIST), will begin publishing in the fall of 2013. The Life Raft Group is pleased to announce the launch of *The GIST Cancer Journal* and will release issues on a quarterly basis. Once launched, the Journal will also be accessible via an interactive website at www.thegistcancerjournal.com.

The Life Raft Group is working in partnership with GUPA, LLC, to develop, produce, and distribute *The GIST Cancer Journal*. The journal will be distributed to clinical oncologists, specific gastroenterologists, and other healthcare professionals directly involved in the care of GIST patients, researchers and educators. GUPA, LLC also publishes *The Kidney Cancer Journal* , the official journal of the Kidney Cancer Association.

Jonathan C. Trent, MD, PhD has been appointed as the GIST journal's Editor-in-Chief. Dr Trent is the Co-Director of the Musculoskeletal Center, Director of the Sarcoma Medical Research Program and professor of medicine at the University of Miami Sylvester Comprehensive Cancer Center. He has published numerous abstracts and research articles in leading journals, as well as book chapters, and is a frequently requested lecturer. He is the chief editor of the sarcoma section of Cancer Investigation and on the editorial board of *The Chinese Journal of Clinical Oncology* and has served as a journal reviewer on a number of journals, including *Nature Medicine, Lancet, Cancer, Clinical Cancer Research*, and *Cancer Research*, and has received a number of honors for his work in cancer research. Dr Trent earned his undergraduate degree in chemistry at Southeastern Oklahoma State University and his MD and PhD in cancer biology from The University of Texas Health Science Center. He completed an internship and residency in internal medicine at The University of Texas Health Science Center, and a fellowship in medical oncology at The University of Texas, MD Anderson Cancer Center while serving as chief fellow. Dr Trent is board certified in internal medicine and medical oncology.

The Life Raft Group is a registered 501(c)3 non-profit organization founded in 2002 and headquartered in Wayne, NJ that operates in over 50 countries worldwide. Its mission is to ensure the survival of patients with GIST through a comprehensive approach connecting individual patients' needs, the worldwide community of GIST advocates and the global health and research environment. Its focus is in three key areas: research, patient support and education, and advocacy. The Life Raft Group funds and manages uniquely coordinated research initiatives that always keep the needs of the GIST patient foremost. It is the only GIST advocacy organization with a dedicated research initiative led by a team of world renowned scientists and clinicians in GIST.

After Stunning Rejection of Tivozanib, a Company Regroups, But Not for Treatment of RCC

CAMBRIDGE, MA—What happens when a pharmaceutical company's lead candidate for treatment of kidney cancer is rejected by the FDA? It begins to restructure. Following the FDA's rejection of tivozanib in June, Aveo Oncology recently reported that it spent $7.9 million in restructuring costs during the second quarter. The Cambridge, Massachusetts drug company abandoned the tivozanib program in kidney cancer and laid off 140 employees in June.

Tivozanib, a tyrosine kinase inhibitor, had raised hopes in the oncology community that it might provide a new treatment with an improved side effect profile compared with other TKIs. However, disappointing results from its Phase 3 study in a comparison with sorafenib led to its rejection by the FDA.

Data from the randomized Phase 3 trial showed that the primary endpoint of progression-free survival for patients with metastatic RCC was significantly greater with tivozanib, at a median of 11.9 months, compared with sorafenib (Nexavar, Onyx Pharmaceuticals), at a median of 9.1 months (hazard ratio [HR], 0.80; $P = .04$).

But the same trial also showed a nonsignificant trend toward worse overall survival among patients assigned to tivozanib after all patients had been followed for at least 2 years. There were 118 deaths among 260 patients in the tivozanib group (45%) compared with 101 of 257 patients in the sorafenib group (39%). The hazard ratio for death was 1.25 ($P = .11$). In each trial group, 21 patients withdrew consent, and 6 were lost to follow-up and were censored at the time of withdrawal or loss to follow-up.

Robert Motzer, MD, an attending physician at the Memorial Sloan-Kettering Cancer Center in New York City, the lead investigator on the Phase 3 trial, said that overall survival data were difficult to interpret. As with other pivotal trials of TKIs for RCC, the overall survival data were confounded by crossover to a second-line therapy, he explained. On the other hand, the data on progression-free survival and the safety profile of the drug were convincing evidence of benefit, said Dr Motzer.

