

THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based Oncology

Smoking and Health: A Public Health Milestone Surgeon General's 'Smoking and Health' Turns 50 From Scientific Triumph to Public Health Success Story

Peter Page

The word "landmark" is not in the title, and strictly speaking it is not the Surgeon General's report but that of an advisory committee to US Surgeon General Luther Terry. Yet "the landmark 1964 Surgeon General's report" is shorthand for the document that would change America's mind about cigarettes, and, in time, the habit of smoking.

"It was a big deal," Tom Glynn, 66, senior director of cancer science and trends for the American Cancer Society, said of the report, which is approaching the 50-year anniversary of its release on January 11, 1964.¹ Glynn grew up in a New York City apartment where both parents smoked and his grandfather puffed a pipe. His father died of lung cancer.

"I remember clearly it got a lot of news ... 1964 was the highpoint, depending on your point of view,



Ads depicting smoking doctors appeared regularly in *JAMA* from 1933 until 1953, fostering an odd relationship between AMA and tobacco companies.

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Accountable Care

The Quest for Better Survivorship: Guidelines Promote More Accountable Cancer Care

Peter Page



Crystal Denlinger, MD

Over the past 20 years, advances in cancer treatment have created a new challenge: How does medicine meet the needs of increasing numbers of patients who survive the disease?

Thanks to earlier detection and more effective therapies, roughly 14 million cancer survivors are now living in the United States, with this population expected to reach 18 million by 2020.¹

The challenges of survivorship were first spotlighted in the 2005 Institute of Medicine (IOM) report, *From Cancer Patient to Cancer Survivor: Lost in Transition*.² The study estimated that 10 million cancer survivors were then alive in the United States; that number had tripled in 30 years. About two-thirds, or more than 6 million people, were older than 65 years.² A large percentage of survivors, particularly those who are older, suffer chronic conditions in addition to cancer. The IOM report detailed systemic shortcomings in coordinating the nation's notoriously uncoordinated healthcare system to provide cancer care for aging patients with

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Provider Perspectives Current Thinking Behind Decision Making in Oncology Clinical Pathway Design

Rhonda Greenapple, MSPH

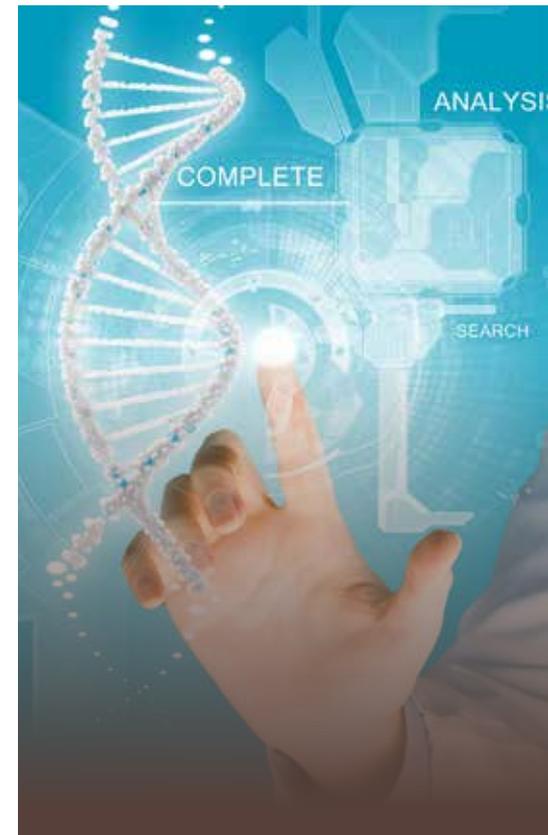
The wide variety and high cost of available treatments for patients with cancer can present challenges to clinicians for deciding upon the most appropriate and cost-effective care.¹ These challenges will only increase with time because recent data show that there are now nearly 1000 medicines and vaccines in the oncology pipeline.² Moreover, the cost for currently available cancer medications increased 22.3% in 2012, with utilization increasing 3.4%.³ Genetically targeted therapies represent much of the increase in the cost of cancer medicines. In 2012, specialty conditions accounted for 24.5% of the drug spend in the United States, with many of the 22 new specialty drugs approved that year costing more than \$10,000 per month of treatment.² The increasing number, type, and cost of cancer therapies confront healthcare providers and payers alike with a pressing need for a method to identify the most effective treatments and reduce cancer care-related costs.

Clinical pathways are a means by which clinicians can arrive at appropriate treatment decisions in cancer care and, at the same time, help reduce costly treatment variation and improve quality of care.¹ In addition, oncology care providers who adhere



Rhonda Greenapple, MSPH

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Also in this issue...

- SP453 FDA Tells Genetic Testing Firm 23andMe to Halt Marketing
- SP456 Safety Concerns Halt Ponatinib Development
- SP456 FDA Approves Ibrutinib for Mantle Cell Lymphoma



Finley Matloff Brawley

- SP441 Genetic Testing Should Come With Counseling
- SP440 Congress Takes Aim at Medicare SGR Formula

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There is a choice

Choose TAFINLAR[®] (dabrafenib) capsules

For the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Limitation of use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma.

Important Safety Information for TAFINLAR

New Primary Cutaneous Malignancies

TAFINLAR results in an increased incidence of cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma. In Trial 1, cutaneous squamous cell carcinomas and keratoacanthomas (cuSCC) occurred in 7% (14/187) of patients treated with TAFINLAR and in none of the patients treated with dacarbazine (DTIC). Across clinical trials of TAFINLAR (n=586), the incidence of cuSCC was 11%. The median time to first cuSCC was 9 weeks (range: 1 to 53 weeks). Of those patients who developed a cuSCC, approximately 33% developed one or more cuSCC with continued TAFINLAR. The median time between diagnosis of the first cuSCC and the second cuSCC was 6 weeks.

In Trial 1, the incidence of new primary malignant melanomas was 2% (3/187) for patients receiving TAFINLAR while no DTIC-treated patient was diagnosed with new primary malignant melanoma. Perform dermatologic evaluations prior to initiation of TAFINLAR, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR.

Tumor Promotion in BRAF Wild-Type Melanoma

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation status prior to initiation of TAFINLAR.

Serious Febrile Drug Reactions

In Trial 1, serious febrile drug reactions, defined as serious cases of fever or fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure in the absence of another identifiable cause (eg, infection) occurred in 3.7% (7/187) of patients treated with TAFINLAR and in none of the patients treated with DTIC. The incidence of fever (serious and non-serious) was 28% in patients treated with TAFINLAR and 10% in patients treated with DTIC. In patients treated with TAFINLAR, the median time to initial onset of fever (any severity) was 11 days (range: 1 to 202 days) and the median duration of fever was 3 days (range: 1 to 129 days).

Withhold TAFINLAR for fever of 101.3°F or greater or for any serious febrile drug reaction and evaluate for signs and symptoms of infection. Refer to Table 1 in the Prescribing Information for recommended dose modifications for adverse reactions. Prophylaxis with antipyretics may be required when resuming TAFINLAR.

Hyperglycemia

Hyperglycemia requiring increase in dose or initiation of insulin or oral hypoglycemic agent therapy can occur with TAFINLAR. In Trial 1, 5 of 12 patients with a history of diabetes required more intensive hypoglycemic therapy while taking TAFINLAR. The incidence of Grade 3 hyperglycemia based on laboratory values was 6% (12/187) in patients treated with TAFINLAR compared to none of the DTIC-treated patients.

Monitor serum glucose levels as clinically appropriate during treatment with TAFINLAR in patients with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia, such as excessive thirst or any increase in the volume or frequency of urination.

Uveitis and Iritis

Uveitis (including iritis) occurred in 1% (6/586) of patients treated with TAFINLAR across clinical trials. Symptomatic treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (eg, change in vision, photophobia, and eye pain).

Glucose-6-Phosphate Dehydrogenase Deficiency

TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Closely observe patients with G6PD deficiency for signs of hemolytic anemia.

Embryofetal Toxicity

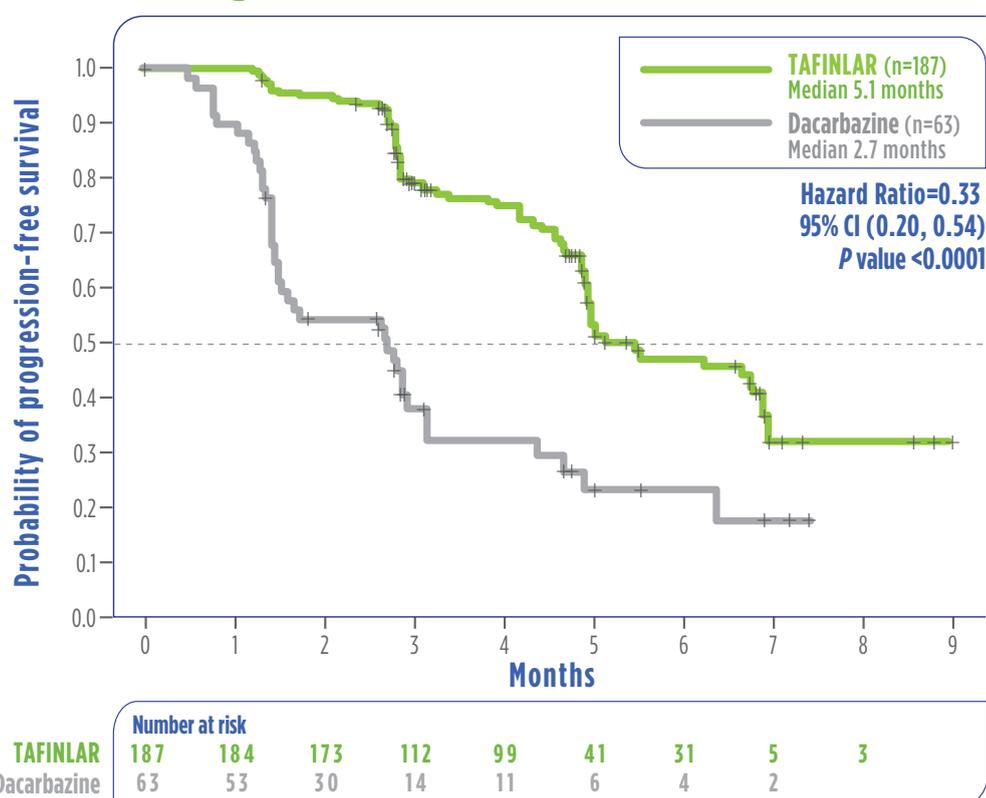
TAFINLAR can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use a highly effective non-hormonal method of contraception during treatment and for 4 weeks after treatment since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant or if pregnancy is suspected while taking TAFINLAR.

Most Common Adverse Reactions

The most common ($\geq 10\%$) adverse reactions (all grades) for TAFINLAR versus dacarbazine included hyperkeratosis (37% vs 0%), headache (32% vs 8%), pyrexia (28% vs 10%), arthralgia (27% vs 2%), papilloma (27% vs 2%), alopecia (22% vs 2%), palmar-plantar erythrodysesthesia syndrome (20% vs 2%), rash (17% vs 0%), back pain (12% vs 7%), cough (12% vs 5%), constipation (11% vs 14%), myalgia (11% vs 0%), and nasopharyngitis (10% vs 3%).

Median progression-free survival (PFS) nearly doubled with TAFINLAR vs dacarbazine¹

Investigator-assessed PFS¹



BREAK-3 study design: A Phase 3, multicenter, randomized, open-label, active-controlled trial in previously untreated patients with BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients were randomized (3:1) to receive TAFINLAR 150 mg orally twice daily (n=187) or dacarbazine 1,000 mg/m² intravenously every 3 weeks (n=63). The main efficacy outcome measure was investigator-assessed PFS.^{1,2}

TAFINLAR significantly extended median PFS to 5.1 months (95% CI: 4.9, 6.9) compared to 2.7 months (1.5, 3.2) with dacarbazine.

The number of PFS events was 78 (42%) and 41 (65%) for TAFINLAR and dacarbazine, respectively.¹

TAFINLAR demonstrated superior objective response rates compared to dacarbazine—**52% vs 17% (95% CI: [44, 59] vs [9, 29], respectively)¹**

- **Complete response:** TAFINLAR—n=6 (3%), dacarbazine—n=0; **partial response:** TAFINLAR—n=91 (48%), dacarbazine—n=11 (17%); **median (95% CI) duration of response:** TAFINLAR—5.6 months (5.4, NR [not reached]), dacarbazine—NR (5.0, NR)

The most common ($\geq 2\%$) adverse reactions (grades 3 and 4) for TAFINLAR versus dacarbazine included cutaneous squamous cell carcinoma (4% vs 0%), back pain (3% vs 0%), pyrexia (3% vs 0%), constipation (2% vs 0%), and palmar-plantar erythrodysesthesia syndrome (2% vs 0%).

Drug Interactions

Effects of Other Drugs on Dabrafenib

Drugs that Inhibit or Induce Drug-Metabolizing Enzymes: Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease, respectively, concentrations of dabrafenib. Substitution of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors (eg, ketoconazole, nefazodone, clarithromycin, gemfibrozil) or strong inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors or loss of efficacy when taking strong inducers.

Drugs that Affect Gastric pH: Drugs that alter the pH of the upper GI tract (eg, proton pump inhibitors, H₂-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability.

Effects of Dabrafenib on Other Drugs

Dabrafenib induces CYP3A4 and may induce other enzymes, including CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UDP glucuronosyltransferases (UGT), and may induce

transporters. Coadministration of TAFINLAR with other substrates of these enzymes, including warfarin, dexamethasone, or hormonal contraceptives, can result in decreased concentrations and loss of efficacy. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

References: 1. TAFINLAR [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013. 2. Hauschild A, Grob J-J, Demidov LV, et al. *Lancet*. 2012;380:358-365.

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Tafinlar[®]
(dabrafenib)
 50 mg, 75 mg capsules

Please see Brief Summary of the full Prescribing Information on the following pages.

To learn more, visit TAFINLARHCP.com

BRIEF SUMMARY

TAFINLAR® (dabrafenib) capsules for oral use

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Cutaneous Malignancies

TAFINLAR results in an increased incidence of cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma. In Trial 1, cutaneous squamous cell carcinomas and keratoacanthomas (cuSCC) occurred in 7% (14/187) of patients treated with TAFINLAR and in none of the patients treated with dacarbazine. Across clinical trials of TAFINLAR (n = 586), the incidence of cuSCC was 11%. The median time to first cuSCC was 9 weeks (range: 1 to 53 weeks). Of those patients who developed a cuSCC, approximately 33% developed one or more cuSCC with continued TAFINLAR. The median time between diagnosis of the first cuSCC and the second cuSCC was 6 weeks.

In Trial 1, the incidence of new primary malignant melanomas was 2% (3/187) for patients receiving TAFINLAR while no chemotherapy-treated patient was diagnosed with new primary malignant melanoma.

Perform dermatologic evaluations prior to initiation of TAFINLAR, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR.

5.2 Tumor Promotion in BRAF Wild-Type Melanoma

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E mutation status prior to initiation of TAFINLAR [see *Indications and Usage (1) and Dosage and Administration (2.1) of full Prescribing Information*].

5.3 Serious Febrile Drug Reactions

In Trial 1, serious febrile drug reactions, defined as serious cases of fever or fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure in the absence of another identifiable cause (e.g., infection) occurred in 3.7% (7/187) of patients treated with TAFINLAR and in none of the patients treated with dacarbazine. The incidence of fever (serious and non-serious) was 28% in patients treated with TAFINLAR and 10% in patients treated with dacarbazine. In patients treated with TAFINLAR, the median time to initial onset of fever (any severity) was 11 days (range: 1 to 202 days) and the median duration of fever was 3 days (range: 1 to 129 days).

Withhold TAFINLAR for fever of 101.3°F or greater or for any serious febrile drug reaction and evaluate for signs and symptoms of infection. Refer to Table 1 for recommended dose modifications for adverse reactions [see *Dosage and Administration (2.3) of full Prescribing Information*]. Prophylaxis with antipyretics may be required when resuming TAFINLAR.

5.4 Hyperglycemia

Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycemic agent therapy can occur with TAFINLAR. In Trial 1, five of 12 patients with a history of diabetes required more intensive hypoglycemic therapy while taking TAFINLAR. The incidence of Grade 3 hyperglycemia based on laboratory values was 6% (12/187) in patients treated with TAFINLAR compared to none of the dacarbazine-treated patients.

Monitor serum glucose levels as clinically appropriate during treatment with TAFINLAR in patients with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

5.5 Uveitis and Iritis

Uveitis (including iritis) occurred in 1% (6/586) of patients treated with TAFINLAR across clinical trials. Symptomatic treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, and eye pain).

5.6 Glucose-6-Phosphate Dehydrogenase Deficiency

TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Closely observe patients with G6PD deficiency for signs of hemolytic anemia.

5.7 Embryofetal Toxicity

Based on its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended clinical dose. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Use in Specific Populations (8.1)*].

Advise female patients of reproductive potential to use a highly effective non-hormonal method of contraception during treatment and for 4 weeks after treatment since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR [see *Drug Interactions (7.2), Use in Specific Populations (8.6)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in another section of the label.

- New Primary Cutaneous Malignancies [see *Warnings and Precautions (5.1)*]
- Tumor Promotion in BRAF Wild-Type Melanoma [see *Warnings and Precautions (5.2)*]
- Serious Febrile Drug Reactions [see *Warnings and Precautions (5.3)*]
- Hyperglycemia [see *Warnings and Precautions (5.4)*]
- Uveitis and Iritis [see *Warnings and Precautions (5.5)*]

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 TAFINLAR was evaluated in 586 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity, including 181 patients treated

for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range: 118 to 300 mg).

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of Trial 1 [see *Clinical Studies (14) of full Prescribing Information*]. Trial 1, a multi-center, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m² intravenously every 3 weeks (n = 63). The trial excluded patients with abnormal left ventricular ejection fraction or cardiac valve morphology (≥Grade 2), corrected QT interval ≥480 milliseconds on electrocardiogram, or a known history of glucose-6-phosphate dehydrogenase deficiency. The median duration on treatment was 4.9 months for patients treated with TAFINLAR and 2.8 months for dacarbazine-treated patients. The population exposed to TAFINLAR was 60% male, 99% white, and had a median age of 53 years.

The most commonly occurring adverse reactions (≥20%) in patients treated with TAFINLAR were, in order of decreasing frequency: hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome (PPES).

The incidence of adverse events resulting in permanent discontinuation of study medication in Trial 1 was 3% for patients treated with TAFINLAR and 3% for patients treated with dacarbazine. The most frequent (≥2%) adverse reactions leading to dose reduction of TAFINLAR were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%).

Table 3. Selected Common Adverse Reactions Occurring in ≥10% (All Grades) or ≥2% (Grades 3 or 4) of Patients Treated with TAFINLAR^a

Primary System Organ Class Preferred Term	TAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4 ^b (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and subcutaneous tissue disorders				
Hyperkeratosis	37	1	0	0
Alopecia	22	NA ^f	2	NA ^f
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system disorders				
Headache	32	0	8	0
General disorders and administration site conditions				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue disorders				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Papilloma ^c	27	0	2	0
cuSCC ^{d,e}	7	4	0	0
Gastrointestinal disorders				
Constipation	11	2	14	0
Respiratory, thoracic, and mediastinal disorders				
Cough	12	0	5	0
Infections and infestations				
Nasopharyngitis	10	0	3	0

^aAdverse drug reactions, reported using MedDRA and graded using CTCAE version 4.0 for assessment of toxicity.

^bGrade 4 adverse reactions limited to hyperkeratosis (n = 1) and constipation (n = 1).

^cIncludes skin papilloma and papilloma.

^dIncludes squamous cell carcinoma of the skin and keratoacanthoma.

^eCases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol.

^fNA = not applicable

Table 4. Incidence of Laboratory Abnormalities Increased from Baseline Occurring at a Higher Incidence in Patients Treated with TAFINLAR in Trial 1 [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3 or 4)]

	Dabrafenib N = 187		DTIC N = 59	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6 ^a	14	2
Increased Alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

^aGrade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

Other clinically important adverse reactions observed in <10% of patients (N = 586) treated with TAFINLAR were:

Gastrointestinal Disorders: Pancreatitis.

Immune System Disorders: Hypersensitivity manifesting as bullous rash.

Renal and Urinary Disorders: Interstitial nephritis.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Dabrafenib

Drugs that Inhibit or Induce Drug-Metabolizing Enzymes: Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease, respectively, concentrations of dabrafenib [see *Clinical Pharmacology (12.3) of full Prescribing Information*]. Substitution of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, gemfibrozil) or strong inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors or loss of efficacy when taking strong inducers.

Drugs that Affect Gastric pH: Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H₂-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of dabrafenib. When TAFINLAR is coadministered with a proton pump inhibitor, H₂-receptor antagonist, or antacid, systemic exposure of dabrafenib may be decreased and the effect on efficacy of TAFINLAR is unknown.

7.2 Effects of Dabrafenib on Other Drugs

Dabrafenib induces CYP3A4 and may induce other enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UDP glucuronosyltransferases (UGT) and may induce transporters. Dabrafenib decreased the maximum concentration (C_{max}) and area under the curve (AUC) of midazolam (a substrate of CYP3A4) by 61% and 74%, respectively [see *Clinical Pharmacology (12.3) of full Prescribing Information*]. Coadministration of TAFINLAR with other substrates of these enzymes, including warfarin, dexamethasone, or hormonal contraceptives, can result in decreased concentrations and loss of efficacy [see *Use in Specific Populations (8.1, 8.6)*]. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary: Based on its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses 3 times greater than the human exposure at the recommended clinical dose of 150 mg twice daily based on AUC. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Warnings and Precautions (5.7)*].

Animal Data: In a combined female fertility and embryofetal development study in rats, developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape at a dabrafenib dose of 300 mg/kg/day (approximately 3 times the human exposure at the recommended dose based on AUC). At doses of 20 mg/kg/day or greater (equivalent to the human exposure at the recommended dose based on AUC), rats demonstrated delays in skeletal development and reduced fetal body weight.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of TAFINLAR have not been established in pediatric patients.

8.5 Geriatric Use

One hundred and twenty-six (22%) of 586 patients in clinical trials of TAFINLAR and 40 (21%) of the 187 patients receiving TAFINLAR in Trial 1 were ≥65 years of age. No overall differences in the effectiveness or safety of TAFINLAR were observed in the elderly in Trial 1.

8.6 Females and Males of Reproductive Potential

Contraception:

Females

Advise female patients of reproductive potential to use highly effective contraception during treatment and for 4 weeks after treatment. Counsel patients to use a non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR [see *Warnings and Precautions (5.7), Drug Interactions (7.1), Use in Specific Populations (8.1)*].

Infertility:

Males

Effects on spermatogenesis have been observed in animals. Advise male patients of the potential risk for impaired spermatogenesis, and to seek counseling on fertility and family planning options prior to starting treatment with TAFINLAR [see *Nonclinical Toxicology (13.1)*].

8.7 Hepatic Impairment

No formal pharmacokinetic trial in patients with hepatic impairment has been conducted. Dose adjustment is not recommended for patients with mild hepatic impairment based on the results of the population pharmacokinetic analysis. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, patients

with moderate to severe hepatic impairment may have increased exposure. An appropriate dose has not been established for patients with moderate to severe hepatic impairment [see *Clinical Pharmacology (12.3) of full Prescribing Information*].

8.8 Renal Impairment

No formal pharmacokinetic trial in patients with renal impairment has been conducted. Dose adjustment is not recommended for patients with mild or moderate renal impairment based on the results of the population pharmacokinetic analysis. An appropriate dose has not been established for patients with severe renal impairment [see *Clinical Pharmacology (12.3) of full Prescribing Information*].

