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Volume 18  
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## Evidence-Based Oncology

Exclusive Conference Coverage From the

1ST ANNUAL

# Translating Evidence-Based Research into Value-Based Decisions in Oncology

BALTIMORE, MD | NOVEMBER 16, 2012



**Clifford Goodman, PhD**, discusses evidence requirements to gain market approval and payments, individualized care decisions, and changes in innovation of cancer care.



**Jeffrey D. Dunn, PharmD, MBA**, addresses defining value and comparative effectiveness research in oncology.



**Bruce A. Feinberg, DO**, talks about the practical application of clinical pathways.



**Ira M. Klein, MD, MBA, FACP**, discusses quality measures in oncology.



**Peter B. Bach, MD, MAPP**, speaks about the evolving payment models in oncology.



**Andrew L. Pecora, MD, FACP, CPE**, talks about the evolution of integrated delivery networks in oncology.



**Michael E. Chernew, PhD**, describes the impact of healthcare reform on benefit design.



**A. Mark Fendrick, MD**, joins the panel to discuss the future of payer management in oncology.

- Evidence requirements, personalized care, and innovation in cancer care
- The importance of quality measures in oncology
- The practical application of clinical pathways
- Current evolution of accountable care organizations

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ADRENALS

# INHIBIT ANDROGEN PRODUCTION AT 3 SOURCES

PROSTATE  
TUMOR TISSUE

TESTES

Janssen Biotech, Inc.

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PHARMACEUTICAL COMPANIES  
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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 (17 $\alpha$ -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 ( $\geq 5\%$ ) 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  $\leq 50$  ng/dL).<sup>1</sup> 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](http://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 ( $\geq 5\%$ ) 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

## ZYTIGA™ (abiraterone acetate)

(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  $\geq 2\%$  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**

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

<sup>1</sup> Adverse events graded according to CTCAE version 3.0

<sup>2</sup> Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

<sup>3</sup> Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness

<sup>4</sup> Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema

<sup>5</sup> Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia

<sup>6</sup> 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).

<sup>7</sup> 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  $\geq 2.5X$  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**

Laboratory Abnormality	Abiraterone (N=791)		Placebo (N=394)	
	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*].

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**SP257 INTRODUCTION****SP258 HEALTHCARE REFORM****Oncology, Innovation, and Healthcare**

This article is based on the keynote address by  
Clifford Goodman, PhD



Recognizing that market conditions will continue to evolve, innovators must make decisions under uncertainty whether to pursue, adjust, or shelve the innovation, and reallocate resources accordingly.

**SP262 COMPARATIVE EFFECTIVENESS RESEARCH****Developing Comparative Effectiveness Research in Oncology**

This article is based on the presentation by  
Jeffrey D. Dunn, PharmD, MBA

**SP264 ONC PATHWAYS****Practical Application of Clinical Pathways**

This article is based on the presentation by  
Bruce A. Feinberg, DO

**SP265 QUALITY CARE****Quality Measures in Oncology**

This article is based on the presentation by  
Ira M. Klein, MD, MBA, FACP



The key to success with quality metrics is adherence. Not just patient adherence but adherence by the medical professionals to quality metrics and pathways-based oncology strategies.

**SP272 PAYMENT MODELS****Innovative Payment Models in Oncology Care**

This article is based on the presentation by  
Peter B. Bach, MD, MAPP

**SP274 INTEGRATED DELIVERY NETWORKS****Data Tracking and Point of Service Decision Support**

This article is based on the presentation by  
Andrew L. Pecora, MD, FACP, CPE



We need a model that lets physicians be physicians and frees them of some of the administrative duties. We also need a model that embraces the multitude of ways that patients are classified and treated.

**SP282 VALUE-BASED INSURANCE DESIGN****Healthcare, the National Debt, and Taxes**

This article is based on the presentation by  
Michael E. Chermew, PhD

**SP286 PAYER MANAGEMENT****Expert Roundtable Panel Discussion: The Future of Payer Management of Oncology**

*“For a drug in oncology that will cure cancer 90% of the time, it should not cost the same as a drug that will extend life by 6 weeks to 6 months.”*

—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, AJMC

*“I think the day of every new drug being simply set to a price that the market will bear, irrespective of the value it delivers, is one that will be seeing its sunset.”*

—Peter B. Bach, MD, MAPP

Director, Center for Health Policy and Outcomes  
Attending Physician  
Memorial Sloan-Kettering Cancer Center

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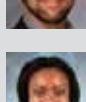
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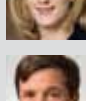
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On Friday, November 16, 2012, *The American Journal of Managed Care (AJMC)* hosted its first annual live meeting, *Translating Evidence-Based Research into Value-Based Decisions in Oncology*. The conference provided an opportunity for key leaders in managed care and oncology to discuss innovative payment models being used by payers and providers and their future impact on the rapidly evolving healthcare system.

The meeting kicked off with a breakfast presentation on cost-effectiveness in oncology, where experts suggested new approaches to incorporating dynamic and patient-centered considerations into value and cost-effectiveness calculations. Dana Goldman, PhD, director of the Leonard D. Schaeffer Center for Health Policy and Economics at the University of Southern California, described the relationship between US income and healthcare spending, and explained how the price of cancer therapy is relative to the value of its results (ie, survival). Yuri Sanchez, PhD, a research economist at Precision Health Economics, discussed the option value of innovation in cancer treatment. Darius Lakdawalla, PhD, director of research at the Leonard D. Schaeffer Center for Health Policy and Economics at the University of California, explored the challenges of measuring the cost-effectiveness of a drug and explained how it evolves over the product's lifecycle. A complete description of the experts' studies and results was published in a recent supplement to *AJMC* (November 2012–Vol. 18, No. 11, Sup.), which is available on [ajmc.com](http://ajmc.com).

Following opening remarks from A. Mark Fendrick, MD, professor of medicine and health management and policy, Schools of Medicine and Public Health, University of Michigan, and co-editor-in-chief of *AJMC*, there was a keynote address from Clifford Goodman, PhD, senior vice president, The Lewin Group, who spoke about evidence requirements to gain market approval and payment, individualized care decisions, and changes in innovation of cancer care.

Dr Goodman's presentation was followed by a session devoted to defining value in cancer care. Jeffrey D. Dunn, PharmD, MBA, formulary and contract manager at SelectHealth, Inc, described comparative effectiveness research in oncology. Bruce A. Feinberg, DO, vice president and chief medical officer, Cardinal Health Specialty Solutions, discussed the practical application of clinical pathways. Ira M. Klein, MD, MBA, FACP, chief of staff, Office of the Chief Medical Officer, Aetna, outlined quality measures in oncology.

The afternoon session focused on the role of innovative payment models in cancer care. Peter B. Bach, MD, MAPP, director, Center for Health Policy and Outcomes and attending physician, Memorial Sloan-Kettering Cancer Center, presented an overview of evolving payment models. Andrew L. Pecora, MD, FACP, CPE, chief innovations officer and vice president of cancer services at John Theurer Cancer Center at the Hackensack University Medical Center and president of Regional Cancer Care Associates, discussed the evolution of an integrated delivery network. Michael E. Chernew, PhD, professor of health care policy, Harvard Medical School, and co-editor-in-chief of *AJMC*, described the impact of healthcare reform on plan design.

The day concluded with all speakers participating in a roundtable discussion on the future of payer management in oncology that was moderated by Dr Goodman. **EBO**

*The conference provided an opportunity for key leaders in managed care and oncology to discuss innovative payment models being used by payers and providers and their future impact on the rapidly evolving healthcare system.*

EDITORIAL MISSION

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

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# Oncology, Innovation, and Healthcare

This article is based on the keynote address by Clifford Goodman, PhD

## The Times Are Changing

Recently, sanofi-aventis was forced to reduce the cost of its new cancer drug Zaltrap by 50% in response to Memorial Sloan-Kettering Cancer Center's decision to not use the drug. The cancer center stated that the new drug was twice as expensive as Avastin (manufactured by Genentech) despite similar efficacy. Both drugs improved median survival by 1.4 months.<sup>1</sup> In the *New York Times* article that reported the story, a senior vice president for oncology at UnitedHealthcare stated that "It was the first time physicians have stood up and said, 'Enough is enough.'" Many believe that this small story in the *New York Times* was a watershed moment. "It is shifting the fulcrum of the return on investment in oncology innovation," remarked Dr Clifford Goodman, PhD, senior vice president at The Lewin Group, at the beginning of his keynote address entitled *Health Care Reform: What Now for Evidence Requirements, Personalized Care, and Innovation in Oncology?*

So what are the marketplace trends affecting innovation in oncology? Dr Goodman outlined 14 such trends:

1. Scientific and technical advances (eg, lower costs for genome sequencing)
2. Diminished blockbuster opportunities
3. Restructuring and consolidating life science industry
4. Changing research and development roles of big and small companies
5. Shifting relative magnitudes of international markets for oncology interventions
6. Varying and unpredictable international intellectual property protection
7. Global effects of reference pricing and other downward price pressure by national and regional health authorities
8. Complex, variable relationships between the evidence requirements of regulators and payers, and greater reliance on health technology assessment
9. Greater demand for evidence of comparative effectiveness of new interventions (not just absolute efficacy versus placebo)
10. Greater emphasis on discerning heterogeneity of treatment effects
11. Increasing patient centeredness, including greater emphasis on patient-reported outcomes
12. Need to validate companion diagnostics (eg, for personalized medicine), including evidence of their impact on treatment decisions and outcomes
13. Increasingly broad and sensitive postmarket detection of adverse events
14. Increasing yet varying demands of payers for demonstrating cost-effectiveness and/or acceptable budget impact

## Innovation Isn't Getting Any Easier

Dr Goodman highlighted why industry faces greater challenges to adding a new oncology drug or procedure into the marketplace. Gaining market approval by the US Food and Drug Administration (FDA) is not the guaranteed ticket to market success. Innovators must pass the scrutiny of regulatory and payment gatekeepers, and the 2 groups often have different evidence requirements (Table).<sup>2</sup> According to Dr Goodman, although payer evidence requirements do not substitute for those of regulators, they are increasingly mediating adoption and use in the marketplace. For example, the main question of regulators continues to be: "Does the drug work?" For payers, it is more likely: "How well does the drug work in the community or general practice compared with standard care?" The answers to these questions often require different types of evidence, which can complicate new therapy development and validation. The evidence could be generated using practical (pragmatic) clinical trials, other nonrandomized controlled trials, adaptive clinical trials, and other trial designs (eg, randomized consent, regression discontinuity, combined single-subject ["n of 1"] trials). Prospective and retrospective observational studies should also be considered, such as population-based longitudinal cohort studies, patient registries, claims databases, clinical data networks, electronic health record data analyses, and passive and active postmarketing surveillance. Dr Goodman also noted that payers may draw on syntheses of existing evidence (eg, systematic reviews, meta-analyses, and modeling). These additional types of studies can supple-

**Table. Differences in Evidence Expectations From Regulators and Payers<sup>2</sup>**

Characteristic	Regulatory Approval	Payment
<b>Research question</b>	Can the drug work?	How well does the drug work in community/general practice compared with standard of care?
<b>Study design</b>	Randomized controlled trials	Randomized controlled trials, pragmatic controlled trials, certain observational studies, other
<b>Patient population</b>	Narrowly selected, similar baseline, limited comorbidities; some stratification	More diverse patients more likely to use drug in community practice; more subgroup analyses
<b>Intervention</b>	Carefully managed/monitored dosing and side effects; expert practitioners	Less carefully managed; wider range of practitioner expertise/experience
<b>Comparator(s)</b>	Placebo or intervention selected to maximize treatment effect	Standard of care/typical therapeutic alternative(s); may use indirect comparisons if direct comparisons unavailable
<b>Compliance</b>	Strictly monitored, enforced	As in community practice; less actively enforced
<b>Outcomes</b>	Intermediate/surrogate end points; health outcomes <sup>a</sup> if feasible in short time frame; little or no economic data	Health outcomes <sup>a</sup> relevant to clinical decisions or policies; more patient centered; often economic
<b>Time frame</b>	Sufficient to detect significant differences in intermediate/surrogate, other end points	Sufficient to detect significant and clinically important differences in health outcomes
<b>Setting of care</b>	Controlled (eg, center of excellence)	Community practice; often diverse
<b>Validity</b>	High internal; low external; often not broadly generalizable	Internal from market approval plus extended external (longitudinal, settings, subgroups)

<sup>a</sup>Health outcomes: mortality, morbidity, adverse events, quality of life, functional status. Adapted from Schumock GT, Pickard AS. *Am J Health Syst Pharm.* 2009;66(14):1278-1286.

ment payers' understanding of how therapies work in more diverse and representative populations. Dr Goodman emphasized that "This does make it more difficult to innovate. It is more demanding of evidence. It is more demanding of continued data generation, collection, analysis, and feedback."

## What to Measure?

Dr Goodman stated that innovation in oncology increasingly calls on researchers to use multiple study designs (as listed above). To illustrate the types

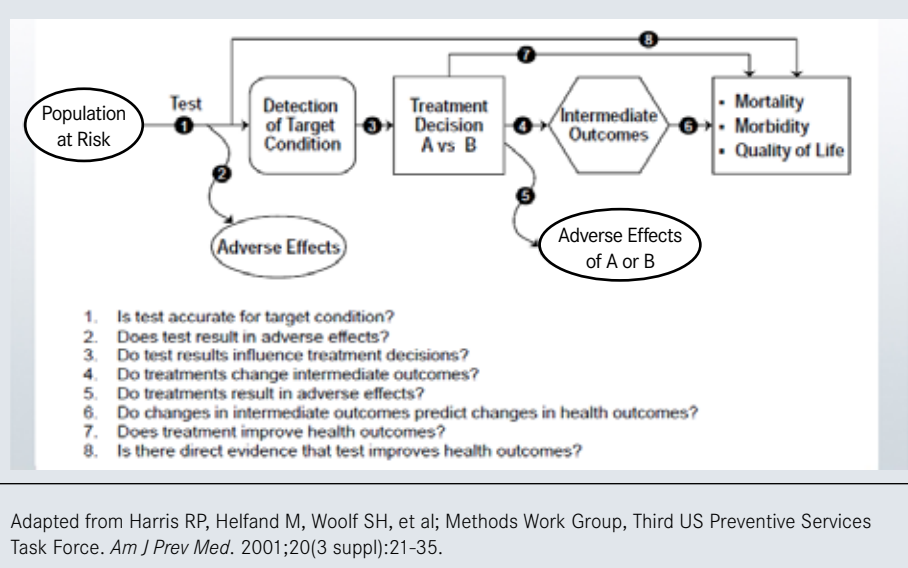
of evidence questions posed by payers, he showed a typical analytic framework for diagnostics and therapeutics (Figure 1).<sup>3</sup> Dr Goodman stressed that test accuracy is often not sufficient for validating tests in clinical use, and that clinicians, payers, and other decision makers also seek direct or indirect evidence linking tests to clinical decisions and health outcomes.

## End Points and Biomarkers

The most sought end point in oncology studies typically is overall survival, de-



Figure 1. Analytical Framework of Evidence Questions<sup>3</sup>



defined as the time from study randomization until death from any cause; it is best measured in the intent-to-treat population. However, the FDA and other parties will analyze other end points, including

- Tumor assessments:
  - Disease-free survival: time from randomization until recurrence of tumor or death from any cause
  - Objective response rate: proportion of patients with tumor size reduction of a predefined amount and for a minimum time period
  - Complete response: no detectable evidence of tumor
  - Time to progression (TTP): time from randomization until objective tumor progression; does not include death
  - Progression-free survival: time from randomization until objective tumor progression or death
- Symptom assessment:
  - Patient perspective of direct clinical benefit
  - Patient symptom assessments and/or physical signs representing symptomatic improvement (eg, weight gain, decreased effusion)
  - Time to progression of symptoms: Similar to TTP, a direct measure of clinical benefit rather than a potential surrogate<sup>4</sup>

Important work on identifying and validating surrogate end points for regulatory purposes and clinical decision-making continues. A recent example is the 2012 FDA guidance on using pathologic complete response as a surrogate end point in neoadjuvant treatment of high-risk early-stage breast cancer to support accelerated FDA approval that would be linked to requirements for subsequent data collection to demonstrate the relationship of the surrogate to health outcomes.<sup>5</sup>

Dr Goodman noted that the validity of surrogates must be continually

scrutinized. For example, although increased bone density has been used as a surrogate end point for osteoporosis medications, it is not necessarily a reliable predictor of decreased fracture rates. Similarly, despite widespread use of prostate-specific antigen levels for clinical decision making, it is often not a reliable predictor of mortality and other outcomes in prostate cancer management.

Genetic testing is also subject to greater scrutiny. Evidence of analytic validity (test accuracy for a genotype) must increasingly be accompanied by evidence of clinical validity (test accuracy for identifying a clinical condition or other phenotype) and, further, evidence of clinical utility (impact on clinical decisions and health outcomes). Although evidence is commonly lacking for clinical utility and clinical validity for assessing risk or otherwise managing disease, it can be lacking for analytic validity as well.<sup>6</sup> Dr Goodman noted that even when such evidence is available, payers recognize that the data trail in practice from patient indications for a test to test ordering to test result to indicated clinical decision is typically incomplete and otherwise poorly documented.

#### Personalized Medicine

Dr Goodman noted that “Personalized medicine is not simply about the genomics.” Personalized medicine is intended to tailor medical care to the particular traits (or circumstances or other characteristics) of a patient that influence response to a healthcare intervention. In addition to genetic traits, these may be sociodemographic, clinical, behavioral, economic, environmental, and other personal traits, as well as personal preferences. Dr Goodman emphasized that, for any form of cancer, there may be a great diversity of such traits—including where and how

people live and what their incentives are—that can affect individual patient response across the broader at-risk population and, therefore, should be weighed in determining optimal care for individuals. Dr Goodman described how the conduct of subgroup analyses in comparative effectiveness research and patient-centered outcomes research to discern heterogeneity of treatment effects reflects, in part, the need to yield evidence to support personalized medicine.

