Bridging the gap between payer and provider perspectives

THE AMERICAN JOURNAL OF MANAGED CARE®

#1 IN CITATIONS & IMPACT FACTOR

Volume 18
Special Issue 4

Evidence-Based Oncology

AMCP Conference Coverage

Achieving Quality and Containing Cost Through Oncology Pharmacy Management

Kim Farina, PhD

In 2011, one large pharmacy benefit manager spent more than $25 per member per year (PMPY) on oncology specialty pharmacy, an increase of $4 PMPY from 2010 (**Table**). Spending is forecasted to exceed $40 PMPY by 2014 (**Figure 1**). Emerging oral cancer drugs are shifting costs from medical benefits to pharmacy benefits. With increasing numbers of expensive specialty pharmacy oncology drugs on the market—and hundreds more in the pipeline—it is clear that improvements in oncology pharmacy management are needed.

At the 2012 Academy of Managed Care Pharmacy Annual Meeting, a panel made up of a patient advocate, a cancer survivorship specialist, health plan representatives, an oncologist, and a health services researcher discussed the desired outcomes of oral oncology drug management, practical next steps, and gaps in and barriers to implementation.

Over the last 10 to 20 years, the introduction of new therapeutic agents has markedly improved overall survival for many types of cancer. In most cases, however, supporting data have not kept up with these advances, leaving knowledge gaps that make coverage and treatment decisions difficult. For many patients,

(continued on page SP150)

Pertuzumab Panel Discussion

Treatment and Cost Implications of Pertuzumab

Providing Access and Controlling Costs in the Era of Targeted Therapies

Pertuzumab, a new HER2-positive breast cancer drug, is being launched at a 31% premium to the price of trastuzumab. This is an aggressive strategy that will substantially increase the cost of treating patients with metastatic HER2-positive breast cancer, while also aiming to deliver the best outcomes for patients.

Pertuzumab will be used as an add-on to trastuzumab to treat patients. Progression-free survival was boosted by 6.1 months when the drugs were used in combination in the CLEOPATRA study.

With payers already anxious about the rising costs in oncology, an 18-month course of the combination treatment is estimated to reach more than $180,000. This cost sets the bar high for the future, as expensive targeted drugs are expected to be used increasingly in combination to deliver the best outcomes.

Michael E. Chernew, PhD

To examine these treatment benefits, cost concerns, and potential insurance coverage strategies, *AJMC*'s co-editor-in-chief, Michael E. Chernew, PhD, professor, department of healthcare policy, Harvard Medical School, moderated a panel discussion with Lee Newcomer, MD, MHA, senior vice president, oncology, UnitedHealthcare, and Sandra M. Swain, MD, medical director, Washington Cancer Institute, Medstar Washington Hospital Center.

(continued on page SP151)

OncPathways®

Implementation of Cancer Clinical Care Pathways

A Successful Model of Collaboration Between Payers and Providers

Bruce A. Feinberg, DO; et al

Despite rising medical costs within the US healthcare system, quality and outcomes are not improving. Without significant policy reform, the cost-quality imbalance will reach unsustainable proportions in the foreseeable future. The rising cost of healthcare in part results from an expanding aging population with an increasing number of life-threatening

Bruce A. Feinberg, DO

diseases. This is further compounded by a growing arsenal of high-cost therapies. In no medical specialty is this more apparent than in the area of oncology. Numerous attempts to reduce costs have been attempted, often with limited benefit and brief duration. Because physicians directly or indirectly control or influence the majority of medical care costs, physician behavioral changes must occur to bend the healthcare cost curve in a sustainable fashion. Experts within academia, health policy, and business agree that a significant paradigm change in stakeholder collaboration will be necessary

(continued on page SP159)

Also in this issue...

AJMC TV

What's this? See page SP148 for information.

Beckie Fenrick, PharmD, MBA, Senior Director, Medical Operations, Care Models and Affordability Solutions, Florida Blue, Discusses Companion Diagnostics for Personalized Medicine in Specialty Pharmacy

Surya Singh, MD, Vice President, Medical Benefit Management, CVS Caremark, Addresses Methods for Managing Oncology Spending in Specialty Pharmacy

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A supplement to
The American Journal of Managed Care

Making PROgress with patient-reported outcomes

How PROs were successfully integrated into the Jakafi® (ruxolitinib) drug development program[1]

A novel approach to engage clinicians and FDA

PROs are an important means to demonstrate treatment benefits in clinical trials.[2,3] Use of a PRO instrument can evaluate symptoms best judged by the patient, whether caused by the disease or treatment toxicity. Assessment of symptom burden is important because it can be a major indicator of disease severity, progression or improvement. Incorporating PROs into a clinical trial program provides a means for evaluating the impact of therapy from the patient's perspective and helps patients and clinicians make better-informed decisions.[4]

TAILORING a PRO tool for myelofibrosis

Myelofibrosis (MF) is a life-threatening, progressive disease characterized by splenomegaly, debilitating symptoms and cytopenias.[5-7] Measures to assess both the splenomegaly and core symptoms of MF were incorporated into the phase III, double-blind placebo-controlled study, COMFORT-I, for Jakafi. Spleen reduction, as measured by imaging (MRI or CT), was the primary and biologic endpoint, and a reduction in total symptom score (TSS), the PRO measure, was a key secondary endpoint.[8,9] The TSS encompassed the following symptoms: abdominal discomfort, pain under left ribs, early satiety, pruritus, night sweats and bone/muscle pain.[9]

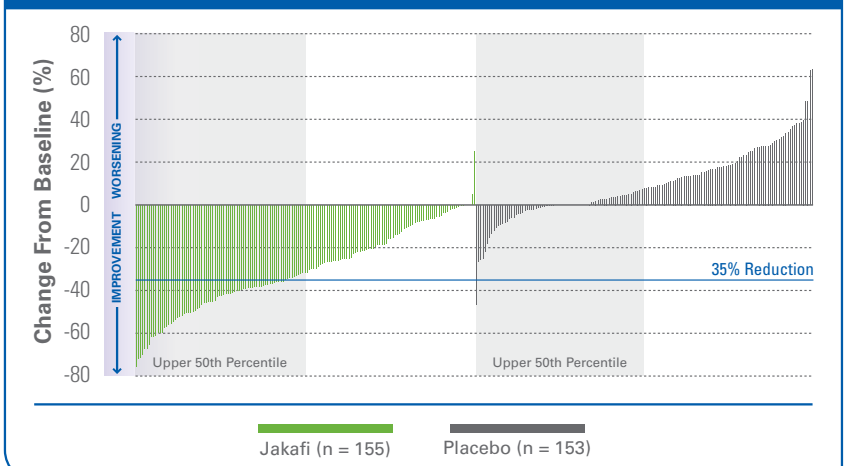
To include PROs in the trial, a novel instrument had to be specifically developed. After patient interviews, advice from clinical experts and extensive input from the FDA, the modified Myelofibrosis Symptom Assessment Form, version 2.0 (modified MFSAF v2.0) was finalized as part of the Special Protocol Assessment prior to the initiation of COMFORT-I. Ultimately, Jakafi was approved by the FDA for the treatment of intermediate or high-risk MF.[1,8] This became Incyte's first approved drug and also the first oncology medicine approved with symptom data in its label since the FDA's draft guidance on PROs was finalized in 2009.[2,4]

Indications and Usage
Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Important Safety Information
- Treatment with Jakafi can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia, which are each dose-related effects, with the most frequent being thrombocytopenia and anemia. A complete blood count must be performed before initiating therapy with Jakafi. Complete blood counts should be monitored as clinically indicated and dosing adjusted as required
- The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache
- Patients with platelet counts <200 × 10^9/L at the start of therapy are more likely to develop thrombocytopenia during treatment. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakafi. If clinically indicated, platelet transfusions may be administered
- Patients developing anemia may require blood transfusions. Dose modifications of Jakafi for patients developing anemia may also be considered
- Neutropenia (ANC <0.5 × 10^9/L) was generally reversible and was managed by temporarily withholding Jakafi
- Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Active serious infections should have resolved before starting Jakafi. Physicians should carefully observe patients receiving Jakafi for signs and symptoms of infection (including herpes zoster) and initiate appropriate treatment promptly
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or in patients with

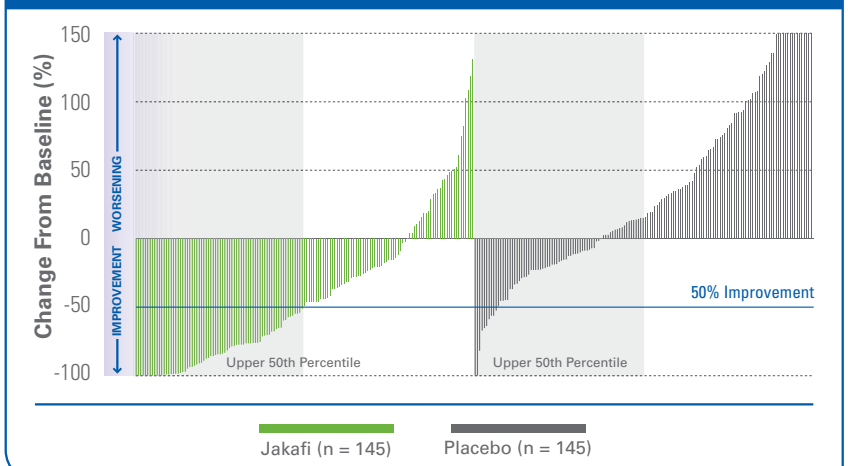
JAKAFI endpoints included both biologic and patient-reported outcomes[8,9]

COMFORT-I: Percent Change in Spleen Volume in Individual Patients From Baseline to Week 24 or Last Observation[9,a]



Each bar represents an individual patient's response.

COMFORT-I: Percent Change in TSS in Individual Patients From Baseline to Week 24 or Last Observation[9,a,b]



Each bar represents an individual patient's response. Worsening of TSS is truncated at 150%.

PROVIDING proof of patient benefit

MF is progressive, and spleen size and symptoms can become increasingly burdensome to patients over time.[5-7] Jakafi is proven to decrease total symptom score in patients with intermediate or high-risk MF—this is an important consideration when evaluating and treating patients.[9] The FDA approval included patients with intermediate-2 risk and high risk, as well as patients with intermediate-1 risk, since intermediate-1 patients may also have symptoms that require treatment. Clinical experience with Jakafi has shown that with the right process, manufacturers can successfully collaborate with regulatory agencies and academic experts to develop relevant and validated PRO instruments that can be incorporated into clinical trials.[1,8] The approval of Jakafi marks a significant milestone in which validated PRO instruments can provide symptom data and demonstrate clinical benefit. The experience with Jakafi may provide a model for the future use of PROs in marketing applications.[8]

renal or hepatic impairment *[see Dosage and Administration]*. Patients should be closely monitored and the dose titrated based on safety and efficacy

- There are no adequate and well-controlled studies of Jakafi in pregnant women. Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus
- Women taking Jakafi should not breast-feed. Discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother

References: 1. McCallister E, et al. *BioCentury*. Reprint from December 5, 2011. **2.** Haley S. *The Pink Sheet*. November 21, 2011;73:47. Symptom Measurement in Clinical Trials. **3.** US Department of Health and Human Services Guidance for Industry: Patient-reported outcome measures: Use in medical product development to support labeling claims. December 2009. **4.** Basch E, et al. Issue brief from Conference on Clinical Cancer Research, November 2011. **5.** Cervantes F, et al. *Blood*. 2009;113:2895-2901. **6.** Mesa RA, et al. *Leuk Res*. 2009;33:1199-1203. **7.** Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. **8.** Deisseroth AB, et al. *Clin Cancer Res*. 2012 Apr 27. (Epub ahead of print). **9.** Jakafi Prescribing Information. Incyte Corporation. November 2011. **10.** Data on File, Incyte Corporation.

[a] As studied in COMFORT-I, a randomized, double-blind, placebo-controlled phase III study with 309 total patients (United States, Canada, Australia). The primary endpoint was the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI or computed tomography (CT). A secondary endpoint was the proportion of subjects with a ≥50% reduction in TSS from baseline to Week 24 as measured by the daily patient diary, the modified MFSAF v2.0.[9,10]

[b] Symptom scores were captured by a daily patient diary recorded for 25 weeks. TSS encompasses debilitating symptoms of MF: abdominal discomfort, pain under left ribs, early satiety, pruritus, night sweats and bone/muscle pain. Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60. At baseline, mean TSS was 18.0 in the Jakafi group and 16.5 in the placebo group.[9,10]

Please see Brief Summary of Full Prescribing Information on the following page.

Incyte

Jakafi™
ruxolitinib (tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

INDICATIONS AND USAGE Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with Jakafi [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Patients with platelet counts of less than 200 X 10^9/L at the start of therapy are more likely to develop thrombocytopenia during treatment. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakafi. If clinically indicated, platelet transfusions may be administered [*see Dosage and Administration (2.2) in Full Prescribing Information*, *and Adverse Reactions*]. Patients developing anemia may require blood transfusions. Dose modifications of Jakafi for patients developing anemia may also be considered. Neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible and was managed by temporarily withholding Jakafi [*see Adverse Reactions*]. Complete blood counts should be monitored as clinically indicated and dosing adjusted as required [*see Dosage and Administration (2.2) in Full Prescribing Information*, *and Adverse Reactions*]. **Infections** Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Active serious infections should have resolved before starting therapy with Jakafi. Physicians should carefully observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly. *Herpes Zoster* Physicians should inform patients about early signs and symptoms of herpes zoster and advise patients to seek treatment as early as possible [*see Adverse Reactions*].

ADVERSE REACTIONS 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 Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 88.7% of patients treated for more than 6 months and 24.6% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In a double-blind, randomized, placebo-controlled study of Jakafi, 155 patients were treated with Jakafi. The most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11.0% of patients treated with Jakafi and 10.6% of patients treated with placebo. Following interruption or discontinuation of Jakafi, symptoms of myelofibrosis generally return to pretreatment levels over a period of approximately 1 week. There have been isolated cases of patients discontinuing Jakafi during acute intercurrent illnesses after which the patient's clinical course continued to worsen; however, it has not been established whether discontinuation of therapy contributed to the clinical course in these patients. When discontinuing therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered [*see Dosage and Administration (2.6) in Full Prescribing Information*]. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23.2	0.6	0	14.6	0	0
Dizziness[c]	18.1	0.6	0	7.3	0	0
Headache	14.8	0	0	5.3	0	0
Urinary Tract Infections[d]	9.0	0	0	5.3	0.7	0.7
Weight Gain[e]	7.1	0.6	0	1.3	0.7	0
Flatulence	5.2	0	0	0.7	0	0
Herpes Zoster[f]	1.9	0	0	0.7	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (0.3%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 4.7% of patients receiving Jakafi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakafi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (16.5% versus 7.2%). **Neutropenia** In the two Phase 3 clinical studies, 1.0% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Worst Hematology Laboratory Abnormalities in the Placebo-controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	69.7	9.0	3.9	30.5	1.3	0
Anemia	96.1	34.2	11.0	86.8	15.9	3.3
Neutropenia	18.7	5.2	1.9	4.0	0.7	1.3

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25.2% of patients treated with Jakafi and 7.3% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 1.9% for Jakafi with 1.3% Grade 3 and no Grade 4 ALT elevations. 17.4% of patients treated with Jakafi and 6.0% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was 0.6% for Jakafi with no Grade 3 or 4 AST elevations. 16.8% of patients treated with Jakafi and 0.7% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was 0.6% for Jakafi with no Grade 3 or 4 cholesterol elevations.

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is predominantly metabolized by CYP3A4. **Strong CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, with Jakafi administration (10 mg single dose) following ketoconazole 200 mg twice daily for four days, compared to receiving Jakafi alone in healthy subjects. The half-life was also prolonged from 3.7 to 6.0 hours with concurrent use of ketoconazole. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding ruxolitinib AUC following concurrent administration with ketoconazole. When administering Jakafi with strong CYP3A4 inhibitors a dose reduction is recommended [*see Dosage and Administration (2.4) in Full Prescribing Information*]. Patients should be closely monitored and the dose titrated based on safety and efficacy. **Mild or moderate CYP3A4 inhibitors:** There was an 8% and 27% increase in the C_{max} and AUC of ruxolitinib, respectively, with Jakafi administration (10 mg single dose) following erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to receiving Jakafi alone in healthy subjects. The change in the pharmacodynamic marker, pSTAT3 inhibition was consistent with the corresponding exposure information. No dose adjustment is recommended when Jakafi is coadministered with mild or moderate CYP3A4 inhibitors (eg, erythromycin). **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, with Jakafi administration (50 mg single dose) following rifampin 600 mg once daily for 10 days, compared to receiving Jakafi alone in healthy subjects. In addition, the relative exposure to ruxolitinib's active metabolites increased approximately 100%. This increase may partially explain the reported disproportionate 10% reduction in the pharmacodynamic marker pSTAT3 inhibition. No dose adjustment is recommended when Jakafi is coadministered with a CYP3A4 inducer. Patients should be closely monitored and the dose titrated based on safety and efficacy.

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made 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 Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of myelofibrosis patients in clinical studies with Jakafi, 51.9% were 65 years of age and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 100 X 10^9/L and 150 X 10^9/L and patients with end stage renal disease on dialysis a dose reduction is recommended [*see Dosage and Administration (2.5) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with any degree of hepatic impairment and with a platelet count between 100 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended [*see Dosage and Administration (2.5) in Full Prescribing Information*].

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THE AMERICAN JOURNAL OF MANAGED CARE

From the Publisher

In this issue of *Evidence-Based Oncology*, readers will have the opportunity to review transcripts from a panel discussion that highlights a growing problem in oncology—controlling costs for expensive targeted drugs while continuing to deliver the best outcomes. To specifically examine the treatment benefits, cost concerns, and potential insurance coverage strategies for pertuzumab, *AJMC*'s Co-Editor-in-Chief, Dr Michael Chernew, moderated this panel discussion with Dr Lee Newcomer, Senior Vice President of Oncology at UnitedHealthcare, and Dr Sandra Swain, Medical Director at Washington Cancer Institute, Medstar Washington Hospital Center.

Successive years of double-digit health insurance premium increases have caused many employers to restructure the health benefit plans that they offer, meaning that employees now have more of a financial stake in their own care. These changes have hit some subsets of patients harder than others. For instance, patients with cancer often rely on specialty pharmacy drugs that offer hope for managing or curing their condition. The problem is that many of these treatments come with a hefty price tag, leaving those patients to make some very difficult decisions.

Pertuzumab, a new HER2-positive breast cancer drug, when combined with trastuzumab plus docetaxel (as compared with placebo plus trastuzumab plus docetaxel) has been shown to significantly prolong progression-free survival when used as a first-line treatment. However, the cost of this combination treatment has been estimated at $180,000.

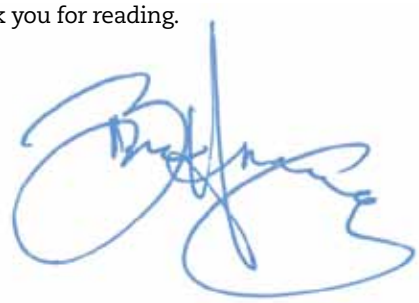
"Sometimes the number you see is a billion dollars to develop a drug," says Dr Swain. "And, many of the drugs that they start developing don't go to market, so then they don't recoup any of those costs for developing those drugs. However, I think that the pricing is as high as the market can bear. And, so there's really no link right now between the pricing and effectiveness of drugs."

So, what is being done to make lifesaving treatments more affordable? There's no shortage of ideas. Drs Chernew, Newcomer, and Swain talk about the emergence of Accountable Care Organizations, bundled payments, and value-based healthcare delivery. However, although these ideas are impactful in theory, there are still difficulties in implementing such strategies, as the panel points out.

Progress is being made in the area of companion diagnostics, which should decrease the population of patients in which particular drugs are tested. This, in turn, will help to control and lower the cost of development. However, one thing is certain, there needs to be a better system in place so that therapeutic breakthroughs are more affordable. After all, there isn't much value in lifesaving treatments if the cost makes it impossible for patients to receive access to them.

These are the type of topics that *Evidence-Based Oncology* and *The American Journal of Managed Care* are continually addressing in an effort to bridge the gap between payers and providers. In addition, *The American Journal of Managed Care* is coordinating its first annual meeting, titled "Translating Evidence-Based Research into Value-Based Decisions in Oncology" in Baltimore, MD, on November 15-16. For more information on this event please contact Christina Doong at cdoong@clinicalcomm.com.

Thank you for reading.



Brian Haug
Publisher

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.

In This Issue...

THE AMERICAN JOURNAL OF MANAGED CARE

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Office Center at Princeton Meadows, Bldg. 300
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Moderated by:

Michael E. Chernew, PhD
Professor of Health Care Policy
Harvard Medical School
Vice Chairman, MEDPAC
Co-Editor-in-Chief, *The American Journal of Managed Care*

A. Mark Fendrick, MD
Professor of Medicine and Health Management and Policy
Schools of Medicine and Public Health
University of Michigan
Co-Editor-in-Chief, *The American Journal of Managed Care*

Speakers:

Peter B. Bach, MD, MAPP
Director, Center for Health Policy and Outcomes
Attending Physician
Memorial Sloan-Kettering Cancer Center
New York, NY

Bruce A. Feinberg, DO
Vice President and Chief Medical Officer
Cardinal Health Specialty Solutions
Dublin, OH

Cliff Goodman, PhD
Senior Vice President & Principal
The Lewin Group
President, Health Technology Assessment International
Falls Church, VA

Ira M. Klein, MD, MBA, FACP
Chief of Staff
Office of the Chief Medical Officer
National Accounts Clinical Sales & Strategy
Aetna, Inc

Andrew L. Pecora, MD
Chief Innovations Officer and Vice President of Cancer Services
John Theurer Cancer Center at Hackensack University Medical Center
Hackensack, NJ

Sean R. Tunis, MD, MSc
President and Chief Executive Officer
Center for Medical Technology Policy
Baltimore, MD

THE AMERICAN JOURNAL OF MANAGED CARE

Achieving Quality
(continued from Cover)

cancer has become a chronic condition requiring long-term therapy. These evolving trends are bringing long-term cost implications. Payers and health plans find themselves attempting to manage practice patterns, provider and patient behavior, treatment options, and quality—a huge administrative cost burden.

Identifying Indicators of Outcomes

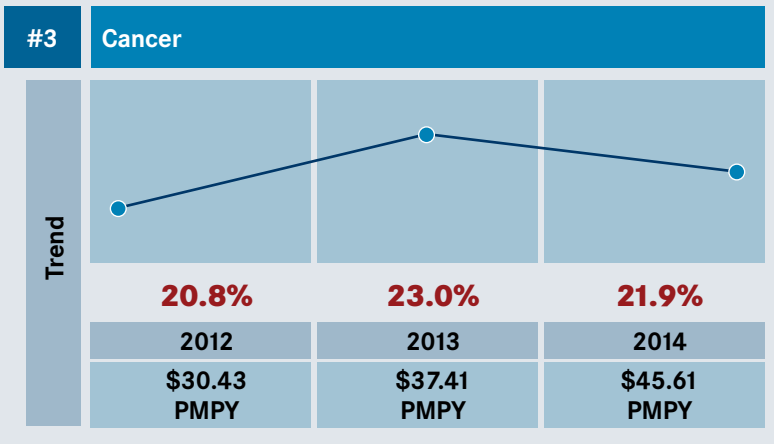
John Cruickshank, DO, MBA, chief medical officer, Lovelace Health Plan, provided an overview of outcome indicators and treatment pathways during the program. "Payers are beginning to expect that improved outcomes by an agent or regimen be demonstrated prior to full reimbursement," he explained. "Historically, the overall survival end point has been the gold standard for oncology drug approval by the FDA, but that is changing rapidly." Recently, approvals have been granted based on surrogate end points, such as objective response rate, progression-free survival, disease-free survival, and time to progression. A major problem with surrogate end points is that they often do not translate into long-term survival benefit. The use of different end points across trials makes comparative analyses difficult.

Table. Components and Drivers of Trend for the Top 10 Specialty Therapy Classes, PBM-Adjusted Claims Only, Ranked by 2011 PMPY Spend

Rank	Therapy Class	PMPY Spend, $	% of Total Specialty Spend	PMPY Change From 2010, $
1	Inflammatory conditions	40.70	23.7	6.13
2	Multiple sclerosis	32.89	19.2	5.56
3	Cancer	25.20	14.7	3.42
4	HIV	18.08	10.5	0.84
5	Growth deficiency	6.72	3.9	0.42
6	Anticoagulants	6.42	3.7	0.31
7	Hepatitis C	6.34	3.7	4.19
8	Transplant	5.63	3.3	–0.10
9	Respiratory conditions	4.65	2.7	0.69
10	Pulmonary hypertension	4.23	2.5	0.11
	Top 10	**150.86**	**88.0**	**21.57**
	Others	**20.65**	**12.0**	**3.45**
	Total	**171.51**	**100.0**	**25.01**

HIV indicates human immunodeficiency virus; PBM, pharmacy benefit manager; PMPY, per member per year.
Source: Reprinted with permission from The Express Scripts Research & New Solutions Lab. 2011 Drug Trend Report. http://www.express-scripts.com/research/research/dtr/archive/2012/dtrFinal.pdf. Published April 2012. Accessed May 21, 2012.

Figure 1. Forecast for the Top Specialty Therapy Classes, 2012-2014



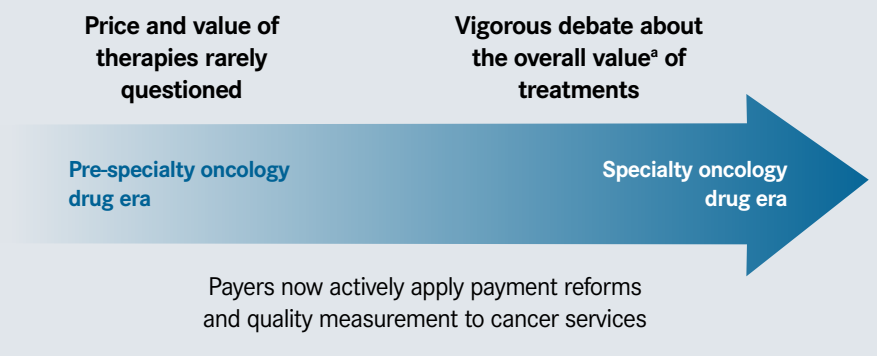
PMPY indicates per member per year.
Source: Reprinted with permission from The Express Scripts Research & New Solutions Lab. 2011 Drug Trend Report. http://www.express-scripts.com/research/research/dtr/archive/2012/dtrFinal.pdf. Published April 2012. Accessed May 21, 2012.

Sidebar: Action Items for Improved Oral Oncology Management Through Treatment Pathways

- Define preferred protocol, based on efficacy, safety, or, as a third-line basis for decision, cost
- Stratify guidelines (eg, NCCN) by costs and survivability rates
- Utilize peer-reviewed data to close gaps between guideline updates
- Develop a standardized care plan that aligns reimbursement with each preferred protocol
- Utilize patient-centered outcomes research as decision support tool to reduce treatment variability
- Reduce large variations in the late stages of care
- Incorporate monitoring and safety checkpoints along the full continuum of care to control cost and enhance quality

NCCN indicates National Comprehensive Cancer Network.

Figure 2. Status of Oncology Treatment Has Changed: Cancer Is Now on the Table



With the introduction of more oncology specialty pharmacy drugs, the mind-set of benefit managers has shifted from one that rarely questioned price and value of therapies to one that engages in vigorous debates about the overall value of cancer treatments. Payers have integrated payment reforms and quality monitoring into their cancer benefit models.
[a]Clinical, pharmacoeconomic, humanistic, societal, etc.
Source: Reprinted with permission from Dunn JD. Applying formulary and benefit design innovations. Presented at: The Academy of Managed Care Pharmacy 24th Annual Meeting and Expo; April 18, 2012; San Francisco, CA.

Implementing Treatment Pathways

The panelists and attendees agreed that standardized treatment pathways that take into account comparative effectiveness and cost data are the ideal foundation for coverage decisions. The consensus among the panel was that preferred pathways will help relax prior authorization requirements and other barriers to approval, thereby lowering cost for managed care organizations while easing access for both patients and providers. Health plans would like to be able to use treatment guidelines or pathway programs for a balance of clinical, qualitative, and economic features to yield the most cost-effective treatment results. Numerous treatment options, a poor evidence base upon which to make decisions, and wide variability in treatment plans present barriers to making this a reality, however.

Existing guidelines do not offer a single drug recommendation in most cases, do not include cost information, and are not always in agreement with one another or with compendia. To achieve desired outcomes, the number of pathways in use must be reduced to a manageable number. Until these challenges are overcome, panelists and attendees both agreed that National Comprehensive Cancer Network (NCCN) guidelines are an excellent resource and that their consistent use as a basis for decision making will reduce barriers to access for appropriate therapies. The panelists summarized other specific suggestions that came out of session workshops (**Sidebar**).

Applying Oncology Formulary and Benefit Design Innovations

The panel discussed innovations in formulary and benefit design models through which to better manage oral oncology drugs. With the introduction of more effective and expensive oncology drugs, vigorous debates have ensued about the overall value of treatments, said Jeffrey Dunn, PharmD, MBA, formulary and contract manger, Select Health Inc (**Figure 2**). Payers are actively applying payment reforms and quality measurement to cancer services.

Health information technology (HIT) is a powerful tool that should be better exploited by pharmacy management. Effective application of HIT can enable rapid identification and incorporation of emerging data and provide a common data platform that supports decision making and patient monitoring.

HIT might also be used to address fragmentation of care between specialty pharmacy and the oncology care team. Fragmentation poses a significant management barrier. For example, logistic procedures may differ from drug to drug or between classes of drugs on both the payer and provider sides of healthcare. This issue is particularly relevant to oncology because the medication regimens of cancer patients frequently evolve.

Dunn emphasized that improved communication and collaboration between plans and oncologists will be vital to success and that achieving desired outcomes will be impossible without them. Successful management of cancer care requires a strategy that supports rather than hinders successful payer/physician collaboration.

The panel supported patients and patient support groups as important stakeholders whose perspectives should be considered during overall benefit design—especially with respect to issues such as copay versus coinsurance, emotional distress, supportive care, advance planning, and the impacts on decision making of dynamics between plans, employer, oncologist, and family/caregivers.

In summary, the panel agreed that a tiered oncology benefit model will undoubtedly be a part of designs going forward. Overcoming barriers will be helped by integration of specialty pharmacy and investing in technology that improves access to data and collaboration. Other valuable approaches discussed included utilization of case management programs and certain aspects of patient-centered medical homes, value-based models, and adaptation of education and disease-management strategies that have been proved effective in other disease states. Furthermore, ownership of outcomes should be shared among key stakeholders, including patients, payers, and healthcare providers. **EBO**

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Treatment and Cost Implications

(continued from Cover)

Dr Chernew: Dr Swain, I am interested in the current treatment landscape for patients with breast cancer. If you have any thoughts on how physicians choose breast cancer treatments for their patients, it would be interesting to hear them.

