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ASCO Strategic Plan Calls on Physicians to Promote Patient Participation in Clinical Trials

EXPERT EDITORIAL

Richard L. Schilsky, MD

Numerous studies over the past several years have demonstrated that the most important factor influencing the likelihood of a patient enrolling in a clinical trial is whether the patient's physician introduces the concept of clinical trials and identifies specific opportunities for patients to participate. A 1999 survey of ASCO members revealed that the majority of oncologists view clinical trials as integral to the practice of oncology, but a much smaller proportion of physicians actively enroll patients in trials. This is a challenge not only to developing new cancer treatments but also to the clinical-trials enterprise itself. Preserving and enhancing the clinical trials system, as well as assisting ASCO members to participate in clinical trials are areas of increased focus for the Society. The Board of Directors has identified desired outcomes and an initial list of action items to guide ASCO's work, but feedback from the membership is critical as we seek to expand the Society's focus in this area.

With an array of challenges and changes facing the clinical-trials enterprise, particularly the National Cancer Institute (NCI)-funded Cooperative Groups, the ASCO Board believes that it is critical to give high priority to activities and programs aimed at supporting

Richard L. Schilsky, MD

the engagement of oncologists in clinical trials. The Board initiated a discussion at its March 2010 strategic planning retreat and approved a final strategic plan regarding clinical trials at its September 2010 meeting. The plan focuses on defining ASCO's role and desired outcomes for cancer clinical trials and determining action steps needed to achieve those outcomes.

The strategic issue statement that guided the Board's discussion was "Clinical trials are the key to building a high-value cancer care system, yet clinical trials remain unavailable to most patients [with cancer]."

The Board was deliberate about focusing the issue statement on clinical trials and not the broader arena of clinical research. Well-designed, prospective clinical trials are necessary to produce definitive data that lead to practice-changing treatments for patients with cancer. The Board recognized that there are many factors that make clinical trials unavailable to patients. In particular, the lack of engagement of oncologists in clinical trials is one of the most significant. This lack of engagement results from the need to meet complex regulatory requirements to conduct clinical trials, the additional time required to talk with patients about trial participation, inadequate reimbursement to support research and regulatory staff, and strict eligibility criteria that eliminate many patients from consideration. ASCO's advocacy efforts and collaborations focus on addressing many of these challenges, but more work remains to be done. The Board also agreed that it is critical for ASCO to focus its communication strategy on the effect of clinical trials on patient outcomes and the resulting improvements in quality and effectiveness of cancer care.

The Board's discussion was informed by the April 2010 Institute of Medicine's (IOM) analysis of the National Cancer Institute's Cooperative Group Program "A National Cancer Clinical Trials System for the 21st

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INSIDE THIS SECTION

Immunotherapy for Melanoma: Sparks Excitement about Potential for Other Cancers, Possible Multipronged Approaches

Enhanced understanding of biology behind tumor resistance and immune system yields potential breakthroughs for metastatic disease

Clinicians treating metastatic melanoma, well known as being poorly responsive to chemotherapy and radiation, added a new treatment option with the approval of ipilimumab in March 2011, and may soon have more agents available with other immunotherapies in development. Researchers believe that advances in the treatment of melanoma can translate into new agents and techniques to treat other forms of cancer as well. Updates on the current state of immunotherapy research, the next challenges to be addressed, and how ipilimumab's approval will affect future treatment options will be discussed in today's Education Session, "Immunotherapy for Advanced and High-risk Melanoma: Lessons Learned and Future Directions," to be held 9:45 AM – 11:00 AM, Room E354a, East Building.

"There is great enthusiasm in the field and huge promise for immunotherapy — first in melanoma, and on the basis of principles [learned there], in other solid tumors," said Session Chair John Kirkwood, MD, of the University of Pittsburgh Medical Center and the University of Pittsburgh Cancer Institute Melanoma Program.

New approaches

Unlike traditional chemotherapy, the goal behind immunotherapy is to reprogram the immune system to recognize and reject cancer cells. Melanoma is a highly immunogenic cancer, and there is some evidence of spontaneous regression and T-cell infiltration into tumors to suggest recognition of melanoma by the immune system at some level, but this response alone is inadequate, said Thomas Gajewski, MD, PhD, of The University of Chicago Medical Center.

What has been determined in the past decade is that melanoma and other cancers can evade immune recognition through a variety of immunosuppressive pathways, and the host becomes tolerant of the cancer, said Suzanne L. Topalian, MD, of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University Medical Center. Immunotherapy is directed at "breaking tolerance" by reactivating the immune system to overcome these resistance mechanisms.

When successful, immunotherapy can lead to complete regression of even advanced disease. Some patients with stage IV metastatic disease for whom other available therapies had failed were treated in trials with interleukin-2 in the 1980s and are still in complete remission more than 20 years later, Dr. Topalian told *ASCO Daily News*.

> **"There is great enthusiasm in the field and huge promise for immunotherapy — first in melanoma, and on the basis of principles [learned there], in other solid tumors."**
>
> — John Kirkwood, MD

"When you consider that these patients were signing on to experimental drug trials because [their disease] had failed all standard therapies and [they] had widely metastatic

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Distinguished Achievement Award Bestowed to Dr. David Khayat for Transforming Cancer Care in France

At a closed reception on Friday, ASCO honored a leader in oncology who has changed the way cancer is fought in France while raising awareness and mentoring others in the future of oncology care. David Khayat, MD, PhD, of Pitié-Salpêtrière Hospital, Paris, received the 2011 Distinguished Achievement Award in recognition of his clinical and research work and his role in promoting oncology care in his home country.

The award salutes an individual who has proven to be as an outstanding leader and mentor in science, practice, or research in any subspecialty of oncology, and whose efforts have benefited ASCO members or their patients. Created in 2009, this award honors individuals who strive to not only treat patients with cancer but also to train and mentor the next generation of oncologists.

Dr. Khayat was honored to receive this award and recognition from ASCO in a closed ceremony Friday night. "I am proud of this award; it means recognition by the international community and people I respect who have contributed so much to the processes we are using today when we treat our patients," he told *ASCO Daily News*. "We are working hard to make France a leading country in the fight against cancer."

An International Leader in the Fight Against Cancer

Dr. Khayat has been instrumental in transforming cancer care in France and advising other nations seeking to improve the care of patients with cancer. He was a Co-Founder of the World Summit Against Cancer in 2000, an event at which more than 100 international political, corporate, and nonprofit organization leaders reaffirmed their commitment to the global eradication of cancer by signing the Charter of Paris Against Cancer. Numerous signing countries went on to develop their own national cancer plans, for which many sought out Dr. Khayat as an advisor.

"The Charter is something I am extremely proud of in my career. Through the Charter, I learned how to set up national cancer plans and integrate measures dealing with screening and organization of care," he said.

In addition to advising countries such as Tunisia, Morocco, and Uzbekistan, Dr. Khayat was appointed by former President Jacques Chirac to lead the development of the French National Cancer Control Plan in 2003. The plan includes 70 resolutions that address prevention, screening, organization of care, research, training, and support. One measure involved establishment of a national cancer institute, for which Dr. Khayat served as president.

The plan has led to amazing progress in cancer care throughout the country. One notable accomplishment, Dr. Khayat said, is the development of a national screening program for breast and colorectal cancer. Screenings are paid for by the government, and results are evaluated and published every year.

David Khayat, MD, PhD

"France is the only country in the world where you have an ongoing screening program for both cancers," he said.

Keeping Patient Rights at the Heart of His Work

Although his national responsibilities required time away from the bedside, Dr. Khayat is a staunch defender of the rights of patients and has made patient-centered care a focus of his work. He is Head of the Department of Medical Oncology at Pitié-Salpêtrière Hospital, where he focuses on developing new agents for breast cancer, colorectal cancer, lung cancer, and melanoma. His laboratory is one of few centers in France fully equipped and heavily involved in the evaluation of new drugs and targeted therapies. The hospital's cancer center is one of the largest in France and treats thousands of patients, offering them access to new therapies through clinical research.

Through his experience caring for patients, Dr. Khayat has spent another part of his career speaking directly to patients, not as a doctor but as an author. He has published novels, a play, and screenplays dealing with cancer care. "All of my literature is focused on trying to explain the issues of cancer care and the right for patients to participate in care and decide their course of treatment," he said. "The way we fight cancer in our country has changed over the past 15 to 20 years, and I use everyday language and stories to help explain this to the public."

Supporting the Next Generation

Early in his career at Pitié-Salpêtrière, Dr. Khayat had the opportunity to work under some of the leading oncologists of the time, including Claude Jacquillat, MD. In turn, Dr. Khayat has been involved in many efforts to develop the next generation of oncologists and share advancements in oncology around the world.

He established the Master of Excellence in Medicine in Oncology, a teaching program to increase the skills and knowledge of young oncologists in France and foster the future opinion leaders that will move French oncology into the future. In addition, he formed the French Federation of Medical Oncologists, a sister organization of ASCO, to bring together professionals throughout the country.

Within ASCO, Dr. Khayat serves as Deputy Editor of International Editions for the *Journal of Clinical Oncology (JCO)*. He has been a driving force in spreading the cutting-edge science published in *JCO* around the world. "I am in charge of the international editions of *JCO*," he said. "We started with only the Spanish edition and now have 17 editions published regularly."

ASCO has meant a great deal to him throughout his career, Dr. Khayat noted, serving to develop his skills and a vast network of colleagues. ●

The Cost of Cancer Care: How Patients Are Coping and How We Can Help

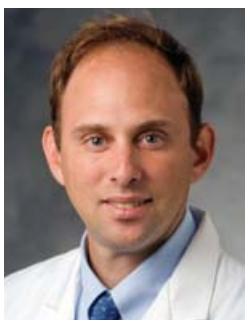
EXPERT EDITORIAL

Jeffrey M. Peppercorn, MD, MPH

Cancer is frequently a devastating diagnosis for patients and their families because of its implications for morbidity and mortality. In the U.S. health care system, the challenge of coping with cancer, and the effect of both disease and treatment, can be compounded by the uncertainty of whether patients will have access to appropriate care and who will pay for it. It is clear that the costs of cancer care are going up, driven in large part by innovation and by our ability to do more for patients. In many settings these costs are being shifted to our patients, with a poorly understood effect on access to care and treatment decisions. There is a clear need to better understand the financial effect of cancer care on our patients and how we as oncologists can best promote informed decision making and access to appropriate care.

What Does Cancer Cost?

The cost of cancer care can be considered in terms of either total spending or the cost of care for an individual patient. On the national level, it is estimated that in 2010, $124 billion was spent on cancer care in the United States. This represents a more than 400% increase



Jeffrey M. Peppercorn, MD, MPH

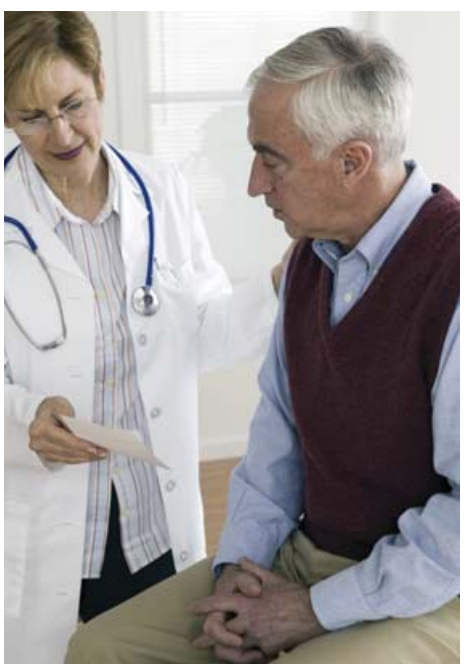
in spending since earlier estimates of $27 billion in 1990.[1] Total spending figures do not directly affect individual patients, but they have focused attention on the need to "bend the curve" of projected growth in health care spending over time.

Increasingly, a favored method to "bend the curve" among insurance providers is to shift more of the costs of care to patients in the form of higher premiums, co-pays, and deductibles. Although the immediate effect of such policies is to shift costs to patients, one of the goals is to make the patient, or "consumer," more sensitive to the cost of care so that he or she has a greater stake in use of the health care system. Out-of-pocket expenses for patients with cancer are increasing faster than overall costs of cancer care.[2] Although increasing patients' exposure to the costs of care can undoubtedly affect health care decisions, whether it leads to higher-quality decisions without adversely affecting outcomes is unclear. As this trend continues, research into the nature and effect of these policies is needed.

How Does Cost Affect Care?

For decades, it has been clear that a lack of health insurance leads to patients with cancer presenting with more advanced stages of disease at the time of diagnosis and to worse outcomes.[3] The recent passage of the 2010 Patient Protection and Affordable Care Act promises to reduce the ranks of the uninsured, currently estimated at more than 50 million people. Given ongoing legal challenges and political controversy, whether the law will survive in its current form and what effect it ultimately will have on access to cancer care and cost remains uncertain. Limitations in access to appropriate cancer care are not restricted to those without health insurance. More than 25 million additional Americans may be considered "underinsured" based on inadequate coverage for medical expenses. Ideology aside, we likely can agree that all patients with cancer should have access to quality health care, and that guaranteed access to screening, timely diagnosis, treatment, and supportive care should be our priority for any emerging policy.

At this time, there is a patchwork of services and support that can provide financial assistance for patients with cancer. Many state, county, and local institutions, including hospitals and some practices, have patient-assistance programs for individuals meeting a threshold of financial need. In addition, pharmaceutical companies often provide assistance or free drugs for patients who are uninsured and who meet financial qualifications. For underinsured patients, there are a number of co-pay assistance foundations, such as the HealthWell Foundation and



Patient Access Network, which help provide access to high-cost medications. ASCO's patient-focused website, Cancer.Net, lists organizations that can provide assistance and information to help patients understand and cope with the costs of care.

Despite the availability of financial assistance programs, one-third of patients with cancer report trouble paying their bills and up to 25% report exhausting their savings.[4] These figures are perhaps not surprising in light of the costs of treatment, particularly

See Cost of Cancer Care, Page 11B

In Advanced Renal Cell Carcinoma...

Indication

VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Important Safety Information

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

Hepatic Effects: Patients with pre-existing hepatic impairment should use VOTRIENT with caution. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended**.

QT Prolongation and Torsades de Pointes: Prolonged QT intervals and arrhythmias, including torsades de pointes, have been observed with VOTRIENT. Use with caution in patients at higher risk of developing QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes within the normal range should be performed.

Hemorrhagic Events: Fatal hemorrhagic events have been reported (all grades [16%] and Grades 3 to 5 [2%]). VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.

Arterial Thrombotic Events: Arterial thrombotic events have been observed and can be fatal. In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack (all grades [3%] and Grades 3 to 5 [2%]) were observed. Use with caution in patients who are at increased risk for these events.

Gastrointestinal Perforation and Fistula: Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula.

Hypertension: Hypertension has been observed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (88% occurred in the first 18 weeks). Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. If hypertension persists despite antihypertensive therapy, the dose of VOTRIENT may be reduced or discontinued as appropriate.