10 OVERDOSAGE

There is no information on overdosage of TAFINLAR.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with dabrafenib have not been conducted. TAFINLAR increased the risk of cutaneous squamous cell carcinomas in patients in clinical trials.

Dabrafenib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay, and was not clastogenic in an in vivo rat bone marrow micronucleus test.

In a combined female fertility and embryofetal development study in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant females at 300 mg/kg/day (which is approximately three times the human exposure at the recommended dose based on AUC).

Male fertility studies with dabrafenib have not been conducted; however, in repeat-dose studies, testicular degeneration/depletion was seen in rats and dogs at doses equivalent to and three times the human exposure at the recommended dose based on AUC, respectively.

13.2 Animal Toxicology and/or Pharmacology

Adverse cardiovascular effects were noted in dogs at dabrafenib doses of 50 mg/kg/day (approximately five times the human exposure at the recommended dose based on AUC) or greater, when administered for up to 4 weeks. Adverse effects consisted of coronary arterial degeneration/necrosis and hemorrhage, as well as cardiac atrioventricular valve hypertrophy/hemorrhage.

17 PATIENT COUNSELING INFORMATION

See *FDA-approved patient labeling (Medication Guide)*.

Inform patients of the following:

- Evidence of BRAF V600E mutation in the tumor specimen is necessary to identify patients for whom treatment with TAFINLAR is indicated [see *Dosage and Administration (2.1) of full Prescribing Information*].
- TAFINLAR increases the risk of developing new primary cutaneous malignancies. Advise patients to contact their doctor immediately for any new lesions or changes to existing lesions on their skin [see *Warnings and Precautions (5.1)*].
- TAFINLAR causes pyrexia including serious febrile drug reactions. Instruct patients to contact their doctor if they experience a fever while taking TAFINLAR [see *Warnings and Precautions (5.3)*].
- TAFINLAR can impair glucose control in diabetic patients resulting in the need for more intensive hypoglycemic treatment. Advise patients to contact their doctor to report symptoms of severe hyperglycemia [see *Warnings and Precautions (5.4)*].
- TAFINLAR may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Advise patients with known G6PD deficiency to contact their doctor to report signs or symptoms of anemia or hemolysis [see *Warnings and Precautions (5.6)*].
- TAFINLAR can cause fetal harm if taken during pregnancy. Instruct female patients to use non-hormonal, highly effective contraception during treatment and for 4 weeks after treatment. Advise patients to contact their doctor if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR [see *Use in Specific Populations (8.1)*].
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With this issue, *Evidence-Based Oncology* marks a milestone: the 50th anniversary of the report to the US Surgeon General, *Smoking and Health*. The 1964 report would change the way the nation thought about cigarettes, even if it took years to drive them from our daily lives. Though smoking may seem like an old story, it is not: Cigarettes cause 1 in 5 American deaths, or 440,000 a year. Many of those deaths are from cancer, especially lung cancer, the incidence of which took off after cigarettes were distributed to troops during World War I. The 1964 report's conclusion that cigarettes caused lung cancer in men and probably in women was the thunderclap that began reversing a half-century of smoking; at their peak, cigarettes were everywhere and 42% of the population smoked; today, most Americans live in places with smoke-free laws and only 19% of us smoke. That is a victory, despite the work that remains.

As the population ages, and treatments improve, we are confronting cancer as a chronic condition. Earlier this year, the National Comprehensive Cancer Network (NCCN) released its first guidelines for survivorship, and they are being implemented around the country. Our story in *EBO* shows how the discussion of survivorship affects the way patients are treated, the way doctors are paid, and the way hospitals are changing systems to better accommodate those living with cancer. It's all part of the movement in medicine to focus our efforts on what makes sense for the patient.

To that end, Congress this month appears ready to repeal and replace the Medicare Sustainable Growth Rate (SGR), a failed mechanism that has not kept pace with the movement away from fee-for-service and toward accountable care. Scrapping SGR and moving toward a system that rewards best practices is essential, but it remains to be seen whether lawmakers can avoid creating a system of winners and losers. It has been good to see groups like the Community Oncology Alliance (COA) and the American Society of Clinical Oncology (ASCO) front and center advocating for a system that will improve care. We will follow this issue and report back in February. As always, look for updates on www.ajmc.com, and thank you for reading.

Sincerely,

Brian Haug
Publisher

Our story in EBO shows how the discussion of survivorship affects the way patients are treated, the way doctors are paid, and the way hospitals are changing systems to better accommodate those living with cancer. It's all part of the movement in medicine to focus our efforts on what makes sense for the patient.

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

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“We are very proud, as an organization, that we were at the table at that meeting when it was agreed to make an objective assessment of the health effects of tobacco.”

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“We are going from the Big C, that automatically killed people and we couldn’t do much about it, to cancer as a chronic disease or a disease we can cure.”

Crystal Denlinger, MD

We hope you enjoy our special report on the 50th anniversary of Smoking and Health. Status in the States will resume in January/February 2014 with a look at cancer care in Washington state.

Oncology Groups Active in Effort to Repeal SGR

Mary K. Caffrey

Talk about a “fiscal cliff.”

The eyes of America’s doctors will be fixed this month on the nation’s capital, as Congress appears poised to repeal the Medicare Sustainable Growth Rate, or SGR. Should lawmakers fail to undo the much-maligned formula, physicians would face Medicare cuts of at least 24% on January 1, 2014.¹ While this seems unlikely, doctors—and oncologists in particular—are learning the cure is hardly without side effects.

A bipartisan proposal unveiled October 30, 2013, would replace SGR with a reimbursement scheme that moves doctors away from fee-for-service and closer to compensation based on quality of care, as envisioned under the Affordable Care Act (ACA). But, to keep a lid on spending, Congress included some pills that doctors may find hard to swallow: a 10-year payment freeze, and, for oncologists, a system of winners and losers; some fear this will discourage sharing best practices and penalize some physicians who are generally doing a good job.²

The fact that the American Medical Association’s (AMA’s)³ House of Delegates supports the proposal and the American Society of Clinical Oncology (ASCO) is “encouraged”⁴ by its broad outlines speaks to the need to get rid of SGR, which has consistently failed to keep up with Medicare Part B expenditures. Doctors want an end to the annual uncertainty of waiting for the Congressional “patch” to cover the mounting SGR shortfall.⁵ Still, both AMA and ASCO, as well as the Community Oncology Alliance (COA),⁵ have expressed reservations with elements of proposal.

The oncology groups cite details of the plan they say will undermine its goal of moving from fee-for-service to payment for quality, as well as aspects they say will hasten the march of cancer treatment into expensive hospital settings.^{1,2} The AMA joins the oncologists in asking whether the 10-year payment freeze, coming on top of Medicare cuts physicians have already endured, will allow practices to invest in technology and other changes needed to move toward new payment models.⁵

After years of waiting for an SGR remedy, however, oncology groups appear willing to work with the current proposal. At the meeting Value-Based Oncology Management in Chicago, Illinois, Ted Okon, executive director of COA, spoke a day before Congress’ proposal was announced. Okon outlined the “destructive” effects that current Medicare reimbursement policies have had on community clinics. Since 2005, after Congress altered Medicare cancer drug reimbursement formula—pegging to average sales price instead of average wholesale price—Okon said 288 clinics have closed, and 469 have been acquired or have a physicians’ services agreement with a hospital.



Ted Okon

“The community share of oncology patients is declining,” Okon said. “More and more I hear physicians say, ‘I give up.’ These are well-run practices.”

Years of uncertainty over Medicare reimbursement have left practices unwilling or unable to make long-term investments, he said. “They say, ‘We strategic plan day-by-day.’”

The Arc of the SGR Shortfall

The problem with SGR dates to 1997, when Congress created the formula in an effort to control spending. The formula was supposed to set realistic yearly and cumulative spending targets; if the cost of care exceeded the target in any given year, rates would be cut the following year to make up the difference.

However, inaccurate forecasts meant actual Medicare Part B spending has exceeded the target for more than a decade. Each year, the “sword of Damocles,” as UCAMA president Ardis Hoven, MD, called it,⁵ would hang over physicians’ heads as they waited for Congress to pass legislation to thwart the automatic triggers that would absorb the accumulating shortfall. Yet the longer Congress failed to fix SGR, the worse the problem grew. In May 2012, in an interview with *Evidence-Based Oncology*, ASCO chief executive officer Allen S. Lichter, MD, called the situation “the classic kick-the-can-down-the-road.”⁶

How big is the problem? Estimates for getting rid of SGR include \$377 billion for

2012 and \$139 billion for 2013,⁸ and there are no good answers on how to address it. When asked how the repeal would be funded, AMA’s Hoven said, “I don’t think we really know.”⁵

Problems with Medicare’s dysfunctional reimbursement model have hit oncology especially hard, and the effects of the federal sequester have only made things worse, Okon explained in Chicago. Oncology’s buy-and-bill system of administering increasingly expensive medications, the diversity of disease states, and the fact that so many cancer patients are older and reliant on Medicare mean an outdated reimbursement model is acutely felt in oncology. According to the American Cancer Society’s 2013 report, 77% of all new cancers are diagnosed in persons 55 years or older.⁷

In his 2012 interview with EBO, ASCO’s Lichter outlined just how an unreformed fee-for-service payment model fails the oncologist, since the total amount of Medicare funding is capped. “Over time, the number of things physicians can do, and the number of patients and the number of medical conditions that we can now affect, has just grown and grown and grown. If the amount of funding to pay the fees is finite, and to some extent the number of things we can do keeps growing and growing, then the fee for each unit of service needs to be cut. That’s essentially, in very broad brush strokes, how the SGR dug the hole that we’re in,” he said.⁶

Meanwhile, the scientific side of cancer treatment—including new therapies and the impact of genetics on treatment—has been transformed. With that transformation has come the call for oncology to move with the rest of medicine toward a payment model that rewards quality. But while multiple pay-for-quality demonstration programs exist in cancer care, as long as Medicare stuck with SGR, change would be difficult.

The lack of resolution has not been good for doctors or patients, Okon told the Chicago gathering. More and more patients have been pushed into hospitals for chemotherapy, where costs are higher. Shortages of key chemotherapy drugs, especially generics, have emerged, along with parts of the country where care is limited.

“If you look at a state like Wyoming, you see we’ve created treatment cracks in rural areas,” Okon said. “Drug shortages have cost lives in this country.”

Oncologists’ Concerns With Proposal

This year, Congress vowed to craft a permanent fix; however, the proposal as drafted did not appear to commit any new funding to closing the shortfall. AMA’s Hoven told *MedPage Today*, “We understand the fiscal issues very clearly, and we understand there are going to have to be offsets,” she said. “But ... to ask physicians to sustain a freeze for another 10 years on top of what they have already sustained, when the cost of care continues to rise ... is not reasonable ei-

“If you look at a state like Wyoming, you see we’ve created treatment cracks in rural areas. Drug shortages have cost lives in this country.”

—Ted Okon,

Community Oncology Alliance

ther. You have to balance the two.”⁵

Beyond the concern with the rate freeze, both ASCO and COA have raised issues with the proposal that the groups feel undermine its expressed goal of moving away from fee-for-service.

ASCO president Clifford A. Hudis, MD, raised many issues in a letter to chairs and ranking members of the Senate Finance and House Ways and Means committees.² Among them:

- The use of a proposed Value-Based Performance (VBP) payment program could end up penalizing practices that are doing good work—and, in fact, improving—but still rank slightly below their peers. Denying these practices resources, especially those located in underserved areas, risks putting them out of business and adding to shortages of oncologists.

- Imposing a VBP program and a rate freeze at once would give practices little time or ability to transition to a pay-for-performance model, including making investments in information technology.

- Lack of detail about quality measures concerns oncologists, who have many subspecialties; ASCO seeks to govern the standards that Medicare will use. For this same reason, ASCO wants to test alternative payment models (APMs) before they are fully implemented.

- Instead of creating a system of winners and losers, ASCO seeks “thresholds”: if the physician or practice met certain standards, reimbursement would be granted; more would be paid to providers that meet a higher standard.²

COA expressed similar concerns in comments to committees, noting that quality measures and APMs that make sense for other medical specialties may not make sense for oncology. COA also expressed concerns about the effect of heavy penalties from VBP on small practices, and the group also warned against giving 1 entity the ability to certify medical homes.

In Chicago, Okon outlined the COA payment reform model: a 4-phase, 5-year model based on 19 quality measures that were developed with input from stakeholders that make up the group’s Oncology Medical Home Steering Committee. COA’s model specifically calls for pay-for-performance, with 50-50 shared savings by the third year. The model also calls for patient satisfaction to be included in any pay-for-performance mechanism.

Most of all, Okon noted, “We are very concerned about the provisions relating to (APMs), and it is difficult to definitely comment on this aspect of the committees’ work until we see legislative language.”¹

Both oncology groups fear that the cost of getting rid of SGR would cause Congress to fold all these liabilities into the new APM models, with little opportunity for the oncologists to respond.^{1,2}

That said, Okon warned that Medicare reimbursement reform must happen. “If the current SGR-based system is not fundamentally fixed, along with the current (sequester) and proposed (Medicare fee schedule) reimbursement cuts to cancer care,” according to Okon, “physician payment reform will become an academic exercise because all cancer care will be shifted into hospitals.”¹

Hearings in Congress on the proposal were scheduled for December 12, 2013, as *Evidence-Based Oncology* was going to press. **EBO**

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Panel Discussion

Genetic Testing Should Come With Counseling

American Cancer Society CMO, Supreme Court Plaintiff Among Experts Who Warn of Consumer Risks

Produced by Nicole Beagin

This fall, *The American Journal of Managed Care* convened a panel of leading medical professionals and genetic counselors to discuss how the exploding field of genetic testing is affecting cancer prevention, diagnosis, and treatment. **Jan Berger, MD, MJ**, president & CEO, Health Intelligence Partners, and editor-in-chief, *The American Journal of Pharmacy Benefits*, served as the moderator for a wide-ranging discussion, including issues that have arisen since June 13, 2013, when the US Supreme Court opened the door to competition in genetic testing with its *Myriad* decision.

Panelists included **Otis Brawley, MD**, chief medical officer, American Cancer Society; **David H. Finley, MD, FACS**, national medical officer, enterprise affordability and policy, Cigna; **Joy Larsen-Haidle, MS**, genetic counselor, Hubert H. Humphrey Cancer Center; **Ellen T. Matloff, MS**, research scientist, Department of Genetics and director, Cancer Genetic Counseling, Yale Cancer Center; and **Rebecca Nagy, MS**, genetic counselor and president, National Society of Genetic Counselors.

The following transcript has been edited for clarity, style, and length. To hear the full discussion, please visit <http://www.ajmc.com/ajmc-tv/panel-discussion/genetic-testing>.

Jan Berger, MD, MJ: Let’s focus first on the unmet needs and challenges. What is the current uptake of genetic testing? We see increased utilization and increased availability. So are we seeing greater use? Is it in the employer market? Is it in the health plan market? Who’s leading the charge in this area? Ellen Matloff, would you get us started?

Ellen Matloff, MS: I think the other genetic counselors on this panel have been much more involved in this area than I have to date, but my group has been able to document over

the years some of the mistakes that are being made in genetic testing and also in prophylactic surgery, as well as surveillance for patients who aren’t getting the genetic counselling they need by a certified provider—both before and after having testing.

Berger: Joy Larsen-Haidle, can you share what are you seeing as a genetic counsellor? Are you seeing an increased uptick in genetic testing?

Joy Larsen-Haidle, MS: Yes, I am. Since the end of June there’s been a significant increase in the number of requests for genetic counselling and genetic testing, as well as differences in the type of testing that

are available. I’ve been a genetic counsellor for 18 years, and it’s been a lovely experience to watch that trend where

genetic counselors have become more integrated in routine medical care. We are part of that conversation when patients and physicians are developing their care plan, and I think that trend will continue. With the court decision and the media attention around BRCA testing that trend will likely continue.

Berger: Dr Brawley, how are you all at the American Cancer Society both impacted by and impacting the current uptick?

Otis Brawley, MD: “Uptick” is actually a very good word. We’ve received many more calls to our 800-number from people seeking information. We have advised people to get genetic counselling before getting genetic testing. One of the tendencies that we’re seeing is that people who want genetic testing without the counseling. They sometimes want it ask for a specific test, and we have people who probably don’t need testing getting BRCA testing. There are those being tested for BRCA who probably should be tested for Li-Fraumini syndrome or other syndromes.



Jan Berger, MD, MJ

Berger: That's interesting that you brought up the counseling before testing. Dr Finley, you know I can't let you go without asking this: Cigna has made a precedent setting move of requiring—not just offering but requiring—genetic counseling by a certified provider prior to breast and colon cancer genetic testing. There's been some noise to this and a bit of pushback. Do you believe other insurers will follow in your footsteps? And also, are there enough genetic counselors to meet the need for this protocol?

David Finley, MD: I don't have a hope whether the other insurers follow or don't follow us. It's not my primary or even secondary focus. I just hope that Cigna's program will succeed in steering people toward genetic counseling and better care. Let me comment on the trend: As a payer we have the advantage of being able to look at claims history and see what's happening in

it's not. I don't think it's one size fits all. In order to make sure that our Cigna customers can get the genetic counseling they need, we have contracted with a genetic counseling firm, IMD, that does these consultations telephonically; if there is a Cigna customer in a market where they cannot get a face-to-face appointment, that person can take advantage of the telephonic counseling with board-certified genetic counselors.

Brawley: If I can just say why women should talk to a genetic counselor before being tested—men for that matter, too, because occasionally we have men who want testing. As a physician, I have had to deal with women who have been tested and ended up with



Otis Brawley, MD

syndrome, but because they've heard about BRCA they insist on getting the BRCA testing. They don't get tested for these other things.

If I could just add one more thing: agree with everything that you said, Dr Finley, and that's one of the motivators behind our program. The other misunderstanding that I believe is out there, but I'd like your comment, is it true that some women misunderstand what the BRCA is and what it does, and they feel that if they're negative for BRCA they don't have to worry about getting breast cancer?

Finley: You're absolutely correct; 95% of women who get breast cancer don't have any of these mutations, and then there are mutations out there that we don't know about yet. I can remember people were concerned when we had BRCA1, and women were tested for BRCA1 and they were so reassured that they tested negative for BRCA1, and then a few months later we had BRCA2; those same women went through the same thing again and finally were found to be positive for BRCA2. There are other mutations out there that we don't know about yet; and 95% of breast cancers are not due to genetic inheritance.

Berger: Those comments are all very, very important; they help us to think through a logical pathway for both educating and utilizing counselors in an appropriate way. I want to reach out to our counselors and ask: being involved with genetic counselors and being genetic counselors, first, is there a concern regarding the availability and number? Second, I want to bring up the telephonic genetic counseling and your thoughts on that.

Larsen-Haidle: Those are very good questions. As Dr Finley had alluded to, in certain markets in the United States there are many genetic counselors. In areas where the coverage isn't what we would like, such as rural areas or certain states, I think the numbers do present a problem. But being able to use the telephone genetic counseling or even tele-genetic services has started to bring down that type of a barrier. Patients don't have to worry

about distance; they can still reach a qualified provider to do that pre-test/posttest counseling and have access to someone to appropriately interpret that results. We do see a difference, at least in my state, between the patients who are in rural areas and their level of resources and access versus the patients that are in metropolitan areas. I think it is an important resource to allow counselors to visit with the patient over the phone and still be reimbursed for that time.

Rebecca Nagy, MS: I agree. The other model that we've adopted is handling tele-genetic counseling by Skype. Our clinic can Skype to several local hospitals, where the patient can come in and sit with the healthcare provider, such as a nurse, who is their local contact person and has some limited expertise in genetics. It offers the benefit of having somebody local—and I think a lot of people in rural areas especially feel comfortable having that contact at a hospital that they're familiar with, as well as a nurse who can help with referrals, while still getting the genetic counseling expertise through the phone or the computer. In terms of quality, I think there is an impression out there to this day that telephone counseling is not as effective as in-person counseling, and we genetic counselors worried about that for a long time. It's been very well studied. When you look at patient satisfaction and patient knowledge, there really isn't significant difference between the patient sitting with you versus being on the telephone. Now, there probably are some areas where it's better to be in person. Some pieces of that counseling occur more effectively when in person. But in terms of how the patients view it, they feel pretty satisfied by the telephone experience.

Berger: That's great to know. I want to turn for a moment to the Supreme Court decision in the *Myriad* case on June 13. I would ask: What have you seen as an impact on what each of you all do? I'd like each of you to comment on this. The press covered the Supreme Court ruling somewhat, but they did more with Angelina Jolie's disclosure (about having a bilateral mastectomy after BRCA testing). Can each of you discuss what the impact of these events has been?

Matloff: We had an unprecedented 3 months because the Supreme Court case went to trial in April, Angelina

I think there is an impression out there to this day that telephone counseling is not as effective as in-person counseling, and we genetic counselors worried about that for a long time. It's been very well studied. When you look at patient satisfaction and patient knowledge, there really isn't significant difference between the patient is sitting with you versus being on the telephone.

—Rebecca Nagy, MS

genetic testing. Our claims data show about a 15% annual uptick in genetic testing. And when I say "about," it's because of the change in coding that's occurred. So, it is an estimate as the coding has changes from 2011 to 2012 to 2013. Our best estimate is a 15% uptick per year. I'm sorry, the last part of your question?

Berger: I asked about the number of genetic counselors.

Finley: I think there are better experts on this panel to answer the question, but the way Cigna looks at it, in some markets, the number of genetic counselors is adequate. In certain markets

mutations of unknown significance, as opposed to a mutation that clearly increases significance by 40% or 80%. And what these women with mutations of unknown significance go through is just terrible—the emotional and mental anguish is terrible. Some of them actually force doctors to do bilateral mastectomies; in at least 3 instances I know of women have gone through this, and 3, 4, 5 years later what was a mutation of unknown significance is now known to be a mutation of no significance. Then you have the other issue that I talked about earlier: those who, based on family history, clearly have a genetic pattern that might be a Lynch syndrome or might be a Li-Fraumini

Jolie made her disclosure in May, and then the Supreme Court decision came out in June. We had a 40% increase in phone calls to our center during this period of time. One of my predictions before the ruling was that if the Supreme Court banned gene patents that within 3 months other laboratories would come forward and offer better, cheaper, faster testing. But wasn't I surprised when we started getting e-mail advertisements within 5 hours of this decision! Other labs had been anticipating this, and they were up and running, not only offering cheaper BRCA testing, but much more comprehensive, better testing. And all of these labs were also offering (to test for) other genes. So as we've discussed, BRCA1 and BRCA2 are not the only 2 genes associated with breast cancer development; some of these panels now include, believe it or not, 40 genes that can be associated in breast cancer development. In my view, having also been in the field for 18 years, the entire playing field changed very, very quickly. We suddenly had all of these options—we could order more testing for less money or certainly the same amount of money that we were taking for BRCA analysis from Myriad. This is both a good and a bad thing.

One of the things that I've found is that we had meetings with our whole staff after doing hours of research into all of the options. What each lab was offering, how much it would cost, what the turnaround time would be, and what techniques they were using. What are the pros and cons of this testing for genes? Some genes are clinically actionable, but others are not, so perhaps we don't want to know about them yet. And I thought to myself, "If we're struggling through this, how is the facility or an independent physician's office with no information about genetics going to now make these decisions—let alone interpret the results?"

Berger: Interesting. What about some of the rest of you all?

Nagy: With the Angelina Jolie news, we did see a brief but limited increase in the number of requests for utilization management. From the Supreme Court what we have gotten is about 4 or 5 inquiries from the labs that are offering the BRCA tests about contracting with us.

Berger: And some of the others? Are you busy? What are you finding?