Dr Swain: There are a lot of different treatment paradigms for breast cancer and it really depends on if you are talking about early stage disease or metastatic disease. Let's start with metastatic disease. Unfortunately, even with some of our very effective treatments, we really don't affect survival in a lot of cases of metastatic breast cancer. However, breast cancer has really been categorized now into different kinds of breast cancer—ER-positive breast cancer, triple negative breast cancer [meaning there is no estrogen receptor or HER2], and HER2-positive breast cancer [in which patients have the HER2 oncogene that is overexpressed]. So, it's very complex; you can't just answer that with 1 answer. The way an oncologist would choose is to look at the biology of the tumor [to see] if it has the receptors or not. For example, if the tumor had the HER receptor with metastatic disease and it was first line you would choose trastuzumab. And, with the recent data in the CLEOPATRA study showing that the addition of pertuzumab to trastuzumab plus docetaxel actually has a large benefit, oncologists would consider this also at this point.

Dr Chernew: So, can you provide a brief overview of the CLEOPATRA trial?

Dr Swain: The CLEOPATRA trial was a prospective, phase 3, randomized study in patients who had not received any chemotherapy for metastatic HER2-positive breast cancer. The study included 808 patients and they were randomized to either receive placebo plus trastuzumab plus docetaxel [control group] or pertuzumab plus trastuzumab plus docetaxel [pertuzumab group]. It was first-line treatment, and the end point of the study was to look at an independently assessed progression-free survival. It really had a spectacular result in my opinion. It was a progression-free survival advantage of 6 months. This was actually a placebo-controlled study, so even though progression-free survival can be a difficult end point, it was clear in this study that there really was a benefit to the addition of the drug pertuzumab. The interim analysis of survival showed a trend in favor of pertuzumab in the initial report that we released at the San Antonio Breast Cancer Symposium and published in the *New England Journal of Medicine* in December 2011, but most recently we've reanalyzed the survival and, actually, a press release came out this past June showing that there was a survival benefit also with the addition of pertuzumab. This top-line data was submitted to a major meeting, so hopefully it will be presented in the next few months.

Dr Chernew: As a first-line treatment, how many breast cancer patients would be eligible? Just the patients who would have the correct target—the HER2 target?

Dr Swain: The patients with HER2-positive overexpression are approximately 15% to 20% of breast cancer. And, the indication is only for patients who have not had previous chemotherapy. It wouldn't be for someone who's had trastuzumab or other drugs or second-, third-, or fourth-line treatments. It's only for first-line treatment.

Dr Chernew: OK, and that would be approximately 15% or less because of the exclusions?

Dr Swain: Maybe a little less than [the general population of patients with breast cancer]. Per year, it would be 15%, but of the patients now, it's certainly going to be less because a lot of patients now would have had other treatments.

Dr Newcomer: The manufacturers are estimating that there would be approximately 8000 women who would have HER2-positive metastatic breast cancer, per year, in the country. That's a fair estimate.

Dr Chernew: One of the biggest challenges—because it sounds, clinically, like there are a lot of optimistic results—is how we might finance access to this treatment. The cost of the pertuzumab and trastuzumab combination is approximately $187,000 for a course of treatment over the entire duration. So, Dr Newcomer, how do you think plans might respond, how do you think oncologists might respond, and what general strategies will be utilized to provide access to this drug?

Dr Newcomer: Well, I am in complete agreement with Dr Swain in that pertuzumab is a good drug. The trial showed a clear benefit and the benefit was probably one of the larger ones we've seen in a long time. Therefore, I would be quite surprised if there wasn't ready access to pertuzumab from any payer for the indication for which it's approved. So, as first-line therapy in combination with trastuzumab and docetaxel, I can't imagine that anyone wouldn't cover that. That said, it's expensive, there's no question. From a total expense though, it's a very small population compared with all of the women with breast cancer. And, the way that we deal with that, as does every payer in the country, is we simply build it into the premium, and the premium for the next quarter goes up. So, there isn't a way to pay for this other than simply passing the costs on in the premium, which means everyone who buys health insurance will see a slight increase.

"There isn't a way to pay for this other than simply passing the costs on in the premium, which means everyone who buys health insurance will see a slight increase."

—Lee Newcomer, MD, MHA
Senior Vice President, Oncology
UnitedHealthcare

Dr Chernew: Do you do modeling—because the population is so small—to show how big that increase might be? Is the premium increase small because of the small number of women, despite the per treatment sticker price?

Dr Newcomer: Yes, we actually do model all new technologies. We generally model them approximately 6 to 12 months prior to their emergence into the market and start building that into the premium in anticipation of the new technology coming on board. I don't know the exact amount for pertuzumab and wouldn't be able to release it anyway, but that is a process that we do routinely, looking for the new drugs coming out or other new technologies, estimating their costs and how many people would be using it, and building that into the premium.

Dr Chernew: In certain cases, and you were very clear in your earlier answer, there's utilization of drugs or, more broadly, new technologies beyond the populations that were originally studied or for whom it was originally approved. Do you think that's a big

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issue in this particular case and, if so, how do you think your plan and other plans might deal with that issue?

Dr Newcomer: I think it clearly is an issue to consider. Every drug that comes to the market eventually finds new uses as further clinical trials are undertaken and they may be reflected on the FDA label. What we've done at UnitedHealthcare is turned to the National Comprehensive Cancer Network (NCCN) recommendations to decide when there is enough evidence for coverage. If the NCCN recommends it in their guidelines, then we provide coverage. Other insurers are examining the evidence, whether using their own staff or other sources, but we are going to see people testing this drug in other indications. They may use it as an adjuvant with trastuzumab. They may try using it in second- and third-line treatments. If the evidence shows there is still a benefit, then I do think you will see a use expand.

Dr Chernew: **Do you think there will be that type of experimentation prior to rigorous studies in those other populations?**

Dr. Newcomer: There already are other people attempting to use it that way, and as I was discussing with Dr Swain prior to the call, almost 90% of our requests for this drug in the first week were for indications other than what the CLEOPATRA trial showed. And, we don't cover in that circumstance until there is proper evidence.

Dr Chernew: **When you say other indications than what the CLEOPATRA trial showed, do you mean indications that were studied and there wasn't an effect or do you mean indications that simply weren't studied in the CLEOPATRA trial?**

Dr Newcomer: In clinical situations that simply weren't examined in the CLEOPATRA trial; for example, patients on their fourth or fifth line of therapy.

Dr Chernew: **More broadly, what drives the cost of drugs in cancer care?**

Dr Swain: Well, I think what the companies say is that it's very expensive to develop these drugs, such as the clinical trials. The CLEOPATRA study was 808 patients—I don't know how many millions of dollars it cost, but it cost a huge amount of money. Sometimes the number you see is a billion dollars to develop a drug. And, many of the drugs that they start developing don't go to market, so then they don't recoup any of those costs for developing those drugs. However, I think that the pricing is as high as the market can bear. And, so there's really no link right now between the pricing and effectiveness of drugs. For example, many of these other drugs that are chemotherapy drugs used for second-, third-, fourth-line treatment in breast cancer don't have survival benefit and are expensive, and yet that really isn't taken into consideration. I think we need to do that, certainly in the future. One of the things that I am very interested in doing is not getting incremental benefits with our drugs. I think what's happened in the past is that a lot of drugs have been approved when it's later-line treatment because there's not a lot of treatment for the patient—the bar is lower. In other words, the benefit is not as great. In addition, the patient may have a lot of toxicity and may not have the benefit, so there's a high cost there, too.

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"We really need to have a high bar for what we consider effective treatment. I think that's where we've gone wrong in the past."

—Sandra M. Swain, MD
Medical Director
Washington Cancer Institute
MedStar Washington Hospital

Dr Chernew: **In this case, it seems pertuzumab provides a lot of value at a very high cost and, if I understand Dr Newcomer's earlier answer, the benefit seems great in this case and the overall population seems relatively small. So, the overall premium impact isn't enormous and he [Dr Newcomer] would expect that there would not be restrictions on access to pertuzumab. Is that generally your sense, Dr Newcomer?**

Dr Newcomer: The restrictions that will be placed will involve ensuring that the HER2 gene is actually overexpressed, so that the drug isn't used on HER2 underexpressed patients. This was a problem when trastuzumab initially came out. I would expect the same thing here. But, within the same criteria that the trial used, I do think there will be readily available coverage.

Dr Chernew: **I think that breakthroughs such as this lead to a lot of excitement. However, it does lead to a general dilemma about financing access to expensive, although I think in this case considered valuable, care.**

Dr Newcomer: First, I would love to hear Dr Swain's opinion and others on whether the CLEOPATRA trial should have had a third arm. That arm would have compared the control regimen used until progression followed by the addition of pertuzumab until the second progression. The study would then compare overall survival between the groups. One way to reduce the total cost of therapy is to use the drugs sequentially rather than as an initial combination. This would reduce the time required to use the more expensive medication if the results were comparable. Yet manufacturers, for obvious reasons, don't ever do that trial. If sequential therapy obtained the same type of responses, it would significantly reduce the amount of drug necessary to treat them.

Dr Swain: I think that's a really good design and that's my criticism of a lot of trials and a lot of combinations. However, with pertuzumab, for example, when it was used as monotherapy, it had a very low response rate. Therefore, in this situation it would be unlikely to have had a benefit. If you use the sequential design, you still end up having the cost, though, because you would end up having both drugs over the lifetime, so I'm not sure it would decrease the cost that much.

Dr Newcomer: Yes, unless you could treat the patient for just 6 months instead of 18 months. So, if the patient got 12 months out of trastuzumab plus docetaxel, then the oncologist was able to add the pertuzumab to those 2 drugs at the time of relapse and get another 6 or 7 months of progression-free survival—that's the kind of scenario I was thinking about. That would mean patients would be treated for only 6 months with pertuzumab instead of 18 months.

Dr Chernew: **Do you think some plans, or I think more relevantly some healthcare providers, would try such a strategy? Or, do you think because of the way the CLEOPATRA trial was designed that it's unlikely?**

Dr Newcomer: I think given the trial design they are almost required to use the 3-drug combination. What I just described needs testing because we don't know if it would work. However, if it did, it would be one way to get the total cost of therapy down.

Dr Swain: And, the problem is that there's a survival benefit now with the 3-drug combination. You don't know if there will be a survival benefit if you're dropping out the newer drug. You may not have the survival benefit. So, I think that providers will go with the indication that's in the trial right now.

Dr Chernew: **So, it's much more likely that the drug's use will be expanded by testing other indications in clinical trial rather than trying to economize by attempting indications that might not be as good?**

Dr Swain: Well, I think that people do need to economize, but definitely expansion is already being tested in the adjuvant setting and in the neo-adjuvant setting. The other issue that we kind of touched on is the length of treatment in these targeted drugs, especially in the adjuvant setting. There are several trials ongoing in the world looking at the length of treatment for trastuzumab, for example, to see if you really need to give a 1-year adjuvant treatment; there are trials looking at 9 weeks. I think those trials are going to be extremely informative, certainly for the adjuvant setting, and may even also help us in the metastatic setting.

Dr Newcomer: I'm in complete agreement. I just want to make very clear, though, that the suggestion I had about the 6 months of therapy after failure could *only* be done in the context of a clinical trial. I'm not recommending that anyone would do that in the clinic today.

Dr Chernew: **Thank you for clarifying. I did not mean to imply anything otherwise.**

Dr. Chernew: There have been many advances recently, as the CLEOPATRA trial illustrates, and we welcome those advances for a whole number of reasons, but it does place some burden on financing. It might be the case that any particular product, such as pertuzumab, doesn't add a lot to the overall premium; however, in combination with technologies, illnesses, and so on, premiums have been rising to rates that people consider difficult to finance. Therefore, how can we support the innovation that we all desire in our healthcare system without having a price tag that we can't afford?

Dr Swain: We really need to have a high bar for what we consider effective treatment. I think that's where we've gone wrong in the past. We've had statistically significant benefits for some of these drugs that may be a month-to-month [or] a couple weeks' benefit if you look at the randomized study, but what does it mean to the patient? It probably doesn't mean a whole lot. I really feel strongly about this issue. We're looking at some of these things in my role as president at the American Society of Clinical Oncology (ASCO) to ensure we set a higher bar and don't have incremental benefits. I think that's where you get into very high costs, is when you are using these drugs

that are marginally effective. We also need to be looking at toxicity issues, which we are doing. For example, in the CLEOPATRA trial, pertuzumab really didn't add a lot of toxicity per se. A few patients developed febrile neutropenia and diarrhea, but not significant toxicity in most cases. We really need to be looking at cost-effectiveness and we really haven't done that well in most of our randomized studies in the past.

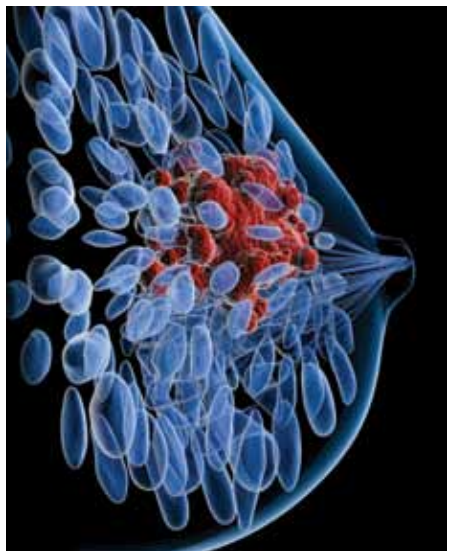
Dr Newcomer: I'm in complete agreement with Dr Swain. We have to do something to reduce the consumption of both drugs and other technologies that aren't really making a big difference. And, that's going to be a very painful thing to do, but there's a reason we have to do it. There are 3 reports recently on the ASCO News website where economists took a look at current trends in medical costs and current trends in US salaries, and what they found is that in 15 years you will have to use your entire US average salary to pay your average US healthcare premium. So, that doesn't leave anything for food, clothing, and shelter. Obviously, we can't do that. And, the only way we are going to be able to bring our healthcare costs down is to eliminate those things of very marginal value. It means we have to say no. And, that's a tough thing for us to do politically in the United States.

Dr Swain: It's very tough and it's also tough for patients in the United States—the American patients expect to be treated. They expect to come into the physician's office and get a drug, antibiotics, or whatever in all aspects of healthcare. We just have to change that culture and educate the population that just because we have a drug doesn't mean it's the right thing to do at that point. And, it is very hard, as I do it in my practice all the time. People don't want to hear "This drug is going to cause you a lot of side effects and it's not going to help you a whole lot."

Dr Chernew: How will utilization responses to innovation be affected by changes in payment models (eg, pay-for-performance, new bundled payments systems)? In general, how will oncology respond as many of these new drugs coming out are applied to cancer?

Dr Newcomer: There's no question that, as we move forward in the United States, we'll see more financing approaches that use budgets. The accountable care organizations are an example and bundled payments may be another. In those systems, a budget would require physicians to separate out those things that are really important from those that either don't have an effect or don't have enough of an effect to be important. I really believe those decisions are best made at the professional level. So, I'm hoping that as we evolve new financing systems that it will be doctors involved in making the decisions. But, I can't emphasize enough, as we both said before, that it's going to be hard. Looking at a patient and saying we aren't going to do some of these things because they just don't have value, even if the patient might want them, is a difficult thing to do.

Dr Swain: I think we are also in an era in which we are looking at quality improvement. One of the things we are doing at ASCO also is the Quality Oncology Practice Initiative program in which we are observing approximately 700 practices, and we have done this at the Washington Cancer Institute, to study different measures and how these different measures can improve the quality. We need to link that now to outcomes, and I think that's really one of the basic areas of research that's being done. If you make these changes, will the outcomes actually be better?



Dr Newcomer: An important part to add to that is that drugs are only one-third of the cost of caring for a patient with cancer. So, if you can anticipate problems, deal with them early, and keep the patient out of a hospital, there will be significant savings in terms of caring for that patient. This isn't all about drugs; it's about how we can improve the whole care process.

Dr Chernew: Some of these other payment models might enable the decisions to reflect these other savings?

Dr Newcomer: Yes, I think that is true as well.

Dr Swain: Something we've done at ASCO is the Choosing Wisely campaign. I know several other organizations have done something similar. We chose 5 common, costly procedures in oncology that are not supported by evidence and that should be questioned; for example, performing surveillance with PET scans or CTs for early breast cancer and prostate cancer, using growth factors when the likelihood of febrile neutropenia is low, or giving drugs in the last days of life when it's really not effective. So, we have really taken this issue on and we are trying to do something as an organization of physicians to try to decrease healthcare costs. I think it's going to take all of us working on this issue—the payers', physicians', and patients' understanding and education of it—to really solve the problem.

Dr Newcomer: I was on the committee that developed the 5 choices and I'm finding, in my current role, people coming back and saying "OK, is it time for us to stop paying for PET scans? We're getting a lot of pushback." Even though ASCO has done a beautiful job of laying out the reasons for why it shouldn't be performed, as we try to put some of that in the field, a lot of providers are pushing back on us and saying it's unfair. And, it just helps illustrate how difficult this is going to be.

Dr Chernew: Do you think there's any role in patient incentives to get patients with cancer more engaged, or isn't it realistic to expect these patients to be engaged in the process, at least in weighing any of the financial ramifications of the decisions?

Dr Swain: Well, I think they are doing that now. They have to do that with some of the copays—they have to look at whether they can afford it. However, we as physicians have to be honest and clear with the patients as to what the benefits are with the treatment being recommended. And, that's why I again get back to having a very high bar. If you administer a treatment, it needs to have really good efficacy for the patient, especially if they are going to be paying some money out of pocket, which happens many times now, especially for oral drugs.

Dr Newcomer: The actual amount of out-of-pocket money for these folks—typically the ceiling is around $5000—is fairly high. It's enough that some patients are forgoing treatment. So, I agree; patients get involved in the economics of some of these decisions pretty early.

Dr Chernew: In a case where the evidence of effectiveness is as strong as it is for pertuzumab, you might think that some different copay structure would be reasonable to avoid placing financial access barriers to very good medications. Do you see that type of differentiation going on now?

Dr Newcomer: Well, what you are describing is called a value-based copayment or value-based coinsurance and the concept is wonderful; putting it into action is really hard, particularly for drugs that have more than 1 cancer where they're active. So, you might give a drug a good rating for effectiveness in 1 cancer, but a very low rating in a second cancer. Trying to keep that simple enough for a patient or consumer to understand and a business office to bill correctly gets to be pretty complex. It's a great idea, but we haven't learned how to simplify it enough to make it work.

Dr Chernew: Drs Newcomer and Swain, do you have any other comments or something you would like to add?

Dr Swain: I think one thing that we didn't really talk about today is the importance of approving companion diagnostics with the newer drugs in oncology. This sets a higher bar for the new drugs that are coming out, plus it decreases the population of patients in which the drug is being tested. Therefore, clinical trials in the future should cost less and, hopefully, the drugs will cost less. So, that's something where research is really important to try to decrease some of these costs.

Dr Chernew: I assume UnitedHealthcare supports the relevant companion diagnostics to assess, for example, whether HER2 is over- or under-expressed in order to get access?

Dr Newcomer: Absolutely, for all the reasons that Dr Swain just mentioned. They make perfect sense. We also didn't address that the pharmaceutical industry is going to have to find a way to lower the costs of drug development. They're a very innovative group and they are finding great drugs. They've got to find a way, then, to make the cost of developing those drugs less as well. So, some of that innovation needs to be turned inward to see if we can reduce the price of those medicines. **EBO**

Participant Affiliations: From the Department of Healthcare Policy, Harvard Medical School (MEC), Boston, MA; UnitedHealthcare (LN), Minneapolis, MN; Washington Cancer Institute, Medstar Washington Hospital Center (SMS), Washington, DC.

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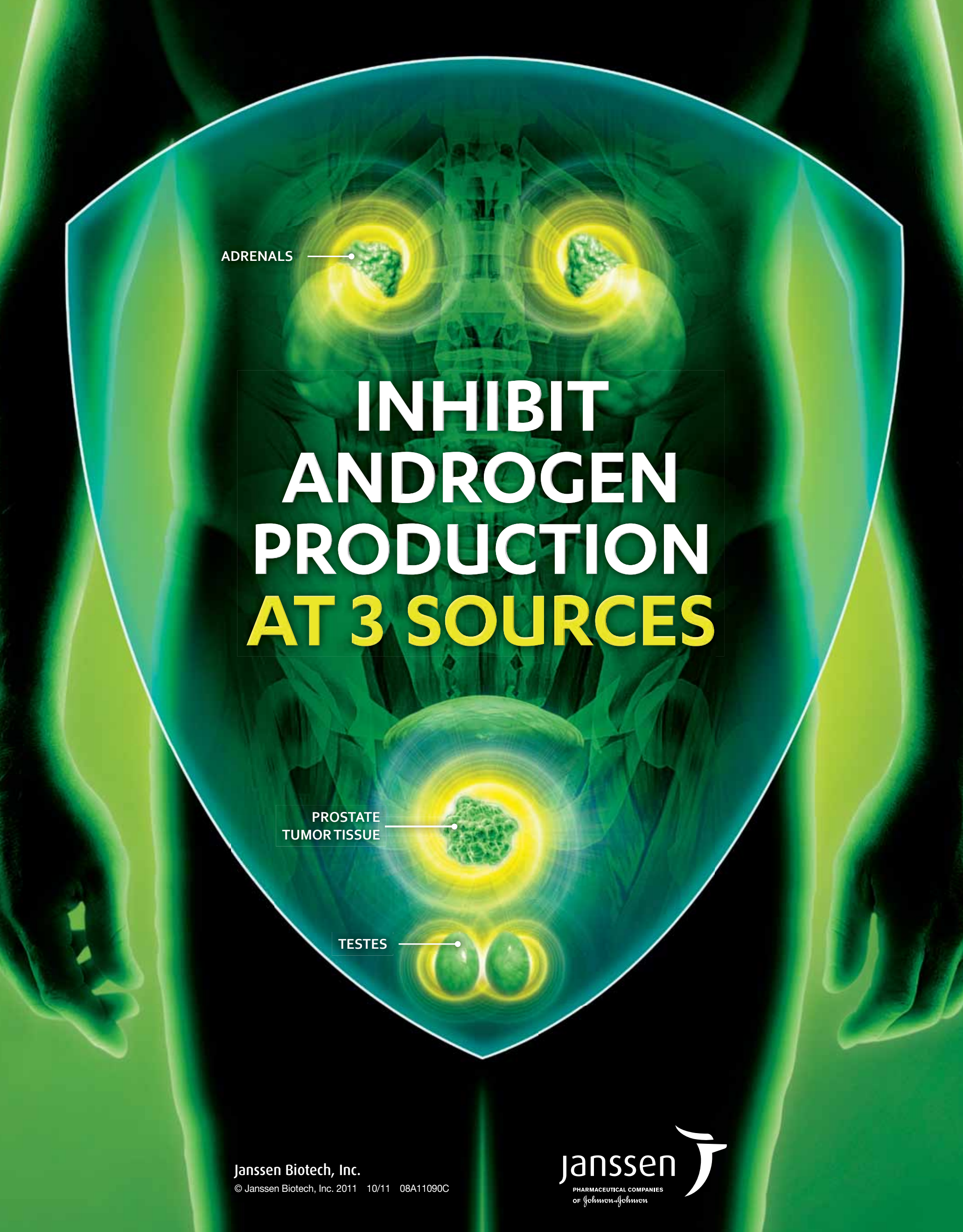

Janssen Biotech, Inc.

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

ORAL THERAPY

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

Mechanism of action

- Abiraterone is an *androgen biosynthesis inhibitor* (ABI) that directly affects the androgen biosynthesis pathway by inhibiting CYP17 (17α-hydroxylase/C17,20-lyase)
  - — Consequently, androgen biosynthesis is inhibited at 3 sources of testosterone production: the testes, adrenal glands, and prostate tumor tissue
- Androgen biosynthesis inhibition with ZYTIGA® results in decreased levels of serum testosterone and other androgens
- At the interim analysis of the pivotal phase 3 study, ZYTIGA® + prednisone showed a statistically significant improvement in median overall survival (OS) compared with the control arm*
  - — Median OS: 14.8 months vs 10.9 months (hazard ratio = 0.646; 95% confidence interval: 0.543, 0.768, $P < 0.0001$)

Important Safety Information

Contraindications—ZYTIGA® may cause fetal harm (Pregnancy Category X) and is contraindicated in women who are or may become pregnant.

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in hypertension, hypokalemia, and fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF < 50% or New York Heart Association (NYHA) Class III or IV heart failure because these patients were excluded from the randomized clinical trial. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

Adrenocortical Insufficiency (AI)—AI has been reported in clinical trials in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids, and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

Hepatotoxicity—Increases in liver enzymes have led to drug interruption, dose modification, and/or discontinuation. Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

Food Effect—ZYTIGA® must be taken on an empty stomach. Exposure of abiraterone increases up to 10-fold when abiraterone acetate is taken with meals. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Use in Specific Populations—The safety of ZYTIGA® in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA®.

Drug Interactions—ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate. Additionally, abiraterone is a substrate of CYP3A4 *in vitro*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution.

Adverse Reactions—The most common adverse reactions (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

***Study Design:** ZYTIGA®, in combination with prednisone, was evaluated in a Phase 3, randomized, double-blind, placebo-controlled, multicenter study in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received prior chemotherapy containing docetaxel (N = 1,195). Patients were randomized 2:1 to receive ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily (n = 797) or placebo orally once daily + prednisone 5 mg orally twice daily (n = 398). Patients were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy and were at castration levels of testosterone (serum testosterone ≤ 50 ng/dL).[1] The primary efficacy endpoint was overall survival.*

Reference: 1. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

Please see adjacent pages for brief summary of full Prescribing Information.

www.zytiga.com

ZYTIGA™ (abiraterone acetate)
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

ZYTIGA in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

CONTRAINDICATIONS

Pregnancy: ZYTIGA may cause fetal harm when administered to a pregnant woman. ZYTIGA is contraindicated in women who are or may become 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 the fetus.

WARNINGS AND PRECAUTIONS

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: Use ZYTIGA with caution in patients with a history of cardiovascular disease. ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Adverse Reactions and Clinical Pharmacology (12.1) in full Prescribing Information]*. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenocortical insufficiency has been reported in clinical trials in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions]*.

Hepatotoxicity: Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred *[see Adverse Reactions]*. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function. Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2) in full Prescribing Information]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Food Effect: ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

Hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess *[see Warnings and Precautions]*.

Adrenocortical insufficiency *[see Warnings and Precautions]*.

Hepatotoxicity *[see Warnings and Precautions]*.

Food effect *[see Warnings and Precautions]*.

Clinical Trial 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.

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N = 791). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 394). The median duration of treatment with ZYTIGA was 8 months.

The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking ZYTIGA).

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly in patients treated with ZYTIGA than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively (see Table 1). In patients treated with ZYTIGA, grades 3 to 4 hypokalemia occurred in 5% of patients and grades 3 to 4 hypertension was reported in 1% of patients *[see Warnings and Precautions]*.

Table 1 shows adverse reactions due to ZYTIGA that occurred with either a ≥ 2% absolute increase in frequency compared to placebo, or were events of special interest (mineralocorticoid excess, cardiac adverse reactions, and liver toxicities).

Table 1: Adverse Reactions due to ZYTIGA in a Placebo-Controlled Phase 3 Trial

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Cardiac disorders				
Arrhythmia[5]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[6]	3.8	0.5	2.8	0
Cardiac failure[7]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[6] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[7] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Cardiovascular Adverse Reactions: Cardiovascular adverse reactions in the phase 3 trial are shown in Table 1. The majority of arrhythmias were grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the ZYTIGA arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity: Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been reported in patients treated with ZYTIGA. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. In the phase 3 trial, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, ZYTIGA was withheld or discontinued. In two instances marked increases in liver function tests occurred *[see Warnings and Precautions]*. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of ZYTIGA, both patients had normalization of their liver function tests and one patient was re-treated with ZYTIGA without recurrence of the elevations.

In clinical trials, the following patients were excluded: patients with active hepatitis, patients with baseline ALT and/or AST ≥ 2.5X ULN in the absence of liver metastases, and patients with ALT and/or AST > 5X ULN in the presence of liver metastases. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption, dose modification and/or discontinuation *[see Dosage and Administration (2.2) in full Prescribing Information and Warnings and Precautions]*. Patients with elevations of ALT or AST > 20X ULN were not re-treated.

Other Adverse Reactions: Adrenal insufficiency occurred in two patients on the abiraterone arm of the phase 3 clinical trial (< 1%).

Laboratory Abnormalities of Interest: Table 2 shows laboratory values of interest from the phase 3 placebo-controlled clinical trial. Grade 3-4 low serum phosphate (7.2%) and potassium (5.3%) occurred more frequently in the ZYTIGA arm.

ZYTIGA™ (abiraterone acetate)

Table 2: Laboratory Abnormalities of Interest in a Phase 3 Placebo-Controlled Clinical Trial

	Abiraterone (N=791)		Placebo (N=394)	
Laboratory Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
High Triglyceride	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Low Potassium	28.3	5.3	19.8	1.0
Low Phosphorus	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

DRUG INTERACTIONS

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category X *[see Contraindications]*. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the potential risk for pregnancy loss. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with ZYTIGA.

Nursing Mothers: ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate 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 ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: ZYTIGA is not indicated in children.

Geriatric Use: Of the total number of patients in a phase 3 trial of ZYTIGA, 71% of patients were 65 years and over and 28% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Patients with Hepatic Impairment: The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Patients with Renal Impairment: In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE: There have been no reports of overdose of ZYTIGA during clinical studies. There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

Storage and Handling: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*. Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations]*.

Manufactured by:
Patheon Inc.
Toronto, Canada

Manufactured for:
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Rationalizing Treatment and Coverage Decisions With Predictive Biomarkers

Kim Farina, PhD

Beyond providing prognostic information, molecular biomarkers can help optimize therapy decisions. Predictive biomarkers are beginning to help physicians assign value to associated therapies in terms of likelihood of benefit and benefit-to-risk profiles for individual patients. A predictive factor is a baseline patient or tumor characteristic that identifies a specific qualitative outcome (eg, response or survival) driven by a treatment.

Healthcare providers and payers hope to be able to use predictive biomarkers to rationally apportion therapy. "We want to enrich the treated population with those who are likely to benefit from therapy," explained Mark Green, MD, chief medical officer, Xcenda, who led the roundtable discussion *Prognostic vs Predictive Biomarkers and the Role of Companion Diagnostic Testing in Payer Decision Making* during the 2012 Academy of Managed Care Pharmacy Annual Meeting. "Individuals likely to benefit should be willing to accept the risks of receiving that therapy, namely: costs for that particular treatment, loss of opportunity to try something else at that point in time, and treatment-related toxicities."

