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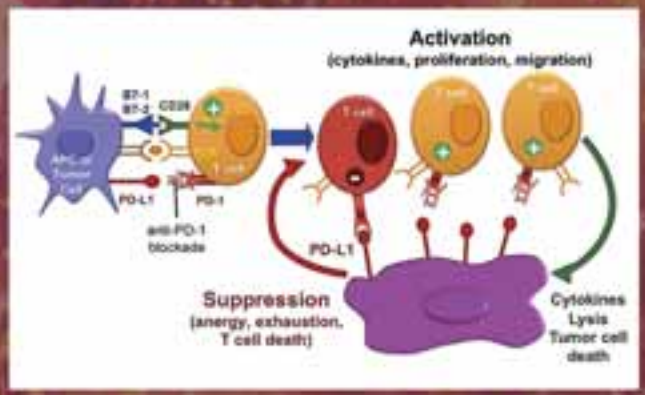
Reinventing Immunotherapy in RCC

- New Science of PD-1 Blockade Rolls Out at ASCO
- Alternate Dosing Strategies for IL-2 Could Improve Outcomes

Lymph Node Dissection in High-Risk Patients: Controversies and Consensus on When It Should be Performed



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**	

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

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

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

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

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

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

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

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

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

Psychiatric disorders: Insomnia (9%)

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

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

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

Renal and urinary disorders: Renal failure (3%)

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

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

Hematologic disorders: Hemorrhage (3%)

Key observed laboratory abnormalities are presented in Table 7.

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

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

CTCAE Version 3.0

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

7 DRUG INTERACTIONS

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

Agents That May Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

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

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

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

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

Agents That May Decrease Everolimus Blood Concentrations

CYP3A4 Inducers

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

Drugs That May Have Their Plasma Concentrations Altered by Everolimus

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

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

Nursing Mothers

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

Pediatric Use

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

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

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

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

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

Geriatric Use

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

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

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

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

Renal Impairment

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

Hepatic Impairment

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

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

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

10 OVERDOSAGE

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

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

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

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

Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

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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
Artist's conception of upregulated T cells (white cells) as part of immune response against a tumor (purple). In a more complex representation (lower right), the PD-1 pathway is illustrated, suggesting how PD-1 blockade can improve the immune response and provide as new treatment streategy. (Illustration, Custom Medical Stock Photo; schematic diagram courtesy of David McDermott, MD)

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KCJ EDITOR'S MEMO

The Renaissance in Immunotherapy: Boosting the Immune Response by Targeting the "Checkpoints" of RCC

Robert A. Figlin, MD

When the American Society of Clinical Oncology (ASCO) announced the studies to be featured as major advances in cancer research as part of its press program this year, our attention focused on a therapy that may have important implications for kidney cancer, among other tumors. Consider the fact that 2 studies featured by ASCO in advance of the meeting were among the 7 selected from 4,500 abstracts to be presented at the scientific sessions. Two of the 7 studies highlighted a new immunotherapy that is under study in kidney cancer and melanoma—an engineered 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.

Results from another phase 1 study show that combination therapy with ipilimumab (Yervoy) and the investigational antibody drug nivolumab led to lasting tumor shrinkage in approximately half of patients with aggressive, advanced melanoma.

Ipilimumab is a standard treatment option for advanced melanoma in many countries. Nivolumab, a PD-1 targeted antibody, has shown promising activity against melanoma and other cancers. Both nivolumab and ipilimumab are antibody drugs that target immune system "gatekeepers" or checkpoints (PD-1 and CTLA-4, respectively) on immune cells, effectively releasing the brakes on the immune system and boosting its ability to fight off cancer. This proof-of-principal study shows that concurrent use of two immune checkpoint antibodies offers a promising strategy for advanced melanoma therapy, and possibly kidney cancer as well. *[See the journal interview with researcher David McDermott, MD, in this issue.]*

After years during which targeted therapy, including the use of tyrosine kinase inhibitors (TKIs), dominated much of the agenda in kidney cancer at ASCO, this year's meeting in some ways represents a striking departure in focus and a return to immunotherapy as a promising avenue for prolonging progression free survival in renal cell carcinoma. This issue of the journal also seizes upon new information in still another area of immunotherapy—the use of interleukin-2 and emerging reports

(continued on page 21)

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

FDA panel votes against approval of tivozanib for RCC

BETHESDA, MD—An FDA advisory panel has raised questions about the approval of tivozanib. The panel voted 13 to 1 that tivozanib, a VEGF inhibitor, did not demonstrate a favorable benefit-to-risk evaluation for the treatment of advanced renal cell carcinoma (RCC) in an adequate and well-controlled trial. The panel noted that while the drug conferred a 20% benefit in delaying disease progression, it increased the risk of death by 25%. Panelists also expressed concern that most of the patients in the late-stage TIVO-1 trial were studied in Central and Eastern Europe and they questioned whether the results would be applicable to the US population.

"If we approve this drug based on this study how would we communicate to patients the potential 25% increase in the risk of death?" asked Jonathan Jarow, Medical Officer at the FDA. Representatives for Aveo Pharmaceuticals, developer of the drug, countered that the lack of a survival benefit was due to the fact that patients in the sorafinib arm whose disease worsened during the study period were permitted to switch to the tivozanib arm. However, Jarow noted that there are 7 other approved drugs to treat RCC on the market, and patients were allowed to cross over in 5 of those trials, "yet none of these trials demonstrated a negative trend for overall survival." Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, added that he was "extremely disappointed" in the information Aveo proposed placing on the drug's label, which he said did not provide patients with adequate survival data.

Pazdur also questioned the design of the trial, as well as why Aveo conducted its clinical trials in central and Eastern Europe, noting that if tivozanib was such a promising product, why were clinicians in the United States not encouraging their patients to enter the trial. Aveo responded that at the time it was enrolling patients, a number of other companies were also enrolling patients in competing trials, forcing Aveo to focus its recruitment efforts on patients oversees.

"While we are disappointed with the outcome of the [panel] vote, we remain confident in the efficacy, safety and tolerability of tivozanib in RCC patients," aid Aveo CEO Tuan Ha-Ngoc, adding that the company "will work closely with the FDA to address the issues discussed by the panel." A final decision by the FDA is expected by July 28.

AUA predicts urologist shortage nationwide

SAN DIEGO—Parts of the United States are running out of urologists, according to findings presented at the 2013 Annual Scientific Meeting of the American Urological Association. The number of urologists in the US peaked in 2008 at 9,852, and is now declining with serious consequences, especially in rural areas, said Raj Pruthi, MD, from the University of North Carolina at Chapel Hill. "We think this is a real problem."

The number of urologists per capita has been declining since at least 1991, he said. And the problem is getting worse; almost half of all urologists are older than age 55, so time is running short to train all the urologists needed to replace them when they retire, he said. Dr Pruthi told *Medscape Medical News*. Research has suggested that members of the millennial generation prefer not to work as many hours as their parents and grandparents, he added, and that could affect urology care. To estimate the number of urologists in coming decades, Dr. Pruthi and his team took the number of urologists in 2009, added new entrants, and then subtracted attrition, related to retirement or breaks in practice, from both training programs and the workforce.

They forecast a 29% reduction in the total number of urologists by 2025.In 2020, there will be about 7500 urologists in the country. The US Health Resources and Services Administration estimates a need for 16,000 urologists that year, said Dr Pruthi. He noted that federal funding for urology residency programs was frozen in 1997.A third of medical students who want to specialize in urology can't get residencies in that specialty, he said. Most residency programs are partially funded by the income from clinical care.

Either implementing a recommendation from the Council of Graduate Medical Education or passing a bill now in the US Senate would increase the number of residency slots by 15%. But even then, there would be a 28% reduction in the supply of urologists by 2025, said Dr Pruthi.

Newly diagnosed kidney cancer in 2013 will reach more than 65,000

ATLANTA—An estimated 65,150 new cases of kidney cancer are expected (see **Figure**, page 28) to be diagnosed in 2013, according to the American Cancer Society (ACS). This estimate includes cancers of the renal pelvis (6%) and Wilms tumor (1%), a childhood cancer that usually develops before age 5. From 2005 to 2009, kidney cancer incidence rates increased by 3.1% per year, primarily due to an increase in early stage disease. Some of the increase in kidney cancer rates, particularly for early stage disease, may be due to incidental diagnosis during abdominal imaging performed for unrelated issues. Based on the most recent years of data, it appears as though the rate may be reaching a plateau after several decades of increase.

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Essential Peer-Reviewed Reading in Kidney Cancer

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

How does age affect treatment trends, outcomes?

Impact of age on treatment trends and clinical outcome in patients with metastatic renal cell carcinoma. Pal SK, Hsu S, Hu J, et al. *J Geriatr Oncol*. 2013;4:128-133.

Summary: Clinical outcomes in older adults with metastatic renal cell carcinoma (mRCC) are poorly understood, particularly in the era of targeted therapies. This study characterized survival and relevant treatment-related variables in a modern series. From an institutional database including 562 patients with RCC, a total of 219 patients with metastatic disease were identified for the current analysis. Survival was assessed in four age-based cohorts: (1) age < 55, (2) age 55-64, (3) age 65-74, and (4) age ≥ 75. The number of lines of therapy rendered was collected for each patient, and the reason for treatment discontinuation was characterized. Of the 219 patients assessed, median age was 58 (range, 26-87), and most patients had clear cell histology (82%) and prior nephrectomy (70.9%). The majority of patients were characterized as intermediate-risk (53%) by MSKCC criteria. Median survival in patients age ≥ 75 was 12.5 months, as compared to 26.4 months for patients age < 75 (P=0.003). Patients age ≥ 75 received fewer lines of systemic therapy as compared to other age-based subsets, and more frequently discontinued therapies due to toxicity.

Conclusion: Older adults represent a unique subpopulation of patients with mRCC, with distinct clinical outcomes. Further research is warranted to better understand the safety and tolerability of current therapies for mRCC in this group.

Adrenalectomy and LND in locally advanced RCC

Systematic Review of Adrenalectomy and Lymph Node Dissection in Locally Advanced Renal Cell Carcinoma. Bekema HJ, Maclennan S, Imamura M, et al. *Eur Urol*. 2013; [Epub ahead of print]

Summary: Controversy remains over whether adrenalectomy and lymph node dissection (LND) should be performed concomitantly with radical nephrectomy (RN) for locally advanced renal cell carcinoma (RCC) cT3-T4N0M0. The objective was to systematically review all relevant literature comparing oncologic, perioperative, and quality-of-life (QoL) outcomes for locally advanced RCC managed with RN with or without concomitant adrenalectomy or LND. Relevant databases were searched up to August 2012. Randomized controlled trials (RCTs) and comparative studies were included. Outcome measures were overall survival, QoL, and perioperative adverse effects. Risks of bias (RoB) were assessed using Cochrane RoB tools. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. A total of 3658 abstracts and 252 full-text articles were screened. Eight studies met the inclusion criteria: six LNDs (one RCT and five nonrandomized studies [NRSs]) and two adrenalectomies (two NRSs). RoB was high across the evidence base, and the quality of evidence from outcomes ranged from moderate to very low. Meta-analyses were not undertaken because of diverse study designs and data heterogeneity. There was no significant difference in survival between the groups, even though 5-yr overall survival appears better for the RN plus LND group compared with the no-LND group in one randomized study. There was no evidence of a difference in adverse events between the RN plus LND and no-LND groups. No studies reported QoL outcomes. There was no evidence of an oncologic difference between the RN with adrenalectomy and RN without adrenalectomy groups. No studies reported adverse events or QoL outcomes.

Conclusion: There is insufficient evidence to draw any conclusions on oncologic outcomes for patients having concomitant LND or ipsilateral adrenalectomy compared with patients having RN alone for cT3-T4N0M0 RCC. The quality of evidence is generally low and the results potentially biased. Further research in adequately powered trials is needed to answer these questions.

