

THE AMERICAN JOURNAL OF MANAGED CARE®



Evidence-Based Oncology

THE IMMUNO-ONCOLOGY SPECIAL ISSUE

Payer Perspective

Issues Impacting Stakeholder Adoption of Immuno-Oncology

BRUCE FEINBERG, DO

Those were heady times. We saw ourselves on the verge of mastering the immune system and, with such mastery, conquering cancer's most elusive trait. Initial clinical trials were not only demonstrating broad antitumor activity, but complete remissions in melanoma, as well as significant responses in other solid tumors and hematologic malignancies. We were witnessing the dawn of a new therapeutic era with a much anticipated arsenal of weapons that would exploit the human immune system and overcome cancer's cloaking device.

My original research in the field was rewarded with manuscripts accepted by the *Journal of Clinical Oncology* and *The Journal of the American Medical Association*, as well as an abstract selected for oral presentation at the American Society of Clinical Oncology's Annual Meeting. The year was not 2013, it was 1986. I was a fellow at MD Anderson Cancer Center in Houston, Texas, in the Developmental Therapeutics Department. Interleukins, interferons, tumor necrosis factor, cytokines, and lymphokines comprised a new language of biologic therapies that would eclipse and replace the cytotoxic and cytostatic traditional chemotherapies of the past. The enthusiasm over this first generation of immuno-oncology agents was eventually tempered by toxicity and limited efficacy, leading to the commercialization of only a handful of agents that would have an impact on relatively small disease populations of hairy cell leukemia, chronic myeloid leukemia, HIV-related lymphoma, localized recurrent bladder cancer, melanoma, and renal cell cancer. Over the subsequent 2 decades, a second

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Provider Perspective

Improving the Value of Immune-Based Therapies

RICHARD W. JOSEPH, MD

BACKGROUND

Immune checkpoint blockade inhibitors are revolutionizing care for patients with metastatic melanoma and other malignancies. The first generation of FDA-approved checkpoint blockade inhibitors targeted the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), while the next generation of inhibitors inhibit either the programmed death 1 (PD-1) receptor or programmed death ligand 1 (PD-L1). These agents act by inhibiting negative regulators of the immune system, thereby providing a net effect of immune stimulation.

In September 2014, the FDA approved the first anti-PD-1 therapy, pembrolizumab (Keytruda), for the treatment of patients with metastatic melanoma who have previously progressed on ipilimumab, with the stipulation that if the patient's tumor harbored a mutation in BRAF, the patient must receive a BRAF inhibitor as well. In December 2014, the FDA approved the second anti-PD-1 agent, nivolumab (Opdivo), for the same indication as pembrolizumab.

Both pembrolizumab and nivolumab have demonstrated a remarkable clinical efficacy-to-toxicity ratio. Specifically, these therapies are providing durable remissions to a substantial minority of patients (20% to 40%) while at the same time proving to be very safe, with very few grade 3/4 (<10%) adverse events. In addition to melanoma, these agents, as well as other anti-PD-1/PD-L1 agents, are showing promising results in multiple other tumor types including lung cancer, bladder cancer, kidney cancer, lymphoma, and many others.

Given the clinical success and low

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Patient Perspective

Patient Cost-Sharing in Oncology and the Patient Access Network Foundation

DAN KLEIN

The Patient Access Network (PAN) Foundation is a charitable organization that provides underinsured patients with the financial support they need to meet cost-sharing requirements for breakthrough therapies and other costly cancer treatments. PAN was established more than 10 years ago, partially in response to the development of the Medicare Part D prescription drug benefit. Since then, PAN has evolved with the Part D program and the trend among public and private payers to develop separate benefit approaches for specialty drugs, including the use of limited distribution channels and higher cost-sharing requirements.

With nearly 60 disease-specific funds, including 25 for oncology, PAN provides cost-sharing assistance for therapies that are used to treat 2 tumor types for which the FDA has approved distinct immuno-oncology agents: 1) for hormone-refractory prostate cancer, the therapeutic cancer vaccine sipuleucel-T, marketed as Provenge; 2) for metastatic melanoma, the T-cell potentiating anti-CTLA-4 monoclonal antibody, ipilimumab, marketed as Yervoy. In addition, PAN provides assistance for 2 other immunotherapies approved for metastatic melanoma: pembrolizumab, marketed as Keytruda; and nivolumab, marketed as Opdivo.

More broadly, the foundation focuses on helping the underinsured meet the high cost-sharing requirements for critical, prescribed therapies. As such, PAN responds to the reality of current

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MONEY WELL SPENT: THE NEED FOR FEDERAL FUNDING IN CANCER RESEARCH

John R. Seffrin, PhD

The CEO of ACS CAN provides insight on the impact of basic and clinical research on cancer care and how his organization is providing a voice in Congress to help patients and research scientists (SP70).

REALITY MEETS ASCO'S POLICY STATEMENT ON MEDICAID REFORM

Ted Okon, MBA

The executive director of Community Oncology Alliance shares his views on ASCO's recent policy statement on Medicaid reform published in *The Journal of Clinical Oncology* (SP73).

ASCO ANNOUNCES IT PARTNER FOR THE CancerLinQ PLATFORM

CancerLinQ, ASCO's clinical decision-making support tool for physicians, will be using the SAP HANA platform to improve cancer care delivery (SP74).

ONCOLOGY STAKEHOLDERS SUMMIT

The last segment from the summit, with discussions on clinical pathway adoption, diagnostic tests, innovation in cancer care, and management of prostate cancer (SP85).

AJMC® Oncology Stakeholders Summit

Oncology Stakeholders Summit Panel



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The Value and Future of Immuno-Oncology

Welcome to the first issue of *Evidence-Based Oncology* for 2015. With the New Year, we are working on a different approach for *EBO*—each issue will bring you articles around an underlying theme. With immuno-oncology (I-O) making rapid strides in cancer treatment, this issue explores our understanding of where I-O presently stands, as well as some questions that remain unanswered regarding this innovative approach in cancer care.

In his cover commentary, Bruce Feinberg, DO, vice president and chief medical officer, Cardinal Health Specialty Solutions, makes a case for the position that I-O has revolutionized cancer care. “What makes immuno-oncology seem so transformative and thereby so appealing is the gestalt of panacea, therapies that are histology agnostic unleashing an immune system to recognize self from abnormal self regardless of cell origin,” he says. However, he thinks the cost of I-O treatment will result in greater scrutiny by payers, because these agents have the potential to transform cancer into a chronic condition.

What are some of the limitations with the drug development approaches with these agents, and what is the current clinical need? Richard W. Joseph, MD, a medical oncologist at the Mayo Clinic in Jacksonville, Florida, examines these issues in his commentary. In his opinion, identifying predictive biomarkers, duration of therapy, and optimal combinations and sequence of therapy is the way forward in I-O. While the agents are currently only approved for advanced melanoma, promising results achieved in other cancers will call for improving their value by answering some of these questions, Joseph believes.

The high cost of cancer care is addressed in the commentary from Dan Klein, president and chief executive officer of the Patient Access Network Foundation, which provides financial support to meet cost-sharing requirements of underinsured patients. He points to the fact that newer oncology treatments—unlike chemotherapy—are a greater cost burden, since they are prescribed as maintenance therapies for longer periods, and thus increase the patient’s financial exposure.

We also bring you the last segment of the Oncology Stakeholders Summit, hosted by *The American Journal of Managed Care* in fall 2014, which brought together leading voices from the clinical and managed care world to discuss some of the most important issues that affect clinicians, payers, and regulators. Stay tuned for updates as we plan more of these discussions in the coming year.

Please look for updates on our live meeting, Patient-Centered Oncology Care (PCOC) 2015, on the events page at www.ajmc.com. On the footsteps of a successful PCOC 2014, we have a great agenda planned and are working toward recruiting leading experts from the healthcare world.

Sincerely,

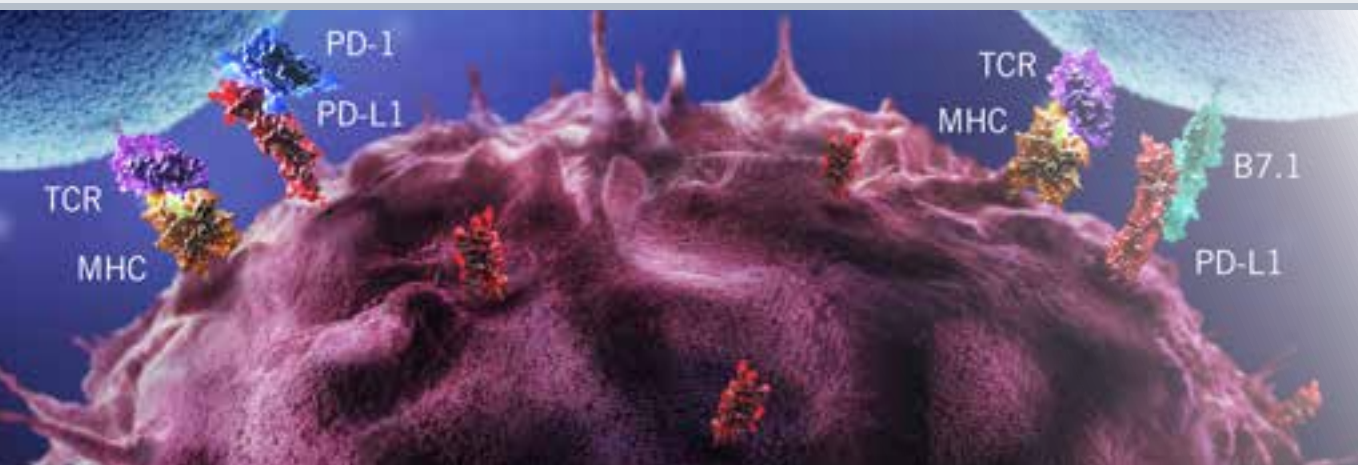
Brian Haug
President, *The American Journal of Managed Care*

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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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The Promise of Immuno-Oncology

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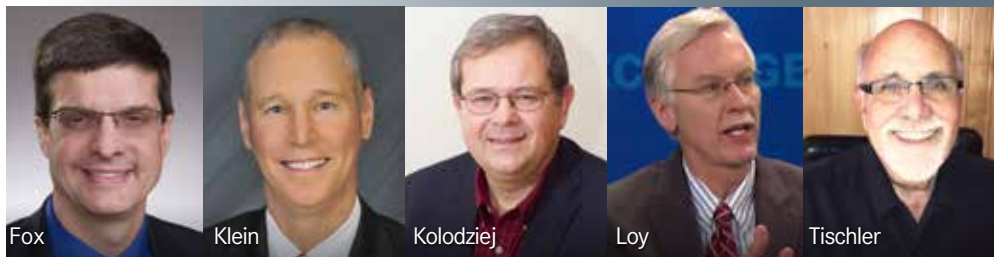
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GRANIX[®] is an option in short-acting G-CSF therapy

- » A 71% reduction in duration of severe neutropenia vs placebo (1.1 days vs 3.8 days, $p < 0.0001$)¹
 - Efficacy was evaluated in a multinational, multicenter, randomized, controlled, Phase III study of chemotherapy-naïve patients with high-risk breast cancer receiving doxorubicin (60 mg/m² IV bolus)/docetaxel (75 mg/m²)¹
- » The safety of GRANIX was established in 3 Phase III trials, with 680 patients receiving chemotherapy for either breast cancer, lung cancer, or non-Hodgkin lymphoma (NHL)¹
- » Now offering a new presentation for self-administration

Indication

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

Important Safety Information

- » **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.
- » **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
- » **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.
- » **Use in patients with sickle cell disease:** Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
- » **Capillary leak syndrome (CLS):** CLS can occur in patients receiving hG-CSFs and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of CLS should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.
- » **Potential for tumor growth stimulatory effects on malignant cells:** The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.
- » **Most common treatment-emergent adverse reaction:** The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

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

For more information, visit GRANIXhcp.com.

Reference: 1. GRANIX[®] (tbo-filgrastim) Injection Prescribing Information. North Wales, PA: Teva Pharmaceuticals; 2014.



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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

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

5.2 Acute Respiratory Distress Syndrome (ARDS)

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

5.3 Allergic Reactions

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

5.4 Use in Patients with Sickle Cell Disease

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

5.5 Capillary Leak Syndrome

Capillary leak syndrome (CLS) can occur in patients receiving human granulocyte colony-stimulating factors and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.6 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

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

6 ADVERSE REACTIONS

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

- Splenic Rupture [see *Warnings and Precautions* (5.1)]
- Acute Respiratory Distress Syndrome [see *Warnings and Precautions* (5.2)]
- Serious Allergic Reactions [see *Warnings and Precautions* (5.3)]
- Use in Patients with Sickle Cell Disease [see *Warnings and Precautions* (5.4)]
- Capillary Leak Syndrome [see *Warnings and Precautions* (5.5)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [see *Warnings and Precautions* (5.6)]

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

6.1 Clinical Trials Experience

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

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

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

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

Additional Adverse Reactions

Other adverse reactions known to occur following administration of human granulocyte colony-stimulating factors include myalgia, headache, vomiting, Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis and thrombocytopenia.

6.2 Immunogenicity

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of GRANIX in pregnant women. In animal reproduction studies, treatment of pregnant rabbits with tbo-filgrastim resulted in increased spontaneous abortion and fetal malformations at systemic exposures substantially higher than the human exposure. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No case of overdose has been reported.



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Product of Israel

GRX-40502 December 2014

This brief summary is based on TBO-004 GRANIX full Prescribing Information.

The Promise of Immuno-Oncology

Surabhi Dangi-Garimella, PhD

Immuno-oncology (I-O) is set to revolutionize the field of cancer care. Harnessing the immune system to attack cancer cells was ideated after scientists discovered the viral origins of some forms of cancer. Cancer vaccines were subsequently developed as prophylactic treatment and as therapy. Currently, 3 prophylactic vaccines approved for use by the FDA against the human papilloma virus (HPV)—responsible for most cases of cervical cancer—are available in the United States: Gardasil (HPV 6, 11, 16, 18), Gardasil 9 (HPV 9), and Cervarix (HPV 16 and 18).¹ Gardasil is a Merck product and Cervarix was developed by Glaxo-SmithKline Biologicals. On the therapeutic front, several companies continue their research efforts, but the lone FDA-approved product is Provenge (sipuleucel-T)² from Dendreon Corporation, indicated for the treatment of asymptomatic or minimally symptomatic, metastatic, hormone-refractory prostate cancer.³ However, the drug's front-end cost (\$93,000) coupled with its complex personalization protocol resulted in a slump in sales, and Dendreon finally filed for bankruptcy late last year.⁴ While CEO W. Thomas Amick has assured that Provenge will remain commercially available to patients and providers during the process, there are reports that Valeant Pharmaceuticals International, Inc would buy the immunotherapy from Dendreon (see page SP76).

Several other cancer vaccines, both prophylactic and therapeutic, are currently under development. Additionally, several clinical trials are ongoing with approved and novel vaccines (Table 1).

UNDERSTANDING CANCER

An early approach that was tried, but failed, was treating patients with cytokines and interferons. The primary reasons for failure included lack of specificity, limited efficacy, and toxicity.⁵ Present-day advances in I-O can be attributed to a paradigm shift in understanding the disease: in the late 1990s and early 2000s, cancer was considered a disease of genetic origins, with specific "hallmarks," including sustained proliferation, resistance to apoptosis, the ability to promote angiogenesis, and the ability to promote invasion and metastasis.⁶ This view disregarded the dynamic nature of the interaction of the tumor with its microenvironment, which included the "normal" cells in the surrounding tissue as well as the immune system.⁷ Discovery of just how the immune system helps tumor cells proliferate and avoid immune detection led to rapid advances in immune-based targeting of cancer and its microenvironment. With this came the understanding that both "passive"

(eg, infusing with antibodies or cytokines) and "active" (eg, vaccines) immunotherapies would be paramount for long-term tumor control or for complete elimination of tumors.⁸

An important and fairly successful outcome of this new wave of thinking has been the tumor-specific monoclonal antibodies that target specific antigens on cancer cells. Several of these antibodies have already been approved by the FDA and are being used as standard treatment in numerous cancer types (Table 2).

THE SCIENCE BEHIND I-O

The biggest advantage of the current immune therapies is that they stimulate the patient's immune system to take charge and the proteins being targeted are not organ-specific. This broadens the scope of the therapy for use in multiple tumor types.

While monoclonal antibodies, which target a specific antigen on a cancer cell, have proven successful in some tumor types, the effect is transient and cure rates are low, most likely due to a compromised immune system. The challenge with antibodies is maintaining a persistent memory response. While T-cells persist longer, the antibody memory response is restricted to a single clone or a few clones, which allows tumor escape.⁸ The newly approved I-O agents are designed to overcome this weakness, raising the possibility of ideal combination immunotherapies.

Usually, the amplitude and quality of an immune response by T cells is a result of the balance between co-stimulatory and inhibitory (immune checkpoint) signals. The immune checkpoints help maintain homeostasis and prevent auto-immunity. However, to avoid immune recognition, tumors dysregulate these checkpoints. Two of the most widely studied inhibitory immune checkpoint receptors in oncology are cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1).⁹ So far, 3 antibodies that target these receptors have been FDA-approved: ipilimumab (CTLA-4 inhibitor) for metastatic melanoma, and pembrolizumab and nivolumab (both PD-1 inhibitors) for metastatic melanoma with disease progression on ipilimumab (Table 3). It's important to note that several other checkpoint inhibitor receptors are expressed on T cells, and molecules targeting these receptors and their ligands are also being evaluated.