Move Forward With VOTRIENT

In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC[1,2]

All patients
9.2 months
(95% CI, 7.4-12.9)
overall median PFS with VOTRIENT (n=290) vs **4.2 months** (95% CI, 2.8-4.2) with placebo (n=145) (*P*<0.001)[2,3]

Treatment-naïve patients
11.1 months
(95% CI, 7.4-14.8)
median PFS with VOTRIENT (n=155) vs **2.8 months** (95% CI, 1.9-5.6) with placebo (n=78) (*P*<0.001)[2,3]

Cytokine-pretreated patients
7.4 months
(95% CI, 5.6-12.9)
median PFS with VOTRIENT (n=135) vs **4.2 months** (95% CI, 2.8-5.6) with placebo (n=67) (*P*<0.001)[2,3]

NCCN Guidelines Category 1 recommendation[4]

- First-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology

Proven safety profile[1,2]

- Most common adverse events observed with VOTRIENT (>20%) were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  - — Grade 3/4 fatigue occurred in 2% of patients; all grades, 19%
  - — Grade 3/4 asthenia occurred in 3% of patients; all grades, 14%

Most common laboratory abnormalities were ALT and AST increases[1]

- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2%
- In clinical trials, 92.5% of all transaminase elevations of any grade occurred in the first 18 weeks of treatment with VOTRIENT
- Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period

Once-daily oral dosing[1]

- The recommended dosage of VOTRIENT is 800 mg once daily without food (at least 1 hour before or 2 hours after a meal)
- Dose modifications, interruptions, and discontinuations may be required in patients with hepatic impairment, drug interactions, and following adverse events
- Forty-two percent of patients on VOTRIENT required a dose interruption; 36% of patients on VOTRIENT were dose-reduced

VOTRIENT is a multitargeted tyrosine kinase inhibitor that is indicated for the treatment of patients with advanced RCC.

Votrient™
pazopanib tablets (200 mg)

Wound Healing: VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.

Hypothyroidism: Hypothyroidism was reported as an adverse reaction in 26/586 (4%). Monitoring of thyroid function tests is recommended.

Proteinuria: Monitor urine protein. Proteinuria was reported in 44/586 (8%) (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for Grade 4 proteinuria.

Pregnancy Category D: VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.

Drug Interactions: CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin): Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors.

CYP3A4 Inducers (such as rifampin): Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT.

CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

Adverse Reactions: The most common adverse reactions (>20%) for VOTRIENT versus placebo were diarrhea (52% vs. 9%), hypertension (40% vs. 10%), hair color changes (depigmentation) (38% vs. 3%), nausea (26% vs. 9%), anorexia (22% vs. 10%), and vomiting (21% vs. 8%).

Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in the VOTRIENT arm versus placebo included increases in ALT (53% vs. 22%), AST (53% vs. 19%), glucose (41% vs. 33%), and total bilirubin (36% vs. 10%); decreases in phosphorus (34% vs. 11%), sodium (31% vs. 24%), magnesium (26% vs. 14%), and glucose (17% vs. 3%); leukopenia (37% vs. 6%), neutropenia (34% vs. 6%), thrombocytopenia (32% vs. 5%), and lymphocytopenia (31% vs. 24%).

VOTRIENT has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients (<1%).

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. VOTRIENT Prescribing Information. Research Triangle Park, NC: GlaxoSmith-Kline; 2010. **2.** Sternberg CN, et al. *J Clin Oncol*. 2010;28(6):1061–1068. **3.** Data on file, GlaxoSmithKline. **4.** Referenced with permission from ©National Comprehensive Cancer Network, Inc 2010. All Rights Reserved. NCCN Guidelines™: Kidney Cancer, V.1.2011. NCCN.org Accessed January 12, 2011. NCCN® and NCCN GUIDELINES™ are trademarks owned by the National Comprehensive Cancer Network, Inc.

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Oncology

Clinical Trials

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Century: Reinvigorating the NCI Cooperative Group Program."[1] Board members reflected on the important contributions of federally funded clinical trials to developing standards of care and on the importance of maintaining a mechanism to conduct clinical trials in the community as well as in academic settings — all an important part of NCI's Cooperative Group Program. The Cooperative Group Program also provides important training and leadership opportunities for investigators and research staff to bolster their career development. Cooperative Group trials complement the drug discovery provided by industry-funded trials and deepen our understanding of how to use approved agents — in combination with one another and with other modalities— to treat cancer and other diseases.

In light of the IOM report, the Board developed tactics and identified desired outcomes in the strategic planning that relate specifically to federally funded clinical trials. ASCO has a unique role to play in championing the role of a publicly funded clinical trials infrastructure, supporting implementation of all of the IOM recommendations to improve the system, and advocating for increased funds to adequately support the cost of conducting clinical trials. In framing the outcomes, the Board focused on the key stakeholders that would have to be involved in order to address the strategic issue statement: oncologists, government agencies, policymakers (chiefly Members of Congress and the Administration), the general public, patients with cancer, and third-party payers or insurers.

The Board has identified several desired outcomes.

- Oncologists routinely discuss clinical trial participation with their patients as a metric of quality cancer care. Physicians view clinical trials participation as integral to quality cancer care and not as a "last resort" option.
- A coordinated, well-funded federal effort ensures that clinical trials are launched, enabled, supported, and completed as quickly as possible and with wide dissemination of results.
- The general public and policymakers view publicly supported clinical trials as essential to the prevention and cure of cancer.
- Patients view trials as a treatment option, seek oncologists offering trials, and actively inquire about clinical trials.
- Health payers encourage and support participation in cancer clinical trials.

These outcomes are listed in priority order, reflecting the groups that ASCO is in the greatest position to influence, as well as the important role that each of the stakeholders has in increasing participation in clinical trials.

ASCO in Action

To help achieve these outcomes, ASCO will conduct a series of initiatives to support

oncologists' engagement in clinical trials. These initiatives will include development of a forum for community-based investigators to network and develop tools and resources to help support effective research programs. ASCO also will develop a self-assessment mechanism to help oncology practices achieve ASCO's exemplary attributes of quality-research sites. ASCO also plans to enhance its educational offerings for investigators and research staff, both in the United States and other countries. Finally, ASCO will examine whether the Society can provide direct assistance to sites that engage in clinical research, particularly through mentorship from experienced research sites.

ASCO is partnering with the IOM to hold two workshops to help promote implementation of the IOM report recommendations among all stakeholders. The first workshop was held in March 2011, and a second workshop is planned for 2012. ASCO is engaging in a communications campaign to shape public opinion and raise awareness among policymakers and the media of the progress made in clinical cancer research, including the launch of a new website, CancerProgress.net. ASCO is also conducting an assessment of the clinical-investigator workforce to develop recommendations for ways to increase support of clinical investigators and enhance the career pipeline. Finally, ASCO plans to engage with the payer community to ensure smooth implementation of the clinical trials coverage requirement that was included in the health care reform law and goes into effect in 2014.

The Board's work was informed by collaboration with ASCO's Cancer Research Committee (CRC). During this period, the CRC was chaired by Theodore S. Lawrence, MD, PhD, of the University of Michigan, Carolyn D. Runowicz, MD, of the Herbert Wertheim College of Medicine at Florida International University, and Neal J. Meropol, MD, of Case Western Reserve University School of Medicine. The CRC prepared background materials and helped prioritized the outcomes and action items.

This strategic plan lays an important foundation for the work of the Society over the next several years. The CRC is partnering with other ASCO committees and advisory groups to implement initiatives that are aimed at achieving the desired outcomes as laid out in ASCO's current strategic plan. ●

About the Author: *Dr. Schilsky is an ASCO Past President. Since 1995, he has served as chairman of the Cancer and Leukemia Group B (CALGB), the largest and oldest cancer clinical trials group in the United States.*

Reference

1. Institute of Medicine. A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. http://www.iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx. Accessed March 17, 2011.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
Adverse Reactions	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[a] %	Grade 3 %	Grade 4 %
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%).

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N = 290)			Placebo (N = 145)		
Parameters	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[a] %	Grade 3 %	Grade 4 %
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Hepatic Toxicity: In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. *[See Dosage and Administration (2.2) and Warnings and Precautions (5.1).]* Hypertension: In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. [*See Warnings and Precautions (5.2).*] QT Prolongation and Torsades de Pointes: In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.3).]* Arterial Thrombotic Events: In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). *[See Warnings and Precautions (5.4).]* Hemorrhagic Events: In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.5).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. Hypothyroidism: In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.7).]* Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. Proteinuria: In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. Lipase Elevations: In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). Cardiac Dysfunction: Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes: In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. CYP3A4 Inhibitors: Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. CYP3A4 Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided *[see Dosage and Administration (2.2)]*. **7.2 Effects of Pazopanib on CYP Substrates:** Results from drug-drug interaction studies conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19 *[see Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events. *[See Clinical Pharmacology (12.3) of full prescribing information.]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category D *[see Warnings and Precautions (5.10)]*. VOTRIENT can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was

Immunotherapy

Continued from Page 1B

disease, that is a significant advance forward," she said.

The limitation of immunotherapy has been the relatively small number of patients who achieve clinical benefit from treatment, as the response rate for interleukin-2, for example, is approximately 16%, with 6% of patients having a complete and durable response. Ipilimumab (anti-CTLA-4), developed by Bristol-Myers Squibb, has a low response rate as monotherapy of approximately 10% to 12%. Laboratory work suggests a much greater effect for other immunotherapy agents such as anti-PD-1 (MDX-1106, also from Bristol-Myers Squibb), and molecularly targeted agents in development, such as PLX4032/RG7204, from Plexxicon/Roche-Genentech, and GSK 2118436 from GlaxoSmithKline, as part of a combinatorial approach either with other immune therapies or with traditional chemotherapy or radiation, Dr. Topalian said.

"Everything that we know from laboratory studies shows that combining some of these drugs will have a synergistic effect and, therefore, will have a much more potent effect on cancer," Dr. Topalian noted.

Ultimately, as more is understood about immunotherapy and how it complements other forms of treatment, there will likely be a multipronged therapeutic approach.

"There are clearly gaps in what we have from chemotherapy and the targeted therapy that has emerged in the past year or two," Dr. Kirkwood said in an interview with *ASCO Daily News*. "My own sense is that the ultimate therapy that we will evolve will be combined-modality therapy."

Clinical Challenges

Pharmacogenetics is already being explored in oncology to determine how a patient's genetic make-up affects how drugs are metabolized and how that, in turn, affects safety and efficacy. Given the role genetics plays in a patient's immune system, this effect is likely to be even more pronounced in immune-modulating agents. Different agents in development have targeted different molecules, so techniques must be developed to determine if a patient is likely to respond to immunotherapy, and, if so, to which agent. In addition, biomarker development is an important aspect of immunotherapy optimization.

In addition, agents that modify a patient's immune system will have a different kind of safety profile. In chemotherapy, side effects only occur during treatment; immunotherapy agents result in more fundamental changes to the immune system. By removing some limits of the immune system and allowing the rejection of resistant tumors, unwanted immune responses could affect normal tissues. For example, in some patients ipilimumab causes colon inflammation and diarrhea, which can be severe enough to cause patients to terminate treatment.

"Ipilimumab is the first in class for these drugs, but there are now other antibodies in development that modulate immune responses that might not be as toxic and seem to have a higher rate of antitumor effects," Dr. Topalian said.

Despite these challenges, the recent advances in immunotherapy offer promise for improved outcomes for patients with advanced disease.

"I consider ipilimumab to be a breakthrough," Dr. Topalian said. "It is a completely different kind of drug than those we previously have used in the clinic. Experience with ipilimumab shows that you can reset the balance of the immune system, and by doing so you can cause rejection of established large disseminated tumors."

The FDA approval of ipilimumab could accelerate the growth of immunotherapy.

"The hope for ipilimumab approval is that it will be a proof of concept that will spark the field," Dr. Gajewski said. "There are many other immune regulatory molecules that can be targeted similarly, that could be even more effective."

Gene expression profiling of the tumor and the tumor microenvironment in patients with melanoma who responded to treatment has found increased T-cell response, suggesting greater immune activity, he said. A similar phenotype also has been identified in subsets of patients with colon cancer, non-small cell lung cancer, and ovarian cancer.

"Now that that commonality is recognized, there is a possibility that you will have that subset of patients in other cancer types that is hard wired to be receptive to immune intervention," Dr. Gajewski said.

Future Developments

Other immunotherapy approaches in development include several melanoma vaccines, including OncoVEX$^{GM\text{-}CSF}$ from Amgen and Allovectin7® from Vical, both in phase III trials. Previous vaccines have had very limited success as monotherapy to cause the regression of advanced metastatic disease, but these vaccines are now being tested in an adjuvant setting to limit the risk of recurrence after complete resection, Dr. Topalian said. Animal models have suggested these vaccines also may be useful to prime the immune system, resulting in a more robust response to immune-modulating antibodies.

Another technique being developed by Steven Rosenberg, MD, PhD, of the National Cancer Institute, is adoptive T-cell transfer, in which T cells are collected from a patient's tumor, reproduced and multiplied in a laboratory, then infused back into the patient. Used in combination with chemotherapy and radiation, this approach has yielded impressive results in some patients, but is a complex and expensive approach that at this time is difficult to reproduce on a large scale. Innovations with gene-modified lymphocyte infusions may provide a generic therapy that is more widely applicable. ●

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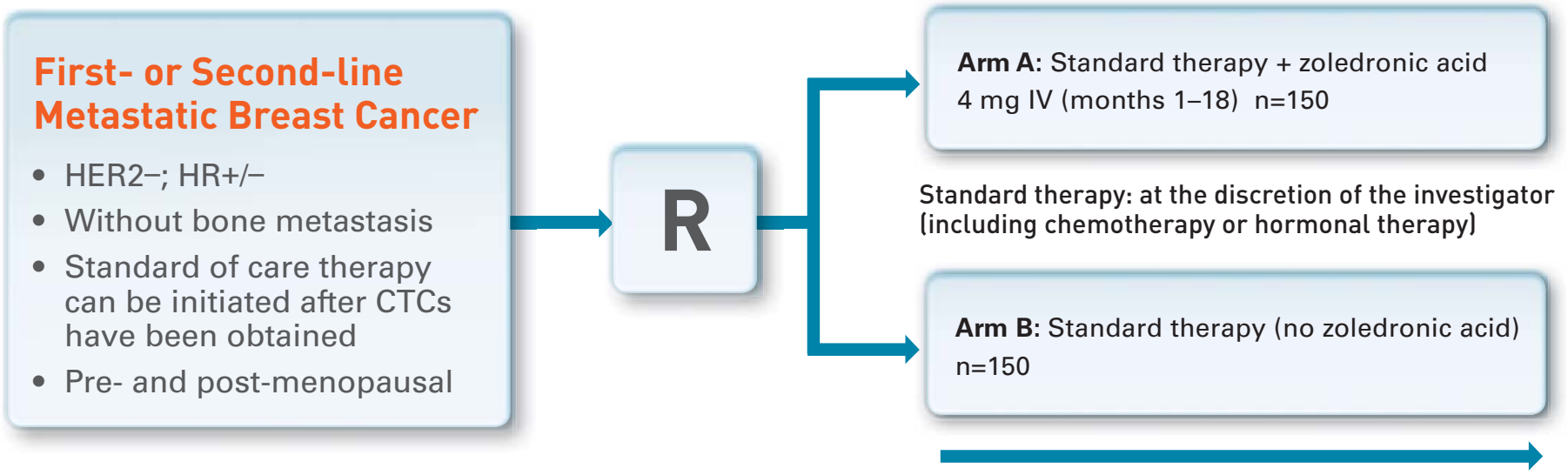

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Reducing Disparities in Cancer Outcomes: A Call to Action

EXPERT EDITORIAL

Blase N. Polite, MD, MPP

If you are poor or an underserved minority and you develop cancer, you are more likely to die from that cancer than if you are rich or white. This is a fact and the current reality of cancer care in the United States, as documented in thousands of peer-reviewed articles, including an Institute of Medicine report.[1] We try a pilot project here or limited public health intervention there, but our efforts thus far have been hopelessly insufficient in addressing the gravity of this situation. I do not deny that there are complexities and nuances to this situation, but if we have the will, there is a way.