Report card on molecular imaging, radionuclide therapy

Molecular imaging and carbonic anhydrase IX-targeted radioimmunotherapy in clear cell renal cell carcinoma. Muselaers S, Mulders P, Oosterwijk E, et al. *Immunotherapy*. 2013;5:489-495.

Summary: Conventional imaging is suboptimal at evaluating disease status in renal cell carcinoma (RCC) because of poor sensitivity. Furthermore, there is an unmet need for the treatment of metastatic RCC, both in terms of improvement of progression-free survival and limitation of toxicity. For this reason, radionuclide imaging and radionuclide therapy are extensively investigated.

Conclusion: This review provides an overview of the current progress in molecular imaging and radionuclide therapy in clear cell RCC and focuses on promising detection and therapy strategies targeting the carbonic anhydrase IX antigen, which is expressed in clear cell RCC.

Novel molecular marker identified

Stearoyl-CoA Desaturase 1 Is a Novel Molecular Therapeutic Target for Clear Cell Renal Cell Carcinoma. von Roemeling CA, Marlow LA, Wei JJ, et al. *Clin Cancer Res*. 2013;19:2368-2380.

Summary: This study's objective was identify Stearoyl-CoA desaturase 1 (SCD1) as a novel molecular target in clear cell renal cell carcinoma (ccRCC) and examine its role in tumor cell growth and viability in vitro and in vivo independently as well as in combination with current U.S. Food and Drug Administration (FDA)-approved regimens. Patient normal and ccRCC tissue samples and cell lines were examined for SCD1 expression. Genetic knockdown models and targeted inhibition of SCD1 through use of a small molecule inhibitor, A939572, were analyzed for growth, apoptosis, and alterations in gene expression using gene array analysis. Therapeutic models of synergy were evaluated utilizing pharmacologic inhibition of SCD1 with the tyrosine kinase inhibitors (TKI) sunitinib and pazopanib, and the mTOR inhibitor temsirolimus. The study identified increased SCD1 expression in all stages of ccRCC. Both genetic knockdown and pharmacologic inhibition of SCD1 decreased tumor cell proliferation and induced apoptosis in vitro and in vivo. Upon gene array, quantitative real-time PCR, and protein analysis of A939572-treated or SCD1 lentiviral knockdown samples, induction of endoplasmic reticulum stress response signaling was observed, providing mechanistic insight for SCD1 activity in ccRCC.

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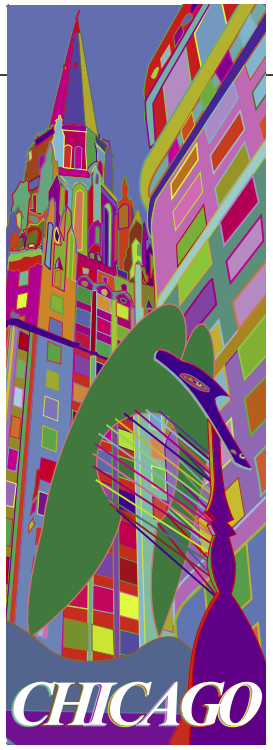

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Exploring the New Science of Immune Checkpoint Blockade With an Anti-PD-1 Antibody

The programmed death -1 (PD-1) pathway has recently been shown to be important in a tumor's ability to evade the immune system. The PD-1 pathway acts as a natural brake on the immune system, hindering the continued proliferation of effector T-cells. Tumors are able to harness this pathway to their advantage to evade detection by the immune system.

In this interview, ***David McDermott, MD****, reviews current thinking on PD-1 blockade and its potential based on clinical trials in which he is participating as an investigator. Dr McDermott is Associate Professor of Medicine, Harvard Medical School and Leader of the Kidney Cancer Program at the Dana-Farber/Harvard Cancer Center, in Boston, Massachusetts.*

KCJ: Why is the PD-1 pathway considered important in the pathogenesis of renal cell carcinoma?

Dr McDermott: It's been known for a while that the ligand for PD-1, known as PDL-1, is expressed by kidney cancer cells. Investigators at the Mayo Clinic have associated PDL-1 expression with more aggressive histologies and worse prognosis in patients with RCC. We think that the PDL-1 expression may defend the tumor against effective recognition by the immune system and allow it to behave more aggressively. Several monoclonal antibodies that can target either PD-1, which is found mostly on T cells, and PDL-1 have recently entered clinical trials. By interrupting the negative interaction, or "immune checkpoint", between the tumor and the immune system it may be possible to allow patient T-cells to be more effective at killing kidney cancer or controlling it.

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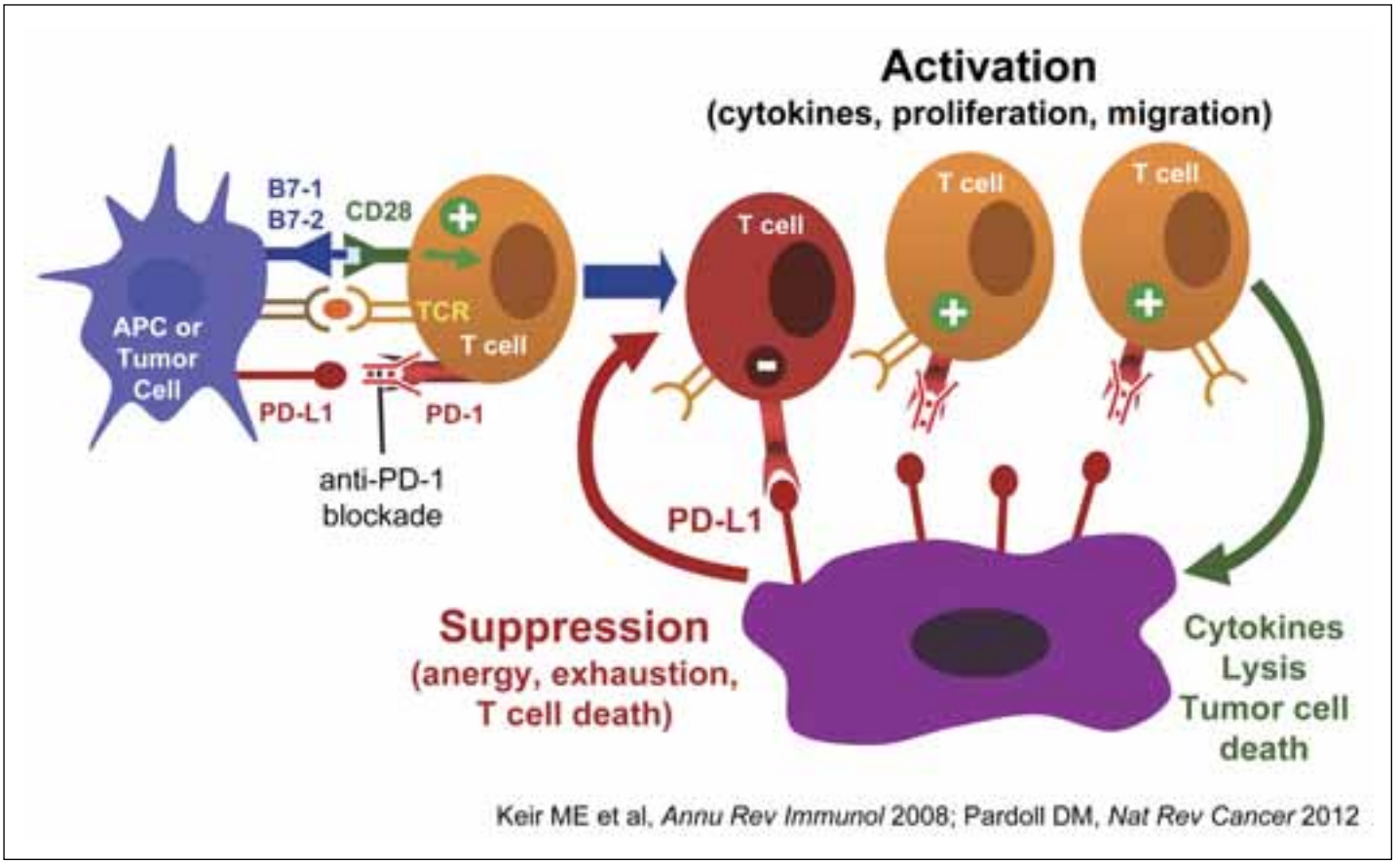
KCJ: How is it related to inhibition of other pathways such as CTLA-4? Is there a parallel to this?

Dr McDermott: Yes, these pathways are both "immune checkpoints." They act as brakes on the immune response to infection and promote tolerance. It turns out that these negative regulatory pathways are more potent than the pathways that stimulate T-cells. Maybe the most important negative regulatory pathway or checkpoint is the CTLA-4 pathway. This critical pathway is found on activated T-cells and normally helps the T cells shut down once the infection is controlled. When that shutdown is blocked with a monoclonal antibody (e.g. ipiliumab) the T cells remain more active and potentially able to recognize tumor and eliminate it. However, this newly active immune system can lead to significant toxicity which mimics autoimmune disease.

For patients with metastatic melanoma, this antibody to CTLA-4 has been shown to improve median survival and leads to lasting remissions of cancer in a small subset of patients. It is now being tested in kidney cancer. PD-1, PDL-1 and CTLA-4 blocking antibodies are part of this larger family of what is called "checkpoint inhibitors".

KCJ: What is your role in the clinical trials and what is the current status of these investigations?

Dr McDermott: Our group at DFHCC has been focusing on improving immunotherapy for kidney cancer for two decades, first with the cytokines (e.g. interleukin-2 and interferon) and now with vaccines and these checkpoint inhibitors. Because of our experience



Programmed death 1 (PD-1) and its ligands, PD-L1 and PD-L2, deliver inhibitory signals that regulate the balance between T cell activation, tolerance, and immunopathology. Immune responses to foreign and self-antigens require specific and balanced responses to clear pathogens and tumors and yet maintain tolerance. Induction and maintenance of T cell tolerance requires PD-1, and its ligand PD-L1 on nonhematopoietic cells can limit effector T cell responses and protect tissues from immune-mediated tissue damage.

with older forms of immunotherapy, we were asked to be involved in some of these recent trials. Because we also take care of patients with melanoma, we participated in early trials of CTLA-4 blockade and then PD-1 and PDL-1 blockade trials as well. We've been encouraging sponsors of these trials to test these agents in kidney cancer. If the trials prove successful, hopefully we will have FDA-approved checkpoint inhibitors for kidney cancer patients in the next few years.

KCJ: Are you the principal investigator for the study on PD-1 blockade?

Dr McDermott: No, the overall PI for the largest PD-1 antibody (nivolumab, Bristol Myers Squibb) trial was Suzanne Topalian, from Johns Hopkins. Our center at the put the most kidney cancer patients on that trial. Therefore, I was asked on behalf of my colleagues to present the kidney cancer portion of that much larger story. There are 34 patients out of approximately 300 patients with kidney cancer on this large trial. There are many cancer centers who participated in this trial and share in the responsibility for this research. These are also several companies developing PD-1 and PDL-1 antibodies (e.g. Merck, Genentech).

KCJ: Is the trial now in Phase 3?

Dr McDermott: Yes, these agents have been tested in Phase 2 and Phase 3. We don't know the results of the Phase 3 trial yet.

KCJ: What can we say about the safety and tolerability of nivolumab, the agent used for PD-1 blockade.

Dr McDermott: When you look at the experience of the 300 or so patients in the Phase 1 trial nivolumab may be less toxic than earlier forms of immune therapy (e.g. IL-2, CTLA-4 blockade). But it does have serious side effects in some patients and needs to be monitored carefully. But this experience is preliminary and obviously much more testing needs to be done.

KCJ: The response rate is 1 in 4 or 1 in 5?

Dr McDermott: The response rate in those 34 patients mentioned previously was 29% with 27% of patients had stable disease lasting over 6 months. A total of 58% of the patients treated with the antibody had some clinical ben-

efit. It is possible that when we get to the Phase 3 that the clinical activity will be less encouraging. That said, some patients experienced anti-tumor effect event after the antibody was discontinued. It will be interesting to follow these patients in the future.

