

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 tri-

als 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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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

"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

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*.

"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

See *Immunotherapy*, Page 8B

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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

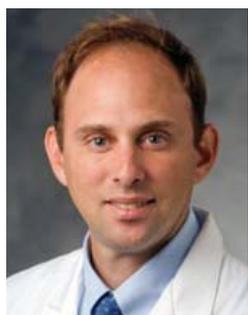
EXPERT EDITORIAL

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.

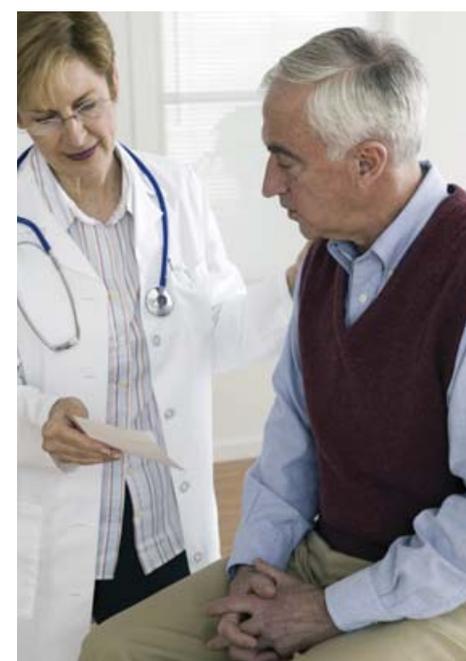
Increasingly, a favored method to "bend the curve" among insurance providers is to shift more of the costs of care to patients in the form of higher premiums, co-pays, and deductibles. Although the immediate effect of such policies is to shift costs to patients, one of the goals is to make the patient, 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 recommendation⁴

- 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 increases¹

- 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 dosing¹

- 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.



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 ($\geq 5\%$) 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: GlaxoSmithKline; 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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 GlaxoSmithKline
Oncology

Clinical Trials

Continued from Page 1B

Century: Reinvigorating the NCI Cooperative Group Program.²¹ 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 un-

derstanding 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

BRIEF SUMMARY

VOTRIENT™ (pazopanib) tablets

The following is a brief summary only; see full prescribing information for complete product 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 (5.1).]

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing: The recommended dose of VOTRIENT is 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal) [see Clinical Pharmacology (12.3) of full prescribing information]. The dose of VOTRIENT should not exceed 800 mg. Do not crush tablets due to the potential for increased rate of absorption which may affect systemic exposure. [See Clinical Pharmacology (12.3) of full prescribing information.] If a dose is missed, it should not be taken if it is less than 12 hours until the next dose. **2.2 Dose Modification Guidelines:** Initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200 mg steps based on individual tolerability. The dose of VOTRIENT should not exceed 800 mg. **Hepatic Impairment:** The dosage of VOTRIENT in patients with moderate hepatic impairment should be reduced to 200 mg per day. There are no data in patients with severe hepatic impairment; therefore, use of VOTRIENT is not recommended in these patients. [See Use in Specific Populations (8.6).] **Concomitant Strong CYP3A4 Inhibitors:** The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations and should be avoided. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of VOTRIENT to 400 mg. Further dose reductions may be needed if adverse effects occur during therapy. This dose is predicted to adjust the pazopanib AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. [See Drug Interactions (7.1).] **Concomitant Strong CYP3A4 Inducer:** The concomitant use of strong CYP3A4 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided. VOTRIENT should not be used in patients who can not avoid chronic use of strong CYP3A4 inducers. [See Drug Interactions (7.1).]

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Effects: In clinical trials with VOTRIENT, hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, was observed [see Adverse Reactions (6.1)]. This hepatotoxicity can be severe and fatal. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Across all monotherapy studies with VOTRIENT, ALT >3 X upper limit of normal (ULN) was reported in 138/977 (14%) and ALT >8 X ULN was reported in 40/977 (4%) of patients who received VOTRIENT. Concurrent elevations in ALT >3 X ULN and bilirubin >2 X ULN regardless of alkaline phosphatase levels were detected in 13/977 (1%) of patients. Four of the 13 patients had no other explanation for these elevations. Two of 977 (0.2%) patients died with disease progression and hepatic failure. 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. Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT return to Grade 1 or baseline. Patients with isolated ALT elevations of >8 X ULN should have VOTRIENT interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with VOTRIENT is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose of no more than 400 mg once daily and measure serum liver tests weekly for 8 weeks [see Dosage and Administration (2.2)]. Following reintroduction of VOTRIENT, if ALT elevations >3 X ULN recur, then VOTRIENT should be permanently discontinued. If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome [see Clinical Pharmacology (12.5) of full prescribing information]. Patients with only a mild indirect hyperbilirubinemia, known Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations. The safety of VOTRIENT in patients with pre-existing severe hepatic impairment, defined as total bilirubin >3 X ULN with any level of ALT, is unknown. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. [See Dosage and Administration (2.2) and Use in Specific Populations (8.6).]

5.2 QT Prolongation and Torsades de Pointes: In clinical RCC studies of VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 11/558 (<2%) of patients. Torsades de pointes occurred in 2/977 (<1%) of patients who received VOTRIENT in the monotherapy studies. In the randomized clinical trial, 3 of the 290 patients receiving VOTRIENT had post-baseline values between 500 to 549 msec. None of the 145 patients receiving placebo had post-baseline QTc values ≥500 msec. VOTRIENT should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. When using VOTRIENT, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g., calcium, magnesium, potassium) within the normal range should be performed. **5.3 Hemorrhagic Events:** In clinical RCC studies of VOTRIENT, hemorrhagic events have been reported [all Grades (16%) and Grades 3 to 5 (2%)]. Fatal hemorrhage has occurred in 5/586 (0.9%) [see Adverse Reactions (6.1)]. 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. **5.4 Arterial Thrombotic Events:** 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. Fatal events have been observed in 2/586 (0.3%). In the randomized study, these events were observed more frequently with VOTRIENT compared to placebo [see Adverse Reactions (6.1)]. VOTRIENT should be used with caution in patients who are at increased risk for these events or who have had a history of these events. VOTRIENT has not been studied in patients who have had an event within the previous 6 months and should not be used in those patients. **5.5 Gastrointestinal Perforation and Fistula:** In clinical RCC studies of VOTRIENT, gastrointestinal perforation or fistula has been reported in 5 patients (0.9%). Fatal perforation events have occurred in 2/586 (0.3%). Monitor for symptoms of gastrointestinal perforation or fistula. **5.6 Hypertension:** Blood pressure should be well-controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy. Hypertension (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mm Hg) 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). [See Adverse Reactions (6.1).] In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced [see Dosage and Administration (2.2)]. VOTRIENT should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT. **5.7 Wound Healing:** No formal studies on the effect of VOTRIENT on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as pazopanib may impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical judgment of adequate wound healing. VOTRIENT should be discontinued in patients with wound dehiscence. **5.8 Hypothyroidism:** In clinical RCC studies of VOTRIENT, hypothyroidism reported as an adverse reaction in 26/586 (4%) [see Adverse Reactions (6.1)]. Proactive monitoring of thyroid function tests is recommended. **5.9 Proteinuria:** In clinical RCC studies with VOTRIENT, proteinuria has been reported in 44/586 (8%) [Grade 3, 5/586 (<1%) and Grade 4, 1/586 (<1%)] [see Adverse Reactions (6.1)]. Baseline and periodic urinalysis during treatment is recommended. VOTRIENT should be discontinued if the patient develops Grade 4 proteinuria. **5.10 Pregnancy:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, VOTRIENT is expected to result in adverse reproductive effects. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking VOTRIENT. [See Use in Specific Populations (8.1).]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience: 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. The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy studies which included 586 patients with RCC. With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly observed adverse reactions (≥20%) in the 586 patients were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled study [see Clinical Studies (14) of full prescribing information]. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of patients on VOTRIENT were dose reduced.

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 implemen-

tation 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

Adverse Reactions	VOTRIENT (N = 290)			Placebo (N = 145)		
	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

Parameters	VOTRIENT (N = 290)			Placebo (N = 145)		
	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-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. ●

reduced fetal body weight, and pre- and post-implantation embryoletality in rats administered pazopanib at doses ≥ 3 mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses ≥ 30 mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses ≥ 100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses ≥ 3 mg/kg/day (AUC not calculated). **8.3 Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VOTRIENT, 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. **8.4 Pediatric Use:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. In repeat-dose toxicology studies in rats including 4-week, 13-week, and 26-week administration, toxicities in bone, teeth, and nail beds were observed at doses ≥ 3 mg/kg/day (approximately 0.07 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13- and 26-week studies with rats. Body weight loss and morbidity were observed at these doses. Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle, broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in rats at ≥ 30 mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks. **8.5 Geriatric Use:** In clinical trials with VOTRIENT for the treatment of RCC, 196 subjects (33%) were aged ≥ 65 years, and 34 subjects (6%) were aged >75 years. No overall differences in safety or effectiveness of VOTRIENT were observed between these subjects and younger subjects. However, patients >60 years of age may be at greater risk for an ALT >3 X ULN. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Hepatic Impairment:** The safety and pharmacokinetics of pazopanib in patients with hepatic impairment have not been fully established. In clinical studies for VOTRIENT, patients with total bilirubin ≤ 1.5 X ULN and AST and ALT ≤ 2 X ULN were included [see *Warnings and Precautions (5.1)*]. An interim analysis of data from 12 patients with normal hepatic function and 9 with moderate hepatic impairment showed that the maximum tolerated dose in patients with moderate hepatic impairment was 200 mg per day [see *Clinical Pharmacology (12.3) of full prescribing information*]. There are no data on patients with severe hepatic impairment [see *Dosage and Administration (2.2)*]. **8.7 Renal Impairment:** Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance ≥ 30 mL/min) were included in clinical studies for VOTRIENT. There are no clinical or pharmacokinetic data in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is unlikely to significantly affect the pharmacokinetics of pazopanib since $<4\%$ of a radiolabeled oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408 subjects with various cancers, creatinine clearance (30-150 mL/min) did not influence clearance of pazopanib. Therefore, renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary.