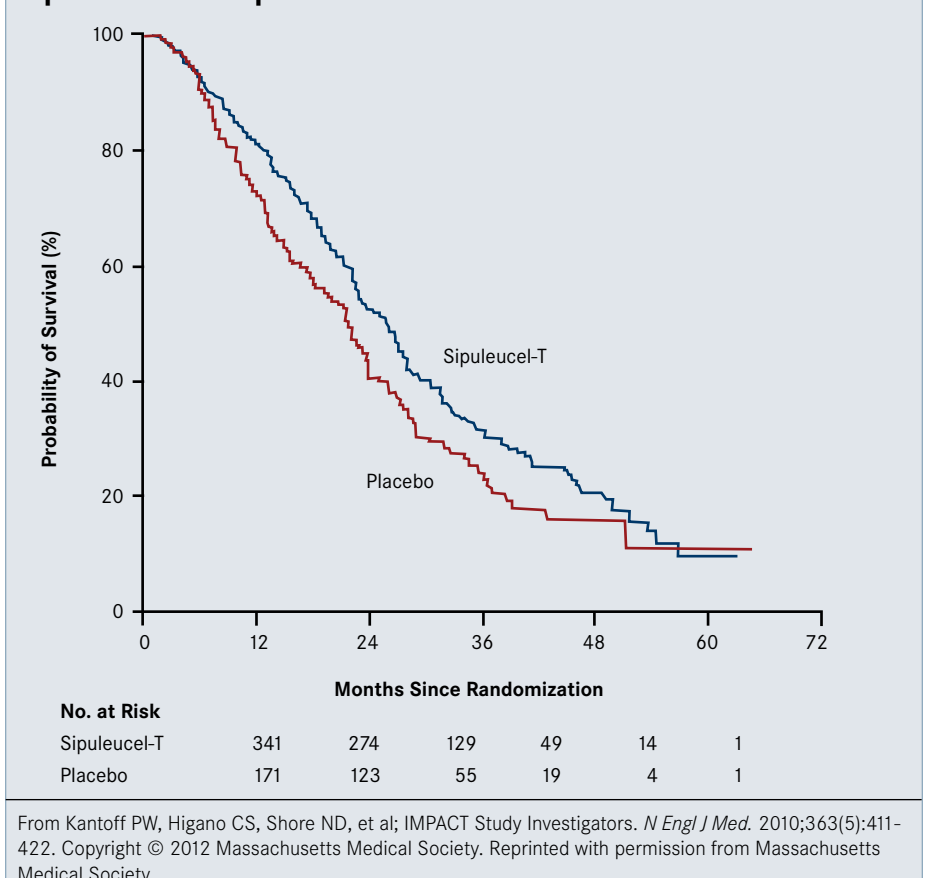
#### Evidence for the Medicare Evidence Development & Coverage Advisory Committee

To illustrate what types of evidence are of increasing interest to payers, Dr Goodman referred to his recent experience on the Medicare Evidence Development & Coverage Advisory Committee (MedCAC), which advises the Centers for Medicare & Medicaid Services about the quality of evidence pertaining to Medicare national coverage determinations. The questions placed before the MedCAC emphasize whether there is adequate evidence to determine whether a technology, therapeutic, or diagnostic has an impact on patient outcomes and, if the evidence is adequate, what it demonstrates. When the available evidence shows favorable impacts on patient outcomes, the MedCAC asks whether it also applies to community-based settings and to Medicare beneficiaries in particular.

Dr Goodman gave 2 examples from the MedCAC. One was pharmacogenomic testing for 5 types of cancer, including HER2/neu for patients with breast cancer who are candidates for trastuzumab and K-RAS for patients with metastatic colorectal cancer who are candidates for cetuximab and/or panitumumab. Rather than focusing on the accuracy of these tests as such, the MedCAC questions addressed the evidence for whether each pharmacogenomic test improves outcomes for patients with cancer whose anticancer treatment strategy is guided by the test results and how well that evidence pertains to Medicare patients in community settings.

In the second example, Dr Goodman discussed how MedCAC examined evidence for FDA-approved Provenge (sipuleucel-T), an immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. The committee examined available evidence about whether the therapy would improve overall survival, control disease-related symptoms, and minimize patient burdens associated with anticancer therapy, including access to care, delivery, and side effects. The MedCAC was generally confident about the quality of the evidence demonstrating some improvement in overall survival and minimizing patient burdens, but not for control of disease-related symptoms. Further, given that

Figure 2. Kaplan-Meier Estimates of Overall Survival With Sipuleucel-T Compared With Placebo<sup>7</sup>



physicians in practice can prescribe FDA-approved therapies for other indications, the MedCAC examined whether the evidence pertaining to the FDA-approved indication was generalizable to 3 off-label uses of Provenge: prostate cancer that has not metastasized; metastatic, castrate-resistant disease with more severe symptoms; and metastatic prostate cancer that has not failed hormonal therapy. The MedCAC expressed low confidence in the evidence supporting all 3 off-label indications. Finally, the MedCAC looked at the generalizability of these findings to patient groups that may have been under-represented in the available clinical trials and community settings. Dr Goodman emphasized that these types of questions are asked as well by public and private sector payers.

Dr Goodman cited Provenge in returning to the theme of innovation and value. Media reports have highlighted the price of Provenge, which was \$93,000 per course of therapy at the time of the MedCAC meeting, and several public commenters raised concerns that this would affect the MedCAC's deliberation. However, he made it clear that the MedCAC does not address matters of cost, and none of its evidence questions addressed the cost of Provenge. What is apparent, though, is that the cost of new cancer therapies is integral to their value. To illustrate, Dr Goodman referred to the survival curves presented at the MedCAC meeting displaying the difference in overall survival between the Provenge treatment group and the placebo group in the pivotal randomized controlled trial (Figure 2).<sup>7</sup> There was a 4.1-month median difference in overall survival. He stated that, while the Medicare program does not consider cost-effectiveness, many cannot help but wonder whether the space between those 2 curves is worth \$93,000. Dr Goodman stated "I will suggest that type of question is being asked more and more, and was probably in the minds of the Memorial Sloan-Kettering folks in the *New York Times* article I showed you earlier."

#### Performance-Based Reimbursement

Paraphrasing a former defense secretary, Dr Goodman said that when it comes to newly approved, and even newly reimbursed, drugs, "We often don't know what we don't know." As noted above, upon regulatory approval, there is often insufficient evidence for how well a drug will work for more diverse patients in real practice, as well as for rare or delayed adverse events. In US and international markets, payment authorities and life sciences companies have been negotiating

various forms of pay-for-performance, risk-sharing, and other types of managed entry for these drugs. For example, in Germany, Roche offered a pay-for-performance arrangement on its drug Avastin for several types of cancer. Payers and cancer care providers get refunds if patients do not respond. As with most deals of this nature, various concerns arise about provider incentives and implications for patient access and health. In any case, such arrangements can enable some market access and payment where there might have been more resistance by payers and other gatekeepers.

Similar deals have been struck for other drugs in various countries. For example, in the United Kingdom, AstraZeneca provides Iressa for free for the first 2 cycles of first-line use in patients with EGFR mutation-positive non-small-cell lung cancer. If the patient responds to treatment, the National Health Service will pay a fixed per-patient price of £12,200, regardless of how long the drug is used.<sup>8</sup>

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#### Disruptive Innovation

Dr Goodman stated that the nature of demand for innovation in healthcare is changing. Beyond new or different, and even in addition to more effective, there is increasing, explicit demand for innovation of value, that is, achieving desirable or acceptable improvement in outcomes per incremental expenditure. Payers and more clinicians and patients want to know "Is it worth it?" Of particular note in healthcare systems undergoing change are "disruptive innovations" that can change

healthcare regulation, payment, delivery, professional training, and other market characteristics. Examples have included diagnostic imaging that replaced exploratory surgery and gene therapy that is replacing some drugs and biologics.

#### Concluding Remarks: Moving Toward Breakthrough Innovations

Dr Goodman concluded with considerations for pursuing breakthrough innovation. Among these are to identify objectives for meeting specific unmet health needs as well as the target users and relevant decision makers for such a breakthrough. This involves identifying the attributes that will distinguish the drug for those target groups, whether this is a clinically meaningful treatment effect, a reduction in adverse events, increased adherence, or a reduction in healthcare utilization or costs. Innovators must anticipate and specify the evidence that will be required to validate these attributes and the feasibility of doing so, including costs, timeline, and other practical aspects. Recognizing that market conditions will continue to evolve, innovators must make decisions under uncertainty whether to pursue, adjust, or shelve the innovation, and reallocate resources accordingly. Dr Goodman made it clear that no one said this would be easy, but that innovation has to reach the higher bar in today's marketplace. **EBO**

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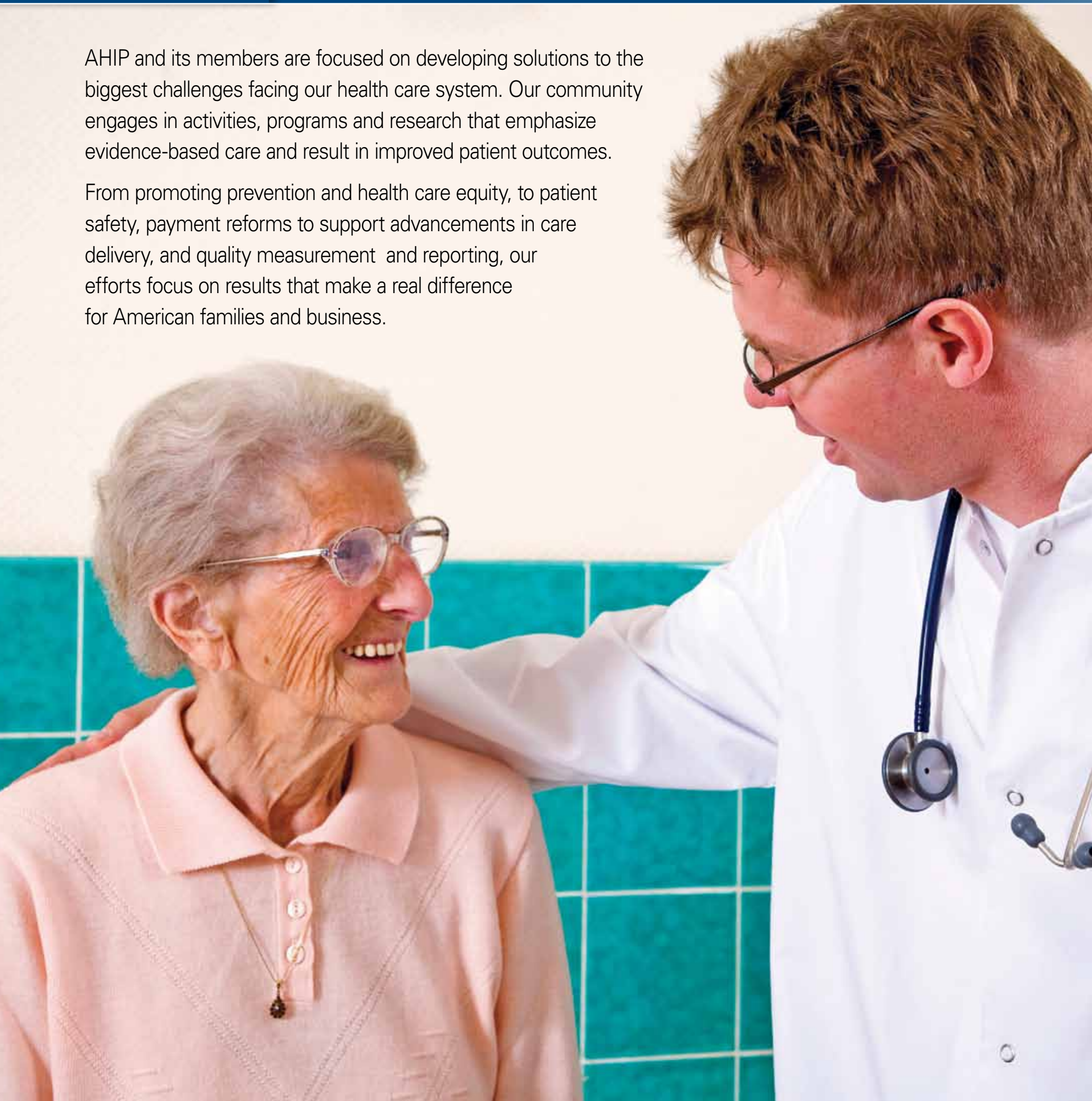
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# Developing Comparative Effectiveness Research in Oncology

This article is based on the presentation by Jeffrey D. Dunn, PharmD, MBA

Cancer is extremely political and extremely emotional. That makes a discussion on the economics of cancer treatment tricky. Further, the cost and value of cancer therapies are not discussed properly. But they need to be discussed. Cancer treatments are expensive and the decisions that need to be addressed (end of life care, expensive side effects, quality of life, treatment efficacy) can significantly impact total costs (Figure).

To introduce these issues, Jeffrey D. Dunn, PharmD, MBA, formulary and contract manager at SelectHealth, Inc, in Murray, Utah, gave a presentation entitled *Defining Value in Cancer: Comparative Effectiveness Research in Oncology*. Dr Dunn said that most people in oncology understand that the complexity of the treatment regimens, bioethics of certain treatment regimens, off-label use of drugs, the lack of consensus among guidelines, and patient education tend to be the topics of discussion, but there needs to be an honest discussion about the cost of care. Cancer is very expensive and the model for cancer care is difficult to fit into a traditional cost-management method. In some cases, cancer is an acute condition; in other cases, the cancer is similar to a chronic condition. And in some cases, it is less about cancer and more about end-of-life care. So, Dr Dunn asked, "Can oncology be considered a value-based disease state?"

According to him, the answer is as complex as the disease. The answer is also dependent on whom you ask. Both payers and clinicians believe costs can be reduced. Payers strongly believe that adoption of clinical pathways will reduce costs (80% of payers believe so)

and improve cancer care (88% of payers believe so). Oncologists also believe that clinical pathways will reduce costs and improve care (61% and 60%, respectively).<sup>1</sup> One way to improve cancer treatment and reduce costs may be the use of comparative effective research (CER).

## CER

The purpose of CER is "to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision makers, responding to their expressed needs about which interventions are most effective for which patients under specific circumstances." Historically, clinical pathways for breast, colorectal, and lung cancers have been in place for a number of years,<sup>2</sup> and pathways for other cancers are being developed. To date, most pathway initiatives have been a collaborative effort between physicians and payers that have utilized the framework of guidelines from the National Comprehensive Cancer Network. CERs can provide great value, but some people confuse CER with restrictions, rationing, or cost-containment issues. Dr Dunn stated that CER is intended to provide real-world evidence on the most cost-effective therapies in an effort to improve outcomes and reduce costs.

## CER Is Local

Good CER requires the engagement of local oncologists. Dr Dunn said that regional variations make it imperative for local oncologists to be involved. Also, the engagement of local oncologists helps develop better working arrangements between oncologists and payers that can allow both parties to be more effective.

With that being said, there are a few disadvantages to tweaking the guidelines to create CER that is more regional. Dr Dunn noted that evidence may need to be "massaged." If a local doctor performs a treatment successfully but it is not in the guidelines, it can be tricky to address that issue. As such, it becomes more difficult to defend certain requests where the data are not black and white, but in a gray area. And that gray area is common in oncology. It has been estimated that one-half to three-fourths of all cancer drugs are used off label.<sup>3</sup> Dr Dunn stated that there are so many new drugs and new treatment ideas being developed that it is difficult for compendia to keep up. That is why local oncologists' input is needed; however, it is also why it can be a struggle to balance what physicians know or think is better in comparison with the guidelines or regulatory agencies.

Dr Dunn said that CER evidence should be based on outcomes (not surrogates), be clinically meaningful, have outcomes that are patient centered, and include costs. He also noted that the CER should be translated into language that can be understood by physicians, payers, and patients.

If done properly, the use of CER as a decision-support tool should:

- Reduce variability in outcomes
- Reduce variability in costs
- Invest in patients' health and improve health outcomes
- Reduce wasteful spending by reducing toxicities

## The Problem With Cancer Evidence

According to Dr Dunn, randomized controlled comparative studies are rare in oncology. In most cases, "We end up relying on cohort studies, population studies, predictive studies, and modeling. So, this is not ideal. And even when we do have randomized controlled trials in oncology, a lot of these are short term and use surrogate efficacy outcomes because they are not long enough or powerful enough to show benefits in survival. They are often limited in sample size and they are often not powered to show statistical improvement over [the] existing standard of care."

## CER and Patient-Centered Outcomes Research

Dr Dunn said there is a growing trend to include patients (and payers) in the

study design using patient-centered outcomes research (PCOR), in which both parties have input into the study's comparators and outcomes. Equally important, both parties may have a better idea of the risks and benefits of a treatment compared with parties that traditionally designed studies. He also noted that PCOR is a new idea to oncology; as a result, it is limited. However, Dr Dunn indicated that the studies have a real-world component to them that is often missing in more traditional trials.

## Estimating Cost of Oncology Treatment

Cost is very difficult to estimate in cancer. This is due to many factors, including treatment regimens that are constantly changing, combination therapy, and new algorithms, all of which can extend the life of patients but create new indirect costs. That is why increasing use of PCOR to obtain real-world data is important. PCOR can also help identify subgroups of treatment responders.

Dr Dunn also noted that PCOR does have its limitations and barriers. Data can be inconsistent or unreliable. Other barriers to success include poor communication that impedes constructive feedback, provider pushback, and incentives that may be misaligned. The key for success is for all parties to be in constant communication to make sure that the data being studied will have value for future clinical pathways.

## Concluding Remarks

Dr Dunn concluded his presentation by reiterating that efficacy and costs need to be addressed when developing CER, and that all parties need to be involved. However, oncology treatment is very complicated. He used a simple example of 3 oncology drugs with sharp differences in daily versus monthly costs. It is up to the physician, payer, and patient to determine which treatment is best, and that is not an easy task. **EBO**

## References

1. The Zitter Group. The Managed Care Oncology Index. Winter 2011. <http://www.zitter.com/OncologyIndex.html>. Accessed November 21, 2012.
2. Danielson E, Demartino J, Mullen JA. Managed care & medical oncology: the focus is on value. *J Natl Compr Canc Netw*. 2010;8(suppl 7):S28-S37.
3. "Off-label" indications for oncology drug use and drug compendia: history and current status. *J Oncol Pract*. 2005;1(3):102-105.

## Figure. Status of Oncology Treatments Has Changed: Cancer Is Now on the Table

Price and value of therapies rarely questioned

Vigorous debate about the overall value<sup>a</sup> of treatments

Prespecialty oncology drug era

Specialty oncology drug era

Payers now actively apply payment reforms and quality measurement to cancer services

<sup>a</sup>Clinical, pharmacoeconomic, humanistic, societal, etc.

# Evidence. Value. Innovation.

## EVIDENCE

Ensure that sound evidence is recognized by independent experts, considered appropriately by private and public payers, reflected adequately in benefit designs, and incorporated into clinical practice.

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## INNOVATION

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# Practical Application of Clinical Pathways

This article is based on the presentation by Bruce A. Feinberg, DO

The cost of care for any patient generally follows a variation of Parkinson's Law. "The more you have available to give to a patient, the more the patient will receive and that requires us to be thinking of different paradigms and not applying medical economics to classical economics," began Bruce A. Feinberg, DO, vice president and chief medical officer, Cardinal Health Specialty Solutions, in his presentation entitled *Practical Application of Clinical Pathways*. Adding to that belief, the more that is spent on medical care, the more likely there will be increased wasteful spending. One way to get around these problems is to use pathways, because they can provide local peer-reviewed guidelines that allow clinicians to treat patients as they see fit. As a result, local clinicians will be better equipped to avoid unnecessary costs since their reference points for care will be local and they will be cognizant of the best way to efficiently treat each patient.