KCJ: Do you envision combining this therapy with other targeted therapies like TKIs or the mTOR inhibitors?

Dr McDermott: Yes, that's actively being done as we speak. There is a Phase 1 trial combining this antibody with sunitinib and pazo-panib as well as ipilimumab. I'm sure other combinations will be considered.

KCJ: There is some talk of combining PD-1 blockade with dendritic cell-based vac-cines.

Dr McDermott: We're doing that at the DFHCC right now. Dr. David Avigan is the principal investigator for a trial combining a dendritic cell/tumor fusion vaccine with a PD-1 antibody. It's an interesting idea that needs to be explored.

KCJ: What can we say about the durability of responses achieved with PD-1 blockade? In what percentage of patients and for how long?

Dr McDermott: Most of the responding patients have durable responses lasting for over a year. That data will be updated at ASCO.

KCJ: You have indicated previously that 30% of patients have "major shrinkage" in their tumor, correct?

Dr McDermott: The 29% is the exact number from the Phase I trial.

KCJ: What is your target date for the completion of the Phase 3 trial?

Dr McDermott: Hopefully the accrual to that trial will be finished this year with results further down the road. The important thing to realize is there are many different trials including the combinations you mentioned. So oncologists should consider whether patients might be candidates or one of the trials. The faster patients are entered on these trials the faster we can get these answers.

KCJ: It sounds like we're at the threshold of a new avenue in treatment, aren't we?

Dr McDermott: We hope so. But that means the Phase 2 and Phase 3 trials need to support Phase 1. We think there will be benefit for a subset of patients with these agents. The question is one, how big is that subset and two, can we identify that group of patients before they receive the treatment? There is a lot of active research in that area as well. KCJ

Kidney Cancer Association Sharpens Its Online Focus, Building a Stronger Global Network of Patient Education, Support and Advocacy

Kidney Cancer Journal *recently interviewed Carrie Konosky, Vice President for Development and Public Affairs for the Kidney Cancer Association. Covering the scope of the Association's activities, she delineated how the KCA is meeting the challenges of the digital age and expanding its program for professionals and patients.*

KCJ: The KCA website suggests that the association has a greater focus on digital and online offerings. How have you expanded and enhanced your programs in this regard?

Ms Konosky: We still offer our primary publication, *We Have Kidney Cancer* updated each year by our Medical Advisory Board and Nurse Advisory Board. This and a number of other publications are available for download or as an e-reader. Some of the publications are now offered for Kindle devices. Some of our in-person, patient support meetings and conferences are videotaped to offer the valuable information to patients across the globe. The topics range from side effects to surgery, nutrition and living with the disease. We have also expanded the online support network. What started as an online message board on our website, has now expanded to sites such as, Facebook and Twitter. We have multiple groups on Facebook, our KCA main page, and some that are more specific such as pages for nutrition, survivors, and care givers. We have also added a live chat application. When someone visits the website and is looking for information they can talk to a member of our staff, who will answer questions or provide assistance in navigating the website.

KCJ: How has the KCA evolved over the last few years as a patient advocacy group and as a resource for kidney cancer information? cancer information?

Ms Konosky: We always try to stay on the cutting edge of technology, to be able to offer patients real time information. There is new information available every day on new treatments, clinical trials, etc. And we want to be able to have patients all over the world access that information as quickly as possible.

The importance of clinical trials is a high priority for the organization. Our medical advisors and Nurse Advisory Board members work with us to better educate patients on this topic. We also have a clinical trials matching service on our website to help patients find a trial that might be right for them. We support the work of young investigators through the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA).

KCJ: What are you doing on the legislative front to advance your agenda for patient advocacy and what obstacles remain to implement important legislation?

Ms Konosky: One thing we're working on in terms of legislation is collaborating with other organizations. Our Board of Directors and advisors recognize the value in working with larger organizations. Some of these may be cancer specific, and others may have a general healthcare focus. There are many organizations that have similar goals and by working together we can make a greater impact.

KCJ: If physicians wish to become more involved in KCA programs what do you recommend?

Ms Konosky: I would recommend visiting our medical

education web site, kidneycancer.com, designed specifically for physicians, nurses, and other health care practitioners. For information on our medical symposia, physicians should visit kidneycancersymposium.com. We host one symposium in the United States each fall and another in Europe in the spring. These meetings are typically one and a half to two-day meetings for physicians and other healthcare professionals.

KCJ: Will you be expanding the CME component of your program?

Ms Konosky: Our medical steering committee is discussing potential ways that we can expand our CME opportunities. In addition to our US and European symposia, we are also exploring the idea of doing similar meetings in Asia and South America.as well.

KCJ: Is the KCA looking for a greater stake in research for renal cell carcinoma through enrollment in clinical trials?

Ms Konosky: The importance of clinical trials is a high priority for the organization. Our medical advisors and Nurse Advisory Board members work with us to better educate patients on this topic. We also have a clinical trials matching service on our website to help patients find a trial that might be right for them. We support the work of young investigators through the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA). Our medical advisors strongly believe in continuing the support of young investigators, to ensure the continued research into treating this disease.

KCJ: In terms of your international involvement, what is the association doing to maintain and encourage a global focus on kidney cancer?

Ms Konosky: One of the things we have done is making our primary publication *We Have Kidney Cancer* available in 13 languages. These translated versions are available as downloadable PDFs on our website, kidneycancer.org. We also work with physicians around the globe, to help them organize their patients or to offer support and educational opportunities in their countries, similar to the conferences we host in the US.

KCJ: How are outreach services such as your patient survivor conferences and support groups expanding?

Ms Konosky: We will continue to do a few regional conferences each year at various institutions across the United States. In addition to videotaping some of these meetings, we have also been testing live webcasting so that we can engage a larger audience in real time. Our goal is to find was to disseminate the information we have to as many patients as possible.

What started as an online message board on our website, has now expanded to sites such as, Facebook and Twitter. We have multiple groups on Facebook, our KCA main page, and some that are more specific such as pages for nutrition, survivors, and care givers.

KCJ: How many patients or members are you serving?

Ms Konosky: We have over 100 support group meetings in the US. Hundreds of patients view the videos online from our larger. In addition our KCA Facebook group has over 65,000 members.

KCJ: Does the KCA anticipate any initiatives to broaden the availability of therapies and make certain medications more affordable to patients when reimbursement is problematic?

Ms Konosky: We direct patients to the different assistance programs that are available, that they may not be aware of. Our government affairs committee also sees accessibility, both in the US and globally as an important agenda item in terms of our advocacy work. KCJ

Optimizing Lymph Node Dissection in RCC: Current Templates and Nomograms for Poor Prognosis Patients

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The optimal contemporary approach to lymphadenectomy during the surgical management of RCC is evolving rapidly and its application in different subsets of patients has produced new guidelines. Recent trials have debunked the misconceptions associated with a large earlier trial suggesting the absence of demonstrated therapeutic benefit. A review of current literature reveals how the approach has changed significantly amid the continued downward stage migration of the disease.

It has been one of the longest running controversies in the surgical management of renal cell carcinoma, now more than 40 years old, and it is still generating debate. But new results on identifying patients most likely to benefit has helped clarify our choices and protocols with regard to the decision on whether—and when—to perform lymphadenectomy at the time of nephrectomy; this topic is increasingly the focus of recent reports that propose criteria for patient selection, delineate the pros and cons of lymphadenectomy in this setting and nomograms to guide clinical decision making. Can the issue be resolved? Perhaps not definitively, but the latest results could provide the impetus for still further study and the validation of various templates for LND.

At the center of the controversy is whether LND is purely an adjunctive staging procedure or has a therapeutic role in the management of the disease.[1]Currently, surgeons do not routinely perform lymph node dissection unless there is gross evidence of lymphadenopathy, as patients without clinical evidence of lymphadenopathy rarely have positive nodes at the time of surgery.[2] Although there are no definitive data indicating an overall survival advantage gained by performing LND in patients with RCC, it is clear that patients with metastatic disease to the regional lymph nodes have a poor overall prognosis.

Current literature suggests a number of different perspectives and epidemiological data that help frame the controversy surrounding LND. Among them are the following:

- The presence of lymph node metastasis in patients with locally advanced RCC is one of the strongest prognostic factors influencing survival. The 5-year survival rate of patients with lymph node-only metastasis ranges from 5% to 38%[3-7]
- Without distant metastatic disease, the incidence of isolated regional lymphatic metastases in patients staged as clinically node negative is rare (1% to 5%).[8,9] These pathologic rates vary, however, depending on such factors as clinical features and the extent of LND performed. Thus, in the absence of distant metastatic disease, nodal metastases can occur more frequently in patients with high stage and grade primary tumors and those with clinical lymphadenopathy.[10]

Given the rare occurrence of isolated lymph node metastases along with the significant stage migration that has occurred in RCC using an "all or none" practice is ill-advised.[1] Delacroix et al suggest that this will either expose a majority of patients to an unnecessary and potentially morbid procedure or may deny some patients from a procedure of potential benefit.[1] There is substantial evidence to show that LND is unnecessary in patients with low-risk primary tumors with clinically negative regional lymph nodes. However, other reports have focused on quantifying a patient's risk for nodal metastases suggested by adverse features.[11,12] A growing body of literature suggests when LND may be appropriate in a given patient and specific subsets for whom aggressive surgical resection involving lymphadenectomy may be indicated.

Keywords: Lymph node dissection; lymphadenectomy; renal cell carcinoma; staging; therapeutic; high risk; nephrectomy

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The EORTC Experience: Interpreting the Results With Caution

The European Organization for Research and Treatment of Cancer (EORTC) trial 30881 offers an excellent starting point from which to analyze data because it is the only large prospective randomized trial assessing the role of LND in RCC.[9] The EORTC compared the long-term results of radical nephrectomy alone (n=389) vs radical nephrectomy with lymphadenectomy (n=383 for patients with clinical N0, M0 disease .

The EORTC study concluded that LND is not therapeutic in the routine management of RCC; however, the group also reported that LND did not increase the morbidity of surgical management. The EOTRC results sparked a great debate over the merits of LND, but before anyone can draw conclusions from its results, it is important to realize that the study was done almost exclusively in patients with low stage, low grade disease. Thus, it is not surprising that there was no benefit to LND because the likelihood of lymph node metastases in these patients or subsequent recurrence of or death from RCC were exceedingly low. Although this was a landmark study, it does not negate the role for LND in RCC.[2] This is particularly apropos in view of the approval of new adjuvant agents, studies nearing completion on targeted therapies that would imply the potential importance of LND either as a therapeutic option or staging procedure. With this in mind, it is important to revisit the debate on LND and explore the impact of other studies.

Ultimately, the benefit of LND in RCC, whether it be therapeutic or purely diagnostic staging accuracy, may only be realized in a select subset of patients. A review of the literature highlights additional areas of controversy and the extent to which templates for lymph node dissection offer guidelines for performing the procedure.

One factor that adds to the controversy surrounding LND at the time of radical nephrectomy is the variability of renal lymphatic drain-age.[2] Therefore, a sentinel or regional lymph node sampling is not adequate for RCC. Currently, we recommend the following templates. For performing LND on the left side the approach includes the paraaortic and preaortic nodes from the crus of the diaphragm to the inferior mesenteric artery. A standard LND on the right includes the paracaval and precaval nodes from the adrenal vein along the vena cava, also down to the level of the inferior mesenteric artery.

Protocols and nomograms for LND

The EORTC adds to a rapidly developing body of literature addressing the question of whether a LND can benefit some subset of patients at the highest risk for metastases.[9] Blute et al[5] proposed a protocol for LND based on pathological features of the primary tumor. The authors determined the primary pathological features of clear cell RCC that are predictive of positive regional lymph nodes at radical nephrectomy and suggested a protocol for the selective use of extended LND.