10 OVERDOSAGE

Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2,000 mg daily and 1,000 mg daily, respectively. Treatment of overdose with VOTRIENT should consist of general supportive measures. There is no specific antidote for overdosage of VOTRIENT. Hemodialysis is not expected to enhance the elimination of VOTRIENT because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenicity studies with pazopanib have not been conducted. However, in a 13-week study in mice, proliferative lesions in the liver including eosinophilic foci in 2 females and a single case of adenoma in another female was observed at doses of 1,000 mg/kg/day (approximately 2.5 times the human clinical exposure based on AUC). Pazopanib did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the in vitro cytogenetic assay using primary human lymphocytes and in the in vivo rat micronucleus assay. Pazopanib may impair fertility in humans. In female rats, reduced fertility including increased pre-implantation loss and early resorptions were noted at dosages ≥ 30 mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC). Total litter resorption was seen at 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC). Post-implantation loss, embryoletality, and decreased fetal body weight were noted in females administered doses ≥ 10 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC). Decreased corpora lutea and increased cysts were noted in mice given ≥ 100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given ≥ 300 mg/kg/day for

26 weeks (approximately 1.3 and 0.85 times the human clinical exposure based on AUC, respectively). Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to 34 weeks (approximately 0.4 times the human clinical exposure based on AUC). Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates and testicular sperm concentrations at doses ≥ 3 mg/kg/day, epididymal sperm concentrations at doses ≥ 30 mg/kg/day, and sperm motility at ≥ 100 mg/kg/day following 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and epididymal weights at doses of ≥ 30 mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC); atrophy and degeneration of the testes with aspermia, hypospermia and cribriform change in the epididymis was also observed at this dose in the 6-month toxicity studies in male rats.

17 PATIENT COUNSELING INFORMATION

See Medication Guide. The Medication Guide is contained in a separate leaflet that accompanies the product. However, inform patients of the following:

- Therapy with VOTRIENT may result in hepatobiliary laboratory abnormalities. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of VOTRIENT and at least once every 4 weeks for the first 4 months of treatment or as clinically indicated. Inform patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away.
 - yellowing of the skin or the whites of the eyes (jaundice),
 - unusual darkening of the urine,
 - unusual tiredness,
 - right upper stomach area pain.
- Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported with VOTRIENT. Patients should be advised how to manage diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Patients should be advised to inform their healthcare providers of all concomitant medications, vitamins, or dietary and herbal supplements.
- Patients should be advised that depigmentation of the hair or skin may occur during treatment with VOTRIENT.
- Patients should be advised to take VOTRIENT without food (at least 1 hour before or 2 hours after a meal).

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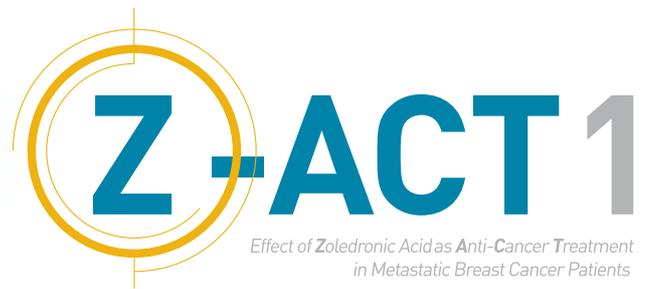


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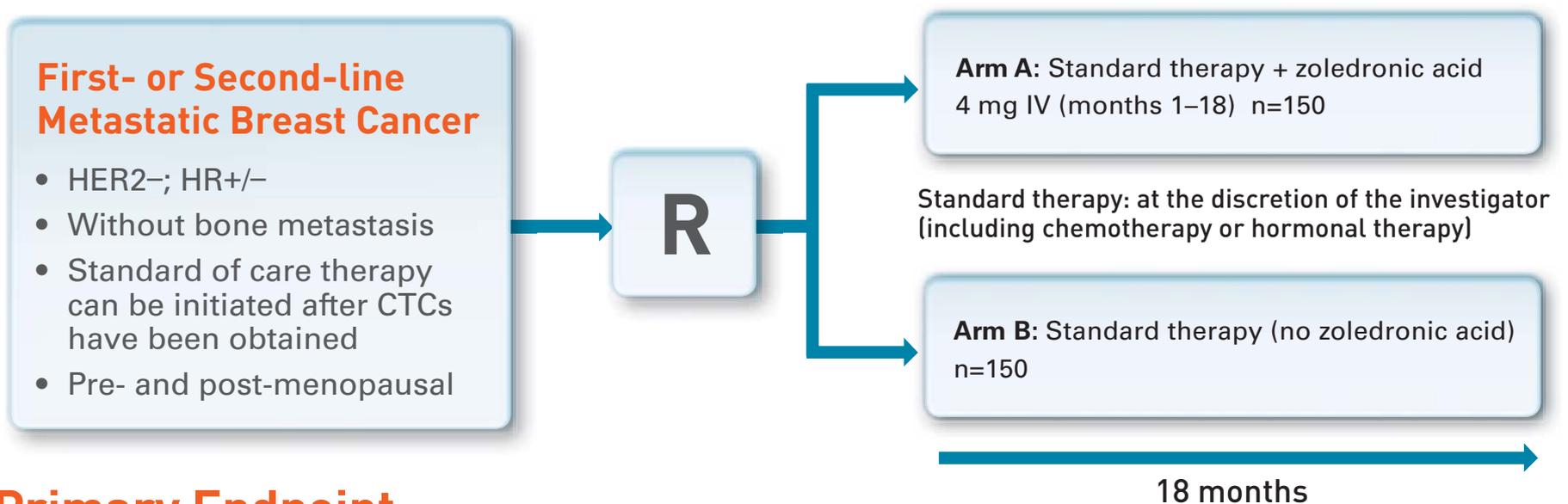
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Study Description

A multicenter, open-label, randomized trial to evaluate the potential anti-cancer effects of zoledronic acid and circulating tumor cell (CTC) measurements in patients with HER2-negative metastatic breast cancer (MBC) without bone metastasis. (Clinical Trial Protocol CZOL446EUS147)

Study Design



Primary Endpoint

Progression-free survival (PFS)

Secondary Endpoint

- Proportion of patients with CTCs ≥ 5 per 7.5 mL of peripheral blood at 1, 2, 4 and 6 months
- Time to progression (TTP)
- Time to development of bone metastasis
- Overall survival (OS)
- Changes from baseline in urinary NTX and its correlation with CTCs
- Change from baseline in Functional Assessment of Cancer Therapy-Bone Pain total score

For more information:

- Call Novartis Oncology at 1-800-340-6843
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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



Blase N. Polite, MD, MPP

with which we apply these tools.

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,

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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 treat-

ing AYA patients with cancer. ASCO and its philanthropic arm, the Conquer Cancer Foundation (formerly known as The ASCO Cancer Foundation®), teamed up with LIVESTRONG® 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 LIVESTRONG 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 spe-



cifically 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

Inability to pay for prescription medications can be a barrier to adherence and must be assessed in clinic.

— Jeffrey M. Peppercorn, MD, MPH

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.

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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(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

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ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

IMPORTANT SAFETY INFORMATION

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/mm³. 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

Albumin (human):

- 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/mm³
- 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/mm³ and platelets recover to >100,000 cells/mm³
- In the case of severe neutropenia (<500 cells/mm³ 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/arthritis (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 colleagues¹⁵ 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-

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Rx Only

(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

Brief Summary of Full Prescribing Information.

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/mm³. 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.

INDICATION:

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS:

ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm³.

WARNINGS:

Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE should not be administered to patients with baseline neutrophil counts of < 1,500 cells/mm³. Frequent monitoring of blood counts should be instituted during ABRAXANE treatment. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³.

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. Administration of paclitaxel protein-bound particles to rats on gestation days 7 to 17 at doses of 6 mg/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE®. 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 (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility** for discussion of effects of ABRAXANE exposure on male fertility and embryonic viability).

Albumin (Human)

ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS:

Drug Interactions

No drug interaction studies have been conducted with ABRAXANE.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4 (see **CLINICAL PHARMACOLOGY**).

Hematology

ABRAXANE® therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of myelotoxicity, 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/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see **DOSAGE AND ADMINISTRATION**).

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 (see **DOSAGE AND ADMINISTRATION**).

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. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m² on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m² basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m²/week in this study (approximately

1 to 5% of the daily maximum recommended human exposure on a mg/m² basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m² and dogs administered 175 mg/m² (see **WARNINGS**).

Pregnancy: Teratogenic Effects: Pregnancy Category D: (See **WARNINGS** section).

Nursing Mothers

It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. 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.

Pediatric Use

The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatric Use

Of the 229 patients in the randomized study who received ABRAXANE, 11% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE.

Ability to Drive and Use Machines

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

ADVERSE REACTIONS:

The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE® or paclitaxel injection for the treatment of metastatic breast cancer.