COMBINATION THERAPIES

Several drug combination therapies are currently in different stages in clinical trials and are providing encouraging results. A phase 1 trial with dual T-cell

TABLE 1. Some of the Ongoing Prophylactic and Therapeutic Cancer Vaccine Trials

	TUMOR TYPE	VACCINE	OBJECTIVE
Prophylactic	Cervical cancer	Gardasil Cervarix	Prevention of sexual transmission of HPV Safety study in 4-to-6-year-old females
Therapeutic	Bladder cancer	BCG + PANVAC MVX-ONCO-1	Test if PANVAC improves efficacy of BCG Safety and tolerability in patients with advanced solid tumors
	Brain cancer	DCVax-L IMA950 multi-peptide vaccine + poly-ICLC	Safety and impact on disease progression Safety, tolerability, and immunogenicity when administered with temozolomide
Breast cancer		NeuVax (Nelipepimut-S)	Safety and efficacy of NeuVax administered with Leukine to prevent breast cancer recurrence
		Allogenic whole-cell vaccine	Improve survival of metastatic epithelial cancer patients
Multiple myeloma		Herpes zoster subunit vaccine	Safety and immunogenicity in adults with blood cancer
		Autologous dendritic cells (Vax-DC/MM)	Safety and efficacy in patients with relapsed or refractory multiple myeloma
Pancreatic cancer		AlgenpanteuceL	Treat borderline resectable or locally advanced unresectable pancreatic cancer

BCG indicates Bacillus Calmette-Guerin; HPV, human papilloma virus.
Source: <http://www.cancer.gov/clinicaltrials>.

TABLE 2. Few of the FDA-Approved Monoclonal Antibodies for Cancer Treatment

BRAND	GENERIC NAME	COMPANY	TUMOR TYPE	APPROVED
Cyramza	Ramucirumab	Eli Lilly	Metastatic NSCLC	2014
			Advanced gastric adenocarcinoma	2014
Blincyto	Bilatumomab	Amgen	ALL	2014
Avastin	Bevacizumab	Genentech	mCRC	2013
Gazyva	Obinutuzumab	Genentech	CLL	2013
Perjeta	Pertuzumab	Genentech	Early-stage breast cancer	2013
Xgeva	Denosumab	Amgen	Giant cell tumor of the bone	2013
Rituxan	Rituximab	Genentech	CLL	2013
			NHL	2012
			Advanced follicular lymphoma	2011
Erbix	Cetuximab		Head and neck cancer	2014
			mCRC	2012

ALL indicates acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; mCRC, metastatic colorectal cancer; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer.
Source: www.fda.gov.

TABLE 3. Immuno-Oncology Checkpoint Inhibitors⁵

GENERIC NAME	BRAND	TARGET	TUMOR TYPE	
Approved				Being developed in
Ipilimumab	Yervoy	CTLA-4	Advanced melanoma	Liver cancer, lung cancer
Pembrolizumab	Keytruda	PD-1	Advanced melanoma following ipilimumab	Recurrent head and neck cancer, malignant glioma, NSCLC, MCC, bladder cancer
Nivolumab	Opdivo	PD-1	Advanced melanoma following ipilimumab	mCRPC, RCC, NSCLC, MM, NHL, HL
Under development				
Tremelimumab		CTLA-4	Malignant mesothelioma, HCC, melanoma	
MPDL3280A		PD-L1	NSCLC, melanoma, RCC, bladder cancer, B-cell lymphoma	
rHIgM12B7		PD-L2	Melanoma	
IMP321		LAG-3	Melanoma, metastatic breast cancer, RCC	

CTLA-4 indicates cytotoxic T-lymphocyte-associated antigen 4; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; LAG-3, lymphocyte activation gene 3; MCC, merkel cell lymphoma; mCRPC, metastatic castration-resistant prostate cancer; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.
Source: www.fda.gov, www.clinicaltrials.gov.

checkpoint inhibitors ipilimumab and nivolumab (targeting CTLA-4 and PD-1, respectively) presented promising 2-year survival rates in patients with advanced melanoma.¹⁰ Numerous other combinations—with dual checkpoint inhibitors, T-cell inhibitors with immune activators, and with chemotherapy—are ongoing in a multitude of tumor types.⁵

FUTURE DIRECTIONS FOR I-O

As several articles in this issue indicate, a big challenge in I-O is identifying the target population for each treatment to enrich the cohort and achieve maximum treatment efficacy. Efforts to monitor the programmed death-ligand expression

in tumors have yielded mixed results, as highlighted in the commentary by Richard Joseph, MD, on page SP97. Efforts to characterize potential biomarkers are ongoing. Challenges include the sequence of therapies and the duration of treatment administration. Identifying biomarkers or alternate clinical endpoints to measure responses to these I-O agents could potentially address the question of treatment duration. **EBO**

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ONCOLOGY MEDICAL HOME

Commission on Cancer and the Oncology Medical Home

Daniel P. McKellar, MD, FACS

Effective January 2015, the Commission on Cancer (CoC) will be accrediting the initial pilot practices for Oncology Medical Home (OMH) recognition. The development of the standards for an OMH has been a collaborative effort among multiple stakeholders. Initial discussions that began 2 years ago with some community-based oncology teams has led to a concerted effort to standardize and endorse quality and value-based cancer care delivered by teams within the community or at other sites of care. Considerable time has been spent to develop the standards and requirements responsible for meaningful improvements in cancer care.

Established by the American College of Surgeons in 1922, the multidisciplinary CoC has been the leader in cancer program improvement. CoC's mission is to improve quality of life and survival for cancer patients. This can be accomplished by:

- establishing standards to ensure quality, multidisciplinary, and comprehensive cancer care delivery in different healthcare settings
- conducting surveys in healthcare settings to assess compliance with standards
- collecting standardized data from accredited healthcare settings to measure the quality of cancer care
- using data to monitor treatment

patterns and outcomes, and enhance cancer control and clinical surveillance activities

- developing effective educational interventions to improve cancer prevention, early detection, cancer care delivery, and outcomes in healthcare settings.

Currently, more than 1500 hospital-based cancer programs are accredited by the CoC. The OMH recognition program is the most recent accreditation program to be implemented by the 54-member cancer care organizations that direct CoC activities. This new model of care is intended to ensure high-quality, measurable cancer care in a more efficient system by improving care coordination, expanding patient access to healthcare



Daniel P. McKellar, MD, FACS

providers, and ensuring that care is delivered in a patient-focused manner.

Medical homes in primary care have been successful in improving the quality of care delivered and reducing the costs of that care. Cancer care practices or centers will need to implement all OMH standards and participate in an onsite survey to review their compliance with standards in 5 domains (Figure):

- patient engagement
- expanded access
- evidence-based medicine
- comprehensive team-based care

“The fresh attention to applicable, meaningful, and measurable improvement in quality and value emphasizes transparency and a better understanding of the processes for those involved in cancer care.”

—DANIEL P. MCKELLAR, MD, FACS

- quality improvement

This program, and subsequent surveys, will promote organizational infrastructure changes in cancer care, resulting in process improvements for components of the 5 domains. These policies and procedures will include evaluation and measurement criteria that will demonstrate the results of the efforts of the centers to comply with these new standards. In this era of increased quality, care coordination, and accountability in healthcare, this will be a welcome addition for all involved—particularly cancer patients and their families.

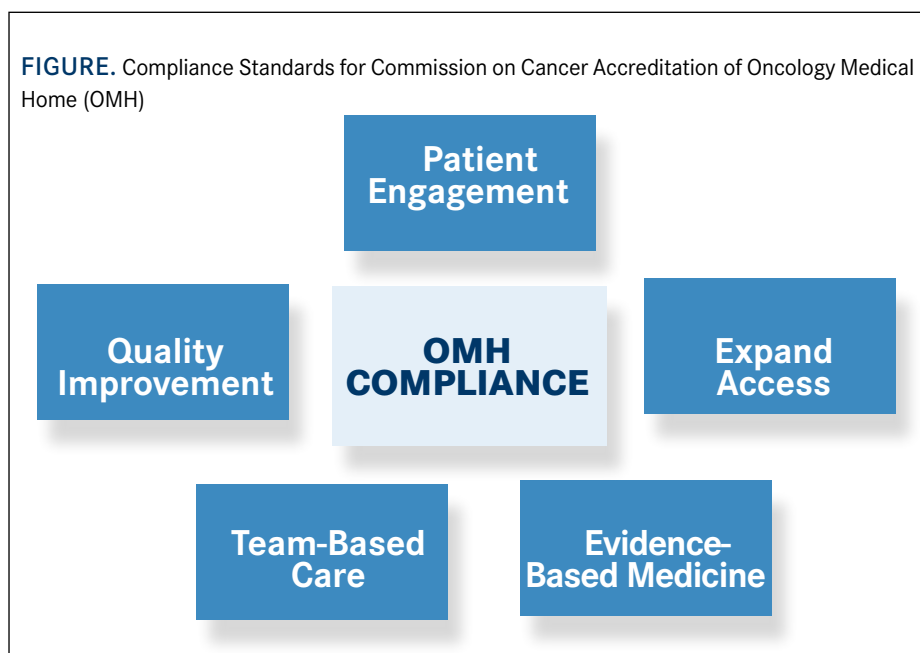
For example, the *patient engagement* domain contains standards specific to educating the patient, providing guidance for managing the financial burden of cancer care, and providing a

documented treatment plan for each patient. Not only will cancer care organizations need detailed, written policies and procedures for each of these processes, they will also have to prove that each required standard was implemented. They will need to demonstrate how they assist with patient education, report whatever aid is offered to patients, and assure that key components and goals of a patient's care plan are shared on a timely basis. These are only a few examples of important issues in cancer patient care that are addressed in the CoC OMH accreditation standards.

The above collaborative effort is in conjunction with other initiatives to identify and promote quality and value in cancer care. These initiatives, and related teams, are working together to provide input, resources, and other standards that are used in the accreditation effort. These resources complement the CoC OMH accreditation program in the following ways:

1. **OMH Steering Committee.** The measurement and overall direction of the oncology medical project is led by a team of thought leaders that includes 16 representatives from the patient, provider, payer, and advocacy communities. The list of objective quality measures in the accreditation program is the direct result of their coordinated vision to improve the quality of care, to deliver efficient care, and to reduce costs.
2. **OMH Implementation Commit-**

FIGURE. Compliance Standards for Commission on Cancer Accreditation of Oncology Medical Home (OMH)



tee. The transition from a legacy-type cancer care system to one with a core emphasis on quantifiable improvement and qual-

ity can be challenging and time-consuming for cancer care teams entrusted with caring for cancer patients and their families. This

leadership team is responsible for identifying resources that could help ease the administrative and financial burdens associated with the transition in care. In fact, it has already identified ways to assist practices with implementing the policies they need to follow to meet the standards described in the CoC OMH accreditation program. The OMH Implementation Committee has also been responsible for the design and deployment of the National Oncology Patient Satisfaction Survey, another standard and key component of the CoC OMH accreditation program.

The CoC OMH accreditation program is deploying at a time when it is crucial to not only improve the quality of cancer care, but also make that care more efficient and cost-effective. This fresh attention to applicable, meaningful, and measurable improvement in qual-

ity and value emphasizes transparency and a better understanding of the processes for those involved in cancer care. The goal for all aspects of this model is to promote quality improvements in cancer care that are better measured, acknowledged, and recognized by all who may be involved in the cancer care system, including cancer care teams, employers, insurance companies, advocacy organizations, and patients and their families. **EBO**

Daniel P. McKellar, MD, FACS, is chair, Commission on Cancer.

PROVIDER RESOURCE

Immuno-Oncology Poised to Revolutionize Patient Care

Lee S. Schwartzberg, MD, FACP

As our understanding of tumor biology and the tumor micro-environment evolves, and an increasing number of immunotherapy approaches become available in oncology, immuno-oncology (I-O) therapy is poised to revolutionize patient care. The past year has brought exciting advancements focused on developing therapies that put the body's immune system to work to fight cancer.

ACCC ESTABLISHES NEW INSTITUTE FOR CLINICAL IMMUNO-ONCOLOGY

The Association of Community Cancer Centers (ACCC) has established the Institute for Clinical Immuno-Oncology (ICLIO) to educate providers about I-O and its implementation and delivery in the community setting. ICLIO will be a catalyst in assuring the availability of, and access to, innovative I-O agents and therapies for patients. This project is made possible by a charitable donation from Bristol-Myers Squibb.

ACCC serves as the leading advocacy and educational organization for the multidisciplinary cancer care team. Approximately 20,000 cancer care professionals from 1900 hospitals

and practices nationwide are affiliated with ACCC. As a national forum for addressing issues that affect community cancer programs, ACCC is recognized as the premier provider of resources for the entire oncology care team. Members include medical and radiation oncologists, surgeons, cancer program administrators and medical directors, senior hospital executives, practice managers, pharmacists, oncology nurses, radiation therapists, social workers, and cancer program data managers. As the healthcare landscape continues to evolve, ACCC helps members go beyond understanding "what" must be done to uncovering "how" to integrate advancements into practice.

ICLIO OPPORTUNITIES

ACCC has identified an advisory committee made up of thought leaders from the I-O field to steer the direction of ICLIO education initiatives. Additionally, ICLIO is convening a cadre of clinician scholars with knowledge of I-O, who will help serve as a resource for the Institute. These clinician scholars will help develop tools to enhance knowledge and understanding about the indications, applications, and

optimal use of I-O therapies within the community and academic settings to benefit patient care, as well as assist in the development of policy initiatives and pertinent educational content as it relates to the evolving I-O landscape.

ICLIO is seeking providers to serve as clinician scholars to provide feedback on information that would be useful to fellow providers, as well as those who want to learn more about I-O. Providers are invited to take a survey about how ACCC can best assist cancer care teams in the implementation of I-O therapy (https://www.surveymonkey.com/s/ICLIO_ACCC).

ICLIO subgroups will focus on topical themes relevant to the multidisciplinary cancer care team to provide information on the development of educational tools. Areas of interest include coverage and reimbursement issues, best practices for management and operations, healthcare policy, and clinical awareness. ICLIO educational resources will include monthly e-courses, journal articles, e-newsletters, a website, and a white paper. The first ICLIO National Education Meeting will take place on October 2, 2015, in Philadelphia, and offer attendees the opportunity to earn continuing medical education/continuing nursing education credits. For more information, visit ACCC's website: <http://www.accc-cancer.org/ICLIO>.

For information on serving as an ICLIO

“ICLIO is seeking scholars to provide feedback on information that would be useful to fellow providers, as well as those who want to learn more about I-O.”

—LEE S. SCHWARTZBERG, MD, FACP

clinician scholar, contact Lorna Lucas at llucas@accc-cancer.org. **EBO**

Lee S. Schwartzberg, MD, FACP, is the ICLIO chair and chief, Division of Hematology Oncology, and professor of medicine, The University of Tennessee, The West Clinic, PC, Memphis, TN.

Money Well Spent: The Need for Federal Funding in Cancer Research

John R. Seffrin, PhD



While many of us struggle each year to keep our personal health resolutions, elected officials face similar challenges: maintaining their commitment to our nation's health. There is real hope for bringing an end to the death and suffering that cancer causes, but doing so requires that we make the fight against cancer a national priority.

In 1971, President Richard Nixon publicly resolved to make a national commitment to defeat cancer when he signed the National Cancer Act. Passage of the Act dedicated federal resources to fight cancer by creating the National Cancer Program, which is led by the National Cancer Institute (NCI). Since the early 1990s, this federal investment in cancer research has led to the development of early detection and treatment tools that have resulted in a 22% drop in death rates in both men and women¹; many cancers are no longer the automatic death sentence they were a generation ago. In fact, since death rates peaked 2 decades ago, we have averted more than 1.5 million cancer deaths. But, we can't rest on our laurels. Answers con-

tinue to elude us when it comes to detecting and treating many types of cancer. To fully maximize our potential for progress, research funding must be dependable and consistent.

Research is not like a light bulb that can be turned on and off depending on when funding becomes available. Patients enrolled in clinical trials who have exhausted other treatment options cannot put their disease on hold while a trial awaits funding. Unfortunately, researchers who are forced to halt multi-year projects when funding runs out must abandon potential discoveries in process. The fact remains that the federal government is, by far, the largest public investor in cancer research and a critical player in our ability to promote discovery in a disease that is forecast to kill more than 589,000 Americans this year.²

On a positive note, research has led to vaccines and early detection tests that can prevent some cancers altogether, as well as treatments that can both increase the number of years of survivorship for millions along with the quality of those years. Targeted and precision therapies for a number of cancers are directly attacking the disease, rather than the patient's entire body—significant progress from the days when those lucky enough to survive the disease were often left with lifelong debilitating side effects.



John R. Seffrin, PhD

Robust and sustained investment in basic science and clinical research is paramount to maximize public and private innovation that has turned the war on cancer into an imminently winnable fight. Government-funded basic research and clinical trials serve as the building blocks for private-sector research and development. This public-private partnership is responsible for bringing promising new lifesaving treatments to patients, and it is essential to ultimately defeating this disease.

In my lifetime, cancer research has gone from a good bet to a sure one. Redoubling the federal investment in cancer research would accelerate progress against the disease and likely result in advances in other diseases, too. Unfortunately, the federal research investment has stagnated in recent years—as the cost of doing research has gone up.