This series included 1652 patients undergoing radical nephrectomy for cM0 clear cell RCC; 58% had lymph nodes submitted for pathologic analysis, of which 93% were pN0, 6% were pN1, and 1% were pN2. The independent predictors of regional lymph node involvement included:

- Presence of nuclear grade3 or 4
- Presence of a sarcomatoid component
- Tumor size ≥10 cm
- Tumor stage pT3 or pT4
- Presence of coagulative tumor necrosis

The likelihood of regional lymph node involvement

Take-Home Messages on Lymphadenectomy at the time of Nephrectomy

In an interview, Bradley C. Leibovich, MD, offered insights on performing lymphadenectomy.

- Most surgeons are comfortable performing a laparoscopic radical nephrectomy even for relatively locally advanced disease. However, most surgeons comfortable with this concept are not comfortable doing a minimally invasive complete retroperitoneal LND or even a relatively incomplete minimally invasive LND. Mobilization of the great vessels to perform a complete LND is challenging for many surgeons to perform open and few can do this with a MIS approach.
- The more nodes one removes the more likely it is one will find positive nodes. There also may be data suggesting that the more nodes one removes, the better the prognosis. Just a lymph node sampling is inadequate.
- What is not clear is whether there is an advantage to the patient, if any, to removing negative lymph nodes. We don't have a good answer to that. The data are equivocal.
- The main message from the available studies is that performance of LND does not significantly, if at all, increase the morbidity of the operation in terms of complication rates, either short term or long term.
- The EORTC study is the only randomized, prospective study in patients undergoing LND or not undergoing LND at the time of nephrectomy. In this study the vast majority of patients had low-stage, low-grade disease and that is why the study showed no benefit from LND. Thus the likelihood of lymph node metastases in these patients or subsequent recurrence or death from kidney cancer are all exceedingly low.
- There are some data to suggest that LND may be beneficial for patients with advanced stage disease. Do you perform LND on everyone or do you do some sort of risk stratification? (We risk stratify.) The problem with using criteria from some studies, such as Blute et al (see reference list in main article), is that the data are all intraoperative pathology findings. At many centers routine frozen sections are not used. Thus, LND is not routinely part of the algorithm for everybody. Most people either do it routinely or they don't do it at all.

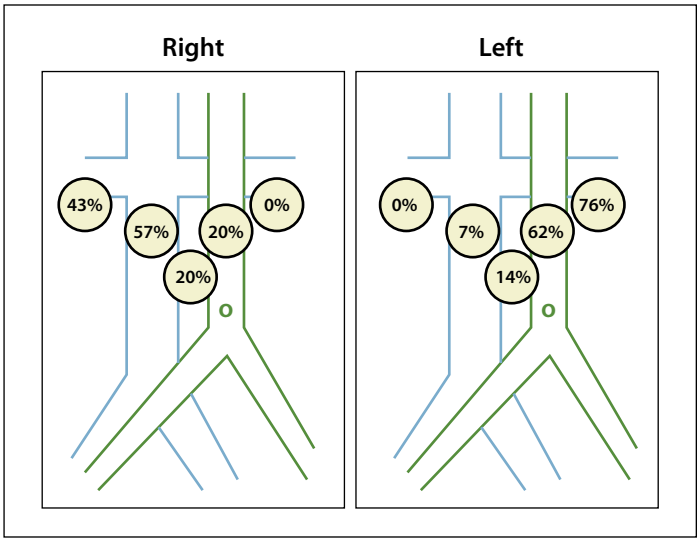

Figure 1. Percentage frequency of involved locations of pathologic lymph node-positive disease based on the side of the primary tumor. (From Crispen PL, Breau RH, Allmer C, et al. *Eur Urol*. 2011; 59:18-23.

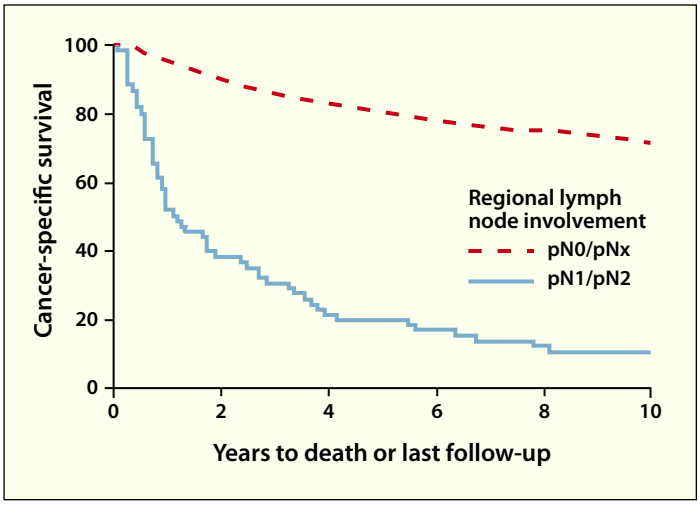

Figure 2. Estimated disease-specific survival according to regional node involvement. (From Blute ML, Leibovich BC, Cheville JC, et al. *J Urol*. 2004;172:465-469.

increased as the number of risk factors increased: regional lymph node involvement was noted in 0.4%, 1%, 4%, 12%, 13%, and 53% of patients with 0, 1, 2, 3, 4, and 5 of these features present. A patient was defined as high risk when at least two adverse features were found. In the series, 621 patients had at least two of these features; 10% (n=62) had regional lymph node involvement detected through LND. Two caveats about this study are one, the data have yet to be validated in an external series and two, its intraoperative protocol required a frozen section analysis at nephrectomy to assess risk. One of the problems then in extrapolating from this study is that many clinicians prefer not to use frozen sections in these cases.

Crispen et al[10] utilized the Blute criteria to determine the utility of the stratification algorithm and reported the frequency and location of nodal metastases in a series of patients. Crispen and colleagues identified 415 patients with clear cell RCC and used the protocol described by Blute et al (**Figure 1**). Of the 415 patients 169 (41%) were identified as high risk because they had two or more of the adverse features identified by Blute. Blute et al also estimated disease-specific survival according to regional node involvement (**Figure 2**).

Hutterer et al[11] provided a preoperative assessment of the risk of lymph node disease in their nomogram based on patient age, symptom classification, and tumor size as possible predictive factors for lymph node metastases in 4658 patients. The primary advantage of this nomogram is the fact that the variables are available in the preoperative setting and therefore facilitates surgical planning as opposed to being dependent on intraoperative frozen pathologic findings. Data were compiled from 7 European centers (n=2522) and was externally validated against patients from 5 other centers (n=2136. Symptoms were classified as asymptomatic, local (flank pain, palpable mass, or hematuria), or systemic (anorexia, asthenia, weight loss). Symptom classification and tumor size were independent predictors of nodal metastases. Although age did not reach the level of independent predictor, it added to the discriminant properties of the model.

A nomogram based on age, symptom classification, and tumor size was 78.4% accurate in predicting the individual probability of nodal metastases. Hutterer et al[11] suggest that their nomogram could help identify patients at low risk of nodal metastases and be useful as a tool to determine the need and extent of nodal staging in patients without known distant metastases.

Consensus on the Role of LND

Optimal patient selection for LND is still somewhat of a work in progress, but multiple retrospective series elucidate the therapeutic benefit in subsets of patients.

Delacroix et al[1] propose the following criteria for selecting patients for LND:

- ***Low-risk localized RCC.*** Patients with clinically localized, low-risk RCC (cT1-2,cN0M0) have a very low risk of harboring micrometastatic disease. In this category, the understaging rate of omitting an LND seems to be approximately 1%. Thus, in clinically localized, low-risk, node-negative RCC, LND does not seem to have a therapeutic benefit nor a staging advantage.
- ***High-risk localized RCC.*** Patients in this category may benefit from resection of isolated nodal metastasis. There are only retrospective data to suggest that this is the case but aside from the potential therapeutic benefit, these patients may require further therapeutic intervention and could be considered for enrollment in adjuvant clinical trials.

Supportive evidence for these approaches come from numerous retrospective reports, as early as 1990[13] when Giuliani et al published their finding on extensive LND in radical nephrectomy. They showed survival in patients with pN+ disease was intermediate between those in

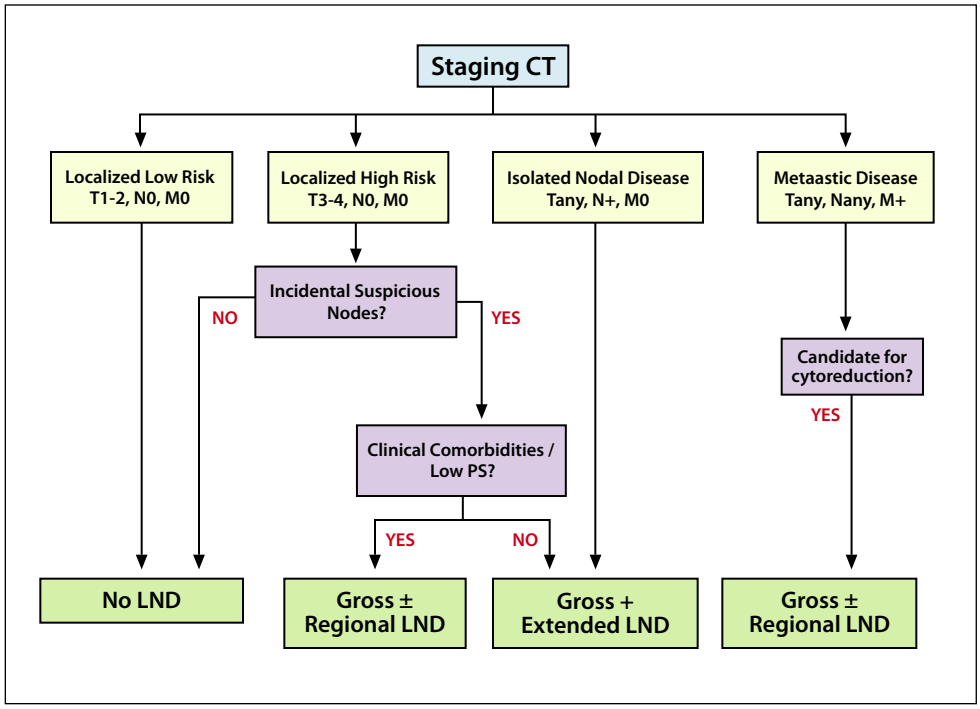

Figure 3. A proposed algorithm for lymph node dissection during radical nephrectomy. (From Crispen PL, Breau RH, Allmer C., et al. *Eur Urol*. 2011;59:18-23.)

whom the tumor was confined to the kidney and those with distant metastatic disease. Subsequently, the authors performed another analysis in 328 patients and confirmed the benefit of LND.

Two critical retrospective reviews by Pantuck et al suggest advantages to LND. They reviewed a large series of nephrectomies with suspected nodal involvement—535 patients with N0M0 disease, 129 with pN+ disease and 236 with distant metastasis only.[14] The authors found that patients with isolated clinical node involvement undergoing LND had a significantly longer survival despite having a worse prognosis after adjusting for Fuhrman grade and T stage. The second report,[3] also based on results gathered at UCLA, included 236 patients with clinical N0M1 RCC and 86 patients with clinical N+M1 disease. In both groups, 65% received postoperative immunotherapy.

Median survival was 20.4 months for patients with N)M1 disease vs 10.5 months in those with N+M1 disease. Patients undergoing nephrectomy with synchronous LND (n=129) had a significant survival advantage (5 months improvement) over patients with clinically positive nodes left in situ. It may be, the authors, concluded that LND may influence the natural history of the disease in metastatic RCC treated with immunotherapy.

In another retrospective analysis based on the SEER database, Whitson et al[15] divided 9586 patients into two cohorts: node-negative (n=8321) and node-positive (n=1265). At a median followup of 3.5 years, 58% of the node-positive patients and 20% of the node-negative patients had died of RCC. An increase in disease-specific survival was seen with the extent of lymphadenectomy in patients with node-positive disease. An increase of 10 lymph nodes in a patient with one positive lymph node was significantly associated with a 10% absolute increase in disease-specific survival at 5 years. Whitson et al suggest that patients at high risk for nodal disease should be considered for LND.