Brawley: The Supreme Court had little effect on us. Long-term, with more

companies in the market and more companies advertising, this could change. Keep in mind, prior to the Supreme Court decision, Myriad had significant advertising campaigns encouraging women to talk to the doctors about BRCA testing. I think you have more companies that are doing that now than you had prior to the Supreme Court decision. After Ms Jolie's announcement—and I should point out that I thought her letter in *The New York Times* was very well written and very responsibly written—we had a large number of calls. We heard from people who suddenly were very interested in BRCA testing, and, unfortunately, not interested in anything but BRCA testing. We've also seen an increase in the number of women getting bilateral mastectomies, which may actually be unfortunate as well. Ms Jolie said it was the right decision for her, but it was not right for every woman, and I think that's absolutely correct. Many women who chose to get a bilateral mastectomy, if they were to sit back, think, and understand everything about it they might choose a different method of treating the present breast cancer.

Berger: Does anybody else have anything else they'd like to share on that?

Larsen-Haidle: I have to echo what everyone has said. Ms Jolie's announcement, which was courageous of her, resulted in a marked increase in the number of calls coming into our office but also in our referring provider network. Most of those calls were women who were what I'll call "the worried well," who had heard about the story and had a concern, but in most cases DNA testing would not have been appropriate for them. The genetic counseling realm helped to put that risk into perspective for them, and to help them understand why testing was not indicated for their family even though it was necessary for Ms Jolie's family. Our volume has sustained about 2½-fold higher than prior to her announcement. Her story raised a lot of general awareness.

I have to agree with what Ms Matloff and Dr Brawley and Dr Finley said about the Supreme Court decision. For us the testing choices have changed dramatically. It becomes important for us to look carefully at each of these panels and ask, what are the genes that are analyzed? How effectively are each of those genes analyzed, compared with what panel fits best with the person that's sitting in front of me? ... So the costs of testing have gone down, but it's

also allowed us to expand and address and on the same test another 20 to 25% of families that have an inherited risk. From the genetic counselor's standpoint, over the last year we've done some careful work trying to identify data. There are some studies out there that do indicate that when the genetic counselor is the person evaluating that family history, that we will identify risk factors that might be missed by other providers without specialized training in genetics. We have to identify those patients and, as Dr Brawley had mentioned, they may not need BRCA testing. They may need testing for Lynch or P53 or some other gene.

Berger: That's a great lead-in to my next question: Let's talk about the providers for a moment. How are they getting their education? How are they keeping up? There may be a number of providers that the patient population would be seeing, whether it's a nurse practitioner, a primary care doctor, an OB-GYN, or potentially somebody with greater specialty. But in the general healthcare area of the family physician, the PCP, or the nurse practitioner, is there confusion? How are they reacting to everything out there?

Brawley: I practice as a medical oncologist, and I'm a firm believer that there are so many things out there that no one person can master everything. So I think it's impossible for a generalist to understand everything that a person needs to understand about genetic counseling or about genetic testing. That's among the reasons I think it is very important for most of us, including myself, to refer patients to a genetic counselor for a conversation, even if that conversation has to happen over a telephone. A genetic counselor brings something to the table that many of us physicians simply cannot.

Nagy: Think about the training. Within the medical school curricula now there is more focus on genetics. There is more than there was maybe 10 years ago.

Berger: That's good to know, because when I trained there was very little, but that was in the dark ages.

Nagy: And it's gotten better over the past 5 years or so; there's more curriculum within the medical schools on this, but it's not enough to really dive deep into the nitty-gritty of the subject. But it's enough to at least make those medical students aware of the complexity, which is a good thing. Unfortunately for physicians who are already in practice, it's really up to them to seek out CME education that would give them a background on genetics. The most unfortunate circumstances occur when a laboratory that may profit from that physician or in a test is providing "education and training." What we're finding is that the education is really geared to the test, and it's not geared to the family history. So they're telling the physician how to order the test and when to order the test, but they're not saying when it might not be appropriate. That's obviously an issue, and it weaves into this whole story of inappropriate testing and improper utilization of tests, unfortunately.

Berger: So is it up to the patients to say to their doctor, "Is this appropriate?" There are a number of places today where we've said the consumer has to be more educated, and has to be the leader of his or her own healthcare. Is this one of those places where it's important?

Nagy: I definitely think it's important. But I also think that some patients won't bring that subject up with their physician, for whatever reason. It may be the physician's responsibility to collect a family history in that office appointment and then know when it would be appropriate to refer the patient to a genetic counselor or geneticist.

Berger: I'd like to concentrate on costs. You hate to have the conversation, but cost is the 800-pound gorilla in the room. We have to be conscious of the limited resources out there. With the increase in utilization and the increase in work that's being done in the labs, what are the current costs that we're seeing associated with genetic testing? Is it going up? Is it going down? Is it staying the same?

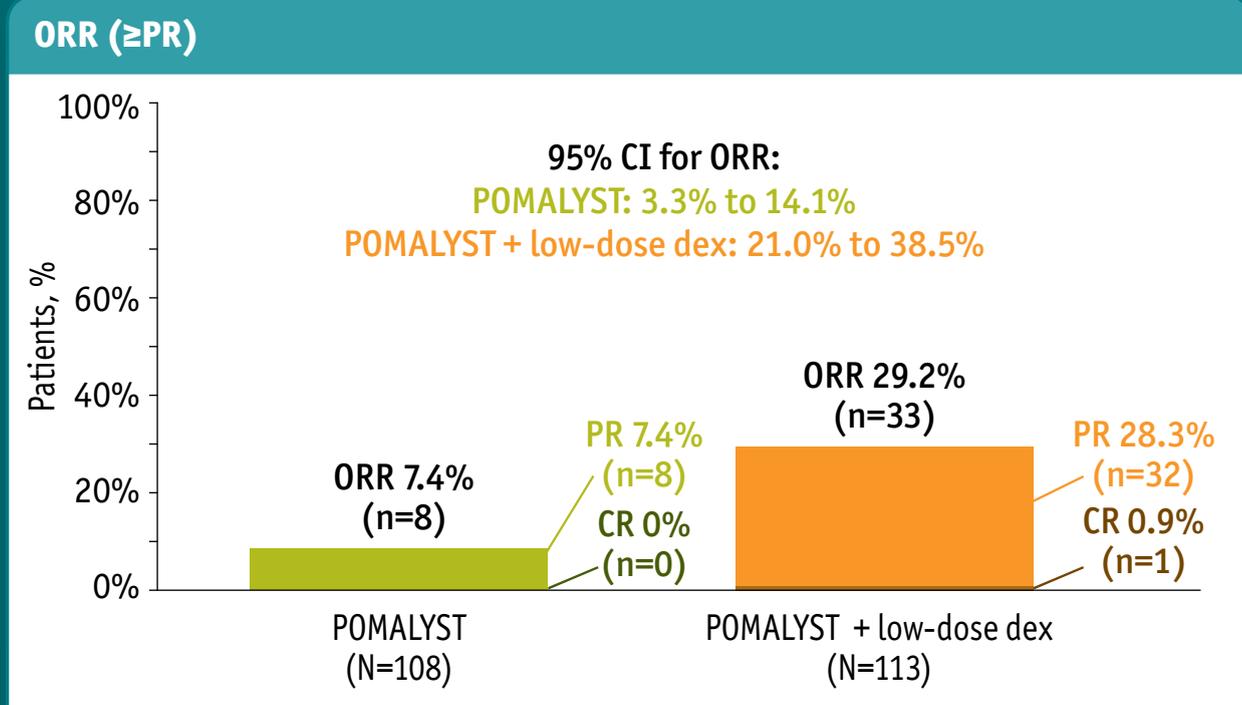


David H. Finely, MD, FACS

POMALYST® (pomalidomide) is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Help give your patients a chance for response

Overall response rate (ORR) of 29.2% was achieved with all-oral POMALYST + low-dose dex



Study design: A Phase II, multicenter, randomized open-label study in patients who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib. The safety and efficacy of POMALYST 4 mg 21/28 days until disease progression was evaluated alone and in combination with low-dose dex: 40 mg per day (patients ≤75 years) or 20 mg per day (patients >75 years) only on Days 1, 8, 15, and 22 for each 28-day cycle. Patients in the POMALYST alone arm were allowed to add low-dose dex upon disease progression.

CI, confidence interval; CR, complete response; Dex, dexamethasone; PR, partial response. Endpoint based on responses assessed by IRAC, based on EBMT criteria.

7.4-month median duration of response (n=33; 95% CI, 5.1 to 9.2) vs NE for POMALYST + low-dose dex and POMALYST, respectively

NE, not established (the median has not yet been reached).

ORR did not differ based on type of prior anti-myeloma therapy



For more information visit www.pomalyst.com
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WARNING: EMBRYO-FETAL TOXICITY and VENOUS THROMBOEMBOLISM

See full prescribing information for complete boxed warning

EMBRYO-FETAL TOXICITY

- POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe life-threatening birth defects
- For females of reproductive potential: Exclude pregnancy before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception

POMALYST is available only through a restricted program called the POMALYST REMS program.

VENOUS THROMBOEMBOLISM

- Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST

CONTRAINDICATIONS

Pregnancy

POMALYST can cause fetal harm when administered to a pregnant female. POMALYST is contraindicated in females who are pregnant. Pomalidomide is a thalidomide analogue, and is teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

POMALYST is only available under a restricted distribution program, POMALYST REMS™.

Please see brief summary of full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, and Important Safety Information on following pages.

 **Pomalyst**[®]
(pomalidomide) capsules

POMALYST® (pomalidomide) is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

- **POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment**
- **Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment**

POMALYST is only available through a restricted distribution program called POMALYST REMS™.

Venous Thromboembolism

- **Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient's underlying risk factors**

CONTRAINDICATIONS: Pregnancy

- POMALYST can cause fetal harm and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus
- Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity

- **Females of Reproductive Potential:** Must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of POMALYST therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- **Males:** Pomalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm
- **Blood Donation:** Patients must not donate blood during treatment with POMALYST and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST

POMALYST REMS Program

Because of the embryo-fetal risk, POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called "**POMALYST REMS.**" Prescribers and pharmacists must be certified with the program; patients must sign an agreement form and comply with the requirements. Further information about the **POMALYST REMS** program is available at [celgeneriskmanagement.com] or by telephone at 1-888-423-5436.

Venous Thromboembolism: Patients receiving POMALYST have developed venous thromboembolic events reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or antithrombotic treatment. The rate of DVT or PE was 3%. Consider anticoagulation prophylaxis after an assessment of each patient's underlying risk factors.

Hematologic Toxicity: Neutropenia of any grade was reported in 50% of patients and was the most frequently reported Grade 3/4 adverse event, followed by anemia and thrombocytopenia. Monitor patients for hematologic toxicities, especially neutropenia, with complete blood counts weekly for the first 8 weeks and monthly thereafter. Treatment is continued or modified for Grade 3 or 4 hematologic toxicities based upon clinical and laboratory findings. Dosing interruptions and/or modifications are recommended to manage neutropenia and thrombocytopenia.

Hypersensitivity Reactions: Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

Dizziness and Confusional State: 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced grade 3/4 dizziness, and 3% of patients experienced grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

WARNINGS AND PRECAUTIONS (continued)

Neuropathy: 18% of patients experienced neuropathy (approximately 9% peripheral neuropathy). There were no cases of grade 3 or higher neuropathy adverse reactions reported.

Risk of Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

ADVERSE REACTIONS

In the clinical trial of 219 patients who received POMALYST alone (n=107) or POMALYST + low-dose dexamethasone (low-dose dex) (n=112), all patients had at least one treatment-emergent adverse reaction.

- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common adverse reactions ($\geq 30\%$) included fatigue and asthenia (55%, 63%), neutropenia (52%, 47%), anemia (38%, 39%), constipation (36%, 35%), nausea (36%, 22%), diarrhea (34%, 33%), dyspnea (34%, 45%), upper respiratory tract infection (32%, 25%), back pain (32%, 30%), and pyrexia (19%, 30%)
- 90% of patients treated with POMALYST alone and 88% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent NCI CTC Grade 3 or 4 adverse reaction
- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common Grade 3/4 adverse reactions ($\geq 15\%$) included neutropenia (47%, 38%), anemia (22%, 21%), thrombocytopenia (22%, 19%), and pneumonia (16%, 23%). For other Grade 3 or 4 toxicities besides neutropenia and thrombocytopenia, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion
- 67% of patients treated with POMALYST and 62% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent serious adverse reaction
- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common serious adverse reactions ($\geq 5\%$) were pneumonia (14%, 19%), renal failure (8%, 6%), dyspnea (5%, 6%), sepsis (6%, 3%), pyrexia (3%, 5%), dehydration (5%, 3%), hypercalcemia (5%, 2%), urinary tract infection (0%, 5%), and febrile neutropenia (5%, 1%)

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with POMALYST. Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Coadministration of POMALYST with drugs that are strong inhibitors or inducers of CYP1A2, CYP3A, or P-gp should be avoided. Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Nursing Mothers: It is not known if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of POMALYST in patients under the age of 18 have not been established.

Geriatric Use: No dosage adjustment is required for POMALYST based on age. Patients greater than or equal to 65 years of age were more likely than patients less than or equal to 65 years of age to experience pneumonia.

Renal and Hepatic Impairment: Pomalidomide is metabolized in the liver. Pomalidomide and its metabolites are primarily excreted by the kidneys. The influence of renal and hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Avoid POMALYST in patients with a serum creatinine >3.0 mg/dL. Avoid POMALYST in patients with serum bilirubin >2.0 mg/dL and AST/ALT >3.0 x ULN.

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



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(continued from SP287)

Matloff: In my opinion there are many, many people having genetic tests that they don't need, and we also have many people who are getting the wrong test or their test result is being misinterpreted. Then, they're having the wrong surgery or they're get-

ting a breast MRI 3 times a year when they don't need it. So it's not only the genetic test, but it's the downstream cost—the wrong surveillance, extra surveillance, the wrong surgeries. At the same time, there are many patients who need genetic testing, but

it's not being offered. It's not being offered to their family members. So there's room to do this much more efficiently. Now with the Supreme Court ruling, I think we can also order the right test and order it more cheaply. I see a lot of room for positive change—

to decrease our costs and to test the right people for the right things.

Finley: I made a comment before about the 15% annual increase in costs. Cost has 2 elements—unit price and utilization. I think that with the

This brief summary does not include all the information needed to use POMALYST® (pomalidomide) safely and effectively. See full prescribing information for POMALYST.

WARNING: EMBRYO-FETAL TOXICITY and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity

- POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.
- Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment [see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.6)].

POMALYST is only available through a restricted distribution program called POMALYST REMS [see Warnings and Precautions (5.2)].

Venous Thromboembolism

- Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient's underlying risk factors [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE 1.1 Multiple Myeloma POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate [see Clinical Studies (14.1)]. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

2 DOSAGE AND ADMINISTRATION 2.1 Multiple Myeloma Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating POMALYST [see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]. The recommended starting dose of POMALYST is 4 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression. POMALYST may be given in combination with dexamethasone [see Clinical Studies (14.1)]. POMALYST may be taken with water. Inform patients not to break, chew or open the capsules. POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal).

2.2 Dose Adjustments for Toxicity
Table 1: Dose Modification Instructions for POMALYST for Hematologic Toxicities

Toxicity	Dose Modification
Neutropenia	
• ANC* < 500 per mL or Febrile neutropenia (fever more than or equal to 38.5°C and ANC < 1,000 per mL)	Interrupt POMALYST treatment, follow CBC weekly.
• ANC return to more than or equal to 500 per mL	Resume POMALYST at 3 mg daily.
• For each subsequent drop < 500 per mL	Interrupt POMALYST treatment
• Return to more than or equal to 500 per mL	Resume POMALYST at 1 mg less than the previous dose

Toxicity	Dose Modification
Thrombocytopenia	
• Platelets < 25,000 per mL	Interrupt POMALYST treatment, follow CBC weekly
• Platelets return to > 50,000 per mL	Resume POMALYST treatment at 3 mg daily
• For each subsequent drop < 25,000 per mL	Interrupt POMALYST treatment
• Return to more than or equal to 50,000 per mL	Resume POMALYST at 1 mg less than previous dose.

*Note: ANC = Absolute Neutrophil Count

For other Grade 3 or 4 toxicities hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion. To initiate a new cycle of POMALYST, the neutrophil count must be at least 500 per mL, the platelet count must be at least 50,000 per mL. If toxicities occur after dose reductions to 1 mg, then discontinue POMALYST.

4 CONTRAINDICATIONS Pregnancy POMALYST can cause fetal harm when administered to a pregnant female [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]. POMALYST is contraindicated in females who are pregnant. Pomalidomide is a thalidomide analogue, and is teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity POMALYST is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death [see Use in Specific Populations (8.1)]. POMALYST is only available through the POMALYST REMS program [see Warnings and Precautions (5.2)]. **Females of Reproductive Potential** Females of reproductive potential must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of POMALYST therapy. Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing POMALYST therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles [see Use in Specific Populations (8.6)]. **Males** Pomalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm [see Use in Specific Populations (8.6)]. **Blood Donation** Patients must not donate blood during treatment with POMALYST and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST.

5.2 POMALYST REMS™ Program Because of the embryo-fetal risk [see Warnings and Precautions

(5.1)], POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called "POMALYST REMS." Required components of the POMALYST REMS program include the following:

- Prescribers must be certified with the POMALYST REMS program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Prescriber agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)] and males must comply with contraception requirements [see Use in Specific Populations (8.6)].
- Pharmacies must be certified with the POMALYST REMS program, must only dispense to patients who are authorized to receive POMALYST and comply with REMS requirements.

Further information about the POMALYST REMS program is available at [celgeneriskmanagement.com] or by telephone at 1-888-423-5436.

5.3 Venous Thromboembolism Patients receiving POMALYST have developed venous thromboembolic events (Venous Thromboembolism [VTEs]) reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or anti-thrombotic treatment; 81% used aspirin, 16% warfarin, 21% heparin, and 3% clopidogrel. The rate of deep vein thrombosis or pulmonary embolism was 3%. Consider anti-coagulation prophylaxis after an assessment of each patient's underlying risk factors.

5.4 Hematologic Toxicity Neutropenia was the most frequently reported Grade 3/4 adverse event (AE), followed by anemia and thrombocytopenia. Neutropenia of any grade was reported in 50% of patients in the trial. The rate of Grade 3/4 neutropenia was 43%. The rate of febrile neutropenia was 3%. Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification [see Dosage and Administration (2.2)].

5.5 Hypersensitivity Reactions. Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

5.6 Dizziness and Confusional State. In the trial, 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced grade 3/4 dizziness, and 3% of patients experienced grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

5.7 Neuropathy In the trial, 18% of patients experienced neuropathy, with approximately 9% of the patients experiencing peripheral neuropathy. There were no cases of grade 3 or higher neuropathy adverse reactions reported.

5.8 Risk of Second Primary Malignancies Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

6 ADVERSE REACTIONS The following adverse reactions are described in detail in other labeling sections:

- Fetal Risk [see Boxed Warnings, Warnings and Precautions (5.1, 5.2)]
- Venous Thromboembolism [see Boxed Warnings, Warnings and Precautions (5.3)]
- Hematologic Toxicity [see Warnings and Precautions (5.4)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.5)]

Supreme Court decision, the unit price is going to go down, certainly for BRCA, but probably for other genetic tests as well. The utilization is in 2 areas. First, as has been said, many people are not tested who should be. So in that way, genetic tests are underutilized. On the

other hand, you have established tests that are overutilized, by the worried well for example. There are genetic labs that are coming up with new tests that have no proven value, but they have direct-to-consumer advertising, as well as relationships with

doctors' facilities and other entities to get their particular test off the ground. So from the payer perspective, I think it's important to address all of these things—the cost and the underutilization by people that should be tested, and the overutilization by people who

shouldn't be tested, and tests that shouldn't be done.

Berger: Are any of the rest of you seeing this? That's a good point that there be overutilization, but there may be underutilization as

- Dizziness and Confusional State [see Warnings and Precautions (5.6)]
- Neuropathy [see Warnings and Precautions (5.7)]
- Risk of Second Primary Malignancies [see Warnings and Precautions (5.8)]

6.1 Clinical Trials Experience in Multiple Myeloma

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. In clinical trial 1, data were evaluated from 219 patients (safety population) who received treatment with POMALYST + Low Dose Dexamethasone (Low dose Dex) (112 patients) or POMALYST alone (107 patients). Median number of treatment cycles was 5. Sixty three percent of patients in the study had a dose interruption of either drug due to adverse reactions. Thirty seven percent of patients in the study had a dose reduction of either drug due to adverse reactions. The discontinuation rate due to treatment-related adverse reaction was 3%. Tables 2, 3 and 4 summarize all treatment-emergent adverse reactions reported for POMALYST + Low dose Dex and POMALYST alone groups regardless of attribution of relatedness to pomalidomide. In the absence of a randomized comparator arm, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

In the clinical trial of 219 patients who received POMALYST alone^a (n=107) or POMALYST + Lowdose Dex (n=112), all patients had at least one treatment-emergent adverse reaction.

Adverse reactions ≥10% in either arm, respectively, included: General disorders and administration site conditions: Fatigue and asthenia (55%, 63%), Pyrexia (19%, 30%), Edema peripheral (23%, 16%), Chills (9%, 11%), Pain (6%, 5%); **Blood and lymphatic system disorders:** Neutropenia (52%, 47%), Anemia (38%, 39%), Thrombocytopenia (25%, 23%), Leukopenia (11%, 18%), Lymphopenia (4%, 15%); **Gastrointestinal disorders:** Constipation (36%, 35%), Diarrhea (34%, 33%), Nausea (36%, 22%), Vomiting (14%, 13%); **Infections and infestations:** Pneumonia (23%, 29%), Upper respiratory tract infection (32%, 25%), Urinary tract infection (8%, 16%); **Musculoskeletal and connective tissue disorders:** Back pain (32%, 30%), Musculoskeletal chest pain (22%, 20%), Muscle spasms (19%, 19%), Arthralgia (16%, 15%), Musculoskeletal pain (11%, 15%), Pain in extremity (5%, 14%), Muscular weakness (12%, 12%), Bone pain (12%, 5%); **Respiratory, thoracic and mediastinal disorders:** Dyspnea (34%, 45%), Cough (14%, 21%), Epistaxis (15%, 11%); **Metabolism and nutritional disorders:** Decreased appetite (22%, 18%), Hyperglycemia (12%, 15%), Hyponatremia (10%, 13%), Hypercalcemia (21%, 12%), Hypocalcemia (6%, 12%), Hypokalemia (10%, 11%); **Skin and subcutaneous tissue disorders:** Hyperhidrosis (6%, 16%), Rash (22%, 16%), Night sweats (5%, 13%), Dry skin (9%, 11%), Pruritus (15%, 11%); **Nervous system disorders:** Dizziness (20%, 17%), Tremor (9%, 13%), Headache (13%, 8%), Neuropathy peripheral (10%, 7%); **Investigations:** Blood creatinine increased (15%, 11%), Weight increased (1%, 11%), Weight decreased (14%, 8%); **Psychiatric disorders:** Insomnia (7%, 14%), Confusional state (10%, 13%), Anxiety (11%, 7%); **Renal and urinary disorders:** Renal failure (15%, 10%).

Grade 3/4 adverse reactions reported in 90% of patients treated with POMALYST^a alone (96/107) and 88% with POMALYST + Low dose Dex (99/112).

Grade 3/4 Adverse Reactions ≥ 5% in either arm, respectively, included: Blood and lymphatic system disorders: Neutropenia (47%, 38%), Anemia (22%, 21%), Thrombocytopenia (22%, 19%), Leukopenia

(6%, 10%), Lymphopenia (2%, 7%); **Infections and infestations:** Pneumonia (16%, 23%), Urinary tract infection (2%, 8%), Sepsis (6%, 3%); **Metabolism and nutritional disorders:** Hypercalcemia (9%, 1%); **General disorders and administration site conditions:** Fatigue and asthenia (11%, 13%); **Investigations:** Blood creatinine increased (6%, 3%); **Respiratory, thoracic and mediastinal disorders:** Dyspnea (7%, 13%); **Musculoskeletal and connective tissue disorders:** Back pain (12%, 9%), Muscular weakness (6%, 4%); **Renal and urinary disorders:** Renal failure (9%, 6%).