Cancer is claiming more than 1600 lives in America every single day.² Meanwhile, in recent years, the budget of the NCI has fallen woefully short of what's needed. For most of the last decade, year over year, NCI funding has failed to keep pace with increased research costs. This stagnated funding has resulted in only 14% of research grant applications receiving support, compared to 24% just a decade ago,³ and the average age of a first-time grant recipient has increased from 37 years in 1980 to 42 years today.⁴ We risk losing promising young researchers to better-resourced research programs overseas, or to other professions altogether, taking with them the lifesaving potential of research never realized.

Past investment in research transformed the way cancer was diagnosed, far beyond the body part where a tumor is found. We now have the ability to develop tests to detect genetic mutations

known to cause certain types of cancers and to tailor therapies that address those same mutations. Yet, we risk squandering our past investment if there is no follow through with funding to make those potential tests and treatments a reality.

Despite the promise of an investment that could yield tremendous dividends for public health, our national commitment to keep up President Nixon's resolution is wavering. We cannot afford to put off until next year, or the next decade, the fight to defeat a disease that is the leading cause of death among adults aged 40 to 79 years and expected to overtake heart disease as the leading cause of death among all Americans within the next several years.

While we remain without effective measures to prevent, detect, and treat some of the most deadly cancers, investing in research is just one piece to solving the cancer puzzle. A discovery is only as valuable as its application, and inadequate funding is allowing promising discoveries to languish in labs. We have an obligation to get new detection tests and treatments from the laboratory to the patient's bedside. Proven ways to prevent cancer or detect it at the earliest, most treatable stages, are seriously underutilized.

On a more critical note, access to quality healthcare remains out of reach for tens of millions of Americans, despite significant progress achieved thanks to key provisions of the Affordable Care Act (ACA). We could prevent roughly half of all cancer deaths by applying what we know works: specifically, getting recommended screening tests and addressing harmful lifestyle factors such as tobacco use, obesity, poor nutrition, and inadequate physical activity. If we want to accelerate progress against cancer, we must realize we already know how to dramatically reduce death and suffering from the disease.

Proven tobacco control measures curb deadly tobacco use. If we increased the number of states and communities with comprehensive smoke-free workplace laws, passed significant tobacco tax increases, and fully funded tobacco prevention and cessation programs, we could perhaps reduce disease and death from tobacco use, which today accounts for 1 in every 5 deaths in the United States.⁵

ACS CAN AND CANCER POLICY

Defeating cancer is as much a matter of public policy as it is of scientific discovery. Lawmakers play a critical role in determining how much progress we can make, as a country, in fighting cancer. The American Cancer Society Cancer Action



CONGRESS, MAKE SURE CANCER RESEARCH INVESTMENTS PAY OFF.
— INCREASE FUNDING FOR NIH. —



Network (ACS CAN) was created to give a voice to those affected by cancer so they can encourage lawmakers at all levels of government to join the fight to make cancer a national priority.

ACS CAN mobilizes cancer advocates in every state and Congressional district nationwide to hold lawmakers accountable to their constituents for the decisions they make related to cancer. The organization works to defeat cancer by helping to protect and increase public investment in ground-breaking medical research and by improving nationwide access to the latest prevention and early detection measures, treatments, and follow-up care that are proven to save lives.

We've long known that increasing access to care is critical to the cancer fight. In 2007, ACS research revealed what had not been proven before: the lack of access to quality healthcare reduces a person's ability to survive cancer.⁶ We knew then that if we didn't see a true systems change in American healthcare policy, we simply could not achieve our goals to save more lives, faster.

During the debate over healthcare legislation in Congress, ACS CAN advocated for critical patient protections. For too long, cancer patients and survivors had been forced to choose between their lives and their life savings, as they were charged unfairly or denied health insurance altogether because of a preexisting condition. ACS CAN staff and volunteers urged lawmakers from both political par-

“Defeating cancer is as much a matter of public policy as it is of scientific discovery. Lawmakers play a critical role in determining how much progress we can make, as a country, in fighting cancer.”

—JOHN R. SEFFRIN, PhD

ties to help ensure all Americans get access to the cancer prevention, early detection, treatment, and follow-up care they need.

Key provisions in the ACA are improving access to care for cancer patients, cancer survivors, and their loved ones. ACS CAN continues to work with elected officials from both parties in Congress and throughout the States to protect critical provisions and improve the law for people with cancer and their families. Lawmakers are being urged to accept federal funds to increase access to Medicaid coverage so our nation's most vulnerable have access to mammograms, colonoscopies, and other lifesaving cancer screen-

ings and treatments they cannot currently afford. Where you live should not dictate whether you have access to care to help prevent, treat, and survive cancer.

Cancer advocates continue to stress to policymakers at every level that there is still much work to be done to eliminate death and suffering from this disease. While we have made strides in making some cancers a chronic condition you can live with, many of the more than 1.6 million diagnosed this year won't be given such promising news. With 1 in 2 men and 1 in 3 women expected to be diagnosed with cancer in their lifetime, now is not the time to relent. Because cancer is primarily a disease of the aged, cancer incidence increases as the population ages. In fact, cancer incidence rates are projected to rise by nearly one-third (31%) by 2025.²

We can—we must—make this century cancer's last. To bring cancer under control as a major public health problem in the United States, we must take 3 critical steps:

- Redouble our efforts to research the causes and cures of cancer
- Promote and elevate prevention into standard practice nationwide
- Ensure access to quality healthcare for all Americans.

If we want to win a final victory in the war on cancer, we must resolve to renew our national commitment to this fight this year. It's a resolution worth keeping. **EBO**

John R. Seffrin, PhD, is CEO of the American Cancer Society Cancer Action Network.

A link to ACS CAN's 2014 report on state legislative activity to reduce cancer incidence and mortality can be found at <http://www.acscan.org/content/wp-content/uploads/2014/08/HDYMU-2014-Report.pdf>.

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Call for Papers

The US National Library of Medicine defines evidence-based medicine as “the process of systematically finding, appraising, and using contemporaneous research findings as the basis of clinical decisions. Evidence-based medicine asks questions, finds and appraises relevant data, and harnesses that information for everyday clinical practice.”

On this basis, *Evidence-Based Oncology* seeks high-quality commentaries and original research reports on cutting-edge clinical, pharmaco-economic, and regulatory topics in cancer care. The objective is to provide patients, clinicians, payers, health plans, and the pharmaceutical community, evidence-based information to aid care decisions. The editors are especially interested in papers that promote dialogue and facilitate communication among stakeholders and healthcare policy makers that would potentially impact the efficiency and outcomes in cancer care. *Evidence-Based Oncology* regularly publishes articles that cover:

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ASCO Demands Medicaid Reform

Surabhi Dangi-Garimella, PhD

The American Society of Clinical Oncology (ASCO) has broadened its reach in recent months with policy statements on healthcare affordability and the value of cancer care. As discussed previously in *Evidence-Based Oncology*,¹ ASCO is constructing a value framework to obtain optimal cancer care outcomes at the lowest possible cost. However, cost is just one aspect of the equation, as was pointed out by Richard L. Schilsky, MD, chief medical officer at ASCO, in the article. The relative value of treatment is defined by both the clinical benefit that it affords and its toxicity, he writes.

While the beginning of 2014 saw the Value in Cancer Care brief issued by ASCO's Value in Cancer Care Task Force,² the end of the year witnessed a paper published by the society in the *Journal of Clinical Oncology* that called for major reform in Medicaid policies in the United States. These recommendations were expected to improve cancer care for the nearly 2.1 million cancer patients or survivors among the approximately 68 million Medicaid enrollees in the United States (see Figure).³ At last count, 28 states had adopted Medicaid expansion and 7 states were in discussions to consider signing up.⁴

With high-quality cancer care for all as their premise, the ASCO policy recommendations were centered on the following key principles:

- Every individual diagnosed with cancer should have health insurance that ensures access to high-quality cancer care by a cancer specialist.
- Medicaid beneficiaries with cancer should receive timely and quality care comparable with those who have private insurance.
- Medicaid payments should be sufficient to ensure that beneficiaries have timely access to quality cancer care. Cancer patients on Medicaid should not face barriers to clinical trial participation.⁵

Several studies have examined the influence of adequate Medicaid benefits and health outcomes of beneficiaries with cancer. Medicaid expansion, for example, improved all-cause survival within 5 years at the county level by more than 6% in the expansion states, with a significant reduction in delays in care.⁶ Another study found that persons diagnosed with cancer who had Medicaid coverage at the time of their diagnosis fared far better than those who were uninsured when diagnosed. The reasoning behind this observation? Individuals without health coverage, who later went on to enroll in Medicaid (likely following their diagno-

sis), presented a more advanced stage of cancer than those who were already covered.⁷

A recent study in the *American Journal of Preventive Medicine* examined the influence of Medicaid expansion on the disparities in preventive care for low-income women. The study assessed pre-Affordable Care Act breast and cervical cancer screening between expansion and nonexpansion states. The results showed that women in states that did not expand Medicaid were less likely to receive recommended mammograms or Pap tests. The authors predicted a high risk of widening healthcare disparities resulting from nonexpansion.⁸ The key recommendations of the executive committee on Medicaid reform have been summarized in the Table.

To allow for optimal patient care, the goal of these ASCO recommendations is to realize an adequate balance between federal and state budgets and fair payments and reimbursements for health service providers. For low-income individuals, Medicaid could be a lifeline. However, to bring healthcare providers on board, many of whom are currently wary of the existing policies, the system is in need of reform, the JCO article previously mentioned concluded. **EBQ**

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FIGURE. Medicaid Enrollees Lack Access to Quality Cancer Care

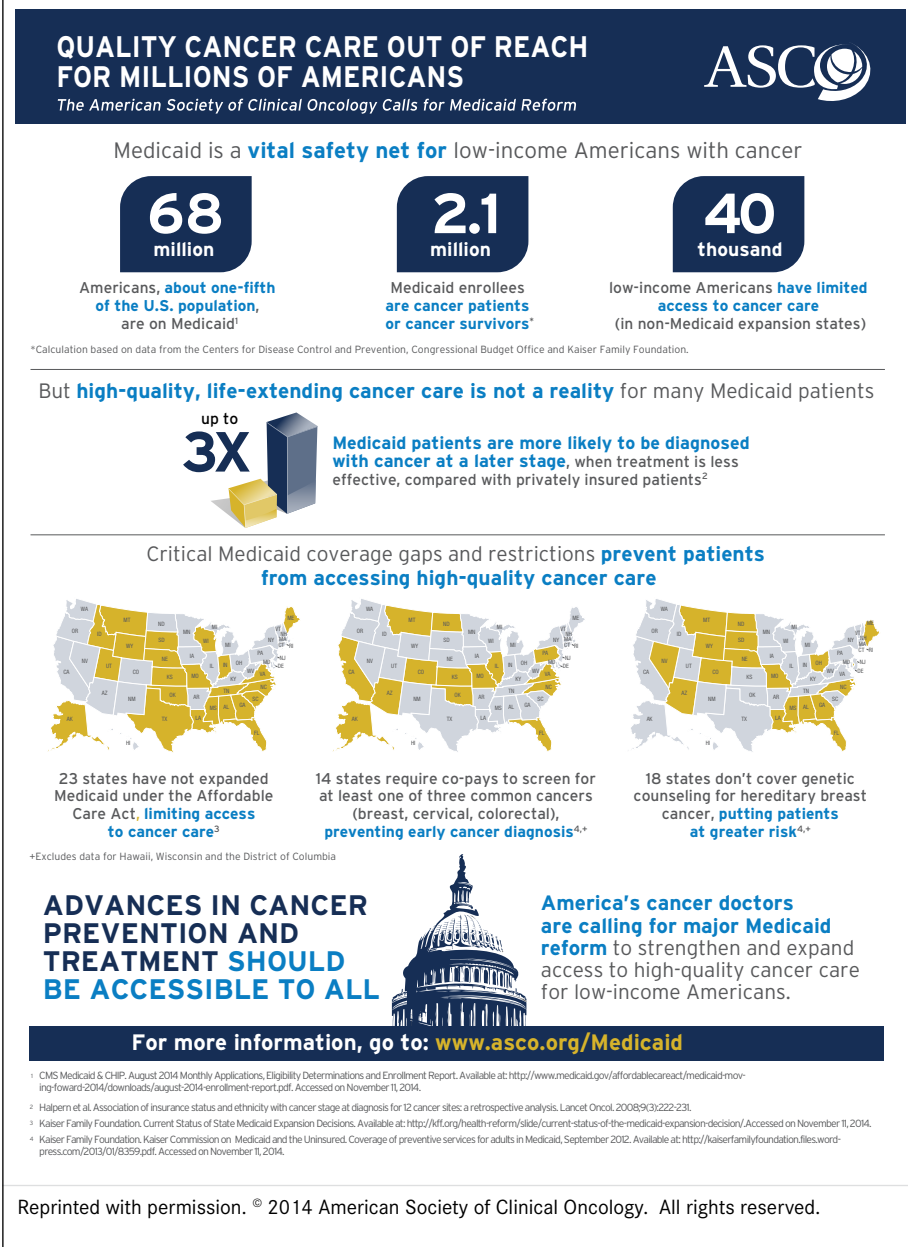


TABLE. ASCO's Policy Recommendations to Improve Access to Quality Care Through Medicaid Reform⁵

TOPIC	RECOMMENDATION
Insurance coverage	Expand coverage to all individuals living below the federal poverty level in all states.
Oral parity	Exempt oral and intravenous cancer medications and supportive care medications from cost-sharing for all Medicaid enrollees.
Clinical trials	Extend clinical trial protection to all enrollees. Dissolve state lines to allow trial participation.
Traditional vs expanded Medicaid	Eliminate barriers between current and newly eligible beneficiaries. Eliminate screening and diagnostic follow-up co-pays for all Medicaid beneficiaries.
Genetic testing	Patients at high-risk for an inherited cancer should not be required to share costs of testing.
304B Drug Pricing Program	Improve the program to incentivize care for uninsured and underinsured Medicaid patients.
Physician reimbursement	Raise Medicaid physician payments to compare with Medicare rates for cancer diagnosis and treatment.
Quality of care	State-run Medicaid programs should meet predefined cancer quality metrics.
Oncology Medical Homes	Oncology practices should be allowed to be designated as medical homes, and should be provided expanded reimbursement for care coordination and patient education.



Reality Meets ASCO's Policy Statement on Medicaid Reform

Ted Okon, MBA

Recently, the American Society of Clinical Oncology (ASCO) published a policy statement on Medicaid reform. The verbatim principles guiding the ASCO Medicaid statement are as follows:

1. No individual diagnosed with cancer should be without health insurance that guarantees access to high-quality cancer care delivered by a cancer specialist.
2. Patients with cancer who have Medicaid should receive the same timely and high-quality cancer care as patients with private insurance.
3. Medicaid payments should be sufficient to ensure that Medicaid patients can have access to quality cancer care.
4. Patients with cancer who have Medicaid should not face insurance barriers to clinical trial participation.¹

On the surface, these principles are admirable. Certainly in this country, especially with world-renowned cancer institutions, no person with cancer should go untreated. Americans of all means should have access to high-quality, accessible, and affordable cancer care. The problem is that the specific ASCO policy recommendations look great on paper but seem unrealistic when one considers their likely implementation and political challenges.

NEED FOR EDUCATION ON CANCER PREVENTION

Before focusing on specific aspects of the ASCO policy recommendations, it's important to note a glaring shortcoming of the ASCO approach to Medicaid reform: failure to at least mention education on cancer prevention. Although one recommendation calls for removal of barriers to "cancer screening and diagnostic follow-up," which would presumably help in detecting early-stage new or recurrent cancers, prevention has not been addressed. Obviously, in view of estimates that half of cancer cases are preventable,² we need a more focused, more realistic effort at prevention



Ted Okon, MBA

education. Although not very beneficial for those who need treatment now, the lack of a forward-looking approach to preventing cancer will overwhelm us. We need a fair balance between cancer's demand and supply sides—in other words, we must look for unique, innovative ways

of lowering the demand for cancer care by reducing the number of new cases rather than focus all our efforts on treatment (the supply side). It is vital that we introduce into the Medicaid program, as well as into all other sources of insurance, education on the personal health responsibility of current beneficiaries, their children, and the generations to come. Admittedly, this is a longer-term fix, but one that must be incorporated into Medicaid reform, because the demand for cancer care services will outstrip the supply of cancer care—especially high-quality, affordable, and accessible cancer care.

IT'S ALL ABOUT THE ECONOMICS

I believe that Medicaid is the "fool's gold" of the Affordable Care Act (ACA). The Obama administration can tout the fact that the Act has led to the insuring of more people, but a significant portion of those are insured under the Medicaid expansion program. The problem, which is inherent in several of the ASCO policy recommendations, is that Medicaid is an insurance program crippled by bad economics. In order to maintain the current program, much less expand it (the first ASCO policy recommendation), its cost needs to be reduced. While there will be additional financial pressure going forward with Medicaid expansion, that reduction is currently being achieved in 2 fundamental ways. First is the reimbursement cut for providers, which is why ASCO recommends raising Medicaid rates to match reimbursement rates provided by Medicare. Second, to regulate the cost of care for cancer patients, access to certain treatments, such as oral cancer drugs, is being restricted via formularies and by higher patient co-payments. Another ASCO recommendation is to ensure access to oral and supportive care medications by containing patients' out-of-pocket expenses and exempting cancer and supportive therapies from patient cost sharing, such as preventive and hospice care services.