Conclusion

The consensus from the literature is that regional LND at the time of radical nephrectomy is not likely to benefit majority of patients with renal tumors. LND is not recommended as standard practice for low-grade, low-stage RCC. However, the recommendations are different for high-risk patients with clinically enlarged lymph nodes. In this setting the staging and prognostic benefit of LND (**Figure 3**) is clear and there is some evidence of potential therapeutic benefit.

Recommendations can best be summarized by the following points:

- cT1N0M0: No LND
- cT2-4N0M0: LND based on risk stratification, surgeon and patient preference
- cTanyN + and or M+: perform LND ; however, no data are available in the era of targeted therapy

References

1. Delacroix SE, Chapin BF, Wood CG. The role of lymph node dissection in renal cell carcinoma. *Urol Clin N Am*. 2011;38:419-428.
2. Jamal JE, Jarrett TW. The current role of lymph node dissection in the management of renal cell carcinoma. *Int J Surg Oncol*. 2011;816926.
3. Pantuck AJ, Zisman A, Dorey F, et al. Renal cell carcinoma with retroperitoneal lymph nodes. Impact on survival and benefits of immunotherapy. *Cancer*. 2003;97:2995-3002.
4. Karakiewicz PI, Trinh QD, Bhojani N, et al. Renal cell carcinoma with nodal metasases in the absence of distant metastatic disease: prognostic indicators of disease-specific survival. *Eur Urol*. 2007;51:1616-1624.
5. Blute ML, Leibovich BC, Cheville JC, et al. A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. *J Urol*. 2004;172:465-469.
6. Delacroix SE, Chapin BF, Chen JJ, et al. Can a durable disease-free survival be achieved with surgical resection in patients with pathological node positive renal cell carcinoma? *J Urol*. 2011;186:1236-1241.
7. Capitanio U, Jeldres C, Patard JJ et al. Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma. *BJU Int*. 2009;103:33-37.
8. Johnson JA, Hellsten S. Lymphatogenous spread of renal cell carcinoma: an autopsy study. J Urol. 1997;157:450-453.
9. Blom JH, van Poppel H, Marechal JM, et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. *Eur Urol*. 2009;55:28-34.
10. Crispen PL, Breau RH, Allmer C, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. *Eur Urol*. 2011;59:18-23.
11. Hutterer GC, Patard JJ, Perotte P, et al. Patients with renal cell carci-

noma nodal metastases can be accurately identified: external validation of a new nomogram. *Int J Cancer.* 2007;121:2556-2561.
12. Thompson R, Raj G, Leibovich BC, et al. Preoperative nomogram to predict positive lymph nodes during nephrectomy for renal cell carcinoma. Presented at the American Urological Association Annual Meeting. Orlando, May 17-22, 2008 [abstract 603].
13. Giuliani L, Giberti C, Martorana G, et al. Radical extensive surgery for renal cell carcinoma: long-term results and prognostic factors. J *Urol.* 1990;143:468-473.
14. Pantuck AJ, Zisman A, Dorey F, et al. Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. *J Urol.*2003;169:2076-2083.
15. Whitson JM, Harris CR, Reese AC et al. Lymphadenectomy improves survival of patients with renal cell carcinoma and nodal metastases. J Urol. 2011;185:1615-1620. KCJ

EDITOR'S MEMO

(continued from page 8)

on how alternate dosing strategies of this cytokine could overcome some of the drawbacks long associated with a therapy associated with significant toxicity.

All of the fanfare surrounding immunotherapy at ASCO and elsewhere does not mean we should overlook the importance of targeted therapies, and there is plenty to cheer about with regard to new data on this front as well. It would be premature to say targeted therapies have not fulfilled their earlier promise, especially when there are signs of improved outcomes through innovative sequencing of these agents.

Have we reached a plateau of efficacy with targeted therapies? Perhaps, and there is indeed evidence to suggest this may be the case. But right now rather than dwell on its use in a disappointing light, it is more important to cheer the new findings on immunotherapy. We might think of immunotherapy as somewhat of a "comeback kid." It has been around for a long time and it is encouraging to see it staging a revival in a different form as a "checkpoint" inhibitor.

Robert A. Figlin, MD
Editor-in-Chief

Deconstructing and Reinventing the IL-2 Paradigm: Can Alternate Dosing Schedules Enhance Tumor Effect?

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In renal cell carcinoma (RCC), patient selection strategies, using clinical and tumor features, are evolving for interleukin-2 (IL-2). Recent reports are taking these strategies further, exploring whether alternative schedules could revamp the paradigm by offering regimens that prove to be less toxic and synchronized to measurements of a patient's immunological response. The emerging concepts, if validated in prospective trials, could dramatically change the treatment landscape for immunotherapy.

Last year marked the 20th anniversary of the clinical introduction and regulatory approval of interleukin-2 (IL-2) for use in cancer therapy, and during this period IL-2 has emerged as the most studied immunotherapy for renal cell carcinoma (RCC). In the ensuing years, through clinical selection, particularly for patients with clear cell RCC and good performance status, the response rate has doubled compared with initial studies (28-30% vs 15%) and stable disease has become a measurable endpoint (44%).[1-4] Nevertheless, the complete response rate remain virtually unchanged (7% for RCC and melanoma). However, the treatment paradigm continues to evolve, and new schedules and approaches are emerging, not yet with enough translational impact to merit application into clinical practice, but creating a stir within the kidney cancer community because of their potential implications for the use of IL-2 therapy.[5] Of interest is the investigation of novel alternate dosing schedules directed at the intrinsic immunologic feature of selected patients [6] that could ultimately better define groups who would benefit from IL-2 treatment and enhance tumor effect.

After 20 years of investigation many important issues still confront the treating physician dealing with a complex treatment regimen—a regimen that has significant issues with toxicity, but that also has potential for outstanding outcomes. Studies have evaluated dose levels, various schedules, cytokine combinations, addition of chemotherapy and different routes of administration.[7-11]

These studies have concluded that the best use of IL-2, producing the best outcomes, remains high-dose treatment, administered by an experienced team in the appropriate setting.[3,4,12-14] Over that period of time, the numbers of doses per course have decreased with an improved toxicity profile, but with enhanced response rate and clinical benefit.[3,4,13-15]

How do we continue to incorporate high-dose IL-2 into the armamentarium for RCC? It has not been and should not be supplanted by newer agents that, while perhaps more manageable and capable of producing positive results in larger numbers of patients, still have as their major benefit stabilization of disease, with some progression-free benefit and likely some additive survival benefit. The therapeutic goal for patients with metastatic RCC should remain the achievement of durable complete responses, measured in terms of years. Our most promising strategy is the development of techniques for identifying those patients who are expected to have a high rate of major responses and complete responses to high-dose IL-2.

Early Studies Established Dose-Response

By the early 1990s, the paradigm for use of IL-2 in metastatic RCC began to emerge, validated by animal and human studies demonstrating a dose-response. Those earlier studies explored a range of issues and different regimens to determine optimal response. Among those were trials that utilized bolus dosing compared with IV continuous infusion and others evaluating subcutaneous administration. Subcutaneous dosing produced outcomes similar to continuous infusion, but at a lower dose.

Keywords: Interleukin-2; immunotherapy; metastatic renal cell carcinoma; alternate dosing; number of dosing.

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High-dose emerged as gold standard early on

The response rate in patients who were treated with high-dose IL-2 was double that seen in patients who were treated with regimens of low-dose intravenous IL-2 or subcutaneous administration of IL-2 alone [13]—and double that seen in patients treated with lower-dose IL-2 plus interferon.[14] In addition, many more durable complete responses were seen in the high-dose IL-2 arms, with many of these responses now surpassing a decade in duration.[13,14] Two recent studies conducted by the Cytokine Working Group (CWG) demonstrated an improved response rate of 28-30% with high-dose IL-2 in patients with metastatic renal cell cancer, using clinical selection critera.[3,4] Studies are ongoing to evaluate biological and immunological parameters that may also impact patient selection for successful IL2 treatment outcomes in these patients.

Numerous additional studies support the use of high-dose bolus IL-2 as the treatment of choice for metastatic RCC. Administration of this regimen has higher response and survival rates when compared to low dose or subcutaneous administration.[16] As referenced above, one of the pivotal papers demonstrated that major tumor regressions, as well as complete respon- ses, were seen with all three regimens tested but IL-2 was more clinically active at maximal doses (720,000 U/kg) vs low dose (72,000 U/kg every 8 hours or a low-dose daily subcutaneous IL-2 regimen.[13] Similarly, in the CWG trial, high dose bolus IL2 was compared to subcutaneous IL2 plus interferon, again with a doubling of response rate and more durable complete and partial responses with the use of high dose IL2.[14]

Since the FDA approval of high-dose IL-2, the paradigm for its use has undergone extensive study with investigators seeking to overcome the limitations of a therapy associated with significant toxicity. Later doses of the approved high-dose regimen (8 hour dosing, 5-day schedule) are typically associated with a higher frequency of major and cumbersome side effects including possible intensive care admission, vasopressor support, as- thenia, capillary leak, and edema.[6,11,15,17] This standard high-dose bolus schedule also requires hospitalization for about 6 days at a time. Key limitations of this schedule (besides the frequency of major response) include that most treatment courses are terminated by an adverse event, and that across a cohort of patients, the cumulative dose delivery is highly variable. Additionally, this schedule is inconvenient for medical staff who must assess patients before each dose, and in some hospitals, the limited availability of monitored beds. Thus necessity and logistics have in some cases led to new empiric schedule alterations.

Some IL2 centers describe alterations in clinical approaches directed at dosing strategies that could maintain efficacy while limiting the adverse effects associated with the approved regimen of high-dose IL-2, with most data being anecdotal. These include a planned extension of time between the two weeks of treatment, and/or a fixed number of doses per week based on data showing the relatively standard reduction in dose numbers administered per course over the last decade, with no reduction in efficacy.[3,4,15]

Acquavella et al[18] reported a prospective high-dose IL-2 program with a modified twice daily dosing schedule, at a dose of 720,000 U/kg, and limited the total number of doses per course to 8, and treated patients in an oncology ward without cardiac monitoring. Hypotension was managed preferentially with normal saline fluid boluses and/or delay in treatment. They conducted a retrospective chart review of 41 consecutive metastatic mela- noma (n=33) and renal cancer (n=8) patients treated with the modified high-dose IL-2 regimen. The median number of IL-2 doses administered in the first cycle was 15. Overall toxicity was similar to published data for the every 8 hour schedule, but only 9.79% of patients required vasopressors. Twenty-four percent of patients were transferred electively or emergently to the intensive care unit. There were no treatment-related deaths. The objective response rate was 12.5% and 0% in melanoma and renal cancer, respectively. Responses were durable, and 2 additional melanoma patients with mixed responses remain disease-free after resection of residual or recurrent sites of disease. Thus, the twice-daily IL-2 regimen had meaningful activity, may be more convenient to administer, reduced the need for elective monitored beds, and may be preferable for development of combinations with newer immune modulators.

Deconstructing the IL-2 Paradigm: Taking a New Direction in Dosing IL-2 Activates Cytotoxic T cells and Regulatory T cells

First described as a T cell growth factor, IL-2 has a wide spectrum of effects in the immune system. Some of the possible mechanisms by which IL-2 carries out its anti-cancer effects include the augmentation of cytotoxic immune cell functions and reversal of T cell anergy, enabling delivery of immune cells and possibly serum components into tumor. IL-2 indirectly limits tumor escape mechanisms such as defective tumor cell expression of Class I or Class II molecules or expansion of regulatory T cells. Indirect effects on the tumor microenvironment are also likely and associated with rather dramatic T cell infiltration during the global delayed type hypersensitivity response that is associated with systemic IL-2 administration.[19]

However, in addition to stimulating lymphocytes to kill tumors via cell-mediated cytotoxicity and possibly other mechanisms (20), IL-2 has been shown to increase T regulatory cells in vivo in patients with renal cell cancer and metastatic melanoma, accompanied by a decrease in natural killer cells and dendritic cells.2[1] Administration of IL-2 acutely also increases the proportion of myeloid-derived suppressor cells in patients with renal cancer who were given IL-2 in a low-dose subcutaneous schedule.[22] Thus, there are competing immunologic effects triggered by IL-2 administration and subsequent cytokines released

in this process. Current research is attempting to maximize the antitumor effect in part by modulating the regulatory cell activity.