It is easy to believe that cancer health disparities have always existed, but the facts dispel this belief. From 1975 to 1982, black males actually had a lower mortality rate for colon cancer than white males, but since that time the gap has widened considerably.[2,3] The same trend is seen in breast cancer. The widening mortality gap holds when you look within disease stage. In fact, worse outcomes are most pronounced for high-risk stages where multimodality therapy is recommended and of clear benefit (node-positive breast cancer is an example). This begs the question, were cancers biologically different in 1975 than they are in 2011? Probably not. In fact, when colon cancer is treated the same way in a cancer clinical trial or in an equal treatment system, disparate outcomes virtually disappear.[4,5] What has changed over time are the tools we have available to prevent, diagnose, and treat these cancers. Regardless of race or socioeconomic status, the tools are basically the same. What varies greatly is the rate and skill with which we apply these tools.

Blase N. Polite, MD, MPP

A common excuse for disparities in care is to blame the patients for not taking responsibility for their health care. The implication is that the system, although not perfect, is sufficient, and that, for whatever reason, individuals simply are not accessing health care resources. Although there may be evidence to support instances of this, I do not believe it is the main reason we have cancer health disparities in this country.

One way to test this theory is to examine regional variations in cancer outcomes. For example, in 2003, black women had a 68% higher breast cancer mortality than white women in the city of Chicago (which has risen to close to 120% in recent years) compared with a 14% difference in New York City.[6] Do black women in New York City develop an innately different form of breast cancer than black women in Chicago? Examine the resources and integration of the Cook County Health System versus those of the New York City Public Health System and you will likely find the real answer.

Solutions to Health Disparities

If we keep the following four principles in mind and target our efforts accordingly, cancer health care disparities can be eliminated: appropriately screen asymptomatic individuals; appropriately diagnose patients who have been screened; appropriately treat, in a timely fashion, patients who have been diagnosed; and appropriately follow and guide patients who have completed treatment. A common element to each of these principles is the term "appropriately" which, of course, is synonymous with "quality." Unfortunately, we know it is the poor and underserved minorities who receive a lack of quality health care.[7,8]

Screening. It is well understood that colon cancer screening saves lives and that colon cancer screening rates are suboptimal for the general population. However, if you lack insurance or, even worse, lack insurance and have no regular health care provider, the rates are abysmal. In the 2001 California Health Interviews Survey, the overall screening rate for colon cancer among individuals ages 50 to 64 was 48%; for uninsured patients it was 26% and for uninsured patients without an identified health care provider, the rate was a mere 8%.[9] Universal health care certainly could help improve cancer screening by providing payment for these procedures. However, the benefits of insurance will be limited without integration of patients into a health system where care can be provided seamlessly.

In 2003, New York City developed a focused campaign to screen more individuals for colon cancer by focusing on colonoscopy, improving tracking systems, and broadly employing patient navigators. As a result, the city's overall colon cancer screening rate went from 40% to 60% in 4 years,

See Reducing Disparities, Page 14B

Focus Under Forty™: ASCO Launches Free Online Education Program to Help Physicians Better Care for Patients Ages 15 to 39

Unlike the progress in cancer survival rates overall, the survival rates for patients ages 15 through 39 who have cancer have not improved in more than 30 years. A new ASCO University® program, Focus Under Forty™, addresses the challenges of treating adolescent and young adult (AYA) patients with cancer.

Acute lymphoblastic leukemia (ALL) is an example of a cancer with a survival rate for young adults that is nearly half that of that for patients younger than 15. "Data from Europe and the United States show that ALL in AYA patients is treated differently than ALL in adults," explained ASCO member Brandon Hayes-Lattin, MD, of the Oregon Health and Science University Knight Cancer Institute , and a member of the task force that planned the Focus Under Forty curriculum. He added, "Patients in the 'in-between' age group of 15 to 20 could be treated for ALL in either the pediatric or adult world, but studies show that patients who received adult treatment fared much worse."

Focus Under Forty addresses these disparities and others by concentrating on the specific challenges of diagnosing and treating AYA patients with cancer. ASCO and its philanthropic arm, the Conquer Cancer Foundation (formerly known as The ASCO Cancer Foundation®), teamed up with LIVE**STRONG**® to develop the program.

Why Do Survival Rates for This Age Group Lag Behind?

A number of interrelated factors have contributed to the lack of progress in cancer care in AYA populations. Delayed diagnosis, limitations in access to care, widely varying referral patterns, and inconsistency in treatment and follow-up care are perhaps the most notable. "These patients are getting lost," said Joyce Reinecke, JD, a cancer and fertility advisor to LIVE**STRONG** who also serves on the joint Focus Under Forty planning task force.

Delayed diagnosis is common because AYA patients typically see themselves as invulnerable, ignoring symptoms or delaying going to a doctor. In addition, providers can often miss a cancer diagnosis because cancer is often not initially suspected in this population. To address delays in diagnosis, Focus Under Forty has educational content designed specifically by and for primary care providers.

Lack of research also contributes to the challenges in treating this population. An exceedingly low rate of participation in clinical trials and the high mobility of this population have hampered research. "The basic biology of cancers in this group differs from that in older patients, and we have a poor understanding of what distinguishes cancers in this population," Dr. Hayes-Lattin noted.

Fertility Preservation

Ms. Reinecke was age 29 when she was diagnosed with leiomyosarcoma. "I wasn't told right after my diagnosis that my planned treatment could put me at risk for infertility. But when I met with several oncologists after surgery to talk about my future treatment, one of the oncology fellows brought this up." Ms. Reinecke and her husband then "scrambled to find an IVF facility" in order to create and then store embryos. They subsequently had twin daughters using a surrogate.

Ms. Reinecke said that breakdowns in communication about fertility preservation for women can often result in a loss of critical few weeks between diagnosis and implementation of chemotherapy or other treatments. "For example, the surgical oncologist might not include fertility preservation in patient discussions because it is not a direct risk of surgery," she pointed out. "However, by the time the patient gets to the medical oncologist, she probably won't have time to

See Focus Under Forty, Page 17B

Cost of Cancer Care

Continued from Page 3B

with novel molecularly targeted agents. Drugs that extend median survival by several months may be priced at as much as $100,000 per patient.[5] In the United States, unlike many countries, cost effectiveness is not considered in drug-approval decisions, and the challenge of assessing value often falls to physicians and patients.[6]

A recent survey of U.S. oncologists found that out-of-pocket costs to patients are considered but rarely discussed directly with patients. Less than half of oncologists responding to the survey reported comfort with making cost-effectiveness decisions.[7] Given the large variations in prescription drug coverage and co-payments, it may be particularly difficult for oncologists to advise their patients regarding the financial effect of oral therapy for cancer or symptom management. Inability to pay for prescription medications can be a barrier to adherence and must be assessed in clinic.

Costs, Compassion at the End of Life

In addition to the general challenge of dealing with costs of care throughout the course of illness, a substantial portion of total spending for cancer care occurs within the last weeks and months of life. What percentage of this care is appropriate and consistent with informed decisions on the part of patients and physicians is unclear, but several studies show that a minority of patients with advanced cancer report even discussing their preferences with their physicians.[8,9] The roughly one-third of patients with incurable cancer who do report such discussions appear to be more likely to have care consistent with their wishes, less likely to be placed on a ventilator or to die in an intensive care unit, more likely to receive hospice care, and more likely to experience lower costs of care in the last weeks of life.[8] The unique clinical circumstances and preferences of the patient and his or her family must guide medical decisions for patients with advanced cancer. Realistic discussions of prognosis, the potential benefits of both disease-directed and palliative therapy, and the likely effect of decisions with regard to symptoms, quality of life, financial costs, and survival can help patients make decisions that best match their goals and preferences.[10]

How We Can Help

The oncology community has the opportunity to help our patients cope with the costs of cancer care both at the bedside and through research and policy initiatives.

The ASCO Task Force on Cost of Cancer Care was established under the leadership of Lowell E. Schnipper, MD, to address mounting concerns over the cost of cancer care and to provide guidance to physicians, patients, and the profession on how to confront issues related to cost. In 2009, the task force published a guidance statement in which Neal J. Meropol, MD, and colleagues advocated for discussion of costs of care between patients and physicians, and the development of educational and clinical support tools to facilitate these discussions.[11] From a research perspective, we need better data on overall costs of care in different cancer settings, drivers of increasing cost, and the effect (or lack thereof) of cost on medical decision making among patients and physicians.

> **Inability to pay for prescription medications can be a barrier to adherence and must be assessed in clinic.**
>
> — Jeffrey M. Peppercorn, MD, MPH

At the bedside, our primary obligation is to consider our patients' well-being, in the fullest sense of the word. This includes determination of the patient's diagnosis, prognosis, and best treatment options, but also consideration of how therapeutic decisions will affect the individual and his or her caregivers financially.

Recognizing the Challenge

The rising cost of cancer care is, in part, a result of our success in developing new and improved means to diagnose and treat disease. Cancer is the leading cause of death of people younger than age 85 in the United States; the fact that cancer care consumes just 5% of total health care spending could be viewed as appropriate, or even inadequate. However, we must recognize the challenge posed by highly expensive novel interventions that offer perhaps months, but rarely years, of improved survival in many settings. In an era of constrained resources on the national and international level, and at a time when we are facing proposals for severe cutbacks in scientific research, there is a need for the oncology community to contribute to finding the solution to this bending of the cost curve while improving quality. Most importantly, we must better prepare ourselves to inform our patients of the direct cost implications of medical decisions and to help ensure that all patients gain access to appropriate cancer care. ●

About the Author: *Dr. Peppercorn, a breast cancer specialist, is an Associate Professor of Medicine in the Division of Medical Oncology at Duke University School of Medicine. He is the Incoming Chair of the ASCO Ethics Committee.*

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WARNING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE.

Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

ADDITIONAL WARNINGS

- The use of ABRAXANE has not been studied in patients with renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL

Pregnancy-Teratogenic Effects: Pregnancy Category D

- ABRAXANE can cause fetal harm when administered to a pregnant woman
- If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus
- Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE

Use in Males:

- Men should be advised to not father a child while receiving treatment with ABRAXANE

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- ABRAXANE contains albumin (human), a derivative of human blood

PRECAUTIONS

Drug Interactions:

- No drug interaction studies have been conducted with ABRAXANE
- Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4

Hematology:

- ABRAXANE therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3
- It is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE
- Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to >100,000 cells/mm^3
- In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended

Nervous System:

- Sensory neuropathy occurs frequently with ABRAXANE
- The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification
- If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE

Hepatic Impairment:

- Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution
- The starting dose should be reduced for patients with moderate and severe hepatic impairment

Injection Site Reaction:

- Injection site reactions occur infrequently with ABRAXANE and were mild in the randomized clinical trial
- Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration

Nursing Mothers:

- It is not known whether paclitaxel is excreted in human milk
- Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE therapy

Ability to Drive and Use Machines:

- Adverse events such as fatigue, lethargy, and malaise may affect the ability to drive and use machines

ADVERSE EVENTS

- Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients in the randomized trial
- These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension
- Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely
- During postmarketing surveillance, rare reports of congestive heart failure and left ventricular dysfunction were observed, primarily among individuals with underlying cardiac history or prior exposure to cardiotoxic drugs

In the randomized metastatic breast cancer study, the most important adverse events included alopecia (90%), neutropenia (all cases 80%; severe 9%), sensory neuropathy (any symptoms 71%; severe 10%), asthenia (any 47%; severe 8%), myalgia/arthralgia (any 44%; severe 8%), anemia (all 33%; severe 1%), nausea (any 30%; severe 3%), diarrhea (any 27%; severe <1%), infections (24%), vomiting (any 18%; severe 4%), and mucositis (any 7%; severe <1%).

Other adverse reactions have included ocular/visual disturbances (any 13%; severe 1%), renal dysfunction (any 11%; severe 1%), fluid retention (any 10%; severe 0%), hepatic dysfunction (elevations in bilirubin 7%, alkaline phosphatase 36%, AST [SGOT] 39%), hypersensitivity reactions (any 4%; severe 0%), cardiovascular reactions (severe 3%), thrombocytopenia (any 2%; severe <1%), and injection site reactions (<1%). In clinical trials and during postmarketing surveillance, dehydration was common and pyrexia was very common. Rare occurrences of severe hypersensitivity reactions have also been reported during postmarketing surveillance.

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.

Reducing Disparities

Continued from Page 10B

and among black patients, it went from 35% to 64%.[10] These simple commonsense strategies can be duplicated tomorrow in every major city in the United States and will save more lives than many of the drug trials being presented at this meeting. The barrier, unfortunately, is our will to do so.

Diagnosis. Getting patients to undergo screening is only half the battle, especially when that screening involves tests which require additional follow-up (e.g., fecal occult blood test [FOBT] and sigmoidoscopy). In a recent survey of primary-care physicians, 25% continue to perform in-office stool screening only, and 18% still advise patients with a positive FOBT to get a repeat FOBT.[11] The rates of these faulty recommendations are higher among older physicians, those in solo practice, and those without board certification. It is often these physicians who are disproportionately caring for minorities and the poor.[12]

Timely treatment. There is ample evidence that poor patients and minorities are less likely to receive appropriate surgical and oncologic care for their cancers.[13,14] Simple interventions can eliminate these disparities. In a landmark study published in 2008, Bickell and colleagues[15] instituted a feedback and tracking registry system in six New York City hospitals for women with stage I and II breast cancer. The computerized registry sent reminders to surgeons that a patient's time for oncology consultation had passed and requested verifications that the consultation had actually occurred. Compared with the pre-registry period, the rates of underuse of therapy (no radiotherapy in breast-conserving treatment, no hormone therapy for estrogen receptor-positive cancer, and no chemotherapy for estrogen receptor-negative cancer) decreased from 34% to 14% for black women and from 23% to 13% for white women. In short, the disparity disappeared. If delivery services can ensure that packages get to the right place at the right time, we as physicians should be able to do the same for our patients with regard to their medical care.