On the other hand, he said, "Individuals whose tumors fail to express a biomarker directly predictive of a reasonable likelihood of response to a certain therapy would be much better served by exploring other therapies and not exposing themselves to an extremely low likelihood of benefit with no reduction in risk." The loss of opportunity for trying an alternative therapy that might offer a better chance for response is a significant risk to this group.

Implications for Payers

When a biomarker test is capable of predicting response to a particular therapy, payers should have the opportunity to incorporate that test into their drug benefit management strategy. It is Dr Green's opinion that by encouraging and covering testing, payers can facilitate rational treatment and coverage decisions. He is expecting that electronic medical records will help bolster awareness, buy-in, and integration of biomarker testing.

According to Green, the field is still finding its way in actualizing the use of biomarkers, not only for therapy selection but for coverage decision making. "It is a new world for providers, payers, patients, and the entire consortium of healthcare stakeholders, but we have to make rational use of them," he commented.

Applying biomarkers in this way, he cautions, will require discipline and biomarker assays of excellent quality that are associated with high reproducibility, specificity, sensitivity, and accuracy. It will also require stakeholders to agree upon test criteria, thresholds, and decisions related to companion diagnostics. Once that happens, according to Green, plans and providers should be in a position to address the optimum strategy for care. "It is evidence-based, it is

Table. Locally Advanced or Metastatic ALK-Positive NSCLC Efficacy Results[a,b]

Efficacy Parameters	Study A (N = 136)	Study B (N = 199)
Objective response rate, CR + PR (95% CI)	50% (42%-59%)	61% (52%-70%)
Number of responders	68	71
Mediation duration of response (weeks)	41.9	48.1

CR indicates complete response; NSCLC, non-small cell lung cancer; PR, partial response.
[a]Investigated in 2 multicenter, single-arm studies (studies A and B).
[b]Investigator-assessed response.
Source: Xalkori [package insert]. New York, NY: Pfizer Labs; 2011. http://labeling.pfizer.com/showlabeling.aspx?id=676. Accessed May 23, 2012.

science-driven, it is an opportunity cost for optimized patient care and it is a responsible behavior. That is what we are striving for and that is where we need to be going," he remarked.

An exciting development in the field of predictive diagnostics is the US Food and Drug Administration (FDA) approval of crizotinib (Xalkori), along with a companion diagnostic test, for patients with ALK-positive locally advanced or metastatic non-small cell lung carcinoma (NSCLC). Although crizotinib costs more than $9000 per month, the response rates in patients with ALK-positive tumors are dramatic. The majority of eligible patients responded to therapy (Table), demonstrating the robust enrichment in likelihood of response achievable with predictive biomarkers.

Why Bother Testing?

Giving these targeted agents a try in everyone is not an advantageous approach for a number of reasons. These drugs are extremely expensive and there is the issue previously raised about giving someone a therapy from which they are not likely to benefit while exposing them to all the associated costs. The overall rate of response to epidermal growth factor receptor (EGFR) inhibitors among patients with advanced NSCLC positive for an EGFR mutation is around 70%, while in patients without an EGFR mutation, it is essentially zero. Use of the EGFR inhibitor gefitinib as initial therapy for patients with EGFR-mutation-negative tumors suggests targeted therapy can actually worsen progression-free survival (Figure). In addition, some trials show that if you don't test and instead simply randomly assign patients to either erlotinib or chemotherapy as first-line therapy, overall survival may be significantly worse in those individuals who are assigned to receive targeted therapy rather than chemotherapy as first-line management. Dr Green elaborated, "So you have to have the test results if you want to use this targeted therapy in the first-line setting and if the patient carries a mutation and you use gefitinib or erlotinib first-line, the likelihood of response is extremely high."

Dr Green reiterated the goal of predictive therapy as, "You want to be able to dichotomize a population into those who have a high likelihood of benefit and those who do not." The key, he says, is to avoid missing that person who has a chance to receive a therapy that may provide a 70% to 80% chance of response and has been shown to remain active at 12 months or longer. "We are looking to be able to rationalize, not in the sense of justify, but in the sense of being able to think clearly of how to assign therapeutic recommendations." **EBO**

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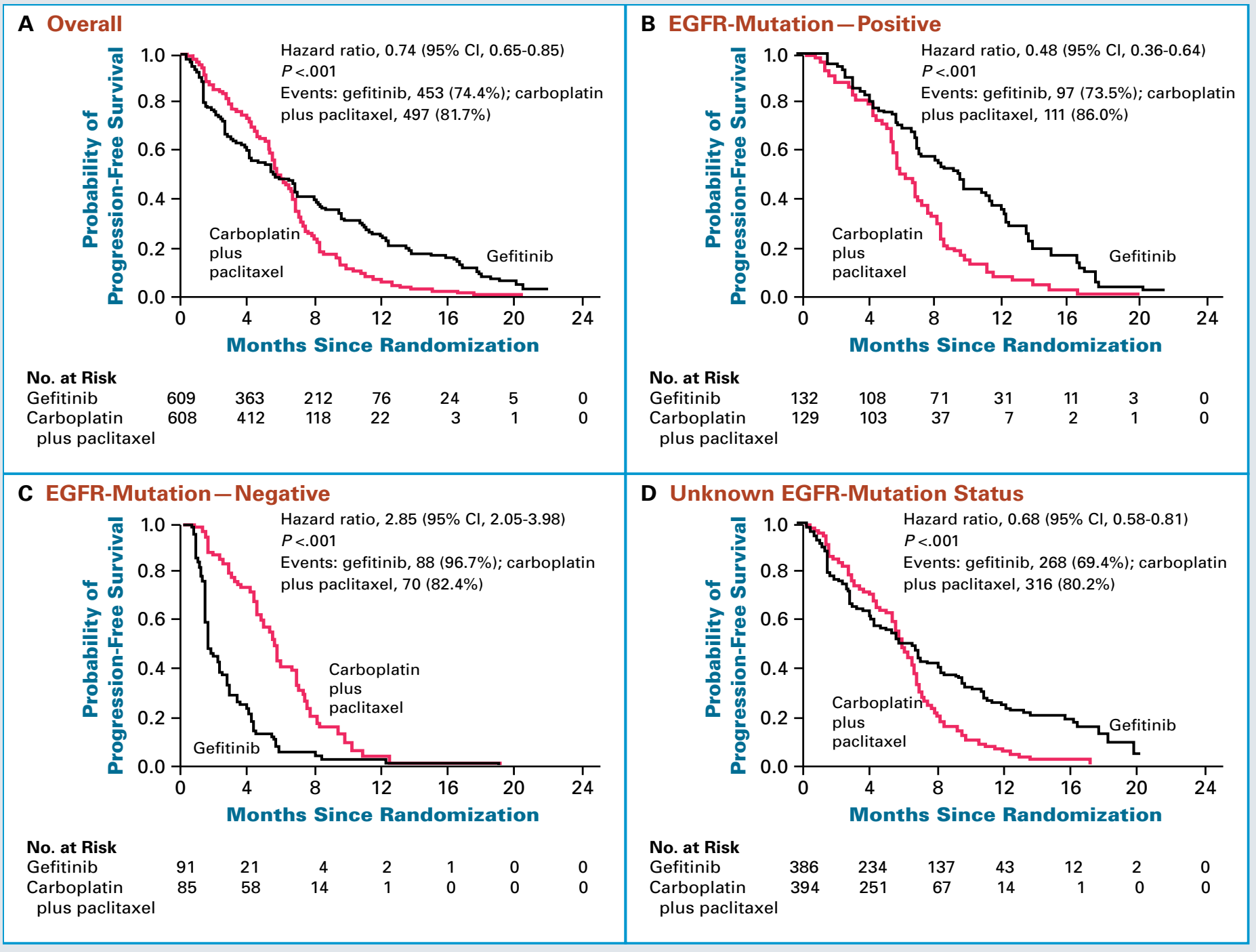
Authorship Information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

Figure. Kaplan-Meier Curves for Primary End Point of Progression-Free Survival in Patients Receiving Either Carboplatin-Paclitaxel or Gefitinib



CI indicates confidence interval; EGFR, epidermal growth factor receptor.

A, Overall population of patients; **B**, patients who were positive for the EGFR mutation; **C**, patients who were negative for the EGFR mutation; and **D**, patients with unknown EGFR mutation status. Analyses were performed on an intention-to-treat population.

Source: Reprinted with permission from Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *New Engl J Med*. 2009;361(10):947-957.

Clinical Care Pathways
(continued from Cover)

Implementation of Cancer Clinical Care Pathways

A Successful Model of Collaboration Between Payers and Providers

Bruce A. Feinberg, DO; James Lang, PharmD, MBA; James Grzegorczyk, MS, RPh; Donna Stark, RPh, MBA; Thomas Rybarczyk, RN, BSN; Thomas Leyden, MBA; Joseph Cooper; Thomas Ruane, MD; Scott Milligan, PhD; Philip Stella, MD; and Jeffrey A. Scott, MD

to accomplish behavioral change. Such a collaboration has been pioneered by Blue Cross Blue Shield of Michigan and Physician Resource Management, a highly specialized oncology healthcare consulting firm with developmental and ongoing technical, analytic, and consultative support from Cardinal Health Specialty Solutions, a division of Cardinal Health. We describe a successful statewide collaboration between payers and providers to create a cancer clinical care pathways program. We show that aligned stakeholder incentives can drive high levels of provider participation and compliance in the pathways that lead to physician behavioral changes. In addition, claims-based data can be collected, analyzed, and used to create and maintain such a program.

The overall incidence of cancer in the United States is projected to increase by 45% in the next 2 decades from 1.6 million in 2010 to 2.3 million in 2030. Direct medical costs associated with cancer are also projected to increase exponentially from $104 billion in 2006 to more than $173 billion in 2020 as a result of increases in both the cost and quantity of cancer therapies.[1] Newer cancer treatments are not only likely to be more expensive than the existing standard of care, but they will expand the pool of available treatment options.[2,3] Despite these rising medical costs and treatment options, quality and outcomes are not improving.[4] Without significant policy reform, the cost-quality imbalance will reach unsustainable proportions in the foreseeable future.[1,4-6]

Many factors play into the rising costs of healthcare, including an aging population, an expanding arsenal of therapeutics for chronic disease states, increasing regulatory demands on stakeholders, inefficiencies in delivery, and archaic information technologies. All of these factors result in significant variations in practice patterns among medical oncologists.[7] Costs can vary dramatically because physicians often treat patients with the same condition differently in choice of drugs, referrals for surgery and radiation, referrals for palliative and end-of-life care, and types of supportive care. Strategies such as prior authorization and decreasing fee schedules have been implemented in an effort to lower healthcare costs.[8-10] However, because neither of these strategies addresses practice variances or the rapidly rising cost of cancer therapeutics, their impact on healthcare costs has been of limited benefit and brief duration.[11]

Clinical pathways are a method to reduce unnecessary and costly treatment variation; however, physician participation is crucial for their success.[1,12] The perceived challenge of cookbook-style medicine to physician autonomy from an external authority, such as insurance companies or academic advisory boards, can be one barrier to pathway adoption among others such as time constraints and comfort with previous practice patterns.[13,14] Without accountability or incentives, physicians might comply partially with the terms of a pathway program or not participate at all. Therefore, a collaborative effort between pathway-developing parties and oncology groups is needed.[15] Physicians directly or indirectly control or influence the majority of cancer care costs.[1] Therefore, physician behavior change can be used as a surrogate marker of cost savings, which can be difficult to demonstrate as a result of evolving patterns of care, new drug technologies, patent expirations, and data capture problems from revenue code and charge bundling to name a few.

This article details a collaborative statewide cancer clinical pathway program in which provider network medical oncology physicians played an integral role in developing oncology clinical pathways. The success of the program was determined by evaluation of physician compliance with the pathways and their behavioral changes in the first year of the program resulting from the inherent difficulties in determining cost savings in this setting.

Collaborative Clinical Pathway Program

In mid-2009, 3 groups—Blue Cross Blue Shield of Michigan (BCBSM; Detroit, Michigan), a large single-state not-for-profit BCBS plan; Physician Resource Management (PRM; Novi, Michigan), a state physician organization; and Cardinal Health Specialty Solutions (CHSS; Dublin, Ohio), an oncology benefit management company (previously P4 Healthcare)—partnered to develop a clinical pathway program whereby physicians would jointly develop the content, structure, and implementation of the program pathways. Involving physicians in the clinical pathways development process would provide an incentive for physicians to participate in the pathways themselves. Care pathways for breast, colon, and lung cancer were developed in the first year of the program and expanded by 5 additional malignancies in the second year. The program would benefit all parties involved in patient care, including patient, provider, and payer, by aiming to improve the consistency and quality of patient care while also reducing costs. The clinical cancer care pathways program was operated and funded through the Oncology Physicians Resources (OPR; West Bloomfield, Michigan) group, an existing statewide physician-owned general purchasing and management organization and subsidiary of the Michigan Society of Hematology and Oncology (MSHO; Rockingham Royal Oak, Michigan). PRM is an administrative arm of OPR and would manage the BCBSM pathway program.

Before the development of this partnership, BCBSM instituted a pay-for-performance program in 2005 for Michigan physicians, the Physician Group Incentive Program (PGIP). This program added a physician organization fee component to each professional service payment. The physician organization component was held in an incentive pool and fully distributed twice each year to physicians who participated in PGIP. It was determined that the BCBSM cancer clinical care pathways program would be placed under the aegis of PGIP and that funding would be paid directly to OPR/PRM according to PGIP bylaws. **Figure 1** presents a schematic of steps involved in the pathways development and the implementation of BCBSM oncology treatment pathways.

Alignment of Stakeholders

One of the first critical steps in the development of the BCBSM pathway program was to align stakeholder incentives so that all interests would be taken into account. BCBSM wanted to develop a program that would improve clinical outcomes with more predictable costs,

Bruce A. Feinberg, DO

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thereby bending the cost curve downward for future oncology care. Oncologists wanted reimbursement stability. CHSS wanted to prove its value-added benefits to the process by not only receiving a fee for service for their technical support but also sharing in both the upside and possible downside of the program results attributable to pathway compliance. All 3 stakeholders agreed that, given the appropriate incentives, provider behavior could be modified in a self-governing process in which claims data would be used to monitor compliance.

Methods

Provider Incentive Program

PRM and BCBSM agreed on ways to reward physicians for using pathways. BCBSM provided each physician participant a $5000 payment for the first year of the pathways program to cover any extra costs involved and to provide a financial incentive to participate and meet approved compliance thresholds. In addition, the reimbursement rate for several generic therapies associated with the specific clinical pathways was increased to remove the perverse incentives created by average sales price–based reimbursement (13 drugs were modified in 2010). Evaluation and management codes would also be increased (10%) for pathway program participants as a result of compliance in year 1. Payments were also made to PRM to serve as the coordinating center for this statewide effort from the BCBSM PGIP incentive pool. With those monies, PRM elected to make payments to physician groups for their participation, support the development of clinical pathways, provide software developed by CHSS, and subcontract with CHSS for additional services. BCBSM incentives and fee schedules were also reviewed to assess how payer incentives aligned with best practices.

Pathway Development

PRM selected regional leaders to serve on a steering committee. The steering committee comprised 12 regional network oncologists from academic-based practices and large and small community-based practices. It was co-chaired by the CHSS chief medical officer and an OPR officer as nonvoting members. On the basis of published scientific and clinical evidence and national guidelines, the steering committee developed the most up-to-date and effective oncology care pathways for breast, lung, and colon cancer and supportive care using granulocyte colony-stimulating factors, erythropoietin stimulating agents, and antiemetics. Treatment, efficacy, toxicity, and cost (in that order of priority) were considered in all pathway regimen selections. National Cancer Institute–designated clinical trials and/or decisions for palliative care were mutually agreed upon to be included in all pathways. The steering committee also embraced molecular diagnostics in breast, colon, and lung cancer as part of the pathways process.

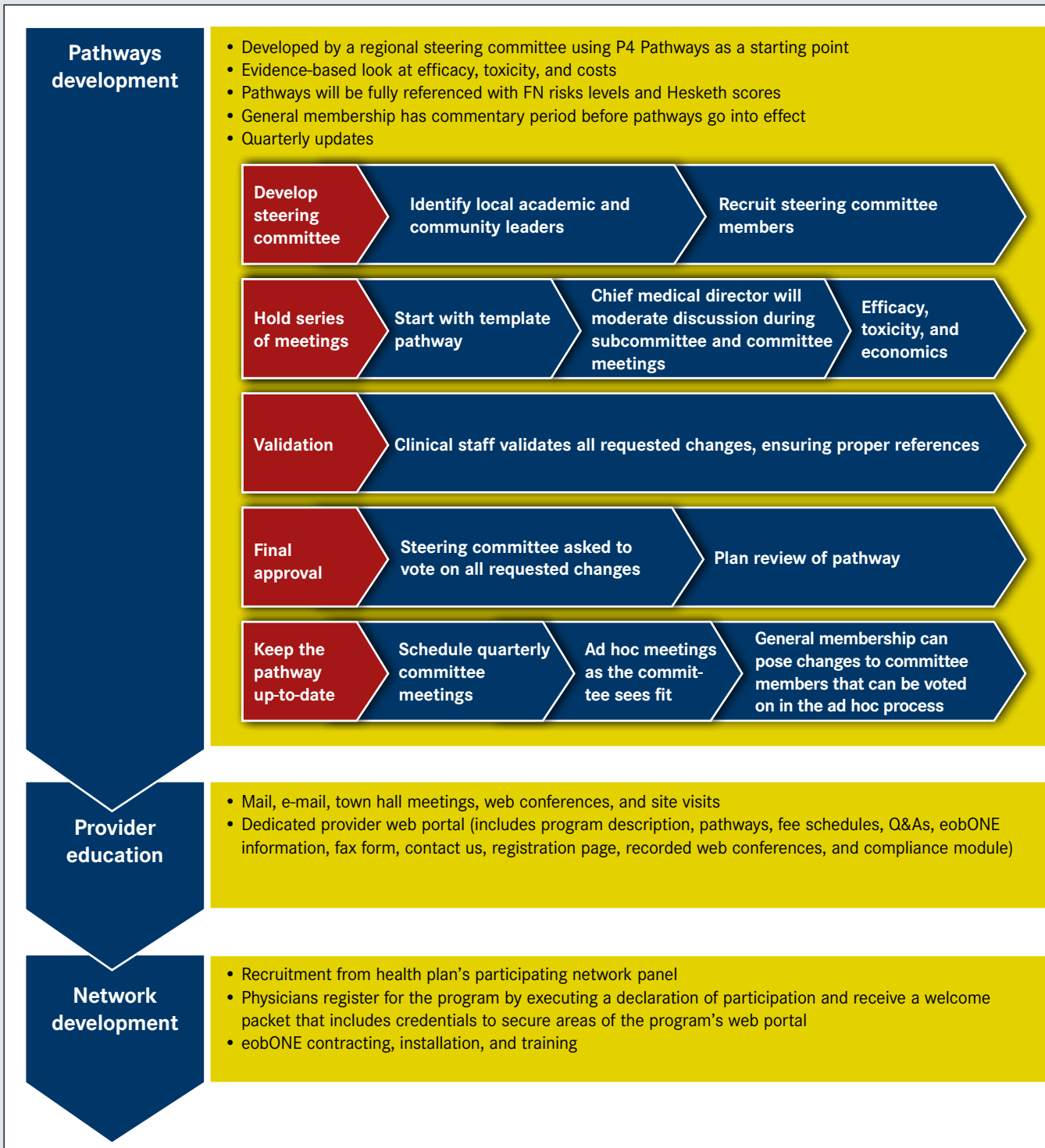
The oncology pathways were introduced to the remaining oncologists within the broader BCBSM network for their review and input. All recommendations were evaluated by the steering committee. These steps were critical and ensured that the valuable experience and expertise of each network physician was considered before pathway adoption. The pathways are organized by line of therapy, and they include molecular profiling, histologic profiling, treatment indication, and stage. The steering committee continues to meet quarterly and on an ad hoc basis.

Before the pathway finalization, the criteria for selection and protocols underwent review by BCBSM; however, BCBSM did not play a role in protocol selection. It was determined from the beginning of this partnership that this statewide initiative would be best positioned for success if BCBSM kept its role to that of an objective third-party funder with a strong interest in the outcomes of the program but with no direct influence in the determination of what ultimately constituted the clinical pathways.

Compliance Monitoring

The BCBSM oncology care pathway program acknowledged that pathways are not a substitute for physician judgment and that some variance can and should be expected to allow for individual treatment on the basis of unique patient needs. Therefore, it was agreed that compliance thresholds for participating physicians should not be set at

Figure 1. Steps Involved in Pathways Development and Implementation of BCBSM Oncology Treatment Pathways

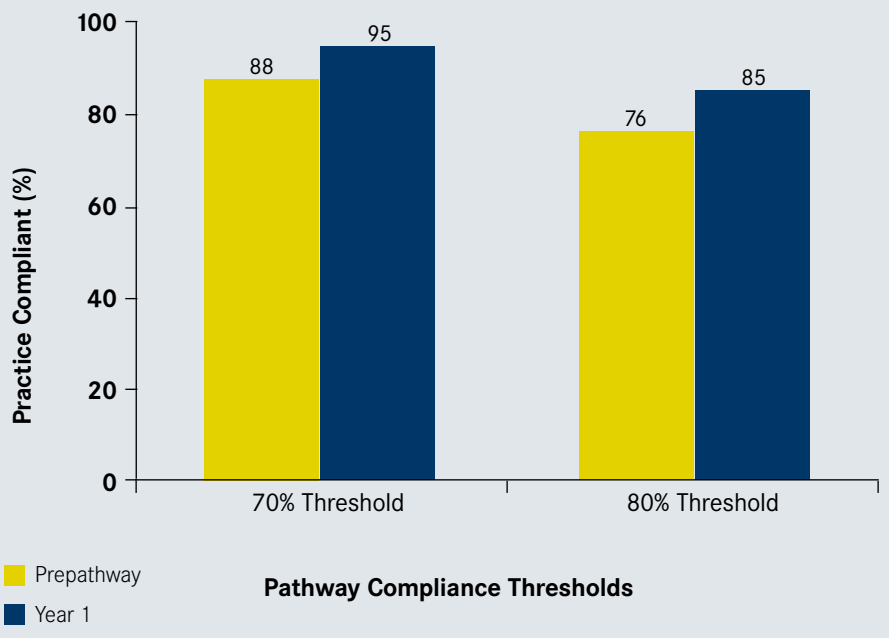


BCBSM indicates Blue Cross Blue Shield of Michigan; FN, febrile neutropenia; Q&As, questions and answers.

100%. For cancer treatment in the adjuvant and metastatic setting for breast, colon, and lung cancer, a 70% compliance rate was set as the threshold for the first year and 80% for subsequent years with reporting on both as a means of communication with and education for the provider network. It was also agreed that an 80% rate of compliance would be appropriate for supportive care in the first and subsequent years. Most pathway deviations would be rendered noncompliant and part of the allowable 30% noncompliance rate. However, an appeals mechanism was put in place via portal. In rare instances, nonpathway approaches could be challenged proactively when standards of care are dynamic (eg, in triple-negative breast cancer). This could be addressed via an ad hoc steering committee meeting or a proactive appeal and would include oversight committee evaluation within 48 hours.

Compliance was measured through claims submitted to a proprietary claims cycle management software tool, eobONE (Cardinal Health; Dublin, Ohio). It was augmented and validated with data directly from the insurer for patients with breast, lung, and colon cancer who started new lines of antineoplastic therapy on or after January 2010. Additionally, physicians could submit information through a secure web portal or fax (eg, clinical trial schema and hospice care notifications). Collecting data in this manner created no additional work for the practices. Physicians were notified of their compliance scores through quarterly reports from CHSS and were allowed to reconcile noncompliant determinations by providing additional data through the appeal section of the CHSS web portal. Aggregated program compliance was presented to BCBSM at quarterly meetings and to participating physicians at semiannual conferences. OPR had the responsibility of notifying and counseling practices with compliance issues.

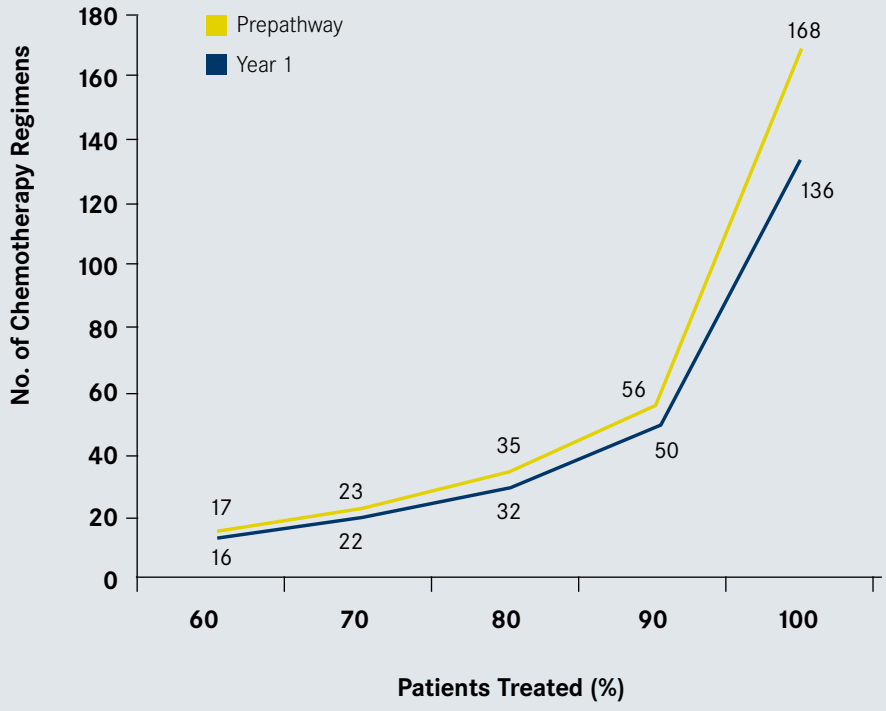
Figure 2. Compliance Levels for Participating Practices



Results

More than 80% of Michigan private practice medical oncologists participated in BCBSM's PGIP in the first year. Prepathway physician practices closely followed pathway guidelines, and baseline pathway compliance was therefore high at 88% when using the 70% threshold. This rate increased steadily in the first year of the program to 95% (Figure 2). Clearest among physician behavioral changes was a reduction in treatment variation. Although pathway guidelines allowed approximately 120 different chemotherapy combinations for breast, colon, and lung cancers, the vast majority of patients were treated with 1 of 30 regimens. Before pathways implementation, the participating physicians accounted for 168 distinct chemotherapy regimens for these cancers. By end of year 1, participating practices had reduced the total number to 136, with nearly all of the reduction affecting 10% of the treated population (Figure 3). The following are other behavioral changes adopted by participants: converting brand regimen to generic when equally effective and equitoxic; converting from more expensive to less expensive brand regimens when the same parameters apply; using molecular diagnostics to appropriately guide therapy; appropriate use of supportive care on the basis of evidence; decreasing lines of therapy when evidence is lacking; limiting late lines of therapy to single-agent cytotoxics; using biologics on the basis of labeling rather than irrational exuberance; and as the result of all the above, lower rates of emergency department (ED) and hospital use.

Figure 3. Reduction in Treatment Variation by Participating Practices



Many healthcare systems are considering clinical pathways as a method to reduce unnecessary and costly treatment variation; however, the extent to which they can effectively do so relies heavily on design and implementation.

Discussion

Behavior Change as a Surrogate for Cost Savings

A recent report by the congressional budget office as well as other peer-reviewed publications have challenged the savings opportunities in payer-mediated provider network guidelines.[16,17] The absence of observed savings is a significant hurdle to overcome as the stakeholders of healthcare delivery explore solutions to bend the cost curve in cancer care. Although we reported being convinced by Gesme and Wiseman[18] in our previously reported analyses that our cancer pathways programs can produce meaningful savings, we also recognize the complexity inherent in such analyses. An in-network concurrent provider control group is the ideal comparator for savings. Unfortunately, this control group is flawed by the small numbers of nonparticipants among community providers, which thereby creates wide CIs, the selection bias inherent in a voluntary participation program (eg, low-cost providers participate, high-cost providers choose not to), and the patient demographic differences among community and academic providers. Concurrent control groups, national or regional, are also compromised, as has been made clear in the wide variations of resource use identified in the Dartmouth Atlas project.[19] Historical controls are equally contentious, given that oncology in particular is such a dynamic specialty with evolving patterns of care, changing label indications, new drugs and technologies, molecular diagnostics, patent expirations, and so on; all of which contributes to an extent of variables that is nearly impossible to account for in comparative analytics. Finally, data capture problems around hospital-based care as a result of revenue codes and charge bundling and around oral therapeutics distributed among multiple plan vendors leave significant data vacuums. In summation, validated savings with the currently available data from payers and providers is virtually impossible. The authors believe that a sustainable reduction in variance inherently improves quality

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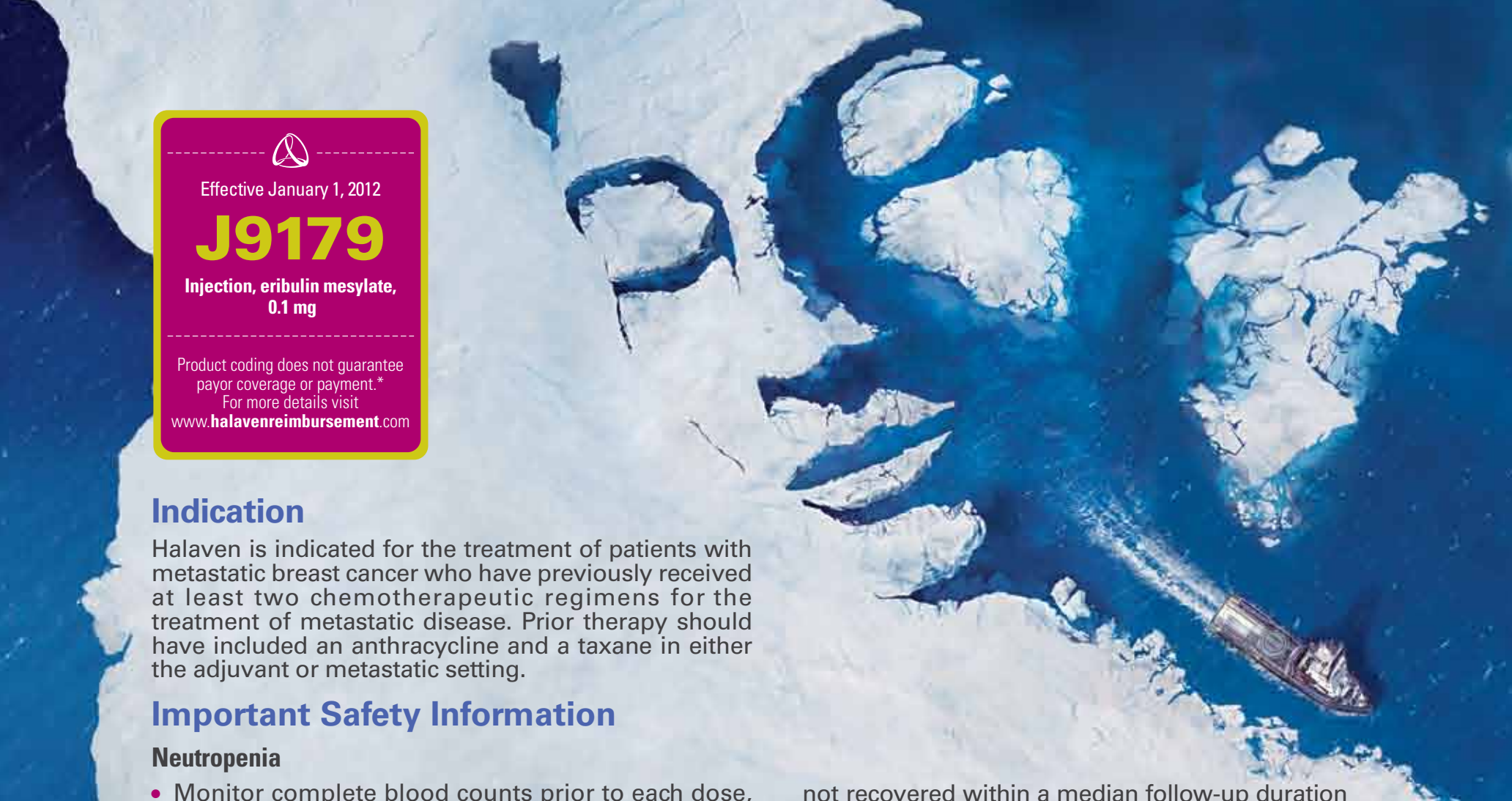

Effective January 1, 2012

J9179

Injection, eribulin mesylate, 0.1 mg

Product coding does not guarantee payor coverage or payment.*
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Indication

Halaven is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

Important Safety Information

Neutropenia

- Monitor complete blood counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days
- Severe neutropenia (ANC <500/mm^3) lasting more than 1 week occurred in 12% (62/503) of patients. Patients with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels
- Grade 3 and Grade 4 neutropenia occurred in 28% and 29%, respectively, of patients who received Halaven. Febrile neutropenia occurred in 5% of patients and two patients (0.4%) died from complications

Peripheral Neuropathy

- Patients should be monitored closely for signs of peripheral motor and sensory neuropathy
- Grade 3 peripheral neuropathy occurred in 8% of patients, and Grade 4 in 0.4% of patients who received Halaven. Delay administration of Halaven until resolution to Grade 2 or less
- Neuropathy lasting more than 1 year occurred in 5% of patients. Twenty-two percent of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days)

Pregnancy Category D

- Halaven is expected to cause fetal harm when administered to a pregnant woman and patients should be advised of these risks

QT Prolongation

- In an uncontrolled ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no prolongation on Day 1. ECG monitoring is recommended for patients with congestive heart failure; bradyarrhythmias; concomitant use of drugs that prolong QT interval, including Class Ia and III antiarrhythmics; and electrolyte abnormalities
- Correct hypokalemia or hypomagnesemia prior to initiating Halaven and monitor electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome

Hepatic and Renal Impairment

- For patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic and/or moderate (CrCl 30-50 mL/min) renal impairment, a reduction in starting dose is recommended

Please see accompanying brief summary of Halaven full Prescribing Information.