Table 3: Frequency of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE® 260/30min ^a (n=229)	Paclitaxel Injection 175/3h ^{c,d} (n=225)
Bone Marrow		
Neutropenia < 2.0 x 10 ⁹ /L < 0.5 x 10 ⁹ /L	80 9	82 22
Thrombocytopenia < 100 x 10 ⁹ /L < 50 x 10 ⁹ /L	2 <1	3 <1
Anemia < 11 g/dL < 8 g/dL	33 1	25 <1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction^e		
All	4	12
Severe ^f	0	2
Cardiovascular		
Vital Sign Changes ^g		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events ^f	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms ^f	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms ^f	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms ^f	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms ^f	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms ^f	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms ^f	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms ^f	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms ^f	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31

(continued)

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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Table 3: Frequency of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule, Continued

	Percent of Patients	
	ABRAXANE® 260/30min ^b (n=229)	Paclitaxel Injection 175/3h ^{c,d} (n=225)
Hepatic (Patients with Normal Baseline)		
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

^a Based on worst grade. ^b ABRAXANE dose in mg/m²/duration in minutes. ^c paclitaxel injection dose in mg/m²/duration in hours. ^d paclitaxel injection pts received premedication. ^e Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing. ^f Severe events are defined as at least grade 3 toxicity. ^g During study drug dosing.

Myelosuppression and sensory neuropathy were dose related.

Adverse Event Experiences by Body System

Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent ABRAXANE® in the randomized controlled trial. The frequency and severity of important adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hematologic

Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm³ (Grade 4) in 9% of the patients treated with a dose of 260 mg/m² compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m².

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m² given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE arm and 1% of patients in the paclitaxel injection arm.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <11 g/dL) was observed in 33% of patients treated with ABRAXANE in the randomized trial and was severe (Hb <8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Rare reports of pancytopenia have been observed in clinical trials and during postmarketing surveillance of ABRAXANE.

Hypersensitivity Reactions (HSRs)

In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of ABRAXANE® in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

During postmarketing surveillance, rare occurrences of severe hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be rechallenged with the drug.

Cardiovascular

Hypotension, during the 30-minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

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.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

During postmarketing surveillance, rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory

Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE in the randomized trial. Rare reports (<1%) of pneumothorax were reported after treatment with ABRAXANE. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE with concurrent radiotherapy.

Neurologic

The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE®. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 2) was observed in either arm of the controlled trial.

Cranial nerve palsies and vocal cord paresis have been reported during postmarketing surveillance of ABRAXANE. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m²). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia

Forty-four percent of patients treated in the randomized trial experienced arthralgia/ myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE® administration, and resolved within a few days.

Hepatic

Among patients with normal baseline liver function treated with ABRAXANE in the randomized trial, 7%,

36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Renal
Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI)
Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of neutropenic enterocolitis (typhilitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
Injection site reactions have occurred infrequently with ABRAXANE and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia

Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE® in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events

Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema. In clinical trials and during postmarketing surveillance of ABRAXANE, dehydration was common and pyrexia was very common.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment: skin abnormalities related to radiation recall as well as reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation. As part of the continuing surveillance of ABRAXANE, skin reactions including generalized or maculo-papular rash, erythema, and pruritus have been observed. Additionally, there have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

Accidental Exposure

No reports of accidental exposure to ABRAXANE® have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

OVERDOSAGE:

There is no known antidote for ABRAXANE overdose. The primary anticipated complications of overdose would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

DOSE AND ADMINISTRATION:

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment treated with ABRAXANE may be at increased risk of toxicities known to paclitaxel. Patients should not receive ABRAXANE if AST > 10 x ULN or bilirubin > 5.0 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 4. The dose of ABRAXANE can be increased up to 200 mg/m² in patients with severe hepatic impairment in subsequent cycles based on individual tolerance. Patients should be monitored closely. (See **CLINICAL PHARMACOLOGY: Hepatic Impairment and PRECAUTIONS: Hepatic Impairment**)

Table 4: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels	Bilirubin Levels	ABRAXANE ^a
Mild	<10 x ULN	>ULN to ≤ 1.25 x ULN	260 mg/m ²
Moderate	<10 x ULN	AND 1.26 to 2.0 x ULN	200 mg/m ²
Severe	<10 x ULN	2.01 to 5.0 x ULN	130 mg/m ² ^b
	> 10 x ULN	OR > 5.0 x ULN	not eligible

^a Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.

^b A dose increase to 200 mg/m² in subsequent courses should be considered based on individual tolerance.

Dose Reduction

Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m² for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m². For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

HOW SUPPLIED:

Product No. 103450

NDC No. 68817-134-50 100 mg of paclitaxel in a single use vial, individually packaged in a carton.

Storage

Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

This Brief Summary is based on the ABRAXANE Full Prescribing Information Revised: March 2010



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U.S. Patent Numbers: 5,439,686; 5,498,421; 6,096,331; 6,506,405; 6,537,579; 6,749,868; 6,753,006



NOW RECRUITING PHASE 3 NON-SMALL-CELL LUNG CANCER (NSCLC)

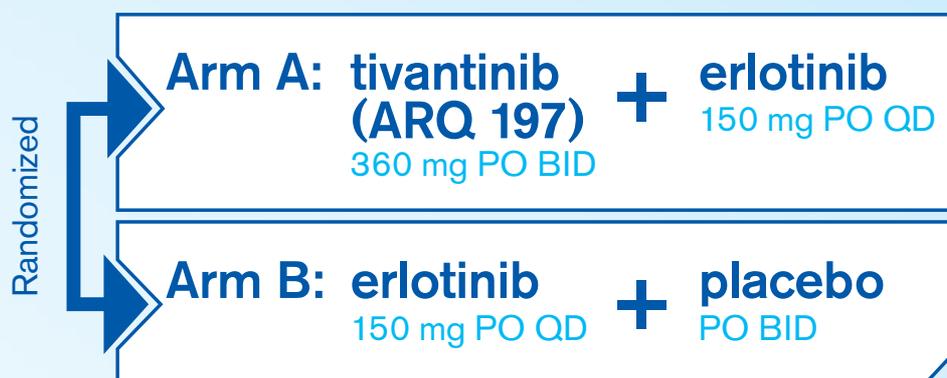
Investigating **c-MET** Inhibition

A global phase 3, randomized, double-blind, placebo-controlled study of tivantinib (ARQ 197) plus erlotinib versus placebo plus erlotinib in previously treated subjects with locally advanced or metastatic, non-squamous NSCLC

NCT01244191

STUDY DESIGN

Patients with non-squamous NSCLC
who progressed after 1 or 2 prior lines of chemotherapy,* stratified by EGFR and KRAS mutation status
(N=988)



*One of which must be a platinum-doublet therapy.

PRIMARY ENDPOINT

- Overall survival

SECONDARY ENDPOINTS

- Progression-free survival
- Overall survival in subjects with EGFR wild type NSCLC

To learn more about this study, please call 1-877-4DS-PROD (1-877-437-7763), e-mail dsus@druginfo.com, or visit www.clinicaltrials.gov/ct2/show/NCT01244191

Please note that tivantinib (ARQ 197) is an investigational agent and is not approved by the FDA or any other worldwide regulatory agency as a treatment for any indication. Efficacy and safety have not been established. There is no guarantee that tivantinib will become commercially available.



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 aid-

ing in the development of novel predictive assays, as well as of new agents and treatment regimens.

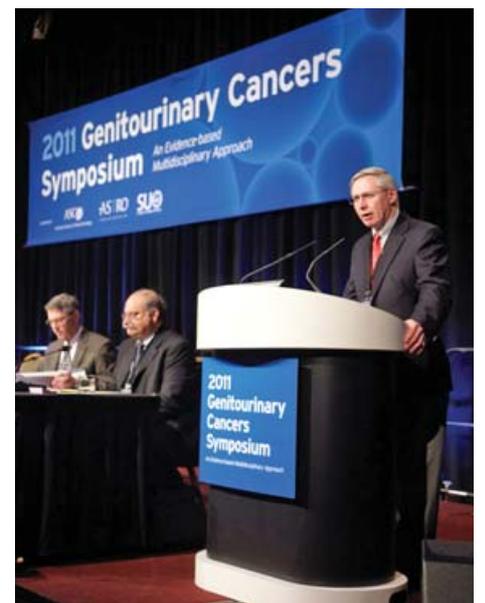
“Dr. Cordon-Cardo’s discussion regarding the stem cell was a very timely subject,” noted Dr. Hussain. “This kind of scientific information and research is critical if we are to significantly affect the outcome from these cancers and improve the care for our patients.”

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.

Genitourinary 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
University of California, San Francisco

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 LIVESTRONG 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 LIVESTRONG. “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 by ASCO 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.

NCCN Thanks Our Colle

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

NCCN works in collaboration with third party organizations to present the NCCN Guidelines™ to international audiences and other medical professionals. Additionally, NCCN collaborates to create and distribute **International Adaptations of NCCN Guidelines**, which may include modifications representative of biologic differences in populations, technology, and regulatory status of agents used in cancer management, such as availabilities of drugs, biologics, devices, and procedures.

Approximately 45% of registered users of NCCN.org reside outside the United States, illustrating the interest and implementation of NCCN resources in the global community.