A detailed commentary of this bimodal activity of IL-2 appeared in a review of literature by Coventry and Ashdown[5] who delineated the spectrum of effect of IL2 in the immune response. They describe a sequential, time-dependent, homeostatic, (**Figures 1, 2**) physiological process, requiring the coordinated and timely interaction of cytokines, their receptors, and the responding cell populations. According to their review, these cytokine/receptor interactions have half-lives of minutes to hours. Both T effector cells and T regulatory cells transiently express the IL-2 receptor for only about 8-12 hours, and both require IL-2 for their activation/expansion and maintenance.[5] With this in mind, they hypothesize that alterations in IL-2 administration schedule may impact more positively on the induction of cytotoxicity.[5]

Why the Cyclical Nature of IL-2 Expression Is a Key Factor

New schedules proposed for the use of IL-2 are beginning to emerge that could, if validated in further trials, support novel concepts in dosing. Among the more intriguing reports within the last few years is a paper by Finkelstein et al.[6] They hypothesized that more frequent planned breaks could preserve or improve planned dose delivery, and result in a more uniform dose delivery across the treated group. They evaluated a new schedule (600,000IU/kg, 8 hours between doses, for 5 doses per course, 4 courses at weekly intervals/cycle - a maximum of 20 doses) of high-dose IL-2 in which they inserted planned breaks while maintaining high cumulative dose delivery.[6]

Target dose delivery was attained: median IL-2 cumulative dose per patient was 11.4 and 10.8 million units/kg (cycles 1 and 2, respectively). Major responses were

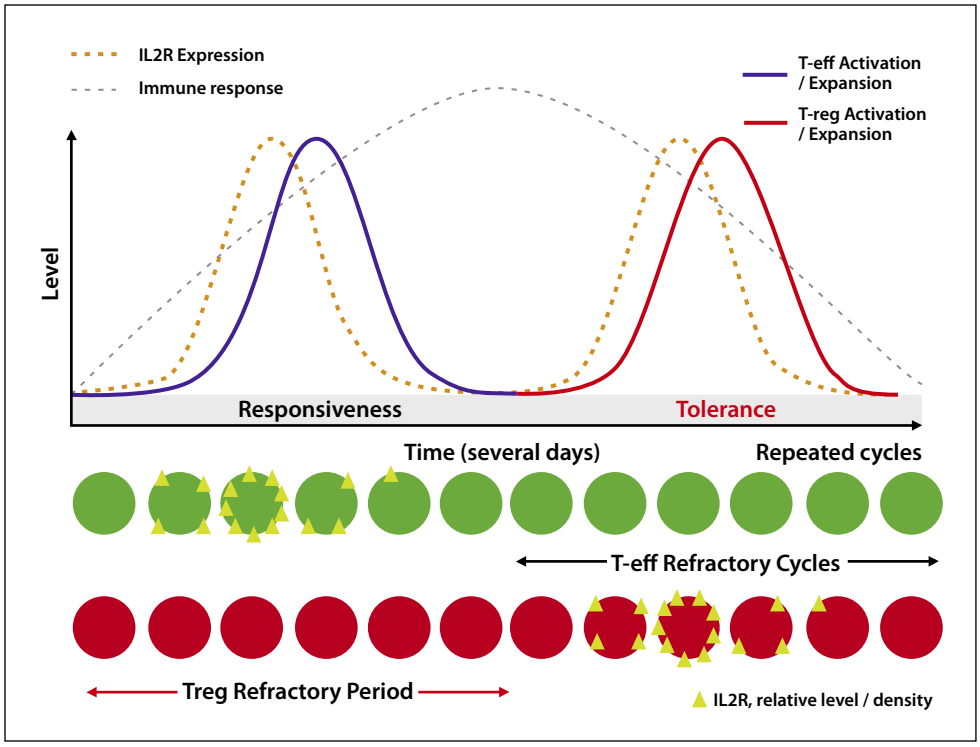

Figure 1. Graph suggests how timing of IL-2 dose may influence T cell effector cells and then regulatory T cells. The sequential rise and fall of receptor density and expansion of alternating opposing T cell populations creates the homeostatic feedback loop of initiation then termination of the immune response. (From Coventry, Ashdown. *Cancer Management and Research*. 2012;4:215-221).

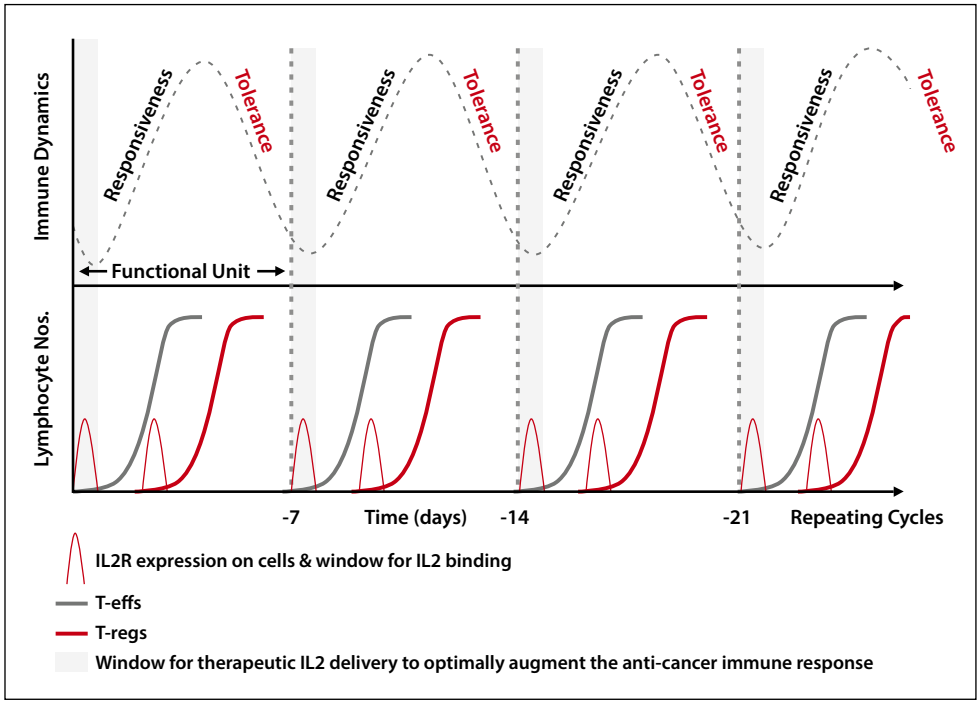

Figure 2. In this graph, the immune response is mapped and consists of different cycles after IL-2 is administered. The graph depicts responsiveness, then tolerance, to antigen stimulation. Chronic antigen persistence and stimulation produces the alternating inflammatory/immune oscillation or cycle (upper portion). The repeating cycle is hypothesized to create recurring narrow therapeutic windows (of approximately 12 hours wide) during which the immune response can be driven in the direction of responsiveness or tolerance. The curves show the predicted positions of maximal susceptibility for therapeutic intervention using agents such as IL-2 (lower portion). (From Coventry, Ashdown. *Cancer Management and Research*. 2012;4:215-221)

observed in patients with kidney cancer (n=20; 3 complete and 2 partial responses) and melanoma (n=16; 1 partial response). Adverse events appeared comparable with those typically associated with high-dose IL-2, with a lesser requirement for vasopressor support. Again, this is a pilot study, with small numbers of patients, but with results consistent with prior literature. Further prospective evaluation based on tolerability and efficacy noted is warranted.

In addition, based on biological evaluations, the authors introduce the hypothesis-generating observation that patients who had more favorable outcomes had high pretreatment DC-to-myeloid-derived suppressor cell (MDSC) ratios, similar to the ratio observed in healthy individuals. However, even in patients with the most favorable outcome, after treatment there were IL-2-induced changes in the DC-to-MDSC ratio, specifically increases in MDSCs. This modified IL-2 schedule is a feasible option, with a more uniform dose delivery over the treatment cycle, a similar toxicity profile, and observed complete, durable response in patients with renal cancer. Pretreatment assessment of DC phenotypic or maturational status may point to predicting response to high-dose IL-2 cytokine immunotherapy in patients with melanoma and kidney cancer.

The applicability of these findings is still controversial at this point, but they raise some tantalizing implications for the selection of patients who may benefit from high-dose IL-2. The plasticity of the DC-to-MDSC ratio is key, according to the authors. Although their data set was small—one of the caveats to interpreting this study—the ratio is consistent with the view that the host immune system features, independent of and perhaps in addition to "tumor features" or clinical features" can be used to define the capacity for clinically useful anticancer responses to therapy.[6] Thus, we need prospective information on the extent to which patients could be selected for immunotherapy based on pretreatment assessment of immune competence. It raises the question of whether treatment with IL-2 could be enhanced if the immune system could be modified or reconstituted. Finkelstein et al propose that the DC-to-MDSC ratio could set the stage for the pursuit of two directions: a) selection of patients with immunological credentials that suggest a higher chance of response to IL-2 therapy, and b) utilize these assays as intermediate laboratory surrogate markers of the effectiveness of pharmacological maneuvers directed at the immune context.

Additionally, Coventry and Ashdown propose that a schedule such as described above could be utilized to capitalize on the bimodal T cell activation noted in the immune response to IL-2.[5]

A New Vision to "Synchronize" the Administration of IL-2

Since its approval as an immune stimulating agent some 20 years ago, the complete response rate in RCC and metastatic melanoma has remained remarkably constant at about 7%, despite improvement in overall response rate and documentation of durable disease stabilization following IL2 treatment. Nevertheless, it is primarily the complete responders and surgical complete responders who are the decades-long survivors after IL2 treatment. The conventional wisdom over the years is that IL-2 is thought to stimulate or initiate the immune response via its stimulation of T effector cells, often being called the "master cytokine." But within the last few years, as the immune system's complexity continues to be delineated, additional information with regard to the mechanisms of IL-2 has surfaced. Although premature to extrapolate to clinical decision making, the new calculus is winning adherents in the oncologic community.

The impetus behind the new thinking is the view that IL-2 may be more than just an immune stimulator, ie the bimodal effect described earlier.[5] Recently IL-2 has been advanced as a potential immune modulator able to "tweak" the immune response selectively to aid transplant tolerance, while others reported this in graft vs host disease and chronic hepatitis C infection.[23-25] Despite the prevailing view in numerous reports that IL-2 activates or augments immune response, the expanded hypothesis suggests an apparent paradoxical role for IL-2 both as a cytokine to drive the immune response in an activated and an inhibitory direction.[5] Coventry and Ashdown refer to the "bimodality" of IL-2 that has created a paradox for understanding its activity.

Seeking to resolve the paradox, Coventry and Ashdown suggest how the immune response needs to be revisited as a "dynamic" entity as opposed to a static process.[5] The response, once triggered, is known to be a sequential, time-dependent, homeostatic, physiological process. This process, note the authors, requires the coordinated and timely interaction of cytokines, their receptors, and the responding cell populations. The half-lives of these interactions are minutes to hours. The coordinated cellular expansions can take several days to rise and fall, a process during which the immune response rises and ends. Both T effector cells and T regulatory cells transiently express the IL-2 receptor for only about 8 to 12 hours, and both require IL-2 for their activation/expansion and maintenance.[5]

A related study (**Figure 3**) by McNally et al described an IL-2 "feedback loop" between T effector and T regulatory cells: the loop apparently can promote or limit the intensity of the immune response.[26] Both of these opposing arms of the immune response are exquisitely sensitive to IL-2 therapy. The intriguing aspect of recent reports, including the review by Coventry and Ashdown, is that investigators are beginning to monitor closely and sequentially map the immune response using serial daily measurements.