In that regard, Dr Feinberg compared clinicians with jazz musicians or chefs. A jazz musician will look at sheet music and a chef will look at a recipe before proceeding. But, both will use their training and experience to expand on what they see in front of them to create music or a meal that is unique to the surroundings. That is what guidelines/pathways can provide to clinicians—a means to provide peer-reviewed guidance while still focusing on the individual patient.

## Pathways

"One of the great misconceptions about pathways is that somehow they represent some alternative universe—and they don't. They are a subset of the universe," said Dr Feinberg. To clarify, Dr Feinberg showed a graphic representation of the universe with areas that depicted the US Food and Drug Administration, the National Comprehensive Cancer Network (NCCN), and others. According to Dr Feinberg, pathways can stretch across those different regulatory bodies and create treatment guidelines that are specific to the clinician's and patient's part of the universe. To illustrate, he said that the NCCN guidelines for adjuvant HER2-negative, node-positive breast cancer has 16 regimens listed. However, most doctors only prescribe 3 or 4 of those regimens on a regular basis. Dr Feinberg's employer, Cardinal Health, would ask the 300 or so physicians in a

given provider network to agree to those same 3 or 4 regimens. By doing that, they believe there will be a reduction in treatment variance that further refines treatment and can lower costs.

## Allowing Physicians to Be Physicians

Cardinal Health is working with physicians to establish them as democratic representatives of their network. Usually, a representative sample of about 12 local physicians (for a network there could be 100 to 300 physicians across the state or geographic area) will develop their own pathway in collaboration with the payer. Dr Feinberg said, "The goal is always best patient outcome." Patient compliance is usually set at 80% for each pathway to allow a 20% leeway for those patients who will require a treatment that deviates from the pathway's suggested treatment options.

Using this setup, all parties should "win." Patients will see better outcomes with more refined care as physicians will be using a specific list of treatment options for a particular population. Also, payers will benefit from lower variance and less cost. Dr Feinberg thinks that pharmaceutical companies will like this model because it will provide a tremendous opportunity to increase accrual rates in clinical trials. He said, "If you have these networks, you have captive audiences to embrace clinical trials," adding, "If we can decrease clinical trial accrual time in this country from 12 years to 6 years, we can halve the cost of drugs when they come to market."

## CareFirst Oncology

To illustrate the efficacy, safety, and cost savings of the pathways approach to healthcare, Dr Feinberg discussed the CareFirst Program. The program started in 2008 with 177 providers; by 2010, it had grown to 229. The key to the success of the program is compliance. In 2008, 77% of the practices were compliant; by 2012, 92% were compliant. Dr Feinberg added that the program only works if all parties are compliant. Therefore, "If a practice is noncompliant for 2 consecutive quarters, they get dropped, and if they then go back into compliance for 2 consecutive quarters, they're allowed back in."

In 2010, the first results from the program were presented at the American Society of Clinical Oncology (ASCO) annual meeting. Scott et al evaluated the

potential cost savings of a payer-based "pay for quality" oncology program that applied clinical pathways.<sup>1</sup> The analysis compared 57 participating practices (176 physicians, 10,432 patients) with 43 non-participating practices (194 physicians, 14,137 patients). The study determined that the estimated cost savings for anti-cancer drugs, supportive care drugs, and non-drug services was over \$12 million. After adjusting for additional fees to participate in the program, the total yearly savings was over \$8.5 million.

## Second Generation

The second generation of CareFirst is a pilot program currently under way that mimics a medical home with the goals of: (1) shifting reimbursement from drugs to cognitive services; (2) aligning incentives; (3) developing a continuous quality improvement (CQI) program; and (4) developing an end-of-life care initiative.

With a reimbursement plan, there is a fee for service, and in oncology those fees are for cognitive patient care, chemotherapy administration, and reimbursement of drug. Given the increasing cost of drugs, those margins have swelled such that the margin on drugs accounts for up to 70% of the oncologist's income. Policy makers are concerned that such reimbursement design incentives more and more expensive (higher-margin) chemotherapy-prescribing behavior. The medical home model realigned incentives by moving the dollars related to drug margin to cognitive services, allowing participating physicians to remain financially whole but without generating income from the sale of drugs.

So far, 14 practices, comprising 31 physicians, in the Maryland/Washington, DC, area have volunteered. Dr Feinberg stated that this pilot program is interesting because there is a possibility that it will dramatically shift how patients are managed and how clinicians treat them. Some of the questions the study was designed to answer include: Will cognitive work increase and at what cost? Will the use of chemotherapy decrease? Will there be a shift away from brand drugs if there are no longer significant margins for brand drug delivery? Will the CQI program decrease emergency department visits and hospitalizations? And will there be an impact on end-of-life care? So far, these questions have not been fully answered, but Dr Feinberg

provided some preliminary data from the pilot study. He cautioned, however, that due to the small sample size, the observed results cannot be considered statistically significant. One interesting observation was that the 31 physicians (in the aggregate) received 4.7% more reimbursement money compared with the year before (prior to joining the pilot program). If those physicians had been in the first-generation program, fees would have been 11% higher. However, when one dives deeper into the data from the aggregate to the individual practice level, there were clear winners and losers based on their patient mix. Dr Feinberg said, "This is where it's really problematic when you look at this kind of modeling, because often it may make sense in the aggregate but it can break down dramatically when you get down to the specifics." Further analysis demonstrated very little difference in physician prescribing behavior as both patient encounters and chemotherapy prescribing remained essentially the same despite the dramatic differences in reimbursement.

While the results from this pilot program may at first appear counterintuitive, it did provide: (1) validation of the unique medical home model among disparate providers; (2) evidence that significant savings (>3:1 return on investment [ROI]) can be achieved in a provider group already compliant with a mature pathways program (note: this was comparing the 4.7% increase in costs with the 11% increase that theoretically did not occur); and (3) a CQI program that directly and favorably impacted patient outcomes and ROI via reduced toxicities, emergency department visits, and hospital admissions.

Dr Feinberg noted that the pilot program will need further enhancements to sustain further savings, but he is very excited that the program can also be used as a springboard for better dialogue about end-of-life care. Whether or not the medical home concept can be exported across the entire plan remains to be determined, according to Dr Feinberg, but he is optimistic that some aspects of this program will lead to innovative programs in the future. **EBO**

## References

1. Scott JA, Wong W, Olson T, Fortner BV. Year one evaluation of regional pay for quality (P4Q) oncology program. *J Clin Oncol*. 2010;28(15 suppl):6013.



To view a video of this presentation, scan here.

# Quality Measures in Oncology

This article is based on the presentation by Ira M. Klein, MD, MBA, FACP

“When we ask people to deliver quality metrics and show what they have done, can we bring that information back to them in a usable format? Can we as payers take it and use it to reward? Can we use it to help pharma companies? Can we use it to help our employer sponsors understand what their costs are? Can we take it back to patients and give them action plans based on it?” asked Ira M. Klein, MD, MBA, FACP, chief of staff, Office of the Chief Medical Officer at Aetna. The answers to these questions were the premise for Dr Klein’s presentation entitled *Quality Measures in Oncology*.

Dr Klein stated the measurement domains for quality metrics: (1) patient experience; (2) value and access; and (3) clinical process and outcome. Furthermore, he noted 6 key questions that help determine the strength of a quality measure<sup>1</sup>:

1. How strong is the scientific evidence supporting the validity of this measure as a quality measure?
2. Are all individuals in the denominator equally eligible for inclusion in the numerator?
3. Is the measure result under control of those whom the measure evaluates?
4. How well do the measure specifications capture the event that is the subject of the measure?
5. Does the measure provide for fair comparisons of the performance of providers, facilities, health plans, or geographic areas?
6. Does the measure allow for adjustment of the measure to exclude patients with rare performance-related characteristics when appropriate?

## Measuring Efficacy and Costs

Dr Klein noted that outcomes can be used to tabulate efficacy and costs of care, but he clarified that more expensive treatment should be given to

some patients if it is deemed appropriate. For example, despite similar efficacy, the cost of treatment options for non-small lung cancer and colon cancer vary tremendously; however, some patients will require more expensive regimens (Table). While treatment will be tailored to the patient, Dr Klein cautioned that “Uniformity builds efficiency and that is what we want.” He also stated that drug shortages, use of generics, and the price of future treatment regimens will also come into play when deciding what is best for the patient with respect to cost and efficacy.

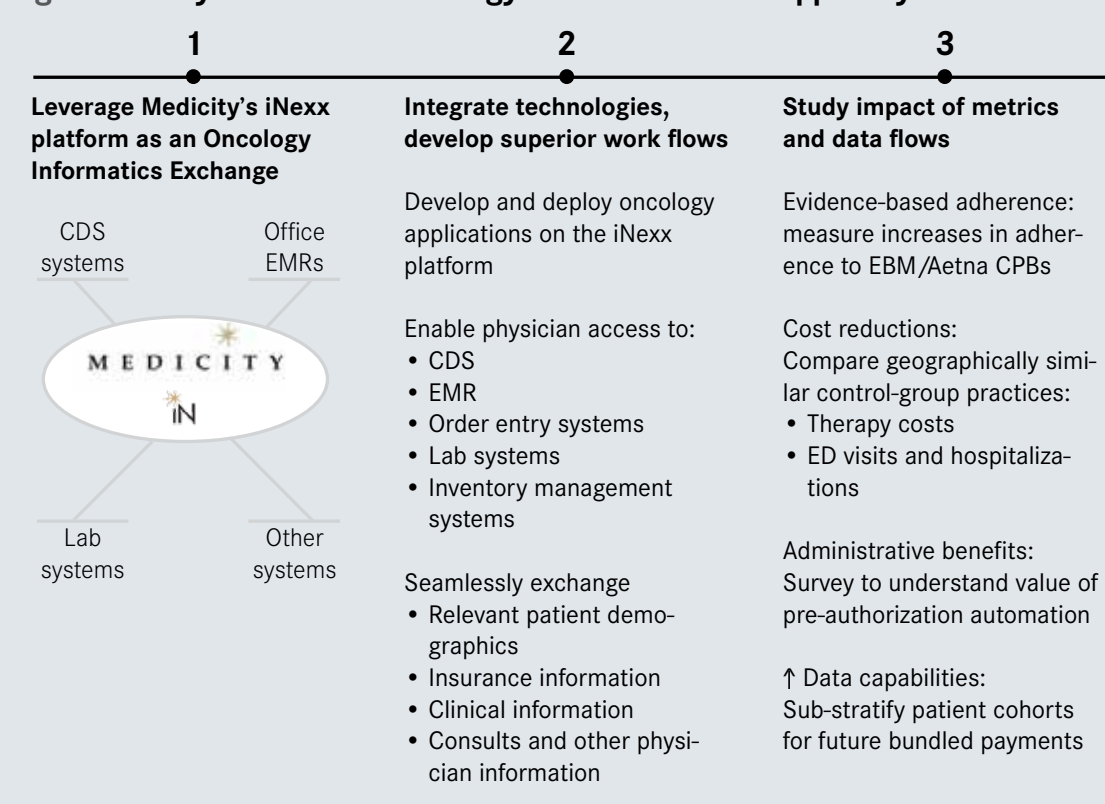
## Adherence

The key to success with quality metrics is adherence. Not just patient adherence but adherence by the medical professionals to quality metrics and pathways-based oncology strategies.

According to Dr Klein, adherence should:

- Enhance patient outcomes and cost-effectiveness of care by applying evidence-based clinical pathways and aligning oncology drug pricing with guidelines. Proper use of guidelines can promote drug pricing to drive selection of the most cost-effective medications, minimize side effects and toxicities, and support clinically appropriate lines of therapy
- Provide community-based care that continues to enable independent quality of life

Figure. Quality Metrics and Oncology Clinical Decision Support System at Aetna



CDS indicates clinical decision support; CPB, clinical policy bulletin; EBM, evidence-based medicine; ED, emergency department; EMR, electronic medical record.

- Provide decision support and care coordination for patients and families to help them make informed choices regarding lines of therapy or access to palliative and hospice care
- Align physician and reimbursement policy with clinical guidelines

## Clinical Decision Support

Adherence to quality metrics also requires a means for the data to be exchanged seamlessly with various parties. At Aetna, Dr Klein said they are planning to use Medicity as an informatics exchange program that allows all parties to have access to the data (Figure).

Using a clinical decision support system, both providers and patients can greatly benefit. Providers receive:

- A flexible clinical decision support platform that can be supported by multiple payers
- Evidence-based guidelines
- Network steerage preferences
- Online access to eligibility data
- Precertification waivers
- Applications that can make work flow easier

Members receive:

- Clinical information

- Social media
- Preferred physicians listing
- Culturally consistent content
- Seamless connection to benefit information
- Support services

The end result is that physicians get an office “that is a happy office, an efficient office. Time is not wasted finding data...or getting approval for things that should be approved based on the information available,” stated Dr Klein. Similarly, patients get information that helps them understand their disease, guidance for getting referrals, and access to patient organizations.

## Concluding Remarks

Dr Klein ended his presentation by stating that for a program to work, patients should always be in the center with all other parties in communication to ensure treatment that is both medically appropriate and cost-effective. **EBO**

## References

1. Agency of Healthcare Research and Quality. Validity of Clinical Quality Measures. <http://www.qualitymeasures.ahrq.gov/tutorial/validity.aspx>. Accessed November 24, 2012.

Table. Varying Costs of Cancer Therapies	
<b>Non-small cell lung cancer</b>	
Alimta + Cisplatin =	<b>\$33,278 (6 cycles)</b>
Carboplatin + Paclitaxel =	<b>\$2047 (6 cycles)</b>
<b>Colon cancer</b>	
Xeloda + Eloxatin =	<b>\$45,877 (8 cycles)</b>
Fluorouracil + Leucovorin + Eloxatin =	<b>\$24,687 (6 cycles)</b>



# DOXIL<sup>®</sup>

(doxorubicin HCl liposome injection)

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## INDICATIONS

- DOXIL<sup>®</sup> is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy
- DOXIL<sup>®</sup> in combination with VELCADE<sup>®</sup> (bortezomib) is indicated for the treatment of patients with multiple myeloma who have not previously received VELCADE and have received at least one prior therapy

## IMPORTANT SAFETY INFORMATION

### BOXED WARNINGS

Cardiotoxicity, infusion reaction, myelosuppression, liver impairment, substitution

- The use of DOXIL<sup>®</sup> may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m<sup>2</sup>
  - Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dose
  - Cardiac toxicity may also occur at lower cumulative doses (400 mg/m<sup>2</sup>) in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy
- Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL<sup>®</sup>. In most patients, these reactions have resolved within several hours to a day once the infusion is terminated. In some patients, reactions resolved with slowing of the infusion rate
  - Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have occurred. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use
  - The initial rate of infusion should be 1 mg/min to minimize the risk of infusion reactions

- Severe myelosuppression may occur
- DOXIL<sup>®</sup> dosage should be reduced in patients with impaired hepatic function
- Accidental substitution has resulted in severe side effects. Do not substitute for doxorubicin HCl on a mg per mg basis

## CONTRAINDICATIONS

- Patients with a history of hypersensitivity reactions to a conventional doxorubicin formulation or the components of DOXIL<sup>®</sup>

## ADDITIONAL SAFETY INFORMATION

- Cardiac function should be carefully monitored
  - Congestive heart failure or cardiomyopathy may occur after discontinuation of anthracycline therapy
  - For patients with a history of cardiovascular disease, or if the results of cardiac monitoring indicate possible cardiac injury, the benefit of therapy must be weighed against the risk of myocardial injury
  - In the randomized multiple myeloma study, 25 patients (8%) in the VELCADE arm and 42 patients (13%) in the DOXIL<sup>®</sup> plus VELCADE arm experienced left ventricular ejection fraction decrease (defined as absolute decrease  $\geq$ 15% over baseline or a  $\geq$ 5% decrease below institutional lower limit of normal)
- Myelosuppression may occur; frequently monitor complete blood count (including platelet count), at least prior to each dose of DOXIL<sup>®</sup>
  - In patients with recurrent ovarian cancer, hematologic toxicity (based on platelet count or absolute neutrophil count) may require dose reduction or delay in administration of DOXIL<sup>®</sup>
  - In patients with multiple myeloma, hematologic toxicity (based on platelet count, absolute neutrophil count, hemoglobin level, or neutropenia with fever) may require dose reduction, delay in administration, or suspension of DOXIL<sup>®</sup> and/or VELCADE



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long-term to ensuring a reliable supply of DOXIL<sup>®</sup>.

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- Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage
- Sepsis occurring during neutropenia has resulted in discontinuation of treatment and, in rare cases, death
- DOXIL<sup>®</sup> may potentiate the toxicity of other anticancer therapies, especially hematologic toxicities, when used in combination with other therapies that suppress bone marrow
- Hand-foot syndrome (HFS) may occur during therapy with DOXIL<sup>®</sup>
  - Based on HFS toxicity grade, dose reduction, delay in administration, or discontinuation of DOXIL<sup>®</sup> may be required
  - HFS was generally observed after 2 to 3 cycles of treatment, but may occur earlier
    - The reaction was mild in most patients, resolving in 1 to 2 weeks
    - The reaction can be severe and debilitating in some patients, resulting in discontinuation of therapy
- DOXIL<sup>®</sup> is an irritant, not a vesicant; use precautions to avoid extravasation
- DOXIL<sup>®</sup> can cause fetal harm when used during pregnancy
- Because of the potential for serious adverse reactions in nursing infants, discontinue nursing during treatment with DOXIL<sup>®</sup>.
- Recall reaction has occurred with DOXIL<sup>®</sup> administration after radiotherapy
- DOXIL<sup>®</sup> may interact with drugs known to interact with the conventional formulation of doxorubicin HCl
- In patients with recurrent ovarian cancer, the most common all-grade adverse reactions (ARs)  $\geq 20\%$  (DOXIL<sup>®</sup> vs topotecan, respectively) included: asthenia (40% vs 51%), fever (21% vs 31%), nausea (46% vs 63%), stomatitis (41% vs 15%), vomiting (33% vs 44%), diarrhea (21% vs 35%), anorexia (20% vs 22%), dyspnea (15% vs 23%), HFS (51% vs 1%), and rash (29% vs 12%)
  - In addition, 19% vs 52.3% reported alopecia (all grades)
  - Grade 3/4 hematologic ARs reported in  $\geq 5\%$  (DOXIL<sup>®</sup> vs topotecan, respectively) were neutropenia (12% vs 76%) and anemia (6% vs 29%)
- In patients with multiple myeloma, the most common all-grade ARs  $\geq 20\%$  (DOXIL<sup>®</sup> plus VELCADE vs VELCADE, respectively) included: neutropenia (36% vs 22%), thrombocytopenia (33% vs 28%), anemia (25% vs 21%), fatigue (36% vs 28%), pyrexia (31% vs 22%), asthenia (22% vs 18%), nausea (48% vs 40%), diarrhea (46% vs 39%), vomiting (32% vs 22%), constipation (31% vs 31%), mucositis/stomatitis (20% vs 5%), peripheral neuropathy (42% vs 45%), neuralgia (17% vs 20%), and rash (22% vs 18%)
  - In addition, 19% vs  $<1\%$  reported HFS

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

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K08D121023

## DOXIL®

(doxorubicin HCl liposome injection)  
for intravenous infusion

**BRIEF SUMMARY. Please see Full Prescribing Information.**

### WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION

1. The use of DOXIL (doxorubicin HCl liposome injection) may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m<sup>2</sup>. In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m<sup>2</sup> or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy [see Warnings and Precautions]. 2. Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. DOXIL should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions [see Warnings and Precautions]. 3. Severe myelosuppression may occur [see Warnings and Precautions]. 4. Dosage should be reduced in patients with impaired hepatic function [see Full Prescribing Information]. 5. Accidental substitution of DOXIL for doxorubicin HCl has resulted in severe side effects. DOXIL should not be substituted for doxorubicin HCl on a mg per mg basis [see Full Prescribing Information].