NCCN Guidelines™ have been translated into the following languages:

Chinese
German
Italian
Japanese
Korean
Polish
Portuguese
Russian
Spanish
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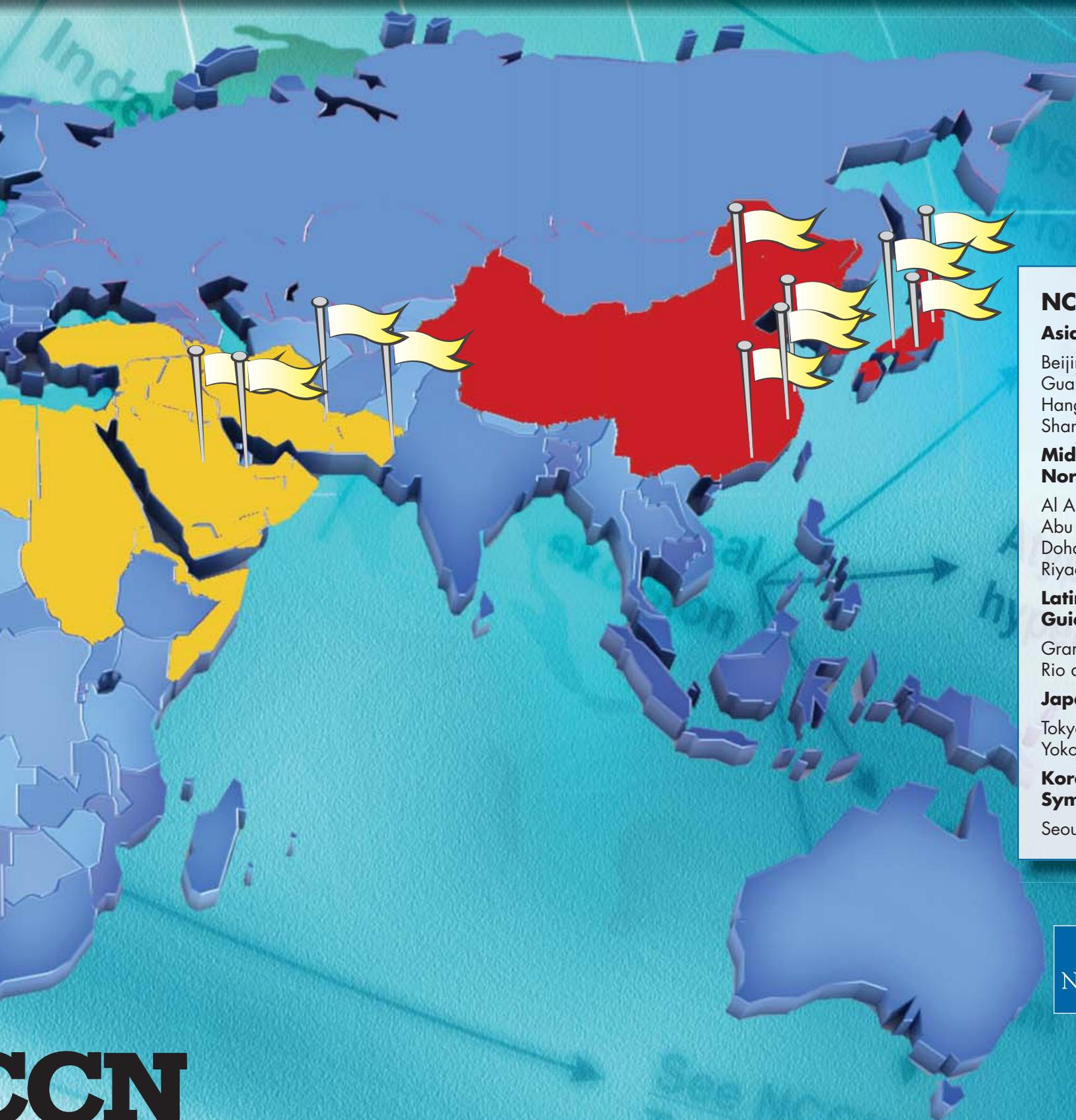
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EGFR Gene Testing before Treatment Recommended for Patients with Advanced Non-small Cell Lung Cancer

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, Maemondo¹ 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. ●

References

1. Maemondo M, Kobayashi K, Oizumi S, et al. Gefitinib or Chemotherapy for Non-Small-Cell Lung Cancer with Mutated *EGFR*. *N Engl J Med*. 2010;362:2380-2388.
2. Zhou C, Yu YL, Chen G, et al. Efficacy results from the randomized phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin (CBDCA) plus gemcitabine (GEM), in Chinese advanced nonsmall-cell lung cancer (NSCLC) patients (pts) with *EGFR* activating mutations. *Ann Oncol*. 2010;21(Supplement 8):Abstract LBA13.
3. EURTAC Press Release. Early successful readout of Tarceva study in a distinct form of lung cancer. January 28, 2011.

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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 com-

mon 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 Gov-

ernment 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

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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

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- ▶ Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting
- ▶ Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting

Important Safety Information

Toxicity in hepatic impairment

- ▶ IXEMPRA (ixabepilone) in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death
- ▶ In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater in patients with hepatic impairment
- ▶ Caution should be used when using IXEMPRA as monotherapy in patients with AST or ALT >5 x ULN. Use of IXEMPRA in patients with AST or ALT >10 x ULN or bilirubin >3 x ULN is not recommended
- ▶ With monotherapy, grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent in patients with hepatic impairment

Contraindications

- ▶ IXEMPRA is contraindicated in patients:
 - with a known history of a severe (CTC grade 3/4) hypersensitivity reaction to agents containing Cremophor[®] EL or its derivatives such as polyoxyethylated castor oil
 - who have a baseline neutrophil count <1500 cells/mm³ or a platelet count <100,000 cells/mm³

Peripheral neuropathy

- ▶ Peripheral neuropathy was common. Patients treated with IXEMPRA (ixabepilone) should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain
- ▶ Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening peripheral neuropathy may require changes in the dose or discontinuation of IXEMPRA
- ▶ Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy

Myelosuppression

- ▶ Myelosuppression is dose-dependent and primarily manifested as neutropenia
- ▶ Patients should be monitored for myelosuppression; frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA
- ▶ Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced. Neutropenia-related deaths occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic

impairment treated with IXEMPRA (ixabepilone) in combination with capecitabine. Neutropenia-related death occurred in 0.4% of 240 patients with IXEMPRA as monotherapy

Hypersensitivity reaction

- ▶ Premedicate with an H₁ and an H₂ antagonist approximately 1 hour before IXEMPRA infusion and observe for hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm)
- ▶ In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (eg, epinephrine, corticosteroids) started
- ▶ Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H₁ and H₂ antagonists, and extension of the infusion time should be considered

Pregnancy

- ▶ Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy or the patient becomes pregnant, the patient should be apprised of the potential hazard to the fetus



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 (ACOG).

Matthew P. Mumber, MD, specializes in radiation oncology at Harbin Clinic Radiation Oncology. He is also the Medical Director at Fuller Cancer Center in Ringgold, 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



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- ▶ who have a baseline neutrophil count <1500 cells/mm³ or a platelet count <100,000 cells/mm³
- ▶ in combination with capecitabine, when AST or ALT is >2.5 x ULN or bilirubin is >1 x ULN due to increased risk of toxicity and neutropenia-related death

Cardiac adverse reactions

▶ Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA (ixabepilone) should be considered in patients who develop cardiac ischemia or impaired cardiac function due to reports of cardiovascular adverse reactions (eg, myocardial ischemia, supraventricular arrhythmia, and ventricular dysfunction). The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group

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▶ The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA were peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional events occurred in ≥20% in combination treatment: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia,

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Reference: 1. IXEMPRA® (ixabepilone) Prescribing Information. Bristol-Myers Squibb; Princeton, NJ.

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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.

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R_x ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: TOXICITY IN HEPATIC IMPAIRMENT
IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity and neutropenia-related death [see Contraindications and Warnings and Precautions].

INDICATIONS AND USAGE

IXEMPRA (ixabepilone) is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

IXEMPRA is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

CONTRAINDICATIONS

IXEMPRA is contraindicated in patients with a history of a severe (CTC grade 3/4) hypersensitivity reaction to agents containing Cremophor® EL or its derivatives (eg, polyoxyethylated castor oil) [see Warnings and Precautions].

IXEMPRA is contraindicated in patients who have a neutrophil count <1500 cells/mm³ or a platelet count <100,000 cells/mm³ [see Warnings and Precautions].

IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN [see Boxed Warning and Warnings and Precautions].

WARNINGS AND PRECAUTIONS

Peripheral Neuropathy

Peripheral neuropathy was common (see Table 1). Patients treated with IXEMPRA should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain. Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening symptoms may require a reduction or delay in the dose of IXEMPRA [see Dosage and Administration (2.2) in Full Prescribing Information]. In clinical studies, peripheral neuropathy was managed through dose reductions, dose delays, and treatment discontinuation. Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. In Studies 046 and 081, 80% and 87%, respectively, of patients with peripheral neuropathy who received IXEMPRA had improvement or no worsening of their neuropathy following dose reduction. For patients with grade 3/4 neuropathy in Studies 046 and 081, 76% and 79%, respectively, had documented improvement to baseline or grade 1, twelve weeks after onset.

Table 1: Treatment-related Peripheral Neuropathy

	IXEMPRA with capecitabine	
	Study 046	IXEMPRA as monotherapy Study 081
Peripheral neuropathy (all grades) ^{a,b}	67%	63%
Peripheral neuropathy (grades 3/4) ^{a,b}	23%	14%
Discontinuation due to neuropathy	21%	6%
Median number of cycles to onset of grade 3/4 neuropathy	4	4
Median time to improvement of grade 3/4 neuropathy to baseline or to grade 1	6.0 weeks	4.6 weeks

^a Sensory and motor neuropathy combined.