The only way to expand Medicaid, or even simply sustain it, is to cut costs by reducing what providers are paid for treating patients covered by Medicaid and restrict the type of cancer care patients receive under Medicaid. The ASCO recommendation of raising Medicaid provider reimbursement to match that of Medicare is not a solution, because Medi-

care is following the downward spiral of Medicaid. Community oncology practices, where the majority of cancer care is still provided, are buckling under the ratcheting down of Medicare payment rates, made worse in 2013 by the Medicare sequestration payment cut. Many community oncology practices struggle as they treat Medicaid patients at unrealistically low reimbursement rates, but the same is becoming true with Medicare patients. As reported by our organization, the Community Oncology Alliance, 331 community oncology practices have closed treatment facilities over the past 8 years, primarily in rural areas, and 544 practices have merged or financially affiliated with hospitals over the same time period.³ The end result of this shifting landscape of cancer care is issues with access to care for patients and higher costs associated with hospital-based cancer care. It is ironic that this shifting landscape has aggravated the Medicaid problem.

Although many of the ASCO recommendations are, superficially, paper fixes to the Medicaid problem, they are simply dead on arrival. That is because it would be up to Congress to find the funding to increase Medicaid payment rates for cancer care, eliminate patient cost sharing, and provide other services such as cancer screening and genetic testing. The reality is that the new Republican-controlled Congress is dealing with a strategy of limiting or curtailing the ACA, not fueling the expansion of Medicaid. Additionally, the way the Congressional Budget Office (CBO) "scores," or economically forecasts, the impact of legislation is amazingly antiquated and myopic. CBO simply looks at costs and not at how higher costs—such as increasing Medicaid payment rates—may actually lead to lower expenditures for Medicaid patients over time. Although some in the current Congress want CBO to introduce so-called "dynamic scoring" in the legislative process, it is not yet a reality.

IDENTIFYING PATIENTS IN NEED

One of the intriguing ASCO recommendations is actually separate, in a way, from the Medicaid program. It is interesting that changes years ago to the Medicaid program dealing with the requirement of pharmaceutical manufacturers to provide best pricing on their drugs gave birth to the 340B drug discount program. The original intent, clearly, was to ensure that patients who were in need but did not qualify for Medicaid did not fall through the "treatment cracks." The 340B program provided safety net hospitals, com-

"I believe that any serious reform to Medicaid with respect to cancer care must be grounded in the reality of today's political environment in Washington. Simply recommending increases in provider payments and patient benefits, while a policy I strongly agree with, is unrealistic, especially while calling for an expansion of Medicaid."

—TED OKON, MBA

munity health clinics, and other specific providers with deep discounts on pharmaceuticals. The numbers indicating how much the program has grown since its inception are staggering, especially among the roughly one-third of hospitals in this country that are eligible for 340B discounts, which translates into upwards of 100% net profit margins on expensive cancer drugs. The problem is that whereas community health clinics, Ryan White HIV/AIDS grantees, and other critical access providers have strict requirements to associate 340B drug discounts with patients in need, hospitals do not.

ASCO recommends that the 340B program be changed so that it is used for its original intent: "To incentivize care for the uninsured and underinsured and Medicaid patients, regardless of care settings." That is intriguing because a possible solution to the Medicaid problem is to create a safety net by fixing the 340B program rather than expand a broken program. This would require that the benefits of the 340B program be more directly associated with patients in need of cancer drugs than with hospitals. Regardless of where patients in need are treated—community cancer clinics or outpatient hospital facilities—they would have access to 340B discounted drugs, which would also lower patient cost sharing. In its current state, patients derive no financial benefit from the 340B program, and,

in fact, as cancer care moves to the hospital setting, numerous studies indicate increased patient costs.

Hospitals that are good stewards of the 340B program, and recognize uninsured and underinsured cancer patients in need, would presumably welcome changes to the critical 340B program to strengthen it and ensure its economic viability. However, the reality is that institutions that derive financial benefit from the hugely profitable 340B program will fight this intriguing ASCO recommendation.

IS THERE A MEDICAL HOME FOR MEDICAID?

ASCO provides a series of specific recommendations relating to introducing medical homes into the Medicaid program for cancer care. Once again, most of these are meant to simply increase reimbursement for important aspects of cancer care. Although well intended, they are not grounded in the reality of the current Congressional and federal budgeting and legislative process. However, I believe

there is merit in introducing the oncology medical home into the fabric of the Medicaid program. Community oncology practices, alongside private insurance payers, have been developing and implementing oncology medical home pilots with early results that are very promising—improving the quality of cancer care while lowering costs. Barbara L. McAneny, MD, has been very successful with the first Medicare-related oncology medical home (OMH), the COME Home project, which is funded by a federal grant from the Centers for Medicare & Medicaid Innovation (CMMI). Recently, US Representative Cathy McMorris Rogers (R-WA) sent out a draft of legislation that would create a national OMH demonstration project for Medicare.⁴ This is in addition to the currently circulating conceptual outline from CMMI about an oncology payment reform project that is, in reality, an OMH. There is no reason why the OMH concept cannot be incorporated into Medicaid in order to enhance the quality of care while managing costs. What it will take is for

state Medicaid programs to think out of the box, just as private payers and now Medicare are doing, to effectively tackle payment challenges in cancer care.

I believe that any serious reform to Medicaid with respect to cancer care must be grounded in the reality of today's political environment in Washington. Simply recommending increases in provider payments and patient benefits, while a policy I strongly agree with, is unrealistic, especially while calling for an expansion of Medicaid. However, it will take innovative approaches to Medicaid, such as introducing the OMH to save the program and make it viable for cancer patients. Additionally, preventing cancer patients in need from falling through the treatment cracks by looking outside the Medicaid program to make the 340B program a true patient safety net, regardless of where cancer patients are treated, is a very promising ASCO policy recommendation. **EBO**

Ted Okon is the executive director of Community Oncology Alliance.

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ASCO Announces Partner for CancerLinQ Platform

Mary K. Caffrey

The American Society of Clinical Oncology (ASCO) announced January 21, 2015,¹ that it would use the SAP HANA platform to develop CancerLinQ, the revolutionary health information technology (HIT) project in which physicians are banding together to improve cancer care delivery.

"In teaming with SAP, we found an ideal company with state-of-the-art technology, a commitment to invest major new resources, and a clear dedication to our patient care mission," ASCO president Peter Paul Yu, MD, FACP, FASCO, said in a statement. "With our cancer expertise complemented by SAP's software and technical insights, CancerLinQ is in a position to make a huge leap toward becoming the platform of choice for oncologists."¹



Peter Paul Yu, MD, FASCO

able in many settings.

In a previous interview with *The American Journal of Managed Care*, Yu described how CancerLinQ would eventually collect data across hundreds of providers and thousands of patients and thus help avoid the bias that can be present in small sample sizes.²

"CancerLinQ will allow us to amass this data, aggregate it and analyze it, and then learn from that," he explained. "If that is then married to clinical decision support, so that information is returned to the doctor at the point of care, it will allow the physician to more rapidly consider choices and make better treatment decisions."²

The idea is to give both doctor and patient a data-driven "second opinion," derived not from a few dozen similar cases presented to a single physician or practice, but from thousands of similar cases involving hundreds of physicians.

SAP HANA has a track record around the world for helping clinicians use technology to improve cancer diagnosis and treatment through flexible, multi-purpose in-memory data management and applications. Its advanced capabilities include predictive text analytics, spatial processing, and data virtualization on



the same architecture. Among the users of SAP HANA is the National Center for Tumor Diseases in Heidelberg, Germany, which uses real-time data analytics to help accelerate cancer research and improve clinical trial matching. In Japan, SAP has teamed with Mitsui Knowledge Industry, trimming the time for an individual patient's genomic analysis for cancer diagnosis from 30 days to 20 minutes.¹

CancerLinQ has been in development for some time, across the tenure of several ASCO presidents. During a March 2013 demonstration in Washington, DC, then-ASCO president elect Cliff Hudis, MD, showed how an oncologist would someday be able to analyze the electronic medical records of millions of cancer patients, find those with characteristics similar to his own patient, and determine how others fared with therapy options, using nothing more than a simple desktop computer. That scenario seemed far off at the time, but now versions of CancerLinQ will be ready in late 2015.^{1,3}

Eight oncology practices in the United States have signed agreements to provide patient records for the first version

of CancerLinQ, and 7 more will soon join, which means 500,000 patient records will populate the first version of the program.¹ Practices providing data represent both major cancer centers and community practices, ensuring an array of data.

While SAP will provide access to customized technologies, CancerLinQ will drive development of the platform with input from physicians, patients, and experts in related disciplines such as quality improvement, epidemiology, and HIT. **EBO**

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FDA Updates

Surabhi Dangi-Garimella, PhD

SANDOZ GETS THE BIOSIMILAR BALL ROLLING

On January 7, 2015, Sandoz, the generics wing of Novartis, announced that the FDA's Oncologic Drugs Advisory Committee (ODAC) has recommended its biosimilar filgrastim (EP2006) for approval in the United States for use in all indications included in the reference product, Amgen's Neupogen.¹ This comes within 6 months of Sandoz filing for approval with the FDA under the biosimilar pathway created in the Biologics Price Competition and Innovation Act of 2009. The drug is already marketed globally in 40 countries under the brand name Zarzio.²

Filgrastim, a granulocyte colony-stimulating factor, is used to prevent infection in individuals with a compromised immune system, a common side effect of chemotherapy in cancer patients. Additionally, persons undergoing a bone marrow transplant, those who suffer from chronic neutropenia (low blood neutrophils), or those undergoing leukapheresis are also treated with this biological.³

According to a report in *The Pink Sheet*, Sandoz had a lot to gain from the global post marketing data on Zarzio, as well as Amgen's Neupogen. The vast foreign-marketing experience brought in by Sandoz helped convince the ODAC panel—the first FDA panel to review a 351(k) application—of the long-term safety and biosimilarity to Neupogen. Among the evidence included in the filing were results from a phase 1 pharmacokinetics/pharmacodynamics study in healthy volunteers and a phase 3 study that compared the Sandoz product with the approved version of Neupogen in the United States in breast cancer patients on myelosuppressive chemotherapy experiencing severe neutropenia. While the massive patient exposure of the Sandoz product outside of the United States provided assurance of product safety, the article also refers to the vast amount of experience brought to the table by parent company Novartis, which was obvious during the presentation, the article says. The panelists were convinced that EP2006 was highly similar to Neupogen, without any clinically meaningful differences.⁴ The Sandoz application, however, does not guarantee smooth sailing for other companies filing biosimilar applications with the FDA.

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NIVOLUMAB SHOWS PROMISE IN NSCLC, AFTER RECENT MELANOMA APPROVAL

Nivolumab (Opdivo), a programmed death 1 (PD-1) immune checkpoint inhibitor developed by Bristol-Myers Squibb (BMS) and approved for metastatic melanoma, is presenting exciting results in non-



The median age of patients in the VISTA¹ trial was 71 years (range: 48-91).

WHAT IS THE VALUE OF ONE YEAR ON VELCADE[®] (bortezomib)?

For patients with previously untreated multiple myeloma, 1 year of treatment with VELCADE in combination with MP* delivered a >1-year sustained median overall survival (OS) advantage.^{1†}

- ▶ At 60.1-month median follow-up: VELCADE (bortezomib)+MP provided a median OS of 56.4 months vs 43.1 months with MP alone (HR=0.695 [95% CI, 0.57-0.85]; $p < 0.05$)
- ▶ At 3-year median follow-up: VELCADE+MP provided an OS advantage over MP that was not regained with subsequent therapies
- ▶ Of the 69% of MP patients who received subsequent therapies, 50% received VELCADE or a VELCADE-containing regimen¹
- ▶ Results were achieved using VELCADE twice weekly followed by a weekly dosing for a median of 50 weeks (54 weeks planned)¹

The additional value of choice of administration.

Subcutaneous VELCADE demonstrated efficacy consistent with IV for the primary endpoints^{2†}:

- ▶ At 12 weeks, subcutaneous VELCADE: 43% achieved overall response rate (ORR) and 7% complete response (CR) vs IV: 42% ORR and 8% CR^{§||}
- ▶ At 24 weeks, subcutaneous VELCADE ± dexamethasone: 53% achieved ORR and 11% CR vs IV: 51% ORR and 12% CR^{§||}

More than 80% of previously untreated patients starting on VELCADE receive subcutaneous administration^{3†}

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

INDICATION

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

CONTRAINDICATIONS

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

WARNINGS, PRECAUTIONS, AND DRUG INTERACTIONS

- ▶ **Peripheral neuropathy:** Manage with dose modification or discontinuation. Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.
- ▶ **Hypotension:** Use caution when treating patients taking antihypertensives, with a history of syncope, or with dehydration.
- ▶ **Cardiac toxicity:** Worsening of and development of cardiac failure have occurred. Closely monitor patients with existing heart disease or risk factors for heart disease.
- ▶ **Pulmonary toxicity:** Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms.

Posterior reversible encephalopathy syndrome:

Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.

▶ **Gastrointestinal toxicity:** Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and anti-diarrheal medications or fluid replacement.

▶ **Thrombocytopenia or Neutropenia:** Monitor complete blood counts regularly throughout treatment.

▶ **Tumor lysis syndrome:** Closely monitor patients with high tumor burden.

▶ **Hepatic toxicity:** Monitor hepatic enzymes during treatment.

▶ **Embryo-fetal risk:** Women should avoid becoming pregnant while being treated with VELCADE. Advise pregnant women of potential embryo-fetal harm.

▶ Closely monitor patients receiving VELCADE in combination with strong **CYP3A4 inhibitors**. Avoid concomitant use of strong **CYP3A4 inducers**.

ADVERSE REACTIONS

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

Please see Brief Summary for VELCADE adjacent to this advertisement.

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

^{*}Melphalan+prednisone.

¹VISTA TRIAL: a randomized, open-label, international phase 3 trial (N=692) evaluating the efficacy and safety of VELCADE administered intravenously in combination with MP vs MP in previously untreated multiple myeloma. The primary endpoint was TTP. Secondary endpoints were CR, ORR, PFS, and overall survival. At a prespecified interim analysis (median follow-up 16.3 months), VELCADE+MP resulted in significantly superior results for TTP (median 20.7 months with VELCADE+MP vs 15.0 months with MP [$p=0.00002$]), PFS, overall survival, and ORR. Further enrollment was halted and patients receiving MP were offered VELCADE in addition. Updated analysis was performed.

²SUBCUTANEOUS VS IV was a randomized (2:1), open-label, non-inferiority phase 3 trial (N=222) in patients with relapsed multiple myeloma designed to establish whether subcutaneous VELCADE (bortezomib) was non-inferior to intravenous administration.² Non-inferiority was defined as retaining 60% of the intravenous treatment effect, measured by ORR, at the end of 4 cycles.² The primary endpoint was ORR at 4 cycles. The secondary endpoints were response rate at 8 cycles, median TTP and PFS (months), 1-year OS, and safety.

³Responses were based on criteria established by the European Group for Blood and Marrow Transplantation.²

[§]82 patients (55%) in the subcutaneous VELCADE group and 39 patients (53%) in the IV group received dexamethasone.

^{||}Out of 275 estimated unique patients receiving VELCADE as of May 2013.³

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small cell lung cancer (NSCLC). Results from CheckMate-017, a randomized, open-label, phase 3 trial, were promising enough for an independent data monitoring committee (DMC) to stop the trial early. The DMC concluded that patients on Opdivo demonstrated superior overall survival (OS) compared with patients in the control arm.¹

The phase 3 study compared Opdivo with docetaxel in previously treated advanced or metastatic squamous cell NSCLC patients. The trial design randomized 272 patients to treatment

with 3 mg/kg nivolumab every 2 weeks or docetaxel 75 mg/m² every 3 weeks, with the primary end point being OS and secondary end points being objective response rate and progression-free survival.¹

In late December 2014, Opdivo received FDA approval for treating patients with advanced melanoma who had advanced after being on ipilimumab.² The approval came 3 months after the first anti-PD-1 agent, Merck's Keytruda, was approved for the same indication. Meanwhile, Eli Lilly and Company has entered into an agree-

ment with BMS to conduct safety, tolerability, and preliminary efficacy studies of Opdivo in combination with Lilly's galunisertib (LY2157299). These studies are expected to improve treatment options for patients with advanced glioblastoma, hepatocellular carcinoma, and NSCLC.³ "Our clinical collaboration with Lilly underscores BMS's continued commitment to explore combination regimens from our immuno-oncology portfolio with other mechanisms of action that may accelerate the development of new treatment options for patients," said Michael Giorda-

no, senior vice president, head of development, oncology, BMS, in a statement.³

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PROVEGE MAY BE BOUGHT BY VALEANT

On January 29, 2015, Dendreon Corporation announced that it had reached an agreement with the Canadian pharmaceutical company Valeant for its troubled prostate cancer vaccine Provenge (sipuleucel-T). Valeant will acquire the worldwide rights for Provenge and some other Dendreon assets for \$296 million, subject to higher bids, Dendreon announced in a press release.¹

While hopes for the immunotherapy were high following its approval by the FDA in 2010, the high cost of treatment and reimbursement ambiguity resulted in a sizable slump in drug sales, forcing Dendreon to declare bankruptcy in November 2014.²

Provenge is an autologous cellular immunotherapy indicated for treating asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. The complex procedure for manufacturing the drug includes collecting a patient's immune cells by leukapheresis, exposing the cells to a recombinant human protein (PAP-GM-CSF) for stimulation, and returning them back to the patient.³ **EBO**

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Brief Summary

INDICATIONS:

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

CONTRAINDICATIONS:

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

WARNINGS AND PRECAUTIONS:

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

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

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

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

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

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

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

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

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

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

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

ADVERSE EVENT DATA:

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

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

In the phase 3 VELCADE+melfhalan and prednisone study in previously untreated multiple myeloma, the safety profile of VELCADE administered intravenously in combination with melfhalan/prednisone is consistent with the known safety profiles of both VELCADE and melfhalan/prednisone. The most commonly reported adverse reactions in this study (VELCADE+melfhalan/prednisone vs melfhalan/prednisone) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), leukopenia (32% vs 28%), vomiting (26% vs 12%), fatigue (25% vs 14%), lymphopenia (23% vs 15%), constipation (23% vs 4%), anorexia (19% vs 6%), asthenia (16% vs 7%), pyrexia (16% vs 6%), paresthesia (12% vs 1%), herpes zoster (11% vs 3%), rash (11% vs 2%), abdominal pain upper (10% vs 6%), and insomnia (10% vs 6%).