Post-treatment guidance. We know that modifiable factors such as comorbidities, diet, physical activity, and obesity may affect not only overall survival but often cancer-specific survival.[16,17] These factors are often concentrated among poor and minority patients. Evidence suggests that colon cancer recurrence and death is significantly decreased when patients walk as little as three times a week at normal pace for 1 hour.[18,19] If we had a drug that produced the same results, it would be a blockbuster. If we, as a health care system, cannot help patients to exercise more, eat better, and strictly control their hypertension and diabetes to help prevent their cancer from returning, then I suspect that we simply have not tried hard enough.

The passage of the Patient Protection and Affordable Care Act in March 2010 created tremendous opportunities to implement the above four principles. ASCO plans to pub-

lish a detailed policy statement in the *Journal of Clinical Oncology (JCO)* discussing opportunities and challenges for addressing cancer care disparities. This policy statement recommends, among other things, improving reimbursement in cancer care, integrating specialty care into the Federal Qualified Health Center model, improving the quality of cancer care, and developing community health teams led by medical oncologists and focusing on the continuum of cancer care to create a seamless cancer care system.

Health disparities in cancer outcomes are undoubtedly complex. However, there are simple, common-sense solutions that could drastically reduce cancer health disparities: enforce stringent quality-of-care standards in areas where we already have the data (e.g., procedure volume and colon cancer screening), implement targeted public health campaigns to dramatically increase screening for preventable cancers, rigorously track and follow up with every patient, and develop survivorship care models that focus on post-treatment lifestyle and health changes. We could begin all of these tomorrow, so why don't we? ●

For more information on disparities in health care, several abstracts within today's Health Services Research Oral Abstract Presentation Session (9:30 AM – 12:30 PM, S404, South Building) address this important and controversial topic. Also, ASCO's efforts in this area are addressed in the article in the Sunday issue of ASCO Daily News*, Section B.*

About the Author: Dr. Polite is an Assistant Professor of Medicine at the University of Chicago Medical Center and a gastrointestinal malignancies specialist. He is a member of the ASCO Health Disparities Advisory Group and the Gastrointestinal (Colorectal) Cancer Track Leader for the Scientific Program Committee, among other committee service.

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2011 Genitourinary Cancers Symposium Builds Off Success of Past Meetings

With several exciting new sessions and many technologic additions, the 2011 Genitourinary Cancers Symposium successfully showcased the latest science and translational research for oncologists and other members of the cancer care community. The cosponsors for the 2011 Genitourinary Cancers Symposium included the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology, and the Society of Urologic Oncology.

"The Symposium accomplished what it was set up to do, which is [to provide] a multidisciplinary interactive setting with a focus on evidence and a balance between didactic and case-based abstract presentations and translational science sessions, while allowing time for attendees to have a dialogue with the presenters," said Symposium Program Committee Chair Maha Hussain, MD, FACP, in an interview with *ASCO Daily News*. "I was very impressed by the number of phase III trials presented and by the breadth of research being presented for the first time at this meeting."

Eight General Sessions featured invited presentations on the latest science and research in genitourinary (GU) cancers. New this year, three of the General Sessions showcased translational research in the areas of renal and prostate cancers and urothelial carcinoma. The Best of Journals Sessions offered attendees the opportunity to hear expert perspectives on recent journal articles of interest in the fields of prostate and renal cancers. This year, these well-attended sessions were held in the General Session Room to accommodate a larger audience.

The Fellows, Residents, and Junior Faculty Networking Luncheon also was well attended. Oncologists in the early phases of their careers listened to select Symposium faculty and committee members give presentations about challenges and successes they have experienced throughout their careers. These presentations were then followed by small-group discussions on experiences, challenges, and other career development topics.

Other highlights of the Symposium program included the Poster Walks, during which expert faculty from various subspecialties led intimate, small groups of fellows, residents, and junior faculty through selected posters while discussing the research presented and putting the findings into the context of the larger educational program of the Symposium. The Symposium's Keynote Lecture, "Stem Cells and Tumorigenesis in GU Tumors," was also a Symposium highlight. Delivered by Carlos Cordon-Cardo, MD, PhD, of Columbia University Medical Center, the lecture focused on exploring tumorigenesis through stem cell research and tumor regrowth in GU cancers. Dr. Cordon-Cardo highlighted how this research is aiding in the development of novel predictive assays, as well as of new agents and treatment regimens.

"Dr. Cordon-Cardo's discussion regarding the stem cell was a very timely subject," noted Dr. Hussain. "This kind of scientific information and research is critical if we are to significantly affect the outcome from these cancers and improve the care for our patients."

Modernizing the Meeting

Several electronic additions were made to this year's meeting, including the choice between USB or print formats of the *Genitourinary Cancers Symposium Proceedings*. In addition, Symposium attendees were able to access the entirety of *Proceedings* electronically at www.gucasym.org.

As another technologic first for the Symposium, all attendees received Virtual Meeting access with their Symposium registration. Virtual Meeting, the largest online collection of oncology-related slides, audio, and video presentations, is a valuable resource for viewing presentations that an attendee may have missed and for reviewing crucial information after the Symposium's conclusion. Access the Virtual Meeting by going to www.gucasym.org.

The technology associated with the Symposium wasn't the only area of change this year. The Genitourinary Cancers Symposium cosponsors incorporated many eco-conscious initiatives, making the meeting more environmentally sensitive than in the past. These changes included: encouraging attendees to bring tote bags to the Symposium in an effort to avoid waste and use fewer shipping resources; distributing lanyards made from 100% bamboo, which is a renewable and sustainable natural resource; providing water coolers instead of distributing bottled water; and reducing paper waste by making Symposium evaluations available online only.

Looking ahead, the 2012 Genitourinary Cancers Symposium will be held February 2-4, 2012, at the San Francisco Marriott Marquis in San Francisco, California. The abstract submitter will be open in early August 2011 and will close at 11:59 PM October 4, 2011. For information about the upcoming Symposium, visit gucasym.org. ●

Merit Awards and Save-the-Date Info

Merit Awards recognize the work of oncology fellows who are first authors on outstanding Genitourinary Cancers Symposium abstracts. These awards provide residents and fellows with the opportunity to present their research and interact with others in their field, as well as further promote clinical research by young scientists.

Genitourniary Cancers Symposium Merit Award application materials must be submitted through the 2012 abstract submitter. Check gucasym.org for updates and application deadlines.

The following are the recipients of the 2011 Genitourinary Cancers Symposium Merit Awards:

Nils Arvold, MD
Harvard Radiation Oncology Program
Arjun Balar, MD
Memorial Sloan-Kettering Cancer Center
Himisha Beltran, MD
Weill Cornell Medical College
Eugene Cha, MD
Weill Cornell Medical College
Brian Chapin, MD
University of Texas M. D. Anderson Cancer Center
Farshid Dayyani, MD, PhD
University of Texas M. D. Anderson Cancer Center
Rian Dickstein, MD
University of Texas M. D. Anderson Cancer Center
Andrew Feifer, MD
Memorial Sloan-Kettering Cancer Center
Terence Friedlander, MD
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Baerin Houghton, BSc(Med), MBBS, FRACP
National Health and Medical Research Council Clinical Trials Centre, University of Sydney
Xuan Huang, MD, PhD
National Cancer Institute
Grant Hunter, MD
Cleveland Clinic
Roberto Iacovelli, MD
Sapienza University of Rome
Daniel Keizman, MD
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
Michelle Kim, MD
University of Texas M. D. Anderson Cancer Center
Stephen Liu, MD
University of Southern California Norris Comprehensive Cancer Center
Sarah Minner, MD
University Medical Center Hamburg-Eppendorf
Timur Mitin, MD, PhD
Brigham and Women's Hospital
Piet Ost, MD
Ghent University Hospital
Sandip Prasad, MD, MPhil
The University of Chicago Medical Center
Sarmad Sadeghi, MD, PhD
Cleveland Clinic Taussig Cancer Center
Mohamed Salem, MD
Cleveland Clinic Foundation and Cleveland Clinic Taussig Cancer Center
Fabio Schutz, MD
Dana-Farber Cancer Institute and Harvard Medical School
Prasanna Sooriakumaran, BMedSci(Hons), BMBS(Hons), PhD, PGC(MedLaw), FRCS(Urol)
Weill Cornell Medical College
Christopher Weight, MD
Mayo Clinic

The 2012 Genitourinary Cancers Symposium will be held February 2-4, 2012, at the San Francisco Marriott in San Francisco, California.

Focus Under Forty

Continued from Page 11B

undertake something like egg banking before treatment."

Focus Under Forty includes two case-based modules that specifically address fertility preservation.

Different Psychosocial and Practical Concerns

Awareness of the significant psychosocial, financial, and practical concerns of this age group is also important. Both Ms. Reinecke and Dr. Hayes-Lattin, who had testicular cancer at age 28, noted that more oncologists should understand the specific challenges faced by AYA patients, whose concerns differ from those of either the child or the older adult with cancer. In addition to fertility preservation, many of these patients have concerns about issues such as body image and relationships.

"You are there in the waiting room and everyone is a generation away from you," Ms. Reinecke said. "It's very scary and isolating to be facing these issues — issues like mortality — and not to have peers there. You are out of sync with your own peers."

New Collaboration

This is the first time ASCO and LIVE**STRONG** have partnered on physician education. "It's exciting to see this collaboration address these critical issues and realize the affect this education can have on patients' lives," said Dr. Hayes-Lattin, who is a senior medical advisor for LIVE**STRONG.** "The goal of Focus Under Forty is to have everyone who interacts with these patients understand what the differences are for this age group and to know that the approach to care should be different."

For more information on Focus Under Forty, hosted byASCO University, visit www.university.asco.org/focusunder40.

Stop by the ASCO University Booth in the Oncology Professionals Hall (Hall A, Level 3, South Building) to see a demonstration of ASCO University's website and the Focus Under Forty Curriculum and to browse slides from the Curriculum that are available in the Oncology Slide Library on the website. ●

This article was adapted from the February 15, 2011 issue of The ASCO Post.

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The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) con to evolve as the standard for clinical practice and policy decision-making.

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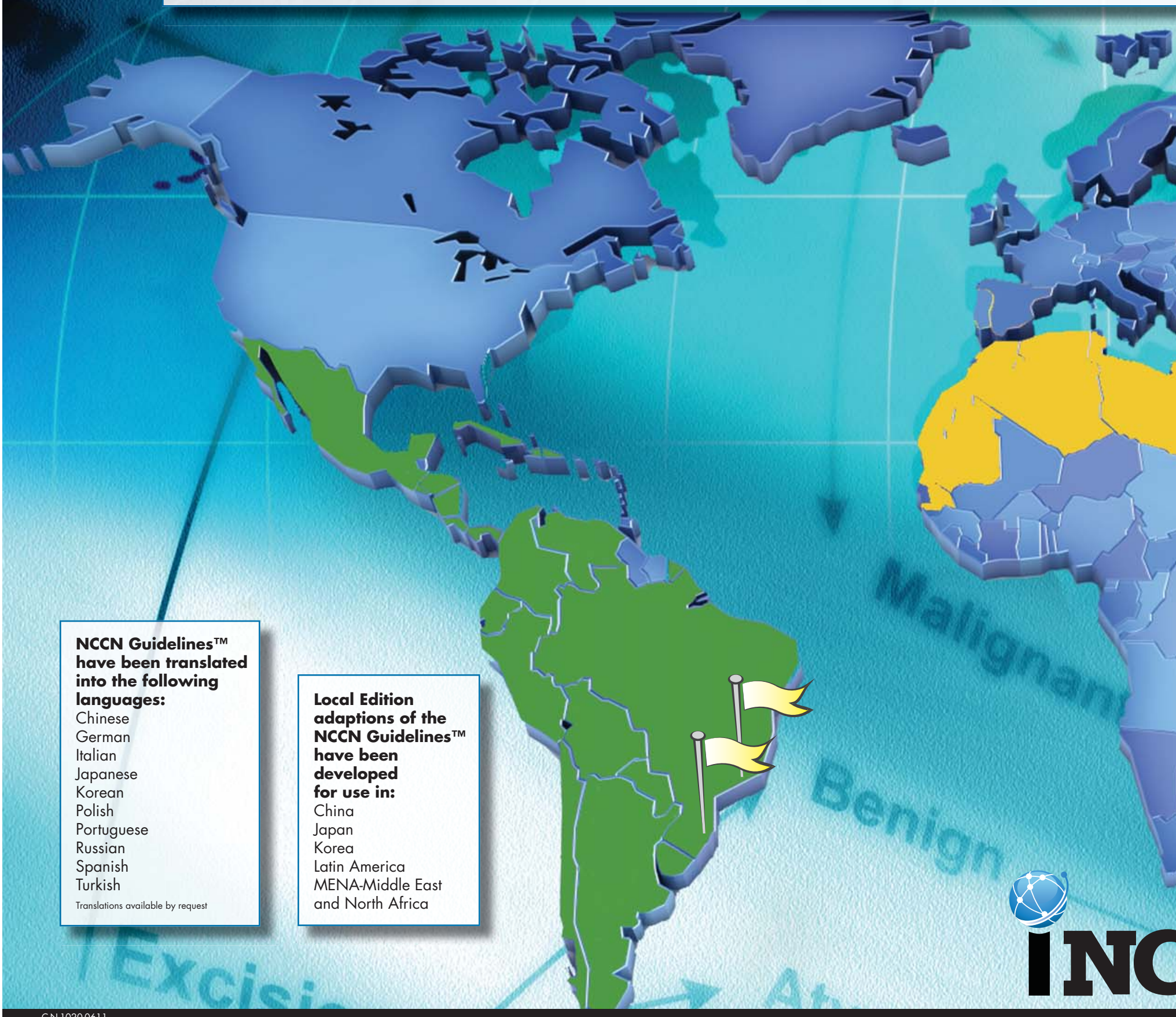

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EGFR Gene Testing before Treatment Recommended for Patients with Advanced Non-small Cell Lung Cancer

Patients with advanced non-small cell lung cancer (NSCLC) should have their tumors tested for mutations in the epidermal growth factor receptor (*EGFR*) gene, which would then determine whether EGFR tyrosine kinase inhibitors (TKIs) or chemotherapy is appropriate first-line therapy. ASCO issued this recommendation in a Provisional Clinical Opinion (PCO), posted to the *Journal of Clinical Oncology* online in April 2011. According to Giuseppe Giaccone, MD, PhD, Chief of the Medical Oncology Branch of the National Cancer Institute (NCI) and Co-Chair of the ad hoc panel that crafted this PCO, *EGFR* mutation testing "should be standard for patients with NSCLC so that they receive the best possible treatment."

EGFR TKIs are currently approved for second-line and third-line treatment of NSCLC. In fact, their use in these settings has been recommended in the ASCO 2009 Guideline Update on Stage IV NSCLC. Patients with advanced NSCLC are typically treated with standard chemotherapy. Now, based on the PCO, EGFR TKIs may be used before chemotherapy in patients with tumors that test positive for *EGFR*-activating mutations.