^b 24% and 27% of patients in 046 and 081, respectively, had preexisting neuropathy (grade 1).

A pooled analysis of 1540 cancer patients treated with IXEMPRA indicated that patients with diabetes mellitus or preexisting peripheral neuropathy may be at increased risk of severe neuropathy. Prior therapy with neurotoxic chemotherapy agents did not predict the development of neuropathy. Patients with moderate to severe neuropathy (grade 2 or greater) were excluded from studies with IXEMPRA. Caution should be used when treating patients with diabetes mellitus or preexisting peripheral neuropathy.

Myelosuppression

Myelosuppression is dose-dependent and primarily manifested as neutropenia. In clinical studies, grade 4 neutropenia (<500 cells/mm³) occurred in 36% of patients treated with IXEMPRA in combination with capecitabine and 23% of patients treated with IXEMPRA monotherapy. Febrile neutropenia and infection with neutropenia were reported in 5% and 6% of patients treated with IXEMPRA in combination with capecitabine, respectively, and 3% and 5% of patients treated with IXEMPRA as monotherapy, respectively. Neutropenia-related death occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with IXEMPRA in combination with capecitabine. The rate of neutropenia-related deaths was higher (29%, 5 out of 17) in patients with AST or ALT >2.5 x ULN or bilirubin >1.5 x ULN [see Boxed Warning, Contraindications, and Warnings and Precautions]. Neutropenia-related death occurred in 0.4% of 240 patients treated with IXEMPRA as monotherapy. No neutropenia-related deaths were reported in 24 patients with AST or ALT >2.5 x ULN or bilirubin >1.5 x ULN treated with IXEMPRA monotherapy. IXEMPRA must not be administered to patients with a neutrophil count <1500 cells/mm³. To monitor for myelosuppression, frequent peripheral blood cell counts are recommended for all patients receiving IXEMPRA. Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced [see Dosage and Administration (2.2) in Full Prescribing Information].

Hepatic Impairment

Patients with baseline AST or ALT >2.5 x ULN or bilirubin >1.5 x ULN experienced greater toxicity than patients with baseline AST or ALT ≤2.5 x ULN or bilirubin ≤1.5 x ULN when treated with IXEMPRA at 40 mg/m² in combination with capecitabine or as monotherapy in breast cancer studies. In combination with capecitabine, the overall frequency of grade 3/4 adverse reactions, febrile neutropenia, serious adverse reactions, and toxicity-related deaths was greater [see Warnings and Precautions]. With monotherapy, grade 4 neutropenia, febrile neutropenia, and serious adverse reactions were more frequent. The safety and pharmacokinetics of IXEMPRA as monotherapy were evaluated in a dose escalation study in 56 patients with varying degrees of hepatic impairment. Exposure was increased in patients with elevated AST or bilirubin [see Use in Specific Populations].

IXEMPRA in combination with capecitabine is contraindicated in patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN due to increased risk of toxicity- and neutropenia-related death [see Boxed Warning, Contraindications, and Warnings and Precautions]. Patients who are treated with IXEMPRA as monotherapy should receive a reduced dose depending on the degree of hepatic impairment [see Dosage and Administration (2.2) in Full Prescribing Information]. Use in patients with AST or ALT >10 x ULN or bilirubin >3 x ULN is not recommended. Limited data are available for patients with AST or ALT >5 x ULN. Caution should be used when treating these patients [see Dosage and Administration (2.2) in Full Prescribing Information].

Hypersensitivity Reactions

Patients with a history of a severe hypersensitivity reaction to agents containing Cremophor® EL or its derivatives (eg, polyoxyethylated castor oil) should not be treated with IXEMPRA. All patients should be premedicated with an H₁ and an H₂ antagonist approximately 1 hour before IXEMPRA infusion and be observed for hypersensitivity reactions (eg, flushing, rash, dyspnea, and bronchospasm). In case of severe hypersensitivity reactions, infusion of IXEMPRA should be stopped and aggressive supportive treatment (eg, epinephrine, corticosteroids) started. Of the 1323 patients treated with IXEMPRA in clinical studies, 9 patients (1%) had experienced severe hypersensitivity reactions (including anaphylaxis). Three of the 9 patients were able to be retreated. Patients who experience a hypersensitivity reaction in one cycle of IXEMPRA must be premedicated in subsequent cycles with a corticosteroid in addition to the H₁ and H₂ antagonists, and extension of the infusion time should be considered [see Dosage and Administration (2.3) in Full Prescribing Information and Contraindications].

Pregnancy

Pregnancy Category D.

IXEMPRA may cause fetal harm when administered to pregnant women. There are no adequate and well-controlled studies with IXEMPRA in pregnant women. Women should be advised not to become pregnant when taking IXEMPRA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Ixabepilone was studied for effects on embryo-fetal development in pregnant rats and rabbits given IV doses of 0.02, 0.08, and 0.3 mg/kg/day and 0.01, 0.03, 0.11, and 0.3 mg/kg/day, respectively. There were no teratogenic effects. In rats, an increase in resorptions and post-implantation loss and a decrease in the number of live fetuses and fetal weight was observed at the maternally

toxic dose of 0.3 mg/kg/day (approximately one-tenth the human clinical exposure based on AUC). Abnormalities included a reduced ossification of caudal vertebrae, sternbrae, and metacarpals. In rabbits, ixabepilone caused maternal toxicity (death) and embryo-fetal toxicity (resorptions) at 0.3 mg/kg/day (approximately one-tenth the human clinical dose based on body surface area). No fetuses were available at this dose for evaluation.

Cardiac Adverse Reactions

The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the IXEMPRA (ixabepilone) in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group. Supraventricular arrhythmias were observed in the combination arm (0.5%) and not in the capecitabine alone arm. Caution should be exercised in patients with a history of cardiac disease. Discontinuation of IXEMPRA should be considered in patients who develop cardiac ischemia or impaired cardiac function.

Potential for Cognitive Impairment from Excipients

Since IXEMPRA contains dehydrated alcohol USP, consideration should be given to the possibility of central nervous system and other effects of alcohol [see Description (11) in Full Prescribing Information].

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections.

- Peripheral neuropathy [see Warnings and Precautions]
- Myelosuppression [see Warnings and Precautions]
- Hypersensitivity reactions [see Warnings and Precautions]

Clinical Trials Experience

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

Unless otherwise specified, assessment of adverse reactions is based on one randomized study (Study 046) and one single-arm study (Study 081). In Study 046, 369 patients with metastatic breast cancer were treated with IXEMPRA 40 mg/m² administered intravenously over 3 hours every 21 days, combined with capecitabine 1000 mg/m² twice daily for 2 weeks followed by a 1-week rest period. Patients treated with capecitabine as monotherapy (n=368) in this study received 1250 mg/m² twice daily for 2 weeks every 21 days. In Study 081, 126 patients with metastatic or locally advanced breast cancer were treated with IXEMPRA 40 mg/m² administered intravenously over 3 hours every 3 weeks.

The most common adverse reactions (≥20%) reported by patients receiving IXEMPRA were peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional reactions occurred in ≥20% in combination treatment: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation. The most common hematologic abnormalities (≥40%) include neutropenia, leukopenia, anemia, and thrombocytopenia.

Table 2 presents nonhematologic adverse reactions reported in 5% or more of patients. Hematologic abnormalities are presented separately in Table 3.

Table 2: Nonhematologic Drug-related Adverse Reactions Occurring in at Least 5% of Patients with Metastatic or Locally Advanced Breast Cancer Treated with IXEMPRA

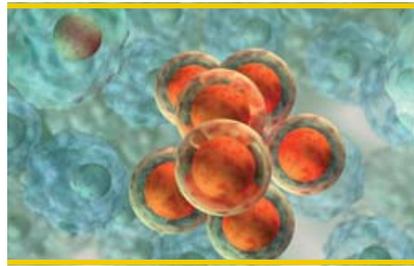
System Organ Class/ Preferred Term	Study 046				Study 081	
	IXEMPRA with capecitabine n=369		Capecitabine n=368		IXEMPRA monotherapy n=126	
	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)
Infections and Infestations						
Upper respiratory tract infection ^b	4	0	3	0	6	0
Blood and Lymphatic System Disorders						
Febrile neutropenia	5	4 ^c	1	1 ^d	3	3 ^d
Immune System Disorders						
Hypersensitivity ^b	2	1 ^d	0	0	5	1 ^d
Metabolism and Nutrition Disorders						
Anorexia ^a	34	3 ^d	15	1 ^d	19	2 ^d
Dehydration ^b	5	2	2	<1 ^d	2	1 ^d
Psychiatric						
Insomnia ^b	9	<1 ^d	2	0	5	0
Nervous System Disorders						
Peripheral neuropathy						
Sensory neuropathy ^{b,e}	65	21	16	0	62	14
Motor neuropathy ^b	16	5 ^d	<1	0	10	1 ^d
Headache	8	<1 ^d	3	0	11	0
Taste disorder ^b	12	0	4	0	6	0
Dizziness	8	1 ^d	5	1 ^d	7	0
Eye Disorders						
Lacrimation increased	5	0	4	<1 ^d	4	0
Vascular Disorders						
Hot flush ^b	5	0	2	0	6	0
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea ^a	7	1	4	1	9	1 ^d
Cough ^b	6	0	2	0	2	0
Gastrointestinal Disorders						
Nausea	53	3 ^d	40	2 ^d	42	2 ^d
Vomiting ^b	39	4 ^d	24	2	29	1 ^d
Stomatitis/mucositis ^b	31	4	20	3 ^d	29	6
Diarrhea ^a	44	6 ^d	39	9	22	1 ^d
Constipation	22	0	6	<1 ^d	16	2 ^d
Abdominal pain ^b	24	2 ^d	14	1 ^d	13	2 ^d
Gastroesophageal reflux disease ^b	7	1 ^d	8	0	6	0
Skin and Subcutaneous Tissue Disorders						
Alopecia ^a	31	0	3	0	48	0
Skin rash ^b	17	1 ^d	7	0	9	2 ^d
Nail disorder ^b	24	2 ^d	10	<1 ^d	9	0
Palmar-plantar erythrodysesthesia syndrome ^{b,f}	64	18 ^d	63	17 ^d	8	2 ^d
Pruritus	5	0	2	0	6	1 ^d
Skin exfoliation ^b	5	<1 ^d	3	0	2	0
Skin hyperpigmentation ^b	11	0	14	0	2	0