In the phase 3 VELCADE subcutaneous vs intravenous study in relapsed multiple myeloma, safety data were similar between the two treatment groups. The most commonly reported adverse reactions in this study were peripheral neuropathy NEC (37% vs 50%), thrombocytopenia (30% vs 34%), neutropenia (23% vs 27%), neuralgia (23% vs 23%), anemia (19% vs 23%), diarrhea (19% vs 28%), leukopenia (18% vs 20%), nausea (16% vs 14%), pyrexia (12% vs 8%), vomiting (9% vs 11%), asthenia (7% vs 16%), and fatigue (7% vs 15%). The incidence of serious adverse reactions was similar for the subcutaneous treatment group (20%) and the intravenous treatment group (19%). The most commonly reported SARs were pneumonia and pyrexia (2% each) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (3% each) in the intravenous treatment group.

DRUG INTERACTIONS:

Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir). Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients. Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur. Efficacy may be reduced when VELCADE is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving VELCADE. St. John's wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and should be avoided. Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients. Co-administration of melfhalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

USE IN SPECIFIC POPULATIONS:

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

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

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

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

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

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

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



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Study Results Support Early Treatment With Abiraterone in Prostate Cancer

Surabhi Dangi-Garimella, PhD

A study published in the journal *Lancet Oncology*¹ presented results showing that the combination of abiraterone acetate with prednisone improved overall survival (OS) in men with chemotherapy-naïve castrate-resistant prostate cancer by more than 4 months. This study, conducted by the Institute of Cancer Research (ICR), London, provides evidence for the value of introducing abiraterone prior to chemotherapy in these patients.

The trial, a placebo-controlled, double-blind, randomized phase 3 study, with crossover, included 1088 asymp-

tomatic or mildly symptomatic patients, who were randomly assigned to the placebo with prednisone group (placebo) or the abiraterone plus prednisone group (abiraterone). End points were progression-free survival and OS. Abiraterone was administered to 44% of patients in the placebo group, either as crossover or as subsequent therapy; 67% of patients in the abiraterone group and 80% in the placebo group were treated with an additional agent(s). Median OS in the placebo group was 30.3 months, compared with 34.7 months in the abiraterone group. Grade 3-4 adverse events with abiraterone included cardiac and liver

toxicity and hypertension.

The group published another study in *Clinical Cancer Research*,² which identified a gene rearrangement that could be used to select the subgroup of patients most likely to benefit from introducing abiraterone early in the treatment regimen.

“Abiraterone has already transformed care for patients with advanced prostate cancer, but the latest trial evidence strengthens the already powerful case for it to be accepted for NHS use earlier in the course of treatment,” said Paul Workman, MD, chief executive of ICR in a statement. **EBO**

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2. Attard G, de Bono JS, Logothetis CJ, et al. Improvements in radiographic progression-free survival stratified by ERG gene status in castration-resistant prostate cancer patients treated with abiraterone. *Clin Cancer Res*. 2015. doi:pil:clincanres.1961.2014.

FDA Approves Palbociclib for Metastatic Breast Cancer

Silas Inman

The FDA has granted an accelerated approval to palbociclib (Ibrance) as a frontline treatment for postmenopausal women with estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer, based on findings from the phase 2 PALOMA-1 trial.

In the open-label phase 2 study, treatment with letrozole plus the novel CDK 4/6 inhibitor palbociclib reduced the risk of disease progression by 51% compared with letrozole alone. The median progression-free survival (PFS) with palbociclib was 20.2 months versus 10.2 months for letrozole alone (Hazard ratio [HR] = 0.488; P = .0004).

Palbociclib was approved under the FDA's Breakthrough Therapy designation and priority review program, which provides an expedited approval process for treatments that provide a substantial benefit over current options. The FDA was not scheduled to make a decision on the drug's application until April 2015. “The addition of palbociclib to letrozole provides a novel treatment option to women diagnosed with metastatic breast cancer,” Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, said in a statement. “The FDA is committed to expediting marketing approval of cancer drugs through our accelerated approval regulations.”

The PALOMA-1 trial randomized 165 postmenopausal patients with ER-positive, HER2-negative advanced

breast cancer in a 1:1 ratio in 2 parts: Part 1 included 66 patients and Part 2 included 99 patients. Continuous daily letrozole was administered at 2.5 mg, with or without palbociclib at 125 mg, daily for 3 weeks followed by 1 week of rest until progression. The primary endpoint was PFS by investigator assessment.

At the final analysis from the trial that was presented at the 2014 Annual Meeting of the American Association of Cancer Research in April 2014, the median overall survival (OS) was 37.5 months with palbociclib compared with 33.3 months with letrozole alone (HR = 0.813; 95% CI, 0.492-1.345; P = .2105). However, this first analysis of OS contained data from only 61 patients (37%) and was not deemed statistically significant. In Part 1 of the study, the median PFS was 26.7 months with palbociclib versus 5.7 months for letrozole alone (HR = 0.299; 95% CI, 0.156-0.572; P = .0001). In the larger Part 2, the median PFS was 18.1 months versus 11.1 months, for palbociclib combination and letrozole, respectively (HR = 0.508; 95% CI, 0.303-0.853; P = .0046). The combination resulted in a response rate of 45% compared with 31% for the monotherapy and the overall clinical benefit rate was 70% versus 44%.

“Palbociclib is the first drug in its

class to be approved by the FDA,” lead investigator Richard Finn, MD, from the Jonsson Comprehensive Cancer Center at UCLA, said in a statement. “What is really remarkable is that we doubled the median progression-free survival. That type of result is not often seen in cancer medicine.”

Inhibition of CDK 4/6 prevents DNA replication by prohibiting progression from G1 to S phase during cell division. Blocking this mechanism prevents tumor cell proliferation through control of the cell cycle. The rationale for the combination of an aromatase inhibitor with palbociclib stemmed from early preclinical evidence suggesting that CDK 4/6 is more active in patients with ER-positive breast cancer, as a result of an intact retinoblastoma pathway.

The rate of grade 3/4 neutropenia was significantly higher in the palbociclib arm compared with letrozole alone (54% vs 1%). Additionally, the rate of grade 3/4 leucopenia (19% vs 0%) and fatigue (4% vs 1%) were higher with palbociclib. No cases of febrile neutropenia or neutropenia-related infections were reported in the study. Altogether, 13% of patients discontinued treatment as a result of side effects in the palbociclib arm compared with 2% for letrozole. The most

frequently reported serious adverse events with the combination were pulmonary embolism (4%) and diarrhea (2%).

A number of phase 2 clinical trials are exploring palbociclib as a treatment for patients with advanced breast cancer. Given the benefit demonstrated in the PALOMA-1 trial, many of these studies will be randomized in a 2:1 ratio favoring treatment with palbociclib. The PALOMA-2 trial is comparing the combination of palbociclib and letrozole with letrozole alone as a frontline treatment for postmenopausal women with ER-positive, HER2-negative advanced breast cancer (NCT01740427). The PALOMA-3 trial is comparing palbociclib plus fulvestrant against fulvestrant alone in women with HR-positive, HER2-negative metastatic breast cancer following progression on prior endocrine therapy (NCT01942135). **EBO**



Richard Pazdur, MD

HHS Announces New Oncology Care Management Initiative

Laura Joszt

A new Affordable Care Act initiative from HHS will better coordinate cancer care with the intention of improving the quality of care provided and reducing the money spent on health-care, according to an announcement from HHS.¹

Cancer cost the United States an estimated \$263.8 billion in medical costs and lost productivity in 2010, with the majority of patients who are diagnosed older than 65 years and Medicare beneficiaries. The Oncology Care Model was developed by the CMS Innovation Center through feedback from the oncology community, patient advocates, and the private sector, with the aim of “better care, smarter spending, and healthier people,” according to HHS.

“We aim to provide Medicare beneficiaries struggling with cancer with high-quality care around the clock and to reward doctors for the value, not volume, of care they

provide. Improving the way we pay providers and deliver care to patients will result in healthier people,” Patrick Conway, MD, CMS chief medical officer and deputy administrator for innovation and quality said in a statement.

CMS will invest in physician-led practices and allow them to innovate and deliver higher-quality care and is seeking participation of other payers. The model will provide episode-based, performance-based payments that incentivize high-quality, coordinated care. Practices that participate in the Oncology Care Model will receive monthly care management payments for each Medicare fee-for-service beneficiary during an episode.

The model will focus on 3 key areas: linking payment to quality of care; improving and innovat-

ing care delivery; and sharing information more broadly to providers, consumers, and others to support better decision



Richard Schilsky, MD, FACP, FASCO

“We are disappointed they have chosen to pursue only one model—and one that continues to rely on a broken fee-for-service system.”

—RICHARD SCHILSKY, MD, FACP, FASCO
CHIEF MEDICAL OFFICER, ASCO

cused on the patient’s needs.”

In response to the HHS announcement, the American Society of Clinical Oncology (ASCO) released a statement that expressed concern about the limited scope of the model. “We are disappointed they have chosen to pursue only one model—and one that continues to rely on a broken fee-for-service system,” said the chief medical officer of ASCO Richard Schilsky, MD, FACP, FASCO, in a statement. In response to a draft version of the model, ASCO says it had urged CMS to test models that would migrate away from the traditional fee-for-service system.² **EBO**

REFERENCES

1. New Affordable Care Act initiative to encourage better oncology care [press release]. Baltimore, MD: HHS; February 12, 2015. <http://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2015-Press-releases-items/2015-02-12.html>.
2. New CMS Oncology Care Model relies on broken fee-for-service system [press release]. Alexandria, VA: American Society of Clinical Oncology; February 12, 2015. <http://www.asco.org/press-center/new-cms-oncology-care-model-relies-broken-fee-service-system>.

while maintaining privacy.

“With the Oncology Care Model, CMS has the opportunity to achieve 3 goals in the care of this medically complex population who are facing a cancer diagnosis: better care, smarter spending, and healthier people,” said Conway. “As a practicing physician and son of a Medicare beneficiary who died from cancer, I know the importance of well-coordinated care fo-

MOLECULAR DIAGNOSTICS

Arguments Taking Shape For and Against FDA Regulation of Diagnostic Tests

Mary K. Caffrey

To supporters, the FDA’s move to regulate thousands of laboratory-developed tests (LDTs) is a logical and necessary step to ensure patient safety. To detractors, it’s an unnecessary overreach that will drive smaller testing labs out of business, causing industry consolidation at the expense of innovation and consumers.

Medical establishment titans stand on opposite sides in this battle, which promises to persist throughout 2015. The next phase will begin after February 2, 2015, as *Evidence-Based Oncology* went to press, when the FDA closes the comment period on its September 30, 2014, draft guidance for regulating LDTs.¹ The FDA has committed to issuing final rules this year, although many signs indicate that the process will be slowed down by administrative challenges or even a lawsuit.

The FDA launched the process with

its July 31, 2014, announcement that after years on the sidelines, it would exercise regulatory authority over diagnostic tests, the importance of which exploded with the rise of personalized medicine. This is especially true in cancer care, as the rise of genomic medicine has allowed clinicians to tailor cutting-edge (and very expensive) treatments to patients based on their genetic characteristics.² Both the American Society of Clinical Oncology (ASCO) and the American Cancer Society Cancer Action Network support the FDA’s action, citing a need for a stronger evidence base in diagnostics.¹

Opposing the FDA’s move are the American Medical Association (AMA) and the Association for Molecular Pathology (AMP), along with the testing industry’s trade group, the American Clinical Laboratory Association (ACLA).³⁻⁵ In a statement accompanying its white

paper, the AMP pointed at the twin forces that threaten to shake out the testing industry: the prospect of increased regulation and the ongoing challenge of winning reimbursement from Medicare.⁴

“The FDA’s new policies will effectively reformulate existing medical device regulations and consider medical professionals as manufacturers which will impose substantially new and duplicative requirements on clinical laboratories and hospitals,” the AMP statement said. “Meanwhile, CMS, who runs Medicare, the nation’s largest insurer and whose actions are frequently mimicked in the private sector, has taken a heavy handed approach in denying coverage or reducing payment for several medically necessary molecular pathology tests.

“Unfortunately, health care providers—those developing and delivering innovative diagnostic tests—along with

patients, who are the ultimate intended beneficiaries, are caught in the middle,” the AMP statement said.⁴

SUPPORT FOR FDA REGULATION

Arguments supporting and opposing FDA oversight were best outlined in a pair of commentaries published January 5, 2015, by *JAMA Oncology*.^{1,3} The dueling viewpoints appeared days before an FDA-sponsored workshop, held January 8 and 9, on how the regulatory process will unfold.⁶

As discussed by Joshua Sharfstein, MD, the FDA’s decision is justified for several reasons:

- There have been some high-profile examples of faulty tests, including an April 2014 failure that required a warning in CDC’s *Mortality and Morbidity Weekly Report*. The lack of FDA oversight raises the specter of cancer patients receiving the wrong

(continued on SP84)



James P. Evans, MD, PhD



Joshua Sharfstein, MD

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Reference: 1. Prosigna [Package Insert]. Seattle, WA: NanoString Technologies, Inc; 2013.

Prosigna is indicated for use in postmenopausal women with hormone receptor-positive, node-negative or node-positive early-stage (stages I and II) breast cancer to be treated with adjuvant endocrine therapy.

Special conditions for use: Prosigna is not intended for diagnosis, to predict or detect response to therapy, or to help select the optimal therapy for patients.

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Indications and Usage

Jakafi is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia ($ANC < 0.5 \times 10^9/L$) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent



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only for who have had intolerant of hydroxyurea¹

illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation

- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

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

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to see Full Prescribing Information and
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* A randomized, open-label, active-controlled phase 3 trial comparing Jakafi with best available therapy in 222 patients. Best available therapy included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). The primary end point was the proportion of subjects achieving a response at week 32, with response defined as having achieved both Hct control (the absence of phlebotomy eligibility beginning at the week 8 visit and continuing through week 32) and spleen volume reduction (a $\geq 35\%$ reduction from baseline in spleen volume at week 32). Phlebotomy eligibility was defined as Hct >45% that is ≥ 3 percentage points higher than baseline or Hct >48% (lower value).

Reference: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation.

Jakafi[®]
ruxolitinib (tablets)



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

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see *Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see *Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than $0.5 \times 10^9/L$) was generally reversible by withholding Jakafi until recovery [see *Adverse Reactions (6.1)*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [see *Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. **Tuberculosis** Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. **PML** Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. **Herpes Zoster** Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [see *Adverse Reactions (6.1)*].

Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of, Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [see *Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly.

Non-Melanoma Skin Cancer Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [see *Warnings and Precautions (5.1)*] • Risk of Infection [see *Warnings and Precautions (5.2)*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see *Warnings and Precautions (5.3)*] • Non-Melanoma Skin Cancer [see *Warnings and Precautions (5.4)*]. 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. **Clinical Trials Experience in Myelofibrosis** The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to $200 \times 10^9/L$) and 20 mg twice daily (pretreatment platelet counts greater than $200 \times 10^9/L$), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [see *Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [see *Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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

Adverse Reactions	Jakafi (N=155)			Placebo (N=151)		
	All Grades ^a (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Bruising ^b	23	<1	0	15	0	0
Dizziness ^c	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections ^d	9	0	0	5	<1	<1
Weight Gain ^e	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster ^f	2	0	0	<1	0	0

^a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

^b includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura

^c includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis

^d includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present

^e includes weight increased, abnormal weight gain

^f includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above $50 \times 10^9/L$ was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of $100 \times 10^9/L$ to $200 \times 10^9/L$ before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than $200 \times 10^9/L$ (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study^a

Laboratory Parameter	Jakafi (N=155)			Placebo (N=151)		
	All Grades ^b (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

^a Presented values are worst Grade values regardless of baseline

^b National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with polycythemia vera resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [see *Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

Adverse Events	Jakafi (N=110)		Best Available Therapy (N=111)	
	All Grades ^a (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Headache	16	<1	19	<1
Abdominal Pain ^b	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness ^c	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea ^d	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema ^e	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster ^f	6	<1	0	0
Nausea	6	0	4	0

^a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

^b includes abdominal pain, abdominal pain lower, and abdominal pain upper

^c includes dizziness and vertigo

^d includes dyspnea and dyspnea exertional

^e includes edema and peripheral edema

^f includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment^a

Laboratory Parameter	Jakafi (N=110)			Best Available Therapy (N=111)		
	All Grades ^b (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

^a Presented values are worst Grade values regardless of baseline

^b National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. **CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention [see *Pharmacokinetics (12.3) in Full Prescribing Information*]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [see *Dosage and Administration (2.3) in Full Prescribing Information*]. **Fluconazole:** The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C9 inhibitor fluconazole at doses of 100 mg to 400 mg once daily, respectively [see *Pharmacokinetics (12.3) in Full Prescribing Information*]. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [see *Dosage and Administration (2.3) in Full Prescribing Information*]. **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [see *Pharmacokinetics (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: Risk Summary There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Animal Data** Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of myelofibrosis patients in clinical studies with Jakafi, 52% were 65 years of age and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 50 X 10⁹/L and 150 X 10⁹/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended [see *Dosage and Administration (2.4) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet

count between 50 X 10⁹/L and 150 X 10⁹/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and hepatic impairment [see *Dosage and Administration (2.4) in Full Prescribing Information*].