References: 1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology™: Breast Cancer.* Version 2.2011. http:NCCN.org. Published January 5, 2011. Accessed October 18, 2011.† **2.** Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2010. **3.** Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. *J Clin Oncol.* 2010;28(11):1958-1962. **4.** Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344(11):783-792. **5.** Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355(26):2733-2743. **6.** von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2–positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 study. *J Clin Oncol.* 2009;27(12):1999-2006. **7.** Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357(26):2666-2676. **8.** Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). *J Clin Oncol.* 2009;27(suppl; abstr 1005). **9.** Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol.* 2010;28(20):3256-3263. **10.** Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol.* 2005;23(24):5542-5551. **11.** Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet.* 2011;377(9769):914-923.

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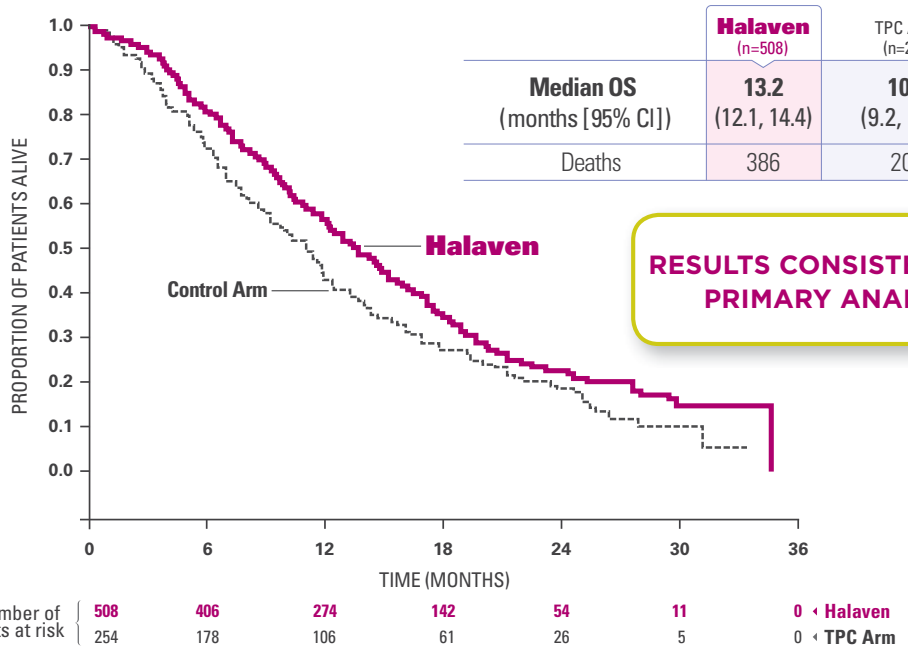
The Phase III EMBRACE* trial met its primary endpoint of overall survival (OS)[2,11]

- In the primary analysis, conducted when ~50% of events (deaths) had been observed, median OS with Halaven vs Control Arm (**T**reatment of **P**hysician's **C**hoice [TPC]) was 13.1 months (95% CI: 11.8, 14.3) vs 10.6 months (95% CI: 9.3, 12.5), HR=0.81 (95% CI: 0.66, 0.99) (*P*=0.041)†[2,11]

UPDATED OVERALL SURVIVAL ANALYSIS (UNPLANNED)†[2]



	Halaven (n=508)	TPC Arm (n=254)
Median OS (months [95% CI])	**13.2** (12.1, 14.4)	**10.6** (9.2, 12.0)
Deaths	386	203

RESULTS CONSISTENT WITH PRIMARY ANALYSIS[2]

Results from an updated, unplanned survival analysis of the Phase III, open-label, multicenter, multinational EMBRACE trial of Halaven vs TPC in patients with MBC (N=762). The primary endpoint was OS. Patients were randomized (2:1) to receive either Halaven 1.4 mg/m^2 IV for 2 to 5 minutes on Days 1 and 8 of a 21-day cycle, or any single-agent therapy, selected prior to randomization. At baseline, all patients had received ≥2 prior chemotherapeutic regimens for metastatic disease and demonstrated disease progression within 6 months of their last chemotherapeutic regimen. All patients received prior anthracycline- and taxane-based chemotherapy, unless contraindicated. Therapies in the TPC Arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxanes [included paclitaxel, docetaxel, nab-paclitaxel, and ixabepilone], 9% anthracyclines, 10% other chemotherapy), and 3% hormonal therapy.[2,11]

CI=confidence interval; HR=hazard ratio.
*EMBRACE=**E**isai **M**etastatic **Br**east Cancer Study **A**ssessing Physician's **C**hoice vs **E**7389 (Eribulin).
†Conducted in the intent-to-treat (ITT) population.

Halaven: Quick administration

- 2- to 5-minute intravenous infusion on Days 1 and 8 of a 21-day cycle[2]

Halaven: Safety profile

- Studied in the Phase III EMBRACE trial[2]

Most Common Adverse Reactions

- Most common adverse reactions (≥25%) reported in patients receiving Halaven were neutropenia (82%), anemia (58%), asthenia/fatigue (54%), alopecia (45%), peripheral neuropathy (35%), nausea (35%), and constipation (25%)
- The most common serious adverse reactions reported in patients receiving Halaven were febrile neutropenia (4%) and neutropenia (2%)
- Peripheral neuropathy (5%) was the most common adverse reaction resulting in discontinuation

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HALAVEN® (eribulin mesylate) Injection BRIEF SUMMARY – See package insert for full prescribing information.

2.2 Dose Modification

Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose delays

- Do not administer HALAVEN on Day 1 or Day 8 for any of the following:
  - ANC <1,000/mm^3
  - Platelets <75,000/mm^3
  - Grade 3 or 4 non-hematological toxicities.
- The Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at a reduced dose as set out in Table 1.
- Do not re-escalate HALAVEN dose after it has been reduced.

Table 1 Recommended Dose Reductions

Event Description	Recommended HALAVEN Dose
Permanently reduce the 1.4 mg/m^2 HALAVEN dose for any of the following:	1.1 mg/m^2
ANC <500/mm^3 for >7 days	
ANC <1,000 /mm^3 with fever or infection	
Platelets <25,000/mm^3	
Platelets <50,000/mm^3 requiring transfusion	
Non-hematologic Grade 3 or 4 toxicities	
Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity	
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue HALAVEN

ANC = absolute neutrophil count.

Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Severe neutropenia (ANC <500/mm^3) lasting more than one week occurred in 12% (62/503) of patients in Study 1, leading to discontinuation in <1% of patients. Patients with alanine aminotransferase or aspartate aminotransferase >3 × ULN (upper limit of normal) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin >1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of HALAVEN and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days. Clinical studies of HALAVEN did not include patients with baseline neutrophil counts below 1,500/mm^3.

5.2 Peripheral Neuropathy

Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients in Study 1. Peripheral neuropathy was the most common toxicity leading to discontinuation of HALAVEN (5% of patients; 24/503). Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

5.3 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

5.4 QT Prolongation

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.

6 ADVERSE REACTIONS

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

• Neutropenia • Peripheral neuropathy • QT interval prolongation

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of HALAVEN was peripheral neuropathy (5%).

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

In clinical trials, HALAVEN has been administered to 1,222 patients with multiple tumor types, including 240 patients exposed to HALAVEN for 6 months or longer. The majority of the 1,222 patients were women (82%) with a median age of 58 years (range: 26 to 91 years). The racial and ethnic distribution was Caucasian (83%), Black (5%), Asian (2%), and other (5%).

The adverse reactions described in Table 2 were identified in 750 patients treated in Study 1. In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 503 patients received HALAVEN, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%)] or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2 Adverse Reactions with a Per-Patient Incidence of at Least 10% in Study 1

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and Lymphatic System Disorders[a]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[b]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders and administrative site conditions				
Asthenia/Fatigue	54%	10%	40%	11%
Mucosal inflammation	9%	1%	10%	2%
Pyrexia	21%	<1%	13%	<1%
Gastrointestinal disorders				
Constipation	25%	1%	21%	1%
Diarrhea	18%	0	18%	0
Nausea	35%	1%	28%	3%
Vomiting	18%	1%	18%	1%
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Investigations				
Weight decreased	21%	1%	14%	<1%
Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Cough	14%	0	9%	0
Dyspnea	16%	4%	13%	4%
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[c]	10%	NA[c]

Table 2 (cont'd)

MedDRA ver 10.0	HALAVEN (n=503)		Control Group (n=247)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Infections and Infestations				
Urinary Tract Infection	10%	1%	5%	0

[a]Based upon laboratory data.

[b]Includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.

[c]Not applicable; (grading system does not specify > Grade 2 for alopecia).

Cytopenias: Grade 3 neutropenia occurred in 28% (143/503) of patients who received HALAVEN in Study 1, and 29% (144/503) of patients experienced Grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients and discontinuation was required in <1% of patients. The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (<500/mm^3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte–macrophage colony-stimulating factor) was used in 19% of patients who received HALAVEN.

Peripheral Neuropathy: In Study 1, 17% of enrolled patients had Grade 1 peripheral neuropathy and 3% of patients had Grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received HALAVEN. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade and 2% (8/503) of patients developed Grade 3 peripheral motor neuropathy.

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of HALAVEN-treated patients experienced Grade 2 or greater ALT elevation. One HALAVEN-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to HALAVEN.

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group:

- **Eye Disorders:** increased lacrimation
- **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth
- **General Disorders and Administration Site Conditions:** peripheral edema
- **Infections and Infestations:** upper respiratory tract infection
- **Metabolism and Nutrition Disorders:** hypokalemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness
- **Nervous System Disorders:** dysgeusia, dizziness
- **Psychiatric Disorders:** insomnia, depression
- **Skin and Subcutaneous Tissue Disorders:** rash

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category D

There are no adequate and well-controlled studies with HALAVEN in pregnant women. HALAVEN is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats that received eribulin mesylate at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In a developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area (mg/m^2). Increased abortion and severe external or soft tissue malformations were observed in offspring at doses 0.64 times the recommended human dose based on body surface area (mg/m^2), including the absence of a lower jaw, tongue, stomach and spleen. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at or above doses of 0.43 times the recommended human dose.

Maternal toxicity of eribulin mesylate was reported in rats at or above doses of 0.43 times the recommended human dose (mg/m^2), and included enlarged spleen, reduced maternal weight gain and decreased food consumption.

8.3 Nursing Mothers

It is not known whether HALAVEN is excreted into human milk. No studies in humans or animals were conducted to determine if HALAVEN is excreted into milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in human milk fed infants from HALAVEN, a decision should be made whether to discontinue nursing or to discontinue HALAVEN taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.

8.6 Hepatic Impairment

Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m^2 is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m^2 is recommended for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C).

8.7 Renal Impairment

For patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function. A lower starting dose of 1.1 mg/m^2 is recommended for patients with moderate renal impairment. The safety of HALAVEN was not studied in patients with severe renal impairment (CrCl <30 mL/min).

10 OVERDOSAGE

Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for HALAVEN overdose.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Hepatic Impairment

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=5) hepatic impairment. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 2.5-fold in patients with mild and moderate hepatic impairment, respectively. Administration of HALAVEN at a dose of 1.1 mg/m^2 to patients with mild hepatic impairment and 0.7 mg/m^2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m^2 to patients with normal hepatic function.

Renal Impairment

No formal PK trials were conducted with HALAVEN in patients with renal impairment. Available data suggests that geometric mean dose-normalized systemic exposure is similar for patients with mild renal impairment (CrCl 50-80 mL/min) relative to patients with normal renal function. However, for patients with moderate renal impairment (CrCl 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function.

12.6 Cardiac Electrophysiology

The effect of HALAVEN on the QTc interval was assessed in an open-label, uncontrolled, multicenter, single-arm dedicated QT trial. A total of 26 patients with solid tumors received 1.4 mg/m^2 of HALAVEN on Days 1 and 8 of a 21-day cycle. A delayed QTc prolongation was observed on Day 8, with no prolongation observed on Day 1. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.4 (19.5) ms.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies have not been conducted with eribulin mesylate.

Eribulin mesylate was not mutagenic in *in vitro* bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

The effects of HALAVEN on human fertility are unknown. Fertility studies have not been conducted with eribulin mesylate in humans or animals. However, nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (mg/m^2) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m^2) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs given 0.64 times the recommended human dose (mg/m^2) weekly for 3 out of 5 weeks, repeated for 6 cycles.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- Advise patients to contact their health care provider for a fever of 100.5°F or greater or other signs or symptoms of infection such as chills, cough, or burning or pain on urination.
- Advise women of childbearing potential to avoid pregnancy and to use effective contraception during treatment with HALAVEN.

Eisai

Clinical Care Pathways
(continued from SP161)

and cost and can only be achieved by changes in physician behavior.

Compliance Monitoring Challenges and Results

The physician-knows-best approach provided challenges in compliance monitoring. To accurately assess treatment practices, the pathways program relied on data provided by BCBSM, captured through eobONE, or submitted directly by physicians in paper-based forms. Even with this tripartite approach, data capture was incomplete. Revenue codes submitted from hospital settings lacked sufficient detail on the type of treatments received. The full treatment picture for patients with multiple insurance plans was incomplete in the BCBSM data. Data from eobONE included all treatments submitted for reimbursement but lacked information on therapies that were self-administered and obtained by the patient through a pharmacy (eg, oral chemotherapies). Fax data received from physicians provided clarity on oral treatments but were limited by accuracy and completeness of input.

Summary

Although we continue to seek solutions to the conundrum of savings measurements in our programs, we believe that behavior change represents an appropriate surrogate that allows payers and providers to collaborate to bend the cost curve while improving quality in cancer care. The costs of cancer care are rapidly increasing and will soon be unsustainable.[1] Many healthcare systems are considering clinical pathways as a method to reduce unnecessary and costly treatment variation; however, the extent to which they can effectively do so relies heavily on design and implementation. Some oncologists have embraced pathways whereas others have resisted, usually as a result of perceived challenges to their autonomy and decision-making ability.[13-15]

For effective cancer care pathway programs, developing parties and oncology groups must collaborate. Oncologists should participate in the development of pathways they believe reflect appropriate care in their community. Moreover, pathway compliance must be monitored and physician behavior validated to achieve success and best practice medicine. Feedback with continual discussions should be provided to participating physicians to keep pathways maintained and current. In addition, the mechanism to collect and disseminate this information must be a seamless, effortless process that healthcare providers perceive as unobtrusive to their office work flow. This article outlined a collaborative model between providers and payers to implement a clinical care pathway program that drives physician behavior. Compliance levels increased from pre- to post-pathways launch and were driven in part by reduced variation in treatment. The program provided standardized treatment options but allowed participating physicians the flexibility to use their own judgment for difficult treatment decisions. Putting this level of control into the physicians' hands played a significant role in the high level of physician participation and compliance.

Creating a standardized approach to patient care through clinical care pathways enables measurement of participation and compliance as well as treatment practices. Additional end points from this database—such as numbers of lines of treatment, brand to generic conversions, use of biologics in multiple lines of therapy, molecular diagnostics to govern care, and acute care interventions in ED and hospital—will be measured in future studies. The results of these analyses will help drive future program design. **EBO**

Moreover, pathway compliance must be monitored and physician behavior validated to achieve success and best practice medicine. Feedback with continual discussions should be provided to participating physicians to keep pathways maintained and current.

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Author Affiliations: From Cardinal Health (BAF, JC, SM, JAS), P4 Healthcare, Dublin, OH; Blue Cross Blue Shield of Michigan (JL, JG, DS, TR, TL, TR), Detroit, MI; Physician Resource Management (PS), Novi, MI.

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Address correspondence to: Bruce A. Feinberg, DO, 7000 Cardinal Place, Dublin, OH 43017; e-mail: bruce.feinberg@cardinalhealth.com.

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THE AMERICAN JOURNAL OF MANAGED CARE

Trends in the *2012 Eisai Oncology Digest*: Counseling and Communication of Cancer Treatment

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Introduction

This is the second article in a 3-part series discussing results from a recent survey of 418 patients with cancer.[1] Patient demographics and details on cancer types and treatment were published in the first article of this series.[2] This article discusses patients' perceptions of the communication and counseling they received during cancer therapy.

It is important for healthcare professionals to communicate effectively with patients in a manner that ensures treatment efficacy, safety, and compliance. Professional organizations, such as the Commission on Cancer (CoC)[3] of the American College of Surgeons and the American Society of Clinical Oncologists (ASCO),[4] continue to call for proper treatment summaries and other forms of communication to be part of treatment plans. Effective communication and counseling should be considered an essential part of cancer treatment to ensure that patients adhere to, and are part of, the treatment plan.

Because cancer can impact patients of all ages, it is imperative for healthcare professionals to know from where patients are getting information and with whom they are sharing that information. Moreover, technology has increased the ways in which healthcare information is communicated. This article highlights patient communication preferences and describes how they have changed in recent years.

Treatment Coordination

An essential part of cancer therapy is coordination of patient care. A variety of people were identified as the primary coordinator of care, including surgeons, oncologists, family members, nursing staff, family physicians, and patient navigators. Of those, patients most often identified surgeons and oncologists/hematologists as the coordinator; patient navigators (eg, social workers, nurse case managers) were identified least often.

It should be noted that the patient navigator is a relatively new role. In 2012, however, the CoC added a new accreditation standard requiring cancer programs to phase in a process for patient navigation by 2015.[3] Therefore, patient navigators will likely increase in prominence over time. Also, patient-centered medical homes, specific to oncology, are embracing the use of a patient navigator–type position to facilitate care coordination and patient involvement.[5,6]

One further interesting observation from the survey was that preferences were different based on sex and age (Table 1). Men and older patients tended to rely on traditional healthcare providers like family physicians for information, whereas women and younger patients were more inclined to get information from patient navigators and oncology nurses.

Treatment Counseling

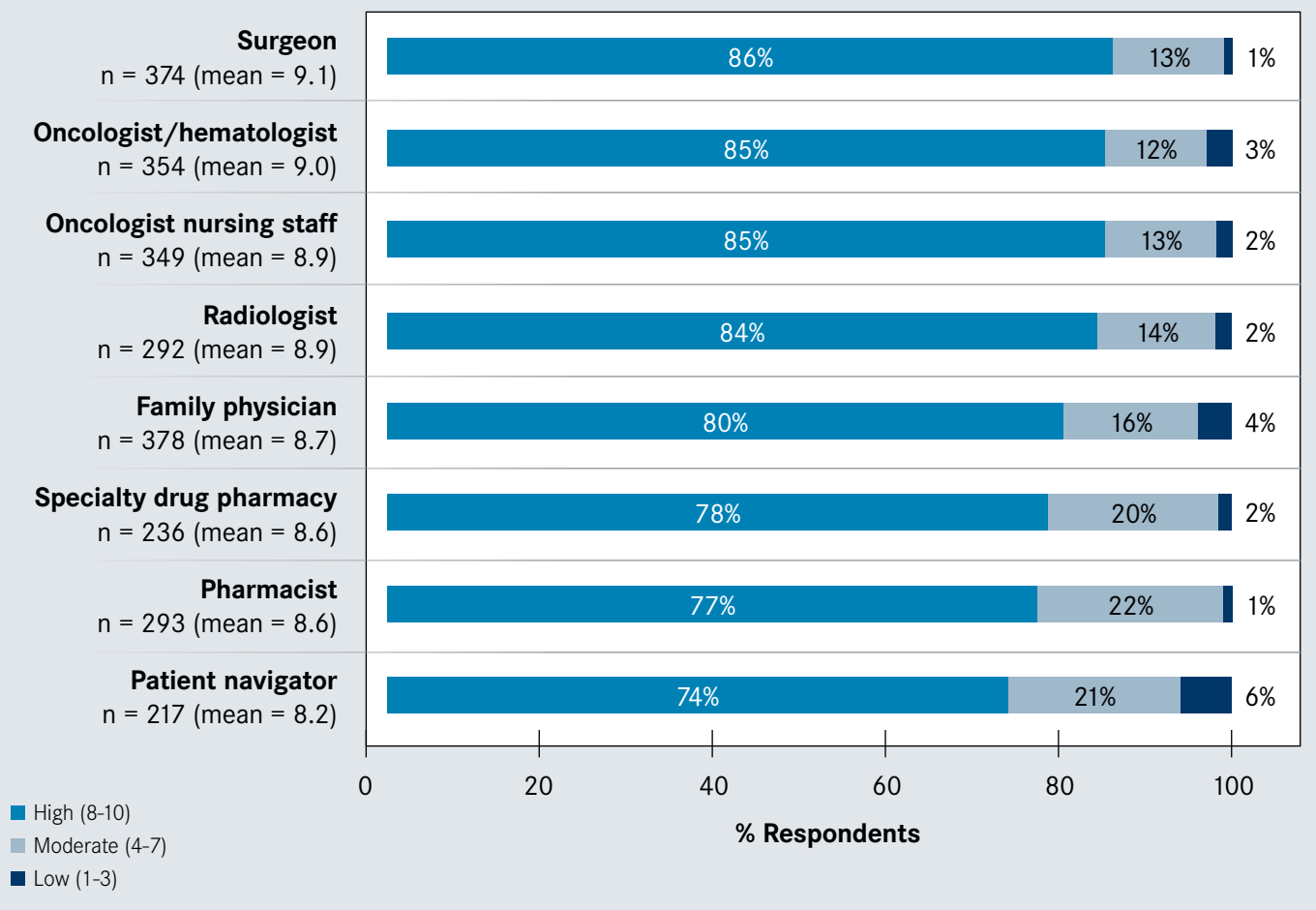
Patients were asked which person on their care team provided treatment counseling, and their level of satisfaction. As shown in Figure 1, most patients gave moderate or high scores of satisfaction to the healthcare professional who provided treatment

Table 1. Main Care Coordinator in the Survey Population

Care Coordinator	Age, y			Sex	
	21-54	55-64	65-84	Male	Female
	% by Age			% by Sex	
Surgeon (n = 137)	29	33	39	47	53
Oncologist (n = 130)	31	33	36	43	57
Family/spouse (n = 109)	39	28	34	51	49
Yourself (n = 95)	30	41	30	35	65[a]
Oncologist's nursing staff (n = 93)	43[a]	32	25	30	70[a]
Family physician (n = 84)	31	31	38	57	43
Patient navigator (n = 43)	54[a]	30	16	33	67

[a]Denotes a statistically meaningful difference between columns/rows (+/- 10% at the 95% confidence level).

Figure 1. Patient Satisfaction With Counseling



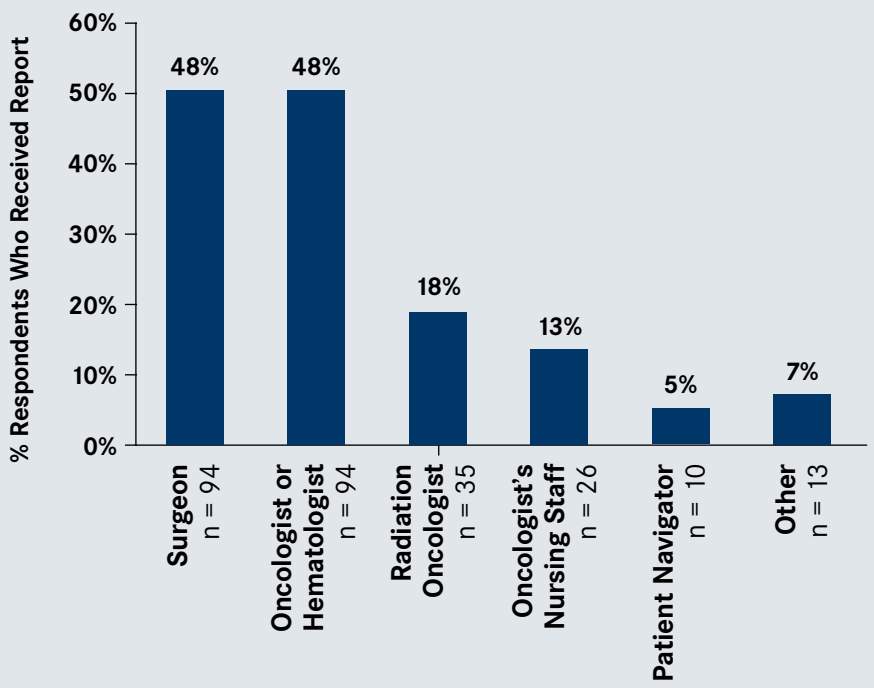
counseling. Surgeons and oncologists received the highest scores for satisfaction.

The list of topics covered during counseling was extensive. Almost all patients (95%) stated that they received information about follow-up care. Most patients also received counseling about pain management (65%), nutrition/exercise (62%), palliative care (51%), and chemotherapy plans (51%). Less than half of the respondents were provided counseling or information on life expectancy, support for family/caregivers, clinical trials, will planning, financial planning, or hospice care.

Table 2. Percentage of Patients Receiving a Cancer Treatment Summary or Follow-up Report

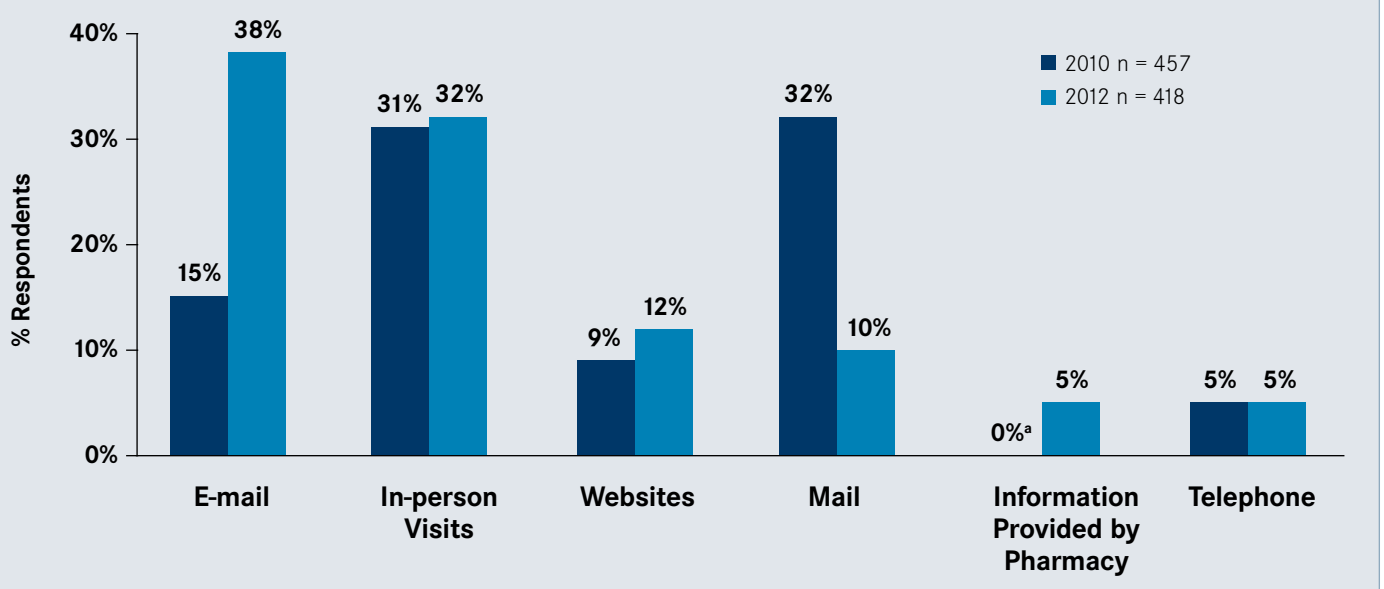
Answer, %	Total (n = 418)	Currently Have Cancer (n = 151)	Cancer Free (n = 267)
Yes (n = 197)	47	49	46
No (n = 189)	45	47	44
Not sure/can't remember (n = 32)	8	4	10

Figure 2. Providers of Treatment Summary and Follow-up Reports[a]



[a]Percentages will add up to greater than 100% due to multiple answers.