The ASCO PCO was based on a "rigorous, evidence-based approach" after evaluating data from five phase III clinical studies. The first study, Iressa Pan-Asia Study (IPASS), showed that gefitinib provides significantly longer progression-free survival (PFS) than chemotherapy for patients with advanced lung adenocarcinoma with mutations in the *EGFR* gene (9.5 months vs. 6.3 months for patients receiving chemotherapy; $p < 0.0001$). Data from IPASS was first assessed by the NCI's Physician Data Query (PDQ) Adult Cancer Editorial Board before ASCO convened its ad hoc panel to review this issue.

IPASS was a phase III, multicenter, open-label study in which patients with advanced NSCLC were randomly assigned to receive gefitinib or the combination of carboplatin and paclitaxel as first-line therapy. Patients receiving gefitinib were 26% less likely to experience disease progression or death. This observation was even more meaningful when the data were analyzed based on the status of *EGFR* gene mutations. In patients with *EGFR* mutations, patients receiving gefitinib were 52% less likely to die or experience disease progression. For patients with tumors that tested negative for mutations in the *EGFR* gene, chemotherapy was significantly more likely to provide longer PFS.

Three other phase III studies also showed that patients with advanced NSCLC and mutations in the *EGFR* gene had a significantly higher response rate and longer progression-free survival from first-line treatment with gefitinib rather than standard chemotherapy. In one of these studies, Maemondo[1] and colleagues reported that PFS doubled when patients with advanced NSCLC and mutations in the *EGFR* gene were treated with gefitinib (10.8 months for gefitinib versus 5.4 for chemotherapy; $p < 0.001$).

Other EGFR TKIs, such as erlotinib, also

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have been found to confer benefit. The panel evaluated emerging data from the OPTIMAL study, which randomly assigned only those patients with mutations in the *EGFR* gene. This phase III study (also known as CTONG 0802) showed that patients treated with erlotinib had a PFS of 13.1 months compared with 4.6 months for patients who received chemotherapy with gemcitabine and carboplatin. With nearly a tripling of the PFS, patients receiving erlotinib were 84% less likely to experience disease progression ($p < 0.0001$).[2]

The PCO acknowledges that patients in IPASS were from China, Japan, Korea, Thailand, and Taiwan. The other four studies were also in Asian populations. Dr. Giaccone indicated that an interim analysis of the European Randomized Trial of Tarceva versus Chemotherapy (EURTAC) study sponsored by the Spanish Lung Cancer Group seem to indicate that non-Asian patients with advanced NSCLC and activating mutations in the *EGFR* gene had longer PFS when they were treated with erlotinib. Although these data are not yet available, the trial was terminated early and may provide support that observations made in Asian populations may also be seen in non-Asians.[3]

This ASCO PCO does not immediately translate into guidelines that change clinical practice but in a companion piece that will be published in the *Journal of Oncology Practice,* panel members Mary Beth Beasley, MD, of Mount Sinai Medical Center, and Daniel T. Milton, MD, of Hematology-Oncology of Indiana, PC, indicate how the PCO may become viable in clinical practice. The report indicates that testing for *EGFR* mutations can be ordered separately at many community cancer centers, with results available in 2 weeks. "If *EGFR* mutational analysis is not covered in a region, it would be appropriate for oncologists and their state professional society to advocate for their patients with insurance companies on this matter, as *EGFR* mutation analysis may enable better care and avoidance of potentially ineffective therapies," the authors concluded. ●

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Please call 1-800-507-5284 or refer to ClinicalTrials.gov for more information (http://www.clinicaltrials.gov/ct2/show/NCT00813943)

The CORE study is in collaboration with the Canadian Brain Tumour Consortium (CBTC).

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President-Elect Brings Pediatric Perspective to ASCO Leadership

In the interview that follows, ASCO President-Elect Michael P. Link, MD, the Lydia J. Lee Professor in Pediatric Cancer at Stanford University School of Medicine, and a member of the medical staff of the Lucile Salter Packard Children's Hospital at Stanford, shared his plans for his transition to the Society presidency and discussed his unique perspective as a pediatric oncologist.


Michael P. Link, MD

Q How did you react when you learned that you had been nominated for the position of ASCO President?

I never dreamt that I would be nominated to be ASCO President. It's an honor, and I'm flattered. To be one of the spokespeople for our Society is a big responsibility, and I hope to serve it well. It also made me realize that ASCO was serious about having a pediatric oncologist as President. Having a "minority" member lead the Society shows exactly how expansive ASCO has become — it is really the Society for all people involved in caring for patients with cancer.

Q What led you to pediatric oncology as a subspecialty?

My brother is a pediatrician, so there was some influence from that quarter. During my first pediatric rotation, I just fell in love with caring for children. After my first rotation on oncology, I was hooked. These kids are faced with a very serious illness, but often they brighten my day as opposed to the other way around. You also develop a very special lifelong relationship with the families. I still communicate with many of the patients I cared for 30 years ago. One of my former patients works here at Stanford, actually, and we meet for coffee and talk about childrearing and other issues that we all face. She never fails to inform me about the consequences of cancer survivorship. Another former patient became a surgeon and called me up to ask me for advice on managing a patient — that was the ultimate compliment. What makes pediatrics magical is that your patients come out on the other end of a serious illness and are able to go on with their lives.

Q What perspective will you bring to Society leadership as a pediatric oncologist?

I've been an advocate for pediatric oncology and children with cancer throughout my career, but it is very true that ASCO leaders should leave our hats at the door — leaders should not feel that they are representatives of a particular specialty or constituency within ASCO. I don't view myself representing pediatrics the way a senator represents Rhode Island — I bring my experience and point of view to help formulate positions that are best for the Society and best for our patients. I believe that all ASCO leaders do the same.

It's clear that many of the advances in oncology were pioneered in pediatrics. Although pediatric oncology is a relatively small piece of the action, we have been on the leading edge of cancer care for quite a while. The multidisciplinary approach to the patient with cancer was pioneered in pediatrics. Many of the issues of survivorship and awareness of late effects of treatment have come from pediatrics and from long-term follow-up of our cured patients. Pediatricians also have led the way in demonstrating the utility of clinical trials.

Something becoming very clear to all of us who care for patients with cancer is the complex heterogeneity of these diseases on the molecular level — that each cancer type is, in reality, a collection of related diseases that may appear the same under the microscope, but which are quite different on the molecular level. It is thus not surprising that different tumors respond very differently to different therapies. Thirty years ago, we were discovering that the most common cancer that pediatricians treat — acute lymphoblastic leukemia — is a heterogeneous collection of diseases with different molecular underpinnings, different clinical presentation, different outcomes, and requiring different intensities of therapy. Something that we've known for a long time in pediatrics is now an important theme in medical oncology as well. Because of the heterogeneity of diseases, we need many more patients than previously thought to do robust clinical trials.

Q How have you been preparing for presidency?

I participated on a number of key committees. For example, as a member of the Government Relations Committee, I received an in-depth understanding of the key issues that relate to medical care and especially oncology care in the United States. It is obvious that health care reform is going to have an enormous effect on our work, and formulating our positions will be critical because the Society advocates for all of us as practitioners. The science of oncology is advancing at such a rapid pace that it is very difficult to keep up. We have to learn to leverage all of our educational resources to keep our members up to speed. Because ASCO is such a heterogeneous organization, we have to focus

See Pediatric Perspective, Page 27B

JOP Announces New Associate Editor and Editorial Board Members

The *Journal of Oncology Practice (JOP)* recently named Jeffery C. Ward, MD, of Puget Sound Cancer Centers an Associate Editor. In addition, *JOP* is delighted to welcome fourteen new members to its Editorial Board — all of whom are highly renowned clinicians and have made many accomplishments and contributions to the field of oncology.

Jeffery C. Ward, MD — *JOP* Associate Editor

The role of *JOP* Associate Editor requires an oncologist who is grounded in practice and familiar with all aspects of running a practice such as practice administration and improvement, billing and reimbursement issues, and quality and efficiency of care. The Associate Editor conducts peer reviews and contributes to content development.

Dr. Ward practices hematology and medical oncology at Puget Sound Cancer Centers, where he serves as Director of Oncology Services at Swedish/Edmonds Hospital in Washington state and Medical Director of Hospice of Snohomish County. *(For more on Dr. Ward's goals for* JOP*, see the article in the Saturday issue of* ASCO Daily News*, Section B.)*

New *JOP* Editorial Board Members

JOP provides oncologists and other oncology professionals with timely, relevant information and tools to enhance practice efficiency and promote high-quality patient care. Accordingly, the role of *JOP*'s Editorial Board is to review clinical research articles to determine if they merit publication and distribution to the cancer treatment community.

Brief biographies of each new Editorial Board Member can be found below.

Thomas A. Aloia, MD, practices at the University of Texas M. D. Anderson Cancer Center. His major specialties include hepatobiliary surgery and cancer, as well as gastrointestinal surgical oncology. Dr. Aloia is the recipient of several clinical and scholastic awards, including the Harry Hutchison Gibson Fellow in Cancer Research.

Robert J. Amato, DO, practices at the University of Texas Medical School at Houston, Division of Oncology in the Department of Internal Medicine. Dr. Amato focuses his research on the perfecting drug combinations to halt the progression of metastatic kidney and prostate cancers, as well as on determining how elements from his current studies may be used to disable other genitourinary cancers.

Edward Paul Balaban, DO, FACP, specializes in hematology and medical oncology and practices in the cancer clinical network associated with the University of Pittsburgh. He is the Immediate Past President of the Pennsylvania Society of Oncology and

Hematology and has served on several ASCO committees including the Clinical Practice Committee and Clinical Practice Guideline Committee. He has also previously served as an Editorial Board member for the *Journal of Clinical Oncology*.

David Coniglio, MPA, PA-C, is an Associate Professor and Academic Coordinator in the Department of Physician Assistant Practice at Campbell University College of Pharmacy & Health Sciences. He has 23 years experience in the care of patients with breast cancer. His areas of clinical and educational interest include: breast cancer, cancer screening and prevention, medical issues in international adoption, evidence-based medicine, test-writing and analysis, medical writing, and educational research. He is also Past President of the Association of Physician Assistants in Oncology.

Patrick A. Grusenmeyer, ScD, is Senior Vice President of Cancer and Imaging Services at Christiana Care Health System and also oversees the Helen F. Graham Cancer Center. Dr. Grusenmeyer is also a Fellow in the American College of Healthcare Executives and is a member of ASCO's Cancer Education Committee and Workforce Advisory Group.

Randall Holcombe, MD, who specializes in hematology and colon cancer, serves as Director of Clinical Cancer Affairs at The Mount Sinai Medical Center. He also serves as Medical Director of the Ruttenberg Treatment Center, Associate Director for Clinical Affairs in The Tisch Cancer Institute, and Director of Gastrointestinal Medical Oncology for the Division of Hematology/Oncology.

Dennie V. Jones, MD, FACP, specializes in hematology, lung cancer, and gastrointestinal oncology. He serves as a Professor of Medicine and Director at the Lung Cancer Multidisciplinary Research and Treatment Program at the University of New Mexico (UNM) Cancer Center. Dr. Jones is also Director in the Clinical Trials Office at UNM Cancer Center, Medical Director of Inpatient Oncology Service at the UNM Hospital, and Medical Director at the New Mexico Cancer Care Alliance.

Sharmila Makhija, MD, an expert in gynecology, is Director and Associate Professor of Gynecology and Obstetrics in the Gynecologic Oncology Division at Emory University School of Medicine. Dr. Makhija is also a Fellow of the American College of Obstetricians and Gynecologists (FACOG).

Matthew P. Mumber, MD, specializes in radiation oncology at Harbin Clinic Radiation Oncology. He is also the Medical Director at Fuller Cancer Center in Ringold, Georgia. Dr. Mumber speaks throughout the country on Integrative Oncology and received the Georgia Cancer Coalition Hamilton Jordan Founder's Award in 2008. Dr. Mumber serves on the Members at Large and Steering Subcommittees of ASCO's Clinical Practice Committee.

Marcus A. Neubauer, MD, a hematologist, serves as Chair of several committees for Kansas City Cancer Center, where he has been on staff for 12 years. He is also a member of the Pharmacy & Therapeutics Committee for U.S. Oncology.

See New JOP *Editorial Members, Page 30B*

Education Session: Targeting Several Stem Cell Pathways Could Provide Clinical Benefit

As the understanding of cancer stem cells continues to grow, the implications both for possible new therapeutic agents and for oncology clinical-trial design grow stronger. Tomorrow's Education Session, "Cancer Stem Cells as a Therapeutic Target: Fact or Fiction?" will discuss some of the possible signaling pathways that could lead to stem cell inhibition, as well as what the stem cell model might mean for our overall understanding of tumor growth and treatment (11:30 AM – 12:45 PM, Room S100A, South Building).

"The cancer stem cell idea really is an old idea, but it is only in the past decade that it has gotten a lot of impetus because of the ability to find these cells in preclinical models," said Max Wicha, MD, of the University of Michigan Cancer Center, in an interview with *ASCO Daily News*. Dr. Wicha, Chair of the Education Session, will discuss the current state of knowledge on cancer stem cells and address whether targeting of these cells is a strong possibility for improving cancer care.

According to Dr. Wicha, it now appears that most cancers have a percentage of cells that exhibit stem cell properties; in other words, he said, "those cancer stem cells have the capacity to renew themselves indefinitely, and those are the same cells that mediate metastasis." Some cancers, such as melanoma, may have too high a percentage of these cell types for it to be meaningful to target them over other tumor cells; however, most other types of cancer — from the leukemias and lymphomas through almost all solid tumor types — generally have only a small percentage of stem cells.

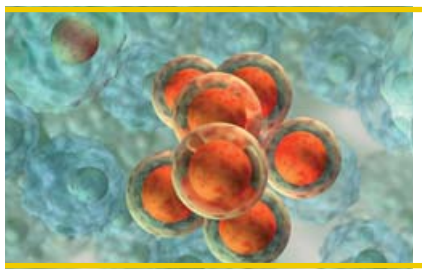
One indicator that targeting of cancer stem cells could provide benefit to patients is the finding that the stem cells appear to be relatively resistant to chemotherapy and to radiation therapy. This could explain why these therapies can often shrink tumor masses but fail to provide substantial patient benefit when the stem cells are largely unaffected.

"Many of the existing therapies may be primarily destroying the more differentiated cells in the tumor, and the stem cells persist and regrow the tumor," said Dr. Wicha.

Joan Seoane, PhD, of the Vall d'Hebron University Hospital Institute of Oncology in Barcelona, will discuss the use of inhibitory agents to target specific signaling pathways that mediate the survival of cancer stem cells.

Some such agents are already in early stages of clinical trials. One agent that inhibits the NOTCH signaling pathway when administered along with standard chemotherapy was well tolerated in a phase I trial of patients with breast cancer, and importantly, biopsies taken before and after the treatment showed a decrease in the percentage of tumor cells with stem cell properties. Normally, that percentage goes up, which would indicate the targeting of non-stem cells in a tumor.