Serious adverse events were reported in 67% of patients treated with POMALYST^a (72/107) and 62% with POMALYST + Low dose Dex (69/112).

Serious Adverse Reactions in 2 or more patients in either arm, respectively, included: Infections and infestations: Pneumonia (14%, 19%), Urinary tract infection (0%, 5%), Sepsis (6%, 3%); **Respiratory, Thoracic and mediastinal disorders:** Dyspnea (5%, 6%); **General disorders and administration site conditions:** Pyrexia (3%, 5%); General physical health deterioration (0%, 2%); **Cardiac Disorders:** Atrial fibrillation (2%, 3%), Cardiac failure congestive (0%, 3%); **Renal and urinary disorders:** Renal failure (8%, 6%); **Gastrointestinal disorders:** constipation (1%, 3%); **Blood and Lymphatic system disorders:** Febrile neutropenia (5%, 1%); **Metabolism and nutrition disorders:** Dehydration (5%, 3%), Hypercalcemia (5%, 2%); **Musculoskeletal and connective tissue disorders:** Back pain (4%, 2%)

^aPOMALYST alone arm includes all patients randomized to the POMALYST alone arm who took study drug; 61 of the 107 patients had dexamethasone added during the treatment period.

Other Adverse Reactions

Other adverse reactions of POMALYST in patients with multiple myeloma, not described above, and considered important: **Ear and Labyrinth Disorders:** Vertigo; **Hepatobiliary Disorders:** Hyperbilirubinemia; **Infections and Infestations:** Pneumocystis jiroveci pneumonia, Respiratory syncytial virus infection, Neutropenic sepsis; **Investigations:** Alanine aminotransferase increased; **Metabolism and Nutritional Disorders:** Hyperkalemia; **Renal and Urinary Disorders:** Urinary retention; **Reproductive System and Breast Disorders:** Pelvic Pain; **Respiratory, Thoracic and Mediastinal Disorders:** Interstitial Lung Disease

7 DRUG INTERACTIONS No formal drug interaction studies have been conducted with POMALYST.

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp).

7.1 Drugs That May Increase Pomalidomide Plasma Concentrations CYP3A, CYP1A2 or P-gp inhibitors: Co-administration of POMALYST with drugs that are strong inhibitors of CYP1A2, CYP3A (e.g. ketoconazole) or P-gp could increase exposure and should be avoided.

7.2 Drugs That May Decrease Pomalidomide Plasma Concentrations CYP3A, CYP1A2 or P-gp inducers: Co-administration of POMALYST with drugs that are strong inducers of CYP1A2, CYP3A (e.g. rifampin) or P-gp could decrease exposure and should be avoided.

Smoking: Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

Dexamethasone: Co-administration of multiple doses of 4 mg POMALYST with 20 mg to 40 mg dexamethasone (a weak inducer of CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category X [see Boxed Warnings and Contraindications (4)]

Risk Summary POMALYST can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants. Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal Data Pomalidomide was teratogenic in both rats and rabbits in the embryofetal developmental studies, when administered during the period of organogenesis. In rats, pomalidomide was administered orally to pregnant animals at doses of 25 to 1000 mg per kg per day. Malformations of absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (vertebral, central and/or neural arches) were observed at all dose levels. There was no maternal toxicity observed in this study. The lowest dose in rats resulted in an exposure (AUC) approximately 85-fold of the human exposure at the recommended dose of 4 mg per day. Other embryofetal toxicities included increased resorptions leading to decreased number of viable fetuses. In rabbits, pomalidomide was administered orally to pregnant animals at doses of 10 to 250 mg per kg per day. Increased cardiac malformations such as interventricular septal defect were seen at all doses with significant increases at 250 mg per kg per day. Additional malformations observed at 250 mg per kg per day included anomalies in limbs (flexed and/or rotated fore- and/or hindlimbs, unattached or absent digit) and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia), moderate dilation of the lateral ventricle in the brain, abnormal placement of the right subclavian artery, absent intermediate lobe in the lungs, low-set kidney, altered liver morphology, incompletely or not ossified pelvis, an increased average for supernumerary thoracic ribs and a reduced average for ossified tarsals. No maternal toxicity was observed at the low dose (10 mg per kg per day) that resulted in cardiac anomalies in fetuses; this dose resulted in an exposure (AUC) approximately equal to that reported in humans at the recommended dose of 4 mg per day. Additional embryofetal toxicity included increased resorption.

8.3 Nursing mothers It is not known if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, 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 Safety and effectiveness of POMALYST in patients below the age of 18 have not been established.

well. ... Cost comes into play across the board. Does anyone else want to comment around current costs and the appropriate resources?

Nagy: One place where inappropriate testing occurs is not just testing the

right person for the right condition, but also using the right test. Once a mutation has been identified in a family, the cost to test unaffected relatives or relatives who may be at risk drops significantly. So, the first test may cost between \$2000 and \$3000 to identify the

mutation in the family, but once that mutation has been identified, other people in the family can be tested for \$400 to \$500, depending on the lab used. We call that cascade testing. In our outside referrals, when genetic testing has been done by a provider who does

not have formal genetics training, over and over again that comprehensive several-thousand-dollar test is being ordered after the mutation has already been identified in the family. For every single person tested in those families, the excess is \$2000 to \$3000. So, that's

8.5 Geriatric use No dosage adjustment is required for POMALYST based on age. Of the total number of patients in clinical studies of POMALYST, 41 percent were 65 and over, while 12 percent were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. In this study, patients greater than or equal to 65 years of age were more likely than patients less than or equal to 65 years of age to experience pneumonia.

8.6 Females of Reproductive Potential and Males POMALYST can cause fetal harm when administered during pregnancy [see *Use in Specific Populations (8.1)*]. Females of reproductive potential must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy. **Females** Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of POMALYST therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed. Females of reproductive potential must have 2 negative pregnancy tests before initiating POMALYST. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing POMALYST. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. POMALYST treatment must be discontinued during this evaluation. **Males** Pomalidomide is present in the semen of males who take POMALYST. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm.

8.7 Renal Impairment Pomalidomide and its metabolites are primarily excreted by the kidneys [see *Clinical Pharmacology (12.3)*]. The influence of renal impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum creatinine greater than 3.0 mg/dL were excluded in clinical studies. Avoid POMALYST in patients with a serum creatinine greater than 3.0 mg/dL.

8.8 Hepatic Impairment Pomalidomide is metabolized in the liver [see *Clinical Pharmacology (12.3)*]. The influence of hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x upper limit normal (ULN) were excluded in clinical studies. Avoid POMALYST in patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x ULN.

10 OVERDOSAGE No specific information is available on the treatment of overdose with pomalidomide, and it is unknown whether pomalidomide or its metabolites are dialyzable.

13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of twelve monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/per day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study. Pomalidomide was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the *in vitro* assay using human peripheral blood lymphocytes and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day. In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of the exposure in patients at the recommended dose of 4 mg/day. When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

17 PATIENT COUNSELING INFORMATION See FDA-approved Patient labeling (*Medication Guide*). **Embryo-Fetal Toxicity** Advise patients that POMALYST is contraindicated in pregnancy [see *Contraindications (4)*]. POMALYST is a thalidomide analog and may cause serious birth defects or death to a developing baby. [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

- Advise females of reproductive potential that they must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy.
- Initiate POMALYST treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use two different forms of contraception including at least one highly effective form simultaneously during POMALYST therapy, during therapy interruption and for 4 weeks after she has completely finished taking POMALYST. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch or implants) and a partner's vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm and cervical cap.
- Instruct patient to immediately stop taking POMALYST and contact her doctor if she becomes pregnant while taking this drug, if she misses her menstrual period, or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.
- Advise patient that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy.
- Advise male patients taking POMALYST that they must not donate sperm [see *Warnings and*

Precautions (5.1) and Use in Specific Populations (8.6)].

- All patients must be instructed to not donate blood while taking POMALYST and for 1 month following discontinuation of POMALYST [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

POMALYST REMS Program Because of the risk of embryo-fetal toxicity, POMALYST is only available through a restricted program call POMALYST REMS [see *Warnings and Precautions (5.2)*].

- Patients must sign a Patient-Prescriber agreement form and comply with the requirements to receive POMALYST. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements and participate in monthly telephone surveys. Males must comply with the contraception requirements [see *Use in Specific Populations (8.6)*].
- POMALYST is available only from pharmacies that are certified in POMALYST REMS program. Provide patients with the telephone number and website for information on how to obtain the product.

Venous Thromboembolism Inform patients of the potential risk of developing venous thromboembolic events and discuss the need for appropriate prophylactic treatment. **Hematologic Toxicities** Inform patients on the risks of developing neutropenia, thrombocytopenia and anemia and the need to report signs and symptoms associated with these events to their health care provider for further evaluation. **Hypersensitivity** Inform patients of the potential for a severe hypersensitivity reaction to POMALYST if they have had such a reaction in the past to either THALOMID® or REVLIMID®. **Dizziness and Confusional State** Inform patients of the potential risk of dizziness and confusion with the drug and to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice. **Neuropathy** Inform patients of the risk of neuropathy and report the signs and symptoms associated with these events to their health care provider for further evaluation. **Second Primary Malignancies** Inform the patient that the potential risk of developing acute myelogenous leukemia during treatment with POMALYST is unknown.

Dosing Instructions Inform patients on how to take POMALYST [see *Dosage and Administration (2.1)*].

- POMALYST should be taken once daily at about the same time each day
- POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal).
- The capsules should not be opened, broken, or chewed. POMALYST should be swallowed whole with water.
- Instruct patients that if they miss a dose of POMALYST, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take POMALYST at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Other Information Advise patients who smoke to stop because smoking may reduce the efficacy of pomalidomide [see *Drug Interactions (7.2)*].

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Summit, NJ 07901

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another place I think where the costs can really get out of hand.

Berger: Dr Finley, I want to go back to you for a moment. ... What are you seeing from Cigna's employer clients around this? Is there conversation? Is there interest? Is there concern?

Finley: We have not heard a lot of feedback from the employer groups. There's 1 large employer group that always has questions when we introduce a new program, and we've heard from them. ... But if we're going to get a lot of questions and pushback or perhaps a pat on the back, I don't know, it hasn't occurred yet. It may not occur until they have cases where there are issues, and they come to us and say, "What about this?" They get more attention once implementation is actually under way. But so far it's been minimal.

Berger: Are any of the rest of you hearing from the employer market or other constituencies?

Brawley: I have not heard from the employer market, but I should note, we have heard from women who have been tested for these genetic mutations who encounter life insurance discrimination. It's illegal to discriminate on the basis of health insurance, but there are other types of insurance that they're having difficulty getting because of a non-genetic mutation. This is something that people frequently don't think about until after they get tested. In some instances it's some of these mutations of unknown significance that are causing people to have difficulty getting insurance.

Berger: It will be interesting to see if the same way we've seen discrimination issues in the employer market and in the medical insurance market, if this eventually extends to the life insurance market. Can we talk about the errors in the genetic test result interpretation? In some cases by having genetic counselors, some of these issues with results of unknown significance can be addressed, but can we talk more broadly about the errors in the results interpretation? Dr Brawley, has there been a lot of conversation at the American Cancer Society around this? Is there concern?

Brawley: There's huge concern that people don't understand the concept of risk. They don't understand what is a

10% increase in relative risk versus an 80% increase in relative risk.

Berger: Is there a concern, not just in interpretation, but that the testing companies and the tests out there are inconsistent? There's been talk in the past that if you get the test from 2 different places you will get 2 different results.

Matloff: I think one of the concerns is that there are also some testing companies offering direct-to-consumer testing. You can order the test online; you can have a kit sent to your home. You can provide a DNA sample by saliva and send it back. Some of those companies have been studied extensively; the Government Accountability Office (GAO) found that if you send the same sample to 4 different laboratories, you will get 4 different sets of results and risks. Some of these companies are dodging FDA and FTC standards by saying they're for entertainment instead of medical use. We recently had a rabbi in our community contact us and say that one of these companies reached out and gave the congregation 100 free

The other area where in the next 5-10 years we'll see a trend is within the pediatric setting, or the NICU setting where a child is born with a condition that looks to be genetic, and that's another area where those whole-exon, whole-genome tests might play a role in diagnosing a child early on.

—Rebecca Nagy, MS

tests, and that he was going to launch it at high holiday services and tell people, "Oh, we've got this testing, and if any of you come back with something, then you can go see a genetic counselor." So I do think there's room for error with unregulated testing. In terms of what I've seen so far, and I'd be interested in what my fellow counselors think, but in terms of BRCA testing, most of the companies that I've seen offering test so far have been through pre-approved laboratories doing quality testing. I haven't had any major concerns in the BRCA market to date.

Nagy: Yes, I agree the companies have done a great job. One concern early on

was that Myriad held a proprietary database and would not share with the public what would characterize uncertain variance, or variance of uncertain significance. The talk was that these other laboratories didn't have enough of those data to be able to call mutations deleterious or just natural polymorphisms or truly uncertain variance. But we've not had that issue come up for us. From what we're hearing, these laboratories have robust data, have variant rates that are very similar to what Myriad is reporting. So I think in my center, our initial hesitancy was 2-fold. It was, "What is their variant call rate?" And then, "What is the insurance coverage within that laboratory?" Over time, those have both been answered.

Berger: We've talked mostly about BRCA and other associated tests with breast cancer and breast cancer risks. Where are some of the other areas you're seeing both today and in the near future as a trend?

Matloff: In the cancer realm, at least at my center specifically, I think there's a lot more awareness of ovarian cancer

we're hearing, neurologists are adopting some of these newer tests, like whole exon, whole genome for their patients who have something clinically, but they just can't figure it out genetically.

Berger: Dr Finley, are you seeing requests in other areas?

Finley: Yes, we are, but it's all over the place. What we've done—as we do for most medical services—we identify the services—in this case genetic tests—that are most frequently requested. And we have to make a determination whether we're going to subject them to utilization review management. So we have about 40 or 50 tests that are on our policy list for which we get frequent requests, and that we have decided it is appropriate to do a utilization management. But I wouldn't say that there has been any that have popped up recently. I'm not aware of any. ...

Nagy: The other area where in the next 5-10 years we'll see a trend is within the pediatric setting, or the NICU setting where a child is born with a condition that looks to be genetic, and that's another area where those whole-exon, whole-genome tests might play a role in diagnosing a child early on. I think its uptick has been relatively slow because the cost is still high, but as that cost comes down I think we'll see a lot more utilization there.

Berger: Let's talk about future trends. If you were to look into your crystal ball in the general area of genetic testing, what do you see coming? Do you think you'll see more requirements of genetic counselling before genetic testing? Do you think more and more people will do these home testing? And although there is a natural inquisitiveness, I can only see that increasing other health-care activities by the so-called "worried well." But what are the other trends you see? I think one of the other issues we should discuss is genetic testing around the right drug, right dose, right time.

Brawley: I'll jump right into that because I treat cancer patients all the time. I am really mortified at some of the things that patients bring to me for second opinions, where they have spent lots of money, sometimes undergone unnecessary biopsies to send fresh tissues to labs to do things which, quite honestly, are experimental. They might ultimately prove to be beneficial,

but they use usually the home-brew loophole in FDA regulation to actually start marketing something that is not ready for prime time.

Nagy: Dr Brawley, I agree with you. In our cancer center we want that to occur still within the research setting. But I do think there is potential for those types of tests in tailoring treatments and opening up clinical trials to not be so focused on the clinical aspects of the patient, but more on the genetic aspects of the tumor. It has great potential. But at our institution we're trying to keep that within the research realm at this point, so that we can gather enough data to show that it has value, and then let it go into the clinical setting at that point.

Berger: Dr Finley, are you seeing people request that kind of genetic testing around medication dosing and right drug at Cigna?

Finley: Yes, we do, and we have policies for the most frequently requested test of that sort. What we do is we apply our general criteria toward medical coverage. The basics are that the service, and in this case we're talking about pharmacogenomics, the service has to be proven by evidence published in the peer-review literature to be associated with beneficial health outcomes. And when we apply those criteria, there aren't that many that have shown to be associated with beneficial health outcomes. They may be reproducible and have other attributes that the manufacturer tout, but at the end of the day can you show that people live longer or shed some of the burden of disease? And the answer is usually no. And if it's no, then we would decline to cover it.

Nagy: Like Dr Finley said, there are some like KRAS ... that we all know and have been well studied and well validated; those are already in the clinical setting. The research that I was talking about is more where they do kind of a whole exon or whole genome on a tissue and it's sort of a fishing expedition. They don't really have a targeted test that they have in mind; it's more, "Let's see what the tumor looks like and see if we can tailor treatment to that patient." And I think that is different. It's

going to take a little more time for us to work through that.

Berger: I appreciate you sharing the differentiated area there because it is very different. Before I close us out, I want to give everybody 30 seconds to give their final thoughts. Why don't we start with Ellen Matloff and then we'll work our around the panel. Any final thoughts to share?



Rebecca Nagy, MS

Matloff: Yes, I think that over the last few months I've done a lot of research myself looking at genetic counselors who either work at insurance companies or work at

laboratories who are helping to review claims coming in for genetic testing to see if, first of all, the right test is being ordered. I've been surprised and, quite frankly, horrified. I'll give you an example. One genetic counselor told me that they frequently get a sample that will come in for a karyotype, a chromosome

radiologic test to get and so I regularly would call the radiologist and say, "This is the problem, this is what I'm looking for, what should I do?" It sounds like this is another area where that kind of advice and support is very important. Joy Larsen-Haidle, do you have any final words?

Larsen-Haidle: I do. I appreciate the opportunity to have this discussion, because it's so important, considering what we are spending. Each of these DNA tests is often a couple of thousand dollars apiece, so for the healthcare resources that we have, it's important for us to start targeting those healthcare dollars toward care that actually makes a difference and improves the health of our patients and the family members. ... There is talk about how having the opportunity for the patients to be working with a genetic counselor on these genetics test, that it improves their understanding of what that result means. It ensures the patient is getting the appropriate testing ordered, and it also improves their compliance with the appropriate surveillance, or it improves their understanding, so they can have a good conversation with their physician about risk reduc-

need to be consulted and really ought to be very heavily involved as gatekeepers in all of these tests, that is for risk assessment. I'll just add that right now, we should have very limited genetic or genomic testing for prognosis as well for...which chemotherapy should be used. There should be some, but it should be very limited.

Berger: I think you bring up a good point; at a time when we're looking at ACOs and we're looking at patient-centered medical homes, it really does take a village, and the genetic counselors are a very important part of that village. With that, Rebecca Nagy, what other final comments would you like to give?

Nagy: All of us in this discussion have experienced quite a bit of change over the last several months, and I think sometimes change makes people uncomfortable. As we go forward with our physician partners we want to make sure they know that genetic counselors, and NSGC as an organization, want to do everything we can to partner with providers to make sure that patients receive the best care. That's what we're all here for. And I think within the framework of the Cigna program, for example, we see this as a partnership where we can provide our expertise, give those providers the genetic information that they need to manage these patients, and then turn that patient over to them for their expertise in managing and following the patient and preventing genetic disease as much as we can.

Berger: Wonderful. Dr Finley, you are last but definitely not least here. What comments can you share with us all?

Finley: Genetic testing and genetic counseling are both areas that are changing very rapidly. It's a complex world, and there are competing interests within that world; there are feelings about how genetic counseling ought to be done, how genetic testing ought to be done. The important point to take away, which was mentioned earlier, there have been a lot of studies on the appropriateness and efficacy of genetic counseling as well as the appropriateness and efficacy of certain genetic tests, and at the end of the day we need to rely on studies that have been published and have gone through peer review. Medical literature should guide us in establishing the direction that we need to go. **EBO**

Each of these DNA tests is often a couple of thousand dollars apiece, so for the healthcare resources that we have, it's important for us to start targeting those healthcare dollars toward care that actually makes a difference and improves the health of our patients and the family members.

—Joy Larsen-Haidle, MS

study, but the indication for testing is whether or not the patient has cystic fibrosis, and that's not a chromosome disorder. So people are not only ordering the wrong test, but they're not going to get an answer to the question that they're asking. So I think that we will probably use genetic counselors in that realm to make sure the right test is being ordered, not only to save healthcare dollars, but to ensure that the patient is getting the test that he or she and the entire family needs.

Berger: That's interesting. It's almost like the older days that I remember when I was unsure which

tion. It also helps for patients to take that same test and share that information with their family members so that same healthcare dollar is expanded further to benefit more people.

Berger: That's wonderful. Thank you. Dr Brawley?

Brawley: I just love the last comment. I think the most important thing you can get from this discussion is that we all need to appreciate that genetic testing is a very complicated thing, and it really needs to stay within the realm of the expert. In my mind genetic counselors are the first experts that really

FDA Tells Direct-to-Consumer Genetic Testing Company to Halt Marketing

Mary K. Caffrey

Federal regulators have ordered the direct-to-consumer genetic testing company 23andMe to stop marketing its saliva-based test without necessary approvals as a medical device, citing the potential for harm to patients who change medication doses or have unnecessary surgeries based on test results.

In a November 22, 2013, letter to 23andMe CEO Anne Wojcicki, the US Food and Drug Administration (FDA) stated that some uses being advertised “are particularly concerning,” including testing for BRCA1 and BRCA2 mutations, which are indicators for breast cancer, as well as sensitivity to certain medications, such as warfarin, a blood thinner that can be prescribed to prevent strokes or heart attacks.¹

The letter warned of the dangers to patients who act on the basis of false negatives or false positives without the assistance of genetic counseling. “For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist,” the letter states.¹

“Assessments for drug responses carry the risks that patients relying on such tests may begin to self-manage their treatments through dose changes or even abandon certain therapies depending on the outcome of the assessment,” continues the letter, which is signed by James L. Woods, deputy director for patient safety and product quality, Office of In vitro Diagnostics and Radiological Health.¹

The FDA’s action comes amid growing concerns by genetic counselors and some health plan experts that direct-to-consumer testing drives poor decisions

by patients, especially if they consult doctors who have limited knowledge of genetics. Ellen T. Matloff, MS, director of Yale Cancer Genetic Counseling, Yale Cancer Center, has repeatedly raised concerns about women who use tests that skirt FDA requirements through an “entertainment” loophole in Federal Trade Commission (FTC) regulations. (See Panel Discussion, SP441.)



Anne Wojcicki

“There’s room for error in unregulated testing,” Matloff said during a panel discussion convened by *The American Journal of Managed Care* earlier this fall. She cited a Government Accountability Office (GAO) study, which found that it was possible to send the same sample to 4 different direct-to-consumer companies and get 4 different results.²

able to send the same sample to 4 different direct-to-consumer companies and get 4 different results.²

Otis Brawley, MD, chief medical officer for the American Cancer Society, shared with the panel that he has treated women who had prophylactic breast removal that later turned out to have been unnecessary. At Patient-Centered Oncology Care 2013, sponsored by *AJMC* in Baltimore, Maryland, on November 14-15, 2013, Jan Berger, MD, MJ, described a situation in which an employer allowed the use of flexible-spending accounts (FSAs) to pay for direct-to-consumer genetic testing. “It was a disaster,” Berger said.

Both the FDA letter¹ and published reports³ describe an agency frustrated with 23andMe after years of negotiations aimed at getting the company to comply voluntarily with the approval process. *The Wall Street Journal* reported

that the FDA issued its warning letter after learning that 23andMe had started

“To 23andMe and to most of its customers, this is information that a per-

“Assessments for drug responses carry the risks that patients relying on such tests may begin to self-manage their treatments through dose changes or even abandon certain therapies depending on the outcome of their assessment.”