Figure 3. Preferred Method of Communication[8]



[a]Not asked in 2010 survey.

Cancer Treatment Reports

Given the CoC's accreditation standard requiring cancer programs to phase in "a process to disseminate a comprehensive care summary and follow-up plan to patients with cancer who are completing cancer treatment,"[3] and the plethora of templates available for treatment planning,[4] patients were asked if they had received a treatment summary or transition plan. As shown in Table 2, only half of respondents received such counseling. This was quite surprising, especially in patients who have completed treatment (ie, the cancer-free group).

Of the 197 patients who received a treatment summary or follow-up report, most obtained the report(s) from their surgeon (48%) or oncologist/hematologist (48%) (Figure 2). Surprisingly, only 18% of reports were communicated by the radiation oncologist, even though more respondents underwent radiation therapy (51%) than chemotherapy (41%). The American Medical Association's (AMA's) Physician Consortium for Performance Improvement developed 2 quality performance measures to document whether the treatment summary was communicated to the patient by the medical oncologist or radiation oncologist, respectively.[7]

Written treatment summaries were well utilized. Most patients (96%) shared the report with other healthcare providers. Summary reports were commonly shared with the patients' family physician (77% of patients) or with other specialists (57%). Sharing the report with a family member was also common (61%), but the reports were rarely communicated to the patient navigator (5%) or pharmacist (5%).

Sources for Health Information

The survey also asked patients how they obtained most of their health information. Most patients (83%) relied on their doctor/doctor's office as their main source of healthcare information. The Internet was the second most common source of healthcare information, with 62% of respondents reporting its use. Common websites for information included WebMD (36%), the Mayo Clinic (13%), the American Cancer Society (12%), and the Leukemia & Lymphoma Society (4%). Survey respondents indicated that e-mail was the preferred method for communication of health information; this is in sharp contrast to 2 years ago, when postal mail was frequently selected (Figure 3).[8]

Conclusion

Results from this survey indicate that surgeons and oncologists are the most likely healthcare professionals to provide counseling and treatment summaries to patients. While counseling was commonly practiced, the required treatment summary report at the end of therapy was only given to half of the patients who participated in this survey. It remains to be seen whether the advent of patient navigators improves patient communication and reporting. However, there appears to be room for improvement based on recommendations by the CoC and the AMA. The last article in this series will examine insurance and cost obstacles in cancer treatment. **EBO**

To request an electronic copy of the 2012 *Eisai Oncology Digest*, please e-mail your request to: eisaioncologydigest@eisai.com.

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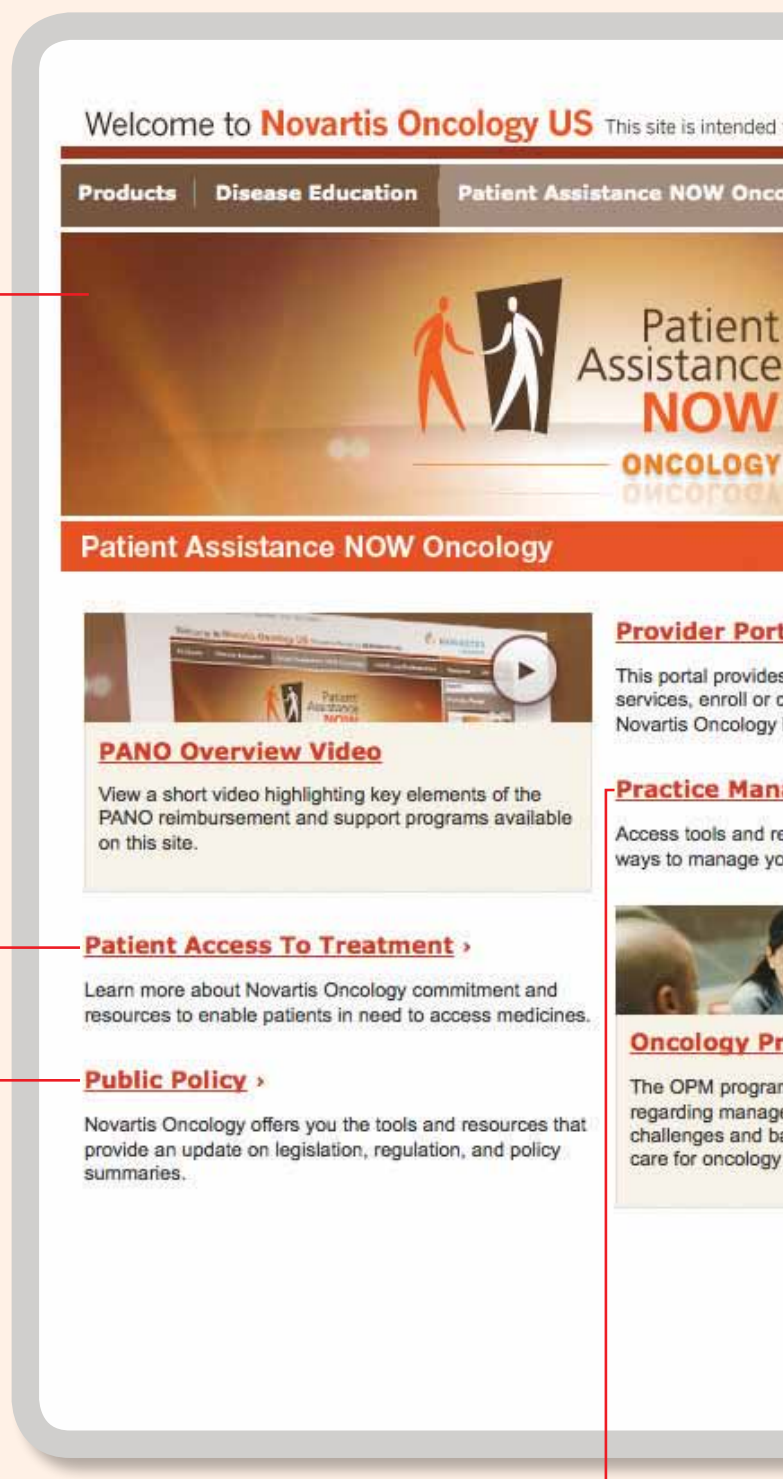

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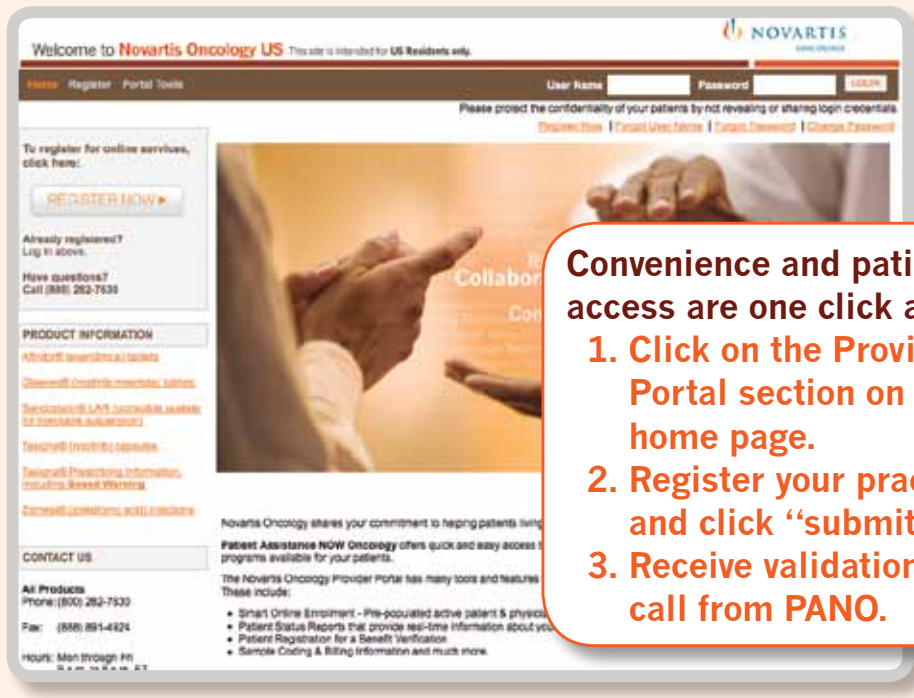

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The Keys to Obtaining Best Value in Non–Small Cell Lung Cancer

Marj P. Zimmerman, MS, BSPharm, RPh; and Stanton R. Mehr

Lung cancer remains a most difficult cancer to treat, because of its seemingly intractable progression and the fact that it is usually diagnosed at a late stage. The prevalence of lung cancer, which is directly related to the incidence of tobacco smoking and unacceptable levels of air pollution, continues to challenge scientists and health economists worldwide.

A Quarter-Million Americans to Be Diagnosed This Year

Lung cancer accounts for 14% of all new cases of cancer today, and of the many forms of lung cancer, non–small cell lung cancer (NSCLC) is the most prevalent, accounting for 85% to 90% of all lung cancer cases.[1] Of patients with NSCLC, adenocarcinomas comprise the greatest proportion (40%), followed by squamous cell tumors (up to 30%) and large-cell tumors (up to 15%), with miscellaneous types comprising the remainder.[1]

According to the American Cancer Society's latest estimates, lung cancer (all forms) will be diagnosed in 226,000 men and women in 2012, and will result in more than 160,000 deaths—this represents 28% of all yearly cancer deaths.[1]

If diagnosed at the earliest stage (1A), the 5-year survival associated with NSCLC is 49%. Those patients whose lung cancer is classified as stage 2 at the time they are diagnosed have a 30% 5-year survival, and this figure drops precipitously with more advanced disease. Despite major gains in our understanding of how NSCLC develops and spreads, survival gains have been slow and incremental. The best chance of a cure is still surgery, which is most effective in the earliest stages of NSCLC.[1]

Multiple Treatments Available and a Full Pipeline of Targets Await

In an effort to gain a foothold in the war on lung cancer, many approaches to treatment of NSCLC have been tried over the last 2 decades. This has resulted in complex treatment algorithms, as reflected in the National Comprehensive Cancer Network guidelines. Treatment considerations can include surgical resection (with or without preoperative chemoradiation) with lymph-node dissection or sampling and followed by adjuvant treatment (typically radiotherapy and/or chemotherapy [often cisplatin and vinorelbine or etoposide]). For patients with inoperable or recurrent disease, first-line chemotherapy may consist of double treatment (usually cisplatin and another agent); bevacizumab plus chemotherapy; cisplatin/pemetrexed; or a combination of cetuximab, vinorelbine, and cisplatin, all of which is partly based on the specific NSCLC subtype (ie, adenocarcinoma vs squamous cell or large cell). Second-line chemotherapy may add crizotinib, docetaxel, erlotinib, or gemcitabine to the mix of options. In addition to the medications already mentioned, patients with advanced or metastatic NSCLC may also receive carboplatin, ifosfamide, irinotecan, or mitomycin. Treatment recommendations will vary based on a finding of adenocarcinoma or squamous cell carcinoma and on the patient's performance status rating.[2] Recent emphasis has been placed on identifying patients who overexpress epidermal growth factor receptor (EGFR). In patients with *EGFR* overexpression and recurrent or advanced disease, targeted monotherapy with erlotinib, a tyrosine-kinase inhibitor, has been found to offer a 2-month survival advantage over patients receiving placebo.[3] Cetuximab, the latest EGFR inhibitor used for NSCLC, works by binding to the extracellular domain of EGFR, blocking activation of the EGFR pathway.

Table. Therapeutic Vaccines and Immunomodulators for NSCLC in Later-Stage Trials

Drug	Type	Company	Phase
CimaVax-EGF	Vaccine	Cuba	III[a]
GSK1572932A	Immune modulator	GlaxoSmithKline plc	III
GV1001	Vaccine	KAEL-GemVax	III
HyperAcute Lung	Vaccine	NewLink Genetics Corp	II
Imprime PGG	Immune modulator	Biothera	II
Lucanix	Vaccine	NovaRx Corp	III
Monatanide IAS 51	Vaccine	SEPPIC	III
Racotumomab	Vaccine	RECOM BIO	III
Stimuvax	Vaccine	Oncothyreon	III
Talactoferrin	Immune system activator	Agennix, Inc	III
TG4010	Vaccine	Transgene	III

NSCLC indicates non-small cell lung cancer.
[a]Developed in Cuba, phase III trials under way (but regulatory approval has not been sought in the United States).
Source: Data from company websites and multiple news sources.

Newer treatments are needed to fight this tenacious cancer, as progress in increasing survival in NSCLC has been challenging. Some promise was seen with vascular-disruptive agents (eg, ASA404) and with other tyrosine-kinase inhibitors (eg, vandetanib and sorafenib), but the outcomes of these trials have been disappointing.[4] It may well be that medications such as these are effective in patients with a specific biomarker that has not yet been recognized—that is, some medications are awaiting identification of a patient subpopulation.

Studies of the use of immunotherapy and therapeutic vaccines in NSCLC have been encouraging. Interest in therapeutic vaccines, some of which are shown in the **Table**, has spread, and the promise of amplifying the body's own defenses is as tantalizing in NSCLC as it is in other cancers. One example is a vaccine called TG4010, which is being tested for use in patients with advanced-stage NSCLC. This vaccine stimulates the immune response of the body to attack the MUC1 protein, which kills the cancer cells.[5] Much of the discovery and investigational work on therapeutic vaccines for NSCLC is being done by smaller companies, with the eventual hope that they will find a marketing partner as clinical trials progress. However, the vaccines, like other modalities in NSCLC, are likely to be used with other therapies. For example, it may be optimal to use therapeutic vaccines in combination with antibodies to amplify the immune response.[6]

Optimizing the Value of Care in NSCLC

This incremental improvement in survival in NSCLC (especially overall survival) has placed payers between the proverbial rock and a hard place. Do they see value in the newer treatments (which are commonly more expensive than older platinum-based therapies),

while seeing a limited survival benefit for only a portion of patients? And, it is exceedingly difficult, from the health plan or insurer's perspective, to restrict cancer therapies shown to have even very limited clinical benefit.

The costs associated with NSCLC can be extensive. In patients with advanced NSCLC (stage IV disease), the average total cost of care was calculated to be $162,134 in a privately insured population, or $10,284 per patient per month. The newer agents (including pemetrexed, biologics, and tyrosine kinase inhibitors) cost an average $10,141 per patient per month (for the duration of their treatments).[7]

As newer agents have been introduced, the cost of treatment for NSCLC has risen. This is likely due to higher prices for new therapies in general and the prevalence of combination regimens in NSCLC. In 2005, the mean drug cost of second-line therapy was $5939; in 2009, it increased to $10,057.[8]

Therefore, payers need to obtain the best value they can from available treatments in NSCLC. New, more effective agents are expected to become available, but one way to increase the value of existing therapies is to better match patients with treatments. Two studies vividly illustrate the point: In one US study of patients receiving second-line therapy for NSCLC, researchers could find no difference in survival outcomes (overall or progression-free survival) among those taking erlotinib, docetaxel, or pemetrexed.[9] However, in an Italian study, patients with NSCLC who did not express the *EGFR* mutation had significantly worse progression-free survival (PFS) when they were given the EGFR inhibitor erlotinib compared with docetaxel as second-line therapy.[10] Furthermore, in a phase III study of an investigational EGFR inhibitor (afatinib), an international team of researchers found a 6.7-month advantage in progression-free survival for patients with the *EGFR* mutation compared with pemetrexed and cisplatin as first-line therapy.[11] High levels of *ERCC1* overexpression can predict a poor response to platinum-based therapy, but high *RRM1* levels are predictive of resistance to gemcitabine-based therapy.[12] Furthermore, low expression of thymidylate synthase may correlate with higher PFS with pemetrexed in patients with adenocarcinoma-type NSCLC.[13]

Researchers are actively evaluating wide panels of serum biomarkers to better understand which therapies may be more effective in certain patients. For example, bevacizumab has been associated with some benefits in NSCLC, and researchers from Rush University in Chicago tested 72 biomarkers from the sera of 93 patients with advanced NSCLC. Of the patients receiving bevacizumab-containing regimens, those with higher serum levels of PDGF-AB/BB had significantly better PFS and overall survival (OS) than the others.[14]

Indeed, clinical investigations are under way to determine whether gene amplifications or mutations, involving such genes as *KRAS, ALK, FGFR1, DDR2*, and *PIK3CA*, to name a few, can predict who will benefit optimally from therapy and even determine which patients with NSCLC have a better prognosis.

Another potentially valuable asset of biomarker identification could be the mediation or avoidance of therapy-associated side effects, which can add significant costs. For example, the occurrence of chemotherapy-associated peripheral neuropathy resulted in $17,344 higher costs compared with those who did not experience peripheral neuropathy.[15]

An important consideration regarding the value of biomarker identification in NSCLC (as well as in most cancers) is the frequency with which the biomarkers appear in the disease. That is, the cost of biomarker identification depends on the cost of the assay to quantify its presence (and of course, the accuracy and sensitivity of the test) and the frequency with which the biomarker can be expected to appear.[16] To illustrate, if one were to screen for a biomarker like *ALK* at an assay cost of $1400 per person, but the biomarker is expected to appear in only 2% of the population, screening in all patients with advanced NSCLC for *ALK*, excluding treatment cost, would be $106,707 per quality-adjusted life-year (QALY). This can drop as low as $4756 per QALY if the biomarker occurs in 36% of patients with NSCLC.[16] Therefore, it makes the most sense to screen for high-frequency gene mutations or amplifications, assuming a treatment benefits a patient with the biomarker (or possibly works better in those without it).

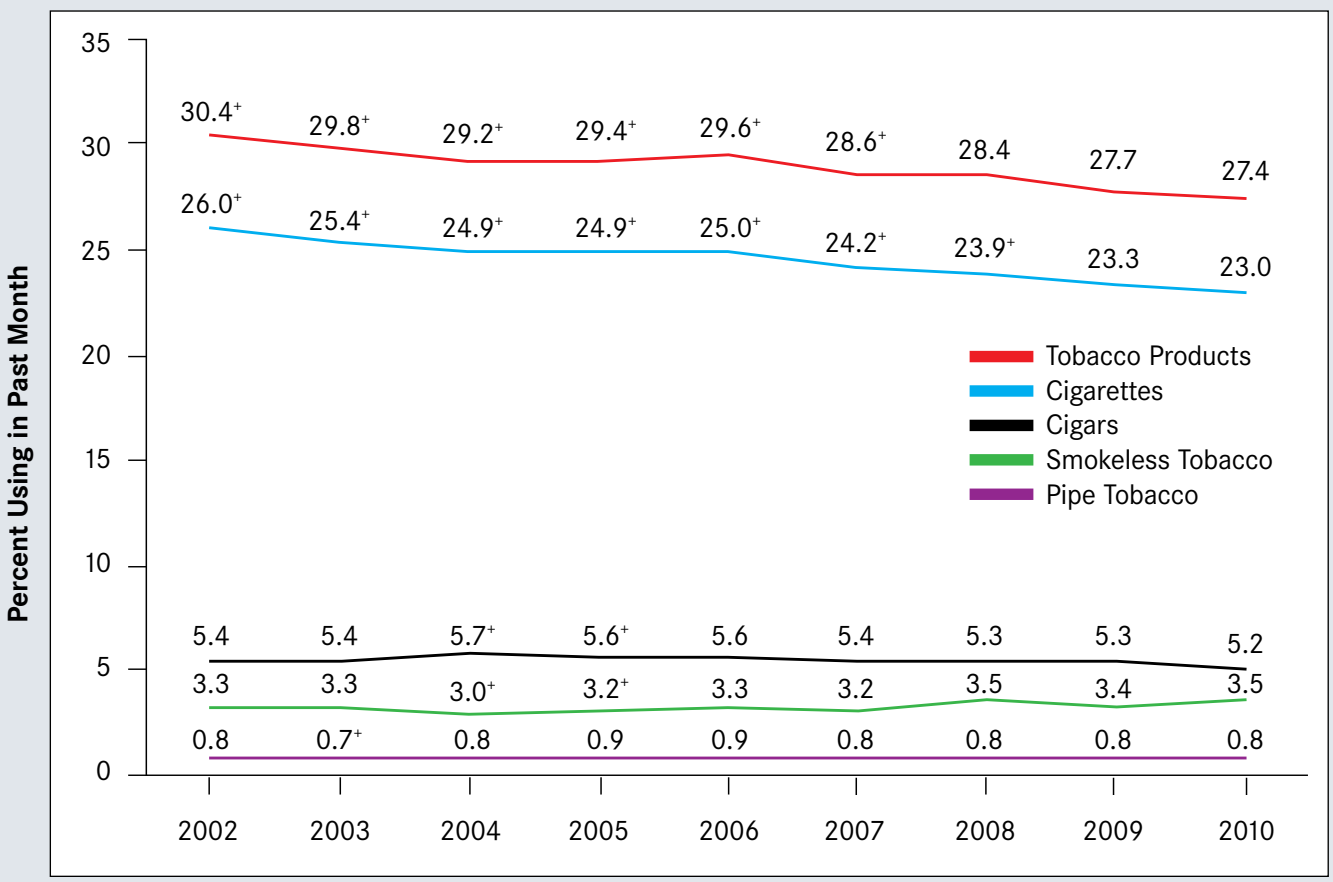
Other NSCLC Cost Drivers

Two definitive drivers of cost of NSCLC (or of lung cancer in general) are the prevalence of cigarette smoking and its diagnosis in relatively late stages. The vast majority of patients are diagnosed not in stage I, when surgery may be curative, but in stages III or IV, when survival is much lower.

Cigarette smoking (including chronic inhalation of secondhand smoke) is estimated to cause 85% to 90% of all lung cancers.[2] The remainder of cases are attributed to environmental factors, such as radon, radiation, or asbestos exposure, and diesel exhaust.[17] Cigarette smoking costs the nation $96 billion annually in direct medical expenditures and $97 billion in lost productivity.[18] According to an actuarial analysis, exposure to secondhand smoke results in over $10 billion annually in US health

If one were to screen for a biomarker like ALK at an assay cost of $1400 per person, but the biomarker is expected to appear in only 2% of the population, screening in all patients with advanced NSCLC for ALK, excluding treatment cost, would be $106,707 per quality-adjusted life-year.

Figure. Past Month Tobacco Use Among Persons 12 Years or Older: 2002-2010



+ indicates that the difference between this estimate and the 2010 estimate is statistically significant at the .05 level.
Source: Reprinted with permission from Substance Abuse and Mental Health Services Administration, Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-41, HHS Publication No. (SMA) 11-4658. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011. http://www.samhsa.gov/data/NSDUH/2k10Results/Web/HTML/2k10Results.htm#Ch4. Accessed July 1, 2012.

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Payer Perspective

Interview with Allan J. Chernov, MD

EBO: **How does Blue Cross and Blue Shield of Texas determine the value of the targeted lung cancer therapies? Are you using a Pharmacy & Therapeutics or technology assessment committee?**

Dr Chernov: Primarily, we use our medical policy process, which is what we call the formal written documents of benefit coverage based on technology assessment. When technologies are drug related, we bring in pharmacy experts to help us make a coverage determination. Technology assessment tends to be easier with drugs, because we can use FDA approval as a reference point for a specific indication. We also evaluate requests—on a case-by-case basis—for off-label uses of these drugs.

EBO: **Does your plan require that patients must undergo biomarker testing or companion tests before receiving targeted agents, such as Erbitux (cetuximab)? Or, is it sort of really up to the doctors' discretion?**

Dr Chernov: This raises 2 questions: (1) Do we pay for those kinds of tests? and (2) Do the tests provide information that will improve outcomes? We evaluate biomarker tests on a separate basis. If we decide that a test will/can help improve patient management, we leave it up to the doctors to decide if it's appropriate for a specific patient.

We have very few prior authorization requirements. We find that when expensive procedures, products, and therapies are being contemplated, physicians tend to ask us to do pre-service review for medical necessity. This tends to work out best for doctors, their patients, and—in a way—for us, because if you can settle the medical necessity for coverage of a service before it is performed and hits our claim system, it is easier to manage. We get many voluntary requests even though we have very few prior authorization requirements.

Would we require a test as a condition for prescribing a drug? It is certainly possible that if the evidence is strong enough we would want to couple coverage for an extremely expensive chemotherapeutic agent with results of a biomarker test. I suspect that as the validity and value of biomarkers emerge for a variety of drugs, we may consider requiring a positive test as a condition of coverage for a specific drug.

EBO: **As the availability of biomarker or companion tests become increasingly available, would you consider developing a specific technology assessment process just for them? Or, would these decisions be handled through existing processes?**

Dr Chernov: The basic principles of technology evaluation apply here, too. We gather the evidence, we look at the published literature, and we look at the clinical impact. The biggest question we try to answer with any new technology is, "So what?" We want to pay for things that make a difference. Unfortunately, it takes time for that evidence to emerge. How do you know that 1 year down the road, it will make a difference in the patient's outcome?

EBO: **New agents introduced to treat non–small cell lung cancer (NSCLC) have generally been associated with modest gains in survival. Does that make it more difficult to determine the value of these agents?**

Dr Chernov: This is a problem in difficult-to-treat cancers that are relatively common. We struggle to find more effective treatments, but the basic principles of evidence still apply. We look for high-quality, well-designed studies. Randomized clinical trials continue to be the gold standard. We are looking for a preponderance of evidence that use of a particular test or procedure is safe, is effective…and has favorable health outcomes.

"The decisions we make today are not for all time. They are based on the strength of today's evidence. That evidence may change next week, next month, and next year. We must be flexible enough to reevaluate our decisions at the appropriate time."

—Allan J. Chernov, MD
Medical Director
Healthcare Quality and Policy
Blue Cross and Blue Shield of Texas

So, I can say that if hypothetical Product X was found—in a sound study with good statistical power—to improve progression-free survival by 8 weeks in NSCLC, and that the product makes a significant difference in patient management, we would tend toward covering it.

We often see passionate proponents of a technology who feel it is just obvious that product X is wonderful. Our job is to be healthy skeptics: Show me! The basic premise is straightforward, but the execution is hard, because we're talking about very complex biological processes. We're talking about complex clinical scenarios. We're talking about things that are difficult to study in a blinded fashion. It may be almost impossible to find comparison groups.

Our job, however, is to do the best we can to evaluate the available evidence and then make a decision. But the available evidence may change tomorrow—a landmark study could be published next week, for example. The decisions we make today are not for all time. They are based on the strength of today's evidence. That evidence may change next week, next month, and next year. We must be flexible enough to reevaluate our decisions at the appropriate time.

EBO: **When considering outcomes from clinical oncology studies, what types of outcomes are you most interested in? Is it overall survival? Is it progression-free survival? Is it a combination, or something else?**

Dr Chernov: Those are the major, standard outcomes measures of success. That's what we look for.

EBO: **Does Blue Cross and Blue Shield of Texas focus specifically on tobacco-use prevention?**

Dr Chernov: We're constantly harping on it. It varies by type of benefit plan; for example, not every self-insured plan covers smoking cessation programs. However, we put our money where our mouth is, because we don't allow smoking in our building and there is a tobacco health insurance surcharge for our own employees who do smoke.

We have a strong commitment to combating smoking. I don't have the numbers, but my understanding is that the smoking rate of our employees has declined significantly with that very powerful incentive because it hits the pocketbook.

EBO: **In an ideal world, where money is no object, what tools would you employ to both prevent lung cancer and to diagnose it earlier?**

Dr Chernov: In the ideal setting, I think it is all about prevention—eliminating smoking and eliminating pollution containing carcinogens. That would have, by far, the most profound impact. Dealing with lung cancer is less about diagnosis and treatment. Once it is present, it is such a terrible, terrible disease. There may be some favorable data emerging about different imaging strategies, especially for high-risk patients. If those prove to be effective, we can certainly get on board and encourage it.

Dr Chernov is medical director, healthcare quality and policy, Blue Cross and Blue Shield of Texas.

expenditures.[19]

The Centers for Disease Control and Prevention found that in 2010, 19.3% of US adults smoked, which represented a decline of 3 million smokers from 2005.[20]

Prevention of NSCLC (or of lung cancer in general) is the favored approach to cost-effective public health; however, smoking in younger people has not decreased substantially. A total of 27.3% of adolescents, teens, and adults reported using tobacco products (including cigarettes, smokeless tobacco, cigars, and pipe tobacco) in 2010.[21] This percentage has declined slowly (**Figure**).

Lung cancer is most often diagnosed late in the disease course. Identification of cancers earlier in high-risk populations (eg, current smokers) could result in more patients diagnosed with stage 1 NSCLC, with greater chance for cure or longer survival. A recent investigation in the use of spiral-computed tomography (which delivers relatively low doses of radiation compared with conventional scanning) in high-risk patients was found to lower mortality but not necessarily costs.[22] This should not be surprising: As patients' tumors are diagnosed early in the course of disease, they may undergo more cycles of chemotherapy and additional therapies in an effort to arrest its spread than a patient whose tumor is identified in stage III or IV. However, the probability for curing these patients with early-stage NSCLC is still greater.

The screening rates for lung cancer are low, either by chest x-ray or low-dose computed tomography (CT) scan. A recent study revealed that only 2.5% of adults underwent a chest x-ray in 2010 specifically to screen for lung cancer, and 1.3% received a low-dose CT examination.[23]

Sniffing Out NSCLC

Patients with lung cancer have compounds (volatile organic compounds) in their exhaled breath that differ from those found in healthy individuals. These aromatic compounds are byproducts of the tumor's metabolism. Hence, these compounds could be used as a biomarker for distinguishing benign from malignant pulmonary nodules. Various tests for analyzing this exhaled air are being explored.

One unique idea is to use sniffer dogs; they have been used in other settings to take advantage of their keen olfactory system. Trials have been conducted that confirm sniffer dogs can identify lung cancer from a breath sample.[24]

Along these same lines, researchers at Israel's Technion Institute are moving forward with the Nano Artificial Nose, which may be able to "smell" lung cancer. It is a breath test that differentiates between benign and malignant pulmonary nodules as well as differentiating between small-cell lung cancer and NSCLC. Some evidence shows that it is also able to identify early cancer from more advanced disease.[25] Early stage trials demonstrate an accuracy of 80% to 90% in differentiating benign from malignant disease. It also demonstrated 90% accuracy in differentiating the 2 types of cancer as well as the progression of the disease.[26]

Knocking On (or Breaking Down) the Door of Progress

Hope remains that the relatively small gains we make with the completion of each new research study will lead to large gains in prevention and survival in the near future. Perhaps the next 5 years will be key to unlocking the secrets of effectively treating NSCLC.

As in most cancers, prevention represents the best value by far in NSCLC. Earliest possible diagnosis, which offers the best chance for a long remission or cure, can only occur with better compliance with screening guidelines and the use of new diagnostic methods. In terms of active treatment, better targeting of existing, expensive biopharmaceuticals and the introduction of new and novel pipeline products hold the keys to better clinical results and value.