Unraveling more of the dynamics of the IL-2 process, it appears that when IL-2 is efficacious, it may be successfully manipulating a pre-existing or endogenous antitumor response in the patients who show durable responses. The key question is how can complete responses become a reality for most or all patients who are

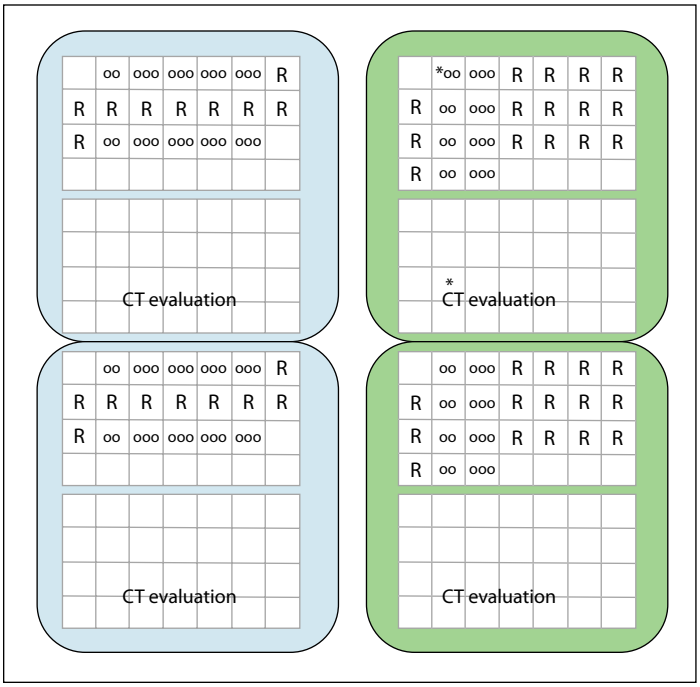

Figure 3. This schematic represents different schedules for administration of IL-2. A proposed new schedule is on the right and the standard schedule is on the left. 1 day=individual small box;1 week=1 row; o=1 dose IL-2. R=rest day within a course; and * represents blood test. Depending on the time of day of the hospital admission, some courses start with 1 dose only on the first day. (From Finkelstein SE, Carey T, Fricke I et al. *J Immunoth*. 2010;33:817-827.)

identified as potential responders. If IL-2 is capable of driving the immune system in either of two separate directions—either responsiveness/activation or tolerance/inhibition then one hypothesis proposes that the timing of IL-2 administration with respect to immune system dynamics when it is used will critically direct the immune response. Based on their literature review, Coventry and Ashdown suggest that serial measurements of the patient's underlying tumor immune response may be able to synchronize therapy with immune fluctuation.

The pattern of each patient's fluctuation in individual immune response can potentially be determined by measuring serum inflammatory markers (C-reactive protein daily or near daily over 2 to 3 weeks). The strategy might consist of the following as recommended by the preliminary studies[5,6]:

Determine fluctuations, then administer IL-2 therapy in a synchronized pulse, and at the predicted time when T effector cells are maximally expressing the IL-2 receptor and T regulatory cells are not.

This approach aims to avoid the T regulatory phase to engineer an extended, predominant T effector response to optimize clinical benefit.

The rationale is that this method counters the repetitive homeostatic attenuation of the immune response arising from chronic persistent antigen load and stimulation.

Conclusion

New concepts are emerging concerning the use of IL-2 therapy, based on observations that alternative dosing schedules appear to be less toxic and more manageable, while providing at least comparable and possibly enhanced tumor efficacy.[6,18]

A biological hypothesis suggests that schedule alterations may augment the cytotoxic component of the bimodal role of IL2 in the immune system, based on the intrinsic immune status of certain patients.

Although still in need of validation, the hypothesis has been advanced that synchronizing the administration of IL-2 to match fluctuations in a patient's immune response could enhance the ability of antitumor effector cells to produce a substantial increase in the complete response rate.

Prospective trials are needed to both investigate an alternative more tolerable schedule, for efficacy and clinical applicability, and to additionally explore the biological evaluation component to determine whether these initial observations of immune synchronization can translate into results with an impact on clinical practice.

References

1. Fisher RI, Coltman CA, Doroshow JH, et al: A phase II clinical trial of interleukin-2 and lymphokine activated killer cellsin metastatic renal cancer. *Ann Intern Med* 1988;108:418-523.
2. Abrams JS, Rayner AA, Wiernik PH, et al. High dose recombinant interleukin-2 alone: a regimen with limited activity in the treatment of advanced renal cell carcinoma. *J Natl Cancer Inst* 1990;82:1202-1206.
3. McDermott DF, Ghebremichael MS, Signoretti S, et al. The high dose aldesleukin (HD-IL-2) "SELECT" trial in patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2010;28:15s (suppl; abstr 4514).
4. Dandamudi UB, Ghebremichael MS, Sosman JA, et al. A phase II study of bevacizumab (B) and high dose aldesleukin (IL-2) in patients with metastatic renal cell carcinoma (mRCC): A Cytokine Working Group Study (CWGS). *J Clin Oncol* 2010;28:15s (suppl; abstr 4530).
5. Coventry BJ, Ashdown, L. The 20th anniversary of interleukin-2 therapy: bimodal role explaining longstanding random induction of complete clinical responses. *Can Man Res*. 2012;4:215-221.
6. Finkelstein SE, Carey T, Fricke I, et al. Changes in dendritic cell phenotype after a new high-dose weekly schedule of interleukin-2 therapy for kidney cancer and melanoma. *J Immunoth*. 2010;33:817-827.
7. Dutcher, JP, Logan T, Gordon M, et al. Phase II Trial of Interleukin 2, Interferon , and 5-Fluorouracil in Metastatic Renal Cell Cancer: A Cytokine Working Group Study. *Clin Cancer Res*. 2000;6:3442-3450.
8. Clark JI, Kuzel TM, Lestingi TM, et al. A multi-institutional phase III trial of a novel inpatient schedule of continuous interleukin-2 with interferon alpha-2b in advanced renal cell carcinoma: major durable responses in a less highly selected patient population. *Ann Oncol*. 2002;4:606-613.
9. McDermott DF, Atkins MB. Application of IL-2 and other cytokines in renal cancer. *Expert Opin Biol Ther*. 2004;4:455-468.
10. Atkins MB, Dutcher JP, Weiss G, et al. Kidney Cancer - The Cytokine Working Group Experience (1986-2001) Part I. IL2 Based Clinical Trials. *Medical Oncology* 2001; 18:189-196.
11. Dutcher JP, Atkins MB, Margolin K, et al. Kidney Cancer -The Cytokine Working Group Experience (1986-2001): Part II: Management of IL-2 Toxicity and Studies with Other Cytokines: *Medical Oncology* 2001; 18: 197-208.
12. Dutcher JP. High-Dose Interleukin-2 Therapy for Metastatic Renal Cell Carcinoma and Metastatic Melanoma: Still the Standard. *Cancernetwork*, April 22, 2011. Cancernetwork.com.
13. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol*. 2003;21:3127-3132.
14. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III

trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2005;23:133-141.
15. Kammula US, White DE, Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. *Cancer* 1998;83:797-805.
16. Patel J, Fishman MN, Goetz D, et al. High-dose bolus interleukin-2: correlating response rate with number of doses received. *J Clin Oncol.* 2013; (suppl 6;abstr 452).
17. Dutcher J. Current status of interleukin-2 therapy for metastatic renal cell carcinoma and metastatic melanoma. *Oncology* (Williston Park). 2002;16(suppl 13):4-10.
18. Acquavella N, Kluger H, Rhee J, et al. Toxicity and activity of a twice daily high-dose bolus interleukin 2 regimen in patients with metastatic melanoma and metastatic renal cell cancer. *J Immunother.* 2008; 31:569-576.
19. Romo de Vivar Chavez A, de Vera ME, Liang X, et al. The biology of interleukin-2 efficacy in the treatment of patients with renal cell carcinoma. *Med Oncol*. 2009;26: Suppl 1:3-12.
20. Smith KA. Rational interleukin-2 therapy. *Cancer J Sci Am*. 1997; 3(suppl 1)S137-S140.
21. van der Vliet HJ, Koon HB, Yue SC, et al. Effects of the administration of high-dose interleukin-2 on immunoregulatory cell subsets in patients with advanced melanoma and renal cell cancer. *Clin Cancer Res*.2007;13:2100-2108.
22. Mirza N, Fishman M, Fricke I, et al. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. *Cancer Res*. 2006;66:9299-9307.
23. Sabatino M, Kim-schulze S, Panelli MC, et al. Serum vascular endothelial growth factor and fibronectin predict clinical response to high-dose interleukin-2 therapy. *J Clin Oncol*. 2009;27:2645-2652.
24. Panelli MC, Nagorsen D, Wang E, et al. Mechanism of immune response during immunotherapy. *Yonsei Med J*. 2004;45:;suppl:15-17.
25. Rangel-Corona R, Corona-Ortega T, Soto-Cruz I, et al. Evidence that cervical cancer cells secrete IL-2, which becomes an autocrine growth factor. *Cytokine*. 2010;50:273-277.
26. McNally A, Hill GR, Sparwasser T, et al. CD4+ CD25+ regulatory T cells control CD8+ T-cell effector differentiation by modulating IL-2 homeostasis. *Proc Natl Acad Sci USA* Proc. 2011;108:7529-7534. **KCJ**

Leading New Cancer Cases and Deaths - 2013 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 238,590 (28%)	Breast 232,340 (29%)	Lung & bronchus 87,260 (28%)	Lung & bronchus 72,220 (26%)
Lung & bronchus 118,080 (14%)	Lung & bronchus 110,110 (14%)	Prostate 29,720 (10%)	Breast 39,620 (14%)
Colon & rectum 73,680 (9%)	Colon & rectu 69,140 (9%)	Colon & rectum 26,300 (9%)	Colon & rectum 24,530 (9%)
Urinary bladder 54,610 (6%)	Uterine corpus 49,560 (6%)	Pancreas 19,480 (6%)	Pancreas 18,980 (7%)
Melanoma of the skin 45,060 (5%)	Thyroid 45,310 (6%)	Liver & intrahepatic bile duct 14,890 (5%)	Ovary 14,030 (5%)
Kidney & renal pelvis 40,430 (5%)	Non-Hodgkin lymphoma 32,140 (4%)	Leukemia 13,660 (4%)	Leukemia 10,060 (4%)
Non-Hodgkin lymphoma 37,600 (4%)	Melanoma of the skin 31,630 (4%)	Esophagus 12,220 (4%)	Non-Hodgkin lymphoma 8,430 (3%)
Oral cavity & pharynx 29,620 (3%)	Kidney & renal pelvis 24,720 (3%)	Urinary bladder 10,820 (4%)	Uterine corpus 8,190 (3%)
Leukemia 27,880 (3%)	Pancreas 22,480 (3%)	Non-Hodgkin lymphoma 10,590 (3%)	Liver & intrahepatic bile duct 6,780 (2%)
Pancreas 22,740 (3%)	Ovary 22,240 (3%)	Kidney & renal pelvis 8,780 (3%)	Brain & other nervous system 6,150 (2%)
All sites 854,790 (100%)	All sites 805,500 (100%)	All sites 306,920 (100%)	All sites 273,430 (100%)

*Excludes basal and squamous cell skin and in situ carcinoma except urinary bladder.

New data from the American Cancer Society show estimated new cases and estimated deaths from kidney cancer in comparison with other cancers.