—James L. Woods,
US Food and Drug Administration,
in letter to 23andMe

a new marketing campaign, including television commercials, after letting 6 months lapse since its last contact with the agency.³

Wojcicki has not commented; the company published the following statement on its website: “We have received the warning letter from the Food and

Drug Administration. We recognize that we have not met the FDA’s expectations regarding timeline and communication regarding our submission. Our relationship with the FDA is extremely important to us and we are committed to fully engaging with them to address their concerns.”⁴

Despite the consensus among genetic counselors that consumers need protection and guidance, the belief that people have

a “right” to their own genetic information, and the ease with which the tests have been ordered, led to some backlash over the FDA decision. In *The New Yorker*, writer David Dobbs described the “cultural clash” between the FDA and Silicon Valley investors, including Google, that backed 23andMe.⁵

son has every right to know,” Dobbs writes. “To the FDA, it is medical advice, which makes 23andMe’s delivery system a medical device.”⁵ **EBO**

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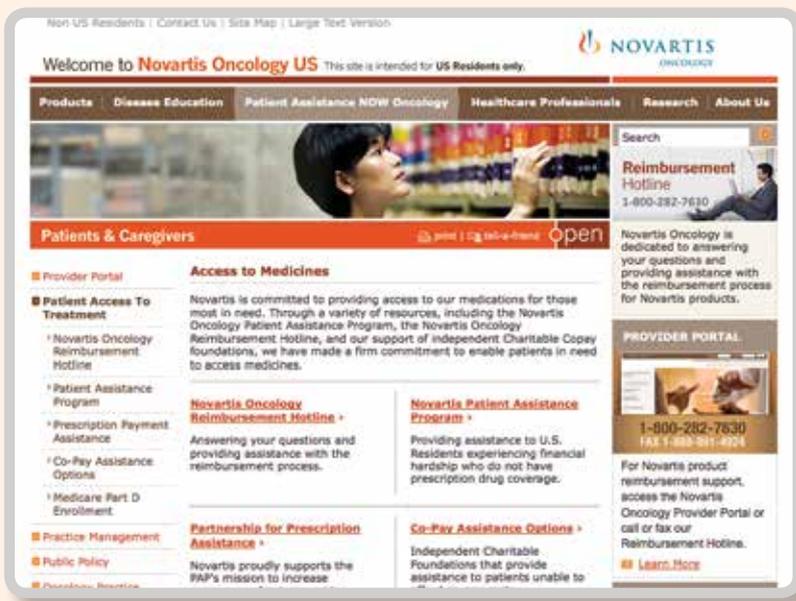
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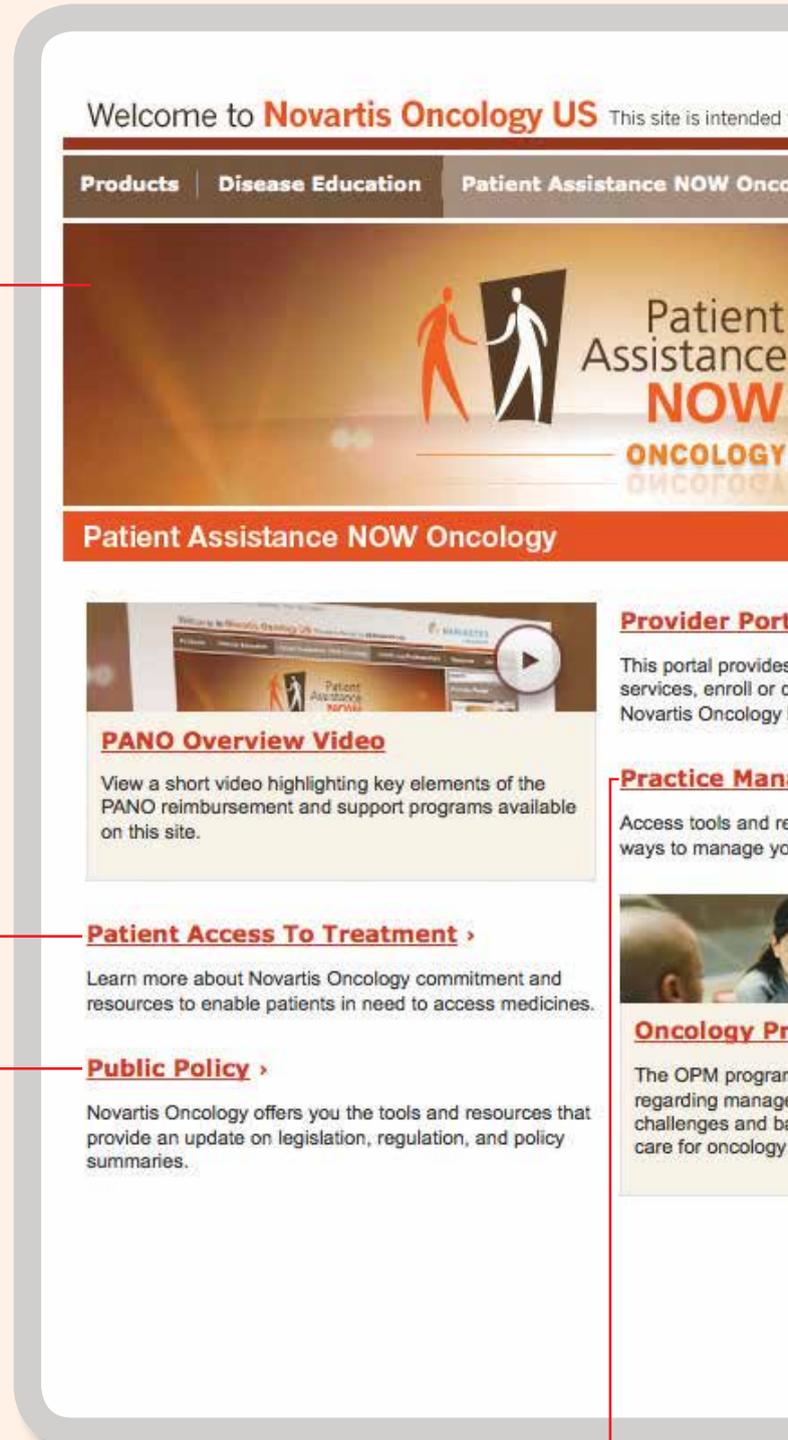


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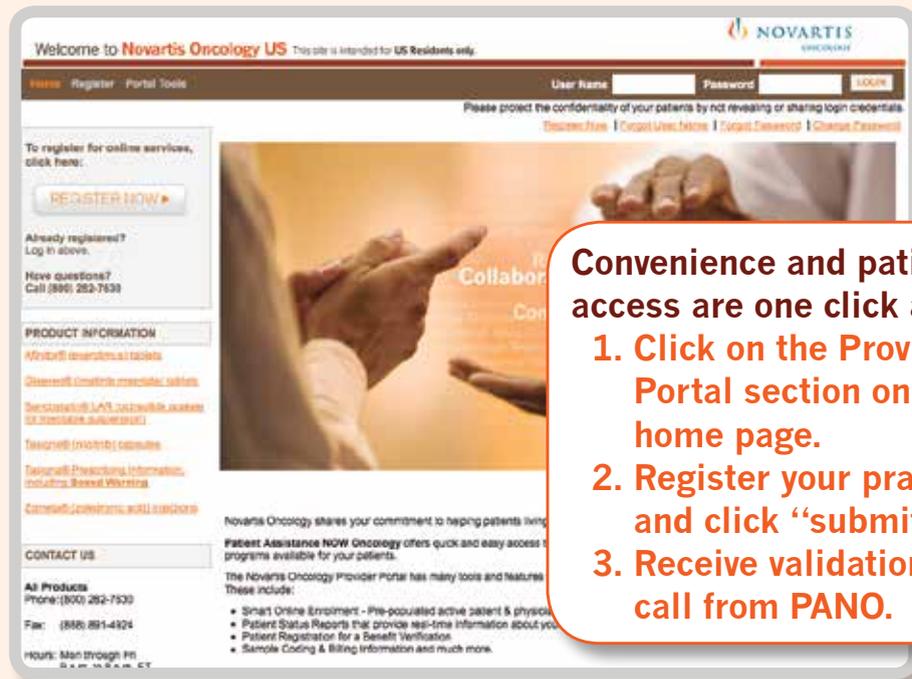
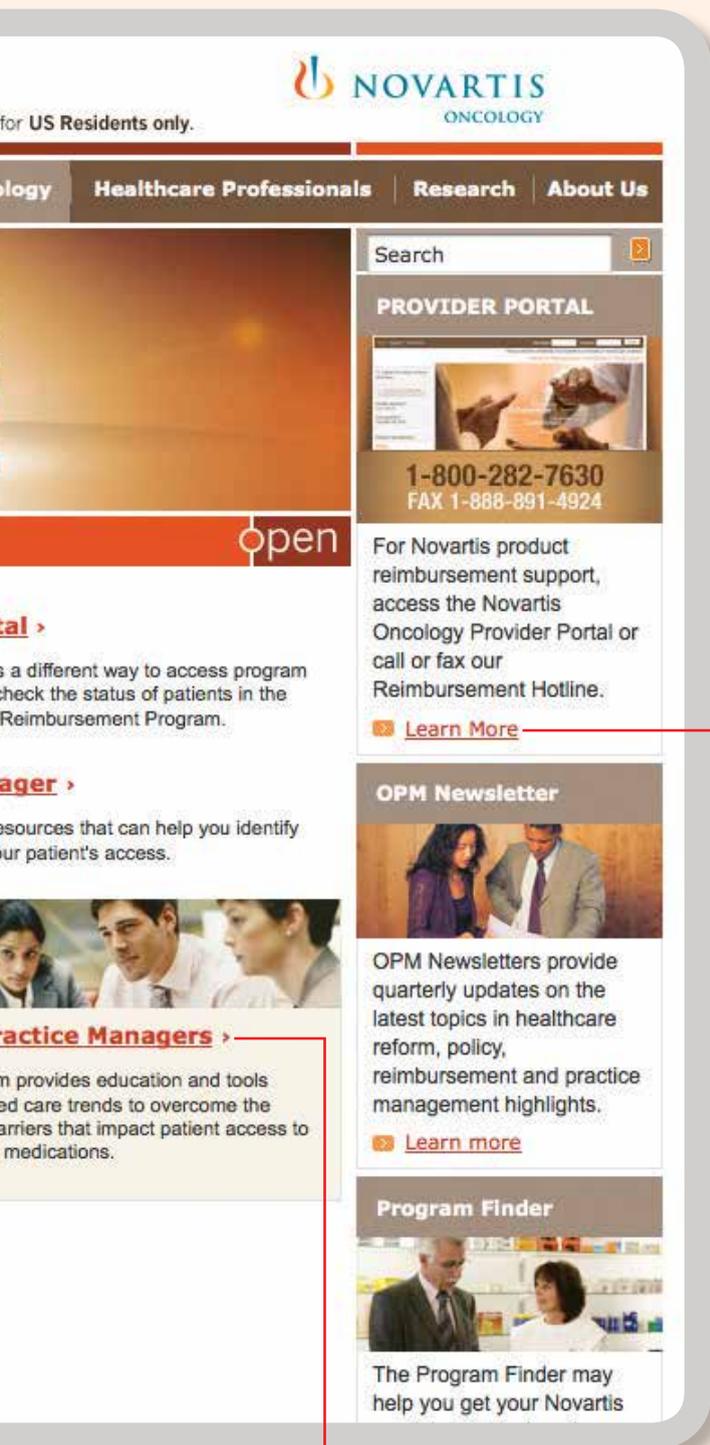
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Safety Concerns Halt Ponatinib Development

Silas Inman

The US Food and Drug Administration (FDA) has placed a partial hold on the clinical development of the BCR-ABL inhibitor ponatinib (Iclusig) as it investigates the high occurrence of arterial thrombosis in patients treated with the drug. As part of this hold, new patient enrollment into all clinical trials investigating ponatinib has been stopped.

Ponatinib was granted accelerated approval in December 2012 at a 45-mg daily dose for patients with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). This approval was based on data from the phase II PACE trial that enrolled patients who were resistant or intolerant to dasatinib or nilotinib, or harbored a T315I mutation.

A Boxed Warning was included in the approval, based on the development of arterial thrombosis in 8% of patients and hepatotoxicity in the trial. However, at an FDA-required median 24-month planned follow-up, the rate of arterial thrombosis had increased to 11.8% in patients treated with ponatinib, warranting the pause in patient enrollment.

Ariad Pharmaceuticals, Inc, the company developing ponatinib, is seeking the

approval of dose modification from the FDA in order to resume its ongoing clinical development program. Additionally, the company is consulting with the FDA on needed adjustments to the drug's prescribing information to reflect the newly discovered increase in toxicity.

"We believe that the actions we are taking will help us ensure the most appropriate and safe use of Iclusig. With two years of follow up, we have learned a great deal about both the efficacy and safety of Iclusig in patients with Philadelphia-positive leukemias," stated Harvey J. Berger, MD, chairman and chief executive officer of Ariad.

The PACE trial was a single-arm investigation of 449 patients, of which 444 were eligible for efficacy analysis. The primary end point for patients with chronic-phase (CP)-CML (n = 267) was major cytogenetic response (MCyR). The primary end point was major hematologic response (MaHR) for patients with accelerated-phase (AP)-CML (n = 83), blast-phase (BP)-CML (n = 62), and Ph+ALL (n = 32).

Ponatinib was approved based on a 10-month analysis of the PACE trial that found that treatment with ponatinib demonstrated a 54% MCyR rate in pa-

tients with CP-CML. Specifically, 70% of the 64 patients with the BCR-ABL T315I mutation achieved MCyR. The MaHR rate was 52% in patients with AP-CML, 31% in patients with BP-CML, and 41% in patients with Ph+ ALL.

At this early follow-up, the median duration of MCyR for patients with CP-CML had not yet been reached. The median duration of MaHR was 9.5 months in patients with AP-CML, 4.7 months in patients with BP-CML, and 3.2 months in patients with Ph+ ALL.

At the 24-month follow up, the PACE trial data demonstrated continued efficacy, even following dose reductions. Overall, 190 patients with CP-CML received a reduced dose of either 30 mg or 15 mg. Despite this reduction, 90% of patients who achieved MCyR maintained this response for a median of 19 months. Furthermore, Ariad noted in a release, for the 35 patients reduced to a 15-mg dose, 94% maintained an MCyR.

The most common adverse events were thrombocytopenia, rash, and dry skin. The most common serious adverse event was pancreatitis, which led to 1 patient discontinuing the drug. At 24 months, serious venous occlusion occurred in 2.9%

of ponatinib-treated patients, compared with 2.2% when the drug was approved. In total, all types of arterial and venous-related adverse events occurred in approximately 20% of ponatinib-treated patients.

"We are focused first and foremost on the needs of cancer patients—to have new medicines that provide both safe and effective treatment of their malignancies. Our unwavering commitment to patients has led us to promptly take the steps we have outlined," Berger said in a statement.

To support the accelerated approval of ponatinib, the phase III EPIC trial was initiated to compare 45 mg ponatinib with imatinib for patients with newly diagnosed CML. As a result of the new safety findings, Ariad, in collaboration with a Data Monitoring Committee, is proposing that the daily dose of ponatinib be adjusted to 30 mg daily in this trial. However, if patients have already achieved a major molecular response, the dose will be further reduced to 15 mg daily. Additionally, the company announced, the eligibility criteria for all ponatinib clinical trials will be modified to exclude patients with prior arterial thrombosis that has resulted in heart attack or stroke. **EBO**

FDA Approves Ibrutinib for Mantle Cell Lymphoma

Silas Inman

Acting ahead of schedule, the US Food and Drug Administration (FDA) has granted an accelerated approval to ibrutinib (Imbruvica) as a treatment for patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, based on a single-arm clinical trial demonstrating a durable improvement in overall response rates (ORRs).

In the phase II trial, labeled PCYC-1104, the oral first-in-class Bruton's tyrosine kinase (BTK) inhibitor ibrutinib demonstrated an ORR of 68%, including a complete response rate of 21%. Moreover, the median duration of response was 17.5 months. Based on these data, the FDA granted ibrutinib a Breakthrough Therapy designation and the eventual approval.

"Imbruvica's approval demonstrates the FDA's commitment to making treatments available to patients with rare diseases," said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "The

agency worked cooperatively with the companies to expedite the drug's development, review and approval, reflecting the promise of the Breakthrough Therapy Designation program."

The PCYC-1104 trial enrolled 111 previously treated patients with relapsed or refractory MCL. The median age of patients was 68 years. According to clinical prognostic factors, 86% of patients had intermediate or high-risk MCL. In general, patients had received a median of 3 prior therapies, including bortezomib. Tumor response was assessed every 2 cycles according to the revised International Working Group for NHL criteria.

In the study, ibrutinib was administered orally at a 560-mg dose. The analysis of the trial was divided into 2 cohorts, based on previous exposure to bortezomib. However, prior treatment with bortezomib was found to have no effect on response to ibrutinib.

According to results published in *The New England Journal of Medicine*,¹ an ORR of 68% was observed in patients treated with ibrutinib (complete response rate

= 21%; partial response rate = 47%). The estimated median duration of response was 17.5 months and the median progression-free survival was 13.9 months. At a median follow-up of 15.3 months, the data for overall survival (OS) were not yet mature. However, the estimated rate of OS at 18 months was 58%.

"This is a meaningful day for previously treated mantle cell lymphoma patients, who are in need of new treatment options," said Michael Wang, MD, an associate professor in the Department of Lymphoma/Myeloma at the University of Texas MD Anderson Cancer Center and lead investigator for the pivotal registration trial PCYC-1104. "With Imbruvica, we now have an important new medicine that is a once-daily oral therapy with a favorable risk-benefit profile."

The most common ibrutinib-related adverse events in the PCYC-1104 trial were mild or moderate diarrhea, fatigue, and nausea. In total, grade 3 or higher hematologic events were infrequent and included neutropenia (16%), thrombocytopenia (11%), and anemia (10%).

"We continue to explore Imbruvica's potential to treat cancer patients in need. Presently we are in the midst of investigating this medicine in numerous additional B-cell malignancies with 37 clinical studies ongoing," said Bob Duggan, CEO and chairman of the board of Pharmacyclics, the company developing the agent.

Ibrutinib is an irreversible small-molecule inhibitor of BTK activity. The agent works by blocking B-cell activation and signaling, which prevents the growth of malignant B cells that overexpress BTK. In general, BTK overexpression is abundant in B-cell malignancies, making this agent an effective treatment for many types of blood cancer.

The FDA is also considering ibrutinib as a treatment for patients with chronic lymphocytic leukemia (CLL), based on the same new drug application that resulted in the MCL approval. **EBO**

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50th Anniversary
(continued from cover)

for smoking in the United States. Most people don't remember, but if you sat in a movie theater, people smoked next to you. People smoked on airplanes; homes were filled with smoke."

As the advisory committee worked feverishly for most of 1963 to prepare the report, the nation's cigarette consumption per capita peaked at 4345, having risen steadily for decades from just 54 in 1900.² What Terry referred to in his foreword as the "tobacco-health controversy," the decades-long lock-step increase in cigarette consumption and lung cancer, was officially unresolved in the view of the US Public Health Service, but Terry was determined that it would be. "The subject does not lend itself to easy answers. Nonetheless, it has been increasingly apparent that answers must be found," he wrote.

Terry released *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*,¹ on a Saturday, timed to roil the Sunday newspapers but not the stock market. The committee's conclusion, that cigarette smoking causes lung cancer in men and probably women, and is among the causes of chronic bronchitis, resounded like a voice from the sky. As Terry expected, headlines with the report's findings blared across the Sunday papers, with *The New York Times* front page referring to the cigarette "peril" and "cancer link cited."³

"I remember debating the news with a group of teenagers the day it came out," recalled Gregory N. Connolly, 64, director for the Center for Global Tobacco Control and professor at the Harvard School of Public Health. "My father eventually quit smoking. The report was a transfer of science to the public that touched every individual."

While the report was a thunderous end to the official uncertainty about whether smoking is unhealthy, its conclusions were not an abrupt departure from medical opinion. In the neutral language of a government report, the committee outlined an unfolding shift in global public health opinion about smoking from studied to alarmed. The committee noted the 1962 report of the Royal College of Physicians in England, which stated, "Cigarette smoking is a cause of lung cancer and bronchitis and probably contributes to coronary heart disease and various other less common diseases."⁴

By the time Terry appointed his advisory committee, the committee noted, the nations of Denmark, Italy, and Great Britain had banned or limited tobacco advertising. Those reports and actions abroad, along with a request

from the Federal Trade Commission (FTC) on whether the science required that cigarettes carry a health warning, were among the reasons Terry listed for appointing the advisory committee.

"Few medical questions have stirred such public interest or created more scientific debate than the tobacco-health controversy. The interrelationships of smoking and health undoubtedly are complex. The subject does not lend itself to easy answers. Nevertheless, it has been increasingly apparent that answers must be found."

from the Foreword, *Smoking and Health*, January 11, 1964
Signed by Luther L. Terry, Surgeon General

Beginning in the 1930s but accelerating through the 1950s, a mountainous body of research had accumulated correlating lung cancer with smoking cigarettes. In 1956, then-surgeon general Leroy E. Burney appointed a scientific study group on smoking and health, drawing from the National Cancer Institute, the National Heart Institute and the American Heart Association, marking the Public Health Service's first involvement in the question. Guided by the study group's conclusion, Burney in 1957 published a statement declaring, "It is clear that there is an increasing and consistent body of evidence that excessive cigarette smoking is one of the causative factors in lung cancer."⁵

What constituted "excessive" Burney did not say, and he dropped the adjective in a second official statement in 1959, writing "the weight of evidence at present implicates smoking as the principal factor in the increased incidence of lung cancer."⁶

A New Approach to Showing "Cause"

In June 1961, a reevaluation of smoking and health was suggested by the American Cancer Society, the American Heart Association, The National Tuberculosis Association (later the American Lung Association) and the American Public Health Association in a letter to President John F. Kennedy. The letter suggested that Kennedy appoint a committee to find "a solution to this public health problem that would interfere least with the freedom of industry or the happiness of individuals."⁷ Terry invited representatives of those same organizations in June 1962⁷ to a meeting for "objective assessment of the nature and magnitude of the health hazards" of smoking after President Kennedy responded to their request for a committee.

"We are very proud, as an organization, that we were at the table at that meeting when it was agreed to make an objective assessment of the health effects of tobacco," said Erika Sward,

assistant vice president of National Advocacy for the American Lung Association. "The 1964 Surgeon General report states very clearly that cigarette smoking is causally linked to lung cancer in men, and they established it as the most important cause of chronic bronchitis and emphysema, which is now known as COPD (chronic obstructive pulmonary disease). It was a landmark report, the first time there was a massive declaration by the federal government that tobacco use was becoming an epidemic."

Terry appointed a committee of 10 eminent specialists, none with expertise in smoking, to work with a small staff and a wide range of consultants to evaluate the available research, draw conclusions, and make recommendations.

"The committee's assignment has been most difficult," the Surgeon General wrote in his foreword, a statement bordering on understatement. Between November 1962 and publication in January 1964, the committee reviewed 7000 studies and consulted with more than 150 experts. The list of acknowledgments covers 9 pages of names.¹

The committee's primary job was to determine if the enormous amount of evidence associating cigarette smoking with disease, particularly but not exclusively lung cancer, supported the conclusion that smoking "caused" the disease. The committee accepted the challenge, stating "statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability." The committee established 5 criteria for building a bridge from association to causation: (1) the consistency of the association; (2) the strength of the association; (3) the specificity of the as-



sociation; (4) the temporal relationship of the association; and (5) the coherence of the association.