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As in most cancers, prevention represents the best value by far in NSCLC. Earliest possible diagnosis, which offers the best chance for a long remission or cure, can only occur with better compliance with screening guidelines and the use of new diagnostic methods.

Crizotinib Active in ALK-Positive Pediatric Cancers

By Silas Inman

Targeting the *ALK* gene with the oral agent crizotinib (Xalkori) slowed or eliminated signs of tumor growth in pediatric patients with aggressive forms of neuroblastoma, anaplastic large cell lymphoma (ALCL), and inflammatory myofibroblastic tumors (IMTs), according to the results of a phase I study. The research was presented at a press conference held in advance of ASCO 2012.

Crizotinib is a small-molecule inhibitor of *ALK* and *c-Met*, and is FDA approved for adults with locally advanced, non–small cell lung cancer that is *ALK*-positive.

The 3 pediatric cancers examined in the trial are associated with mutations in the *ALK* gene, thus making them susceptible to *ALK* inhibition. ALCL, a type of non-Hodgkin lymphoma, harbors an *ALK* mutation in approximately 80% to 95% of tumors. Additionally, half of IMTs and 14% of neuroblastomas are known to contain *ALK* rearrangements.

A total of 70 children with refractory solid tumors and ALCL were enrolled in the dose escalation and pharmacokinetic trial, but only 42 were evaluable. Patients received one of 6 doses of crizotinib twice daily. Not all participants were required to harbor a known *ALK* mutation; as such, 19 patients in the neuroblastoma arm had an unknown *ALK* status.

The most impressive findings from the trial came in the ALCL arm. These 8 patients all had an *ALK* mutation and were heavily pretreated, with 88% (n = 7) experiencing a complete response to treatment. Patients remained on treatment for as long as 18 months.

"Our trial shows that crizotinib appears to have a high degree of activity in children with anaplastic large cell lymphoma, the majority of which are driven by the *ALK* oncogene," said lead author, Yael Mossé, MD, from The Children's Hospital of Philadelphia, Pennsylvania, who spoke at the ASCO press conference. "A larger anaplastic large cell lymphoma trial is currently in development to move this therapy upfront for newly diagnosed patients."


Yael Mossé, MD

Among the 7 patients with IMTs who were enrolled in the trial, most benefited, with results ranging from tumor shrinkage to complete tumor regression. Responses have lasted for up to 2 years, and all patients are still receiving therapy. No available anticancer agents have previously been found to be effective in this disease.

Two of the 27 patients with neuroblastoma had a complete response, and 8 had stable disease. Among neuroblastoma patients with an *ALK* abnormality, 2 of 8 experienced a complete response. Responders have remained on therapy for 9 months to more than 2 years without progression.

Patients with neuroblastoma treated with higher doses of crizotinib experienced demonstrable results. In some cases, these patients received 280 mg/m^2 of crizotinib twice daily, or approximately twice the recommended adult dosage. The researchers speculated that some neuroblastoma patients with known *ALK* mutations did not respond to treatment because they received lower doses of the drug.

"This story is really a glimpse at the new paradigm for our understanding of cancer and for drug development," said Michael Link, MD, outgoing ASCO president. "We now understand that it is not sufficient to identify a tumor based on the histology or the organ of origin, as we did traditionally. Tumors are heterogeneous, and we need to understand the particular molecular driver of the tumor to select appropriate therapy."

The Children's Oncology Group is developing a phase III trial to test crizotinib in *ALK*-positive children with ALCL. Additionally, separate phase II trials are planned to further investigate *ALK* inhibition in neuroblastoma and IMT. **EBO**

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Study Supports Feasibility of Routine Molecular Screening of NSCLC in Community Setting

By Ben Leach

Widespread molecular screening of non–small cell lung cancer (NSCLC) is feasible and can be performed outside of large academic medical centers, according to a multicenter study conducted in Germany that was presented at ASCO 2012.

One of the main drivers of doing such a study was to determine the effectiveness of biomarkers, since many effective treatments for patients with NSCLC are targeted therapies that are most effective in patients with certain mutations. For example, erlotinib (Tarceva) targets the *EGFR1* molecule, and crizotinib (Xalkori) targets the *ALK* gene.

"High quality molecular diagnostics and personalized treatment approaches present a significant benefit for patients," said Thomas Zander, MD, University Hospital in Cologne, Germany. "At last year's ASCO meeting, [studies of] large networks for molecular screening testing were presented, which consisted of several highly specialized comprehensive cancer centers spread all over the United States, but it meant that getting access to molecular diagnostics was only available to a minority of patients in this country."

In order to perform the study, researchers established the Network Genomic Medicine Lung Cancer molecular screening network, which included community hospitals in the Cologne-Bonn region of Germany, where approximately 2.5 million residents could potentially receive screening. Thus far, 1782 samples from residents of the Cologne-Bonn region have been collected. The authors estimate that this accounts for between 60% and 70% of all NSCLC samples in the region. Samples of tumors of patients with lung adenocarcinoma—the most common form of NSCLC—were screened for *ALK* translocations, mutations in *KRAS*, *EGFR*, *BRAF*, and *PIK3CA*, and amplification of *ERBB2*, while squamous cell samples were also screened for *FGFR1* amplifications. Of the Cologne-Bonn region samples, Dr Zander reported that approximately 77% of samples were suitable for molecular analysis.

Among the adenocarcinoma samples tested, *KRAS* mutations were detected in 32% of samples, *EGFR* mutations were detected in 13% of samples, *ALK* mutations in 3%, *BRAF* mutations in 2%, *PIK3CA* mutations in 2%, and *ERBB2* mutations in 2%. The researchers were able to note that in patients with the micropapillary subtype of adenocarcinoma, which accounted for between 30% and 32% of all adenocarcinoma cases identified, *EGFR* mutations were highly enriched. Out of the 500 squamous cell samples, 78 were found to have *FGFR1* amplifications. The researchers found that approximately 40% of all NSCLC samples collected had tractable lesions.


Thomas Zander, MD

The molecular screening findings helped the community hospitals determine patient treatment. For example, patients with *ALK* mutations were given crizotinib, and patients with EGFR mutations were given *EGFR*-TKI treatment. Additionally, patients were also referred to clinical trials that involved investigational treatments that correlated with the genetic profile of their tumors. **EBO**

Zander T, Heukamp LC, Bos MCA, et al. Regional screening network for characterization of the molecular epidemiology of non−small cell lung cancer (NSCLC) and implementation of personalized treatment. *J Clin Oncol*. 2012;30(suppl; abstr CRA10529).

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Mossé photo courtesy of Children's Hospital of Philadelphia

Oncology Leaders Praise Health Law Ruling—With Caveats

By Beth Fand Incollingo

Leaders in the oncology care and research communities largely applauded the recent US Supreme Court ruling that largely upheld the Affordable Care Act (ACA), mixing their optimism with a measure of caution over the impact of the contentious healthcare legislation on clinical practice.

Organizations dedicated to fighting cancer, including the American Society of Clinical Oncology (ASCO) and the American Cancer Society, called the decision a positive development for healthcare providers, researchers, and patients, despite concerns about the ramifications of continued political battling over the law.

ASCO President Sandra M. Swain, MD, medical director of the Washington Cancer Institute at MedStar Washington Hospital Center, said in a statement that the ACA offers a number of provisions that protect those who have cancer or are at risk for cancer.

These include free preventive screenings, the elimination of lifetime limits within health insurance plans, the opportunity for people to get private health insurance regardless of pre-existing conditions, and coverage for participation in clinical trials.

Earlier this year, ASCO said that the ACA had the potential to help reduce racial and economic disparities in cancer care.

"Although the Supreme Court's recent decision largely upheld the ACA, the national policy debate will continue over how to shape our healthcare system and provide Americans with access to health insurance in the future," Dr Swain said. "We urge Congress and other policymakers to recognize and protect the safeguards that are especially important to Americans who are facing life-threatening forms of cancer."

Maurie Markman, MD

Maurie Markman, MD, senior vice president for clinical affairs and national director for medical oncology at Cancer Treatment Centers of America in Philadelphia, believes that the law will have a positive impact, but that there are still questions about how the ACA will accommodate the continued rapid advancement of cancer research while controlling costs and providing care for more patients.

"I'm cautiously optimistic, but only as long as the discussion continues," said Dr Markman, who is editor-in-chief of *OncologyLive* magazine. "We have to constantly put patients in the forefront, improving their duration and quality of life. The worst would be to develop a bureaucracy that will prevent treatments from changing, but I know that won't happen—Americans won't allow it."

Andrew L. Pecora, MD, chief innovations officer and vice president of Cancer Services at John Theurer Cancer Center at Hackensack University Medical Center in New Jersey, also had a mixed view.

"It will be good all the way around to have people who don't have access to insurance get that access. It will increase access to life-extending and life-saving therapies," said Dr Pecora, who is editor-in-chief of *Oncology and Biotech News*. "The concern is that it's not clear how we're going to avoid falling into the trap that has occurred in Great Britain, where at the end of the day you have rationing of cancer therapies by small groups deciding based on economics whether someone should have access to something that's proven to be of benefit."

Andrew L. Pecora, MD

Moy et al discussed the anticipated effects of the ACA on the oncology community in an article that appeared in the 2012 Educational Book that ASCO presented in June at its annual meeting.

Their concerns about the law include a decrease in oncology provider participation in Medicaid as reimbursement levels drop; continued poor cancer outcomes among Medicaid patients; and the lack of a mandate for insurers to cover follow-up testing of abnormalities found in cancer screenings.

At the same time, the ACA holds promise, the authors wrote, because it will help close the Medicare "donut hole" gap in prescription drug coverage, important for those taking expensive oral cancer therapies; it will no longer require children who want hospice services to forgo curative services; it gives patients the right to a timely external appeal of coverage decisions; and it prevents insurers from denying coverage for clinical trial costs, which could ultimately increase minority participation in trials.

"Although the Supreme Court's recent decision largely upheld the ACA, the national policy debate will continue over how to shape our healthcare system and provide Americans with access to health insurance in the future."

—Sandra M. Swain, MD
Medical Director
Washington Cancer Institute
MedStar Washington Hospital Center

The American Association for Cancer Research also sees positives in the ACA.

According to the organization's website, the law calls for the establishment of the Patient Centered Outcomes Research Institute to compare the clinical effectiveness of treatments, which will help researchers focus on valuable therapies; grants to help speed the translation of basic scientific discoveries into treatments; and $15 billion over 10 years committed to cancer prevention.

Congress enacted the ACA in 2010 with the aim of increasing the number of Americans covered by health insurance and decreasing the cost of healthcare. Its constitutionality was challenged by 26 states, several individuals, and the National Federation of Independent Business, which argued that it was a costly, unconstitutional usurpation of individual rights.

In its 5-4 decision, the Supreme Court upheld the central tenet of the act: that individuals be required to buy their own health insurance if they are not insured by an employer or government program, and are not otherwise exempt from the rule.

Starting in 2014, the penalty for not complying will be a "shared responsibility payment" to the federal government; the court majority said they regarded that payment as a tax that Congress has the power to levy.

But the court struck down another core provision of the act, making it optional. That provision would have required states to accept additional federal funding and expand their Medicaid programs to cover the healthcare needs of adults with incomes up to 133% of the federal poverty level.

The court deemed the provision unconstitutional because states that did not comply would have faced the loss of all their federal Medicaid funding, amounting to a denial of their right to choose whether to accept grant funding and conditions for its use.

John R. Seffrin, PhD, chief executive officer of the American Cancer Society, praised the court's decision.

John R. Seffrin, PhD

"The ruling is a victory for people with cancer and their families nationwide, who for decades have been denied health coverage, charged far more than they can afford for life-saving care and forced to spend their life savings on necessary treatment, simply because they have a pre-existing condition," he said. **EBO**

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THE AMERICAN JOURNAL OF MANAGED CARE

How Can We Get Better Value in End-of-Life Care?

Stanton R. Mehr

Today's healthcare controversies often lead to explosive debates. Few discussions in healthcare can be as incendiary as those concerning the care provided at the end of life. Addressing the real systemic problems seen during a patient's last weeks is complicated by (1) erroneous, dire characterizations of health reform legislation resulting in "death panels"; (2) the latest evidence of the great health expenditures in the last weeks of life; and (3) questions about care quality in patients with terminal illness.

The philosophy of "keeping hope alive" despite the almost certain likelihood of near-term mortality fuels efforts to continue to try new active treatments right up until the end. On a population-wide basis, fiscal concerns and clinical facts show that this way of thinking cannot be supported for long.

High Costs and Variation in Services

The last year of life is associated with high health expenditures in the United States, and the costs are increasingly focused on patients' last few months. According to a 2002 landmark study, the last month of life accounts for fully one-third of the health resources expended during the final 12 months.[1]

In another investigation of 230,000 Medicare patients who died as a result of congestive heart failure from 2000 to 2007, researchers found that the rate of hospitalization in the last 6 months of life was approximately 80%.[2] In their study, published in 2011 in the *Annals of Internal Medicine*, 50% of the patients spent time in the hospital's intensive care unit (ICU), and mean length of stay in the ICU increased as the study progressed. By 2007, ICU stays for these terminal patients reached nearly 5 days. This translated to an average cost per patient of $36,000 (in 2007).[2]

Complicating the issue is the variance in most healthcare costs from one geographic location to another. The same is true with end-of-life care. In 2008, the Dartmouth University group led by Jan Wennberg, MD,[3] revealed that in patients with serious chronic diseases (including cancer) treated at one of 3000 hospitals, costs per patient in the last 2 years of life ranged from $53,432 (Mayo Clinic) to $105,000 (New York University Medical Center). Compared with lower-cost centers, the higher-cost institutions were associated with longer hospital stays, greater ICU use, more doctor and specialist visits, and greater use of other hospital-provided services. The researchers could find no difference in patient outcomes among the centers studied. They speculated that medical centers that received capitated payments or paid their physicians on a salary basis may be less likely to order unnecessary (or nonbeneficial) tests and procedures at the end of life.

Another study found that in-hospital end-of-life care was 65% greater in Los Angeles than in San Diego, and this was principally related to the more aggressive care observed in the Los Angeles institutions.[4] The researchers found that "San Diego residents are significantly more likely to die with the assistance of hospice services and less likely to spend time in hospitals and intensive care units during the last 2 years of life."

"The greatest challenge is the statutory requirement for patients to give up insurance coverage for life-prolonging/disease-modifying treatment once they elect hospice. This is a very difficult decision for patients, families, and oncologists."

—Diane Meier, MD
Professor of Geriatrics and Palliative Medicine
Mount Sinai School of Medicine

Palliative Care, Hospice Care, and the End of Life

In patients with advanced metastatic disease, palliative therapy may be the only remaining option: Relieve the symptoms, ease the pain, and provide the best supportive care possible, with "the goal of improving quality of life for both the patient and the family," said Diane Meier, MD, professor of geriatrics and palliative medicine at the Mount Sinai School of Medicine in New York City.

Palliative care is provided by a team of doctors, nurses, and other specialists who work with a patient's other doctors to provide an extra layer of support. Dr Meier told *Evidence-Based Oncology*, "Palliative care is appropriate at any age and at any stage in a serious illness, and can be provided together with curative treatment." The **Sidebar** provides some of the key recommendations from the American College of Physicians, which are backed by solid evidence.

The demand for palliative care has increased significantly, according to a 2012 national poll. The surveyors found that 71% believe that "It is more important to enhance the quality of life for seriously ill patients, even if it means a shorter life."[5]

Ample evidence exists that hospice care plays a highly cost-effective role in end-of-life care. It seems that payers agree: "Commercial and government payers reimburse palliative care as in any other physician or advanced practice nurse services. For patients who are clearly dying, hospice is the most appropriate model of palliative care. It is covered by virtually all payers in the United States," said Dr Meier.

Although few would dispute the cost-effectiveness of palliative care, perhaps the most challenging issue is convincing providers, patients, and their families to avail themselves of hospice services earlier in the course of serious disease. Patients eligible for hospice services are generally considered to have a life expectancy of 6 months or less. Why don't more people use hospice services? Dr Meier responded, "The greatest challenge is the statutory requirement for patients to give up insurance coverage for life-prolonging/disease-modifying treatment once they elect hospice. This is a very difficult decision for patients, families, and oncologists." She added, "Because palliative care services can be delivered at the same time as active cancer treatment, there is no need to choose between approaches—it is sometimes easier for the team to address achievable goals of care earlier in the disease course, and this influences the understanding of and acceptability of hospice for many patients and families."

The physician has a great deal of influence in the patient/family's decision to use hospice services. "The decision to enter hospice is a deeply personal one for both the patient and his or her family," according to Val Halamandaris,

(continued on page SP180)

NOW APPROVED

PERJETA™
pertuzumab

Indication

PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Important Safety Information

Boxed WARNING: Embryo-Fetal Toxicity

- **Exposure to PERJETA can result in embryo-fetal death or birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception**

Additional Important Safety Information

- Left ventricular dysfunction, including cases of congestive heart failure and decreases in left ventricular ejection fraction (LVEF), occurred in patients in the PERJETA-treated group. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within your institution's normal limits. Discontinue PERJETA and trastuzumab if the LVEF has not improved or has declined further
- PERJETA has been associated with infusion and hypersensitivity reactions/anaphylaxis. When all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group (≥1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting
- Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy
- The most common adverse reactions (>30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy

Please see following brief summary of Prescribing Information, including Boxed WARNING, for additional Important Safety Information.

Demonstrating the Value of Innovation

Genentech
A Member of the Roche Group

PERJETA™ (pertuzumab)
INJECTION, FOR INTRAVENOUS USE
INITIAL U.S. APPROVAL: 2012

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

Exposure to PERJETA can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception. (5.1, 8.1, 8.6)

1 INDICATIONS AND USAGE

PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

PERJETA can cause fetal harm when administered to a pregnant woman. Treatment of pregnant cynomolgus monkeys with pertuzumab resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death. If PERJETA is administered during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Verify pregnancy status prior to the initiation of PERJETA. Advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720 *[see Patient Counseling Information (17)]*.

Monitor patients who become pregnant during PERJETA therapy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of intravenous hydration in the management of oligohydramnios due to PERJETA exposure is not known.

5.2 Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. In the randomized trial, PERJETA in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic left ventricular systolic dysfunction (LVSD) or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel *[see Clinical Studies (14.1)]*. Left ventricular dysfunction occurred in 4.4% of patients in the PERJETA-treated group and 8.3% of patients in the placebo-treated group. Symptomatic left ventricular systolic dysfunction (congestive heart failure) occurred in 1.0% of patients in the PERJETA-treated group and 1.8% of patients in the placebo-treated group *[see Adverse Reactions (6.1)]*. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

PERJETA has not been studied in patients with a pretreatment LVEF value of ≤ 50%, a prior history of CHF, decreases in LVEF to < 50% during prior trastuzumab therapy, or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent.

Assess LVEF prior to initiation of PERJETA and at regular intervals (e.g., every three months) during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is < 40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold PERJETA and trastuzumab and repeat LVEF assessment within approximately 3 weeks. Discontinue PERJETA and trastuzumab if the LVEF has not improved or has declined further, unless the benefits for the individual patient outweigh the risks *[see Dosage and Administration (2.2)]*.

5.3 Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis

PERJETA has been associated with infusion and hypersensitivity reactions *[see Adverse Reactions (6.1)]*. An infusion reaction was defined in the randomized trial as any event described as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. The initial dose of PERJETA was given the day before trastuzumab and docetaxel to allow for the examination of PERJETA-associated reactions. On the first day, when only PERJETA was administered, the overall frequency of infusion reactions was 13.0% in the PERJETA-treated group and 9.8% in the placebo-treated group. Less than 1% were grade 3 or 4. The most common infusion reactions (≥ 1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion reactions in the PERJETA-treated group (≥ 1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting.

In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.8% in the PERJETA-treated group and 9.1% in the placebo-treated group. The incidence of Grade 3 – 4 hypersensitivity/anaphylaxis reactions was 2% in the PERJETA-treated group and 2.5% in the placebo-treated group according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI - CTCAE) (version 3). Overall, 4 patients in PERJETA-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions *[see Dosage and Administration (2.2)]*.

5.4 HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for PERJETA therapy because these are the only patients studied and for whom benefit has been shown *[see Indications and Usage (1) and Clinical Studies (14)]*. In the randomized trial, patients with breast cancer were required to have evidence of HER2 overexpression defined as 3+ IHC by Dako Herceptest™ or FISH amplification ratio ≥ 2.0 by Dako *HER2* FISH PharmDx™ test kit. Only limited data were available for patients whose breast cancer was positive by FISH but did not demonstrate protein overexpression by IHC.

Assessment of HER2 status should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Left Ventricular Dysfunction *[see Warnings and Precautions (5.2)]*
- Infusion-Associated Reactions, Hypersensitivity Reactions/ Anaphylaxis *[see Warnings and Precautions (5.3)]*

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.

In clinical trials, PERJETA has been evaluated in more than 1400 patients with various malignancies and treatment with PERJETA was predominantly in combination with other anti-neoplastic agents.

The adverse reactions described in Table 1 were identified in 804 patients with HER2-positive metastatic breast cancer treated in the randomized trial. Patients were randomized to receive either PERJETA in combination with trastuzumab and docetaxel or placebo in combination with trastuzumab and docetaxel. The median duration of study treatment was 18.1 months for patients in the PERJETA-treated group and 11.8 months for patients in the placebo-treated group. No dose adjustment was permitted for PERJETA or trastuzumab. The rates of adverse events resulting in permanent discontinuation of all study therapy were 6.1% for patients in the PERJETA-treated group and 5.3% for patients in the placebo-treated group. Adverse events led to discontinuation of docetaxel alone in 23.6% of patients in the PERJETA-treated group and 23.2% of patients in the placebo-treated group. Table 1 reports the adverse reactions that occurred in at least 10% of patients on the PERJETA-treated group.

The most common adverse reactions (> 30%) seen with PERJETA in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI - CTCAE (version 3) Grade 3 – 4 adverse reactions (> 2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%).

Table 1 Summary of Adverse Reactions Occurring in ≥ 10% of Patients on the PERJETA Treatment Arm in the Randomized Trial

Body System/ Adverse Reactions	PERJETA + trastuzumab + docetaxel n=407		Placebo + trastuzumab + docetaxel n=397	
	Frequency rate %		Frequency rate %	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
General disorders and administration site conditions				
Fatigue	37.6	2.2	36.8	3.3
Asthenia	26.0	2.5	30.2	1.5
Edema peripheral	23.1	0.5	30.0	0.8
Mucosal inflammation	27.8	1.5	19.9	1.0
Pyrexia	18.7	1.2	17.9	0.5
Skin and subcutaneous tissue disorders				
Alopecia	60.9	0.0	60.5	0.3
Rash	33.7	0.7	24.2	0.8
Nail disorder	22.9	1.2	22.9	0.3
Pruritus	14.0	0.0	10.1	0.0
Dry skin	10.6	0.0	4.3	0.0
Gastrointestinal disorders				
Diarrhea	66.8	7.9	46.3	5.0
Nausea	42.3	1.2	41.6	0.5
Vomiting	24.1	1.5	23.9	1.5
Constipation	15.0	0.0	24.9	1.0
Stomatitis	18.9	0.5	15.4	0.3
Blood and lymphatic system disorders				
Neutropenia	52.8	48.9	49.6	45.8
Anemia	23.1	2.5	18.9	3.5
Leukopenia	18.2	12.3	20.4	14.6
Febrile neutropenia*	13.8	13.0	7.6	7.3
Nervous system disorders				
Neuropathy peripheral	32.4	3.2	33.8	2.0
Headache	20.9	1.2	16.9	0.5
Dysgeusia	18.4	0.0	15.6	0.0
Dizziness	12.5	0.5	12.1	0.0
Musculoskeletal and connective tissue disorders				
Myalgia	22.9	1.0	23.9	0.8
Arthralgia	15.5	0.2	16.1	0.8
Infections and infestations				
Upper respiratory tract infection	16.7	0.7	13.4	0.0
Nasopharyngitis	11.8	0.0	12.8	0.3
Respiratory, thoracic and mediastinal disorders				
Dyspnea	14.0	1.0	15.6	2.0
Metabolism and nutrition disorders				
Decreased appetite	29.2	1.7	26.4	1.5
Eye disorders				
Lacrimation increased	14.0	0.0	13.9	0.0
Psychiatric disorders				
Insomnia	13.3	0.0	13.4	0.0

*In this table this denotes an adverse reaction that has been reported in association with a fatal outcome

The following clinically relevant adverse reactions were reported in < 10% of patients in the PERJETA-treated group:

Skin and subcutaneous tissue disorders: Paronychia (7.1% in the PERJETA-treated group vs. 3.5% in the placebo-treated group)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (5.2% in the PERJETA-treated group vs. 5.8% in the placebo-treated group)

Cardiac disorders: Left ventricular dysfunction (4.4% in the PERJETA-treated group vs. 8.3% in the placebo-treated group) including symptomatic left ventricular systolic dysfunction (CHF) (1.0% in the PERJETA-treated group vs. 1.8% in the placebo-treated group)

Immune system disorders: Hypersensitivity (10.1% in the PERJETA-treated group vs. 8.6% in placebo-treated group)

Adverse Reactions Reported in Patients Receiving PERJETA and Trastuzumab after Discontinuation of Docetaxel

In the randomized trial, adverse reactions were reported less frequently after discontinuation of docetaxel treatment. All adverse reactions in the PERJETA and trastuzumab treatment group occurred in < 10% of patients with the exception of diarrhea (19.1%), upper respiratory tract infection (12.8%), rash (11.7%), headache (11.4%), and fatigue (11.1%).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to PERJETA.

Patients in the randomized trial were tested at multiple time-points for antibodies to PERJETA. Approximately 2.8% (11/386)

of patients in the PERJETA-treated group and 6.2% (23/372) of patients in the placebo-treated group tested positive for anti-PERJETA antibodies. Of these 34 patients, none experienced anaphylactic/hypersensitivity reactions that were clearly related to the anti-therapeutic antibodies (ATA). The presence of pertuzumab in patient serum at the levels expected at the time of ATA sampling can interfere with the ability of this assay to detect anti-pertuzumab antibodies. In addition, the assay may be detecting antibodies to trastuzumab. As a result, data may not accurately reflect the true incidence of anti-pertuzumab antibody development.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies to PERJETA with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

There are no adequate and well-controlled studies of PERJETA in pregnant women. Based on findings in animal studies, PERJETA can cause fetal harm when administered to a pregnant woman. The effects of PERJETA are likely to be present during all trimesters of pregnancy. Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on C_{max}. If PERJETA is administered during pregnancy, or if a patient becomes pregnant while receiving PERJETA, the patient should be apprised of the potential hazard to the fetus.

If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720 *[see Patient Counseling Information (17)]*.

Animal Data

Reproductive toxicology studies have been conducted in cynomolgus monkeys. Pregnant monkeys were treated on Gestational Day (GD)19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on C_{max}. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85% for dams treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on C_{max}). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

8.3 Nursing Mothers

It is not known whether PERJETA is excreted in human milk, but human IgG is excreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from PERJETA, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of PERJETA and the importance of the drug to the mother *[See Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 402 patients who received PERJETA in the randomized trial, 60 patients (15%) were ≥ 65 years of age and 5 patients (1%) were ≥ 75 years of age. No overall differences in efficacy and safety of PERJETA were observed between these patients and younger patients.

Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

8.6 Females of Reproductive Potential

PERJETA can cause embryo-fetal harm when administered during pregnancy. Counsel patients regarding pregnancy prevention and planning. Advise females of reproductive potential to use effective contraception while receiving PERJETA and for 6 months following the last dose of PERJETA.

If PERJETA is administered during pregnancy or if a patient becomes pregnant while receiving PERJETA, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720 *[see Patient Counseling Information (17)]*.

8.7 Renal Impairment

Dose adjustments of PERJETA are not needed in patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) or moderate (CLcr 30 to 60 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CLcr less than 30 mL/min) because of the limited pharmacokinetic data available *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab.

10 OVERDOSAGE

No drug overdoses have been reported with PERJETA to date.

Genentech

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PERJETA™ (pertuzumab)
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

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End-of-Life Care
(continued from page SP176)

president of the National Association for Home Care and Hospice (NAHC). "The factors that lead to the decision will vary on a case-by-case basis. Physicians play a pivotal role in hospice—they are frequently the most knowledgeable about a patient's condition and prognosis, and are frequently the source of education about and referral to hospice for care." He added that generally, an individual will choose hospice "when he or she comes to believe that hospice will afford them a better quality of life, and a higher level of participation in their lives, for the remainder of their days."

"We are already seeing the beginnings of a very public debate about individual self-determination and making advance decisions about how we—as individuals—want to be cared for toward the end of our lives."

—Val Halamandaris
President, National Association for Home Care and Hospice

Sidebar. Keys to Palliative End-of-Life Care in Cancer

Patients with advanced, terminal cancer should be:

- Regularly evaluated for pain, dyspnea, and depression
- Prescribed treatments proven to be effective in managing pain; these include nonsteroidal anti-inflammatory drugs, opioids, and bisphosphonates (which may be effective in relieving bone pain in patients with metastatic breast cancer or advanced myeloma)
- Given treatments to effectively manage their dyspnea (eg, opioids in patients with unrelieved dyspnea, and oxygen for short-term relief of hypoxemia)
- Prescribed treatments to treat depression (in patients with cancer, this may include tricyclic antidepressants, selective serotonin reuptake inhibitors, or psychosocial intervention)
- Counseled to complete advance care planning, including advance directives, to address specific issues such as tube feeding, or continuation or discontinuation of chemotherapy

Source: Data from Qaseem A, Snow V, Shekelle P, et al. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2008;148(2):141-146.

Roughly 82% of all hospice services are provided at home, not in hospice facilities, according to the NAHC.[6] The concept of hospice, first introduced in 1972 in Connecticut,[6] is not one of care based only in a separate facility, but of comprehensive palliative services that can be given anywhere.

Medicare accounts for the lion's share of financing for hospice services (**Table**), and therefore, the vast majority of providers seek Medicare certification. The NAHC estimates that in January 2010, 3407 hospices were Medicare-certified, with 66% of these being free-standing facilities, 17% being home health agency–based, 15% being hospital-based, and less than 1% based in skilled nursing facilities. Of total Medicare expenditures, hospice care accounts for roughly 3%. In terms of Medicaid, the Center for Medicare & Medicaid Services does not mandate hospice benefits, but as of 2010, Oklahoma and New Hampshire were the only state programs to specifically exclude it.

Interestingly, patients with cancer comprise a much smaller proportion of patients receiving facility-based hospice services (10%) than those receiving hospice services in the community (42%).[7] According to the Medicare Payment Advisory Commission, the percentage of patients with cancer utilizing any hospice services is increasing each year.[7]

Table. Distribution of Hospice Primary Payment Source, 2008

Source of Payment	Percentage
Medicare	84.3%
Medicaid	5.1%
Private Insurance	7.8%
Other	2.8%

Source: Data from NHCPO Facts and Figures: Hospice Care in America. National Hospice and Palliative Care Organization, October 2009.