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.



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(continued from SP78)

“In the interest of patients and their continued access to critical laboratory testing services, it is incumbent upon the FDA to reverse course and withdraw its proposed agency overreach.”

—STEVE RUSCKOWSKI
CEO, QUEST DIAGNOSTICS

therapy or false positives that lead to unnecessary treatment.

- The FDA has no authority to require reporting of adverse events; thus, thousands of patients may be affected or harmed before a problem comes to light. Sharfstein cited a case involving a suspect test for directing statin therapy that was given to 150,000 patients before flaws were uncovered.¹
- Lack of regulation results in a lack of evidence to guide clinicians.¹ Disagreements over standards of evidence have also created unpredictability and unevenness of reimbursement criteria among insurers, who must decide whether to pay for the tests. Since 2011, the emerging bar of “clinical utility” has frustrated many test manufacturers; some argue that CMS’ chief Medicare contractor in this realm, Palmetto GBA, makes impractical demands regarding evidence for reimbursement.⁷
- Sharfstein asserts that proposed carve-outs for tests for rare diseases, for which no other LDT is available, and plans to phase in regulations will address worries about patient access to tests in the short term.¹

ASCO provided high-profile support for the FDA’s effort with comments submitted to the House Committee on Energy and Commerce, Health Subcommittee, which had released a white paper on creating a new regulatory framework for the tests December 9, 2014.⁸

“In contemporary oncology practice, a patient’s treatment options are increasingly driven by detection of molecular abnormalities in the tumor that drive treatment selection,” ASCO president Peter P. Yu, MD, FASCO, said in a letter to the subcommittee. “ASCO believes that

the tests used to detect those abnormalities must be of the highest quality and thoroughly validated before being offered to doctors and patients. Our patients depend on high quality tests as much as they depend on carefully studied, safe and effective drugs to achieve the best possible outcomes.” Also, ASCO sent Cancer Research Committee Chair Edward Kim, MD, to participate in the FDA workshop.⁸

ARGUMENTS AGAINST FDA OVERSIGHT

The case against regulation, made in *JAMA Oncology* by James P. Evans, MD, PhD, and Michael S. Watson, PhD, is summed up this way: the testing industry includes many small hospital and academic research labs, which are responsible for much of the innovation of recent years but would lack the financial resources to meet the bar of FDA regulation. Forcing these groups to do so would stifle progress in genomic medicine, which would harm the very consumers that regulators say they want to help.³

The AMA’s early statement on FDA oversight, which came the day after the July 31, 2014, announcement, echoed this concern. The AMA “believes that laboratory developed testing (LDT) services offer patients access to safe and high quality diagnostic services that are essential to patient care,” said Barbara L. McAneny, MD, chair of the AMA board. “This proposal adds an additional layer of regulatory requirements which may result in patients losing access to timely life-saving diagnostic services and hinder advancements in the practice of medicine.”⁹

Evans and Watson point to the example of tests for BRCA1 and BRCA2, which were only available through Myriad Genetics until the US Supreme Court largely unraveled the company’s monopoly in 2013. Labs rushed into the market, and the results have given patients choices and forced down the price of the tests themselves. Adding FDA approval on top of existing requirements, which are covered in the Clinical Laboratory Improvement Act (CLIA) of 1988, would reconsolidate the industry, Evans and Watson argue.

They acknowledge, however, that the genetic-based tests that direct cancer care are more complex than the vast majority of LDTs that could come un-

der the FDA’s umbrella. Their solution is to update the CLIA with requirements specific to genetic tests, not add a new regulatory layer.³

Finally, Evans and Watson question whether the FDA has the authority to regulate tests as “medical devices.” Rather, they write, tests are “procedures” that depend not only on technology but also on the expertise of the laboratory, and this will be a poor fit for FDA-style rule making. They predict, as oth-

ers do, that “Given the questionable legitimacy of the FDA’s proposed action, if these changes are implemented, they will most certainly trigger expensive and time-consuming legal challenges.” Such challenges would most likely come from the ACLA, according to press accounts.⁵

ACLA RESPONDS TO FDA

The testing industry appears ready to push back hard against the FDA. The ACLA released its own white paper January 7, 2015, the day before the agency’s workshop, which it described as a “systematic and detailed rejection of the (FDA) proposal.” The document was developed with former solicitor general Paul D. Clement and Harvard constitutional law expert Laurence H. Tribe, and appears to outline arguments that would be used in administrative or legal challenges against the FDA’s attempt to regulate the industry.¹⁰

As expected, a chief argument involves the FDA’s classification of tests as “medical devices.” Other arguments raised by the ACLA include:

- FDA regulation of LDT interferes with the practice of medicine.
- The ACLA asserts that the FDA’s use of guidance documents bypasses the Administrative Procedure Act (APA), which outlines the process that agencies must use in crafting regulations.

While this last item might seem like a procedural argument, the ACLA indicates that it is critical: failure to oppose the FDA’s use of the guidance document at this stage would lay the groundwork for regulation of the industry outside APA’s scope going forward. However, there is some irony to the ACLA arguments in the white paper: it cites CMS’ long-standing ability to regulate the market through CLIA, though test makers have spent plenty of time complaining about CMS reimbursement.

“In the interest of patients and their continued access to critical laboratory testing services, it is incumbent upon the FDA to reverse course and with-

draw its proposed agency overreach,” said Steve Rusckowski, chairman of the ACLA Board of Directors and CEO of Quest Diagnostics.¹⁰ **EBO**

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Michael S. Watson, PhD



Steve Rusckowski

The Use and Implementation of Standardized Treatment Pathways

Sejal Saraiya, PharmD

As the burden of the cost of cancer therapy grows both for payers and for society as a whole, cost-effectiveness discussions are on the rise among all stakeholders. Organizations such as the American Society of Clinical Oncology (ASCO) have joined the discussion and are developing frameworks that could help physicians and patients reach treatment decisions together. Payers are analyzing various models to maintain quality of care while providing incentives to physicians for following certain clinical pathways and bundling payments instead of paying for each episode of care.

The pros and cons associated with developing clinical pathways were discussed by a group of payer representatives during a Peer Exchange convened by *The American Journal of Managed Care* in September 2014. Titled “Oncology Stakeholders Summit: Evidence-Based Decisions to Improve Quality and Regulate Costs,” its participants included John L. Fox, MD, MHA, senior medical director and associate vice president of medical affairs at Priority Health; Ira M. Klein, MD, MBA, FACP, national medical director, clinical thought leadership, Office of the Chief Medical Officer, Aetna Inc; Michael Kolodziej, MD, national medical director for oncology strategies, Aetna Inc; Bryan Loy, MD, physician lead—cancer, Humana; and Irwin W. Tischler, DO, national medical director, oncology, Cigna. The session was moderated by Peter Salgo, MD, professor of medicine and anesthesiology at Columbia University and associate director of surgical intensive care at NewYork-Presbyterian Hospital.

Dr Salgo asked the panel whether clinicians prefer utilizing pathways proposed by payers or implementing their own. Dr Tischler responded that clinicians prefer their own pathways, especially if the pathway proposed by a payer differs greatly from their own and is not backed by evidence. According to Tischler, treatment should be individualized for the patient based on efficacy, toxicity, and cost, in that order; it also needs to follow guidelines developed by the National Comprehensive Cancer Network (NCCN) and ASCO. Dr Fox reminded the panel that companies such as the American Pathway Company provide payers a template for developing pathways, which can then be augmented with experience from providers using some of these pathways. He added, however, that providers need to be given the necessary latitude to individualize treatment for patients. Dr Loy agreed

that pathways need to be effective, non toxic, and cost-effective, with allowance for variance. Dr Kolodziej pointed out 2 benefits to the pathway programs: first, the establishments would be following the same set of rules with regard to efficacy and toxicity, and second, they allow for physician performance measurement.

The panelists were then asked to discuss appropriate tools to measure pathway adherence. Dr Klein acknowledged the importance of the tools in providing a feedback loop for the process. Fox added that collecting data is challenging, especially with the increasing number of pathways. While Tischler suggested the need for a genomic component to the diagnosis, which, he said, could also confirm feedback for the individual patient, Loy argued that there has to be an intention to treat associated with the mutation testing. He listed 2 primary concerns: ordering and not using the test results, and treating without gathering all the diagnostic information.

Salgo then guided the discussion toward the use of generics over brand name drugs, and whether that is a cost-effective way of treating patients. “How do you ensure the 2 are equivalent and that they maintain efficacy?” Kolodziej responded that a study in advanced lung cancer showed that carboplatin/paclitaxel and carboplatin/pemetrexed were equivalent. Pointing to the fact that each protocol may be different, Kolodziej explained that some pathways include branded drugs and some have generics. Klein reminded everyone that when talking about pathways, the regimen should ideally be guided by efficacy, safety and toxicity, and economics—in that order. He said that there is difficulty, however, with this approach because in certain cancers such as non-small cell lung cancer, optimal therapy hasn’t been determined, but there is a lot of discussion on the cost associated with the therapeutic choices.

Salgo asked the panelists whether providers were concerned with not getting paid if they deviated from the pathway to individualized treatment. “Providers should use pathways to reduce variance and therefore improve quality of care; however, they should always individualize therapy to the patient,” said Klein. Fox asserted that while NCCN in-

cludes multiple first-line therapies in its guidelines, providers get incentive payments if they follow their preferred regimens 80% of the time. Salgo then asked the panelists the outcome of providers using the newer immunotherapies that are more expensive, and which may not be part of a recommended clinical pathway. Tischler indicated that targeted agents, requested in a reasonable setting, would never be denied. Klein, however, insisted that providers should attempt to follow pathways, because there are those that often get their patients off of pathways, citing that their patients are sicker.

When discussing the evaluation of safety in clinical pathways, Klein recommends consumers should advocate for pathways because it puts some guardrails on the use of evidence-based medicine “which is what we want.” Loy added that the patient and the provider have to think about the entire chemotherapy plan, including the support drugs and antiemetics. When discussing the question of safety, you have to also ask what the total cost of care would be—what the avoidable consequences are with therapy and how they can be managed. Loy shared that Humana works with ASCO and NCCN to update, modify, and clarify questions about its pathways.

When asked if pathways could be used to reduce treatment complications, Fox responded that pathways are a great help for oncology infusion nurses who don’t have to worry about different regimens and can fully understand the treatment and associated side effects when it comes to dealing with only a handful of pathways. There is evidence that pathways reduce emergency department visits, he added, although “Whether or not that’s due to fewer complications, it’s not clear.”

Salgo then asked the panel whether employers can participate in making pathway recommendations. Loy responded in the affirmative, saying that employers can make recommendations to payers, and they can influence educa-

tion, screenings, and diagnostic testing. Employers can influence what they expect from payers, including work policies such as: short-term disability, payment policies, return to work policies, and setting the tone and culture within their organizations. Salgo asked about Well-Point’s quality initiative, which offers enhanced reimbursement to oncologists who follow planned treatment regimens in an effort to control costs. Kolodziej clarified that the program, which is targeted for breast, colon, and lung cancer patients in a few states, offers payers access to a portal in which clinical information is entered and a small number of treatment choices are offered. If you choose to use one of these treatment options, the payer will get reimbursed a management fee for that patient for that month, he explained. This tool can also be used to adjudicate prior authorization, Kolodziej said, adding, “Data are being collected on patients treated with the preferred treatment choice and on patients that are being prior authorized.” Doctors are given an incentive to use the selected pathways, which may include standard of care drugs and likely cheaper generics, which would steer providers to less expensive options, Kolodziej said. He added that this is based on the prejudice that oncologists make therapeutic decisions based on the margin of the agents. There is contrary evidence indicating that the doctors prescribed differently based on a fixed margin.

Klein summed up the discussion by saying that we need to learn from the various models being evaluated; “However, ablating the margin or the decision making of choosing drug regimens and supportive agents may not be ideal.” Loy agreed there were other elements of the total cost of care that came out of the study, and he suggested the need for a dialogue regarding the variance in treatment as a whole. **EBO**

Please visit Peer Exchange on AJMC TV to view the discussion (<http://www.ajmc.com/ajmc-tv/peer-exchange/>).

AJMC® Oncology Stakeholders Summit

ONCOLOGY STAKEHOLDERS SUMMIT PANEL



Fox

Klein

Kolodziej

Loy

Tischler

Innovation and the Role of Alternative Markers of Efficacy

Sejal Saraiya, PharmD

There is no arguing that early diagnosis and improved treatment measures have had a positive impact on cancer survival. While personalized medicine has helped identify the right patient population and target a regimen using biomarkers, immunooncology (I-O) has revolutionized the treatment approach in advance solid tumors, boosting the body's immune system to mobilize a more resilient response. However, as drug development is a lengthy process, in 1992, the FDA instituted the Accelerated Approval Program to enable the quicker approval of drugs that treat serious conditions and that fill an unmet medical need, based on a surrogate end point.¹

A payer and an oncologist deliberated the role of these surrogate markers that are commonly finding their way into clinical trials, and their influence on innovation in drug development, during a Peer Exchange convened by *The American Journal of Managed Care* in November 2014. The panel discussion, which was a part of the Oncology Stakeholders Summit, saw participation by Ira M. Klein, MD, MBA, FACP, national medical director, Clinical Thought Leadership, Office of the Chief Medical Officer, Aetna Inc; and Richard W. Joseph, MD, assistant professor, Division of Medical Oncology, Mayo Clinic. The session was moderated by Peter Salgo, MD, professor of medicine and anesthesiology at Columbia University and associate director of surgical intensive care at NewYork-Presbyterian Hospital.

Dr Salgo began the discussion by asking the panel's opinion on how different stakeholders—providers, the FDA, payers, and the pharmaceutical industry—would define the value of such innovative approaches in oncology. Dr Klein was of the opinion that while each entity has a mission of improving patient outcomes, each must balance this with a business mission. As an entity, patients are “all-in,” he said; they understand the value of cancer care because they are paying the initial costs. The FDA understands the value, as it encourages the science to move forward and accept breakthrough therapies, even though regulators primarily approve drugs based on efficacy and safety. The payer, on the other hand, is invested in understanding value deployed through integrated delivery systems. Payers, Klein said, are framing models that measure value. Dr Joseph presented the example of pembrolizumab, which was recently approved for advanced melanoma. The trial, he said, was part of the

expanded access program, which allows patients free access to the drug, adding that while the trial started in April 2014, the drug was approved in September 2014. During that time period, the trial participants did not have to worry about co-payments. However, following the approval, questions remain on treatment duration and the ultimate decision rests with the patients: some patients might improve on the drug and want to continue the regimen, while others might feel great but opt out once they have to share the cost through



Richard W. Joseph, MD

Richard W. Joseph, MD, said that physicians face a dilemma when choosing among new cancer therapies. Citing the example of melanoma, for which 3 good drugs were approved over the last 3 years, he asked, “How do we know which one to pick first? We have no idea.”

a co-pay, Joseph pointed out. Therefore, he believes that multistakeholder decisions would contribute to a more value-based system.

Salgo asked the panel whether conducting clinical trials in cancer patients who have the worst prognosis and have failed other therapies can impact the value of a treatment. Not really, said Joseph, because patients willing to participate in the trials have failed standard therapy and are willing to try an experimental drug. He went on to say that these patients are among the healthier participants, as it takes about a month to screen them for the trial. If their condition worsens during that period, they may not be enrolled because they have to meet the same eligibility criteria as for other trials, he added. Salgo played the devil's advocate and asked if there is a possibility that the drug might be

over valued since these patients don't have “real-life issues” in a controlled clinical trial. Klein disagreed, saying that payers believe the FDA approved the medication for a particular indication and therefore it will be covered. Klein alluded to the fact that both public and private payers are quite constrained with respect to setting guidelines on the usage of approved drugs. He pointed out that off-label use of approved drugs, a common practice, can prove expensive, especially with some of the newer oncology drugs.