(Continued)

^a System organ class presented as outlined in Guidelines for Preparing Core Clinical Safety Information on Drugs by the Council for International Organizations of Medical Sciences (CIOMS). ^b A composite of multiple MedDRA Preferred Terms. ^c NCI CTC grading for febrile neutropenia ranges from Grade 3 to 5. Three patients (1%) experienced Grade 5 (fatal) febrile neutropenia. Other neutropenia-related deaths (9) occurred in the absence of reported febrile neutropenia [see Warnings and Precautions]. ^d No grade 4 reports. ^e Peripheral sensory neuropathy (graded with the NCI CTC scale) was defined as the occurrence of any of the following: areflexia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, hyporeflexia, neuralgia, neuritis, neuropathy, neuropathy peripheral, neurotoxicity, painful response to normal stimuli, paresthesia, paresthesia, peripheral sensory neuropathy, polyneuropathy, polyneuropathy toxic and sensorimotor disorder. Peripheral motor neuropathy was defined as the occurrence of any of the following: multifocal motor neuropathy, neuromuscular toxicity, peripheral motor neuropathy, and peripheral sensorimotor neuropathy. ^f Palmar-plantar erythrodysesthesia (hand-foot syndrome) was graded on a 1-3 severity scale in Study 046.

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



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— Max Wicha, MD

normal somatic stem cells unharmed.

“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.” ●

Table 2: Nonhematologic Drug-related Adverse Reactions Occurring in at Least 5% of Patients with Metastatic or Locally Advanced Breast Cancer Treated with IXEMPRA (ixabepilone)

System Organ Class ^a / Preferred Term	Study 046				Study 081	
	IXEMPRA with capecitabine n=369		Capecitabine n=368		IXEMPRA monotherapy n=126	
	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)
Musculoskeletal, Connective Tissue, and Bone Disorders						
Myalgia/arthralgia ^b	39	8 ^d	5	<1 ^d	49	8 ^d
Musculoskeletal pain ^b	23	2 ^d	5	0	20	3 ^d
General Disorders and Administrative Site Conditions						
Fatigue/asthenia ^a	60	16	29	4	56	13
Edema ^a	8	0	5	<1 ^d	9	1 ^d
Pyrexia	10	1 ^d	4	0	8	1 ^d
Pain ^b	9	1 ^d	2	0	8	3 ^d
Chest pain ^b	4	1 ^d	<1	0	5	1 ^d
Investigations						
Weight decreased	11	0	3	0	6	0

^a System organ class presented as outlined in Guidelines for Preparing Core Clinical Safety Information on Drugs by the Council for International Organizations of Medical Sciences (CIOMS). ^b A composite of multiple MedDRA Preferred Terms. ^c NCI CTC grading for febrile neutropenia ranges from Grade 3 to 5. Three patients (1%) experienced Grade 5 (fatal) febrile neutropenia. Other neutropenia-related deaths (9) occurred in the absence of reported febrile neutropenia [see *Warnings and Precautions*]. ^d No grade 4 reports. ^e Peripheral sensory neuropathy (graded with the NCI CTC scale) was defined as the occurrence of any of the following: areflexia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, hyporeflexia, neuralgia, neuritis, neuropathy, neuropathic peripheral, neurotoxicity, painful response to normal stimuli, paresthesia, paresthesia, peripheral sensory neuropathy, polyneuropathy, polyneuropathy toxic and sensorimotor disorder. Peripheral motor neuropathy was defined as the occurrence of any of the following: multifocal motor neuropathy, neuromuscular toxicity, peripheral motor neuropathy, and peripheral sensorimotor neuropathy. ^f Palmar-plantar erythrodysesthesia (hand-foot syndrome) was graded on a 1-3 severity scale in Study 046.

Table 3: Hematologic Abnormalities in Patients with Metastatic or Locally Advanced Breast Cancer Treated with IXEMPRA

Hematology Parameter	Study 046				Study 081	
	IXEMPRA with capecitabine n=369		Capecitabine n=368		IXEMPRA monotherapy n=126	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia ^a	32	36	9	2	31	23
Leukopenia (WBC)	41	16	5	1	36	13
Anemia (Hgb)	8	2	4	1	6	2
Thrombocytopenia	5	3	2	2	5	2

^a G-CSF (granulocyte colony stimulating factor) or GM-CSF (granulocyte macrophage stimulating factor) was used in 20% and 17% of patients who received IXEMPRA in Study 046 and Study 081, respectively.

The following serious adverse reactions were also reported in 1323 patients treated with IXEMPRA as monotherapy or in combination with other therapies in Phase 2 and 3 studies.

Infections and Infestations: sepsis, pneumonia, infection, neutropenic infection, urinary tract infection, bacterial infection, enterocolitis, laryngitis, lower respiratory tract infection

Blood and Lymphatic System Disorders: coagulopathy, lymphopenia

Metabolism and Nutrition Disorders: hyponatremia, metabolic acidosis, hypokalemia, hypovolemia

Nervous System Disorders: cognitive disorder, syncope, cerebral hemorrhage, abnormal coordination, lethargy

Cardiac Disorders: myocardial infarction, supraventricular arrhythmia, left ventricular dysfunction, angina pectoris, atrial flutter, cardiomyopathy, myocardial ischemia

Vascular Disorders: hypotension, thrombosis, embolism, hemorrhage, hypovolemic shock, vasculitis

Respiratory, Thoracic, and Mediastinal Disorders: pneumonitis, hypoxia, respiratory failure, acute pulmonary edema, dyspnea, pharyngolaryngeal pain

Gastrointestinal Disorders: ileus, colitis, impaired gastric emptying, esophagitis, dysphagia, gastritis, gastrointestinal hemorrhage

Hepatobiliary Disorders: acute hepatic failure, jaundice

Skin and Subcutaneous Tissue Disorders: erythema multiforme

Musculoskeletal, Connective Tissue Disorders, and Bone Disorders: muscular weakness, muscle spasms, trismus

Renal and Urinary Disorders: nephrolithiasis, renal failure

General Disorders and Administration Site Conditions: chills

Investigations: increased transaminases, increased blood alkaline phosphatase, increased gamma-glutamyltransferase

Postmarketing Experience

Radiation recall has been reported during postmarketing use of IXEMPRA. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Effect of Other Drugs on Ixabepilone

Drugs That May Increase Ixabepilone Plasma Concentrations

CYP3A4 Inhibitors: Co-administration of ixabepilone with ketoconazole, a potent CYP3A4 inhibitor, increased ixabepilone AUC by 79% compared to ixabepilone treatment alone. If alternative treatment cannot be administered, a dose adjustment should be considered. The effect of mild or moderate inhibitors (eg, erythromycin, fluconazole, or verapamil) on exposure to ixabepilone has not been studied. Therefore, caution should be used when administering mild or moderate CYP3A4 inhibitors during treatment with IXEMPRA, and alternative therapeutic agents that do not inhibit CYP3A4 should be considered. Patients receiving CYP3A4 inhibitors during treatment with IXEMPRA should be monitored closely for acute toxicities (eg, frequent monitoring of peripheral blood counts between cycles of IXEMPRA) [see *Dosage and Administration (2.2) in Full Prescribing Information*].

Drugs That May Decrease Ixabepilone Plasma Concentrations

CYP3A4 Inducers: IXEMPRA is a CYP3A4 substrate. Co-administration of IXEMPRA with rifampin, a potent CYP3A4 inducer, decreased ixabepilone AUC by 43% compared to IXEMPRA treatment alone. Other strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifabutin, and phenobarbital) may also decrease ixabepilone concentrations leading to subtherapeutic levels. Therefore, therapeutic agents with low enzyme induction potential should be considered for coadministration with IXEMPRA. St. John's Wort may decrease ixabepilone plasma concentrations unpredictably and should be avoided. If patients must be co-administered a strong CYP3A4 inducer, a gradual dose adjustment may be considered [see *Dosage and Administration (2.2) in Full Prescribing Information*].

Effect of Ixabepilone on Other Drugs

Ixabepilone does not inhibit CYP enzymes at relevant clinical concentrations and is not expected to alter the plasma concentrations of other drugs [see *Clinical Pharmacology (12.3) in Full Prescribing Information*].