In the Next Decade

The aging of the baby boom generation will touch end-of-life care in a big way, Mr Halamandaris believes. "We will see much greater demand from the aging population for hospice and palliative care, for not only cancer, but a variety of diagnoses." He told *Evidence-Based Oncology*, "In the coming years, hospices will continue to expand their scope of services so that they are not only providing care at the very end of life, but are engaged earlier on in the terminal disease process."

No doubt, more focus will be placed on the completion of advance directives (eg, to forgo extraordinary measures when hope for longer life expectancy with an acceptable quality is vanishing). This may avoid tube feeding, mechanical ventilation, and other life-sustaining measures when the body begins the last phase of life. Mr Halamandaris added, "We are already seeing the beginnings of a very public debate about individual self-determination and making advance decisions about how we—as individuals—want to be cared for toward the end of our lives. Hospices and palliative care organizations will have an important role in educating the public about the options available to them."

In any case, policy makers will need to engage the public much better than in the past. David Nash, MD, MBA, dean, Jefferson School of Population Health, Philadelphia, thinks "It will become more apparent that our spending is untenable and the trade-offs will become painful. Only then," he believes, "will the public regard the end-of-life discussion as routine and commonplace."

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Down the Road for Breast Cancer

Targeted Therapies to Further Improve Outcomes

Michael Marlan Mohundro, PharmD; and Brice Labruzzo Mohundro, PharmD

Highlights From the Future of Breast Cancer 11th International Congress

Scan for additional content.

Julie R. Gralow, MD, director, breast medical oncology, Seattle Cancer Care Alliance (SCCA), discusses a group of clinical trials, currently being conducted by SCCA, that are investigating the agent T-DM1 (trastuzumab emtansine) for patients with HER2-positive metastatic breast cancer, following the administration of 2 prior HER2-targeted therapies (http://bit.ly/PngOs5)

Introduction

Breast cancer, the most common malignancy in developed countries, manifests most often in women, but in rare instances can also occur in men.[1,2] The National Cancer Institute estimates that in 2012, more than 225,000 new breast cancer cases in women and 2000 cases in men will occur, as well as 39,510 deaths attributed to breast cancer in women and 410 deaths in men.[1] Due to improved screening and available treatment options, the 5-year survival rate for women diagnosed with breast cancer between 1999 and 2006 was 90%, compared with 75% for those diagnosed between 1975 and 1977.[3] Despite this increase in survival, advancements in the treatment of breast cancer are still needed. Forthcoming treatments for patients with breast cancer include new monocolonal antibodies, new tyrosine kinase inhibitors (TKIs), and progesterone receptor antagonists, among others which are currently being investigated in clinical trials.

Breast cancer develops in breast tissue, primarily the mammary gland ducts and lobules.[1] Approximately 20% of regional stage disease cases will advance to metastatic breast cancer (MBC).[2] For patients with MBC, available treatment options include chemotherapy, endocrine therapy, monoclonal antibodies targeting growth factors, and TKIs, in addition to supportive measures.[2] MBC is not considered a curable disease; therefore, goals of treatment include improving quality of life, prevention and palliation of symptoms, reduction of drug-related toxicities, and prolongation of survival.[2,4] Several factors must be considered when choosing a treatment regimen. These factors include estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor (HER) 2/*neu* status, duration of the relapse-free interval since primary diagnosis and since completion of adjuvant therapy for breast cancer, location and extent of metastases, previous treatments used (Were they effective? Were they tolerated by the patient?), patient symptoms, patient preferences, expected adverse effects, and availability and access to treatments.[2]

Monoclonal Antibodies

Monoclonal antibodies being investigated for breast cancer include agents targeting vascular endothelial growth factor (VEGF), HER2, and CD3. HER2 is one of several receptors that its downstream signaling pathways promote cell proliferation and survival.[4] Overexpression of HER2 occurs in approximately 15% to 20% of breast cancers and has been linked to poor clinical outcomes. However, this has made it an attractive target for research and drug development.[4] Use of monoclonal antibodies engineered to target the HER2 receptor has been a particularly successful approach in the treatment of breast cancer. Specifically, the development of trastuzumab has been a significant advance represented in the treatment of breast cancer; however, cardiac toxicity, tumor resistance, and lack of effect on brain metastases limit its utility in therapy.

Further research has expanded the focus on the entire family of epidermal growth factor receptors (EGFRs) and signal transduction mechanisms. Another monoclonal antibody under development is pertuzumab, which has been characterized as a HER dimerization inhibitor and interacts with a different binding site than that of trastuzumab.[5] Dimerization between HER2 and HER3 has been shown to promote tumor progression through signal transduction via the PT3K/AK7 pathway.[5] Initial phase I and II trials evaluating pertuzumab showed it was well tolerated along with demonstrating positive results in trastuzumab-refractory patients.[5] Additionally, synergistic results were observed in another phase II trial using pertuzumab in combination with trastzumab.[5] The clinical evaluation of pertuzumab and trastuzumab (CLEOPATRA) is an ongoing, phase III randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of adding pertuzumab to current standard of care in patients with HER2-positive MBC in previously untreated patients with breast cancer.[5,6] Hopefully, results from this study will shed more light on the effect of this agent.

As mentioned above, resistance to trastuzumab has remained a difficult therapeutic challenge to overcome in the treatment of breast cancer. In development is a unique agent that combines the fungal toxin DM1 (maytansine) and trastuzumab through a chemically derived conjugation.[5] This novel approach has given renewed hope to improving outcomes and overcoming resistance. The mechanism of action of this drug does not rely on signal transduction, but simply the overexpression of HER2.[5] Trastuzumab primarily acts as a carrier agent to deliver maytansine, which is a potent cytotoxic agent acting as an inhibitor of cellular microtubule assembly.[5] Multiple phase II and phase III trials are under way. A phase II trial comparing trastuzumab-DM1 with trastuzumab/docetaxel has reported preliminary results. While relative risks were comparable between the 2 arms, recent evidence suggests progression-free survival (PFS) was significantly longer in the trastuzumab-DM1 study group. Further research is ongoing with 2 phase III trials studying trastuzumab-DM1 in patients with MBC. EMILIA is an open-label study evaluating capecitabine (CAP)/lapatinib against trastuzumab-DM1 in patients that have previously received trastuzumab.[7] In another approach, MARIANNE is a phase III trial studying 3 treatment groups as first-line therapy for HER2-positive MBC. One treatment group includes the use of trastuzumab plus a taxane with the second utilizing trastuzumab-DM1 and pertuzumab. The final treatment group will examine the use of trastuzumab-DM1 alone.[8]

Two additional monoclonal antibodies under development include ramucirumab and ertumaxomab. Ramucirumab blocks the interaction between all known VEGFs and VEGFR-2, which has been shown to inhibit angiogenesis and tumor growth in preclinical studies with VEGF-A.[9] In contrast to bevacizumab that targets only VEGF-A, ramucirumab could theoretically inhibit angiogenesis more effectively. Additionally, it is believed that the toxicity profile for ramucirumab will be more favorable due to its specificity and lack of off-target toxicities as seen with the TKIs. The primary side effects that have been identified include hypertension, vascular thrombotic events, and proteinuria, which are consistent with other agents targeting this same pathway.[9] Ongoing studies of ramucirumab include phase II studies evaluating ramucirumab/CAP and ramucirumab/eribulin as well as a phase III randomized, double-blind study evaluating PFS of ramucirumab/docetaxel compared with docetaxel monotherapy in treatment-naïve patients with HER2-negative, unresectable, locally recurrent breast cancer or MBC.[10-12] Ertumaxomab has been developed to target both HER2 receptors and the CD3 antigen that is expressed on T-cells. Aggregation and activation of T-cells, macrophages, dendritic cells, and natural killer cells results from the formation of the HER2-ertumaxomab-CD3 complex.[5] This leads to tumor cell death via phagocytosis, and phase I studies have demonstrated a wide range of activity against HER-2–positive cell lines.[5] Phase II trials in MBC in patients that had already received trastuzumab further support the evaluation of ertumaxomab in future studies.[5] In this study median time to progression (TTP) was 65.5 days. Most adverse effects were mild or moderate, usually resolving in 1 day. The most frequently observed adverse effects were pyrexia, headache, chills, and vomiting.[13]

Insulin-like growth factor type-1 receptor (IGF-1R) aids cell proliferation and survival and is overexpressed in many tumor types.[14] Cixutumumab is an IGF-1R monoclonal antibody. Researchers believe combining cixutumumab with mammalian target of rapamycin (mTOR) inhibitors may enhance the effects of mTOR inhibition. A phase I study evaluating the tolerability and activity of the mTOR inhibitor temsirolimus with cixutumumab demonstrated the combination was tolerable in patients with advanced cancer.[15] An ongoing phase II study is investigating whether cixutumumab with or without antiestrogen therapy increases PFS in patients with hormone receptor (HR)-positive advanced breast cancer (ABC) or MBC who have progressed disease on antiestrogen therapy.[16]

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Tyrosine Kinase Inhibitors

In 2007, the US Food and Drug Administration (FDA) approved lapatinib, the first TKI for use in ABC or MBC in combination with CAP.[17,18] Since that time, there has been intense study utilizing this drug class. Research has resulted in numerous targets being identified.[19] Although significant results have been seen with response rate (RR), PFS, and TTP, improvements in overall survival (OS) have not improved with the addition of lapatinib to therapeutic regimens. Understanding the complex nature of cancer and signaling pathways, it is not unexpected that redundant mechanisms exist that can overcome targeted inhibition using a single agent.[20] Using combinations to avoid dose-limiting toxicities, metronomic dosing, and single agents targeted at multiple receptors are all strategies under review to improve effectiveness and ultimately OS. Due to their small molecular weight, many of the TKIs theoretically can cross the blood-brain barrier, unlike larger monoclonal antibodies such as trastuzumab.[17] This pharmacokinetic advantage is being studied in patients specifically with brain metastasis.[17]

Afatinib and neratinib utilize the same targets as lapatinib, but in contrast to lapatinib irreversibly bind and inhibit the EGFR and HER2 receptors.[20] In theory, they have a therapeutic advantage, as kinase activity would be eliminated until a new receptor could be created.[20] Both drugs are currently in phase III development with favorable results from phase II studies.[21] Both drugs are orally active and share diarrhea as the primary dose-limiting toxicity. However, it should be noted that dose-limiting skin rashes were also associated with afatinib.[20]

Other targets of TKIs being heavily studied are the VEGF family of receptors in an attempt to halt angiogenesis.[22] Angiogenesis is believed to be integral to the growth and metastasis of solid tumors based on the theory that neovascularization is necessary to support oxygen and nutrient needs.[22] Unfortunately, recent phase III studies involving sunitinib

Date Updated	Company	Product	Mechanism of Action	Indication(s)	Stage	License/ Partners	PDUFA Date
7/30/12	Boehringer Ingelheim	afatinib	Irreversible dual receptor inhibitors (EGFR/HER2)	AC; (m)BC; NSCLC; SCC of head and neck	Phase III	N/A	N/A
7/16/12	Pfizer	axitinib	VEGF receptor inhibitors	AC; ACC; AML; (a)HCC; (a)NSCLC; malignant mesothelioma; (m)CRC; (m)melanoma; (m)RCC; (m)thyroid cancer; recurrent glioblastoma	Phase II	N/A	N/A
8/7/12	ImClone Systems	cixutumumab	Insulin-like growth factor type-1 receptor antibody	(a)HCC; CRC; Ewing's sarcoma; (m)BC; (m) prostate cancer; (m)/recurrent SCC of head and neck; neuroendocrine tumors; NSCLC	Phase II	N/A	N/A
7/12	Novartis	everolimus	mTOR inhibitor	(a)H2N-BC with exemestane	Approved 7/2012	N/A	N/A
4/28/11	Fresenius Biotech	ertumaxomab	HER2/CD3	(a)/(m)BC	Phase II	N/A	N/A
8/1/12	Sanofi-Aventis	iniparib	PARP inhibitor	(m)H2N-BC; (m)NSCLC	Phase III	N/A	N/A
4/05/12	Bayer	lonaprisan	Progesterone receptor antagonist	(m)BC	Phase II	N/A	N/A
6/19/12	Pfizer	neratinib	Irreversible dual receptor inhibitors (EGFR/HER2)	(a)/(m)H2P-BC	Phase III	Puma Biotechnology	N/A
8/2/12	AstraZeneca	olaparib	PARP inhibitor	(a)BRCA-positive BC; (a)/recurrent/relapsed OC; CRC; GC	Phase II	N/A	N/A
8/2/12	GlaxoSmithKline	pazopanib	VEGF receptor inhibitors	(a)/(m)RCC; NSCLC; ovarian/fallopian tube/ primary peritoneal cancer; soft tissue sarcoma	Phase III	N/A	N/A
6/08/12	Genentech	pertuzumab	HER2	(m)H2P-BC	Approved 6/2012	N/A	N/A
8/3/12	Janssen Products	pegylated doxorubicin	Anthracycline	Relapsed MM	Phase III	N/A	N/A
8/02/12	Eli Lilly and Company	ramucirumab	Anti-VEGF	(m)CRC; NSCLC	Phase III	N/A	N/A
8/03/12	Merck	ridaforolimus	mTOR inhibitors	(a)endometrial carcinoma; (a)sarcoma; (m) bone/ soft-tissue sarcoma; (m)H2P-BC; PC; refractory/ relapsed leukemia	Phase II	ARIAD Pharmaceuticals	N/A
8/01/12	Bayer	sorafenib	pan-VEGFR inhibitor, RAF kinase inhibitor, platelet derived growth factor receptor	(a)HCC; (a)melanoma; (a)/(m)RCC; NSCLC	Phase III	Onyx Pharmaceuticals	N/A
7/23/12	Pfizer	sunitinib	VEGF receptor inhibitors	(a)BC; (a)/(m)RCC; GIST; HCC; (m)PC; NSCLC; pancreatic carcinoma	Phase III	N/A	N/A
8/02/12	Pfizer	temsirolimus	mTOR inhibitors	(a)RCC; BC; MCL; renal transplant	Phase III	N/A	N/A
8/07/12	Genentech	trastuzumab-emtansine	HER2	(a)GC; (a)/(m)H2P-BC	Phase III	N/A	N/A
7/24/12	Abbott	veliparib	PARP inhibitor	(a)NSCLC; brain metastases from NSCLC; CRC; HCC; (m)BC; (m)melanoma;(m)pancreatic cancer; OC; solid tumor cancers	Phase II	N/A	N/A

(a) indicates advanced; (m), metastatic; AC, adenocarcinoma; ACC, adenoid cystic carcinoma; AML, acute myeloid leukemia; BC, breast cancer; CRC, colorectal cancer; GC, gastric cancer; GIST, gastrointestinal stromal tumor; H2N, HER2-negative; H2P, HER2-positive; HCC, hepatocellular carcinoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, prostate cancer; PDUFA, prescription drug user fee act; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.

showed either inferior or comparable outcomes with increased toxicities, such as anorexia, fatigue, mucositis, diarrhea, and nausea.[22,23] These results have effectively halted drug development for MBC.[22,23] Although these initial results have been discouraging, other VEGFR inhibitors have shown promise in recent trials. Sorafenib is an orally bioavailable pan-VEGFR inhibitor that also inhibits RAF kinase and platelet-derived growth factor receptor (PDGFR), giving it both antiproliferative and anti-angiogenic properties.[22] In early trials studying patients with breast cancer who had been previously treated, it was shown to have limited effectiveness as the sole therapeutic agent. However, in combination with other chemotherapeutic agents, phase IIb trials showed significant improvements in overall outcomes.[22]

Additional VEGF inhibitors under investigation include pazopanib and axitinib. Both molecules have proven inhibitory activity against all identified forms of VEGFR, as well as PDGFR and c-KIT. Results from a recent phase II trial in combination with docetaxel in patients with MBC showed significant improvements in RR, but failed to show a significant difference in median TTP against placebo.[21,22] Pazopanib, another multi-target TKI, is being evaluated in combination with lapatinib in a phase II trial as a first-line therapy for HER2-positive breast cancer and in a phase III trial for HER2-positive inflammatory breast cancer. Initial results from the phase II trial indicate a better RR and 12-week PFS with combination therapy.[21,22] A phase II study of axitinib plus docetaxel versus docetaxel plus placebo in patients with MBC did not demonstrate a statistically significant difference in TTP.[24]

Other multitargeted TKIs under development include cediranib, motesanib (AMG-706), and vandetanib, but early trials have shown added toxicity with limited results.[21,22] Further studies are needed to determine the place of TKIs in breast cancer.

Poly (ADP-ribose) Polymerase Inhibitors

In determining effective cell targets for chemotherapeutic drugs, research has increasingly focused on analysis of the receptor profile of healthy cells versus cancerous cells.[21] The genetic profile and receptor expression of the cancer being treated is becoming more important in determining which drugs will lead to successful outcomes.[18] Triple negative breast cancer (TNBC) is one of the more aggressive, lethal, and subsequently difficult to treat cancer subtypes.[25] Characterized through immunochemistry as lacking the ER, PR, and HER2 genes, TNBC does not respond to mainstay endocrine therapy, leaving limited therapeutic options.[25,26] TNBC accounts for approximately 15% of all breast cancers and has been associated with poorer clinical outcomes.[21,25,26] Although a small subset of patients respond extremely well to chemotherapy and have a good prognosis, frequently patients relapse and subsequently have a short median time of survival.[25,26] As many as 10% of breast cancer cases can be attributed to a hereditary mutation in genes that encode proteins integral to DNA repair, BRAC1 or BRAC2.[21] Patients with mutations in these genes are more likely to have TNBC and are consequently not good candidates for currently available customized therapy.[21]

Poly ADP ribose polymerase 1 (PARP1) is part of a family of enzymes that help maintain genomic integrity in cells.[26] Inhibitors of this enzyme are under development, as scientific analysis has determined that PARP is upregulated in breast cancer, as well as many other cancers.[21] It is theorized that cancer cells already have defects in 1 DNA repair mechanism, and thus attacking an upregulated compensatory pathway would be an effective treatment strategy. This theory has been validated in preclinical studies involving tumor cell lines with BRAC mutations.[25,26] Through inhibition of the PARP enzyme, the strategy known as synthetic lethality is leveraged to cause cell death. Synthetic lethality refers to the situation in which cell death occurs due to the loss of 2 gene products, whereas the loss of one or the other would not have a detrimental effect.[25,27] Additionally, PARP inhibition is theorized to enhance the cytotoxicity of DNA, damaging radiation treatment and chemotherapy.[25] Preclinical studies involving iniparib and veliparib in combination with ionizing radiation, as well chemotherapy such as carboplatin, had supported the theory that PARP inhibitors potentiate the effects of DNA-damaging therapeutic agents.[25]

Although early phase I and phase II trials involving olaparib, veliparib, and iniparib have all shown promise, results from recent phase III trial involving iniparib in patients with triple negative MBC have been disappointing.[21,25,26] Benefit appears to be limited to patients with confirmed BRAC1 or BRAC2 mutations, but further studies will help determine the primary role of PARP inhibitors in breast cancer.[26] Adverse events that have been reported include nausea and fatigue; however, severe toxicities related to myelosuppression have also been documented.[26] Both olaparib and veliparib are orally bioavailable, while iniparib is given intravenously.[25]

mTOR Inhibitors

Letrozole and anastrozole, both aromatase inhibitors, are the mainstay of therapy in patients with HR-positive ABC in postmenopausal patients. The problem with these agents is that not all patients will respond to their effects and others ultimately relapse due to acquired resistance.[28] One potential mechanism of resistance is thought to be due to the mTOR signaling pathway, with evidence suggesting an association involving the mTOR pathway and ER signaling. The mTOR inhibitors are being studied to determine their effect on assisting endocrine therapies to increase their effectiveness. Everolimus, ridaforolimus (formerly deforolimus), and temsirolimus are mTOR inhibitors being studied in breast cancer. A phase III randomized trial of 724 patients with HR-positive ABC with recurrence or progression while receiving an aromatase inhibitor evaluated the effect of everolimus/exemestane versus exemestane monotherapy on PFS. The investigators determined PFS to be increased by 4 months for patients receiving therapy with everolimus/exemestane. At the time the manuscript was submitted it was too early to determine OS; however, at that time 10.7% of patients in the combination group had died, compared with 13% receiving monotherapy.[28] Based upon the results of this study, everolimus was approved by the FDA in July for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane after failing letrozole or anastrozole therapy.[29]

Based on the literature, it is becoming more apparent that tailored therapies will continue to grow based on the increased understanding of the mechanisms of oncogenesis and causes of drug resistance.

PIK3CA mutations have been associated with ER-positive breast cancer. An open label phase II study evaluating temsirolimus in patients with MBC hypothesized that patients with a PIK3CA mutation would respond to temsirolimus; however, the results of the study demonstrated a minimal effect in this subset of patients.[30] Another phase II study that proposed letrozole with 10 mg daily or 30 mg intermittent temsirolimus showed tolerability and clinical activity and early results suggested better PFS with combination arms.[31] Unfortunately, HORIZON, a phase III study evaluating letrozole with temsirolimus, was terminated early because it was believed the combination treatment was unlikely to achieve the targeted level of efficacy compared with letrozole alone.[32] Ongoing studies with temsirolimus include a phase I/II study evaluating combination treatment with neratinib in patients with HER2-amplified MBC or TNBC and a phase I/II trial of cixutumumab and temsirolimus in patients with locally recurrent or MBC.[33,34] A phase II study involving ridaforolimus with dalotuzumab in ER–positive breast cancer is ongoing.[35]

Progesterone Antagonists

The role of progesterone in breast cancer is controversial; however, evidence suggests selective PR antagonists may prevent tumor progression. The first PR antagonist on the market was mifepristone, which is not used for the treatment of breast cancer, but instead termination of intrauterine pregnancy.[36] Lonaprisan is an orally bioavailable type III PR antagonist that differs from mifepristone due to its purely antagonistic effects. Unlike mifepristone, lonaprisan does not convert to a progesterone agonist when exposed to protein kinase A activators and is highly receptor selective.[37,38] An in vitro study demonstrated lonaprisan strongly inhibited cell proliferation of breast cancer cell lines by blocking them in the G0/G1 phase. Additionally, lonaprisan also induced a biological aging-like phenotype.[38] A phase II study investigating the efficacy, safety, and tolerability of lonaprisan 25 mg versus 100 mg daily as a second-line endocrine therapy for postmenopausal women with HR-positive MBC randomized 69 patients and was completed in April 2011. The primary end point of the study was not met, thus suggesting lonaprisan had limited activity as second-line endocrine therapy in MBC.[39]

Pegylated Liposomal Doxorubicin

A study evaluating a non-anthracycline regimen in early HER2-positive breast cancer found estimated disease-free survival rates at 5 years were highest in the group of patients receiving doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks with 52 weeks of trastuzumab.[40] Unfortunately, combination anthracycline plus trastuzumab therapies have been limited due to the cardiotoxic effects of these drugs.[41] Pegylated liposomal doxorubicin (PLD) contains doxorubicin molecules encapsulated in a bilayer sphere of lipids, which is surrounded by a dense layer of polyethylene glycol. The size of the liposomes prevents the doxorubicin from entering the heart and gastrointestinal tract and selectively deposits the liposome into the tumor.[42] PLD is an approved treatment in Europe as monotherapy for MBC in patients at risk of heart problems, but it has not received FDA approval in the United States.[43] A phase II study evaluating PLD plus carboplatin versus PLD plus carboplatin and trastuzumab demonstrated

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better median OS durations (33 months) and better median PFS (10 months) with the PLD, carboplatin, and trastuzumab treatment. Grades 3/4 treatment-related toxic effects in this group were neutropenia (35%), thrombocytopenia (17%), and fatigue (13%); however, minimal cardiac toxicity was noted.[44] A phase III study demonstrated that PLD and CAP had similar TTP when used as first-line therapy in patients with MBC; however, patients administered PLD had better tolerability than patients receiving CAP.[45] Several studies evaluating PLD in various types of patients with breast cancer are ongoing.[46]

Conclusion

Over the past 2 decades, major advances have been seen in the detection, prevention, and treatment of breast cancer, with mortality steadily declining. Numerous new drugs are under development and new targets continue to be identified to focus research efforts. Although early detection and preventative strategies, such as lifestyle modification, remain critical strategies in the overall battle against breast cancer, significant results have been reported from recent drug studies, providing hope to patients who have failed currently available treatments. Based on the literature, it is becoming more apparent that tailored therapies will continue to grow based on the increased understanding of the mechanisms of oncogenesis and causes of drug resistance. A patient's tumor receptor profile (ie, HER2, PR, ER) and genetic markers, such as BRAC1 and BRAC2, have helped to ensure successful treatment strategies. PARP inhibitors have shown limited success in patients specifically with BRAC mutations and, to date, TKIs have had mixed results; however, toxicity remains a concern. The monoclonal antibodies appear to have the greatest potential for coming to market in the short term. Pertuzumab has been recently approved for use with trastuzumab, paving the way for the approval of novel chemotherapy conjugate trastuzumab-DM1. If the results from trials translate to clinical practice, this is likely to improve outcomes. However, the majority of improvements seen have been isolated to PFS with limited or no increases in OS. With an 18-month course of treatment with trastuzumab/pertuzumab estimated at approximately $187,000 (more than $10,000 per month) and 28 days of everolimus being $7500, results over the long term and additional clinical trials should be watched closely.[47,48] Other agents are expected to be costly as well. Given the FDA's decision to revoke the breast cancer indication for bevacizumab, caution is warranted in order to fully understand the side-effect profiles and efficacy of these drugs in the postapproval phase. **EBO**

Author Affiliations: Our Lady of the Lake Regional Medical Center (MMM), Baton Rouge, LA; and University of Louisiana at Monroe College of Pharmacy—Baton Rouge Campus (BLM), Baton Rouge, LA.

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Authorship Information: Concept and design (BLM); acquisition of data (BLM); analysis and interpretation of data (MMM, BLM); drafting of the manuscript (MMM, BLM); and critical revision of the manuscript for important intellectual content (MMM, BLM).

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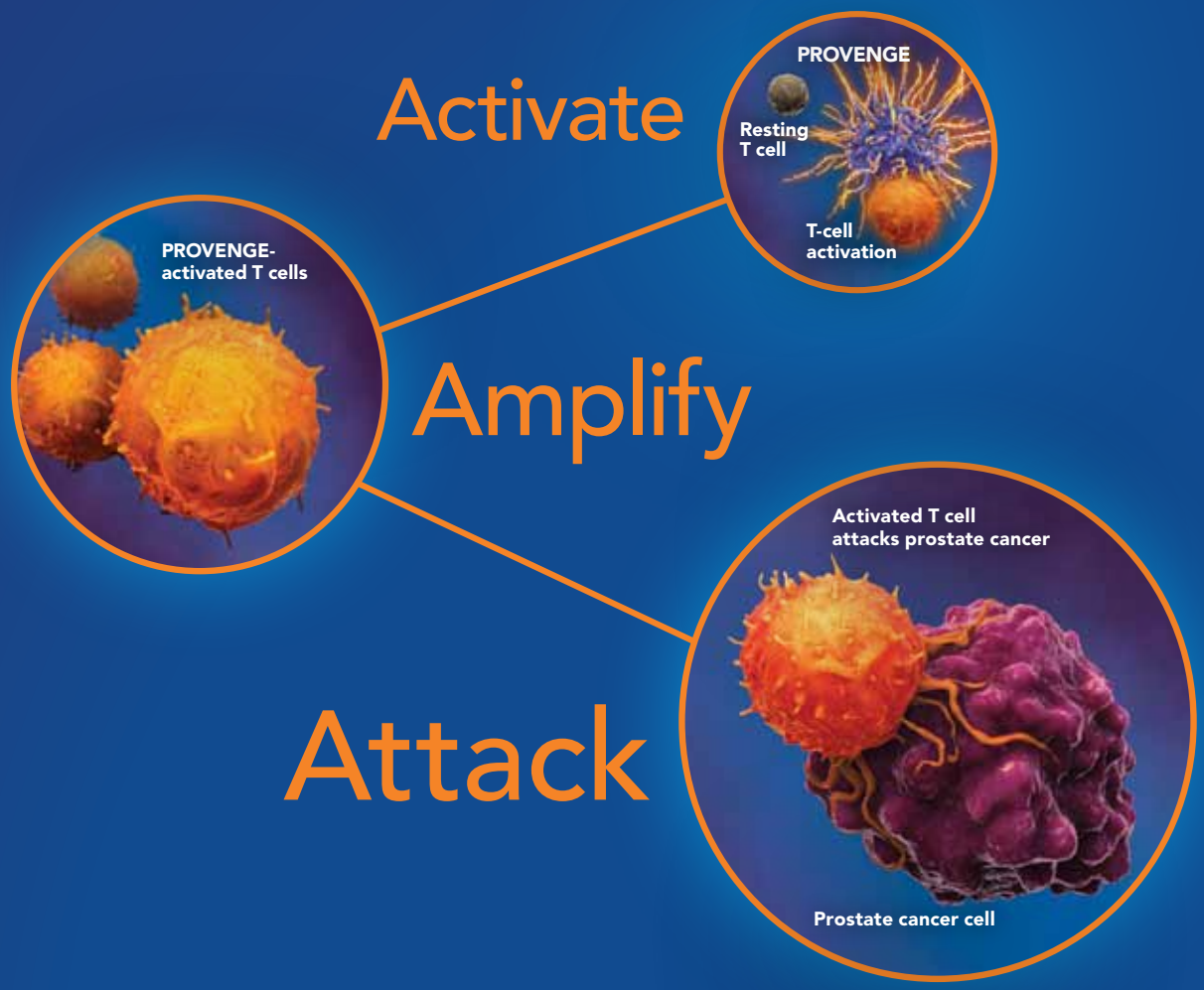
In advanced prostate cancer

TREAT FIRST LINE WITH PROVENGE TO



EXTEND SURVIVAL

>2 years	Extends median survival beyond 2 years[1]
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 ≥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 ≥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 ≥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 ≥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 ≥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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How Payers and Oncologists Really Feel About Oncology Pathways

Kim Farina, PhD

According to the 2011 *Managed Care Benefit Design Index*, cancer was the top-ranked management priority among payers (**Figure 1**). Mark Zitter, CEO, The Zitter Group, explained the reason for their concern: "Typically it is often cost-related and challenge-of-management-related, so this is clearly an issue for payers."

To keep abreast of practice and management trends in oncology, The Zitter Group issues the *Managed Care Oncology Index (MCOI)*, the results of a semiannual survey of 100 payers, 100 oncologists, and 100 oncology practice managers.

During a session titled *Oncology Pathway Development and Implications for Managed Care* at the 2012 Academy of Managed Care Pharmacy Annual Meeting, Zitter presented 2011 *MCOI* data and reviewed the rationale underlying clinical pathway use, current utilization trends, perspectives on pathway use, and implications for managed care pharmacy.