**INDICATIONS AND USAGE: Ovarian Cancer:** DOXIL (doxorubicin HCl liposome injection) is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. **Multiple Myeloma:** DOXIL in combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

**CONTRAINDICATIONS:** DOXIL (doxorubicin HCl liposome injection) is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of DOXIL [see Warnings and Precautions].

**WARNINGS AND PRECAUTIONS: Cardiac Toxicity:** Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m<sup>2</sup>. Lower (400 mg/m<sup>2</sup>) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered DOXIL only when the potential benefit of treatment outweighs the risk. Cardiac function should be carefully monitored in patients treated with DOXIL. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with DOXIL. If these test results indicate possible cardiac injury associated with DOXIL therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury. In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m<sup>2</sup>, or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL was 11%. In this study, cardiotoxicity was defined as a decrease of >20% from baseline if the resting left ventricular ejection fraction (LVEF) remained in the normal range, or a decrease of >10% if the resting LVEF became abnormal (less than the institutional lower limit of normal). The data on left ventricular ejection fraction (LVEF) defined cardiotoxicity and congestive heart failure (CHF) are in the table below.

**Table 1: Number of Patients With Advanced Breast Cancer**

	DOXIL (n=250)
Patients who Developed Cardiotoxicity (LVEF Defined)	10
Cardiotoxicity (With Signs & Symptoms of CHF)	0
Cardiotoxicity (no Signs & Symptoms of CHF)	10
Patients With Signs and Symptoms of CHF Only	2

In the randomized multiple myeloma study, the incidence of heart failure events (ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac failure, acute pulmonary edema and pulmonary edema) was similar in the DOXIL+bortezomib group and the bortezomib monotherapy group, 3% in each group. LVEF decrease was defined as an absolute decrease of ≥ 15% over baseline or a ≥ 5% decrease below the institutional lower limit of normal. Based on this definition, 25 patients in the bortezomib arm (8%) and 42 patients in the DOXIL+bortezomib arm (13%) experienced a reduction in LVEF.

**Infusion Reactions:** Acute infusion-related reactions were reported in 7.1% of patients treated with DOXIL in the randomized ovarian cancer study. These reactions were characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolved when the rate of infusion was slowed. In this study, two patients treated with DOXIL (0.8%) discontinued due to infusion-related reactions. In clinical studies, six patients with AIDS-related Kaposi's sarcoma (0.9%) and 13 (1.7%) solid tumor patients discontinued DOXIL therapy because of infusion-related reactions. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the DOXIL liposomes or one of its surface components. The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions [see Full Prescribing Information].

**Myelosuppression:** Because of the potential for bone marrow suppression, careful hematologic monitoring is required during use of DOXIL, including white blood cell, neutrophil, platelet counts, and Hgb/Hct. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or delay or suspension of DOXIL therapy. Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage. Development of sepsis in the setting of neutropenia has resulted in discontinuation of treatment and, in rare cases, death. DOXIL may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when DOXIL is administered in combination with other agents that cause bone marrow suppression. In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. In the three single-arm studies, anemia was the most common hematologic adverse reaction (52.6%), followed by leukopenia (WBC <4,000 mm<sup>3</sup>; 42.2%), thrombocytopenia (24.2%), and neutropenia (ANC <1,000; 19.0%). In the randomized study, anemia was the most common hematologic adverse reaction (40.2%), followed by leukopenia (WBC <4,000 mm<sup>3</sup>; 36.8%), neutropenia (ANC <1,000; 35.1%), and thrombocytopenia (13.0%) [see Adverse Reactions]. In patients with relapsed ovarian cancer, 4.6% received G-CSF (or GM-CSF) to support their blood counts [see Full Prescribing Information]. For patients with AIDS-related Kaposi's sarcoma who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse reaction at the recommended dose of 20 mg/m<sup>2</sup> [see Adverse Reactions]. Leukopenia is the most common adverse reaction experienced in this population; anemia and thrombocytopenia can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to DOXIL. Eleven patients (1.6%) discontinued study because of bone marrow suppression or neutropenia. Table 10 presents data on myelosuppression in patients with multiple myeloma receiving DOXIL and bortezomib in combination [see Adverse Reactions].

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**Hand-Foot Syndrome (HFS):** In the randomized ovarian cancer study, 50.6% of patients treated with DOXIL at 50 mg/m<sup>2</sup> every 4 weeks experienced HFS (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 23.8% of the patients reporting HFS Grade 3 or 4 events. Ten subjects (4.2%) discontinued treatment due to HFS or other skin toxicity. HFS toxicity grades are described in *Dosage and Administration* section [see Full Prescribing Information]. Among 705 patients with AIDS-related Kaposi's sarcoma treated with DOXIL at 20 mg/m<sup>2</sup> every 2 weeks, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing. In the randomized multiple myeloma study, 19% of patients treated with DOXIL at 30 mg/m<sup>2</sup> every three weeks experienced HFS. HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage HFS [see Full Prescribing Information]. The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

**Radiation Recall Reaction:** Recall reaction has occurred with DOXIL administration after radiotherapy.

**Fetal Mortality: Pregnancy Category D:** DOXIL can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If DOXIL is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs in the first few months following treatment with DOXIL, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy during treatment with Doxil. [see Full Prescribing Information].

**Toxicity Potentiation:** The doxorubicin in DOXIL may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin HCl. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver have been reported to be increased by the administration of doxorubicin HCl.

**Monitoring: Laboratory Tests:** Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of DOXIL [see Warnings and Precautions].

**ADVERSE REACTIONS: Overall Adverse Reactions Profile:** The following adverse reactions are discussed in more detail in other sections of the labeling. • Cardiac Toxicity [see Warnings and Precautions] • Infusion reactions [see Warnings and Precautions] • Myelosuppression [see Warnings and Precautions] • Hand-Foot syndrome [see Warnings and Precautions]

The most common adverse reactions observed with DOXIL are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia. The most common serious adverse reactions observed with DOXIL are described in Section *Adverse Reactions in Clinical Trials*. The safety data described below reflect exposure to DOXIL in 1310 patients including: 239 patients with ovarian cancer, 753 patients with AIDS-related Kaposi's sarcoma and 318 patients with multiple myeloma.

**Adverse Reactions in Clinical Trials:** Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice. The following tables present adverse reactions from clinical trials of DOXIL in ovarian cancer, AIDS-Related Kaposi's sarcoma, and multiple myeloma.

**Patients With Ovarian Cancer:** The safety data described below are from 239 patients with ovarian cancer treated with DOXIL (doxorubicin HCl liposome injection) at 50 mg/m<sup>2</sup> once every 4 weeks for a minimum of 4 courses in a randomized, multicenter, open-label study. In this study, patients received DOXIL for a median number of 98.0 days (range 1-785 days). The population studied was 27-87 years of age, 91% Caucasian, 6% Black and 3% Hispanic and other. **Table 2** presents the hematologic adverse reactions from the randomized study of DOXIL compared to topotecan.

**Table 2: Ovarian Cancer Randomized Study Hematology Data Reported in Patients With Ovarian Cancer**

	DOXIL Patients (n = 239)	Topotecan Patients (n = 235)
Neutropenia		
500 - <1000/mm <sup>3</sup>	19 (7.9%)	33 (14.0%)
<500/mm <sup>3</sup>	10 (4.2%)	146 (62.1%)
Anemia		
6.5 - <8 g/dL	13 (5.4%)	59 (25.1%)
<6.5 g/dL	1 (0.4%)	10 (4.3%)
Thrombocytopenia		
10,000 - <50,000/mm <sup>3</sup>	3 (1.3%)	40 (17.0%)
<10,000/mm <sup>3</sup>	0 (0.0%)	40 (17.0%)

**Table 3** presents a comparative profile of the non-hematologic adverse reactions from the randomized study of DOXIL compared to topotecan.

**Table 3: Ovarian Cancer Randomized Study**

Non-Hematologic Adverse Reaction 10% or Greater	DOXIL (%) treated (n = 239)		Topotecan (%) treated (n = 235)	
	All grades	Grades 3-4	All grades	Grades 3-4
<b>Body as a Whole</b>				
Asthenia	40.2	7.1	51.5	8.1
Fever	21.3	0.8	30.6	5.5
Mucous Membrane Disorder	14.2	3.8	3.4	0
Back Pain	11.7	1.7	10.2	0.9
Infection	11.7	2.1	6.4	0.9
Headache	10.5	0.8	14.9	0
<b>Digestive</b>				
Nausea	46.0	5.4	63.0	8.1
Stomatitis	41.4	8.3	15.3	0.4
Vomiting	32.6	7.9	43.8	9.8
Diarrhea	20.9	2.5	34.9	4.2
Anorexia	20.1	2.5	21.7	1.3
Dyspepsia	12.1	0.8	14.0	0
<b>Nervous</b>				
Dizziness	4.2	0	10.2	0
<b>Respiratory</b>				
Pharyngitis	15.9	0	17.9	0.4
Dyspnea	15.1	4.1	23.4	4.3
Cough increased	9.6	0	11.5	0
<b>Skin and Appendages</b>				
Hand-foot syndrome	50.6	23.8	0.9	0
Rash	28.5	4.2	12.3	0.4
Alopecia	19.2	N/A	52.3	N/A

The following additional adverse reactions (not in table) were observed in patients with ovarian cancer with doses administered every four weeks.

Incidence 1% to 10%: **Cardiovascular:** vasodilation, tachycardia, deep thrombophlebitis, hypotension, cardiac arrest. **Digestive:** oral moniliasis, mouth ulceration, esophagitis, dysphagia, rectal bleeding, ileus. **Hemic and Lymphatic:** ecchymosis. **Metabolic and Nutritional:** dehydration, weight loss, hyperbilirubinemia, hypokalemia, hypercalcemia, hyponatremia. **Nervous:** somnolence, dizziness, depression. **Respiratory:** rhinitis, pneumonia, sinusitis, epistaxis. **Skin and Appendages:** pruritus, skin discoloration, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, dry skin, herpes simplex, fungal dermatitis, furunculosis, acne. **Special Senses:** conjunctivitis, taste perversion, dry eyes. **Urinary:** urinary tract infection, hematuria, vaginal moniliasis.

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**Patients With Multiple Myeloma:** The safety data below are from 318 patients treated with DOXIL (30 mg/m<sup>2</sup> as a 1-hr i.v. infusion) administered on day 4 following bortezomib (1.3 mg/m<sup>2</sup> i.v. bolus on days 1, 4, 8 and 11) every three weeks, in a randomized, open-label, multicenter study. In this study, patients in the DOXIL + bortezomib combination group were treated for a median number of 138 days (range 21-410 days). The population was 28-85 years of age, 58% male, 42% female, 90% Caucasian, 6% Black, and 4% Asian and other. Table 4 lists adverse reactions reported in 10% or more of patients treated with DOXIL in combination with bortezomib for multiple myeloma.

**Table 4: Frequency of treatment emergent adverse reactions reported in ≥ 10% patients treated for multiple myeloma with DOXIL in combination with bortezomib, by Severity, Body System, and MedDRA Terminology.**

Adverse Reaction	DOXIL + bortezomib (n=318)			Bortezomib (n=318)		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
<b>Blood and lymphatic system disorders</b>						
Neutropenia	36	22	10	22	11	5
Thrombocytopenia	33	11	13	28	9	8
Anemia	25	7	2	21	8	2
<b>General disorders and administration site conditions</b>						
Fatigue	36	6	1	28	3	0
Pyrexia	31	1	0	22	1	0
Asthenia	22	6	0	18	4	0
<b>Gastrointestinal disorders</b>						
Nausea	48	3	0	40	1	0
Diarrhea	46	7	0	39	5	0
Vomiting	32	4	0	22	1	0
Constipation	31	1	0	31	1	0
Mucositis/Stomatitis	20	2	0	5	<1	0
Abdominal pain	11	1	0	8	1	0
<b>Infections and infestations</b>						
Herpes zoster	11	2	0	9	2	0
Herpes simplex	10	0	0	6	1	0
<b>Investigations</b>						
Weight decreased	12	0	0	4	0	0
<b>Metabolism and Nutritional disorders</b>						
Anorexia	19	2	0	14	<1	0
<b>Nervous system disorders</b>						
Peripheral Neuropathy*	42	7	<1	45	10	1
Neuralgia	17	3	0	20	4	1
Paresthesia/dysesthesia	13	<1	0	10	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough	18	0	0	12	0	0
<b>Skin and subcutaneous tissue disorders</b>						
Rash**	22	1	0	18	1	0
Hand-foot syndrome	19	6	0	<1	0	0

\*Peripheral neuropathy includes the following adverse reactions: peripheral sensory neuropathy, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, and neuropathy NOS.

\*\*Rash includes the following adverse reactions: rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, exfoliative rash, and rash generalized.

**Post Marketing Experience:** The following additional adverse reactions have been identified during post approval use of DOXIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Musculoskeletal and Connective Tissue Disorders:* rare cases of muscle spasms. *Respiratory, Thoracic and Mediastinal Disorders:* rare cases of pulmonary embolism (in some cases fatal). *Hematologic disorders:* Secondary acute myelogenous leukemia with and without fatal outcome has been reported in patients whose treatment included DOXIL. *Skin and subcutaneous tissue disorders:* rare cases of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

**DRUG INTERACTIONS:** No formal drug interaction studies have been conducted with DOXIL. DOXIL may interact with drugs known to interact with the conventional formulation of doxorubicin HCl.

**USE IN SPECIFIC POPULATIONS: Pregnancy:** Pregnancy Category D [see Warnings and Precautions]. DOXIL is embryotoxic at doses of 1 mg/kg/day in rats and is embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about one-eighth the 50 mg/m<sup>2</sup> human dose on a mg/m<sup>2</sup> basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, discontinue nursing during treatment with DOXIL.

**Pediatric Use:** The safety and effectiveness of DOXIL in pediatric patients have not been established.

**Geriatric Use:** Of the patients treated with DOXIL in the randomized ovarian cancer study, 34.7% (n=83) were 65 years of age or older while 7.9% (n=19) were 75 years of age or older. Of the 318 patients treated with DOXIL in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% were 75 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

**Hepatic Impairment:** The pharmacokinetics of DOXIL has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Thus, DOXIL dosage should be reduced in patients with impaired hepatic function [see Full Prescribing Information].

Prior to DOXIL administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin [see Full Prescribing Information].

**OVERDOSAGE:** Acute overdosage with doxorubicin HCl causes increases in mucositis, leucopenia, and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions, and symptomatic treatment of mucositis.

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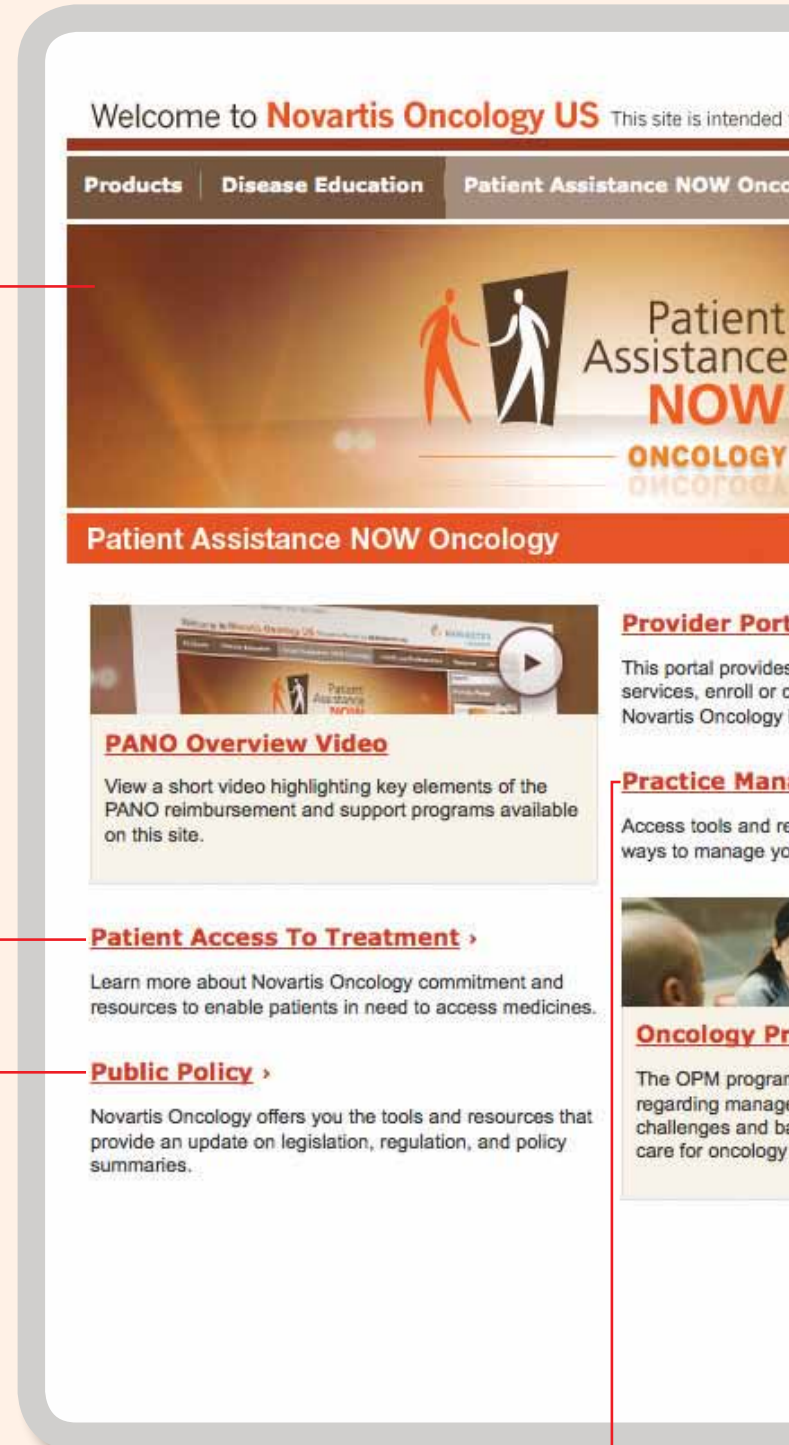