Capecitabine

In patients with cancer who received ixabepilone (40 mg/m²) in combination with capecitabine (1000 mg/m²), ixabepilone C_{max} decreased by 19%, capecitabine C_{max} decreased by 27%, and 5-fluorouracil AUC increased by 14%, as compared to ixabepilone or capecitabine administered separately. The interaction is not clinically significant given that the combination treatment is supported by efficacy data.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Nursing Mothers

It is not known whether ixabepilone is excreted into human milk. Following intravenous administration of radiolabeled ixabepilone to rats on days 7 to 9 postpartum, concentrations of radioactivity in milk were comparable with those in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ixabepilone, a decision must be made whether to discontinue nursing or to discontinue IXEMPRA (ixabepilone) taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of IXEMPRA did not include sufficient numbers of subjects aged sixty-five and over to determine whether they respond differently from younger subjects.

Forty-five of 431 patients treated with IXEMPRA in combination with capecitabine were ≥65 years of age and 3 patients were ≥75. Overall, the incidence of grade 3/4 adverse reactions were higher in patients ≥65 years of age versus those <65 years of age (82% versus 68%) including grade 3/4 stomatitis (9% versus 1%), diarrhea (9% versus 6%), palmar-plantar erythrodysesthesia syndrome (27% versus 20%), peripheral neuropathy (24% versus 22%), febrile neutropenia (9% versus 3%), fatigue (16% versus 12%), and asthenia (11% versus 6%). Toxicity-related deaths occurred in 2 (4.7%) of 43 patients ≥65 years with normal baseline hepatic function or mild impairment.

Thirty-two of 240 breast cancer patients treated with IXEMPRA as monotherapy were ≥65 years of age and 6 patients were ≥75. No overall differences in safety were observed in these patients compared to those <65 years of age.

Hepatic Impairment

IXEMPRA was evaluated in 56 patients with mild to severe hepatic impairment defined by bilirubin levels and AST levels. Compared to patients with normal hepatic function (n=17), the area under the curve (AUC_{0-24h}) of ixabepilone increased by:

- 22% in patients with a) bilirubin >1 - 1.5 x ULN or b) AST >ULN but bilirubin <1.5 x ULN;
- 30% in patients with bilirubin >1.5 - 3 x ULN and any AST level; and
- 81% in patients with bilirubin >3 x ULN and any AST level.

Doses of 10 and 20 mg/m² as monotherapy were tolerated in 17 patients with severe hepatic impairment (bilirubin >3 x ULN).

IXEMPRA in combination with capecitabine must not be given to patients with AST or ALT >2.5 x ULN or bilirubin >1 x ULN [see *Boxed Warning, Contraindications, and Warnings and Precautions*]. Dose reduction is recommended when administering IXEMPRA as monotherapy to patients with hepatic impairment [see *Dosage and Administration (2.3) in Full Prescribing Information*]. Because there is a need for dosage adjustment based upon hepatic function, assessment of hepatic function is recommended before initiation of IXEMPRA and periodically thereafter.

Renal Impairment

Ixabepilone is minimally excreted via the kidney. No controlled pharmacokinetic studies were conducted with IXEMPRA in patients with renal impairment. IXEMPRA in combination with capecitabine has not been evaluated in patients with calculated creatinine clearance of <50 mL/min. IXEMPRA as monotherapy has not been evaluated in patients with creatinine >1.5 times ULN. In a population pharmacokinetic analysis of IXEMPRA as monotherapy, there was no meaningful effect of mild and moderate renal insufficiency (CrCl >30 mL/min) on the pharmacokinetics of ixabepilone.

OVERDOSAGE

Experience with overdose of IXEMPRA is limited to isolated cases. The adverse reactions reported in these cases included peripheral neuropathy, fatigue, musculoskeletal pain/myalgia, and gastrointestinal symptoms (nausea, anorexia, diarrhea, abdominal pain, stomatitis). The highest dose mistakenly received was 100 mg/m² (total dose 185 mg).

There is no known antidote for overdose of IXEMPRA. In case of overdose, the patient should be closely monitored and supportive treatment should be administered. Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with ixabepilone have not been conducted. Ixabepilone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in an *in vitro* cytogenetic assay using primary human lymphocytes. Ixabepilone was clastogenic (induction of micronucleus) in the *in vivo* rat micronucleus assay at doses ≥0.625 mg/kg/day.

There were no effects on male or female rat mating or fertility at doses up to 0.2 mg/kg/day in both males and females (approximately one-fifteenth the expected human clinical exposure based on AUC). The effect of ixabepilone on human fertility is unknown. However, when rats were given an IV infusion of ixabepilone during breeding and through the first 7 days of gestation, a significant increase in resorptions and pre- and post-implantation loss and a decrease in the number of corpora lutea was observed at 0.2 mg/kg/day. Testicular atrophy or degeneration was observed in 6-month rat and 9-month dog studies when ixabepilone was given every 21 days at intravenous doses of 6.7 mg/kg (40 mg/m²) in rats (approximately 2.1 times the expected clinical exposure based on AUC) and 0.5 and 0.75 mg/kg (10 and 15 mg/m²) in dogs (approximately 0.2 and 0.4 times the expected clinical exposure based on AUC).

Animal Toxicology

Overdose

In rats, single intravenous doses from 60 to 180 mg/m² (mean AUC values ≥8156 ng•h/mL) were associated with mortality occurring between 5 and 14 days after dosing, and toxicity was principally manifested in the gastrointestinal, hematopoietic (bone-marrow), lymphatic, peripheral-nervous, and male-reproductive systems. In dogs, a single intravenous dose of 100 mg/m² (mean AUC value of 6925 ng•h/mL) was markedly toxic, inducing severe gastrointestinal toxicity and death 3 days after dosing.

PATIENT COUNSELING INFORMATION

[see *FDA-Approved Patient Labeling in Full Prescribing Information*]

Peripheral Neuropathy

Patients should be advised to report to their physician any numbness and tingling of the hands or feet [see *Warnings and Precautions*].

Fever/Neutropenia

Patients should be instructed to call their physician if a fever of 100.5° F or greater or other evidence of potential infection such as chills, cough, or burning or pain on urination develops [see *Warnings and Precautions*].

Hypersensitivity Reactions

Patients should be advised to call their physician if they experience urticaria, pruritus, rash, flushing, swelling, dyspnea, chest tightness or other hypersensitivity-related symptoms following an infusion of IXEMPRA [see *Warnings and Precautions*].

Pregnancy

Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid nursing during treatment with IXEMPRA [see *Warnings and Precautions and Use in Specific Populations*].

Cardiac Adverse Reactions

Patients should be advised to report to their physician chest pain, difficulty breathing, palpitations or unusual weight gain [see *Warnings and Precautions*].

IXEMPRA® (ixabepilone) for injection Manufactured by: Baxter Oncology GmbH, 33790 Halle/Westfalen, Germany

DILUENT for IXEMPRA Manufactured by: Baxter Oncology GmbH, 33790 Halle/Westfalen, Germany

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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 Ben-

dell, 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.

When PTCL Returns...

BE READY WITH FOLOTYN

(pralatrexate injection)

*Demonstrated response in relapsed
or refractory PTCL¹*

27% overall
response rate
(CR+CRu+PR)
by central review
(95% CI, 19-36)*

Of the responders, **66%**
responded within Cycle 1*
– Median time to first
response was 45 days
(range=37-349 days)

9.4-month median
duration of response by central
review (range=1-503 days)*
– 12% (95% CI, 7-20) of
patients had responses
lasting ≥14 weeks
(range=98-503 days)

Demonstrated
response in
PROPEL—
the largest prospective
single-arm, open-label
clinical trial in PTCL

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 B₁₂ 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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Please see accompanying brief summary
of Prescribing Information.

FOLOTYN
(pralatrexate injection)

www.FOLOTYN.com

Brief summary of Full Prescribing Information for FOLOTYN® (pralatrexate injection)—Please consult Full Prescribing Information.

INDICATIONS AND USAGE

FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression

FOLOTYN can suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Dose modifications are based on ANC and platelet count prior to each dose.

Mucositis

Treatment with FOLOTYN may cause mucositis. If ≥Grade 2 mucositis is observed, omit dose and follow guidelines in Table 1.

Dermatologic Reactions

FOLOTYN has been associated with severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (14/663 patients [2.1%]) and post marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN). These reactions may be progressive and increase in severity with further treatment, and may involve skin and subcutaneous sites of known lymphoma. Patients with dermatologic reactions should be monitored closely, and if severe, FOLOTYN should be withheld or discontinued.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in patients with lymphoma receiving FOLOTYN. Patients receiving FOLOTYN should be monitored closely and treated for complications.

Folic Acid and Vitamin B₁₂ Supplementation

Patients should be instructed to take folic acid and receive vitamin B₁₂ to potentially reduce treatment-related hematological toxicity and mucositis.

Pregnancy Category D

FOLOTYN can cause fetal harm when administered to a pregnant woman. FOLOTYN was embryotoxic and fetotoxic in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Decreased Renal Function

Although FOLOTYN has not been formally tested in patients with renal impairment, caution is advised when administering FOLOTYN to patients with moderate to severe impairment. Monitor patients for renal function and systemic toxicity due to increased drug exposure.

Elevated Liver Enzymes

Liver function test abnormalities have been observed after FOLOTYN administration. Persistent liver function test abnormalities may be indicators of liver toxicity and require dose modification. Monitor patients for liver function.

ADVERSE REACTIONS

The most common adverse reactions observed in patients with peripheral T-cell lymphoma (PTCL) treated with FOLOTYN were mucositis, thrombocytopenia, nausea, and fatigue.