But 13 of the 14 memebers of the FDA's Oncologic Drugs Advisory Committee voted "no" to the question "Has the applicant demonstrated a favorable benefit-to-risk evaluation for the treatment of renal cell carcinoma in an adequate and well-controlled trial?"

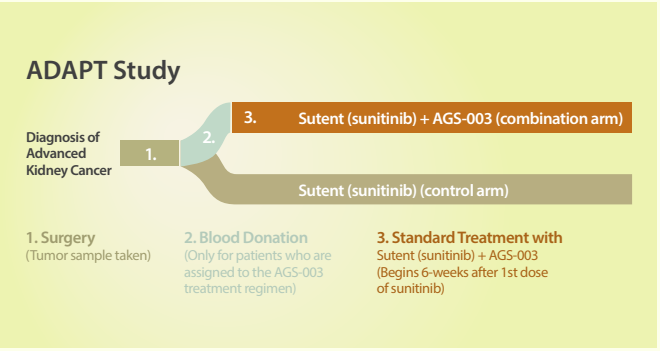
Only 1 panel member, Dan Lumley, a patient representative from Kansas City, Missouri, voted to recommend approval, based on a favorable adverse effect profile of tivozanib compared with other TKIs already approved for treatment of advanced RCC.

Among the panel members' concerns, apart from the survival signal, were the trial design, which allowed for crossover of sorafenib-treated patients to tivozanib, but not vice versa, and the fact that 80% of patients in the trial were enrolled in central and eastern Europe, where clinical care and the patient population are different from those in the United States.

"We are moving forward as an organization and are firmly focused on executing our revised business strategy," said Tuan Ha-Ngoc, president and CEO, in a statement. "We continue to advance our programs in clinical development, including tivozanib in colorectal and breast cancer, which are currently in Phase 2 studies. Additionally, we are moving forward with AV-203, our ERBB3 inhibitory antibody candidate, which is currently in Phase 1 development. While the recent setback related to the tivozanib Complete Response Letter and the company's strategic restructuring was challenging, we remain confident about the company's future prospects and we will continue to work toward our goal of bringing clinically meaningful treatments to patients with cancer."

Argos Therapeutics Expands Ongoing Pivotal Phase 3 ADAPT Study for Personalized Immunotherapy as Part of Vaccine Initiative

DURHAM, NC–— A pivotal trial evaluating a vaccine for renal cell carcinoma (RCC) has hit another benchmark to determine its efficacy. Argos Therapeutics Inc., a biopharmaceutical company focused on the development and commercialization of fully personalized immunotherapies for the treatment of cancer and infectious diseases using its Arcelis™ technology platform, has expanded its ADAPT Phase 3 clinical study for AGS-003 to additional top cancer centers in the United States and Canada and will soon be expanding into Europe and Israel.



The two arms of the ADAPT Study, a protocol evaluating a personalized immunotherapy, AGS-003.

More than 50 sites have been activated and more than 30 subjects have been enrolled in North America. The study is expected to expand to more than 120 global sites by early Fall 2013. The Phase 3 ADAPT clinical study is evaluating AGS-003, an investigational, fully personalized immunotherapy designed to stimulate a tumor-specific T-cell response. AGS-003 is being evaluated in combination with standard surgery followed by targeted drug therapy in this study to determine its potential to extend overall survival in newly-diagnosed, unfavorable risk metastatic renal cell carcinoma (mRCC) patients. Secondary endpoints in this study include progression-free survival, safety, overall response and immune response.

The ADAPT study is a randomized, multicenter, open-label clinical trial, expected to enroll 450 patients in approximately 120 sites, mostly in North America, under an approved Special Protocol Assessment by the FDA. Argos Therapeutics expects to initiate the majority of all trial sites,

including approximately 90 in the United States and 30-40 globally by September of 2013.

The ADAPT study will enroll synchronous, mRCC patients who present with 1-4 baseline Heng risk factors who are good candidates for surgery followed by standard targeted drug therapy. The validated Heng risk model utilizes six risk factors which predict survival for mRCC patients treated with standard targeted therapy. The study will exclude patients with five or more Heng risk factors because these poor risk patients are not expected to respond well to standard treatments and may progress too quickly to benefit from a novel immunotherapy like AGS-003.