"Science at the time was looking at the mechanistic link," said Connolly, of the Harvard School of Public Health. "We wanted to know what in smoking triggered what cell in the lung so we could show cause. It was a very clinical

(continued on page SP460)



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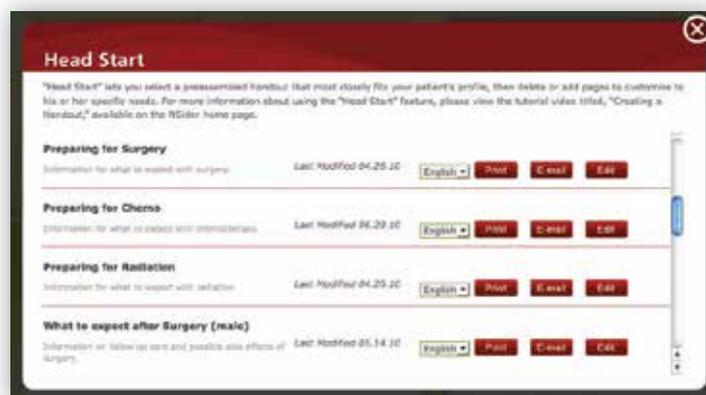


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(continued from SP457)

perspective. This report really invented modern epidemiology, determining cause by looking at large population data.”

Taking on Big Tobacco

The economic significance of the tobacco industry and the ubiquitous nature of smoking caused the committee to shroud its deliberations in secrecy. Most of its work was done deep in the National Library of Medicine (NLM).

The import of the committee’s work soon became apparent to Don Sho-

pland, who in the spring of 1962 was newly graduated from high school and beginning his first adult job at the NLM.

“There were locked files, administrative confidential files, that sort of thing,” said Shopland, who only months before had begun working at the library. Soon, he was working full

smoking.” Pearson cited concerns of the US Department of Agriculture on tobacco crop prices, as well as the FTC’s need for guidance on the need for warning labels and other regulatory issues.⁸

“When we submitted the report to the government printing office, it was

to Your Health.”) The law required the FTC to report annually on the effectiveness of the warning, and for HEW, of which the surgeon general was a part, to report annually to the Congress on the health consequences of smoking.¹¹

The Public Health Cigarette Smoking Act of 1969 banned cigarette advertising on television and radio, and the package label changed to the sterner “Warning: The Surgeon General Has Determined that Cigarette Smoking Is Dangerous to Your Health,” but precluded states and localities from regulating other forms of advertising such as billboards and promotions.¹¹ The industry remained largely unregulated by the federal government¹² until 2009, when President Barack Obama signed the Family Smoking Prevention and Tobacco Control Act that brought cigarettes under purview of the US Food and Drug Administration (FDA), although this groundwork was laid in 1996 by former FDA commissioner David Kessler, MD, a pediatrician.¹³

“After the 1964 report Terry called for remedial action. What happened was Congress exempted tobacco from every health and safety law,” said Connolly of the Harvard School of Public Health.

AMA and Big Tobacco: It’s Complicated

One of the first studies to link cigarette smoking and cancer was coauthored in 1939 by Alton Ochsner, MD, founder of the famed Ochsner Clinic in New Orleans, Louisiana. Early on, Ochsner was ridiculed for his aggressive promotion of his findings, but he became one of the nation’s earliest advocates against cigarette smoking.¹⁴ Most in the medical profession did not see much harm in moderate cigarette use, and many doctors smoked themselves, a fact that the tobacco companies would use

“For the bulk of the population of the United States, the relative cause of cigarette smoking as a cause of chronic broncho-pulmonary disease is much greater than atmospheric pollution or occupational exposures.”

from The Effects of Smoking: Principal Findings, Smoking and Health, 1964

time for the committee. In 1966, he joined the National Clearinghouse on Smoking and Health, and he later became director of the Office of Smoking and Health (OSH), where he helped write 20 more reports on smoking to Congress.

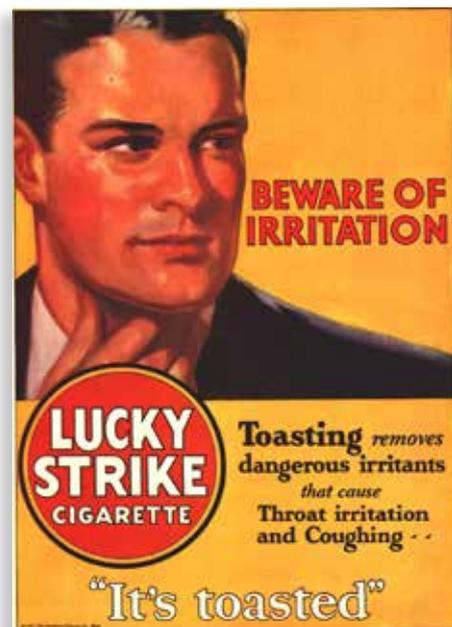
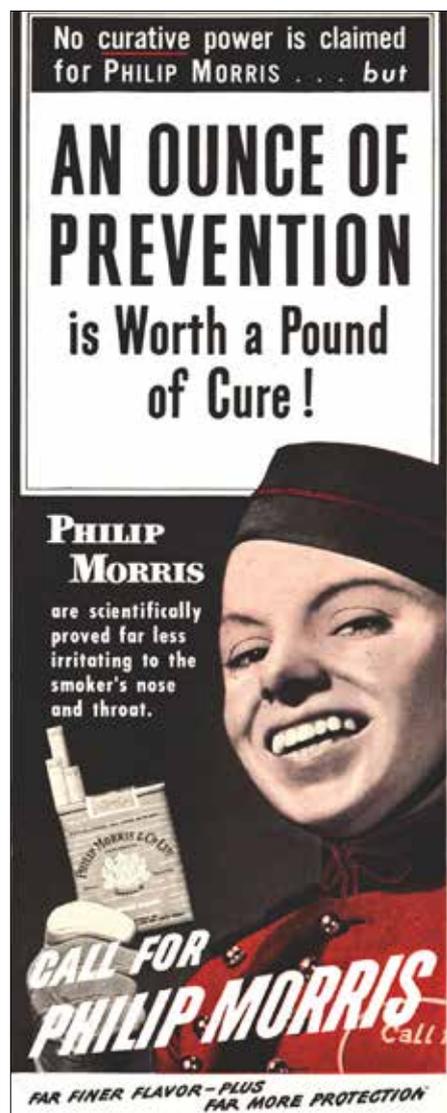
“There was constant tension around the work,” Shopland said. “We worked 7 days a week from August or September when I started, for the rest of the year, often until midnight. I recall having off Christmas Day, Thanksgiving, and a half-day the day of Kennedy’s funeral. It was a very intense time.”

The legendary investigative journalist, Drew Pearson, outlined in an October 1963 column the pressure on the committee, and the federal government’s lack of enthusiasm for regulating tobacco and smoking. Pearson correctly reported the committee would link smoking and cancer. He quoted US Secretary of Health, Education, and Welfare (HEW) Anthony Celebrezze, a pack-a-day smoker, who didn’t “consider it the proper role of the federal government to tell people to stop

the only non-military report that was printed ‘Top Secret,’” Shopland said. “The tobacco companies were major industries, almost like General Motors. (The committee) took great pains to make sure nothing leaked out that would affect the stock market. They were afraid what would happen to the tobacco industry and related industries for paper, packaging, Wall Street. Tobacco reached deep into society.”

As it turned out, the regulatory fallout from the 1964 report had little immediate effect on most smokers, with the per capita consumption remaining around 4000 cigarettes for another decade,⁹ or on the industry, which remained profitable and politically potent.

In June 1964, the FTC relied upon the surgeon general’s report to require health warnings on cigarettes while it considered restrictions on cigarette advertising.¹⁰ In 1965, Congress passed the Federal Cigarette Labeling and Advertising Act (which precluded any package warning except “Caution: Cigarette Smoking May Be Hazardous



to their advantage as health concerns about cigarettes grew.¹⁵

Tobacco companies courted physicians as soon as health concerns arose. One way was placing advertising in the *Journal of the American Medical Association (JAMA)*, which accepted tobacco ads for 20 years starting in 1933.¹⁶ Eventually, tobacco companies used depictions of physicians in the ads themselves; “More doctors smoke Camels” became a classic. When research by Ochsner and others led to a December 1952 *Reader’s Digest* article, “Cancer by the Carton,”¹⁷ it caused a temporary dip in cigarette sales and an immediate response from both JAMA and the tobacco companies. JAMA stopped accepting tobacco ads. But the industry formed the Tobacco Industry Research Committee (TIRC) to both award research grants and advance the industry’s position.¹⁸ Advertising strategy shifted from overt representation of doctors to the promotion of filtered or “safer” cigarettes, which were buoyed by their “studies” and Hollywood actresses who crowed that these new models were “just what the doctor ordered.”¹⁹

The connections among Big Tobacco, the advertising industry, and physicians did not ebb overnight. Pushed

by Ochsner, in 1952 the American Cancer Society began a long-term study to prove cigarettes caused cancer.²⁰ JAMA published Ochsner’s findings and Burney’s 1959 statement on tobacco, but when necessary the industry simply bypassed this outlet and sent favorable study results directly to physicians. Big Tobacco was so entrenched in American culture that Ochsner was warned before an appearance on *Meet the Press* not to state that there was a causal link between cigarettes and lung cancer.²⁰

By 1964, as *Smoking and Health* rocked the country, the AMA seemed poised to issue a report on cigarette smoking

after the Surgeon General’s report was unveiled, the AMA accepted \$10 million from tobacco companies, which it would combine with \$500,000 of its own funds for research grants. Ochsner publicly called the AMA “derelict.”²⁰ A decade would pass before the AMA would issue an official statement on smoking and health, and the group opposed early efforts to regulate cigarette advertising.¹⁹

Secondhand Smoke Dangers

While the 1964 report told smokers the dangers of cigarettes, in the 1970s the Surgeon General began warning America’s nonsmokers about the dangers of

of smokers having the right to pollute the air,” Shopland recalled. “We started getting mail from around the country supporting him. That first raised the idea that being around smoking was not a good idea.”

The 1972 report²¹ contained 3 chapters on “environmental tobacco smoke,” giving momentum to the nascent movement to restrict indoor smoking. By the end of the 1970s, 18 municipalities around the nation had passed indoor smoking ordinances. The 1986 report was entirely about secondhand smoke,²² accelerating the momentum of nonsmokers pressing

(continued on page SP465)

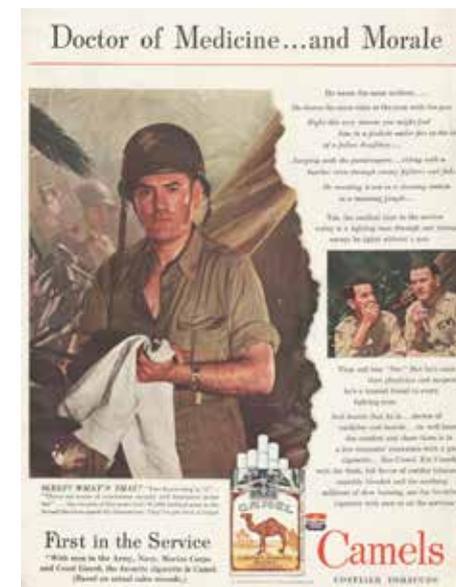
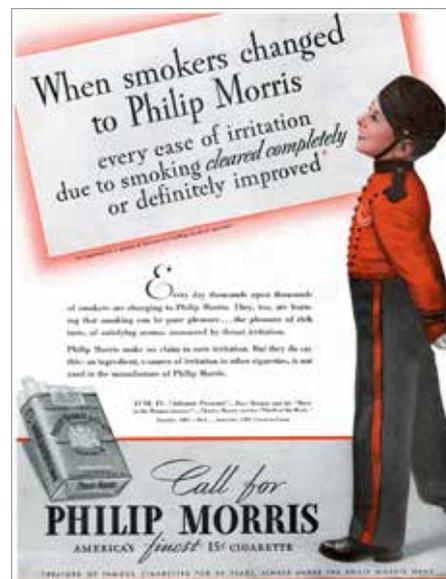
“Cigarette smoking is associated with a 70 percent increase in the age-specific death rates of males, and to a lesser extent with increased death rates in females. The total number of deaths causally related to cigarette smoking in the U.S. population cannot be accurately estimated. In view of the continuing and mounting evidence from many sources, it is the judgment of the Committee that cigarette smoking contributes substantially to mortality from certain specific diseases and to the overall death rate.”

Smoking and Health, January 11, 1964.

and cancer. For 2 years, however, the physicians’ group had been fighting another battle: President Kennedy’s proposal to create Medicare. Although the AMA denied the charge, US Rep. Frank Thompson (D-NJ) and others accused the group of striking a deal with lawmakers from the tobacco states: if the AMA held its tongue on cigarettes, the legislators would fight Medicare.¹⁹ On February 7, 1964, less than a month

smoke-filled rooms. Shopland recalled Surgeon General Jesse Steinfeld mentioning the health effects on nonsmokers when presenting the 1971 report to the National Interagency Council on Smoking and Health.

“The entire report was about smokers, but at the end of his presentation he said it was his opinion nonsmokers needed a bill of rights, that nonsmokers had the right to clean air instead





The median age of patients in the VISTA[†] trial was 71 years (range: 48-91).

Indication and Important Safety Information for VELCADE[®] (bortezomib)

INDICATION

VELCADE (bortezomib) is indicated for the treatment of patients with multiple myeloma.

CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

WARNINGS, PRECAUTIONS, AND DRUG INTERACTIONS

- ▼ **Peripheral neuropathy:** Manage with dose modification or discontinuation. Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.
- ▼ **Hypotension:** Use caution when treating patients taking antihypertensives, with a history of syncope, or with dehydration.

- ▼ **Cardiac toxicity:** Worsening of and development of cardiac failure have occurred. Closely monitor patients with existing heart disease or risk factors for heart disease.
- ▼ **Pulmonary toxicity:** Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms.
- ▼ **Posterior reversible encephalopathy syndrome:** Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.
- ▼ **Gastrointestinal toxicity:** Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement.
- ▼ **Thrombocytopenia or Neutropenia:** Monitor complete blood counts regularly throughout treatment.
- ▼ **Tumor lysis syndrome:** Closely monitor patients with high tumor burden.
- ▼ **Hepatic toxicity:** Monitor hepatic enzymes during treatment.

In treating multiple myeloma

What is the value of VELCADE® (bortezomib)?

- ▼ Overall survival advantage
- ▼ Defined length of therapy
- ▼ Medication cost

IF YOU DEFINE VALUE AS AN OVERALL SURVIVAL ADVANTAGE:

VELCADE (bortezomib) combination delivered a >13-month overall survival advantage

- ▼ At 5-year median follow-up, VELCADE+MP* provided a median overall survival of 56.4 months vs 43.1 months with MP alone (HR=0.695 [95% CI, 0.57-0.85]; $p<0.05$)[†]
- ▼ At 3-year median follow-up, VELCADE+MP provided an overall survival advantage over MP that was not regained with subsequent therapies

IF YOU DEFINE VALUE AS DEFINED LENGTH OF THERAPY:

- ▼ Results achieved using VELCADE twice-weekly followed by weekly dosing for a median of 50 weeks (54 planned)¹

IF YOU DEFINE VALUE AS MEDICATION COST:

- ▼ Medication cost is an important factor when considering overall drug spend. The Wholesale Acquisition Cost for VELCADE is \$1,544 per 3.5-mg vial as of July 2013
- ▼ When determining the value of a prescription drug regimen, it may be worth considering medication cost, length of therapy, and dosing regimens. This list is not all-inclusive; there are additional factors to consider when determining value for a given regimen

- ▼ **Embryo-fetal risk:** Women should avoid becoming pregnant while being treated with VELCADE. Advise pregnant women of potential embryo-fetal harm.
- ▼ Closely monitor patients receiving VELCADE in combination with strong **CYP3A4 inhibitors**. Avoid concomitant use of strong **CYP3A4 inducers**.

ADVERSE REACTIONS

Most commonly reported adverse reactions (incidence $\geq 20\%$) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

Please see Brief Summary for VELCADE on the next page of this advertisement.

For Reimbursement Assistance, call 1-866-VELCADE (835-2233), Option 2, or visit VELCADEHCP.com.

Reference: 1. Mateos M-V, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol.* 2010;28(13):2259-2266.

*Melphalan+prednisone.

[†]**VISTA TRIAL:** a randomized, open-label, international phase 3 trial (N=682) evaluating the efficacy and safety of VELCADE administered intravenously in combination with MP vs MP in previously untreated multiple myeloma. The primary endpoint was TTP. Secondary endpoints were CR, ORR, PFS, and overall survival. At a prespecified interim analysis (median follow-up 16.3 months), VELCADE+MP resulted in significantly superior results for TTP (median 20.7 months with VELCADE+MP vs 15.0 months with MP [$p=0.00002$]), PFS, overall survival, and ORR. Further enrollment was halted and patients receiving MP were offered VELCADE in addition. Updated analysis was performed.

 **VELCADE**[®]
(bortezomib) FOR INJECTION

INDICATIONS:

VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma. VELCADE for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

CONTRAINDICATIONS:

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

WARNINGS AND PRECAUTIONS:

Peripheral Neuropathy: VELCADE treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain, or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs intravenous, the incidence of Grade ≥2 peripheral neuropathy events was 24% for subcutaneous and 39% for intravenous. Grade ≥3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in the intravenous treatment group. Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule. In the VELCADE vs dexamethasone phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension: The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

Cardiac Toxicity: Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing, heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤1% for each individual reaction in the VELCADE group. In the dexamethasone group, the incidence was ≤1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Pulmonary Toxicity: Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology, such as pneumonitis, interstitial pneumonia, and lung infiltration have occurred in patients receiving VELCADE. Some of these events have been fatal. In a clinical trial, the first two patients given high-dose cytarabine (2 g/m² per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease. In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt, comprehensive, diagnostic evaluation is conducted.

Posterior Reversible Encephalopathy Syndrome (PRES): Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome

(RPLS)) has occurred in patients receiving VELCADE. PRES is a rare, reversible, neurological disorder, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.

Gastrointestinal Toxicity: VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting, sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt VELCADE for severe symptoms.

Thrombocytopenia/Neutropenia: VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern, with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice-weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia was related to pretreatment platelet count. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of bleeding (≥Grade 3) was 2% on the VELCADE arm and <1% on the dexamethasone arm. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE. Platelet counts should be monitored prior to each dose of VELCADE. Patients experiencing thrombocytopenia may require change in the dose and schedule of VELCADE. Gastrointestinal and intracerebral hemorrhage has been reported in association with VELCADE. Transfusions may be considered.

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with VELCADE therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

Hepatic Toxicity: Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt VELCADE therapy to assess reversibility. There is limited re-challenge information in these patients.

Embryo-fetal: Pregnancy Category D. Women of reproductive potential should avoid becoming pregnant while being treated with VELCADE. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m² based on body surface area caused post-implantation loss and a decreased number of live fetuses.

ADVERSE EVENT DATA:

Safety data from phase 2 and 3 studies of single-agent VELCADE 1.3 mg/m²/dose administered intravenously twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously-treated multiple myeloma (N=1008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

In the integrated analysis, the most commonly reported (≥10%) adverse reactions were nausea (49%), diarrhea NOS (46%), fatigue (41%), peripheral neuropathies NEC (38%), thrombocytopenia (32%), vomiting NOS (28%), constipation (25%), pyrexia (21%), anorexia (20%), anemia NOS (18%), headache NOS (15%), neutropenia (15%), rash NOS (13%), paresthesia (13%), dizziness (excl vertigo 11%), and weakness (11%). Eleven percent (11%) of patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (4%) and neutropenia (2%). A total of 26% of patients experienced a serious adverse reaction during the studies. The most commonly reported serious adverse reactions included diarrhea, vomiting, and pyrexia (3% each), nausea, dehydration, and thrombocytopenia (2% each), and pneumonia, dyspnea, peripheral neuropathies NEC, and herpes zoster (1% each).

In the phase 3 VELCADE+melfalhan and prednisone study in previously untreated multiple myeloma, the safety profile of VELCADE administered intravenously in combination with melfalhan/prednisone is consistent with the known safety profiles of both VELCADE and melfalhan/prednisone. The most commonly reported adverse reactions in this study (VELCADE+melfalhan/prednisone vs melfalhan/prednisone) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), leukopenia (32% vs 28%), vomiting (26% vs 12%), fatigue (25% vs 14%), lymphopenia (23% vs 15%), constipation (23% vs 4%), anorexia (19% vs 6%), asthenia (16% vs 7%), pyrexia (16% vs 6%), paresthesia (12% vs 1%),

herpes zoster (11% vs 3%), rash (11% vs 2%), abdominal upper (10% vs 6%), and insomnia (10% vs 6%).

In the phase 3 VELCADE subcutaneous vs intravenous relapsed multiple myeloma, safety data were similar between the two treatment groups. The most commonly reported reactions in this study were peripheral neuropathy NEC (35% vs 30%), thrombocytopenia (30% vs 34%), neutropenia (27% vs 27%), neuralgia (23% vs 23%), anemia (19% vs 23%), diarrhea (19% vs 28%), leukopenia (18% vs 20%), nausea (16% vs 16%), pyrexia (12% vs 8%), vomiting (9% vs 11%), asthenia (16%), and fatigue (7% vs 15%). The incidence of serious reactions was similar for the subcutaneous treatment (20%) and the intravenous treatment group (19%). The commonly reported SARs were pneumonia and pyrexia (2% vs 2%) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (3% each) in the intravenous treatment group.

DRUG INTERACTIONS:

Bortezomib is a substrate of cytochrome P450 enzyme 3A4 and 1A2. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in patients. Monitor patients for signs of bortezomib toxicity. Consider a bortezomib dose reduction if bortezomib must be administered in combination with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, voriconazole, posaconazole, and isavuconazole). Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients. Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur. Exposure may be reduced when VELCADE is used in combination with CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving VELCADE. St. John's wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and should be avoided. Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients. Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely clinically relevant.

USE IN SPECIFIC POPULATIONS:

Nursing Mothers: It is not known whether bortezomib 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 VELCADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of VELCADE in children has not been established.

Geriatric Use: No overall differences in safety or effectiveness were observed between patients ≥age 65 and younger patients receiving VELCADE; but greater sensitivity of some individuals cannot be ruled out.

Patients with Renal Impairment: The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. Since dialysis may remove VELCADE concentrations, VELCADE should be administered after the dialysis procedure. For information concerning dosing in patients with renal impairment, see manufacturing prescribing information.

Patients with Hepatic Impairment: The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Starting dose should be reduced in those patients with moderate and severe hepatic impairment.

Patients with Diabetes: During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving VELCADE. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose and adjustment of the dose of their antidiabetic medication.

Please see full Prescribing Information for VELCADE at VELCADEHCP.com.



(continued from SP461)

for clean indoor air. In 1995, California became the first state to pass a law regulating indoor smoking. Currently, 81.5 percent of the US population lives in a locality where indoor smoking is restricted; in many places, outdoor smoking is restricted as well.²³

"You saw America acting as it usually does on social change," said Connolly. "At the community level people said they'd had enough; they deserved clean indoor air, they wanted an end to marketing to children. They combined the science from the Surgeon General with moral virtue. Smoking rates plummeted in America because of what common citizens did, not what Washington did. It's the best public health story of the last century."