Other pathways could be targeted as well, including the Hedgehog- and Wnt-signaling pathways. Michael Kahn, PhD, of the University of Southern California, will speak at the session about the Wnt/B-catenin signaling pathway and about some promising indications that targeting of this pathway could eliminate cancer stem cells while leaving normal somatic stem cells unharmed.



"The cancer stem cell model suggests that response rate is not really a good endpoint because it is an endpoint of bulk tumor cells and not of stem cells. So if these stem cell models are right, we're going to have to figure out better ways to design trials."

— Max Wicha, MD

"There are two highly related [beta-catenin] co-activator proteins: CBP and P300," Dr. Kahn explained to *ASCO Daily News*. "The choice of which partner beta-catenin associates with seems to make a huge difference in whether the cells make symmetric divisions and maintain their level of potency or make asymmetric divisions." According to Dr. Kahn, CBP/catenin-mediated transcription is associated with a nondifferentiative process, whereas p300/catenin-driven transcription initiates differentiation.

Dr. Kahn and colleagues have developed a compound that appears to target only symmetrically dividing cells, that is, the cancer stem cells. "In mouse models, we have been able to basically eliminate these cancer stem cells without having any deleterious effects on the endogenous stem cell populations," he said. The compound has entered phase I testing, and safety and pharmacokinetic data should be available soon.

Dr. Kahn said there is even some early data to suggest that the compound might ameliorate some of the toxicities associated with chemotherapeutic agents when given together. "I think this is a very attractive way to target cancer stem cells, and, on top of that, the treatment has beneficial effects," he said.

Dr. Wicha said that if some of these agents are effective and the cancer stem cell model proves to be correct, it will not only provide new therapies but will also require a rethinking of how cancer trials are conducted. "Right now, the registration and then approval of drugs is largely based on the RECIST [Response Evaluation Criteria in Solid Tumors], which mainly involves tumor measurement criteria, and one looks at the response rate of tumors [to determine efficacy]," he said. "But the cancer stem cell model suggests that response rate is not really a good endpoint because it is an endpoint of bulk tumor cells and not of stem cells. So if these stem cell models are right, we're going to have to figure out better ways to design trials."

In spite of the possible implications for trial design, Dr. Wicha said that if one major trial can show substantial clinical benefit with an agent targeting cancer stem cells, then there will be an explosion of interest across many tumor types. "You would have to have rigorous proof in clinical trials that if you knock down the stem cells, the patients live longer. [Survival is] really the bottom line." ●

Pediatric Perspective

Continued from Page 23B

on those issues that unify us, such as clinical trials infrastructure and access to care, and be strong advocates for them.

Q You've served on a variety of committees throughout your ASCO membership. Do any experiences stand out?

Most exciting for me was the time I spent on the Board of Directors [1999-2002], being in a position to learn about the issues confronting the Society and our patients on a strategic level. I've been an associate editor for the *Journal of Clinical Oncology* (*JCO*) for almost 10 years. I've watched it grow to be the most influential of all the oncology journals — that is a wonderful development. I've served on the faculty for the ASCO/American Association for Cancer Research Workshop: Methods in Clinical Cancer Research, in Vail, Colorado, and it is still one of the most amazing experiences I've had. As a result, I've brought a Fundamentals of Clinical Trials course to the ASCO Annual Meeting for those who don't have the chance to go to Vail.

I think I've gotten more out of ASCO than it's gotten out of me, which is why it's a great privilege to serve. ●

This article was adapted from the July 2010 issue of ASCO Connection.

Psychosocial Screening: Addressing Distress in your Patients

Screening for signs of distress may affect the quality of life on for patients with cancer

In recent years, the concept that cancer care treatment involves more than the clinical treatment of the disease has gained greater attention within the oncologic community. Increasingly, medical guidelines and recommendations are calling on oncologists to screen their patients with cancer for psychosocial concerns, such as depression and anxiety, financial issues, a lack of support system, or other signs of distress that might affect the patient's overall well-being and quality of life. An overview of how to screen for psychosocial issues will be discussed during today's Education Session, "Assessing Patients' Psychosocial Needs: How to Do this in (Your Busy) Practice." The session will be held 9:45 AM – 11:00 AM, Room S100a, South Building.

In 2007, The Institute of Medicine released a report, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs." In it, the organization warned that left unaddressed, psychosocial issues in patients with cancer could lead to problems such as increased suffering and anxiety or reduced adherence to medication. According to the report, the addressing of these needs begins when oncologists first screen for psychosocial issues in all patients so it is essential that they recognize the risk factors for these issues when they present in their patients.[1]

Michelle Naughton, PhD, of Wake Forest University School of Medicine, will serve as Chair of the Session and will discuss what types of psychosocial morbidity might be affecting patients with cancer and what some of the risk factors are for these conditions.

"There is a lot of emphasis on treating the physical disease in patients with cancer, and physicians in general are not well trained to look at psychologic morbidity that might be associated with cancer," Dr. Naughton said in an interview with *ASCO Daily News*.

Although psychosocial concerns cover a range of conditions, depression and anxiety are among the most frequently discussed, Dr. Naughton said. Depression and anxiety can interplay with symptoms, can affect social relationships, and can even affect survivorship treatment adherence. These types of distress can affect a patient during cancer treatment, and also later, during post-treatment cancer survivorship, according to Dr. Naughton.

Recognizing the Symptoms

In 2007, a study published in *Supportive Oncology*, surveyed oncologists about their awareness and adherence to National Comprehensive Cancer Network guidelines on psychosocial distress and screening. Of 1,000 oncologists surveyed using an anonymous questionnaire, only 33% reported screening for distress in their patients.[2] Although time often is an issue when it comes to screening for psychosocial distress, several patient self-report measures exist that can aid physicians in screening, according to Paul Jacobsen, PhD, of H. Lee Moffitt Cancer Center & Research Institute. Dr. Jacobsen will discuss these screening tools and the challenges that exist in the implementation of these tools.

Dr. Jacobsen told *ASCO Daily News* that "there is evidence to suggest that the quality of psychosocial care is less than optimal nationwide. There are two keys to improving this quality. One is to recognize patients in needs of these services, and the second is matching these patients to the needed services."

Putting Strategies into Practice

According to Dr. Jacobsen, data from the ASCO's Quality Oncology Practice Initiative has shown that methods like providing feedback to oncologists on the quality of their psychosocial care can be helpful in identifying the need for improvement efforts. However, Dr. Jacobsen also will discuss data that suggests this supportive feedback may not be completely addressing the problem.

"For example, data shows that assessment of emotional well-being lags behind assessment of pain," Dr. Jacobsen said.

David Goldstein, MD, of Prince Wales Hospital, Sydney, Australia, will provide an international perspective on the issue and will review not only how to identify those in need of psychosocial care, but also how to respond to these patients in a practical way, even with limited resources and time. Although oncologists practicing in large academic centers have a wide variety of support and resources to help patients with psychosocial needs, the same cannot be said for oncologists in smaller or more rural practices. Dr. Goldstein will discuss strategies that have been tested to increase support for those with psychosocial needs, as well as which strategies have been most successful among community practices.

"These techniques are practical and can be done in any size oncology practice," Dr. Goldstein said in an interview with *ASCO Daily News*. "There appear to be ways to improve the holistic nature of our cancer care without compromising our ability to meet the essential tasks we already must do as front-line practitioners."

Moving forward, it is important that oncologists are actively examining the quality of the psychosocial care within their own practices.

"Oncologists should be asking, 'How are we doing in addressing these issues?'" Dr. Jacobsen said. "And if they are not doing well, they need to begin to figure out what can be done to improve the situation given the things they will have learned during this Education Session." ●

References

1. *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs.* Institute of Medicine (U.S.) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting. Adler NE, Page AEK, eds. Washington DC: National Academies Press (U.S.); 2008.
2. Pirl WF, Muriel A, Hwang V, et al. Screening for psychosocial distress: A survey of national oncologists. *J Support Oncol.* 2007;5(10):499-504.

Community Oncology Research Grants Promote Clinical Trial Development in Community Practice

To support the development of high-quality clinical trials programs, ASCO and the Conquer Cancer Foundation (formerly known as The ASCO Cancer Foundation®) are pleased to present the fourth annual Community Oncology Research Grants (CORGs) to the following practices:

- Cancer Care Specialists of Central Illinois, and
- Newark Beth Israel Medical Center Cancer Center.

Each practice will receive up to $30,000 to pursue activities related to the improvement of its clinical research programs. These practices were recognized Saturday, June 4 during the Clinical Trials Team Reception.

"Quality cancer research in the community setting is necessary for advancing cancer therapy for patients," said Johanna Bendell, MD, Chair of the CORG Review and Selection Subcommittee in an interview with *ASCO Daily News*. "The CORG award provides community sites that are performing high-quality clinical research the opportunity to improve their programs to achieve the Exemplary Attributes of Clinical Trial Sites. The awardees also serve as models through which other community sites can learn to grow their programs to further develop excellent research in the community setting."

The Foundation and ASCO chose to base the grant criteria on ASCO's Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites, published in the May 20, 2008, issue of the *Journal of Clinical Oncology (JCO)* and available at www.asco.org/researchsources. The applicants were asked to identify at least one area for improvement from the categories as described in the statement, including:

- diversification of clinical trial enrollment;
- high accrual activity;
- participation in the clinical trials process (including trial development, implementation, and analysis);
- formal maintenance of high educational standards;
- quality assurance measures;
- multidisciplinary involvement in the research setting; and
- clinical trials awareness programs.

To apply for the CORG, the following criteria were required: practices are community-based, with at least one ASCO member and at least one member of an ASCO State/Regional Affiliate involved in the research program; practice investigators are in good standing with the research community and produce high-quality audit reports; and practices comply with Good Clinical Practice standards, as developed by the International Conference on Harmonisation.

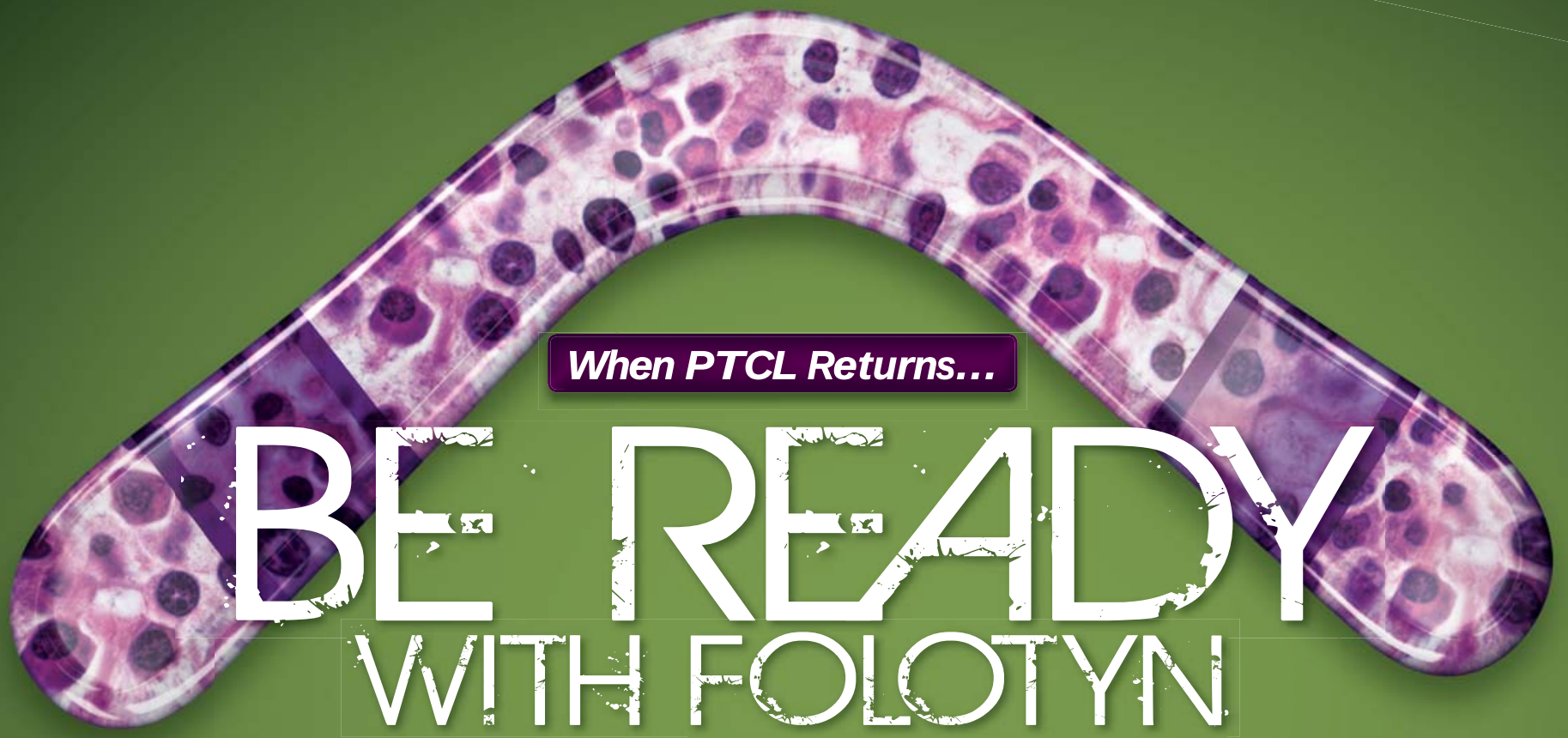
Eligible practices were then asked to complete an online application, which was peer reviewed and scored by members of the CORG Review and Selection Subcommittee. Dr. Bendell serves as Chair for this subcommittee, and the other members of this subcommittee were James Bearden, MD; William Demas, MD, FACR; Matthew Galsky, MD; Thomas Marsland, MD, Martha Mims, MD, PhD; and Preston Steen, MD.

The application required practices to thoughtfully consider four core components:

- identify and discuss the areas in which the practice could improve its clinical research programs,
- develop an implementation plan to bring the improvements to fruition,
- develop an assessment plan to evaluate the effectiveness of the activities, and
- create an accounting of how the practice planned to use the $30,000 grant.

See CORG, Page 35B

The indication for FOLOTYN is based on overall response rate.
Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.



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- *12% (95% CI, 7-20) of patients had responses lasting ≥14 weeks (range=98-503 days)*

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Important Safety Information

Warnings and Precautions

FOLOTYN may suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Monitor blood counts and omit or modify dose for hematologic toxicities.

Mucositis may occur. If ≥Grade 2 mucositis is observed, omit or modify dose. Patients should be instructed to take folic acid and receive vitamin B_{12} to potentially reduce treatment-related hematological toxicity and mucositis.

Fatal dermatologic reactions may occur. Dermatologic reactions may be progressive and increase in severity with further treatment. Patients with dermatologic reactions should be monitored closely, and if severe, FOLOTYN should be withheld or discontinued.

Tumor lysis syndrome may occur. Monitor patients and treat if needed.

FOLOTYN can cause fetal harm. Women should avoid becoming pregnant while being treated with FOLOTYN and pregnant women should be informed of the potential harm to the fetus.

Use caution and monitor patients when administering FOLOTYN to patients with moderate to severe renal function impairment.