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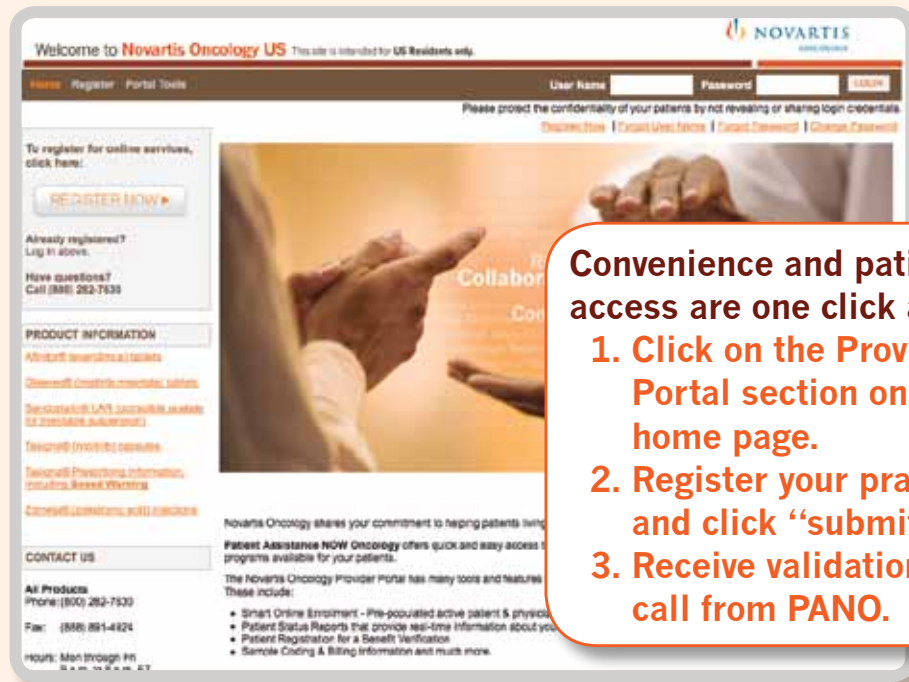
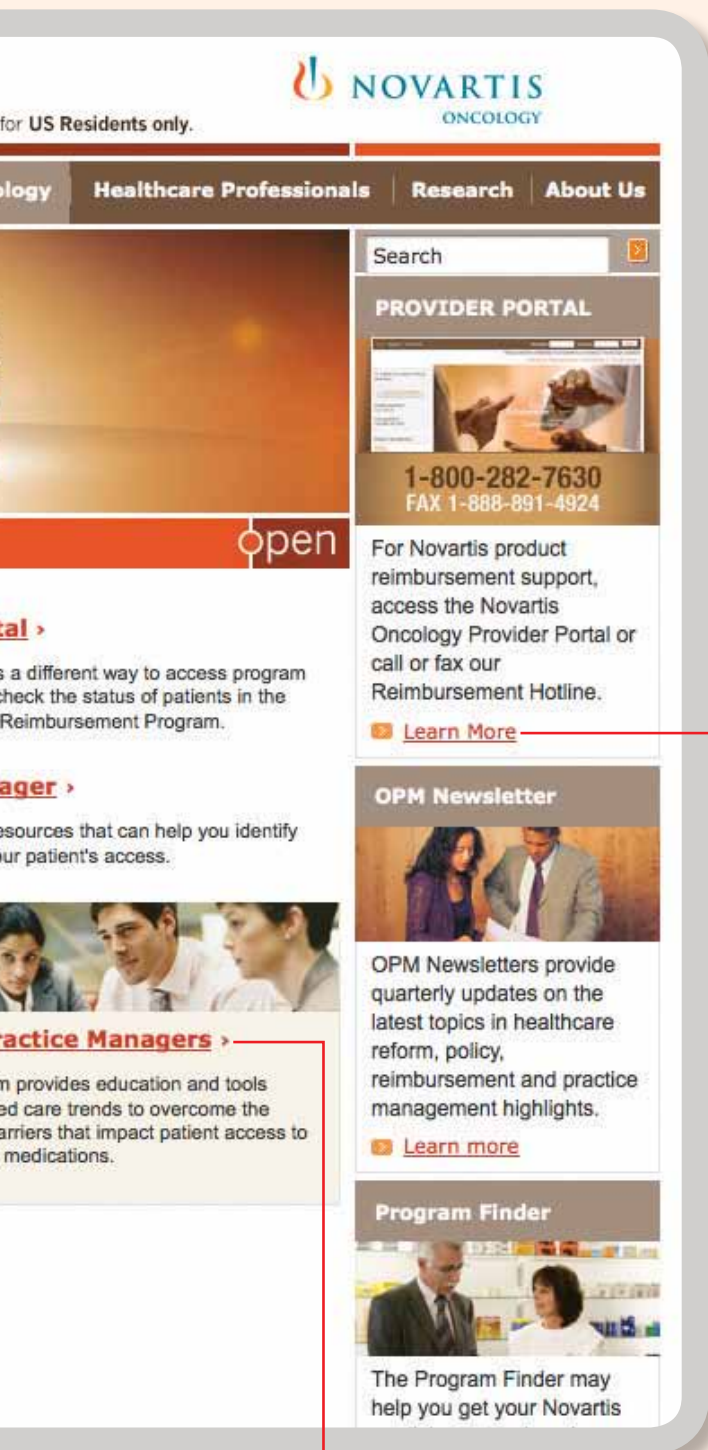
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# Innovative Payment Models in Oncology Care

This article is based on the presentation by Peter B. Bach, MD, MAPP

Payment reform is a necessity in today's healthcare environment. One of the leading experts in payment reform is Peter B. Bach, MD, MAPP, director, Center for Health Policy and Outcomes and attending physician at Memorial Sloan-Kettering Cancer Center. In his presentation entitled *Innovative Payment Models in Oncology Care*, Dr Bach stated that there are numerous payment models available but they tend to fall into 1 of 3 categories: episode-based payment, disintermediation, and cost sharing.

## Episode-Based Payment

In this model, the provider (eg, oncologist) is given a single payment for the care of a patient during an "episode of care." The oncologist can then disperse the funds as he/she sees fit. In this model, the clinician assumes some of the risk and will look at the costs of care and efficacy and determine a treatment regimen based partially on both. As shown in the **Table** and **Figure**, the costs of different treatments vary greatly. An oncologist will need to take into account the costs of treatment and other expenses and determine the drug regimen that is best suited for a patient. If a more expensive treatment regimen is used, the oncologist will have a net loss. As such, the oncologist is at risk in this model.

Dr Bach stated there are many concerns for implementing this method.

First, it is not clear what the payment should be. The allocated funds may focus on the cost of medication but that may be only a small portion of the overall cost of care. Also, Dr Bach indicated that some cancer treatments have been well studied and compared with others, making it is easier to make an informed decision, while others have not. He also cautioned that some may view this model as the least costly alternative payment. But that is not necessarily the case. To better illustrate how the payment would be determined, Dr Bach said: "Episode-based payments, like patient perspective care or hospital payments, [are] based on average behavior."

If most oncologists use more expensive regimens, then the average will be high and that will determine how much the oncologist will be given for the episode. In other words, the payment is not an arbitrary number but one calculated from recent behavior.

## Disintermediation

A second payment model discussed by Dr Bach was the disintermediation model, which theoretically should be cheaper since it takes out the "middle-

man." Disintermediation in medicine would also take out the profit margin, as consumers buy directly from manufacturers. In 2003, the Medicare Modernization Act included a disintermediation program called the Competitive Acquisition Program (CAP). Dr Bach noted that CAP failed due to administrative reasons, but recently it has garnered renewed interest.

Another disintermediation program is the United Healthcare Demonstration, in which doctors pay invoice prices for can-

cer medications. In this setup, clinicians can receive a management fee but no profit from the drugs directly. Pathways are an outgrowth of the United Healthcare Demonstration, and represent contracts with providers to use certain regimens (ie, low-cost regimens).

## Cost Sharing

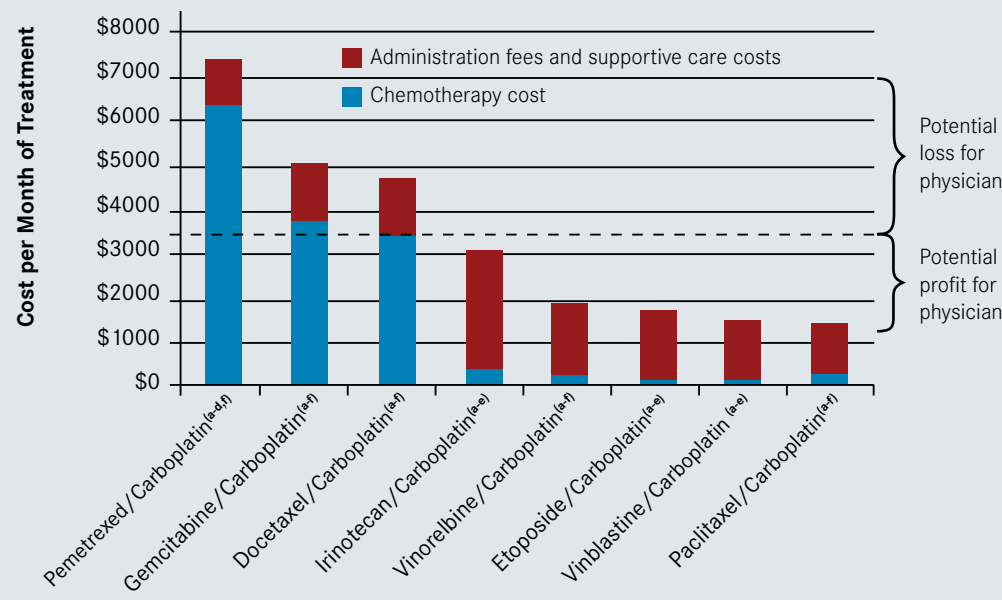
Cost sharing moves the risk away from the provider and places it more on the patient.

Dr Bach noted 3 views on cost sharing:

1. Consumerism is good. Consumers know how to shop for everything else, so they can shop for healthcare.
2. Consumerism is silly. Because medications are so expensive, the consumer cannot really comprehend how to share the cost.
3. Consumerism is economically of little relevance. Consumers are indifferent to who spends the money since all the money is going toward healthcare instead of somewhere else.

He stated that the RAND Health Insurance experiment found that cost sharing did not work.<sup>1</sup> Also, with this model, there is a concern that patients will not go in for regular or routine check-ups due to copays. Dr Bach stated that he is of the mind-set that consumerism is silly and that he is not a strong advocate for this model.

**Figure. Potential Outcomes for Physicians Treating Lung Cancer in an Episode-Based Payment Model**



**Table. Cost of Chemotherapy in Metastatic Non-Small Cell Lung Cancer**

Name	Total Chemotherapy Drug Cost	Monthly Chemotherapy Drug Cost	Total Cost (12 Weeks)	Monthly Cost
Pemetrexed/Cisplatin <sup>a-d,f</sup>	\$16,913.37	\$6105.91	\$19,594.13	<b>\$7073.69</b>
Gemcitabine/Cisplatin <sup>a-f</sup>	\$9745.83	\$3518.35	\$13,303.24	<b>\$4802.61</b>
Docetaxel/Cisplatin <sup>a-f</sup>	\$8916.64	\$3219.00	\$11,647.20	<b>\$4204.77</b>
Irinotecan/Cisplatin <sup>a-e</sup>	\$934.60	\$337.40	\$7984.63	<b>\$2882.54</b>
Vinorelbine/Cisplatin <sup>a-f</sup>	\$519.45	\$187.53	\$4929.03	<b>\$1779.43</b>
Etoposide/Cisplatin <sup>a-e</sup>	\$217.06	\$78.36	\$4453.86	<b>\$1607.89</b>
Vinblastine/Cisplatin <sup>a-e</sup>	\$183.97	\$66.41	\$3741.38	<b>\$1350.68</b>
Paclitaxel/Cisplatin <sup>a-f</sup>	\$518.45	\$187.17	\$3578.70	<b>\$1291.95</b>

<sup>a</sup>National Comprehensive Cancer Center.

<sup>b</sup>American College of Chest Physicians.

<sup>c</sup>Cancer Care Ontario.

<sup>d</sup>Alberta Health Services.

<sup>e</sup>Australian National Health and Medical Research Council.

<sup>f</sup>National Institute for Health and Clinical Excellence.

**What Remains to Be Accomplished?**

Dr Bach ended his presentation with an overview of the questions that “keep him up at night” while wrestling with how best to create better payment plans.

1. Why can't we get along? He said that most payment plans require a fundamental agreement on what constitutes the standard of care. That is difficult to achieve.
2. How large could shifts be from

payment changes, and should we worry? Dr Bach asked, if the various parties can agree on what constitutes the standard of care, will the shift be large or small? If it is too small, it will not be enough to

reduce the total costs that continue to rise. But, if it is too large to allow us to save the money we need to save to fix the system, then will that lead to us to stray from the goal of improving healthcare? Finding that balance is difficult.

3. Can we switch from eliminating “waste” to reducing “marginally beneficial?” Dr Bach said there is constant talk to reduce wasteful spending, but we should focus more on reducing medications that are marginally beneficial. He cited the drug Avastin as a good example of a drug that is marginally beneficial in patients with breast cancer and also illustrates how all parties are not in agreement. In November 2011, the US Food and Drug Administration issued a statement saying that Avastin has not been shown to be safe and effective in patients with breast cancer.<sup>2</sup> In 2012, the National Comprehensive Cancer Network's guidelines for breast cancer included Avastin as a preferred agent.<sup>3</sup> Dr Bach asked: “How are we going to design programs to save money when we can't even get agreement between 2 respected bodies?” **EBO**

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## Data Tracking and Point of Service Decision Support

This article is based on the presentation by Andrew L. Pecora, MD, FACP, CPE

“I’ve been treating patients since 1983. I’ve never had a patient come up to me and say, ‘I want to die cost efficiently.’ Never. Not once.” Those were the opening remarks from Andrew L. Pecora, MD, FACP, CPE, chief innovations officer and vice president, cancer services, John Theurer Cancer Center at the Hackensack University Medical Center in Hackensack, New Jersey and president of Regional Cancer Care Associates, during his presentation entitled *Translating Evidence-Based Research into Value-Based Decisions in Oncology-Integrated Delivery Networks*. This statement made it clear that there is a disconnect between patients and payers.

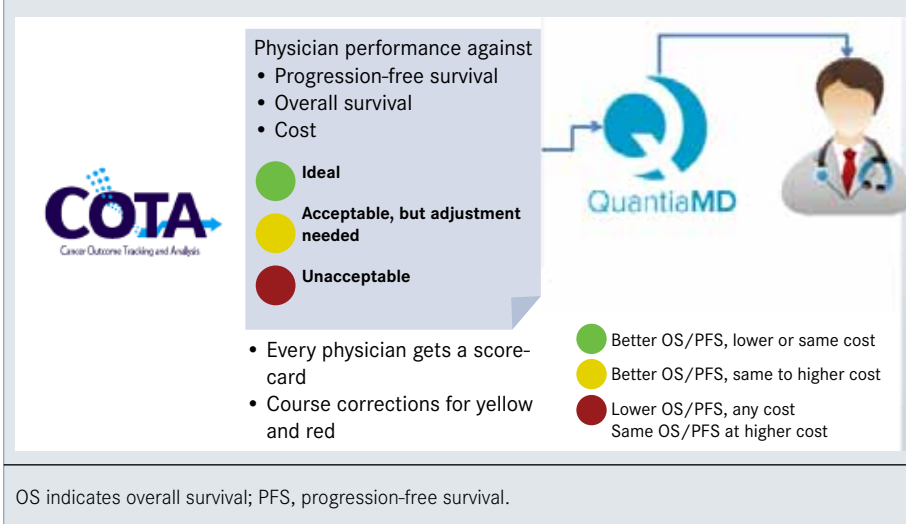
Adding to the problem, the person in the middle, the physician, is being asked to do more and more. To illustrate, Dr Pecora said that as an administrator in the hospital, he has to ask his doctors to be “really good internists because you are giving people chemotherapy that may cause side effects and you have to assess their medical condition, whether they can get their drugs, have a toxicity, and do all those things. You also have to be an oncologist and understand the drugs and write the orders. You have to be a molecular biologist now because of all the pathways and you have to read about these things and really understand them so that you know you are ordering the relevant test so that you give the right drug and not the wrong one. You have to be an informatics expert because everyone is going into electronic medical records

and using pathways. You have to be a social scientist and an economist now since society has now made you responsible for the cost of care of delivery. You have to be an end-of-life specialist. You have to be a pre-certification expert and, by the way, you have to meet all of the quality standards that everyone is promoting—there are about 50 of them now. You have to take time to talk to the patient and be nice to them.”

After going through that list of responsibilities, Dr Pecora ended with, “And by the way, don’t make a single mistake.... And do this in 15 minutes. And do it 30 or 40 times a day.” He asked, “How can any human being do that?” Yet, this is what is being asked of physicians and he is concerned that we are continuing to add to their responsibilities.