Partial Nephrectomy Underutilized, Patients Often Uninformed About Options, Says MSKCC Survey

[Editor's Note: the following news item is adapted from information provided by Memorial Sloan-Kettering Cancer Center.]

NEW YORK, NY— A recent survey led by investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) and the National Kidney Foundation has found that many patients with small kidney tumors are not told that a partial nephrectomy can save their lives while preserving kidney function.

Radical nephrectomy is required for massive kidney tumors but the procedure can increase a patient's risk of developing chronic kidney disease and subsequent cardiovascular complications.

"Physicians, patients, and caregivers alike need to be better educated about kidney-sparing strategies and the consequences of radical nephrectomy for small kidney tumors," said Paul Russo, MD Attending Surgeon, MSKCC and Professor, Weill Cornell College of Medicine.

"This will help patients make the most informed treatment decision for both their cancer and long-term health, and possibly avoid the complications of chronic kidney disease."

Low Awareness of Treatment Options

Dr Russo surveyed 365 people with kidney cancer and 52 caregivers about their understanding of kidney-sparing surgical options and the risk factors for chronic kidney disease. Findings from this survey were published in the *American Journal of Kidney Diseases*. Dr Russo and his team found that more than a quarter of the patients said they were not told about partial nephrectomy, its benefits, and whether they were a candidate for such an operation. As a result, less than 20% of those kidney cancer patients with early-stage kidney tumors underwent a partial nephrectomy, while 80% had their entire kidney removed. Patients who underwent radical nephrectomy were also unaware of their risk for developing or worsening chronic kidney disease.

At Memorial Sloan-Kettering, more than 90% of patients with small kidney tumors are treated with partial nephrectomy. Dr Russo and his team also promote active surveillance as an approach for small renal tumors in the elderly and patients with other health complications. In these patients, the risks associated with surgical intervention and hospitalization are far greater than the risks of significant tumor progression or spread in their lifetimes.

Better Education Needed

Memorial Sloan-Kettering surgeons have been instrumental in pioneering research to define the optimal treatment for kidney tumors. They have found that in nearly half the patients with small kidney tumors, the tumors are indolent or benign, with little or no potential to spread to other parts of the body. Studies conducted here and at other institutions have demonstrated that in patients with small kidney tumors, partial nephrectomy is as effective as radical nephrectomy at controlling cancer, while preserving kidney function and preventing the complications of chronic kidney disease.

About 70% of patients diagnosed with kidney cancer each year have a kidney tumor that is considered small, making those patients candidates for this procedure. And nearly one-third of patients with kidney cancer already have evidence of preexisting chronic kidney disease, which can be made worse by radical nephrectomy. Dr Russo and his team perform more than 300 partial nephrectomies per year and have expanded their kidney-sparing surgical program to include larger tumors and those located deep inside the kidney or adjacent to critical blood vessels. Their research data indicates that just as with smaller tumors, partial nephrectomy in these more complicated cases is as effective as radical nephrectomy at controlling cancer, with the added benefit of preserving kidney function.

According to Dr Russo, "Treatment at a high-volume hospital with a robust multidisciplinary research team is a definite advantage for patients with kidney tumors."

Kidney Cancer Progression Linked to Shifts in Tumor Metabolism; The Cancer Genome Atlas Identifies Genomic Alterations Tied to Tumor Aggressiveness

ROCKVILLE, MD—Investigators in The Cancer Genome Atlas (TCGA) Research Network have uncovered a connection between how tumor cells use energy from metabolic processes and the aggressiveness of clear cell renal cell carcinoma (ccRCC). Their findings demonstrate that normal metabolism is altered in ccRCC tumor cells, and involves a shift from using one metabolic pathway to another. This change – termed a metabolic shift – correlates with tumor stage and severity in some cases.

Researchers also found mutations in a pathway that may cause increased aggressiveness in this cancer. Taken together, the findings may offer new insight into underlying disease mechanisms and potential treatments as well as an understanding of how some cancer cells can shift from

using normal metabolic pathways to alternative pathways, thereby providing a growth advantage to tumor cells. In general, changes in metabolic enzymes that promote growth of the tumor are associated with worse patient outcomes in this disease. This latest TCGA research supports previous evidence of a metabolic shift in a different subtype of kidney cancer.