According to Klein, the FDA has come a long way from simply approving drugs for their efficacy and safety. Narrow indications and the high costs of biologics have resulted in the FDA being more nuanced with drugs showing minimal or no incremental benefit. He suggested that the data from off-label use of drugs should be captured. Joseph agreed, adding that as a physician, he'd appreciate some prescribing flexibility. Salgo raised the economic argument that expensive therapies are worth it because they'll be a tremendous cost saving down the road. Joseph agreed, pointing to ipilimumab as a case study. He said that 20% of melanoma patients treated with ipilimumab are alive at 5 years, and it's worth the upfront cost when we see how these people will be contributing to society. He admitted that while 80% of patients on the treatment did not make it to the 5-year mark, there is hope that the newer I-O agents like nivolumab and pembrolizumab will shift the bar to include quality-adjusted life-years (QALYs) in the equation.

QUALITY, SAFETY, AND COST OF CARE

Salgo next asked the experts if they thought comparative effectiveness research (CER) and innovation clash at the federal or clinical level, and how the 2 could be reconciled. Klein disagreed, saying that innovative therapies like I-O will move through clinical trials quickly and even gain FDA approval, as they are prospective studies that collect data in real time. CER, on the other hand, evaluates what's already been done, although the caveat with CER is identifying the right control cohort: are we comparing the people who were treated pre- and post treatment or are 2 different sets of people being compared, he asked.

Underscoring the value of CER, Joseph hoped there were ethical ways of converting this retrospective method to being prospective. Both Klein and Joseph wish to see a more active influence of CER data, both in the clinic setting and in forming reimbursement policies. While the National Institute for Health and Care Excellence (NICE, which provides national care guidance in the United Kingdom) has adopted CER into practice in Europe, “In the United States, we are not really willing to jump over to that, and I think that's actually more a societal issue than it is a clinical or medical issue,” Klein feels.

The discussion then turned toward the question that was the elephant in the room. Salgo asked the panelists how physicians can find evidence-based data that can help them develop a therapeutic regimen. This is a study that physicians have to conduct themselves on their patients because the data is just not out there. Joseph agreed that physicians do face this dilemma. Citing the example of melanoma, for which 3 good drugs were approved over the last 3 years, he asked, “How do we know which one to pick first? We have no idea.” Then there's the cost discussion. When asked to comment on the cost versus benefit of some of the newer I-O agents, Joseph answered that while these drugs are expensive, close to \$10,000 per month for the melanoma agents, “If you look at the 5-year survival, and the need for further therapy, then the immunotherapies will probably come out ahead.” From the payer perspective, Klein hopes for additional evidence that could prevent an unnecessary burden on the system. “Once the evidence is in, then a coverage policy will be developed,” he said.

When it comes to measuring QALY, though, Klein said that it's a heterogeneous system with the various insurance groups involved; everyone is moving toward achieving a goal through their own, separate distinct business model. He added that these decisions need to be made at the population level, not the individual patient level. For Joseph, his practice, as yet, has not been affected by QALY measures.

Salgo asked the panel how they foresee the Affordable Care Act affecting the value of innovation, to which Klein responded that there has to be an obvious connection between patients, payers, and research. He referred to the model pilots being launched and funded by the Center for Medicare and Medicaid Innovation, aimed at saving healthcare dollars. Pointing to the need to look at our

“When patients who previously needed someone to assist them into the office because of burden of disease then walk upright into the office, that’s a good index.”

—IRA M. KLEIN, MD, MBA, FACP

healthcare system in its entirety, he said, “Instead of discussing the specifics of drugs that cost \$10,000 per therapy, maybe we should step back, make an overall observation, and discuss what is going on in our system and whether we can reduce waste.” And where does the patient fit in the discussion of innovation? Klein thinks that our heterogeneous payment system has so far prevented a formula that could embrace both clinical and economic goals.



Ira M. Klein, MD, MBA, FACP

When asked if bundled payments would impact innovation, Joseph, who agrees with the principle, said that it could improve physician efficiency with more tests to support their therapeutic choices. However, he also thinks the system has problems, which, according to Klein are associated with the execution and governance of bundle payments and the resulting financial responsibilities. He believes in shifting the risk onto a provider or delivery organization, which is what accountable care organizations (ACOs) are about. ACOs need to have in-

depth knowledge of the clinical condition of the population they service, so they can risk-adjust based on the cost of treating that population, said Klein.

SURROGATE MARKERS AND INNOVATION

As the discussion transitioned to the impact of innovation on the drug approval process, Salgo said that back in 1992, the FDA accepted surrogate endpoints as a way to adopting the accelerated drug approval process. While overall survival (OS) is the benchmark used to measure drug efficacy in oncology, several disease progression-based end points—such as progression free survival (PFS), time to treatment failure, and time to progression—are currently being used. Salgo asked the experts to provide their insights and experience

with using these endpoints in drug development. Klein said that a colleague who is involved in clinical policy prefers to rely only on OS because the other endpoints can be conflicting. Joseph, on the other hand, believes that every therapy needs a different endpoint. Citing the example of BRAF inhibitors, he said that they shrunk the tumors, improved quality of life, and were effective for 6 to 8 months. Patients also had better PFS, which then raised an ethical question of whether the patient on chemotherapy who progresses should

be given the BRAF inhibitor, Klein said. This makes it difficult to assess the endpoint because 1 patient started earlier on the “good drug”. Joseph believes that quicker endpoints for drugs that are clearly effective would be a plus. “Are 2 surrogate end points better than 1? Is that where we should be going? Is it more efficient?” asked Salgo. Klein argued that surrogate markers have changed the picture because they measure quality of life, a metric that is dependent on the measurement approach. He said that with surrogate markers, we end up paying for quality of life, not cure or long-term remission. Joseph challenged Klein’s argument, saying that we are really paying for survival; it can be challenging to show OS in patients, he reasoned, especially if the study design includes crossover.

When asked about other endpoints such as objective response rate (ORR) and disease free survival (DFS), Joseph said that ORR is an imperfect science. Citing the example of BRAF inhibitors, he said while 90% of the patients have a reduced tumor burden, only 50% meet the ORR criteria. He said he would rather evaluate drugs based on a patient’s performance status, which is subjective, and Klein agreed. “When patients who previously needed someone to assist them into the office because of burden of disease then walk upright into the office, talk about their daily activities, self-care, and walk back to the car and drive themselves home, he can say that’s a goodness index,” Klein added. DFS, Joseph said, is similar to PFS, but is used more in the adjuvant setting.

VALIDATING AND ADOPTING PROS

Patient reported outcomes (PROs) are gaining increasing attention in mainstream discussions. When asked to provide insight on the value and validation of PROs, since they are an indicator of

the patients’ perceived quality of life, Joseph referenced the COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma) trial, which compared pazopanib and sunitinib in kidney cancer. While both drugs were equally efficacious, pazopanib was better tolerated, based on patient observation and physician objective findings, Joseph said, adding that he likes the idea of patient-based reporting. Klein said that PROs can be validated with quantity, if we can get enough surveys and if we can conduct quality-of-care studies. He thinks that surrogate markers, overall, would be valuable information for informing patient quality-of-life and independent-living decisions.

In closing, Klein summarized that we have a lot to learn with alternative markers of efficacy and there is discrepancy between cost and the final output. But he believes that the impact of these innovations will be felt over time as they are probably still in their infancy. Joseph concluded that, for a melanoma physician, I-O is an exciting field. While he has witnessed the benefits of the innovative therapy, he thinks it will be some time before payers recognize the benefits of I-O. There are still some data needed, he added, including duration of treatment and the need to make treatments more affordable. **EBO**

Please visit **Managed Care Insights on AJMC TV** to watch the expert interviews (<http://www.ajmc.com/insights>).

REFERENCE

1. Accelerated Approval Program. FDA website. <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm313768.htm>. Accessed January 28, 2015.

Payers Evaluate the Clinical Utility of Diagnostic Tests

Surabhi Dangi-Garimella, PhD

Diagnostic tests play a critical role in this era of personalized medicine, as they guide physician decision making, particularly in oncology. Molecular tests generate data that are expected to improve patient outcomes. Research has shown that use of molecular diagnostic testing has increased 20% to 30% each year, while the number of therapeutic decisions based on these tests increased 200% during a recent 3-year period.¹ However, like with most innovations, molecular diagnostic testing does not come without costs.

What are the factors that influence reimbursement and policy decisions for diagnostic tests? What evidence is needed to ensure payment? How is the value

of a diagnostic test determined? These were some of the questions addressed by payer representatives from leading managed care companies during the Oncology Stakeholders Summit: Insights discussion organized by *The American Journal of Managed Care*. The participants included John L. Fox, MD, MHA, senior medical director and associate vice president of medical affairs at Priority Health; and Bryan Loy, MD, physician lead—cancer, Humana. Peter Salgo, MD, professor of medicine and anesthesiology at Columbia University and associate director of surgical intensive care at NewYork-Presbyterian Hospital, interviewed the experts individually.

Currently, physicians can choose

from 3 tests to assess distant recurrence in early-stage breast cancer: MammaPrint (Agendia, 70 genes), Prosigna (Nanostring, 50 genes), and Oncotype DX (Genomic Health, 21 genes). The 3 gene panels have only 12 common genes, none of which are shared across the board. Both MammaPrint and Oncotype DX are covered by Medicare and by a few commercial carriers; Prosigna is covered by UnitedHealth-



Bryan Loy, MD

care but not yet covered by Medicare. While MammaPrint, a laboratory-developed test (LDT), is a microarray that is offered as a service, Oncotype DX, also an LDT, is an RT-PCR assay that can be conducted in a laboratory but is also offered as a centralized service. Prosigna, which is based on the PAM50 gene signature, is an FDA-approved kit that is decentralized.²

Salgo asked the experts whether they saw any advantage of a (continued on page **SP92**)

DISCOVERING HOW FAR THERAPY CAN GO

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA[®]. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA[®].

The mechanism for the bleeding events is not well understood. IMBRUVICA[®] may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding IMBRUVICA[®] for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA[®] therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA[®]. Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA[®]. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA[®], particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA[®] treatment and dose modification.

Second Primary Malignancies - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA[®]. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11%).

IMBRUVICA® (ibrutinib) is the first and only FDA-approved therapy for use in patients with Waldenström's macroglobulinemia (WM)

IMBRUVICA® is approved for use in 4 indications

IMBRUVICA® is indicated for the treatment of patients with

Mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Chronic lymphocytic leukemia with 17p deletion.

Waldenström's macroglobulinemia (WM).

Tumor Lysis Syndrome - Tumor lysis syndrome has been reported with IMBRUVICA® therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA®. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions ($\geq 25\%$) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash. Seven percent of patients receiving IMBRUVICA® discontinued treatment due to adverse events.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid co-administration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

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Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

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INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials [see *Clinical Studies (14.1) in Full Prescribing Information*].

Chronic Lymphocytic Leukemia: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy [see *Clinical Studies (14.2) in Full Prescribing Information*].

Chronic Lymphocytic Leukemia with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion [see *Clinical Studies (14.2) in Full Prescribing Information*].

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) [see *Clinical Studies (14.3) in Full Prescribing Information*].

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding [see *Clinical Studies (14) in Full Prescribing Information*].

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. [See *Adverse Reactions*]. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Monitor patients for fever and infections and evaluate promptly.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification [see *Dosage and Administration (2.3) in Full Prescribing Information*].

Second Primary Malignancies: Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Use in Specific Populations*].

ADVERSE REACTIONS

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

- Hemorrhage [see *Warnings and Precautions*]
- Infections [see *Warnings and Precautions*]
- Cytopenias [see *Warnings and Precautions*]
- Atrial Fibrillation [see *Warnings and Precautions*]
- Second Primary Malignancies [see *Warnings and Precautions*]
- Tumor Lysis Syndrome [see *Warnings and Precautions*]

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

Clinical Trials Experience: Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administrative site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3

IMBRUVICA® (ibrutinib) capsules

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Mantle Cell Lymphoma (N=111) (continued)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia: The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and Study 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	Dyspepsia	13	0
Infections and infestations	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General disorders and administrative site conditions	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin and subcutaneous tissue disorders	Bruising	54	2
	Rash	27	0
	Petechiae	17	0
Respiratory, thoracic and mediastinal disorders	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Nervous system disorders	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17	2
Neoplasms benign, malignant, unspecified	Second malignancies*	10*	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17	8

*One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions

Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2.

Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2

System Organ Class ADR Term	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Fatigue	28	2	30	2
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term. The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

* Based on laboratory measurements per IWCLL criteria

Waldenström's Macroglobulinemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial (≥ 20%) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 7 and 8 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63) (continued)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
General disorders and administrative site conditions	Fatigue	21	0
	Musculoskeletal and connective tissue disorders	21 13	0 0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The system organ class and individual ADR terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 8: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. 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.

Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A Inhibitors: In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity [see Dosage and Administration (2.4) in Full Prescribing Information].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A [see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

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

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

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

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) [see Clinical Studies (14.2) in Full Prescribing Information].

Of the 63 patients treated for WM, 59% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.

IMBRUVICA[®] (ibrutinib) capsules

Renal Impairment: Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CL_{cr}) > 25 mL/min. There are no data in patients with severe renal impairment (CL_{cr} < 25 mL/min) or patients on dialysis [see *Clinical Pharmacology (12.3) in Full Prescribing Information*].

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of IMBRUVICA has not been evaluated in patients with hepatic impairment. Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) [see *Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information*].

Females and Males of Reproductive Potential: Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm [see *Use in Specific Populations*].

Plasmapheresis: Management of hyperviscosity in patients with WM may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- **Hemorrhage:**
Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see *Warnings and Precautions*].
- **Infections:**
Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see *Warnings and Precautions*].
- **Atrial Fibrillation:**
Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see *Warnings and Precautions*].
- **Second primary malignancies:**
Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see *Warnings and Precautions*].
- **Tumor lysis syndrome:**
Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation [see *Warnings and Precautions*].
- **Embryo-fetal toxicity:**
Advise women of the potential hazard to a fetus and to avoid becoming pregnant [see *Warnings and Precautions*].
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day [see *Dosage and Administration (2.1) in Full Prescribing Information*].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose [see *Dosage and Administration (2.5) in Full Prescribing Information*].
- Advise patients of the common side effects associated with IMBRUVICA [see *Adverse Reactions*]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see *Drug Interactions*].
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

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(continued from page SP87)

decentralized test versus a centralized LDT. Both payers agreed that being decentralized is a definite advantage for a diagnostic test, with a faster turnaround time and ease of access. Fox, however, did not see any direct advantage to the patient. The fact that a patient may not immediately be initiated on treatment following the results of the test means that a decentralized test does not necessarily serve them. He went on to add, "I'm indifferent as a payer to what test I pay for if the costs are the same," and that he did not believe decentralizing would influence the cost of the test.



John L. Fox, MD, MHA

parison of these tests would be the ideal way to determine which one is optimal. A paper published in the *Journal of Clinical Oncology* in 2013 assessed the mRNA of 1017 estrogen receptor-positive breast cancer patients treated with anastrozole or tamoxifen in the Armidex, Tamoxifen, Alone or in Combination (ATAC) trial. The trial found that the risk-of-recurrence score provided by PAM50 added prognostic information far beyond the clinical treatment score in all the different subsets evaluated. Additionally, the

test categorized fewer patients in the gray "intermediate-risk" category compared with Oncotype DX.⁵

Fox said he is more concerned about patients being placed in the appropriate risk category than about the actual number of patients being classified as "high" versus "intermediate" versus "low" risk. Proper patient stratification is key, he affirmed.

Both panelists agreed that a test that can determine the response to treatment can be defined as being "predictive." Fox would ideally like to see the test define optimal and personalized therapy for a patient, not just response to chemotherapy. "If I could acquire information that was easily understood by both the patient and the provider, and it was clinically meaningful, being able to provide that level of context, I think, would be the most valuable," said Loy. **EBO**

Please visit Managed Care Insights on AJMC TV to watch the expert interviews (<http://www.ajmc.com/insights>).

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FDA GUIDELINES FOR DIAGNOSTIC TESTS

The FDA recently announced that it would issue guidance for the development, review, and approval of companion diagnostics, while also publishing a risk-based oversight framework for LDTs.^{3,4} The decision was based on the increasing reliance of physicians on diagnostic test results to make treatment decisions. Would payers welcome this increased oversight on diagnostics? Would it influence payer policies?

According to Loy, providers may not necessarily understand the rigors of these tests, and they have to rely on the decisions made by the pathologist on where and by whom the tumor sample is tested, resulting in a lack of transparency on the analytical and clinical validity of the test. "I think that the value in having a more rigorous and well-defined FDA process will help in the planning stages," said Loy. "Many of these folks developing these tests are largely growing out of the laboratory industry, and they don't necessarily have the deep pockets." He emphasized that without stifling innovation, streamlining and regulating the process would guarantee reliable tests. Fox believes that FDA scrutiny would ensure the clinical and analytical validity of the test.

VALUE PROPOSITION OF A NEW DIAGNOSTIC TEST

Competition is always good, and it helps level the playing field—a monopoly is not ideal for growth and innovation. "Now, all of a sudden, you've got a discussion around price point, accessibility, decentralization, how interpretable the information is, ease of doing business, and the ability to generate sufficient turnaround time in order for them to get out in front and not delay therapy. All those become extremely important pieces of the discussion, above and beyond just the evidence base," stressed Loy.

Fox said that a head-to-head com-

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- How the President's Precision Medicine Initiative Will Learn From Oncology Practice
- The Patient Lens on Precision Medicine
- **Panel:** Reimbursement Challenges for Oncology Innovations: Who Pays?