Instead, Dr Pecora stated, we need a model that lets physicians be physicians and frees them of some of the administrative duties. We also need a model that embraces the multitude of ways that patients are classified and treated. Conventional models may combine patients bluntly, such as “All breast cancer patients are the same.” Instead, Dr Pecora argued for a system that segregates patients into more realistic diagnostic and prognostic groupings. He believes this will be the key to better outcomes and better ways to measure outcomes. For example, Dr Pecora stated that there are 3 pages of tests for leukemia that allow clinicians to place patients in the correct treatment group. “Once you segregate people and better refine your segregation, you have a group of

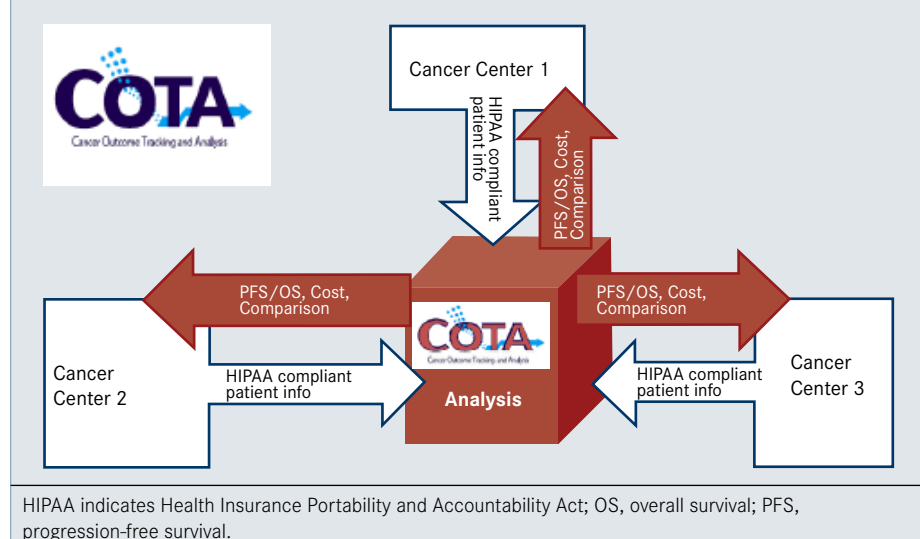
Figure 2. Tracking Patients’ Progress With COTA and QuantiaMD



patients where biologic variability goes down and therefore you can measure, with greater fidelity, the outcome of what you are doing,” he said, and that “The absolute key to this is to track in real time the things that matter,” adding that the 2 things that matter are overall survival and progression-free survival. Those are the outcomes that physicians are selling and the patients are buying (ie, survival). And the product of survival needs to be properly tracked and it needs to be tracked in a manner that frees a physician to do his/her job. That is the reasoning behind Cancer Outcomes Tracking and Analysis (COTA), a point-of-service decision-support tool. It groups patients based on diagnostics and treatment, and tracks them in real time so that the medical staff can make more informed decisions quicker. As a result, the staff has more time to focus on caring for its patients.

physicians to provide (and monitor) point-of-service decision support. He compared the setup to a global positioning system (GPS). The physician knows where they are starting in a patient’s treatment plan and they know the final destination (survival and a reasonable cost). Daily tracking of patients’ cost and outcomes allow physicians to map the progression of treatment. Dr Pecora noted that a good GPS will only make noise if the traveler goes off target. Similarly, a good point-of-service system will remain quiet if the patient is proceeding as planned and red flags will pop up if there is deviation from the target. This can be measured in different ways, but Dr Pecora showed examples in which both outcomes and costs are monitored to allow all parties to know how the patient is progressing compared with similar patients (Figure 2).

Figure 1. Cancer Outcomes Tracking and Analysis Decision Support Tool



### Tracking Outcomes That Matter

COTA tracks patients in groups that are applicable and compares each patient’s outcomes with similar patients. The segregation of patients is based on many factors such as histology, stage, genomics, epigenetics, proteomics, relapse, and re-segregation with new information. Furthermore, patient data are tracked daily with a focus on reporting outcomes that matter the most (ie, progression-free survival, overall survival, and cost). Using this setup, outcomes for each patient and each cancer center can be compared with other centers with similar patient populations (Figure 1).

Dr Pecora stated that COTA, along with its QuantiaMD system, allows

### Concluding Remarks

Dr Pecora concluded his presentation by cautioning the audience: “We do not want to be in a setting where we are creating that moral double jeopardy for our physicians and nurses where they have to decide between ‘I think this is best’ and ‘I don’t know if they can afford it.’ We don’t need to go there.” But he said he remains optimistic, adding: “I think you will see solutions come into the marketplace that heretofore were not even considered in medicine and I think one of them is that we will move from selling services to selling products. And by selling products you are accountable for the 2 things that matter—the outcome and the cost.” **EBO**





ADVANCING SCIENCE  
IN METASTATIC MELANOMA

# The science of immunotherapy

## The significance of long-term survival

Median overall survival: YERVOY + gp100 arm: 10 months (95% CI: 8.5, 11.5); gp100: 6 months (95% CI: 5.5, 8.7); YERVOY alone: 10 months (95% CI: 8.0, 13.8). YERVOY + gp100: hazard ratio (HR) vs YERVOY=1.04 (95% CI: 0.83, 1.30),  $P=0.76$ ; HR vs gp100: HR=0.68 (95% CI: 0.55, 0.85),  $P=0.0004$ ; YERVOY vs gp100: HR=0.66 (95% CI: 0.51, 0.87),  $P=0.0026$  (not adjusted for multiple comparisons).<sup>1,2</sup>

### Indication

YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

#### **WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

YERVOY can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs) and thyroid function tests at baseline and before each dose.

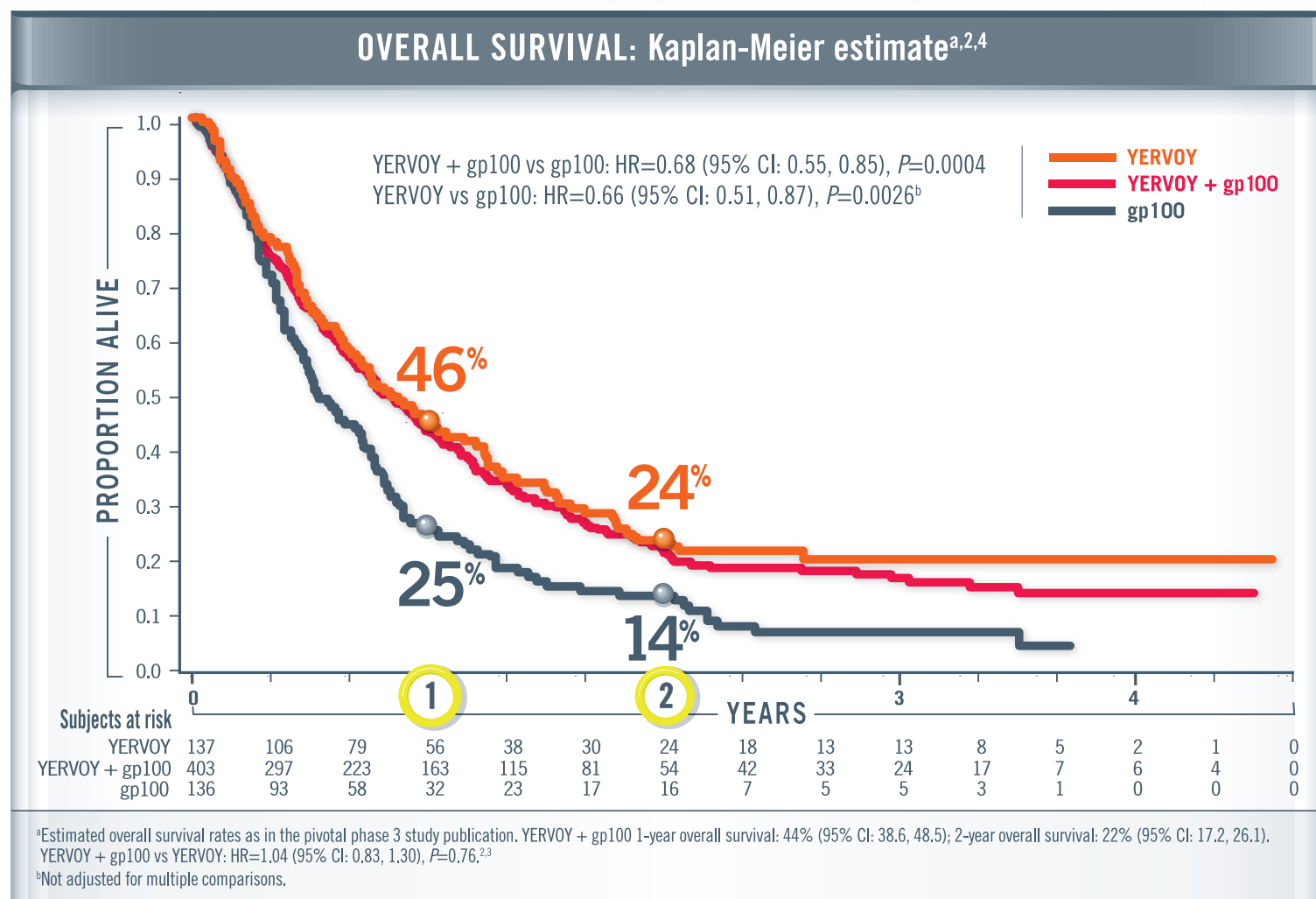
Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Please see detailed Important Safety Information continued on following pages.

Please see brief summary of Full Prescribing Information on adjacent pages, including **Boxed WARNING** regarding immune-mediated side effects.

# The significance of a long-term survival benefit

**YERVOY (ipilimumab): The first and only immunotherapy to deliver a significant long-term survival benefit in metastatic melanoma in a phase 3 study<sup>3</sup>**



A phase 3, double-blind, double-dummy study that randomized 676 patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin (IL-2), dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive YERVOY 3 mg/kg in combination with an investigational gp100 peptide vaccine (gp100) (n=403), YERVOY 3 mg/kg (n=137), or gp100 (n=136). The primary endpoint was overall survival in the YERVOY + gp100 arm vs the gp100 arm.<sup>3</sup>

## Estimated overall survival in the YERVOY pivotal phase 3 study publication

- The YERVOY overall survival curve separated at approximately 16 weeks and remained separated throughout the study period<sup>2</sup>
- Overall survival rate at 1 year was 46% (95% CI: 37.0, 54.1) in the YERVOY arm vs 25% (95% CI: 18.1, 32.9) in the gp100 arm<sup>2,4</sup>
- Overall survival rate at 2 years was 24% (95% CI: 16.0, 31.5) in the YERVOY arm vs 14% (95% CI: 8.0, 20.0) in the gp100 arm<sup>2,4</sup>
- Median overall survival in the YERVOY + gp100 arm was 10 months (95% CI: 8.5, 11.5), 6 months (95% CI: 5.5, 8.7) in the gp100 arm, and 10 months (95% CI: 8.0, 13.8) in the YERVOY arm

Please see Important Safety Information, including **Boxed WARNING regarding immune-mediated side effects**, and brief summary of Full Prescribing Information on adjacent pages.

# Important Safety Information

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## Recommended Dose Modifications

Withhold dose for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving <7.5 mg prednisone or equivalent per day.

Permanently discontinue YERVOY (ipilimumab) for any of the following:

- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day
- Failure to complete full treatment course within 16 weeks from administration of first dose
- Severe or life-threatening adverse reactions, including any of the following
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency ( $\geq 7$  over baseline), stool incontinence, need for intravenous hydration for >24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  - AST or ALT  $>5\times$  the upper limit of normal (ULN) or total bilirubin  $>3\times$  the ULN
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full-thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations
  - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Severe immune-mediated reactions involving any organ system
  - Immune-mediated ocular disease which is unresponsive to topical immunosuppressive therapy

## Immune-mediated Enterocolitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening or fatal (diarrhea of  $\geq 7$  stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) patients
- Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis
- Infliximab was administered to 5 of 62 (8%) patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids
- Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms
- Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to  $\leq$ Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients
- Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent)

## Immune-mediated Hepatitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations  $>5\times$  the ULN or total bilirubin elevations  $>3\times$  the ULN; Grade 3-5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%



Important Safety Information continued on following page.

To learn more, visit [www.YERVOYinformation.com](http://www.YERVOYinformation.com)  
or call Medical Information at  
1-855-YERVOY1(1-855-937-8691).

**YERVOY**<sup>™</sup>  
(ipilimumab)  
Injection for intravenous infusion

# Important Safety Information (cont'd)

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## Immune-mediated Hepatitis (cont'd):

- 13 (2.5%) additional YERVOY (ipilimumab)-treated patients experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations  $>2.5\times$  but  $\leq 5\times$  the ULN or total bilirubin elevation  $>1.5\times$  but  $\leq 3\times$  the ULN; Grade 2)
- Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution
- Permanently discontinue YERVOY in patients with Grade 3-5 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids
- Withhold YERVOY in patients with Grade 2 hepatotoxicity

## Immune-mediated Dermatitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) patients
  - 1 (0.2%) patient died as a result of toxic epidermal necrolysis
  - 1 additional patient required hospitalization for severe dermatitis
- There were 63 (12%) YERVOY-treated patients with moderate (Grade 2) dermatitis
- Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated
- Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY in patients with moderate to severe signs and symptoms
- Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically. Administer topical or systemic corticosteroids if there is no improvement within 1 week

## Immune-mediated Neuropathies:

- In the pivotal Phase 3 study in YERVOY-treated patients, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported
- Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported
- Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes
- Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities)

## Immune-mediated Endocrinopathies:

- In the pivotal Phase 3 study in YERVOY-treated patients, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients
  - All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism
  - 6 of the 9 patients were hospitalized for severe endocrinopathies
- Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) YERVOY-treated patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome

Important Safety Information continued on following page.

# Important Safety Information (cont'd)

## Immune-mediated Endocrinopathies (cont'd):

- Median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of YERVOY (ipilimumab)
- Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism
  - Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms should be considered immune-mediated
  - Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland
- Withhold YERVOY in symptomatic patients. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. Long-term hormone replacement therapy may be necessary

## Other Immune-mediated Adverse Reactions, Including Ocular Manifestations:

- In the pivotal Phase 3 study in YERVOY-treated patients, clinically significant immune-mediated adverse reactions seen in <1% were: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia
- Across the clinical development program for YERVOY, immune-mediated adverse reactions also reported with <1% incidence were: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis
- Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions
- Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy

## Pregnancy & Nursing:

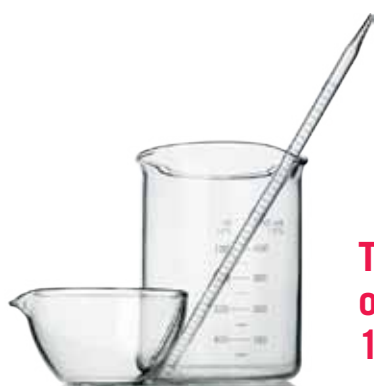
- YERVOY is classified as pregnancy category C. There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus
- Human IgG1 is known to cross the placental barrier and YERVOY is an IgG1; therefore, YERVOY has the potential to be transmitted from the mother to the developing fetus
- It is not known whether YERVOY is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY

## Common Adverse Reactions:

- The most common adverse reactions ( $\geq 5\%$ ) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%)

Please see brief summary of Full Prescribing Information on adjacent pages, including **Boxed WARNING** regarding immune-mediated side effects.

**References:** 1. YERVOY package insert. Princeton, NJ: Bristol-Myers Squibb Company. 2. Data on file. YERV 008. Bristol-Myers Squibb Company. Princeton, NJ. April 2011. 3. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723. 4. Wolchok JD, Weber JS, Hamid O, et al. Ipilimumab efficacy and safety in patients with advanced melanoma: a retrospective analysis of HLA subtype from four trials. *Cancer Immun.* 2010;10:9-14.



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or call Medical Information at  
1-855-YERVOY1 (1-855-937-8691).

**YERVOY**<sup>™</sup>  
(ipilimumab)  
Injection for intravenous infusion

**YERVOY™ (ipilimumab) Injection, for intravenous infusion****Rx ONLY**

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

**WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

**YERVOY (ipilimumab) can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.**

**Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. [See Dosage and Administration (2.2) in Full Prescribing Information]**

**Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose. [See Warnings and Precautions]**

**INDICATIONS AND USAGE**

YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

YERVOY can result in severe and fatal immune-mediated reactions due to T-cell activation and proliferation. [See Boxed Warning]

**Immune-mediated Enterocolitis**

In Study 1, severe, life-threatening, or fatal (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3–5) immune-mediated enterocolitis occurred in 34 (7%) YERVOY-treated patients, and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) YERVOY-treated patients. Across all YERVOY-treated patients (n=511), 5 (1%) patients developed intestinal perforation, 4 (0.8%) patients died as a result of complications, and 26 (5%) patients were hospitalized for severe enterocolitis.

The median time to onset was 7.4 weeks (range 1.6–13.4) and 6.3 weeks (range 0.3–18.9) after the initiation of YERVOY for patients with Grade 3–5 enterocolitis and with Grade 2 enterocolitis, respectively.

Twenty-nine patients (85%) with Grade 3–5 enterocolitis were treated with high-dose (≥40 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 2.3 weeks (ranging up to 13.9 weeks) followed by corticosteroid taper. Of the 28 patients with moderate enterocolitis, 46% were not treated with systemic corticosteroids, 29% were treated with <40 mg prednisone or equivalent per day for a median duration of 5.1 weeks, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 of the 62 patients (8%) with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

Of the 34 patients with Grade 3–5 enterocolitis, 74% experienced complete resolution, 3% experienced improvement to Grade 2 severity, and 24% did not improve. Among the 28 patients with Grade 2 enterocolitis, 79% experienced complete resolution, 11% improved, and 11% did not improve.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients.

Withhold YERVOY dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than one week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent. [See Dosage and Administration (2.2) in Full Prescribing Information]

**Immune-mediated Hepatitis**

In Study 1, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations of more than 5 times the upper limit of normal or total bilirubin elevations more than 3 times the upper limit of normal; Grade 3–5) occurred in 8 (2%) YERVOY-treated patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4% of YERVOY-treated patients. An additional 13 (2.5%) patients experienced moderate hepatotoxicity manifested by liver function test abnormalities (AST or ALT elevations of more than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of more than 1.5 times but not more than 3 times the upper limit of normal; Grade 2). The underlying pathology was not ascertained in all patients but in some instances included immune-mediated hepatitis. There were insufficient numbers of patients with biopsy-proven hepatitis to characterize the clinical course of this event.

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Permanently discontinue YERVOY in patients with Grade 3–5 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold YERVOY in patients with Grade 2 hepatotoxicity. [See Dosage and Administration (2.2) in Full Prescribing Information]

**Immune-mediated Dermatitis**

In Study 1, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) YERVOY (ipilimumab)-treated patients. One (0.2%) patient died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis. There were 63 (12%) patients with moderate (Grade 2) dermatitis.

The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 3.1 weeks and ranged up to 17.3 weeks from the initiation of YERVOY.

Seven (54%) YERVOY-treated patients with severe dermatitis received high-dose corticosteroids (median dose 60 mg prednisone/day or equivalent) for up to 14.9 weeks followed by corticosteroid taper. Of these 7 patients, 6 had complete resolution; time to resolution ranged up to 15.6 weeks.

Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 2.1 weeks, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four (70%) patients with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

Permanently discontinue YERVOY in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. [See Dosage and Administration (2.2) in Full Prescribing Information]

For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

**Immune-mediated Neuropathies**

In Study 1, one case of fatal Guillain-Barré syndrome and one case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold YERVOY dosing in patients with moderate neuropathy (not interfering with daily activities). [See Dosage and Administration (2.2) in Full Prescribing Information]

**Immune-mediated Endocrinopathies**

In Study 1, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3–4) occurred in 9 (1.8%) YERVOY-treated patients. All 9 patients had hypopituitarism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and one case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of YERVOY.

Of the 21 patients with moderate to life-threatening endocrinopathy, 17 patients required long-term hormone replacement therapy including, most commonly, adrenal hormones (n=10) and thyroid hormones (n=13).