Investigators used data generated by TCGA, a collaborative effort funded by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health. The results of this study were published online June 23 in *Nature*. "Because of TCGA's comprehensive characterization of kidney tumors and correlating that with patient survival data, researchers now can begin applying this knowledge to validating prognostic biomarkers and identifying new therapeutic strategies for this disease," said NIH Director, Francis S. Collins, MD, PhD.

The study examined nearly 450 ccRCC tumors and matched each with a normal sample from the same patient. When researchers looked at the amounts of specific proteins expressed in cancer cells, they found that low levels of one protein essential to cell metabolism (AMPK) and high levels of another (acetyl-CoA carboxylase) were associated with worse patient outcomes. "Earlier findings from the characterization of other types of cancers have given us important clues as to how to design better therapies for these cancers," said NCI Director Harold Varmus, MD. "The new results from the TCGA analysis of clear cell renal cell carcinomas provide an explanation for how mutations in certain genes can alter chromosome chemistry to produce changes in enzyme levels that affect cell metabolism in ways correlated with clinical outcomes. These findings will stimulate some novel ideas about therapies for other lethal cancers."

In addition to the connection between metabolic shift and tumor aggressiveness, TCGA Research Network scientists discovered that, in some cases, the metabolic shift may be caused by changes in the PI3K cellular pathway, which helps regulate cell metabolism. The investigators observed a number of changes in P13K pathway genes and its regulators in tumor cells, including DNA mutations in protein-coding areas, as well as other changes affecting gene expression. They found such alterations in the PI3K pathway — or its partner pathways, AKT and mTOR — in 29% of tumor samples. AKT and mTOR also are essential for regulating cellular metabolism.

The effects of these changes show the importance of the PI3K/AKT/mTOR pathways. For example, researchers found a decrease in factors that activate tumor suppressor genes – the genes that produce proteins aimed at blocking tumor development. At the same time, factors that turned on genes that inhibit the PI3K pathway were blocked. Both of these changes promote activity in the PI3K/AKT/mTOR pathways. The results suggest the pathways' potential as therapeutic targets with inhibitor drugs.

"These findings illustrate how large, multi-dimensional datasets obtained from the rigorous analyses of hundreds of tumors can be mined to uncover new insights into cancer biology," said NHGRI Director Eric Green, MD, Ph.D. "By creating these types of datasets, TCGA has advanced our fundamental understanding of this type of cancer."

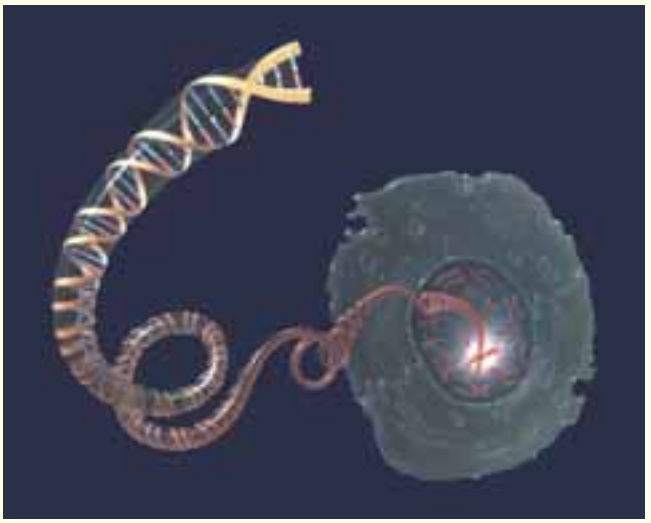


Illustration depicting DNA molecule unwinding from a chromosome inside the nucleus of a cell.

W. Marston Linehan, MD, chief of the NCI Urologic Oncology Branch and one of the study's leaders, sees several implications from the results. "The finding of a metabolic shift in the aggressive tumors could provide the foundation for the development of a number of novel approaches to therapy for patients with advanced kidney cancer," said Dr Linehan. New therapies are especially important since advanced kidney cancer is often resistant to chemotherapy. TCGA data offer insights into various global processes occurring in kidney cancer and can show how different tumor pathways intersect.