The single greatest blow against cigarette sales in the United States was landed in 1998 when the nation's 4 largest manufacturers—Phillip Morris USA, R.J. Reynolds Tobacco Company, Brown & Williamson, and the Liggett Group—signed the "master settlement agreement" with 46 states. The agreement guarantees billions of dollars in annual payments to offset Medicaid costs for smoking-related disease. The agreement limits tobacco advertising, with particular restrictions on the use of cartoon characters and other devices for marketing to children. And, it forced the permanent dismantling of the Council for Tobacco Research, the successor to the TIRC.²⁴

A Permanently Altered Landscape

Knowledge of the dangers of cigarette smoking have seeped into the public consciousness to a degree unthinkable in 1964. This has allowed research priorities to shift as well, as studies turn to issues surrounding public education and health disparities; it is well documented that the effects of smoking hit hardest on low-income groups and the developing world.²⁵ In fact, in October 2013, the American Thoracic Society and the European Respiratory Society published a statement in *The American Journal of Respiratory Critical Care Medicine* announcing the creation of a committee to address the fact that lower-level socioeconomic groups are 14 times more likely than higher-level groups to suffer from respiratory ailments, with cigarette smoking being a major reason.²⁵

In recent decades, the AMA has joined with other medical groups to combat cigarette smoking, especially among the young. In September 2009, the AMA praised the FDA for a ban on flavored cigarettes, after numerous studies in which "the evidence shows that young smokers are the primary

"Lung cancer deaths, less than 3,000 in 1930, increased to 18,000 in 1950. In the short period since 1955, deaths from lung cancer rose from less than 27,000 to the 1962 total of 41,000. This extraordinary rise has not been recorded for cancer of any other site. Deaths from arteriosclerotic, coronary, and degenerative heart disease rose from 273,000 in 1940, to 396,000 in 1950, and to 578,000 in 1962.

Reported deaths from chronic bronchitis and emphysema rose from 2,300 in 1945 to 15,000 in 1962.

The changing patterns and extent of tobacco use are a pertinent aspect of the tobacco-health problem.

Nearly 70 million people in the United States consume tobacco regularly. Cigarette consumption in the United States has increased markedly since the turn of the Century, when per capita consumption was less than 50 cigarettes a year. Since 1910, when cigarette consumption per person (15 years or older) was 138, it rose to 1,365 in 1930, to 1,828 in 1940, to 3,322 in 1950 and a peak of 3,986 in 1961. The 1955 Current Population Survey showed that 68 percent of the male population and 32.4 percent of the female population 18 years of age and over were regular smokers of cigarettes."

from Background and Highlights, Smoking and Health, 1964

users of flavored tobacco products."²⁶ Much of today's policy focus is on stopping young people from picking up the habit; last month, the New York City Council raised to 21 the age at which it is legal to buy cigarettes.²⁷

Clinically, smoking still kills. The most recent data sheet from the Centers for Disease Control and Prevention (CDC), published August 1, 2013, states that 440,000 deaths, or 1 in 5 in the United States, are caused by smoking.²⁸ This includes 90% of all deaths from COPD.²⁸ Many were already smokers in their twenties when the 1964 report came out, who have been unable to quit, and now suffer its health effects in their old age.²⁹

The 1964 report was the first big step in a very long trek to a smoke-free society, said Glynn of the American Cancer Society, who is working on commemorating the 50th anniversary.

"I grew up in a small New York City apartment with 2 cigarette smokers and my grandfather smoking a pipe. No one thought a thing about

it," Glynn said. "We went from 42% of the population then (smoking) to 19% now. That is a huge public health success. Probably between 8 and 12 million lives have been saved since the publication of that report, but we still have 44 million people smoking, even though 70% of them say they want to stop. Our work remains to get people to stop smoking, period. I know that sounds obvious, but that's the work, still." **EBO**

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(continued on page SP468)

Take a bite out of G-CSF acquisition costs*



*Based on wholesale acquisition cost (WAC) of all short-acting G-CSF products as of November 11, 2013. WAC represents published catalogue or list prices and may not represent actual transactional prices. Please contact your supplier for actual prices.

Indication

- » GRANIX™ (tbo-filgrastim) Injection is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Important Safety Information

- » **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.
- » **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
- » **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

GRANIX™ is a new option in short-acting G-CSF therapy

- » FDA approved through the rigorous BLA[†] process
- » Teva's filgrastim, the same compound as GRANIX, was first introduced in Europe in 2008 and is available in 39 countries outside the US[‡]
- » GRANIX is an option for hospitals and payers to consider when determining health system budgets

A unique J-code is expected for GRANIX in January 2014

[†]Biologics License Application.

[‡]As of November 2013.

Important Safety Information (continued)

- » **Use in patients with sickle cell disease:** Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
- » **Potential for tumor growth stimulatory effects on malignant cells:** The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.
- » **Most common treatment-emergent adverse reaction:** The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

Please see brief summary of Full Prescribing Information on adjacent page.

For more information, visit GRANIXhcp.com.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR GRANIX™ (tbo-filgrastim) Injection, for subcutaneous use
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GRANIX is indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Allergic Reactions

Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Use in Patients with Sickle Cell Disease

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

5.5 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which GRANIX acts has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.

6 ADVERSE REACTIONS

The following potential serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [see Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome [see Warnings and Precautions (5.2)]
- Serious Allergic Reactions [see Warnings and Precautions (5.3)]
- Use in Patients with Sickle Cell Disease [see Warnings and Precautions (5.4)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [see Warnings and Precautions (5.5)]

The most common treatment-emergent adverse reaction that occurred at an incidence of at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group was bone pain.

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 clinical practice.

GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin's lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin's lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. Both GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of $\geq 10,000 \times 10^6/L$ after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the

recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

In clinical studies, leukocytosis (WBC counts $> 100,000 \times 10^6/L$) was observed in less than 1% patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7 DRUG INTERACTIONS

No formal drug interaction studies between GRANIX and other drugs have been performed.

Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of GRANIX in pregnant women. In an embryofetal developmental study, treatment of pregnant rabbits with tbo-filgrastim resulted in adverse embryofetal findings, including increased spontaneous abortion and fetal malformations at a maternally toxic dose. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In the embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure (AUC_{0-24}) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

It is not known whether tbo-filgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

8.4 Pediatric Use

The safety and effectiveness of GRANIX in pediatric patients have not been established.

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

8.6 Renal Impairment

The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No case of overdose has been reported.



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Sicor Biotech UAB
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Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Product of Israel
FIL-40046

July 2013

This brief summary is based on TBO-003 GRANIX full Prescribing Information.

About the Photos

Images of these vintage tobacco ads are courtesy of the Stanford Research into the Impact of Tobacco Advertising (SRITA). The need to regulate cigarette advertisements to eliminate false medical claims was a driving force behind the 1964 report to the Surgeon General. Ads depicting doctors smoking, including many shown here, appeared regularly in the *Journal of the American Medical Association* between 1933 and 1953.

For more, see srita.stanford.edu.

Pathways Survey
(continued from cover)

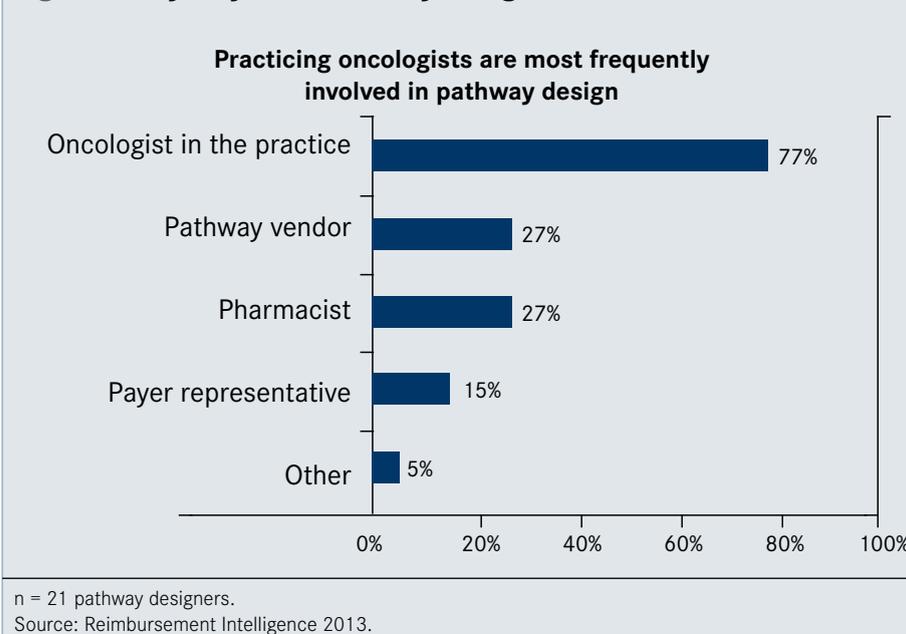
to clinical pathways can benefit from financial and administrative incentives offered by payers.⁴ When pathways were first introduced, however, oncologists were concerned that they would face payer-imposed limitations to exercising their clinical judgment when treating patients.⁵ Nevertheless, clinical pathways have gained traction in the healthcare marketplace as payers have sought to collaborate with providers in the design and implementation of clinical pathways. Accordingly, physician involvement in the development of clinical pathways is now recognized as critical to their adoption and success.¹

Reimbursement Intelligence (RI), a market access consulting firm, completed an online survey in August 2013 of 50 oncology providers representing independent community practices, hospital-affiliated practices, physician network-affiliated practices, and hospitals/academic medical centers. In addition, 20 in-depth interviews were conducted with a subset of respondents responsible for pathway design. The objective was to learn more about the decision-making process in clinical pathway development.

The Model of Cancer Care Is Shifting to Clinical Pathways

The development of clinical pathways can be seen as a shift toward a new model for making cancer care treatment decisions, based on increasingly restrictive decision-making criteria. At the broad end of the decision criteria spectrum, for example, are earlier models such as that used by Medicare. This decision model determines coverage using the compendia of authoritative sources, which determines the level of clinical evidence to support on- and off-label uses of oncology drugs. Somewhat more focused recommendations for treatment, although still broad in nature, are those written by professional societies with National Comprehensive Cancer Network guidelines most prominent. These recommendations are utilized to determine coverage of a product by a private payer. Now, with the advent of clinical pathways, we are seeing highly specific recommendations for patient management being developed by providers for use in their particular organizations. Pathways are becoming increasingly prevalent, as evidenced by the majority of RI survey respondents reporting that they currently utilize pathways in the treatment of breast, lung, and colorectal cancers.

Figure 1. Key Players in Pathway Design



Oncology Providers Lead the Way in Developing of Pathway Design

There has been an influx of pathway design companies available to assist payers and oncology practices. Pathway companies can track and report utilization and identify benchmarks of adherence to pathways. They can also identify where there may be inappropriate or excessive utilization of treatments and services such as colony-stimulating factors and imaging.

Survey questions about pathway design showed that 45% of the pathway users developed their own pathways, with the remainder of pathway users receiving pathway design assistance from pathway vendors such as US Oncology and Via Oncology (28% and 14% of users, respectively). This extensive use of pathway design assistance may reflect oncology providers' ability to

customize their pathways even within a system that uses a pathway vendor. Oncology providers want to make sure the pathways reflect the needs of the patient population within their practice, and many pathway design companies allow some flexibility regarding drugs that are not on pathway.

Figure 1 reinforces that oncologists, not payers, are the key players in pathway design. Those who participated in the design of clinical pathways were most often oncologists within the practice (77%), followed by pathway vendors (27%), pharmacists (27%), and payer representatives (15%). Oncologists' leadership ensures the pathways reflect the latest clinical treatment.

Safety and Efficacy Are Top Considerations for Inclusion of Treatments, Followed by Cost

Figure 2. Safety/Tolerability Considerations for Pathway Placement

	Safety/Tolerability Consideration	
	Overall Rank	Average Rank
Trial design (RCT, non-inferiority, AE framework selected, etc)	1	3.6
Time on market	2	3.8
Real-world performance (non-trial based data)	3	4.1
Discontinuation rates	4	5.0
Sample size	5	5.1
Concomitant therapies	6	5.8
Length of follow-up	7	5.8
Hospitalization rates	8	6.0
Validated PROs/third-party verification	9	6.3
Frequency of ER visits	10	6.6

AE indicates adverse events; ER, emergency department; PRO, patient reported outcomes; RCT, randomized controlled trial. n = 21 pathway designers.
Source: Reimbursement Intelligence 2013

So how do pathway users decide upon a given treatment regimen versus another in designing a clinical pathway? In mid-2009, a statewide collaboration between Blue Cross Blue Shield of Michigan (a single-state, not-for-profit BCBS plan), Physician Resource Management (a state physician organization), and Cardinal Health Specialty Solutions (an oncology benefit management company) created a clinical pathway program in which physicians developed the content, structure, and implementation of the program.¹ In this program, pathway regimen selections were considered in order of descending priority starting with treatment efficacy, then toxicity, then cost. Decision making was similar in the 2010 program, a collaboration between Aetna and The US Oncology Care Network, wherein efficacy was given first priority, toxicity was second, and if both efficacy and toxicity were similar, then

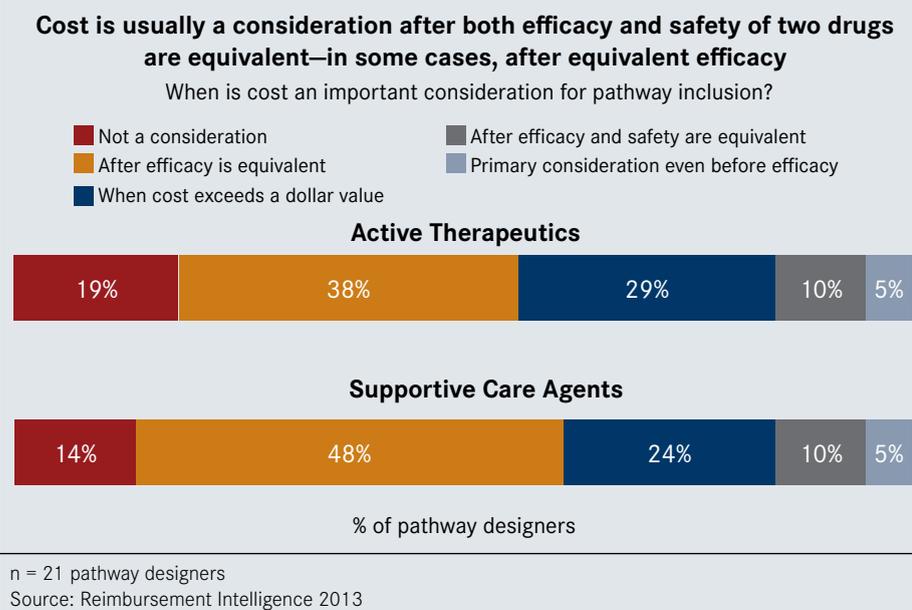
Pathways are becoming increasingly prevalent, as evidenced by the majority of survey respondents reporting that they currently utilize pathways in the treatment of breast, lung, and colorectal cancers.

the lower-cost regimen was preferred for incorporation into the pathway.⁵

Given that many pathway designers placed safety immediately after efficacy as a consideration in selecting treatment, a natural question arises as to which factors carry the most weight in evaluating the relative safety and tolerability of different drugs being considered for placement on pathways. The RI survey results shown in Figure 2 indicated that clinical trial design was the top safety/tolerability consideration for pathway placement, followed by the amount of time a drug was on the market, and real-world performance of the drug.

Interestingly, the aforementioned 2 successful pathway collaborations reflect trends later identified in the RI survey, which found that clinical data showing clear treatment superiority were most

Figure 3. Pathway Designers' Considerations for Inclusion of Drugs on Pathways



influential on the decision to place a product on pathway for 67% of pathway designers surveyed. Also, **Figure 3** shows that if both efficacy and safety of 2 active therapeutics were equivalent, cost then became a consideration for 38% of pathway designers surveyed, and 29% considered cost after efficacy alone was shown to be equivalent. Similar results were found when both efficacy and safety of 2 supportive care agents were equivalent, with cost then becoming a consideration for 48% of pathway designers surveyed, and 24% considering cost after efficacy alone was shown to be equivalent.

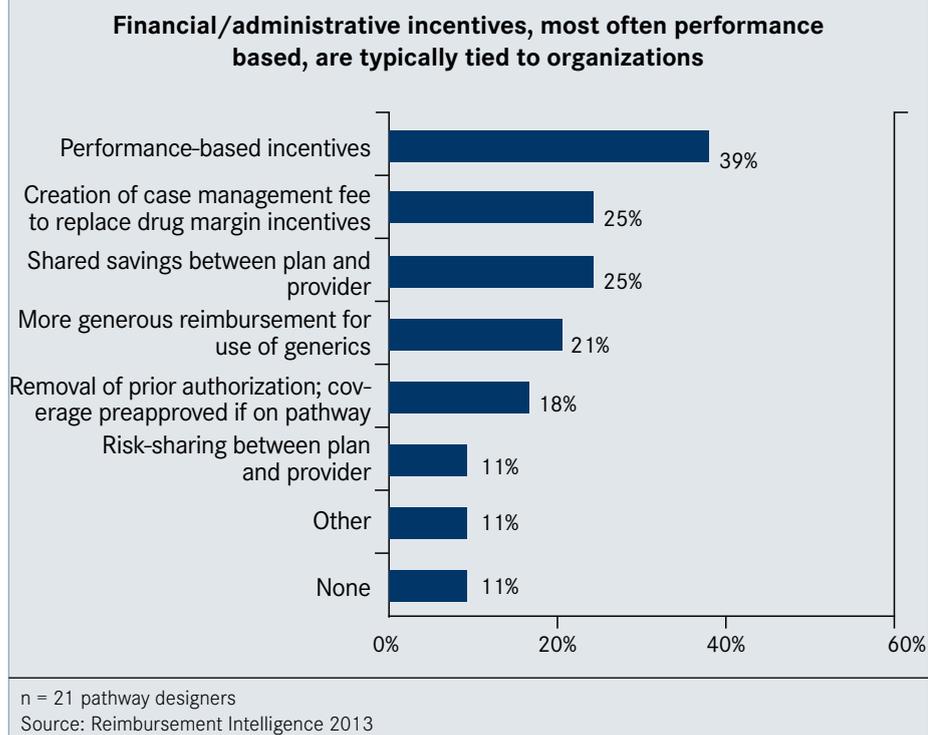
It has been well documented that the high cost of cancer care can be an impediment to patients receiving neces-

sary treatment.^{6,7} Physicians must necessarily be cognizant of expensive costs that might impact their patients' ability to adhere to treatment. For this reason, cost is becoming an increasingly important consideration in clinical pathway design. The RI survey found that when cost factors became a consideration, drugs costs were ranked as the greatest contributing cost consideration for on-pathway placement, followed by overall cost of care, and the cost to patient.

Financial and Administrative Incentives Are Primarily Performance-Based and Tied to Organizations

As previously mentioned, payers are of-

Figure 4. Incentives Offered to Providers Using Pathways



fering financial and administrative incentives to oncology care providers who adhere to clinical pathways. Examples of such incentives can be found in the pathway collaboration between Blue Cross Blue Shield of Michigan and Oncology Physician Resource, a physician-owned practice management entity. Each oncologist who signed up to use the pathway received a \$5000 incentive payment; also, the reimbursement rate for generics was increased, and physicians were promised a certain percentage of any savings related to expenditures for chemotherapy and supportive medications.⁸

It has been well documented that the high cost of cancer care can be an impediment to patients receiving necessary treatment. Physicians must necessarily be cognizant of expensive costs that might impact their patients' ability to adhere to treatment.

The responses to the RI survey showed that incentives for adherence to clinical pathways were tied to the oncology practice as a whole for 46% of pathway users surveyed, while 29% of pathway users had incentives tied to both the oncology practice as a whole and the individual oncologists in the practice.

Figure 4 details the variety of incentives most commonly offered to providers, as indicated by the respondents to the RI survey. Incentives were performance-based in 39% of the organizations surveyed, suggesting that payers and providers place great importance on patient outcomes. The creation of a case management fee to replace drug margin incentives was found in 25% of provider organizations surveyed. Shared savings between payer and provider was an incentive for 25% of pathway users surveyed, and more generous reimbursement for the use of generics was an incentive for 21% of users. Payer coverage was pre-approved for 18% of provider organizations, essentially creating another incentive: removal of the requirement for prior authorization for on-pathway treatment. Finally, risk-sharing between payer and provider was an incentive among 11% of pathway users.

Summary

Clinical pathways represent a shift in how cancer care decisions are made, moving from the use of general guidelines for providing treatment to more specific considerations based upon ef-

ficacy, safety, and cost. Pathways utilization is increasing, particularly in the treatment of breast, lung, and colorectal cancer. Pathway design companies can provide assistance in pathway design, monitoring services, and may offer some flexibility to oncologists in making treatment decisions. Oncologists' buy-in is seen as essential to the success of pathways and the primary participants in pathway design are most often the oncologists within the practice adopting the pathway. Participation in pathways is being incentivized by payers who offer incentive payments, increased reim-

bursement rates, case management fees, shared savings, pre-approved coverage, and risk sharing. **EBO**

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Survivorship

(continued from cover)

complex physical and psychosocial conditions. The study found primary care physicians (PCPs) seldom received explicit guidance from oncologists for survivors in remission and lacked evidence-based best practices.²

A 2012 report on survivorship published by the American Cancer Society (ACS)³ estimated 13.7 million Americans with a history of cancer were alive on January 1, 2012, and nearly 18 million will be alive January 1, 2022. Prostate cancer is the most common diagnosis for men; at 43% of all cancers for men it is almost 3 times as common as the next 2 diagnoses combined, which are colorectal (9%) and melanoma of the skin (7%). Similarly for women, breast cancer at 41% is more than twice as common as uterine corpus (8%) and colorectal (8%) cases combined.³

The 2012 ACS report concluded, “It is increasingly important to understand the unique medical and psychosocial needs of survivors and be aware of resources that can assist patients, caregivers, and health care providers in navigating the various phases of cancer survivorship.”¹

“We are going from the Big C, that automatically killed people and we couldn’t do much about it, to cancer as a chronic disease or a disease we can cure. It is still scary, but it is not the automatic death sentence it once was,” said Crystal Denlinger, MD, an oncologist at Fox Chase Cancer Center in Philadelphia, Pennsylvania. Denlinger, who specializes in treating gastrointestinal cancers, chaired the National Comprehensive Cancer Network (NCCN) panel on survivorship guidelines and coauthored their publication in the *Journal of the National Comprehensive Cancer Network* in May 2013.⁴ A patient-friendly version now appears on the NCCN website.⁵

“We are getting better at what we are doing, but we were all focused on treating the cancer and not the fallout of the treatment,” she said.

Survivorship Demands a Plan

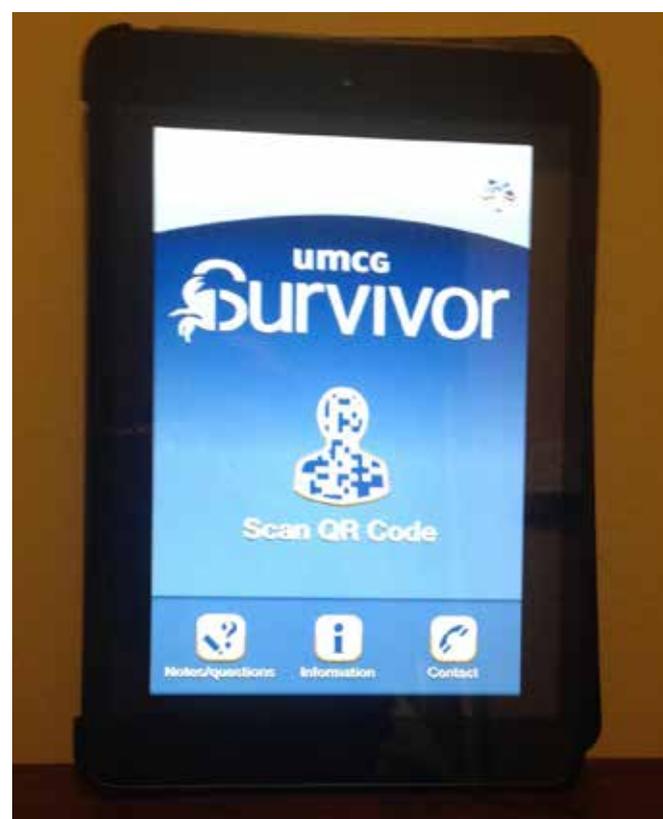
The NCCN guidelines for cancer survivorship planning and care are intended for both oncologists and PCPs treating cancer survivors. The algorithms in the guidelines make recommendations for addressing anxiety and depression, cognitive function, exercise, fatigue, immunizations and infections, pain, sexual function, and sleep disorders in patients who have survived breast cancer, chronic myelogenous leukemia (CML), colon cancer, Hodgkin lymphoma, melanoma, non-Hodgkin lymphomas, non-small cell lung cancer (NSCLC), prostate can-

cer, small cell lung cancer, and thyroid carcinoma.⁵

Denlinger said the guidelines will help care providers fulfill a crucial recommendation from the 2005 IOM report: each cancer patient should receive a “survivorship care plan” that includes diagnosis and content of follow-up visits, tips on maintaining a healthy lifestyle and preventing recurrent or new cancers, legal rights affecting employment and insurance, and the availability of psychological and support services.