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold YERVOY dosing in symptomatic patients. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. [See Dosage and Administration (2.2) in Full Prescribing Information]

**Other Immune-mediated Adverse Reactions, Including Ocular Manifestations**

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients in Study 1: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Across the clinical development program for YERVOY, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. [See Dosage and Administration (2.2) in Full Prescribing Information]

## ADVERSE REACTIONS

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

- Immune-mediated enterocolitis [see *Warnings and Precautions*].
- Immune-mediated hepatitis [see *Warnings and Precautions*].
- Immune-mediated dermatitis [see *Warnings and Precautions*].
- Immune-mediated neuropathies [see *Warnings and Precautions*].
- Immune-mediated endocrinopathies [see *Warnings and Precautions*].
- Other immune-mediated adverse reactions, including ocular manifestations [see *Warnings and Precautions*].

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared with rates in other clinical trials or experience with therapeutics in the same class and may not reflect the rates observed in clinical practice.

The clinical development program excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Exposure to YERVOY (ipilimumab) 3 mg/kg for four doses given by intravenous infusion in previously treated patients with unresectable or metastatic melanoma was assessed in a randomized, double-blind clinical study (Study 1). [See *Clinical Studies (14)* in Full Prescribing Information] One hundred thirty-one patients (median age 57 years, 60% male) received YERVOY as a single agent, 380 patients (median age 56 years, 61% male) received YERVOY with an investigational gp100 peptide vaccine (gp100), and 132 patients (median age 57 years, 54% male) received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses (range 1 to 4 doses). YERVOY was discontinued for adverse reactions in 10% of patients.

The most common adverse reactions ( $\geq 5\%$ ) in patients who received YERVOY at 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis.

Table 1 presents selected adverse reactions from Study 1, which occurred in at least 5% of patients in the YERVOY-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3–5 events.

**Table 1: Selected Adverse Reactions in Study 1**

System Organ Class/ Preferred Term	Percentage (%) of Patients <sup>a</sup>					
	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg+gp100 n=380		gp100 n=132	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
<b>Gastrointestinal Disorders</b>						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
<b>Skin and Subcutaneous Tissue Disorders</b>						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0
<b>General Disorders and Administration Site Conditions</b>						
Fatigue	41	7	34	5	31	3

<sup>a</sup> Incidences presented in this table are based on reports of adverse events regardless of causality.

Table 2 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from Study 1.

**Table 2: Severe to Fatal Immune-mediated Adverse Reactions in Study 1**

	Percentage (%) of Patients	
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg+gp100 n=380
<b>Any Immune-mediated Adverse Reaction</b>	15	12
<b>Enterocolitis<sup>a,b</sup></b>	7	7
<b>Hepatotoxicity<sup>a</sup></b>	1	2
<b>Dermatitis<sup>a</sup></b>	2	3
<b>Neuropathy<sup>a</sup></b>	1	<1
<b>Endocrinopathy</b>	4	1
Hypopituitarism	4	1
Adrenal insufficiency	0	1
<b>Other</b>		
Pneumonitis	0	<1
Meningitis	0	<1
Nephritis	1	0
Eosinophilia <sup>c</sup>	1	0
Pericarditis <sup>a,c</sup>	0	<1

<sup>a</sup> Including fatal outcome.

<sup>b</sup> Including intestinal perforation.

<sup>c</sup> Underlying etiology not established.

Across clinical studies that utilized YERVOY (ipilimumab) doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence less than 1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appear to be dose dependent.

### Immunogenicity

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed in the dose cohort with the lowest trough levels. In this analysis, 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to YERVOY with the incidences of antibodies to other products may be misleading.

### DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with YERVOY.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

##### Pregnancy Category C

There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a combined study of embryo-fetal and peri-postnatal development, severe toxicities including increased incidences of third-trimester abortion, stillbirth, premature delivery, low birth weight, and infant mortality occurred following intravenous administration of ipilimumab to pregnant cynomolgus monkeys every 21 days from the onset of organogenesis through parturition at doses of 2.6 or 7.2 times the recommended human dose of 3 mg/kg (by AUC). [See *Nonclinical Toxicology (13.2)* in Full Prescribing Information]

In genetically engineered mice in which the gene for CTLA-4 has been deleted (a “knockout mouse”), offspring lacking CTLA-4 were born apparently healthy, but died within 3–4 weeks due to multi-organ infiltration and damage by lymphocytes.

Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

#### Nursing Mothers

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

#### Pediatric Use

Safety and effectiveness of YERVOY have not been established in pediatric patients.

#### Geriatric Use

Of the 511 patients treated with YERVOY at 3 mg/kg, 28% were 65 years and over. No overall differences in safety or efficacy were reported between the elderly patients (65 years and over) and younger patients (less than 65 years).

#### Renal Impairment

No formal studies of YERVOY in patients with renal impairment have been conducted. [See *Clinical Pharmacology (12.3)* in Full Prescribing Information]

#### Hepatic Impairment

No formal studies of YERVOY in patients with hepatic impairment have been conducted. [See *Clinical Pharmacology (12.3)* in Full Prescribing Information]

### OVERDOSAGE


There is no information on overdosage with YERVOY.

### PATIENT COUNSELING INFORMATION

See *MEDICATION GUIDE* in Full Prescribing Information.

- Inform patients of the potential risk of immune-mediated adverse reactions.
- Advise patients to read the YERVOY Medication Guide before each YERVOY infusion.
- Advise women that YERVOY may cause fetal harm.
- Advise nursing mothers not to breast-feed while taking YERVOY.

Manufactured by: Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

 Bristol-Myers Squibb  
Princeton, NJ 08543 U.S.A.



To view a video of this presentation, scan here.

# Healthcare, the National Debt, and Taxes

This article is based on the presentation by Michael E. Chernew, PhD

“Don’t fool yourself into thinking that this debate is about value and cancer care or about healthcare...This is fundamentally a debate about taxes,” stated Michael E. Chernew, PhD, professor of health care policy, Harvard Medical School, and co-editor-in-chief of *The American Journal of Managed Care*.

During his presentation entitled *Controlling Health Care Spending Growth: the Role of Benefit Design and Payment Reform*, Dr Chernew noted that while we can all discuss the various means to improve how we monitor and track outcomes and costs of care, the healthcare system is strongly linked to our national debt. To illustrate, he showed the figures for federal spending on health as a percentage of gross domestic product (Figures 1 and 2).

According to Dr Chernew, is that it retains many of the pathologies currently present in the healthcare system. The fee-for-service system “is anywhere between inane and unmanageable,” he stated, adding that “Issues about site of care, issues about how many different codes there are for very similar things, issues about how to depreciate big equipment...lowering payments in fee for service does not solve all those issues.”

Another payment reform is bundled payments such as episode bundles (which group patients based on illness) or patient bundles (which group patients based on geography or other demographics). Dr Chernew said that patient bundles are less complicated than episode bundles, and that accountable care organizations are a form of a pa-

scenarios that are dependent on policies and bureaucrats. Some examples of how to do this include:

1. *Higher co-premiums/premium support.* Dr Chernew said this is an easy design to visualize, as customers pay higher premiums while the government pays a fixed amount for care.
2. *Higher copays, co-insurance, or deductibles.* With this option, the customer pays more at the point of service. One concern with this design is that it will reduce the use of high-value services.
3. *Reference pricing.* This design sets prices on various treatments and if patients want additional or alternative care, they have to pay extra.
4. *Tiered networks.* With this method, patients may be asked to bear an increased share of the costs of care for higher-tier care (ie, higher copays for nonformulary drugs or experimental drugs).
5. *Value-based insurance design.* Using this design, copayments are aligned with value. Dr Chernew is in favor of this design but is concerned that it may be difficult to implement.

Dr Chernew noted that benefit design changes can support efforts to control the public spending problem. However, if not designed properly, they can lead to other problems in the end.

Episode-based bundled payment may work for the certain common conditions, but may have limited value in less common ones. He is concerned that bundled payments may become political and pit innovation against higher taxes.

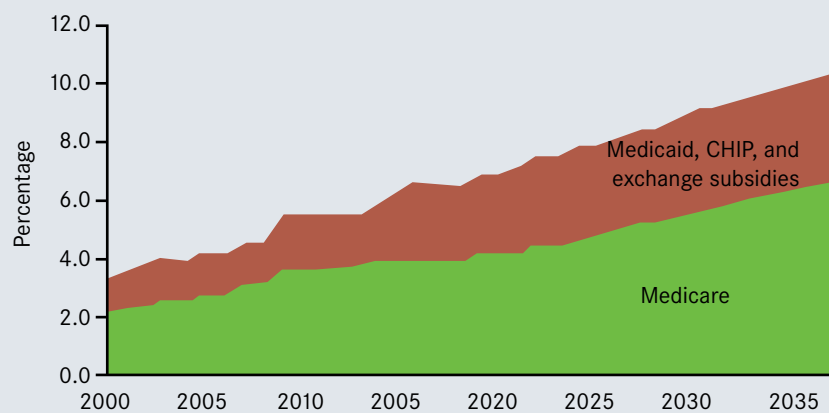
Dr Chernew also stated that cost-sharing strategies may work, particularly those that reduce payer spending. The major concern with cost-sharing is that it transfers a lot of risk to individuals and it may exacerbate disparities. On the plus side, however, those concerns may be mitigated if a value-based insurance design is used. Such plan designs will be valuable to address all areas of cancer.

Finally, he said that there are other strategies being examined. It is unlikely they will have substantial effects. Innovations in the future will likely fall under 1 of 2 general categories: (1) more consumerism; or (2) broader payment. Dr Chernew concluded, “The challenge we face is that as we move away from a world in which value was the closing word of every argument...to one in which presumption or proof of value is going to be more important, we must navigate these waters in a way that does not dampen innovation and prevent us from having better treatments in the future.” **EBO**

#### References

1. Baicker K, Skinner J. Health Care Spending Growth and the Future of U.S. Tax Rates. <http://www.nber.org/programs/ag/rrc/NB11-14%20Baicker,%20Skinner%20WP.pdf>. Published September 2011. Accessed November 30, 2012.

**Figure 1. Federal Spending on Health as a Percentage of GDP**



Source: Congressional Budget Office. The 2012 Long-Term Budget Outlook. [http://cbo.gov/sites/default/files/cbofiles/attachments/06-05\\_long-term\\_budget\\_outlook\\_2.pdf](http://cbo.gov/sites/default/files/cbofiles/attachments/06-05_long-term_budget_outlook_2.pdf)  
CHIP indicates Children’s Health Insurance Program; GDP, gross domestic product.

Dr Chernew noted that if we continue to finance higher healthcare spending by taxes, marginal tax rates of high income earners could rise to 70% by 2060.<sup>1</sup> He stated that the key is to not reduce spending on healthcare. Instead, we should slow down the growth in spending. According to Dr Chernew, there are several ways to slow growth. The first way is payment reform.

#### Slowing Spending Growth

##### Payment Reform

One goal of payment reform is to simply pay less to both providers and plans.

The problem with paying less, ac-

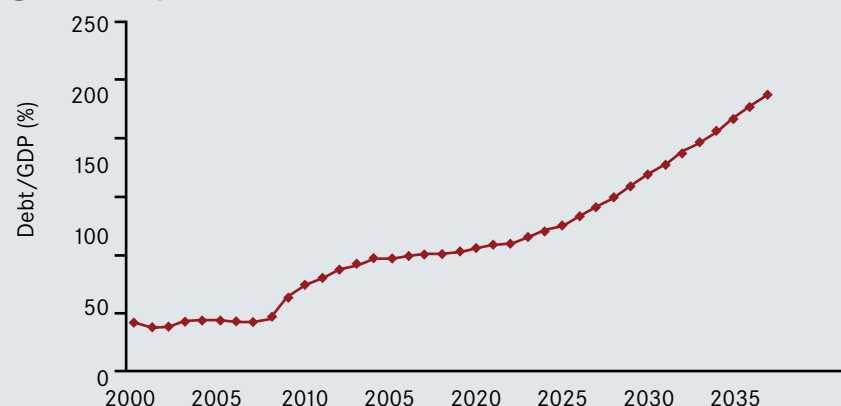
cordant to Dr Chernew, is that it retains many of the pathologies currently present in the healthcare system. The fee-for-service system “is anywhere between inane and unmanageable,” he stated, adding that “Issues about site of care, issues about how many different codes there are for very similar things, issues about how to depreciate big equipment...lowering payments in fee for service does not solve all those issues.”

Another payment reform is bundled payments such as episode bundles (which group patients based on illness) or patient bundles (which group patients based on geography or other demographics). Dr Chernew said that patient bundles are less complicated than episode bundles, and that accountable care organizations are a form of a pa-

##### Benefit Design

Another option to slow spending growth is benefit design. Dr Chernew said that some people believe the best way to reform the system is to let consumers vote with their pocketbook instead of the above payment-reform

**Figure 2. Projected US Debt**



Source: Congressional Budget Office. The 2012 Long-Term Budget Outlook. [http://cbo.gov/sites/default/files/cbofiles/attachments/06-05\\_long-term\\_budget\\_outlook\\_2.pdf](http://cbo.gov/sites/default/files/cbofiles/attachments/06-05_long-term_budget_outlook_2.pdf).  
GDP indicates gross domestic product.



# Coming Spring 2013

## Specialty Practice Recognition

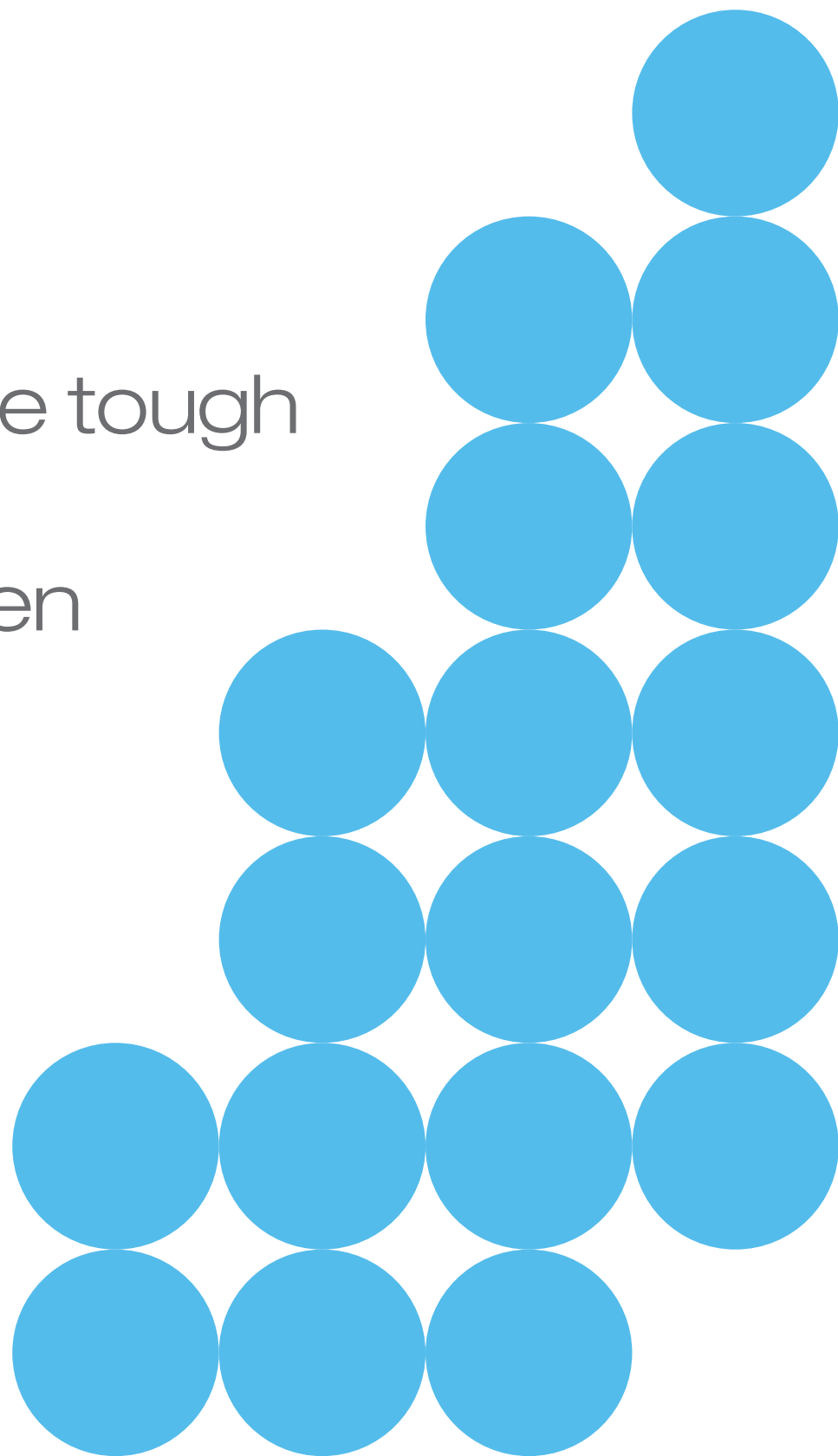
Built on the success of NCQA's acclaimed Patient-Centered Medical Home, this program highlights the role of specialists in the coordination and delivery of patient-centered care.