"The molecular analysis of this disease impacts understanding of all cancers through furthering insights into the role of metabolic perturbation in malignancy," said Richard A. Gibbs, PhD, another lead investigator in the project and director of the Human Genome Sequencing Center at Baylor College of Medicine, Houston.

"The TCGA findings offer new insights into why some kidney cancers are more aggressive and presents opportunities to develop therapeutics addressing these findings," said Robert A. Figlin, MD, Editor-in-Chief of *Kidney Cancer Journal*. "The metabolic shift in some tumors may explain their aggressiveness. The authors note that the PI3K/AKT/mTOR pathway may be especially important in this metabolic shift. Caution must always be considered in these findings because to date the benefits of targeting this pathway have not met with the robust benefits that might

be suggested by the TCGA analysis. Future efforts may suggest additional targets that might offer the poor risk patients better options. It may also help to define the at risk populations of patients following potentially curative surgery who might benefit from additional treatment options.

NCI estimates that nearly 65,000 people in this country will be diagnosed with ccRCC in 2013, and more than 13,000 people will die from the disease. More than 50% of patients with early stage renal cell cancer are successfully treated with current therapies. To date, the TCGA Research Network has generated data and published analyses on glioblastoma multiforme, ovarian serous adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, invasive breast cancer, acute myeloid leukemia, and endometrial cancer. TCGA-generated data are freely available at the TCGA Data Portal and CGHub.

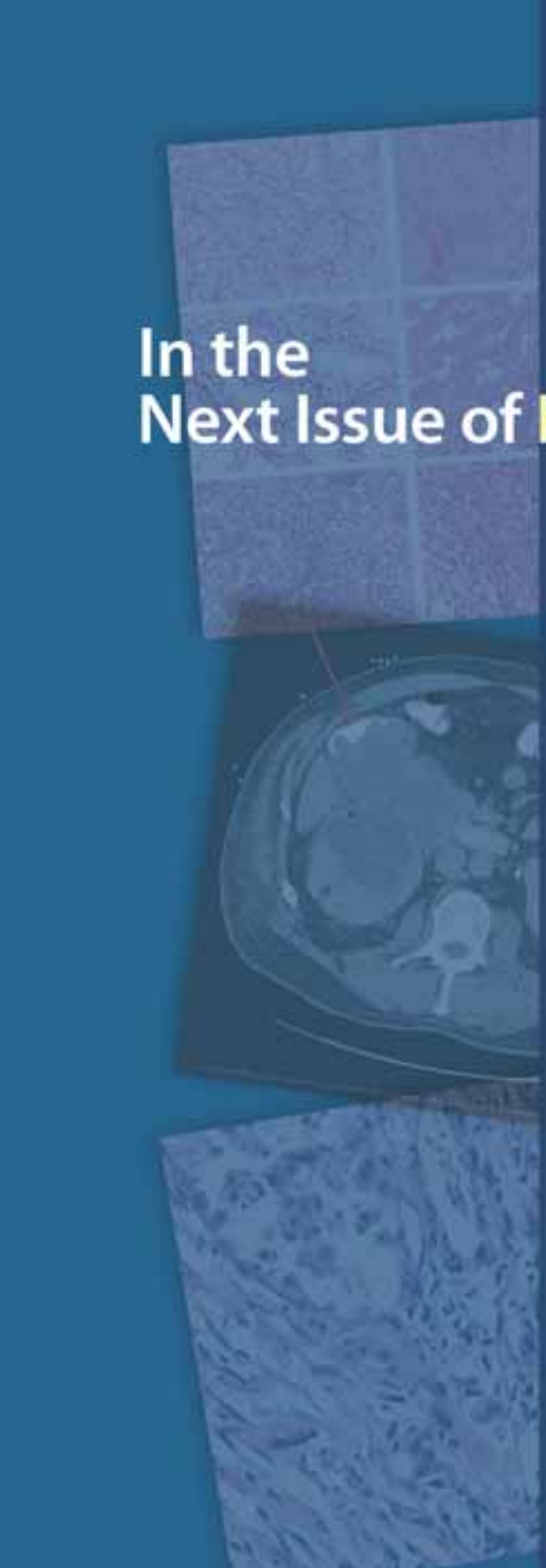
Oncology Business Review: A Digital Resource Analyzing a Broad Spectrum of Clinically Related Content and Trends