Elevated liver function test abnormalities may occur and require monitoring. If liver function test abnormalities are ≥Grade 3, omit or modify dose.

Adverse Reactions

The most common adverse reactions were mucositis (70%), thrombocytopenia (41%), nausea (40%), and fatigue (36%).The most common serious adverse events are pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

Use in Specific Patient Populations

Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother.

Drug Interactions

Co-administration of drugs subject to renal clearance (e.g., probenecid, NSAIDs, and trimethoprim/sulfamethoxazole) may result in delayed renal clearance.

Please see FOLOTYN Full Prescribing Information.

*Per independent central review

Reference: 1. FOLOTYN Prescribing Information. Allos Therapeutics, Inc., 2011.

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New *JOP* Editorial Members

Continued from Page 25B

Maura Polansky, MS, PA-C, is Director of the Physician Assistant educational programs at the University of Texas M. D. Anderson Cancer Center. She specializes in gastrointestinal medical oncology. Ms. Polansky is a founding member of the American Academy of Physician Assistants.

Nicholas J. Robert, MD, an expert in breast cancer and hematology, is Co-Chair of the Breast Committee of the U.S. Oncology Research Network. He is also Chair of both the Cancer Committee and Research Committee of Inova Fairfax Hospital's Cancer Center in Virginia. Additionally, Dr. Robert serves as Medical Director of Research at Fairfax Northern Virginia Hematology.

William R. Robinson, MD, is a Professor of Gynecologic Oncology in the Department of Obstetrics and Gynecology at Tulane University School of Medicine. He has written more than 50 scientific publications and held multiple professional leadership roles, including President of the Western Association of Gynecologic Oncologists and Chair of the Chemoprevention Subcommittee of the Gynecologic Oncology Group.

Gamini S. Soori, MD, FACP, FRCP, who specializes in medical oncology and hematology, is Medical Director of Alegent Health Bergan Mercy Cancer Center and Chair of its Oncology Committee. Dr. Soori is also a Clinical Professor of Medicine at Creighton University School and serves on ASCO's By-laws Committee. ●

Introducing Newest *JCO* Editors

In addition to the changes to the new Associate Editor and Editorial Board members for the *Journal of Oncology Practice* (*JOP*), the *Journal of Clinical Oncology* (*JCO*) recently named two new Associate Editors.

Melissa M. Hudson, MD, recently began her term as a *JCO* Associate Editor, replacing 2011-2012 ASCO President Michael P. Link, MD. She is Director of the Cancer Survivorship Program and Co-Leader of the Cancer Prevention & Control Program at St. Jude Children's Hospital.

In addition to her work at St. Jude Children's Hospital, Dr. Hudson is 2011-2012 Chair of ASCO's Cancer Survivorship Committee, 2010-2013 Associate Editor on the Cancer.Net Editorial Board, and is a member of *ASCO Connection* Editorial Board.

Danny Rischin, MD, was named *JCO* Associate Editor, replacing Arlene A. Forastiere, MD, who is retiring from *JCO*. Dr. Rischin specializes in head and neck cancers and is an Associate Professor in the Department of Medical Oncology at Peter MacCallum Cancer Centre in Melbourne, Australia. ●

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Education Session Highlights Promising Studies from 2010 in NSCLC

Today's Education Session, "Recent Advances in Non-small Cell Lung Cancer: Best of 2010 Basic and Clinical Research in Lung Cancer" (3:00 PM – 4:15 PM, Hall D2, East Building) will highlight just that — basic and clinical research in lung cancer that may have significant implications for treating patients. The topics will range from screening for lung cancer to individualizing therapy for patients with advanced non-small cell lung cancer (NSCLC).

Screening for lung cancer has not enjoyed the success observed with early screening for breast and colorectal cancer. The lack of success was partially attributed to the ineffectiveness of chest x-rays to identify early events. The National Lung Screening Trial (NLST) has showed that low-dose computed tomography (CT) might be better than chest x-rays to reduce overall mortality and lung cancer-specific mortality. However, Greg Kalemkerian, MD, of the University of Michigan Comprehensive Cancer Center, and a presenter at the session will argue that, "the 20% reduction in lung cancer-specific mortality using low-dose CT scans is encouraging, as is the 7% reduction in all-cause mortality. However, the risks and cost-effectiveness of CT screening require further assessment prior to its routine use for screening in clinical practice."

Clinical Benefits of Adjuvant Chemotherapy

On the front lines of research related to improving outcomes for patients with early-stage NSCLC, the Education Session will highlight data from a meta-analysis suggesting that adding chemotherapy after surgical resection with or without radiation therapy offers a survival advantage for patients.[1] This is good news for patients with early NSCLC. For patients with early-stage disease, 5-year survival rates lag behind those seen for other cancers such as breast and colon cancer. A limited meta-analysis in 2008 concluded that cisplatin-based chemotherapy following complete resection improved 5-year overall survival by 5.4%.[2]

In 2010, the NSCLC Meta-analysis Collaborative Group reported on two meta-analyses. Data from this report, which showed that 5-year overall survival improved by 4%, will be presented. According to Dr. Kalemkerian, "This report provides the best evidence that patients with stage IB and stage II/III benefit from platinum-based chemotherapy when done after surgery with or without radiation therapy." Although the advantage appears to be small, it translates to approximately 15,000 lives saved annually if the procedure is adopted. However, the advantage of chemotherapy is not clear for patients with stage IA disease or for patients who are older than age 70.

Disease Management at the Molecular Level

Treating NSCLC may now be ready for individualizing patient care based on the molecular features of NSCLC. Several molecular mutations have been identified in NSCLC. The biggest finding in basic science that will significantly affect clinical practice is based on the *ALK* translocation, which results in a fusion of two genes, *EML4* and *ALK*, and is seen in 4% of all patients with NSCLC. The EML4-ALK fusion protein was first shown to induce the malignant transformation of murine fibroblasts. Now, only 3 years after this report, a phase I/II study shows that approximately 60% of patients treated with crizotinib, a tyrosine kinase inhibitor (TKI) with activity against ALK, showed a high objective response rate.[3] Crizotinib will benefit only those patients with NSCLC that harbors the *ALK* translocation, which is more commonly seen in patients who were never-smokers or light smokers. Pasi Janne, MD, of the Dana-Farber Cancer Institute, who will also be presenting at the Education Session told *ASCO Daily News* that "this represents a paradigm shift in treating patients with NSCLC. Despite the rare occurrence of the *ALK* translocation, if you find the mutation, crizotinib may be a very good therapy for these patients."

Also at the molecular level, several studies reported in 2010 concluded that patients with NSCLC with activating mutations in the epidermal growth factor receptor *(EGFR)* gene should be treated with EFGR TKIs before chemotherapy. Currently, patients with advanced NSCLC are first treated with chemotherapy, and EGFR TKIs are reserved for treatment at relapse. Data will be presented at the session from trials such as the IPASS, OPTIMAL, and Japanese Study Group showing that patients with mutations in the *EGFR* gene have significantly higher chances for longer progression-free survival (PFS). The OPTIMAL study, for example, showed that an 84% PFS improvement was seen when patients with an *EGFR* mutation were treated with erlotinib compared with chemotherapy with gemcitabine and carboplatin. Although these studies were undertaken in Asian populations, data from a European study may suggest similar benefits for Caucasians. Dr. Kalemkerian told *ASCO Daily News* that "these observations suggest that molecular testing will be important in treating patients with advanced NSCLC. Although EGFR TKIs are not yet approved for the first-line treatment of patients with advanced NSCLC, most oncologists are using them for first-line treatment when molecular testing indicates a mutation." ●

References

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3. Kwak EL, B Y-J, Camidge R, et al. Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer. *N Engl J Med*. 2010;363(18):1693-1703.

SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

LEAD WITH EFFICACY.
LEAD WITH SUTENT.
(SUNITINIB MALATE)

SUTENT: PROVEN EFFICACY IN 1ST-LINE ADVANCED RCC VS IFNα*

MORE THAN DOUBLED MEDIAN PFS
- 11 months vs 5 months with IFNα (95% CI: 9.8, 11.7 and 3.8, 5.5, respectively; *P*<.000001)
- 58% reduced risk of progression or death (HR=0.42; 95% CI: 0.32, 0.54)

DEMONSTRATED 5-FOLD HIGHER ORR
- 39% vs 8% with IFNα (95% CI: 34.0, 44.3 and 5.7, 11.8, respectively; *P*<.000001) in the second analysis (June 2007)[1]
- 28% vs 5% with IFNα (95% CI: 23.0, 32.3 and 3.3, 8.1, respectively; *P*<.001) in the first analysis (November 2005)

ALSO ACHIEVED MORE THAN 2 YEARS' MEDIAN OS
- 26.4 months vs 21.8 months with IFNα (HR=0.82; 95% CI: 0.673, 1.001; *P*=.051)[1]

AN ESTABLISHED SAFETY PROFILE
- The most common adverse reactions (ARs) occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%)

ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Reference: 1. Data on file. Pfizer Inc, New York, NY.

Please see study description and brief summary, including boxed warning, on the following page.

*All data are from the large (N=750), phase 3, randomized, multicenter trial comparing SUTENT with IFNα in patients with treatment-naïve metastatic RCC.

Important safety information

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Left ventricular ejection fraction declines to below the lower limit of normal have occurred. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including torsades de pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension may occur. Monitor blood pressure and treat as needed.

Hemorrhagic events including tumor-related hemorrhage, some of which were fatal, have occurred. Perform serial complete blood counts (CBCs) and physical examinations.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of hypothyroidism or hyperthyroidism and treat per standard medical practice.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.

CBCs and serum chemistries should be performed at the beginning of each treatment cycle.

Dose adjustments are recommended when administered with CYP3A4 inhibitors or inducers.

The most common grade 3/4 ARs (occurring in ≥5% of SUTENT patients) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).

The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients receiving SUTENT vs IFNα) included lymphocytes (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%).

capsules
SUTENT®
sunitinib malate
The Proven Path

Results of the phase 3, randomized, multicenter, international trial. 750 treatment-naïve patients were treated with either 50-mg SUTENT once daily in cycles of 4 weeks on/2 weeks off, or 9 MIU IFNα 3 times per week (administered subcutaneously) until disease progression or study withdrawal. Primary endpoint was progression-free survival, and secondary endpoints included objective response rate by Response Evaluation Criteria in Solid Tumors, overall survival, and safety.

SUTENT® (SUNITINIB MALATE) CAPSULES, ORAL

Brief Summary of Prescribing Information

WARNING: HEPATOTOXICITY

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. *[See Warnings and Precautions]*

INDICATIONS AND USAGE: SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

DOSAGE AND ADMINISTRATION

Recommended Dose. The recommended dose of SUTENT for advanced RCC is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

Dose Modification. Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure.
Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.
Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

Pregnancy/Pregnancy Category D. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.
Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Left Ventricular Dysfunction. In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Cardiovascular events, including heart failure, myocardial disorders and cardiomyopathy, some of which were fatal, have been reported through post-marketing experience. More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or interferon-α (IFN-α).
In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.
Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

QT Interval Prolongation and Torsade de Pointes. SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.
SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered.

Hypertension. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.
Of patients receiving SUTENT for treatment-naïve RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naïve RCC patients (13%) on SUTENT compared to 1/360 patient (<1%) on IFN-α. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naive RCC study. Four treatment-naïve RCC patients, including one with malignant hypertension, discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 32/375 treatment-naïve RCC patients (9%) on SUTENT and 3/360 patients (1%) on IFN-α.

Hemorrhagic Events. Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naïve RCC, 140/375 patients (37%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in gastrointestinal stromal tumor (GIST) or RCC patients included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. Most events in RCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient.
Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.
Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Thyroid Dysfunction. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.
Hypothyroidism was reported as an adverse reaction in sixty-one patients (16%) on SUTENT in the treatment-naïve RCC study and in three patients (1%) in the IFN-α arm.
Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Adrenal Function. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.
Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies.
Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Laboratory Tests. CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 577 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of GIST or an active-controlled trial (n=375) for the treatment of RCC. The patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.
The most common adverse reactions (≥20%) in patients with GIST or RCC are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in *Warnings and Precautions*. Other adverse reactions occurring in RCC studies are described below.

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

Adverse Reactions in the Treatment-Naïve RCC Study. The as-treated patient population for the treatment-naive RCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 - 46.1) for SUTENT treatment and 4.1 months (range: 0.1 - 45.6) for IFN-α treatment. Dose interruptions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 24% for IFN-α. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 77% versus 55% of patients on SUTENT versus IFN-α, respectively. The following table compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α*

	SUTENT (n=375)		IFN-α (n=360)	
Adverse Reaction, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any	372 (99)	290 (77)	355 (99)	197 (55)
Constitutional				
Fatigue	233 (62)	55 (15)	202 (56)	54 (15)
Asthenia	96 (26)	42 (11)	81 (22)	21 (6)
Fever	84 (22)	3 (1)	134 (37)	1 (<1)
Weight decreased	60 (16)	1 (<1)	60 (17)	3 (1)
Chills	53 (14)	3 (1)	111 (31)	0 (0)
Chest Pain	50 (13)	7 (2)	24 (7)	3 (1)
Influenza like illness	18 (5)	0 (0)	54 (15)	1 (<1)
Gastrointestinal				
Diarrhea	246 (66)	37 (10)	76 (21)	1 (<1)
Nausea	216 (58)	21 (6)	147 (41)	6 (2)
Mucositis/stomatitis	178 (47)	13 (3)	19 (5)	2 (<1)
Vomiting	148 (39)	19 (5)	62 (17)	4 (1)
Dyspepsia	128 (34)	8 (2)	16 (4)	0 (0)
Abdominal pain[c]	113 (30)	20 (5)	42 (12)	5 (1)
Constipation	85 (23)	4 (1)	49 (14)	1 (<1)
Dry mouth	50 (13)	0 (0)	27 (7)	1 (<1)
GERD/reflux esophagitis	47 (12)	1 (<1)	3 (1)	0 (0)
Flatulence	52 (14)	0 (0)	8 (2)	0 (0)
Oral pain	54 (14)	2 (<1)	2 (1)	0 (0)
Glossodynia	40 (11)	0 (0)	2 (1)	0 (0)
Hemorrhoids	38 (10)	0 (0)	6 (2)	0 (0)
Cardiac				
Hypertension	127 (34)	50 (13)	13 (4)	1 (<1)
Edema, peripheral	91 (24)	7 (2)	17 (5)	2 (1)
Ejection fraction decreased	61 (16)	10 (3)	19 (5)	6 (2)
Dermatology				
Rash	109 (29)	6 (2)	39 (11)	1 (<1)
Hand-foot syndrome	108 (29)	32 (8)	3 (1)	0 (0)
Skin discoloration/ yellow skin	94 (25)	1 (<1)	0 (0)	0 (0)
Dry skin	85 (23)	1 (<1)	26 (7)	0 (0)
Hair color changes	75 (20)	0 (0)	1 (<1)	0 (0)
Alopecia	51 (14)	0 (0)	34 (9)	0 (0)
Erythema	46 (12)	2 (<1)	5 (1)	0 (0)
Pruritus	44 (12)	1 (<1)	24 (7)	1 (<1)
Neurology				
Altered taste[d]	178 (47)	1 (<1)	54 (15)	0 (0)
Headache	86 (23)	4 (1)	69 (19)	0 (0)
Dizziness	43 (11)	2 (<1)	50 (14)	2 (1)
Musculoskeletal				
Back pain	105 (28)	19 (5)	52 (14)	7 (2)
Arthralgia	111 (30)	10 (3)	69 (19)	4 (1)
Pain in extremity/ limb discomfort	150 (40)	19 (5)	107 (30)	7 (2)
Endocrine				
Hypothyroidism	61 (16)	6 (2)	3 (1)	0 (0)
Respiratory				
Cough	100 (27)	3 (1)	51 (14)	1 (<1)
Dyspnea	99 (26)	24 (6)	71 (20)	15 (4)
Nasopharyngitis	54 (14)	0 (0)	8 (2)	0 (0)
Oropharyngeal Pain	51 (14)	2 (<1)	9 (2)	0 (0)
Upper respiratory tract infection	43 (11)	2 (<1)	9 (2)	0 (0)
Metabolism/Nutrition				
Anorexia[e]	182 (48)	11 (3)	153 (42)	7 (2)
Hemorrhage/Bleeding				
Bleeding, all sites	140 (37)	16 (4)[f]	35 (10)	3 (1)
Psychiatric				
Insomnia	57 (15)	3 (<1)	37 (10)	0 (0)
Depression[g]	40 (11)	0 (0)	51 (14)	5 (1)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), dyspnea (<1%), asthenia (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%)
[b]Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%), abdominal pain (<1%), and depression (<1%)
[c]Includes flank pain
[d]Includes ageusia, hypogeusia and dysgeusia
[e]Includes decreased appetite
[f]Includes one patient with Grade 5 gastric hemorrhage
[g]Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented below.

Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve RCC Patients Who Received SUTENT or IFN-α

	SUTENT (n=375)		IFN-α (n=360)	
Laboratory Parameter, n (%)	**All Grades***	**Grade 3/4*[a]**	**All Grades***	**Grade 3/4*[b]**
Gastrointestinal				
AST	211 (56)	6 (2)	136 (38)	8 (2)
ALT	192 (51)	10 (3)	144 (40)	9 (2)
Lipase	211 (56)	69 (18)	165 (46)	29 (8)
Alkaline phosphatase	171 (46)	7 (2)	132 (37)	6 (2)
Amylase	130 (35)	22 (6)	114 (32)	12 (3)
Total bilirubin	75 (20)	3 (1)	8 (2)	0 (0)
Indirect bilirubin	49 (13)	4 (1)	3 (1)	0 (0)
Renal/Metabolic				
Creatinine	262 (70)	2 (<1)	183 (51)	1 (<1)
Creatine kinase	183 (49)	9 (2)	40 (11)	4 (1)
Uric acid	173 (46)	54 (14)	119 (33)	29 (8)
Calcium decreased	156 (42)	4 (1)	145 (40)	4 (1)
Phosphorus	116 (31)	22 (6)	87 (24)	23 (6)
Albumin	106 (28)	4 (1)	72 (20)	0 (0)
Glucose increased	86 (23)	21 (6)	55 (15)	22 (6)
Sodium decreased	75 (20)	31 (8)	55 (15)	13 (4)
Glucose decreased	65 (17)	0 (0)	43 (12)	1 (<1)
Potassium increased	61 (16)	13 (3)	61 (17)	15 (4)
Calcium increased	50 (13)	2 (<1)	35 (10)	5 (1)
Potassium decreased	49 (13)	3 (1)	7 (2)	1 (<1)
Sodium increased	48 (13)	0 (0)	38 (10)	0 (0)
Hematology				
Neutrophils	289 (77)	65 (17)	178 (49)	31 (9)
Hemoglobin	298 (79)	29 (8)	250 (69)	18 (5)
Platelets	255 (68)	35 (9)	85 (24)	2 (1)
Lymphocytes	256 (68)	66 (18)	245 (68)	93 (26)
Leukocytes	293 (78)	29 (8)	202 (56)	8 (2)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (14%), lipase (3%), neutrophils (2%), lymphocytes (2%), hemoglobin (2%), platelets (1%), amylase (1%), ALT (<1%), creatine kinase (<1%), creatinine (<1%), glucose increased (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), and sodium decreased (<1%)
[b]Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lymphocytes (2%), lipase (1%), neutrophils (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%) and hemoglobin (<1%)

Venous Thromboembolic Events. Thirteen (3%) patients receiving SUTENT for treatment-naïve RCC had venous thromboembolic events reported. Seven (2%) of these patients had pulmonary embolism, one was Grade 2 and six were Grade 4, and six (2%) patients had DVT, including three Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve RCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, all Grade 4.

Reversible Posterior Leukoencephalopathy Syndrome. There have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Pancreatic and Hepatic Function. If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve RCC compared to 1 (<1%) patient receiving IFN-α. Hepatotoxicity was observed in patients receiving SUTENT *[See Boxed Warning and Warnings and Precautions]*.

Post-marketing Experience. The following adverse reactions have been identified during post-approval use of SUTENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. Cases of myopathy and/or rhabdomyolysis with or without acute renal failure, in some cases with fatal outcome, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice. Thrombotic microangiopathy has been reported in patients on SUTENT. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician. Cases of fatal hemorrhage associated with thrombocytopenia have been reported. Pulmonary embolism, in some cases with fatal outcome, has been reported. Cases of renal impairment and/or failure, in some cases with fatal outcome, have been reported. Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome. Hypersensitivity reactions, including angioedema, have been reported. Cases of fistula formation, sometimes associated with tumor necrosis and/or regression, in some cases with fatal outcome, have been reported.

DRUG INTERACTIONS/CYP3A4 Inhibitors. Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors.

CYP3A4 Inducers. CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers.

In Vitro Studies of CYP Inhibition and Induction. *In vitro* studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

USE IN SPECIFIC POPULATIONS

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

Nursing Mothers. Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether sunitinib or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, 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 *[see Nonclinical Toxicology]*.

Pediatric Use. The safety and efficacy of SUTENT in pediatric patients have not been established.
Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

Geriatric Use. Of 825 GIST and MRCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

Hepatic Impairment. No dose adjustment is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. A few cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of SUTENT in an attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although definitive carcinogenicity studies with sunitinib have not been completed, carcinoma and hyperplasia of the Brunner's gland of the duodenum have been observed at the highest dose tested in H2ras transgenic mice administered doses of 0, 10, 25, 75, or 200 mg/kg/day for 28 days. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.
Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.
Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was approximately 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10 mg/kg/day dose produced a mean AUC that was approximately 25.8 times the AUC in patients administered the RDD).

PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin Effects. Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

Other Common Events. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Concomitant Medications. Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Drug Interactions]*.

Rx only Revised: July 2010

Education Session: Future Role of Antiangiogenic Drugs in Breast Cancer Treatment Examined

In December, the U.S. Food and Drug Administration (FDA) announced that it was beginning the process of removing the breast cancer indication from the label of bevacizumab, an antiangiogenic drug that was granted accelerated approval for the treatment of metastatic breast cancer in February 2008. The regulatory agency said the decision was based on the review of data from four clinical trials that indicated that the drug did not prolong overall survival and did not sufficiently delay progression of the disease to outweigh known adverse effects. This decision, along with other high-profile failures or modest results of antiangogenic drugs for the treatment of breast cancer, has left the use of these therapies for the treatment of breast cancer in question. Tomorrow's Education Session, "Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?", will address the current controversy surrounding the use of angiogenesis drugs to treat breast cancer and will help to clarify what could be the limitations of the current generation of antiangiogenic drugs for the treatment of the disease. The session will be held 8:00 AM – 9:15 AM, Room E354a, East Building.

Maura Dickler, MD, of Memorial Sloan-Kettering Cancer Center, will serve as Chair of the Session and will consider the current clinical data using antiangiogenic therapy. She will focus on potential lessons learned from these trials for both oncologists and basic scientists, as well as on how they can put these data into context in order to make the best decision for patients as the oncology community grapples with the future of these agents in breast cancer.

"We are hoping to step back and try to learn what went awry from these seemingly well-designed randomized trials," Dr. Dickler said in an interview with *ASCO Daily News*. "I will briefly review the clinical data, evaluate whether hypothesized mechanisms of resistance are supported by clinical data, and discuss potential factors that may have affected the lack of benefit in overall survival."

Bevacizumab was granted accelerated approval by the FDA based on the results of the E2100 trial. This trial examined the use of the drug in combination with weekly paclitaxel in chemotherapy-naive patients with HER2-negative metastatic breast cancer. Patients assigned the drug combination had a 4.5-month improvement in progression-free survival compared with patients assigned weekly paclitaxel alone; however, there was no increase in overall survival on the combination.

Bevacizumab's approval was controversial because it was based on data from clinical trials that showed improvements in progression-free survival, in contrast to overall survival, the gold-standard for most drug approvals.

Controversial Decision

Bevacizumab's approval was controversial because it was based on data from clinical trials that showed improvements in progression-free survival, in contrast to overall survival, the gold-standard for most drug approvals. Also controversial was the FDA's decision to grant the accelerated approval despite a 5-4 recommendation by the Oncologic Drugs Advisory Committee against its approval.

Accelerated approval requires a drug's manufacturer to submit data from additional clinical trials to support the drug's receipt of full approval status. According to the FDA, data from the AVADO and RIBBON-1 trials failed to further support bevacizumab's approval for breast cancer treatment. In the double-blind, placebo-controlled AVADO trial, patients assigned the combination of bevacizumab and docetaxel had a less than 1 month improvement in progression-free survival. In the RIBBON1 trial, patients assigned a combination of bevacizumab and taxane/anthracycline-based chemotherapy had a 1.2-month increase in progression-free survival. Neither trial indicated that combination treatment improved overall survival. In addition, bevacizumab was associated with serious adverse effects such as hypertension, febrile neutropenia, and bleeding.

Robert S. Kerbel, PhD, of the Sunnybrook Research Institute/Odette Cancer Center, Canada, who has worked in the field of antiangiogenic therapy for the past 20 years, will discuss some of the scientific issues and problems about the role of angiogenesis in breast cancer, as well as how the field may need to move forward to improve the effect of antiangiogenic drug-based therapies for the treatment of with breast cancer, especially those with metastatic disease.

Dr. Kerbel also will discuss the issue of resistance to antiangiogenic drugs that may develop very quickly, especially in patients with breast cancer.

"It is possible that antiangiogenic drugs may induce an initial benefit by slowing down tumor growth, but that in doing so, they may actually alter the natural history of the disease in such as way as to make the cancer a bit more aggressive later on, so that the overall net benefit is compromised, or even lost in the case of overall survival," Dr. Kerbel told *ASCO Daily News*.

If that is the case, other approaches to the use of antiangiogenic drugs, such as low-dose metronomic chemotherapy, or more powerful preclinical trials using improved animal models such as the ones that involve treating established metastatic disease might help to better define how and if this class of drugs can be used effectively in the treatment of breast cancer.

Examining the Data

Daniel Sargent, PhD, of the Mayo Clinic, Rochester, will focus on statistical issues related to the choice of a primary endpoint in metastatic disease. Specifically, he will discuss the pros and cons of the frequently used endpoints, such as overall survival and progression-free survival.

"It is a worthy question to ask [whether] we need overall survival improvement for our drugs to be valuable to our patients," Dr. Dickler said in an interview with *ASCO Daily News*. "Is progression-free survival enough? And, if overall survival is what we are hoping for, why are we designing studies that are not powered to answer that question?"

Overall, the Education Session will help attendees put all available information into perspective, as the status of bevacizumab remains in flux in the United States (bevacizumab is still approved in Europe). Although the FDA made the decision to remove the breast cancer indication from the drug label in December, it has had no immediate effect. The drug's manufacturer may still be granted a trial to appeal the FDA's decision. ●

ASCO's Medical Oncology In-training Exam Helps Evaluate Graduate Training Programs

Fellows and training program directors can always benefit from tools to help evaluate their progress within a fellowship program. ASCO offers the Medical Oncology In-Training Examination (MedOncITE) as a tool for training program directors and fellows, nationally and internationally, to assess their knowledge and evaluate their program against others.

ASCO's MedOncITE assesses trainees' knowledge of a clinical oncology subspecialty, establishes consistency in educational standards across training programs, identifies areas of strength and weakness in individual programs, and stimulates intraprogrammatic reading and discussion.

The In-training Exam uses the American Board of Internal Medicine's Oncology Board Exam as a starting point to develop the questions. The exam has nine content areas that focus on specific diseases, basic science principles, and legal or ethical issues.

The Web-based exam is 200 questions and lasts 6 hours. For program directors, the exam helps establish consistency in educational standards across training programs and serves as a benchmark and tool to improve training. Results are compared with national outcomes in the score reports.

Katherine Reeder-Hayes, a member of ASCO's Career Development Subcommittee, sat for the exam in 2009 as part of her fellowship program. She told *ASCO Daily News* many of her peers used the results "to identify weaknesses so that they can concentrate on those areas when preparing for their board exams."

The exam is not pass/fail but is designed to be a teaching tool. Taking it cold, without studying, would provide the best snapshot of the training program. The percentage of questions answered correctly will be given, and teaching points are provided for items answered incorrectly.

Jae Park, MD, said that the exam can be taken to assess a trainee's knowledge at baseline, but he said some test takers may benefit from a small amount of study in areas with which they are least familiar.

"I think you get more out of the test by preparing a little, especially if it's been a while since you've taken care of patients with a particular disease type," he said in an interview with *ASCO Daily News*. "I used [*ASCO-SEP®: Medical Oncology Self-evaluation Program*] as my study guide. The questions at the end of *ASCO-SEP* helped me get a sense of the types of questions that may be asked in the exam."

In 2010, the exam was piloted internationally in Ireland. With the success of the pilot, the 2011 exam was opened to all international programs. Three international programs registered and about 20 program directors sat for the exam alongside their fellows in 2011.

The exam costs $250 per fellow and $50 for program directors.

The next exam will be held February 28, 2012 and February 29, 2012. Registration opens in November 2011. For more information and registration, visit www.asco.org/medoncite. ●

CORG

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Although the areas for improvement were based on the *JCO* Statement, in general, practices were unlimited in the kinds of activities they could propose and were not required to have already achieved any of the exemplary attributes. A practice interested in increasing clinical trials awareness could use the funds for marketing pieces designed to reach an underrepresented demographic, other investigators, or the general community. A practice concerned with ensuring the formal maintenance of high educational standards could earmark part of the grant budget to keep the certifications of clinical research assistants current.

As part of the grant terms, practices are expected to submit 6- and 12-month reports detailing and evaluating the expenditures and progress of their activities. A cumulative 18-month report will ask questions about the practices' grant experience and the effect of the grant on their practice.

For the latest information on CORG, visit the Cancer Professionals section on the Foundation's website at www.conquercancerfoundation.org. The 2011 CORG is supported by Novartis Oncology. ●

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