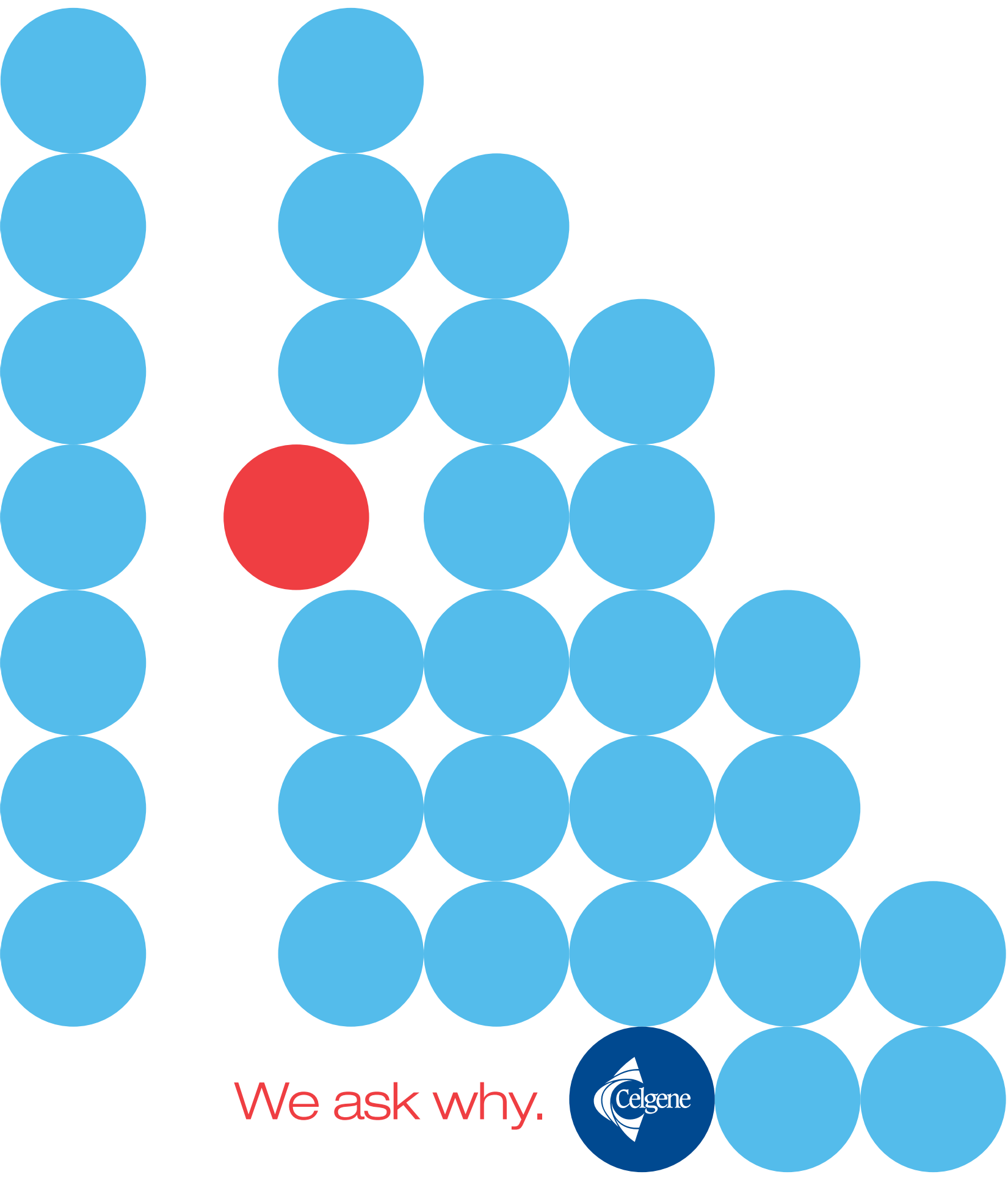
Learn more at [www.ncqa.org/spr](http://www.ncqa.org/spr).



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To view a video of this panel discussion, scan here.

## Expert Roundtable Panel Discussion: The Future of Payer Management of Oncology

The meeting concluded with all participants on stage to field questions on a variety of topics. The moderator of the event was Clifford Goodman, PhD, senior vice president of The Lewin Group, and the panel included:

Peter B. Bach, MD, MAPP, director, Center for Health Policy and Outcomes, attending physician, Memorial Sloan-Kettering Cancer Center; Michael E. Chernew, PhD, professor of health care policy, Harvard Medical School, and co-editor-in-chief, *The American Journal of Managed Care*; Jeffrey D. Dunn, PharmD, MBA, formulary and contract manager at SelectHealth, Inc; Bruce A. Feinberg, DO, vice president and chief medical officer, Cardinal Health Specialty Solutions; A. Mark Fendrick, MD, professor of medicine and health management and policy, Schools of Medicine and Public Health, University of Michigan and co-editor-in-chief of *The American Journal*

ments than about new delivery systems. Dr Bach said, "On the pharmaceutical side, the returns on investment in research and development are already gone, and most of the big companies are not investing in that and shareholders aren't giving them credit for it." Instead, companies will find innovative ways to produce competitive drugs more cheaply. "I think the day of every new drug being simply set to a price that the market will bear, irrespective of the value it delivers, is one that will be seeing its sunset," speculated Dr Bach.

Dr Chernew added there may be a decline in innovative medicines as it becomes harder to show a drug's "value." He said: "The ability to make money on a drug that is perceived as a marginal improvement, I believe, is going to be a lot harder in the future unless the companies can find ways to cut money out from other parts of the system, maybe unrelated to oncology....And I do think

**Moderator: What do payers expect to see insofar as the pipeline for innovation?**

Dr Klein said that at Aetna, "What we're trying to do is migrate at least a third of our business from the traditional insurance business over to the health-care services business. And the way to do that is to be an aggregator and processor of important health information. And the way we're doing it is with a health information portal." He added that the goal is to create a system that centers on the clinician and the patient. "What you get out of that is the ability to take lab, claims, pharmacy data, and also genetic testing data, put it through a logic engine filter, and bring it to an oncologist who, at the point of decision for care, can then actually prescribe the tailor-made, personalized medication therapy."

**Moderator: Do clinicians feel threatened or constrained by the cost pressure that may affect innovation?**

As a clinician, Dr Pecora did not say whether he felt threatened or constrained. He was, however, concerned that the discussion about innovation was focused on innovating payment strategies instead of innovating treatment strategies. Dr Pecora said, "The pace of discovery and our ability to open up the black box now is much greater than it's ever been and that's only going to accelerate. So we don't want to put reimbursement strategies in place that slow that down." Dr Pecora believes those innovations will lead to more cost efficient ways to treat cancer.

**Moderator: Will new healthcare payment plans still have room for expensive cancer drugs?**

Dr Feinberg said that he was not sure how much the new payment plans would be willing to accommodate new innovative but expensive drugs. However, he did caution that we still have much to learn about how all of us pay for certain procedures or medications. Dr Feinberg stated: "As we remove all financial incentives and we see marginally neutral responses to drugs, we're starting to see behavior that maybe isn't as predictable. We're not seeing the shift away from certain things, and I think it's because it's driven by habit. It's driven by psychology. It's driven by a selective learning process in which it reinforces their worldview that I'm going to treat it that way. And I think that is a piece that we're not addressing as we continue to focus on the financial modeling."

**Moderator: As new drugs enter formularies and old drugs are removed, are the rules of engagement changing?**

Dr Dunn of SelectHealth, Inc, stated that the rules are dramatically changing since their business model is changing. He said, "If you look at the estimations on what's going to happen to the pharmacy budget over the next 3 to 4 years, half our budget is going to be in specialty. And this is different than it was 3 or 4 years ago because there's been an obvious move toward oral pharmacy specialty drugs....And so how benefits are designed around that has to change." To adapt to these new trends, Dr Dunn said they have acknowledged that within 5

*"I think the day of every new drug being simply set to a price that the market will bear, irrespective of the value it delivers, is one that will be seeing its sunset."*



—Peter B. Bach, MD, MAPP

Director, Center for Health Policy and Outcomes  
Attending Physician  
Memorial Sloan-Kettering Cancer Center,

of *Managed Care*; Ira M. Klein, MD, MBA, FACP, chief of staff, Office of the Chief Medical Officer, Aetna; and Andrew L. Pecora, MD, FACP, CPE, chief innovations officer and vice president of cancer services, John Theurer Cancer Center at the Hackensack University Medical Center and president of Regional Cancer Care Associates.

**Moderator: If we are indeed experiencing some kind of turning point or even tipping point in the way oncology care is being priced, what do you expect will be the effect on what is innovated or how it is innovated in cancer care?**

Dr Bach answered this question by stating that the most notable innovation in cancer may be less about new treat-

that will have an effect on innovation, and I think that's a shame and something we have to think about going forward."

Dr Klein was more optimistic and noted that as we continue to subtype various cancers, the drugs will be more specific to a smaller cohort of patients: "The nature of biologic drugs is that they're going to be applicable to a much narrower cohort of patients. So I think on a just-dollar basis, there's no such thing as a huge blockbuster drug now because there's no such thing as a huge applicable population. There's going to be segments." He added: "If there is an ability to efficiently generate a good match for a specific tumor subtype, I think those products will be successful."

*"The pace of discovery and our ability to open up the black box now is much greater than it's ever been and that's only going to accelerate. So we don't want to put reimbursement strategies in place that slow that down."*

—Andrew L. Pecora, MD, FACP, CPE

Chief Innovations Officer and Vice President of Cancer Services  
John Theurer Cancer Center  
Hackensack University Medical Center  
President Regional Cancer Care Associates





**“For a drug in oncology that will cure cancer 90% of the time, it should not cost the same as a drug that will extend life by 6 weeks to 6 months.”**

—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, *AJMC*

years they want to have a trend to be consumer price index plus 1%. “So we are heavily jumping into the accountable care organization model, redesigning benefit designs, collaboration, payment reform.”

**Moderator: What does value-based insurance design mean in the context of specialty pharma now?**

Dr Fendrick, co-editor-in-chief of *The American Journal of Managed Care*, pointed out that this question deals with some very tricky issues that may not be easily measured for cancer care. He said, “For a drug in oncology that will cure cancer 90% of the time, it should not cost the same as a drug that will extend life by 6 weeks to 6 months.” Dr Fendrick further noted that with cancer care, there is a lot of nuance associated with care. “Every stakeholder involved with cancer care understands that clinical nuance is better than the status quo of one-size-fits-all.” Furthermore, “Things that are profitable...are [those] that produce the outcomes that they’re supposed to produce, like better education or transportation or other types of things. In healthcare, that is hardly ever the case. The things that produce the most health for the money, you know them, we’ve known them, they are things that are typically and traditionally underpaid. And those that would have the most marginal cost-effectiveness ratios, or whatever measure you put on them, tend to be the most profitable.”

**Moderator: Do you see a pathway to implementing value-based insurance design in specialty pharma?**

Dr Dunn stated that his company has attempted to apply value-based insurance design (VBID) to conditions such as asthma and diabetes but they did not see an improvement in compliance and employers were reluctant to pay for it. However, Dr Dunn thinks that VBID may work in specialty pharmacies. “I think VBID is more applicable, actually, to specialty than it is in some of those wider, broader categories. But it’s a little bit different definition of VBID. It’s more

of the pathway. It’s the more cost-effectiveness/comparative effectiveness research type approach.”

Dr Klein added that VBID is designed to provide incentives to change behavior and while it is a logical means to reduce healthcare costs, employers are reluctant to pay for this arrangement.

Dr Fendrick echoed those sentiments by concluding, “The idea of clinical nuance and value-based insurance design, it’s like apple pie, it’s intuitive, it makes sense. It’s been relatively slow to adopt.”

**Moderator: Can you comment on the perceived lack of transparency that occurs with pathways?**

Dr Feinberg disagreed that there was a lack of transparency: “In our case, every one of our contracts that’s done on a regional basis, the pathways are then disseminated to the entire provider network. The steering committees then meet on a quarterly basis and review new information like new labeling, new drug introduction, black box warnings, etc, and they update accordingly.” In addition, he said that physicians in their group have a “tremendous sense of comfort in knowing that a group of their peers endorses what they’re going to do, that not every situation is a situation that you see 10 times, 100 times a year, sometimes not even a lifetime.”

Dr Dunn also stated that he felt that his company’s pathways are transparent. “The policies and procedures would be publicized and published because our organization is risk averse, and it’s an evidence-based organization. So we’re not going to put out something that is not backed up with evidence,” he said, adding, “What’s not going to probably be shared publicly, initially, is the reporting incentive type piece, how are providers doing.”

Dr Chernew applauded the organizations that promote transparency but was concerned that the fundamental question was not being properly addressed. “I think most patients, for example, won’t be able to evaluate them [pathways]. And they certainly won’t be able to evaluate them where they’re

making a choice about what delivery system to be in.”

**Moderator: How is cancer care going to change the most as a result of the factors we discussed today?**

- “The organizations in which oncologists work are going to be bigger and more heavily managed,” stated Dr Chernew.
- “There will be information and incentives placed on the actual consumer to go to places like centers of excellence,” said Dr Fendrick.
- According to Dr Klein, “People are

years from now we’ll be sitting here having this exact same discussion.”

- “We’re going to worry a lot more about disparities. We will have mechanisms that are going to make it difficult for some segments of our population to get access to all those treatments,” stated Dr Chernew.

**Better:**

- According to Dr Klein, “We’ll have taken information from individual patients that includes not just their disease and stage, but also their tumor marker status, other biologic marker status, their performance

**“We’ll have taken information from individual patients that includes not just their disease and stage, but also their tumor marker status, other biologic marker status, their performance status at time of diagnosis, their demographic information. We will have taken that for hundreds of thousands of people and we will have sorted it and attached it to different regimens, and we will understand from comparative effectiveness research what works best.”**

—Ira M. Klein, MD, MBA, FACP

Chief of Staff  
Office of the Chief Medical Officer  
Aetna



going to start demanding more value for every dollar they spend. And the only way that can be validated or have it be transparent and uniform for all is to create a cost equivalent so that people can look at what they’re getting for what they pay.”

- “There’s been a meaningful discussion among stakeholders to go beyond price to this issue of value and not just the lowest price provider, which gives me some optimism moving forward,” stated Dr Fendrick.

**Moderator: What do you think will be worse and better about cancer care in the year 2020?**

**Worse:**

- “As the baby-boomer bulge moves into retirement, I don’t think that we’re going to see as much of the healthy elderly as we think,” replied Dr Klein.
- According to Dr Dunn, “My fear is 8

status at time of diagnosis, their demographic information. We will have taken that for hundreds of thousands of people and we will have sorted it and attached it to different regimens, and we will understand from comparative effectiveness research what works best.”

- “Things like payment reform, benefit design changes, investments in health information technology will all lead us to evidence-based formularies which are going to improve outcomes and lower costs,” said Dr Dunn.
- Dr Fendrick stated that Section 2713 of the Affordable Care Act mandates that primary preventive services, including cancer screening, will be without cost sharing to any American. He is hopeful that we will see meaningful reductions in preventable cancers.
- According to Dr Chernew, “Treatments are going to be much better.” **EBO**

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

**Rx Only**

**BRIEF SUMMARY – See full Prescribing Information for complete product information**

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

**DOSAGE AND ADMINISTRATION**

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

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

**CONTRAINDICATIONS:** None.

**WARNINGS AND PRECAUTIONS**

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

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

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

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

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

**ADVERSE REACTIONS**

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

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

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

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

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

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

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

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

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
<b>Any Adverse Event</b>	<b>591 (98.3)</b>	<b>186 (30.9)</b>	<b>291 (96.0)</b>	<b>97 (32.0)</b>
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](http://www.fda.gov/medwatch).**

**Dendreon Corporation  
Seattle, Washington 98101**

**References:** 1. Kantoff PW, Higano CS, Shore ND, et al; for the IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363:411-422.  
2. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. V.3.2012. National Comprehensive Cancer Network Web site. [www.nccn.org](http://www.nccn.org). Accessed April 26, 2012.

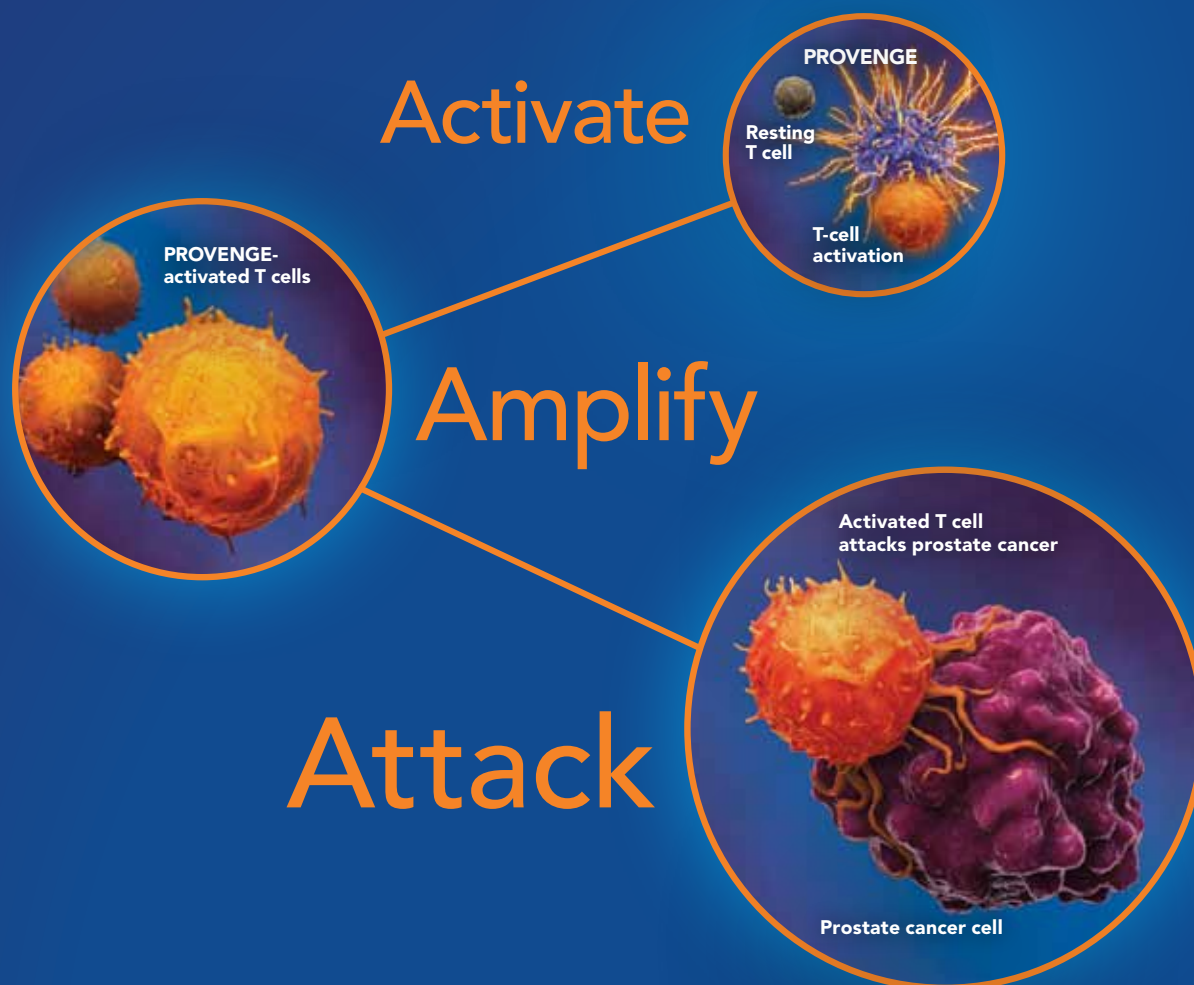
**Dendreon**  
*Targeting Cancer, Transforming Lives®*

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**PROVENGE®**  
(sipuleucel-T)

In advanced prostate cancer

# TREAT FIRST LINE WITH PROVENGE TO



## EXTEND SURVIVAL

> 2<sup>years</sup>

Extends median survival beyond 2 years<sup>1</sup>

1<sup>st</sup>  
and only

First and only FDA-approved immunotherapy for advanced prostate cancer

1<sup>st</sup>  
line

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

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

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

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

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

[www.PROVENGE.com](http://www.PROVENGE.com)

**PROVENGE**<sup>®</sup>  
(sipuleucel-T)