SAUSALITO, CA—An explosion of digital information often leaves clinicians struggling to keep pace with new developments, but one source has been tracking trends for thousands of providers and may be an important adjunct to one's knowledge base. *Oncology Business Review* calls itself "the most comprehensive digital platform for oncology focused news and information." Its mission is to:

- aggregate, customize and prioritize daily oncology news and publications (OBR Daily for industry and providers, RSS newsfeeds)
- research, develop and publish original content (OBR green)
- create and produce customized training programs for pharmaceutical professionals (Oncology Business Dynamics)
- conduct, interpret, analyze and produce original research (On-Telligence)
- publish informational resources and editorial perspective to our websites (OBR Radar, Pipeline Online, Blog, Twitter, OBR Finance, News Pulse, KOL Commentary, and others)

"We build OBR green from scratch every issue," according to a spokesperson. "We pick up the phone, go to the meetings, ask the important questions, research relevant facts, provide commentary and ideas from our interviews, and add a pinch of our own provocative editorial. In each issue of OBR green we balance the topical business matters with the evolving science that we love about the oncology industry. Everyday we compile, filter, and prioritize the day's oncology news while also providing unique insights and editorials to complement the fast moving oncology news. Our readership, loyal users, and testimonials grow every week, month, and year because of the quality we put into building OBR daily everyday."

Further information is available through OBR's website: http://obroncology.com/. KCJ



In the Next Issue of Kidney Cancer Journal

- The importance of inhibiting systemic autophagy during interleukin-2 (IL-2) immunotherapy and its effect on tumor regression
- The latest findings on a novel clinical strategy to enhance the efficacy of high dose IL-2 immunotherapy for patients with cancer
- Why partial nephrectomy is underutilized, patients often uninformed about options
- Results of a new Memorial Sloan-Kettering Cancer Center survey on the low awareness of treatment options

Kidney Cancer

clinic. However, no other familial ccRCC predisposing genes are frequently mutated in sporadic ccRCC. With the development of massively parallel sequencing, a plethora of somatically mutated genes has been identified. Most genes are mutated at low frequencies, but three genes are mutated in more than 10% of ccRCC, PBRM1 (mutated in 50%), BAP1 (15%), and SETD2 (15%). Like VHL, all three genes are 2-hit tumor suppressor genes. Furthermore, these three genes are within a 50-Mb region on the short arm of chromosome 3p that encompasses VHL and is deleted in 90% of ccRCC.
Conclusion: PBRM1 mutations tend to anticorrelate with BAP1 mutations in ccRCC and that PBRM1- and BAP1-mutated tumors exhibit different biology and are associated with markedly different outcomes. This established the foundation for the first molecular genetic classification of sporadic ccRCC. The author reviews the evidence that implicated PBRM1 and BAP1 as renal cancer driver genes, provides an update on the function of the gene products, and speculates on how mutations in these genes may be exploited therapeutically.

Targeting the Hepatocyte Growth Factor/c-Met Signaling Pathway in Renal Cell Carcinoma. Harshman LC, Choueiri TK. *Cancer J*. 2013;19:316-323.
Summary: The product of a proto-oncogene, the c-Met protein is a transmembrane receptor tyrosine kinase. Its only known ligand, hepatocyte growth factor/scatter factor, regulates cell growth, motility, migration, invasion, proliferation, and angiogenesis. Dysregulation of c-Met and hepatocyte growth factor have been observed in both clear cell and nonclear cell renal cell carcinomas (RCCs), although only papillary RCCs harbor activating mutations in the MET gene. In clear cell RCC, there is evidence of a direct link between loss of von Hippel-Lindau and up-regulation of c-Met.
Conclusion: As in other cancers, high expression of c-Met correlates with worse outcomes in RCC. In vitro and in vivo preclinical RCC models demonstrate cancer control with small molecule and antibodies against c-Met. Given these findings, the c-Met pathway is a logical therapeutic target in RCC, and several agents are in clinical testing with early signs of efficacy. Ongoing clinical trials hope to define patients who will benefit based on predictive biomarkers. Immune checkpoint inhibitors may play a key role in the future of management of solid tumors including kidney cancer. KCJ