MEDICAL INTELLIGENCE *(continued from page 9)*

The ACS also estimates 13,680 deaths from kidney cancer are expected to occur in 2013. Death rates for kidney cancer decreased by 0.5% per year from 2005 to 2009.

Durability of vaccine's immune response validated; markers for overall survival confirmed

DURHAM, NC—Argos Therapeutics Inc. has announced it has validated the durability of the immune response for metastatic renal cell carcinoma (mRCC) patients treated with AGS-003. Additionally, the company confirmed the correlation between specific immune markers and overall survival in these patients is statistically significant. The data from these studies were presented during two poster sessions at Keystone Symposia´s Understanding Dendritic Cell Biology to Advanced Diseases Therapies Conference in Keystone, Colorado.

Argos is 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. Charles Nicolette, PhD, Chief Scientific Officer and Vice President of Research and Development of Argos, stated, "The validated durability of the immune response to AGS-003, and the established correlation between certain immune markers and overall patient survival, helps to characterize with further specificity the updated overall survival data from our Phase 2 trial, which we presented at this year´s Genitourinary Cancers Symposium. The data we presented at the Keystone Symposia confirms the accuracy of the Phase 2 results and the importance of the ADAPT Phase 3 clinical trial."

The two posters were entitled, "Autologus Dendritic Cell Therapy AGS-003, Induces Strong Durable Immune Responses in Patients with Advanced Renal Cell Carcinoma" and "Multi-Functional Cytotoxic T-Cell Subsets as Immune Correlates with Clinical Outcomes in a Phase II Study of AGS-003, an Autologous Dendritic Cell-Based Therapy Administered To Newly Diagnosed, Metastatic RCC Patients." The latter demonstrated that a specific tumor-reactive cytotoxic T-cell (CTL) subset (CD28+/CCR7+/CD45RA-) displaying a broad Markers of Immune Function (MIFs) profile correlates with long-term overall survival in patients treated with AGS-003. The former outlines that one patient treated long-term with AGS-003, with greater than 30 months overall survival, maintained the presence of CD28+/CCR7+/CD45RA- CTLs outwards to 3 years post initial treatment.

To further evaluate and validate the potential clinical and immunologic effects of AGS-003, Argos Therapeutics is currently enrolling patients in the ADAPT Phase 3 clinical study for AGS-003. The ADAPT study is a randomized, multicenter, open-label clinical trial expected to enroll 450 patients in

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approximately 120 global sites, mostly in North America, under an approved Special Protocol Assessment by the Food and Drug Administration. The study is designed to examine the potential for AGS-003 plus standard targeted drug therapy to extend overall survival versus standard therapy alone in newly diagnosed patients with unfavorable risk mRCC.

Long-term success rate high with renal cryoablation

NEW ORLEANS—Percutaneous renal cryoablation may serve as an effective, minimally-invasive treatment for small renal masses, according to findings presented at the Society of Interventional Radiology's 38th Annual Scientific Meeting.

The study included 33 men and 17 women with small renal tumors. The patients had a mean tumor diameter of 2.7 cm (range 1.1-4.9 cm). Among these tumors, 28 masses (54%) were exophytic, 21 (40%) were mixed, and three (6%) were central. Clinical success was defined as the absence of previously identified contrast enhancement , according to Thomas Jefferson University researchers. Under computed tomography guidance, 52 masses were treated using 2-5 cryoprobes. The median follow-up was 36 months (range 12-57 months). Clinical success was achieved in 51 cases (98%). One patient experienced local recurrence after 13 months and underwent salvage cryoablation. This same patient developed a distant metastasis after an additional 34 months. KCJ

JOURNAL CLUB *(continued from page 10)*

Furthermore, combinatorial application of A939572 with temsirolimus synergistically inhibited tumor growth in vitro and in vivo.
Conclusion: Increased SCD1 expression supports ccRCC viability and therefore the authors propose it as a novel molecular target for therapy either independently or in combination with an mTOR inhibitor for patients whose disease cannot be remedied with surgical intervention, such as in cases of advanced or metastatic disease.

Role of mutated genes delineated in clear cell RCC

Adverse Outcomes in Clear Cell Renal Cell Carcinoma with Mutations of 3p21 Epigenetic Regulators BAP1 and SETD2: a Report by MSKCC and the KIRC TCGA Research Network. Hakimi AA, Ostrovnaya I, Reva BA, et al. *Clin Cancer Res*. 2013;[Epub ahead of print]
Summary: The purpose was to investigate the impact of newly identified chromosome 3p21 epigenetic tumor suppressors PBRM1, SETD2, and BAP1 on cancer specific survival (CSS) of 609 clear cell renal cell carcinoma (ccRCC) patients from two distinct cohorts. Select sequencing on 3p tumor suppressors of 188 patients who underwent resection of primary ccRCC at the Memorial Sloan-Kettering Cancer Center (MSKCC) was performed to interrogate the genotype-phenotype associations. These findings were compared to analyses of the genomic and clinical dataset from our non-overlapping The Cancer Genome Atlas (TCGA) cohort of 421 primary ccRCC patients. 3p21 tumor suppressors are frequently mutated in both the MSKCC (PBRM1, 30.3%; SETD2, 7.4%; BAP1, 6.4%) and the TCGA (PBRM1, 33.5%; SETD2, 11.6%; BAP1, 9.7%) cohorts. BAP1 mutations are associated with worse CSS in both cohorts (MSKCC, p=0.002, HR 7.71 (2.08-28.6); TCGA, p=0.002, HR 2.21 (1.35-3.63)). SETD2 are associated with worse CSS in the TCGA cohort (p=0.036, HR 1.68 (1.04-2.73)). On the contrary, PBRM1 mutations, the second most common gene mutations of ccRCC, have no impact on CSS.
Conclusion: The chromosome 3p21 locus harbors three frequently mutated ccRCC tumor suppressor genes. BAP1 and SETD2 mutations (6-12%) are associated with worse CSS, suggesting their roles in disease progression. PBRM1 mutations (30-34%) do not impact CSS, implicating its principal role in the tumor initiation. Future efforts should focus on therapeutic interventions and further clinical, pathologic and molecular interrogation of this novel class of tumor suppressors.

Axitinib validated as second-line therapy

Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomized phase 3 trial. Motzer RJ, Escudier B, Tomczak P, et al. *Lancet Oncol*. 2013;14:552-562.
Summary: Eligible patients had clear cell metastatic renal cell carcinoma, progressive disease after one approved systemic treatment, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1; 723 patients were stratified by ECOG PS and previous treatment and randomly allocated (1:1) to receive axitinib (5 mg twice daily; n=361) or sorafenib (400 mg twice daily; n=362). The primary endpoint was PFS assessed by a masked, independent radiology review committee. The study assessed patient-reported outcomes using validated questionnaires. Baseline characteristics and development of hypertension on treatment were studied as prognostic factors. Efficacy was assessed in the intention-to-treat population, and safety was assessed in patients who received at least one dose of the study drug. Median overall survival was 20.1 months with axitinib and 19.2 months with sorafenib. Median investigator-assessed PFS was 8.3 months with axitinib and 5.7 months with sorafenib (P<0·0001). Patient-reported outcomes scores were similar in the treatment groups at baseline, were maintained during treatment, but decreased at end-of-treatment. Common grade 3 or higher treatment-related adverse events were hypertension (60 [17%]), diarrhea (40 [11%]), and fatigue (37 [10%]) in 359 axitinib-treated patients and hand-foot syndrome (61 [17%]), hypertension (43 [12%]), and diarrhea (27 [8%]) in 355 sorafenib-treated patients. In a post-hoc 12-week landmark analysis, median overall survival was longer in patients with a diastolic blood pressure of 90 mm Hg or greater than in those with a diastolic blood pressure of less than 90 mm Hg: 20.7 months vs 12.9 months (10·1-20·4) in the axitinib group (p=0·0116), and 20.2 months (17.1-32.0) vs 14.8 months (12.0-17.7) in the sorafenib group (one-sided P=0·0020).
Conclusion: Although overall survival, a secondary endpoint for the study, did not differ between the two groups, investigator-assessed PFS remained longer in the axitinib group compared with the sorafenib group. These results establish axitinib as a second-line treatment option for patients with metastatic renal cell carcinoma. KCJ

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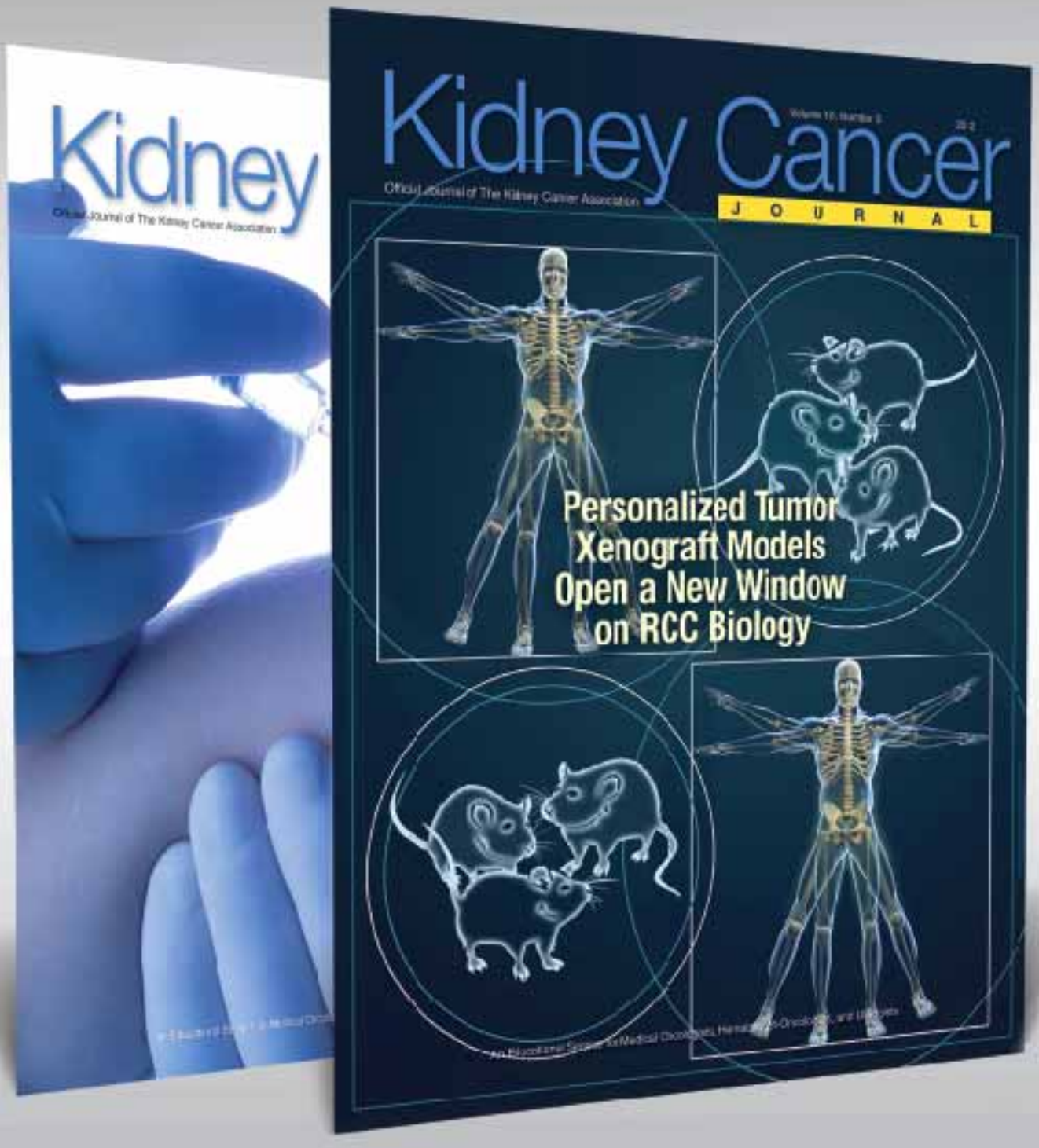

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