Survey respondents estimated that 16% to 23% excess cost can be eliminated from cancer treatment without adversely affecting quality of care or health outcomes. The cause of excess spending most commonly cited by payers and oncologists was excessive end-of-life treatment (35% payers, 30% oncologists). Other contributors to wasteful spending include inappropriate drug use and diagnostic testing, suboptimal distribution of prescription drugs, and utilization management requirements.

Payers are employing a number of traditional benefit management approaches to control spending. Prior authorization is by far the most commonly employed strategy. In cancer care, payers use prior authorization as a way to ensure appropriate utilization. Ultimately, payers and doctors agree that it is the doctors who drive treatment decisions. Hence, it seems logical that doctors should drive cost reduction. That, explained Zitter, is where clinical pathways come into play.

Doctors don't like the typical payer responses to increased oncology costs: reimbursement reductions, prior authorizations, and specialty pharmacy or other site-of-care mandates. Pathways offer a more palatable alternative toward reducing practice variation, improving outcomes, and reducing cost.

A pathway represents an evidence-based approach to care that focuses on a specific disease or patient group with a relatively predictable course. For each disease or patient group, the pathway specifies which interventions to perform and in which sequence to use them. Pathway generation and maintenance requires a process for evaluating therapies and clinical approaches.

Forty percent of the payers surveyed already had pathways in place and the majority of those who did not indicated that they were likely to implement clinical treatment pathways in the near future (within 18 months of survey). Breast, lung, and colorectal cancers were the tumor types most commonly covered by clinical pathways (**Figure 2**). Payers and oncologists were optimistic that cancer care guidelines will improve the quality of cancer care and reduce cancer costs.

Pathways are typically developed by individual provider groups or national organizations (eg, National Comprehensive Cancer Network, American Society of Clinical Oncology), not by health plans. Nearly 80% of payers agreed that they would rather enforce externally produced cancer care guidelines than create and enforce internally created pathways. Indeed, nearly 70% of those who had already adopted clinical pathways indicated that a third party pathway organization was responsible for pathway management. Although managed care is not typically involved in pathway development, pharmacists can play a significant role in informing the development process by providing data, vetting the pathways, and assisting with pathway enforcement.

Several reasons were cited among those who had chosen not to adopt clinical pathways. The most common were that their organizations had not reached consensus on which pathways to develop and that the management techniques in place were considered effective. Interestingly, these were also the top 2 reasons cited by oncologists who were not planning to adopt clinical pathways in the next 2 years. Adoption of clinical pathways does not necessarily mean that traditional management approaches need to be abandoned. About half of the payers integrated treatment algorithms into their existing prior authorization process.

Ultimately, for clinical pathways to be effective, the oncologists have to be using them. With that in mind, health plans are devising a number of ways to incentivize pathway use. According to payers surveyed, higher drug reimbursements and reduced administrative requirements (eg, prior authorization) are the most frequently applied incentives for physicians who adhere to pathways. Less commonly used incentives are expedited utilization reviews and reimbursement processing, in-network requirements, and preferred provider status within network. According to the *MCOI*, getting doctors on pathway may not be too difficult. The oncologist respondents found pathways influential and were in favor of their use. Of 60 oncologists surveyed, just less than half said they plan on adopting pathways within the next 2 years. **EBO**

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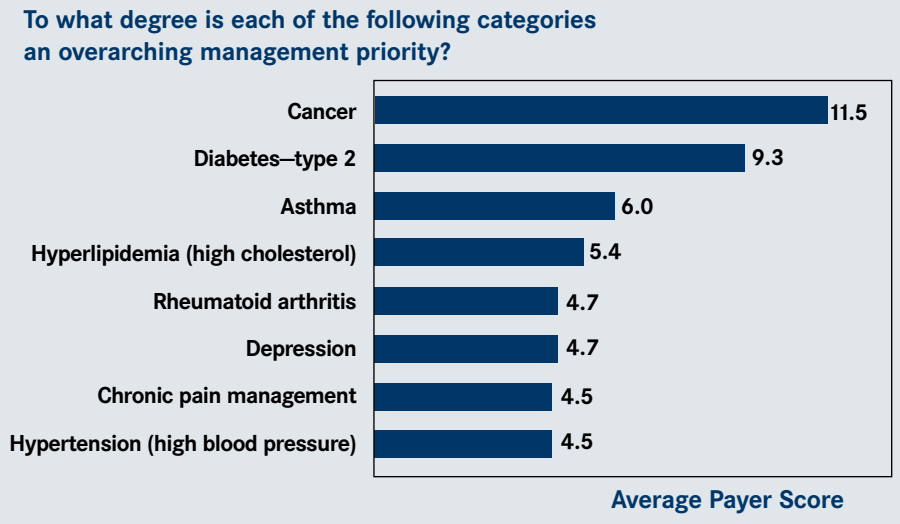
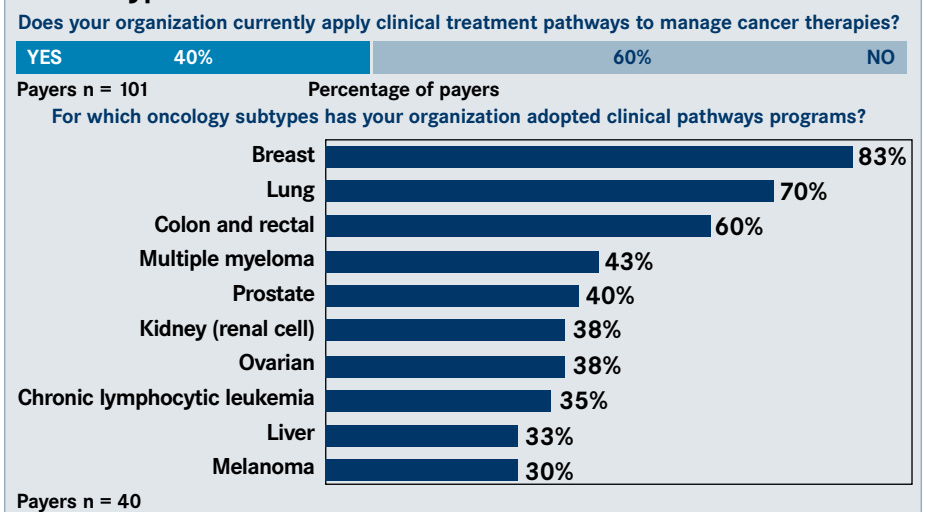
Figure 1. Cancer Is Payers' Number 1 Management Priority



According to the *Managed Care Benefit Design Index, Fall 2011* (a survey of payers, N = 101), cancer topped the list of payers' management priorities for the first time.
Source: Reprinted with permission from The Zitter Group. *Managed Care Benefit Design Index*. Fall 2011.

Figure 2. Payers Have Adopted Pathways for the Most Common Cancer Types



Among the 40% of payers who have adopted clinical oncology pathways, breast, lung, and colorectal cancer were the most commonly covered tumor types.
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Value-Based Care SP189

Partnering With a Payer to Develop a Value-Based Medical Home Pilot: A West Coast Practice's Experience

Linda D. Bosserman, MD, FACP; Diana Verrilli; and Wendy McNatt

The Wilshire Oncology Medical Group has worked in many payment systems during its 54-year history. Our experiences have led us to develop a medical oncology home pilot to offer a transparent, high-quality, high-value cancer program in partnership with our largest California health plan, Anthem Blue Cross WellPoint. Changes in how we were paid by independent physician associations were the catalyst of a 20-year process of re-engineering our care delivery while maintaining participation in clinical trials. We became pioneers in staffing models and the use of an oncology electronic medical record (EMR) system. The EMR prompted us to be diligent in the evaluation and monitoring of both practice and clinical data and allowed us to use data at the practice level to create ongoing programs for continuous quality improvement.[1,2] By 2006, we had transitioned to a customizable oncology-specific EMR standardized to incorporate treatment protocols on the basis of evidence-based medicine. We began analyzing our data to benchmark the care we provided against national guidelines.[3-5] Today as a member of the nation's largest network of community-based oncologists, we continue to document our adherence to Level 1 Pathways and the costs and quality of care we provide[6-10] and to study complex quality issues in cancer.[11]

We next planned how we could better serve the preferred provider organization health plans in our market. Our goal was to demonstrate that we could deliver a comprehensive plan of care and manage their patients with cancer while creating significant savings for the patients who were facing growing copay burdens[12,13] and the health plans that could save in lowered direct and management costs for therapy and supportive care, lessening avoidable urgent, emergency hospital care and futile, toxic therapies at the end of life. The practice would benefit from these cost savings through value-based reimbursement and lessened management by the health plan.

Four years ago, we contacted the senior leadership of the largest preferred provider organization in our market. We wanted to explore how we might share our work with the health plan and develop what we initially called a 'pay differently for better outcomes' plan. Despite the fact that our comprehensive approach did not fit into their previous oncology management models, the medical directors of this payer believed our proposal had merit and initiated what became a series of ongoing meetings between our groups. This led to an agreement to validate our clinical and claims data, which brought the health plan analysts and actuaries into the discussions. These talented professional actuaries were able to build models to analyze regimens by patient and regional groups, supportive care drugs, and days of emergency department (ED) care differentiated by weekday versus weekend and evaluate global hospital claims data. They validated the patient data we could rapidly pull on a real-time basis from our EMR and billing reports; whereas this proved to be a complex, time-consuming undertaking for the health plan.

We worked with medical directors whose expertise and interests were not initially in oncology but who listened and learned. A major breakthrough came with the understanding of why we cannot get oncology and value reporting down to 4 or 5 simple data points. They came to understand that cancer is not simple; you need about 10 to 20 data points to fully assess whether the right patient got the right treatment for his disease subtype in the right setting at the right cost with a measurable outcome. This information then enabled refinements and understanding of what the health plan and the health system were providing to patients. This led to site visits to our practice by the medical directors, their actuaries, and their administrators to see firsthand what it was we were talking about. They saw and talked to our patients, reviewed the issues of their diagnoses, staging, tumor subtypes, comorbidities, and psychosocial needs. They saw our specialized oncology nurses in action and talked to them about their work. They talked to members of our administrative, front desk, intake, billing, disability, medical assistant, licensed vocational nurse, and midlevel provider staff. This engagement made a huge difference during our subsequent meetings. Because most health plan medical directors are not oncologists, most of what we do is not granular to them. Our team process built strong working relationships with the health plan medical directors, actuaries, and payer teams. We have recently welcomed 2 additional medical directors to the team. They bring experienced medical leadership and expertise in oncology, as well as health outcomes, to the team.

During our 4 years of collaboration, we have developed a medical oncology pilot that has required great trust on all sides and the sharing of detailed presentations on the basis of verifiable data. At the practice, we came to understand and respect the many challenges health plans have, especially those related to state requirements like those in California and their need to address their responsibilities to another level of oversight—their parent organization.

The next step was to agree on a conceptual framework for payments. First, we agreed the health plan *wants* doctors to coordinate and deliver quality cancer care to their members. This required us to break out the work, people, documentation, reporting, and analytics for our pilot. Second, we agreed the health plan *wants* to pay for their members to get high-value care—high-quality care at the best overall price with high patient satisfaction. Third, we agreed that the evaluation and management (E&M) code payment system does not cover the additional complex work involved in creating comprehensive care plans or for comprehensive care management. Comprehensive care plans involve medical, surgical, radiation oncology, often other specialists, sometimes inpatient, sometimes outpatient care, clinical trials when appropriate, supportive care, psychosocial care, rehabilitation, recovery, survival, and at times, end-of-life care. Paying for a clearly coordinated comprehensive plan ensures the most efficient care for patients who then have a clear plan to navigate and a team to look to as they move through their care. Then, once on the often highly toxic and costly

Linda D. Bosserman, MD, FACP

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We expect to have a validated, transparent, and accountable medical oncology home model that is scalable and available to others in our state and across our country.

cancer care plan, personalized education and expectant management can minimize suffering and speed interval care in the outpatient setting to minimize avoidable ED and hospital care. End-of-life care was another area in which better data were needed to determine why people get third-line therapy or beyond for some cancers even though many studies show patients would choose hospice and palliative care if they were better informed about the futility of many end-stage therapies. We were able to show the time and motion work for the care management that goes on for each cycle of care beyond the standard E&M visit and beyond the underfunded infusion codes and drug margins no longer covered by average sales price (ASP) plus 6% to 10%.

Our teams met almost monthly during 2009 and 2010 until our work was validated and the health plan agreed to proceed with what we now call the Medical Oncology Home Pilot. Legal and technical considerations delayed the launch until August 2011. An initial federal waiver was needed for some patients to participate in a pilot, and a payment system had to be worked out within the current information technology capabilities and coding systems for the health plan. Health plans in California are required to provide the same quality of care to all members. Therefore, pilots likely to provide a much higher level of care for some patients versus others can have specific funding challenges (especially those funded through federal dollars).

Since our agreement to move forward in 2010, our group affiliated with the US Oncology Network (The Woodlands, Texas), which is supported by McKesson Specialty Health (The Woodlands, Texas). This has been key to expanding the progress of our pilot. Just as our pilot was launched, the health plan, like many nationwide, was seeing community doctors migrate to large hospital systems, which have higher costs to health plans and patients but provide financial stability to providers. The greater understanding of the care and costs community oncologists have traditionally coordinated and managed has made health plans realize that their ratcheting down of payments for E&M codes, inadequate infusion payments, and ASP plus 6% or even ASP plus 10% reimbursements have not adequately covered the cancer services that patients need. It has also incentivized more high-cost ED and hospital care and duplication among the many caregivers when care is not coordinated. Our national network affiliation has given the practice access to experts in health plan relations, a larger medical home team, and a sophisticated actuarial team to expand our analytic capabilities for benchmarking our pilot regionally and nationally. We are also collecting data on practice administrative and delivery costs and the potential cost savings to patients and the health plan to enable future refinements of medical oncology home payments. Our aggregate team now has weekly calls and quarterly or more meetings with the health plan team to review and benchmark the results. Our first 3 months of data exceeded our goals. Our 6-month reports in February will meet or exceed our expectations, with full benchmarking data expected shortly thereafter.

Although the path has been long, we are hopeful that our pioneering efforts can launch others into making value-based cancer care a reality. It has been essential to have a clear vision that, as oncology specialists, we know the field—what and how we can best coordinate, provide, document, and report as high-quality care for our patients with cancer at the lowest cost that also supports high patient satisfaction. It has taken a leap of faith on the part of both our practice and the health plan to be totally transparent on the processes, working to understand and fund the full costs of delivering care. We expect to have a validated, transparent, and accountable medical oncology home model that is scalable and available to others in our state and across our country. We hope the sharing of these pioneering efforts will encourage others to reach out to their payers to further expand these efforts. **EBO**

Author Affiliations: From Wilshire Oncology Medical Group (LDB, WM), The Woodlands, TX; McKesson Specialty Health (DV), The Woodlands, TX.

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Linda D. Bosserman, MD, FACP, is president, Wilshire Oncology Medical Group, an affiliate of the US Oncology/McKesson Specialty Health Network, The Woodlands, TX. Diana Verrilli is vice president, payer and revenue cycle services, McKesson Specialty Health, The Woodlands, TX. Wendy McNatt is practice director, Wilshire Oncology Medical Group, an affiliate of the US Oncology/McKesson Specialty Health Network, The Woodlands, TX.

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Oncology Patient–Centered Medical Home

John D. Sprandio, MD, FACP

In the current dynamism of health system restructuring in the aftermath of healthcare reform, community-based oncology practices and institutionally based cancer programs have a significant opportunity to lead positive change that will position them better in the new world order. This article presents the oncology patient–centered medical home as a physician-driven, patient-focused value proposition that can really make a difference for patients, oncologists, and the cost of healthcare.

Before 2008, approximately 85% of all cancer care in the United States was delivered in a community setting by independent practitioners. The remaining patients received care from institutionally based cancer programs. An admittedly flawed chemotherapy reimbursement model provided medical oncology practices a steady revenue stream that allowed practices to assume an increasing degree of responsibility and expense for supporting, educating, and navigating patients through an increasingly complex cancer care delivery system. Private and institutionally based practices flourished, and in many cases, patient care was enhanced.

Times have changed. The Medicare Modernization Act passed in 2003 put into motion fundamental changes in the methodology of chemotherapy drug reimbursement. These changes fully impacted oncology practices in 2008, with independent community-based practices being the most economically vulnerable.[1] It is now widely recognized by providers and payers that the current net reimbursement to independent practices for evaluation and management services, plus the remnants of the buy-and-bill method of paying for chemotherapeutic agents, has not kept pace with the complexity of tasks required of medical oncologists if they are to maintain existing levels of service. More importantly, the current reimbursement model virtually eliminates the ability of community-based oncology practices to answer the urgent call of healthcare reform to deliver improved quality and value while focusing on patient needs and the delivery of consistent care. Many institutional programs, on the other hand, still have the resources to focus on care coordination, patient safety, evidence-based guidelines, and preparing for more integrated payment models, including participation in accountable care organizations (ACOs).

In March 2011, the Community Oncology Alliance (COA) reported a significant shift in the site of care delivery from the community to institutionally based cancer programs with a further trend in the closure of private practice sites and the pervasive financial instability of those still operating.[1] Best guesstimates today from COA suggest that 65% of cancer care is delivered by independent community-based physicians and 35% by their institutionally based counterparts (T. Okon, personal communication, January 2012). In retrospect, before 2008, one could argue that neither site of care was optimally delivering consistent, standardized, coordinated cancer care to the most vulnerable segment of our healthcare system's patient population. Many stakeholders would argue that cancer care has become more fragmented and less coordinated in both settings since 2008.

The Response

Community-based physicians have not led the response to the current economic challenges confronting their practices. Third-party vendors promoting chemotherapy pathway programs and institutionally based cancer programs are seizing that opportunity.

Pathway Programs

The chemotherapy pathway programs have had some positive effects in partially addressing quality of care and cost issues.[2] However, this approach can only provide a limited advancement of the value proposition from a patient service, disease management, and long-term payer perspective as a result of the inherent need to design the pathway intervention to be minimally disruptive to a practice's operations to promote physician acceptance and implementation. The payers and the pathway vendors have largely enjoyed the positive economic effect; the impact for the practices, which have already been economically deflated by the effects of the Medicare Modernization Act, is often neutral. Pathway programs offer the opportunity to lock in to current reimbursement levels, but this, unfortunately, does not support current or future practice infrastructure needs. This strategy is still effectively centered around a modified buy-and-bill drug reimbursement model, devoid of a patient-centered value proposition. It has become clear that the impact of a pathways program on the total cost of cancer care delivery is finite—in the 1% to 3% range, according to a 2011 analysis by McKinsey & Company.[3] This, alone, is not the answer to the escalating total cost of cancer care.

Hospital- and Academic-Based Programs. By leveraging existing favorable contracts with payers and extending the 340B chemotherapy pricing program to extended—and unintended—patient populations, institutional programs are consolidating their markets by virtue of their ability to offer economic shelter to independent practices. According to COA, the number of community-based physicians entering into employment or management arrangements with institutionally based programs accelerated in 2011.[1] This shift in the site of care delivery has been accompanied by substantial—sometimes spectacular—increases in the cost of care, often without demonstrable enhancement of quality and with a resulting diminution of value. This is not the answer to the escalating total cost of cancer care.

Independent Community-Based Practices. Independent practices are considering several strategic options in the search for economic predictability or a sustainable business model: contractual alignment (employment, management arrangement) with community or academic institutions, integrated delivery systems, or accountable care organizations; participation in vendor-driven programs to stabilize revenue; association with a larger regional/national network of medical oncologists for negotiating purposes; regional consolidation under a single tax ID for the purpose of negotiations with payers; alignment with a multispecialty, physician-centric ACO; participation as an individual practice in a regional ACO; and engagement in physician-directed care transformation to deliver a new value proposition to payers and begin to define and demonstrate value in cancer care.

The last option offers potentially the most important opportunity for real

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clinical and financial change. But it provides a dual challenge. First, it requires nothing short of a substantial, disruptive, and coordinated response by the practice to re-engineer the delivery of care. Second, it requires the creation of a sustainable business model for independent community-based practices by actively engaging with payers in the development of new payment methodologies that will support these different processes of care capable of producing remarkable results.

Oncology Patient–Centered Medical Home

A physician-led response built around the National Committee for Quality Assurance's (NCQA's) standards for the primary care patient-centered medical home (PCMH) program has been created to address these challenges. The NCQA standards provide a template that calls for a physician-led care team to direct disease management, care coordination, the standardization to the evidence base, and patient engagement and education.[4] Results from primary care PCMH projects suggest elements of the model have a positive effect on quality, cost, and satisfaction of the patient and the clinical team.[5,6]

In 2010, Consultants in Medical Oncology and Hematology (CMOH)—a 9-physician, single-specialty practice outside of Philadelphia—became the first oncology practice recognized by the NCQA as a level III PCMH.[7] The growing national attention focused on this model has, in large part, stemmed from CMOH's success in effectively minimizing unnecessary resource use. CMOH has lowered emergency department visits by 68%, hospital admissions per patient treated with chemotherapy per year by 51%, and the length of stay for admitted patients by 21%. CMO has also seen a 22% reduction in outpatient visits per patient per year in the general (hematology and oncology) patient population and a 12% reduction in outpatient visits per patient per year in the chemotherapy subpopulation. CMOH has demonstrated that the processes of improving the delivery of cancer care and reducing unnecessary use (waste) are intertwined; they are one and the same.

The aggregated economic savings to CMOH's payers is estimated to be in the range of $1 million per physician per year. The magnitude of the savings is a reflection of the cost of caring for a concentrated population of clinically vulnerable, older, chronically ill patients with multiple comorbid conditions and unique psychosocial needs. Although CMOH is in the process of replicating this model in other practices, the data presented, thus far, are from the single practice. This begs the question of the validity and reproducibility of this model.

Validity

CMOH's internal data have recently been directly compared with the internal cost and use data of a national payer. The results of that comparison were consistent with CMOH's own data. The necessary validation of this model can only occur with the cooperation of payers and significant expansion of the model to other practices.

Reproducibility

The Congressional Budget Office's Lessons from Medicare's Demonstration Projects identified several successful components of the demonstration projects, including the ability to "gather timely data on the use of care, especially hospital admissions; the focus on transitions in care settings, especially primary care to specialist referral; using a team-based care approach; targeting interventions toward high-risk enrollees; limit the cost of [and insertion of third parties into the] intervention."[8(p8)] None of the disease management and care coordination demonstration pilots outlined in the report reduced Medicare spending. In part, this resulted from the use of costly third-party vendors. These vendors were required because the physicians involved were not called upon to transform the delivery of care within their own practice and needed outside intervention, thus negating savings from decreased use.

Bohmer[9] suggests that, instead of only focusing on the problems of definition and measurement of value in healthcare, it is equally important to understand how "health care delivery organizations reliably deliver higher value."[9(p2045)] He proposes that the ability to disseminate and consistently deliver high-value clinical innovation and system improvement is based on similar, portal habits of care management: extensive specification and planning, micro system design, measurement and oversight, and commitment to ongoing process improvement.

Many organizations engage in some or most of these habits, which explains the common response from oncologists after the presentation of CMOH's results: "I think we do that." Bohmer points out that high-value organizations "systematically . . . integrate [all 4 habits] into a comprehensive system for clinical management that is focused more on clinical processes and outcomes."[9(p2045)] The oncology PCMH (OPCMH) model with re-engineered processes of care on the basis of the NCQA template, the merger of operational and clinical decisions, and the developed infrastructure support facilitate the baking of these 4 habits into the practices' "structures, culture, and routines, [with the understanding that these are] not simply short-lived projects."[9(p2045)] CMOH has replicated this model of care in another similar-size practice; its performance is currently under evaluation.

Summary

"The good news is: the possibility of change has never been greater. The bad news: if it's going to be the right change, the burden is yours," stated Berwick in this year's closing remarks of the Institute for Healthcare Improvement National Forum. "If improvement [of care delivery] is the plan, then we own the plan. Government can't do it. Payers can't do it. Regulators can't do it. Only the people who give the care can improve the care . . . . It is not possible to claim that we do not know what to do. We have the templates."[10(p8)] Using the NCQA template, the CMOH integrated team of caregivers developed exactly what Berwick has called for: "An electronic line-of-sight contact with each other all day long, weaving a net of help and partnership with patients and families."[10(p8)] The template exists.

Without payer support, there will be further loss of community-based practices; costs will escalate, and the value of the delivered care will decline...

Oncologists know what to do. We need to move quickly to define, measure, and maximize the value of the OPCMH model to become responsible, accountable, and able to achieve the goals of better cancer care, better health, and lower cost through improved delivery of care.

Payers need to respond quickly to develop a contractual platform around this model so that it can be expanded and verified. It potentially provides a sustainable business model for the community oncologist because it transforms the delivery of cancer care within the practice without the need for insertion of a costly third-party vendor. It can also provide a framework for the improvement of cancer care delivery by all oncology care providers. Under the current fee-for-service system, the OPCMH model is economically unsustainable. Without payer support, there will be further loss of community-based practices; costs will escalate, and the value of the delivered care will decline, thus forcing arbitrary reductions in funding without full consideration of the clinical implications. The patient-centered healthcare reform initiative in cancer care will be lost. **EBO**

Author Affiliation: From Consultants in Medical Oncology and Hematology, Drexel Hill, PA.

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Medical Drug Benefit Management in the Pathway Era

Kim Farina, PhD

Payers have exhausted traditional oncology benefit management options. Many of their strategies to control utilization have led to unintended consequences, such as driving poor utilization over to the medical side of the equation. As a result, payers are starting to turn to vendors for turn-key solutions to both pharmacy and medical benefits management. During a roundtable discussion, *Changing the Oncology Drug Reimbursement Paradigm Through Pathway Driven Oncology Management*, at the 2012 Academy of Managed Care Pharmacy Annual Meeting, William Sullivan, principal consultant, Specialty Pharmacy Solutions, LLC, provided an update on the state of oncology management.

What Is Driving Change?

Payers are under constant pressure to deliver savings to their accounts. New therapies and price of therapy are also important factors. The choice of chemotherapy is a huge cost determinant for the total cost of care. Additionally, efforts to manage oncology through traditional case management have been, for the most part, unsuccessful. "Payers just don't have the sophistication internally to really drill down deep into managing oncology patients and the science of oncology, for example, diagnostic testing and genetics," explained Sullivan. Oncology management extends beyond the medical and pharmacy arenas and involves cognitive, psychosocial, nutrition, hospice, and palliative aspects of care.

Another contributor to payers' desire for a new management paradigm is excess waste. In a recent *Managed Care Oncology Index* report by The Zitter Group, oncologists recognized an average 18% excess cost that could be immediately eliminated and 15% of them attributed the waste to inappropriate drug utilization. Sullivan talked about some of the reasons for inappropriate utilization. Overutilization is common during late-stage disease and upon treatment failure. Prescribing patterns of oncologists are slow to change. A number of published studies have demonstrated the difficulties oncologists face in keeping their practices up-to-date with the evidence base. Additionally, fewer oncologists are practicing in the community setting—over 300 practices closed within the last 2 years, with many of those oncologists moving to hospital-based practice. This has increased the work burden on remaining community oncologists and has caused some redirection of community oncology patients to the hospital outpatient setting.

One situation that has been on everyone's mind lately is the parity between pharmacy and medical benefits. Drugs which fall under pharmacy benefit plans, particularly oral anticancer drugs, can be associated with extremely high out-of-pocket costs for patients. On the medical side, infusible drugs may not represent optimal alternatives, but they are certainly less expensive. Concern has risen about patients being driven to certain medical alternatives simply because they are cheaper. "In fact, there is going to be a lot of legislation popping up about pharmacy and medical benefit parity," stated Sullivan.

Who Is Delivering Innovation?

A number of third-party vendors offer oncology management services to health plans (Table 1). Pharmacy benefit managers and specialty pharmacy both operate with a clear patient focus. Integrated single specialty providers (ISSPs), on the other hand, are third-party oncology management vendors seeking to create behavioral change around comprehensive guidelines/pathways with a focus on the oncologist, not patients.

ISSPs target both medical and pharmacy benefit management and policy to reign in total costs and increase quality and consistency of care. They are developing strategic and tactical programs to ensure appropriateness, minimize waste, and monitor and measure program compliance. This is being executed through the use of pathways and additional strategies in alignment with the pathway initiatives (Table 2). Sullivan explained, "It is a complicated recipe. Pathways are the primary ingredient, but there are about a dozen other components."

The ISSPs in operation are citing savings of 25% in the first year for health plans that follow their complete recommended program, according to Sullivan. Health plans are not always willing to jump in with both feet right away and often prefer to start with a scaled-down version. Sullivan estimates that each individual strategy has the potential to save 0.5% to 1% annually. Generally, providers that comply with established practice standards will enjoy shared savings and other incentives.

Next Frontiers: Pay for Performance, ACOs, Medical Homes

The next frontier in healthcare revolves around the concept of quality. "Oncology management can actually fit into these models (ie, pay for performance, accountable care organizations [ACOs], and medical homes) pretty well," said Sullivan. For one thing, a quality-driven model necessitates standards of quality—oncology clinical pathways represent those standards. Additionally, cancer patient populations are amenable to actuarial forecasting based on the number of cancer patients, stratified by type and stage of disease. "You can actually calculate cost factors associated with oncology pretty easily," explained Sullivan. "You pretty much know what the course of disease will be based on progression and response to care."

"Pathways will lower total cost of care because quality inevitably always does," remarked Sullivan. Lower total cost of care turns into net savings and net savings turns into shared savings, which benefits everyone. **EBO**

Table 1. Oncology Management Third-Party Vendors

Pharmacy benefit managers	• Target pharmacy and medical benefits • Base therapy management guidelines • Restrict services • Focus on patients
Specialty pharmacies	• Target oral pharmacy management • Base management on guidelines, in some cases • Reactive to plan • Focus on patients • Offer oncology-specified enhanced services
Integrated single specialty providers	• Target both medical and pharmacy benefit • Base management on comprehensive pathways • Adhere to behavior change model • Focus on oncologists • Utilize management and policy interventions

Source: Reprinted with permission from Sullivan W. Changing the oncology drug reimbursement paradigm through pathway driven oncology management. Presented at: The Academy of Managed Care Pharmacy 24th Annual Meeting and Expo; April 20, 2012; San Francisco, CA.

Table 2. Oncology Management Is Multifaceted

Strategy	Methods
Practice standards	Pathways
Reimbursement and compensation	Rational reimbursement, repricing
Formulary management	Lowest cost drug, rebates
Benefit design	Normalization of product selection bias
Distribution channel management	Optimization of site of administration
Medical management	Prior authorization, site of service
Diagnostics management	Proactive utilization management, cost management
Waste management	Dose management, split first fills
Health plan operations	Block units, claims scrubbing
Case management	Cognitive services, hospice, palliative care
Specialty management	Radiology, laboratory, etc
Pay for performance, accountable care organizations, and medical homes	Diverse methodologies

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