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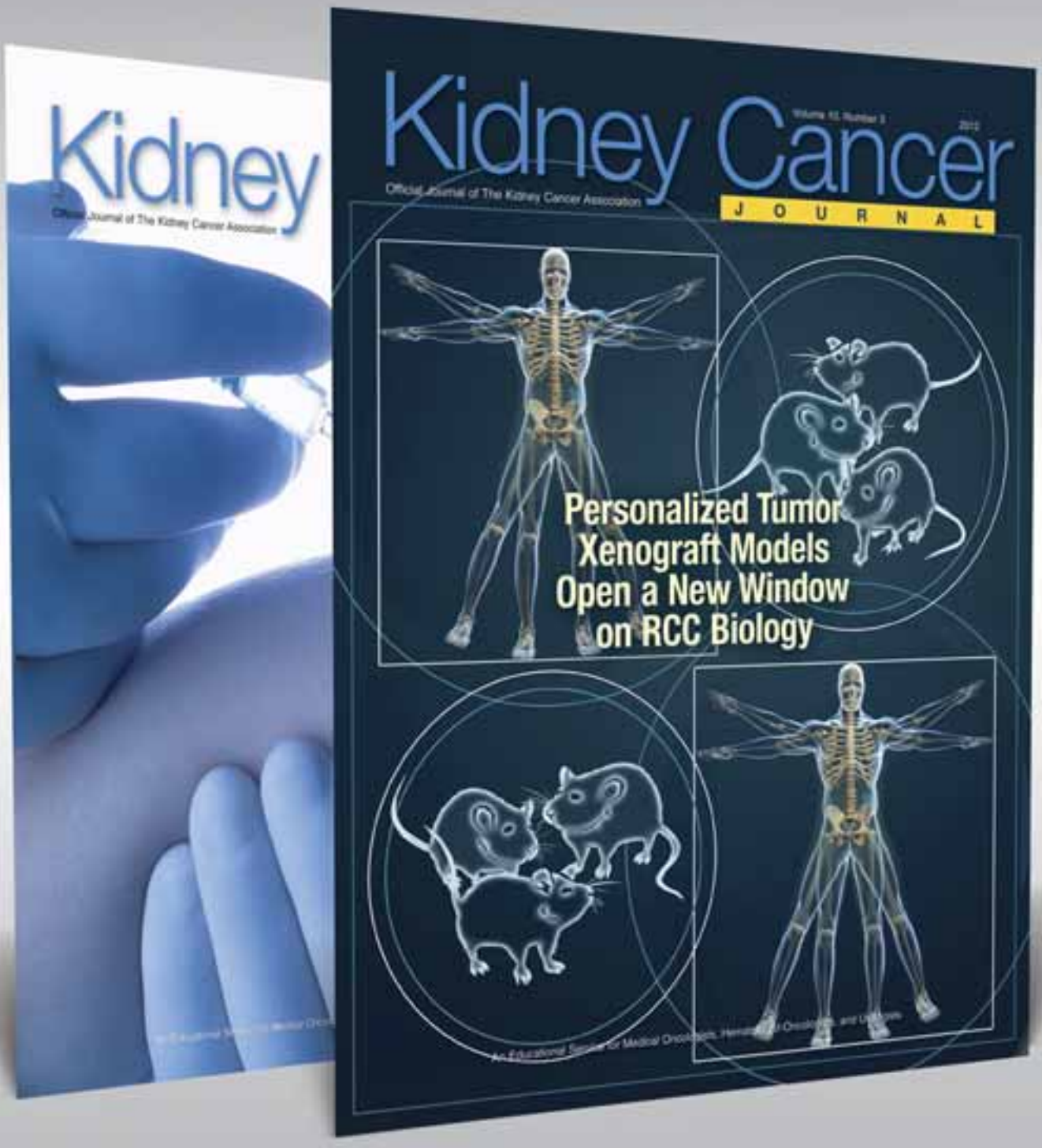

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