Clinical Trials Experience

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

The safety of FOLOTYN was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m² once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range 1-540 days).

Most Frequent Adverse Reactions

Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥10% of patients)

Preferred Term	N=111					
	Total		Grade 3		Grade 4	
	N	%	N	%	N	%
Any Adverse Event	111	100	48	43	34	31
Mucositis ^a	78	70	19	17	4	4
Thrombocytopenia ^b	45	41	15	14	21	19 ^c
Nausea	44	40	4	4	0	0
Fatigue	40	36	5	5	2	2
Anemia	38	34	17	15	2	2
Constipation	37	33	0	0	0	0
Pyrexia	36	32	1	1	1	1
Edema	33	30	1	1	0	0
Cough	31	28	1	1	0	0
Epistaxis	29	26	0	0	0	0
Vomiting	28	25	2	2	0	0
Neutropenia	27	24	14	13	8	7
Diarrhea	23	21	2	2	0	0
Dyspnea	21	19	8	7	0	0
Anorexia	17	15	3	3	0	0
Hypokalemia	17	15	4	4	1	1
Rash	17	15	0	0	0	0
Pruritus	16	14	2	2	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0

Preferred Term	N=111					
	Total		Grade 3		Grade 4	
	N	%	N	%	N	%
Liver function test abnormal ^a	14	13	6	5	0	0
Abdominal pain	13	12	4	4	0	0
Pain in extremity	13	12	0	0	0	0
Back pain	12	11	3	3	0	0
Leukopenia	12	11	3	3	4	4
Night sweats	12	11	0	0	0	0
Asthenia	11	10	1	1	0	0
Tachycardia	11	10	0	0	0	0
Upper respiratory tract infection	11	10	1	1	0	0

^a Stomatitis or mucosal inflammation of the gastrointestinal and genitourinary tracts

^b Five patients with platelets <10,000/μL

^c Alanine aminotransferase, aspartate aminotransferase, and transaminases increased

Serious Adverse Events

Forty-four percent of patients (n=49) experienced a serious adverse event while on study or within 30 days after their last dose of FOLOTYN. The most common serious adverse events (>3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all FOLOTYN trials at doses ranging from 30 to 325 mg/m².

Discontinuations

Twenty-three percent of patients (n=25) discontinued treatment with FOLOTYN due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6%, n=7) and thrombocytopenia (5%, n=5).

Dose Modifications

The target dose of FOLOTYN was 30 mg/m² once weekly for 6 weeks in 7-week cycles. The majority of patients (69%, n=77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

Post Marketing Experience

Toxic epidermal necrolysis has been identified during post approval use of FOLOTYN. 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 (see *Warnings and Precautions*).

DRUG INTERACTIONS

In vitro studies indicate that pralatrexate is not a substrate, inhibitor, or inducer of CYP450 isoenzymes and has low potential for drug-drug interactions at CYP450 isoenzymes. No formal clinical assessments of pharmacokinetic drug-drug interactions between FOLOTYN and other drugs have been conducted. The effect of co-administration of the uricosuric drug probenecid on pralatrexate pharmacokinetics was investigated in a Phase I clinical study. Co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure.

Due to the contribution of renal excretion (approximately 34%) to the overall clearance of pralatrexate, concomitant administration of drugs that are subject to substantial renal clearance (eg, NSAIDs, trimethoprim/sulfamethoxazole) may result in delayed clearance of pralatrexate.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D (see *Warnings and Precautions*).

FOLOTYN can cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and fetotoxic in rats at IV doses of 0.06 mg/kg/day (0.36 mg/m²/day or about 1.2% of the clinical dose on a mg/m² basis) given on gestation days 7 through 20. Treatment with pralatrexate caused a dose-dependent decrease in fetal viability manifested as an increase in late, early, and total resorptions. There was also a dose-dependent increase in post-implantation loss. In rabbits, IV doses of 0.03 mg/kg/day (0.36 mg/m²/day) or greater given on gestation days 8 through 21 also caused abortion and fetal lethality. This toxicity manifested as early and total resorptions, post-implantation loss, and a decrease in the total number of live fetuses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers

It is not known whether pralatrexate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from this drug, a decision should be made whether to discontinue nursing or to discontinue FOLOTYN, taking into account the importance of FOLOTYN to the mother.

Pediatric Use

Pediatric patients were not included in clinical studies with FOLOTYN. The safety and effectiveness of FOLOTYN in pediatric patients have not been established.

Geriatric Use

In the PTCL efficacy study, 36% of patients (n=40) were 65 years of age and over. No overall differences in efficacy and safety were observed in patients based on age (<65 years compared with ≥65 years).

No dosage adjustment is required in elderly patients with normal renal function.

Hepatic Impairment

Formal studies have not been performed with FOLOTYN in patients with hepatic impairment. Patients with the following laboratory values were excluded from the pralatrexate lymphoma clinical trials: total bilirubin >1.5 mg/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN); and AST or ALT >5 × ULN if documented hepatic involvement with lymphoma.

Renal Impairment

See Warnings and Precautions.

OVERDOSAGE

No specific information is available on the treatment of overdosage of FOLOTYN. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Based on FOLOTYN'S mechanism of action the prompt administration of leucovorin should be considered.

PATIENT COUNSELING INFORMATION

See FDA-approved Patient Package Insert.

Patients should be instructed to read the Patient Package Insert carefully.

DOSE AND ADMINISTRATION

FOLOTYN should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Peripheral T-cell Lymphoma

The recommended dose of FOLOTYN is 30 mg/m² administered as an intravenous (IV) push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection, USP IV line once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity.

Vitamin Supplementation

Patients should take low-dose (1.0-1.25 mg) oral folic acid on a daily basis. Folic acid should be initiated during the 10-day period preceding the first dose of FOLOTYN, and dosing should continue during the full course of therapy and for 30 days after the last dose of FOLOTYN. Patients should also receive a vitamin B₁₂ (1 mg) intramuscular injection no more than 10 weeks prior to the first dose of FOLOTYN and every 8-10 weeks thereafter. Subsequent vitamin B₁₂ injections may be given the same day as treatment with FOLOTYN (see *Warnings and Precautions*).

Monitoring and Dose Modifications

Management of severe or intolerable adverse reactions may require dose omission, reduction, or interruption of FOLOTYN therapy.

Monitoring

Complete blood cell counts and severity of mucositis should be monitored weekly. Serum chemistry tests, including renal and hepatic function, should be performed prior to the start of the first and fourth dose of a given cycle.

Dose Modification Recommendations

Prior to administering any dose of FOLOTYN:

- Mucositis should be ≤Grade 1.
- Platelet count should be ≥100,000/μL for first dose and ≥50,000/μL for all subsequent doses.
- Absolute neutrophil count (ANC) should be ≥1,000/μL.

Doses may be omitted or reduced based on patient tolerance. Omitted doses will not be made up at the end of the cycle; once a dose reduction occurs for toxicity, do not re-escalate. For dose modifications and omissions, use the guidelines in Tables 1, 2, and 3.

Table 1 FOLOTYN Dose Modifications for Mucositis

Mucositis Grade ^a on Day of Treatment	Action	Dose upon Recovery to ≤Grade 1
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m ²
Grade 3	Omit dose	20 mg/m ²
Grade 4	Stop therapy	

^a Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

Table 2 FOLOTYN Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon Restart
Platelet <50,000/μL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m ²
	3 weeks	Stop therapy	
ANC 500-1,000/μL and no fever	1 week	Omit dose	Continue prior dose
	1 week	Omit dose, give G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
ANC 500-1,000/μL with fever or ANC <500/μL	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF support	20 mg/m ² with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Stop therapy	

Table 3 FOLOTYN Dose Modifications for All Other Treatment-related Toxicities

Toxicity Grade ^a on Day of Treatment	Action	Dose upon Recovery to ≤Grade 2
Grade 3	Omit dose	20 mg/m ²
Grade 4	Stop therapy	

^a Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

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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 Alegen 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 shown 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 *EGFR* 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

1. Kalemkerian GP. Adjuvant therapy for non-small-cell lung cancer. *Lancet*. 2010; 375:1230-1231.
2. NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet*. 2010;375:1267-1277.
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.

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ONE POINT, ONE PARTNER, MANY NEEDS

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 IFN α *

MORE THAN DOUBLED MEDIAN PFS

- 11 months vs 5 months with IFN α (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 IFN α (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 IFN α (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 IFN α (HR=0.82; 95% CI: 0.673, 1.001; $P=.051$)¹

AN ESTABLISHED SAFETY PROFILE

- The most common adverse reactions (ARs) occurring in $\geq 20\%$ of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFN α) 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 $<1\%$)

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

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.

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 $\geq 5\%$ 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 $\geq 5\%$ of patients receiving SUTENT vs IFN α) 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%).

 **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 IFN-α 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).

DOSE 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-naïve 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-naïve 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*

Adverse Reaction, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	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

^aGrade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), dyspnea (<1%), asthenia (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%)

^bGrade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%), abdominal pain (<1%), and depression (<1%)

^cIncludes flank pain

^dIncludes ageusia, hypogeusia and dysgeusia

^eIncludes decreased appetite

^fIncludes one patient with Grade 5 gastric hemorrhage

^gIncludes 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

Laboratory Parameter, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades*	Grade 3/4**	All Grades*	Grade 3/4**
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

^{*}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%)

^{**}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-∞} 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-∞} 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.

Physcal 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 physcal 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 overdose 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</}

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 antiangiogenic 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-naïve patients with HER2-negative metastatic breast

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.

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.

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 a 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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