“The survivorship care plan that delineates what is required for follow-up has gained a lot of traction,” she said. “A lot of people are struggling with how to put together these care plans when, for many patients, the information is scattered across multiple offices and multiple systems.”

The Commission on Cancer, which certifies most US cancer care centers, has made survivorship care plans a certification requirement beginning in 2015.⁶ “A few decades ago, a patient surviving cancer 5 years was a success, but now people are surviving longer and longer,” said Sarah R. Arvey, PhD, director of Research and Evaluation at the LIVESTRONG Foundation in Austin, Texas. “Once treatment is completed, patients and the primary care physicians should receive a list of what happened to you in the hospital, and the known risks of those medicines and treatments. You need to walk out of there with a plan. With electronic medical records this will become easier.”



A survivor app aids patient planning.

LIVESTRONG has developed a survivorship care planning template that, along with templates from the American Society of Clinical Oncology (ASCO) and National Coalition for Cancer Survivorship, is recommended in the new survivorship care plan requirement.⁶

Linking Survivorship to Payment

Survivorship planning and care is rising as a priority, because the transition from a fee-for-service reimbursement system to an accountable care system demands increasing

correlation between results and what gets paid for, said Bo Gamble, director of strategic practice initiatives for the Community Oncology Alliance (COA).

“Healthcare is the last industry without metrics to determine what is good care or not such good care,” Gamble said. “We’ve seen a mass exodus of oncologists from community practice to hospitals, mainly for reasons of reimbursement. Patients and their insurers are paying almost double for hospital care. We want to develop the measures to make valid comparisons and create some healthy competition to improve care.”

In 2012, Gamble and COA launched the Oncology Medical Home Initiative to explore with medical providers and payers what constitutes quality cancer care. He reports a high level of agreement and strong commitment to developing survivorship as part of standard care.

“We asked the question, ‘What do you need in cancer care?’ The answer from everybody is the best quality care at the least cost with a good survivorship program that includes quality of life,” Gamble said. “Payers, providers, patients, everyone answered the same. The payers said—and this was profound—they don’t

want to give the impression (they) are about withholding care.”

In fact, when Gamble detailed COA’s effort to develop 19 standards of cancer on October 30, 2013, at the meeting Value-Based Oncology Management in Chicago, Illinois, he noted that payers were the first to ask that survivorship be included in the standards.

Ira Klein, MD, chief of staff to the chief medical officer for Aetna and active in the Oncology Medical Home Initiative, said survivorship programs will succeed by empowering patients with information they can both understand and apply, while providing metrics for evaluating the costs and benefits of various treatments.

“We are looking for where what makes the most sense financially is what’s best for the patient. We want to arrange things so we encourage health, because being healthiest is what is cheapest, and when we have illness we pay for what works and not just everything people do,” Klein said.

“The survivorship care plan that delineates what is required for follow-up has gained a lot of traction.”

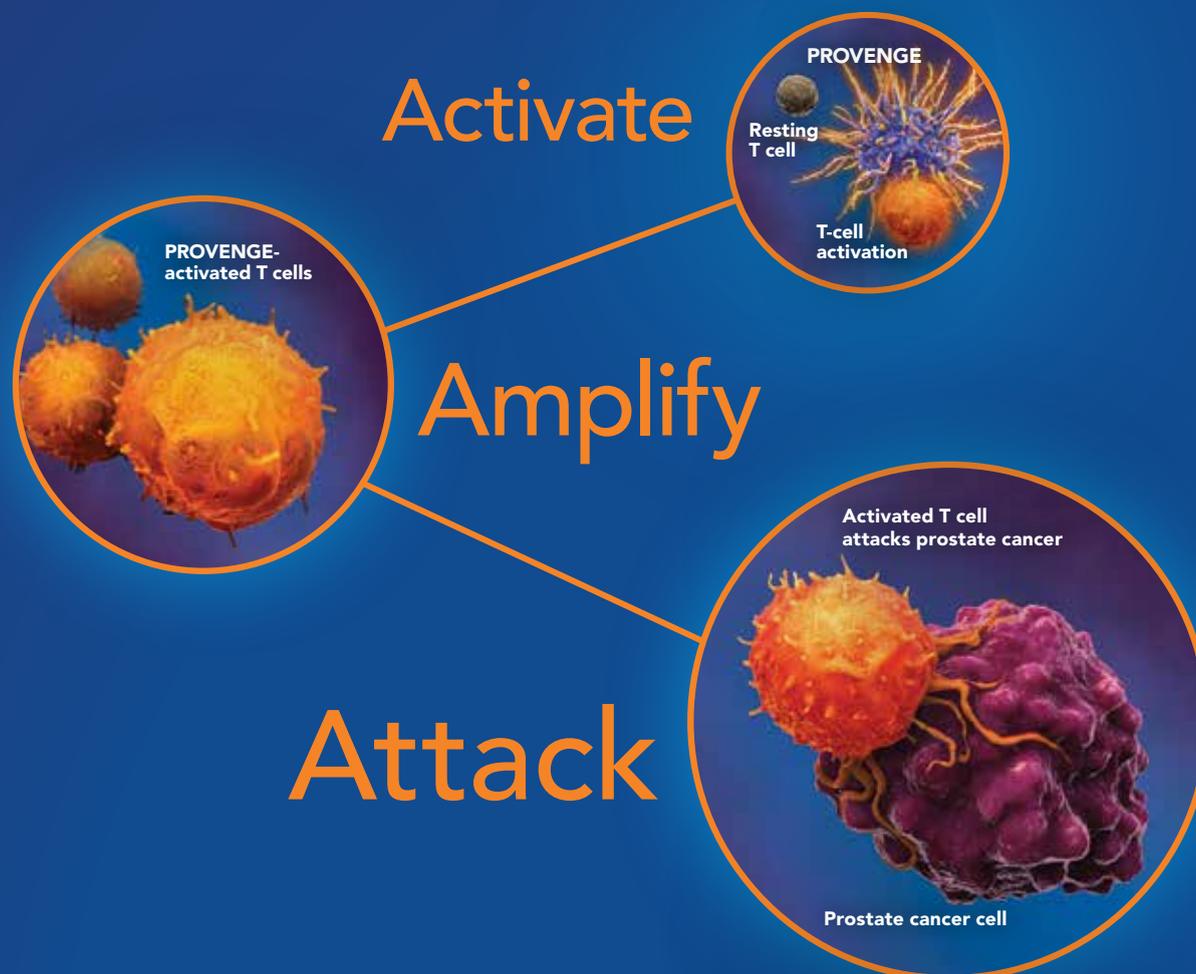
—Crystal Denlinger, MD,
Chair, NCCN Survivorship Guidelines
Committee.

“As we move from the very individualistic model of health care to population health care, the people who pay for the service recognize continuity of care is important,” he continued. “Once cancer patients are in remission they need a navigator to help with self-management, help organizing records of their treatment, access to information on how to improve their health, how to manage long-term side effects. Maybe anxiety and depression will be issues; they may still be obese; they may not exercise and still smoke.”

(continued on page SP475)

In advanced prostate cancer

TREAT FIRST LINE WITH PROVENGE TO



EXTEND SURVIVAL

>2^{years}

Extends median survival beyond 2 years¹

1st
and only

First and only FDA-approved immunotherapy for advanced prostate cancer

1st
line

First-line treatment for men with asymptomatic or minimally symptomatic metastatic CRPC (NCCN Category 1 recommendation)²

INDICATION: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

IMPORTANT SAFETY INFORMATION: PROVENGE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases. In controlled clinical trials, serious adverse events reported in the PROVENGE group included acute infusion reactions (occurring within 1 day of infusion) and cerebrovascular events. Severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

The most common adverse events (incidence $\geq 15\%$) reported in the PROVENGE group were chills, fatigue, fever, back pain, nausea, joint ache, and headache.

For more information on PROVENGE, please see Brief Summary of Prescribing Information on adjacent page.

www.PROVENGE.com

PROVENGE®
(sipuleucel-T)

**PROVENGE® (sipuleucel-T)
Suspension for Intravenous Infusion**

Rx Only

BRIEF SUMMARY – See full Prescribing Information for complete product information

INDICATIONS AND USAGE: PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

DOSAGE AND ADMINISTRATION

- **For Autologous Use Only.**
- The recommended course of therapy for PROVENGE is 3 complete doses, given at approximately 2-week intervals.
- Premedicate patients with oral acetaminophen and an antihistamine such as diphenhydramine.
- Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag.
- **Do Not Initiate Infusion of Expired Product.**
- Infuse PROVENGE intravenously over a period of approximately 60 minutes.
- **Do Not Use a Cell Filter.**
- Interrupt or slow infusion as necessary for acute infusion reactions, depending on the severity of the reaction.

(See Dosage and Administration [2] of full Prescribing Information.)

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

- **PROVENGE is intended solely for autologous use.**
- **Acute infusion reactions** (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the PROVENGE group developed an acute infusion reaction.

In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the PROVENGE group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

Closely monitor patients with cardiac or pulmonary conditions. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.

- **Handling Precautions for Control of Infectious Disease.** PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Universal precautions should be followed.
- **Concomitant Chemotherapy or Immunosuppressive Therapy.** Use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given concurrently with the leukapheresis procedure or PROVENGE has not been studied. PROVENGE is designed to stimulate the immune system, and concurrent use of immunosuppressive agents may alter the efficacy and/or safety of PROVENGE. Therefore, patients should be carefully evaluated to determine whether it is medically appropriate to reduce or discontinue immunosuppressive agents prior to treatment with PROVENGE.
- **Product Safety Testing.** PROVENGE is released for infusion based on the microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion. If the sterility results become positive for microbial contamination after PROVENGE has been approved for infusion, Dendreon will notify the treating physician. Dendreon will attempt to identify the microorganism, perform antibiotic sensitivity testing on recovered microorganisms, and communicate the results to the treating physician. Dendreon may request additional information from the physician in order to determine the source of contamination.

(See Warnings and Precautions [5] of full Prescribing Information.)

ADVERSE REACTIONS

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 evaluation of PROVENGE is based on 601 prostate cancer patients in the PROVENGE group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologous peripheral blood mononuclear cells.

The most common adverse events, reported in patients in the PROVENGE group at a rate $\geq 15\%$, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the PROVENGE group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the PROVENGE group compared with 3.6% of patients in the control group.

Serious adverse events were reported in 24.0% of patients in the PROVENGE group and 25.1% of patients in the control group. Serious adverse events in the PROVENGE group included acute infusion reactions (see Warnings and Precautions), cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE was discontinued in 1.5% of patients in Study 1 (PROVENGE group n=341; Control group n=171) due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤ 1 day following a leukapheresis procedure in $\geq 5\%$ of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in $\geq 5\%$ of patients in the PROVENGE group of randomized, controlled trials of men with prostate cancer. The population included 485 patients with metastatic castrate resistant prostate cancer and 116 patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and 90.6% of patients were Caucasian.

Table 1 Incidence of Adverse Events Occurring in $\geq 5\%$ of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	591 (98.3)	186 (30.9)	291 (96.0)	97 (32.0)
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)

(Table 1 continued on next page.)

Table 1 Incidence of Adverse Events Occurring in ≥5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

*Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events. In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were reported in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

(See Adverse Reactions [6] of full Prescribing Information.)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**Dendreon Corporation
Seattle, Washington 98101**

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Dendreon
Targeting Cancer, Transforming Lives®

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P-A-05.12-145.01

PROVENGE
(sipuleucel-T)

(continued from SP471)

Dexter Shurney, MD, is chief medical director for Cummins, Inc, a leading global corporation headquartered in Columbus, Indiana, designing, manufacturing, selling, and servicing diesel engines and related technology. The company's healthcare system covers 110,000 people and is about equally divided between employees and their families, Shurney said. The company is lending its perspective to the Oncology Medical Home Initiative because it already follows that mode for coordinated primary and cardiac care.

"We have a lifestyle approach to primary and cardiac care that encourages wellness. We know foods that contribute to heart disease contribute to obesity and diabetes," Shurney said. "We would expect the oncologists to have a lifestyle approach to survivorship, particularly making sure patients don't get a second cancer or it is caught early if they do. Our population will include children, some very young who require long-term follow up, and employees who want to get back to work as much as we want them back.

"Once people are in remission, what are the lifestyle adoptions they need to make? That is the conversation we are looking to measure, to see if that hap-

it, so it just doesn't happen," said Shelley Fuld Nasso, chief executive officer of the National Coalition for Cancer Survivorship. "For this to be common practice, we have to compensate physicians for their time."

Avery, of LIVE-STRONG, said it takes about 3 hours per patient to assemble their survivorship care plan.

"How can you get this done and get reimbursed for it?" she asked. "We have tools, the jewel being our free patient navigation services. We can help cancer clinics meet the needs of survivors."

Nasso pointed to Journey Forward, a project to integrate data from cancer registries to speed plan preparation for 2 audiences, the patient and the primary care physician (PCP) who will care for the survivor once the cancer is in remission.

"We need the NCCN guidelines to reach primary care physicians who are treating cancer survivors, and we need



Amy Berman

A new IOM report issued this year, *Delivering High Quality Cancer Care: Charting a New Course for a System in Crisis*,⁸ tempers optimism nurtured by increasingly effective treatments. The nation can anticipate 1.6 million new cancer cases annually with more than half striking people older than 65 years, with comorbidities common in this population. Treatment, already costly, is skyrocketing with each new therapy. The 2013 IOM report found that living with cancer is frequently grueling mentally, emotionally, and financially for patients and their

families.⁸ Screening programs have led to more overdiagnosis than cures while encouraging overtreatment of patients faced with bewildering and scary choices.⁹ For all the progress, cancer will likely surpass heart disease as the nation's leading cause of death this decade.¹⁰

"We are in a new payment environment that presents a great opportunity to raise the quality floor," said Amy Berman, a senior program officer at the John A. Hartford Foundation. Her focus is on the health and healthcare of older adults, evaluating both the cost and effectiveness of care.

Berman has become her own best case study. Three years ago she was diagnosed with stage IV inflammatory breast cancer. The first oncologist she consulted recommended aggressive treatment including surgery, chemotherapy, and radiation that he conceded would not cure her. She declined, pursued palliative care, and remains at her job. During her keynote address in Baltimore, Maryland, at Patient-Centered Oncology Care 2013, sponsored by *The American Journal of Managed Care*, Berman told a rapt audience about visiting the Great Wall of China and staying active as an advocate for palliative care.

The NCCN survivorship guidelines are a good start, she said, toward a frank discussion about what outcomes survivors can expect in exchange for the misery and cost of cancer treatment. She cites research that found patients who received palliative care frequently had better outcomes with standard treatment than patients who did not.¹¹

"People need an open conversation about the likely course of the disease,

not just their diagnosis," she said. "My prognosis, the likely course of my disease, is that about 11% of people live 5 years. What do I want my next couple of years to look like and feel like? A curative approach that doesn't cure will take away time from my family, cause me pain, and put me in the hospital where I am exposed to other infection.

"I take medications with the least side effects to hold the cancer at bay and, 3 years out, I feel great, I've saved about \$500,000 and I have a great life," Berman said. "But if I hadn't understood the likely course of this disease, I might have thrown everything at it." **EBO**

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"We need the NCCN guidelines to reach primary care physicians who are treating cancer survivors, and we need patients to get something, understandable to them, that says, 'This is what you are facing; these are the side effects you should expect; this is when you need to call us.'"

—Shelley Fuld Nasso

pens," he said. "We don't want people discharged without looking at what they might be doing that contributed to their cancer."

Moving Mountains—of Data

Lack of information is not the obstacle to writing a survivorship care plan. The biggest barriers are logistical and institutional; they include the technical challenge of coordinating the specifics of patient treatment with established best practices and documented side effects of medicines and treatment, and then paying care providers for it.

"There is no reimbursement for putting together a plan the patient can take away. ... Physicians aren't paid for

patients to get something, understandable to them, that says, 'This is what you are facing; these are the side effects you should expect; this is when you need to call us,'" Nasso said. "I think it will get easier to create survivorship care plans as electronic record keeping improves."

Care Without Cure

In 1959 the *British Medical Journal* published a study that found cancer patients did better when doctors told them the truth about their diagnosis.⁷ Today, cancer is not always the disease doctors sometimes hide from doomed patients, but, even with better results from oncology, it remains perhaps the most dreaded diagnosis.

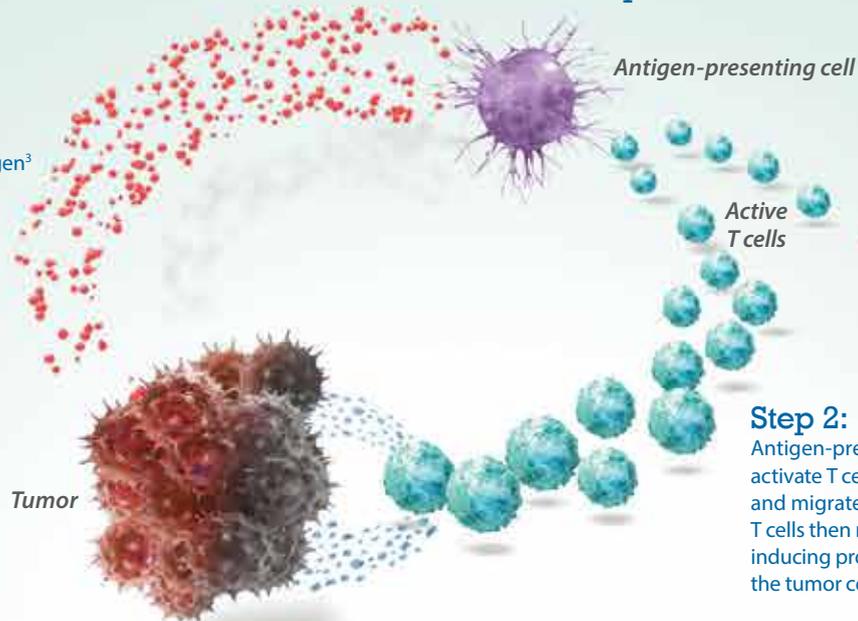
In the research of advanced cancers

What if inhibiting the PD-1 checkpoint pathway played an important role in restoring immune response to tumor cells?

In a normal state, the immune system recognizes tumors and can mount an active antitumor response^{1,2}

Step 1:

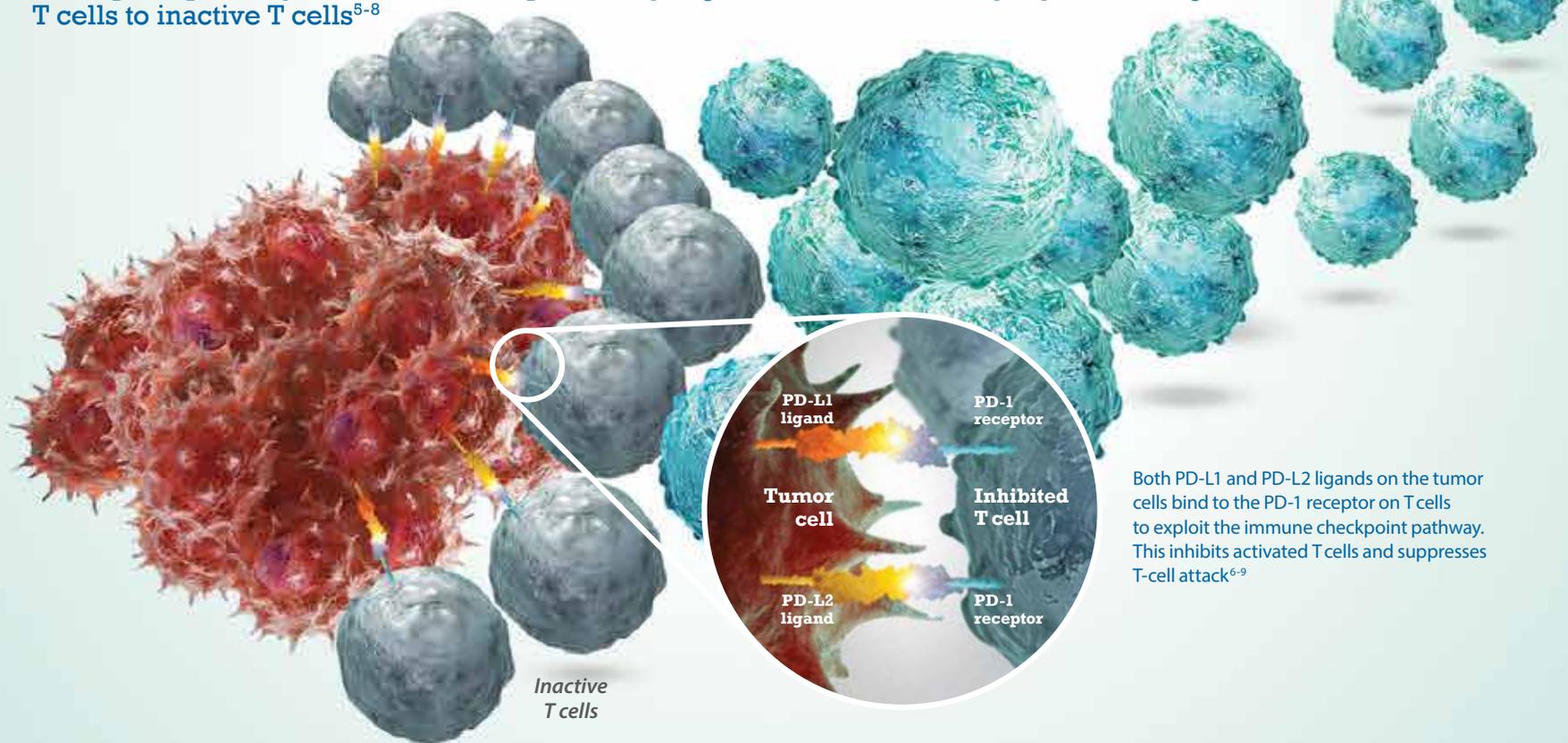
Tumor releases antigen³



Step 2:

Antigen-presenting cells activate T cells that proliferate and migrate to the tumor. T cells then release apoptosis-inducing proteins, which attack the tumor cells^{3,4}

One way that tumors can evade normal immune attack is through exploitation of the PD-1 checkpoint pathway via the PD-1 receptor, a key regulator of T-cell activity, by converting active T cells to inactive T cells⁵⁻⁸



Both PD-L1 and PD-L2 ligands on the tumor cells bind to the PD-1 receptor on T cells to exploit the immune checkpoint pathway. This inhibits activated T cells and suppresses T-cell attack⁶⁻⁹

Bristol-Myers Squibb is researching ways to block the interaction between the PD-1 receptor and PD-L1 and PD-L2 ligands to restore T-cell activation, which may play a role in helping the body fight cancer.^{8,10}

PD-1=programmed death 1; PD-L1=programmed death 1 ligand 1; PD-L2=programmed death 1 ligand 2.

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Immuno-Oncology