Session 3: The Future of Immunology

- Are We Close to the Big "C": Cure?
- Evaluation of Options and Outcomes in a "Me Too" Market
- **Panel:** The Role of PBMs in Managing High-Cost Treatment Options

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- **Panel:** Navigating the Conflict of Personalized Medicine vs Population Management

Session 5: Accountable Care in Oncology

- **Panel:** Evolution of the ACO Model to Meet the Needs of Oncology Patients and Payers

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New Standards of Care in the Management of Prostate Cancer

Surabhi Dangi-Garimella, PhD

With increasing evidence that prostate-specific antigen (PSA) is not an ideal marker for prostate cancer, research efforts are focused on identifying efficient biomarkers for disease diagnosis as well as response to treatment. Additionally, this form of cancer is known to rapidly adapt and develop resistance to androgen-deprivation therapy (ADT), the most commonly used hormone therapy for prostate cancer.

To shed some light on the current status of prostate cancer diagnosis, and to gain insight into the clinical pathways followed to treat the resistant form of the disease, *The American Journal of Managed Care* invited comment from Ira M. Klein, MD, MBA, FACP, national medical director, Clinical Thought Leadership, Office of the Chief Medical Officer, Aetna Inc; and Christopher Sweeney, MBBS, associate professor, Department of Medicine, Harvard Medical School, and medical oncologist, Dana-Farber Cancer Institute. Peter Salgo, MD, professor of medicine and anesthesiology at Columbia University and associate director of surgical intensive care at NewYork-Presbyterian Hospital, interviewed Klein, while Silas Inman, director, editorial and multimedia, OnLive, interviewed Sweeney.

The discussion started with the experts being asked to comment on new and emerging diagnostic and prognostic markers in prostate cancer, to which both Sweeney and Klein responded by saying that currently there is nothing beyond PSA, although this antigen “has a terrible track record in terms of its predictive value, and we have a lot of people getting unnecessary prostate biopsies,” according to Klein. He went on to add that for individuals with high PSA levels whose biopsies come back positive, traditional methods of Gleason score and tumor morphology follow. Klein emphasized that the patient’s age is an important consideration when choosing the treatment pathway

because a balance between life expectancy and aggressiveness of treatment is vital. With respect to epigenetic markers to understand disease progression, Klein thinks we are in the very early stages, at least when it comes to prostate cancer; current epigenetic data on prostate cancer are not sufficient to determine which patients with metastatic disease will progress, which might be due to tumor heterogeneity.

Salgo asked Klein whether patients who might develop ADT resistance can be identified, and whether tumor heterogeneity might be the driving force. According to Klein, it’s a tough predicament because we currently cannot identify hormone-resistant patients prior to initiating hormone therapy. While tumor heterogeneity is known to exist in prostate cancer, it’s not well defined. “Some of the trials that are ongoing are evaluating this,” Klein added, combining androgen blockade with traditional chemotherapy and comparing the response with androgen blockade alone. According to Sweeney, while the time frame for progression to resistance on luteinizing hormone-releasing hormone (LHRH) agonists is variable, very few patients progress within the first 6 months. Sweeney affirmed, however, that it is possible to identify and segregate patients based on the rate at which their disease will progress—a finding from the “ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease” (CHAARTED) study. “One feature that we presented in the CHAARTED studies, which has also been seen in other studies, is that patients who have a higher volume of disease at presentation have a shorter time to progression,” said Sweeney. Thus, the extent of disease that the patient presents with prior to starting therapy, and the impact on PSA after initiating therapy, determine the time to progression, he said. Tumor heterogeneity could be a risk factor for differential responses to therapy—an area of research actively being pursued. One

such finding is the expression of a splice variant of the androgen receptor (AR), a truncated form which functions independent of androgen and drives cancer progression independent of the blocking testosterone or the wild-type AR, he said. Sweeney highlighted a study in *The New England Journal of Medicine* that found patients expressing this truncated AR resistant to both abiraterone and enzalutamide,¹ and he believes this is a promising biomarker that could help distinguish between good and poor responders.



Christopher Sweeney, MBBS

Inman asked about the use of combination therapies in prostate cancer and where the field currently stands. Sweeney, who has played a major role in the CHAARTED study since its inception in 2004, responded that the study has reported promising results from combining hormones with chemotherapy early in treatment, adding that ongoing trials are evaluating the introduction of enzalutamide or abiraterone early in treatment. Another trial, said Sweeney, is studying androgen deprivation in combination with enzalutamide and docetaxel at initiation, to target the less resistant cells, based on the hypothesis that “It would delay progression further and improve survival even further.”

Inman asked Sweeney to provide details on CHAARTED, a randomized phase 3 study comparing androgen deprivation with or without docetaxel, followed by a lag period, and then hormone therapy alone. The results were quite encouraging among patients with a high-volume disease (liver or lung metastases and ≥4 bony metastases), Sweeney said, with high-volume patients showing an increase in median survival from 32 months to 49 months. Early chemotherapy resulted in a 40% reduction in the risk of death, suggesting that high-volume patients treated with the combination lived longer, he said. With the low-volume patients, Sweeney continued, 70% were still on the study without disease progression at 4 years, independent of chemotherapy, indicating that the response to chemotherapy in this population would need a longer follow-up. He agreed that in older patients with a low-volume disease, aggressive chemotherapy may not be an ideal choice.

The discussion then moved to sequencing therapies in prostate cancer; current National Comprehensive Cancer Center (NCCN) guidelines have no recommenda-

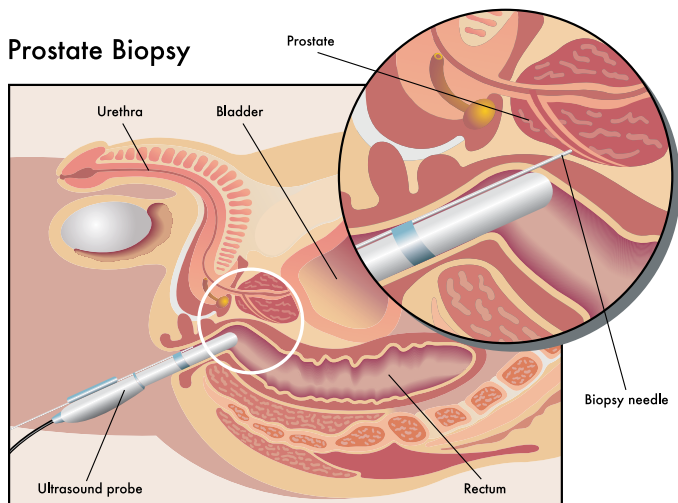
tions for the sequencing of antiandrogens (enzalutamide) with androgen synthesis inhibitors (abiraterone), pre- or post chemotherapy. Klein said that Aetna works with consultants who have pointed to the lack of information on some of these agents for recommending a sequence of drugs to use in treatment regimens. However, he alluded to the fact that abiraterone has been approved and has been in use for some time now, while enzalutamide is a fairly new drug but should be accessible in the near future. Prospective trials evaluating the combination of abiraterone and enzalutamide in advanced prostate cancer have not been conducted; Klein said that while that is important, other aspects of the disease such as low-versus high-volume disease burden, performance status, and disease stage are also critical. Sweeney thinks that publishing results from trials like CHAARTED in peer-reviewed journals can definitely impact clinical guidelines. He added, though, that he knows from conversations that the strength of these trial data has convinced regulators, clinicians, urologists, medical oncologists, and radiation oncologists to adopt the combination therapy in their practices. “It’s going to be easier if it’s on the guidelines and it’s actively being reviewed by the guidelines committees, but it hasn’t reached [that point] yet. I know a number of hospitals have actually put it on their pathways as the preferred choice for high-volume disease and an item to be discussed for patients with low-volume disease. But each country is weighing it out differently,” Sweeney added. When attempting to sequence drugs like abiraterone and enzalutamide, there are strategies to individualize, based on health status, despite the lack of data.

Klein concluded that we have not moved too far from older treatments like ketoconazole, LHRH agonists such as leuprolides, and the trileptins. The current options for patients, per NCCN guidelines, include docetaxel, cabazitaxel, and abiraterone, he said, in addition to the immunotherapy, Provenge. According to Klein, a better understanding of disease genomics, along with additional information on evidence-based therapy can improve the prognosis for the advanced prostate cancer patient. **EBO**

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Issues Impacting Stakeholder Adoption of Immuno-Oncology
(CONTINUED FROM COVER)

generation of development, pioneered by Steven A. Rosenberg, MD, PhD, at the National Cancer Institute (NCI), heralded a future for vaccine-based therapy, which failed to materialize. Eventually, researchers explained the failure of these first 2 forays into immuno-oncology by elucidating the mechanisms by which tumors evaded the activated and enriched T-cells: the tumors subverted immune checkpoint pathways and other immunoregulatory mechanisms.

Now, nearly 30 years later, we find ourselves at a similar junction in the history of cancer and drug discovery, filled with promise and triumph as science conquers another frontier. How is this third generation of immuno-oncology different? Why is this scientific breakthrough more transcendent? What will be the response of stakeholders—patients, providers, and payers—to the emergence of this new class of therapeutics? Are these times and circumstances really so different? Such are the questions before us.

Stakeholder adoption of new therapeutics classically hinges on the quality valuation triad of efficacy, toxicity, and cost. But as we have learned from experience and the discipline of behavioral economics, our choices of treatment are often more complex. We are immersed in an era of precision medicine and targeted drug development, being convinced that each cancer has its unique gene signature and thereby represents an N of 1. Tumors that appear phenotypically identical are genetically distinct, owing to the differential expression of multiple mutated genes (from 10 to >100), without a clear distinction of the most critical gene(s). Targeted treatment of such patients has produced some dramatic responses, albeit transient and without cures.¹ Thus, the allure of precision medicine combined with targeted therapy is becoming tarnished by tumor adaption to pathway interference, resulting in the lack of a durable response—reminiscent of the limitations of traditional chemotherapy. What makes immuno-oncology seem so transformative and, thereby, so appealing is the gestalt of panacea, therapies that are histology agnostic unleashing an immune system to recognize self from abnormal self regardless of cell origin. Even more so today than in the 1980s, we are rightly captivated by the promise of an arsenal of broadly active antitumor drugs that demonstrate rapid and durable responses with limited grade 3-4 toxicity.

A corollary to the perception of immuno-oncology as the anticipated evolution of cancer treatment is its equally compelling mechanism of action. Stakeholders

“I believe that the parallel to hepatitis C agents cannot be overstated and that the recent market response should be viewed seriously as multiple PD-1 pathway drugs with similar indications will likely enter the market in the next 2 years.”

—BRUCE FEINBERG, DO



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are much more likely to embrace treatments that intellectually and emotionally appeal to them. Many complex multicellular regulatory events keep the immune system from overreacting to a stimulus or mistaking a component of itself for a dangerous invader. Most notable among the “antigen presenting cell-T-cell-microenvironment” that regulates inflammatory responses in the tissues is the programmed cell death protein 1 (PD-1) pathway. One or both of the PD-1 ligands, PD-L1 and PD-L2, which are expressed on cells in the tissues, bind to PD-1 receptors on T-cells and inhibit their function. Blocking this interaction between PD-1 and its ligands can result in T-cell activation and a more florid tissue inflammatory response.² Although this third generation of immuno-oncology truly began with the FDA’s approval of the vaccine sipuleucel-T (Provenge) in

2010 and the immunostimulatory cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody ipilimumab (Yervoy) in 2011, the PD-1 pathway drugs are driving our current interest in immuno-oncology, as response rates with ipilimumab and sipuleucel-T have been modest at best.^{3,4}

EFFICACY

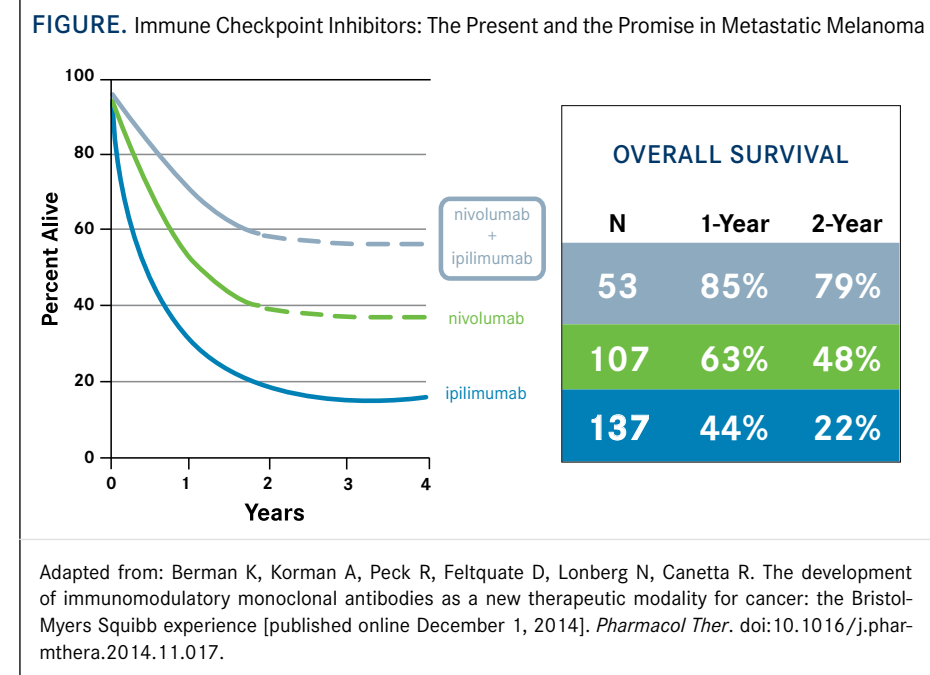
Despite the increasing impact of cost on treatment considerations and toxicity on prescribing patterns, efficacy remains the most critical driver of new therapeutic adoption. Recently published reports provided additional data on the efficacy of immune therapy; specifically, on the role of antibodies blocking the PD-1 receptor pathway in the treatment of metastatic cancer. Robert et al described an improved objective response rate (ORR) (40%) and 1-year survival rates (72.9%) among patients with untreated metastatic melanoma that received the anti-PD-1 drug nivolumab compared with dacarbazine.⁵ Ansell et al reported a remarkably high ORR of 87% among heavily pretreated patients with Hodgkin’s lymphoma receiving nivolumab.⁶ In September 2014, another anti-PD-1 drug, pembrolizumab (Keytruda), was granted accelerated approval in the United States, but only for the treatment of metastatic melanoma in patients with progressive disease after treatment with the current standard of care, ipilimumab (an anti-CTLA-4 antibody) and a BRAF-targeted agent (for tumors with a V600 mutation).⁷ Breakthrough Therapy designation for pembrolizumab in advanced non-small cell lung cancer was supported by response data from the ongoing phase 1b KEYNOTE-001 study.⁸ Pembrolizumab, like other drugs in the PD-1 pathway, is actively being studied as monotherapy and in combination across more than 30 types of cancers. But such robust responses, as has been published by Roberts and Ansell et al, is

not the case in all tumors studied.^{5,6} In the KEYNOTE-012 trial, pembrolizumab resulted in a meager 18.5% response rate in women with triple-negative breast cancer.⁹ Similar response rates with PD-1 inhibitors in other solid tumors may diminish their current popularity.

Efficacy, in and of itself, may be seen as a complex triad of factors including time, depth, and duration of response. One of the most striking observations from the checkpoint-inhibitor clinical trials is the early objective responses and durable tumor control and survival. The vast majority of responders do so rapidly with upwards of 80% maximum tumor shrinkage, including complete response, within 12 weeks of initiation.¹⁰ Unleashing a memory immune response may also result in long-term disease stabilization as T-cells are stimulated by peptide ligands, resulting in memory that may be lifelong. Maturing data in more than 4800 patients have shown that approximately 1 in 5 patients treated with ipilimumab has the potential to survive for at least 3 years, and up to 10 years, from treatment initiation, which more than doubles results with conventional drugs.¹¹ Although the PD pathway may be the poster child for this third generation of immuno-oncology due to its compelling mechanism of action and impressive clinical trial survival data, the field of immuno-oncology is becoming incredibly crowded and competitive, especially for the first generation of targets (eg, CTLA-4, PD-1/PD-L1, TIM3, LAG3, OX40, etc).

TOXICITY

When treatment is not curative, toxicity becomes a significant factor in stakeholder adoption. There was early recognition that stimulating the immune system might result in autoimmune events: as expected, enterocolitis, hepatitis, dermatitis, pneumonitis, endocrinopathy, and neuropathy have been the most common autoimmune-related adverse events (AEs) observed. Rate of AEs with single agent immuno-oncology regimens have ranged from 46% to 64% for any grade event and 6% to 18% for grade 3-4 events.¹⁰ In the KEYNOTE-012 trial, 18 of the 32 treated patients experienced a treatment-related AE.⁹ Four patients had grade 3 events, which included anemia, headache, aseptic meningitis, and pyrexia; 1 patient had a grade 4 event. A concern for increased toxicity with combination therapy was corroborated when grade 3-4 toxicities were observed in 62% of patients treated with the combination of ipilimumab and nivolumab.¹² The unusual constellation of autoimmune AEs may pose a dilemma for oncologists not accustomed to identifying and managing such conditions. Despite low levels of serious AEs with single-agent PD-1 treatment, the toxicity profile and early safety signals with combination



therapies may limit stakeholder adoption.

COMPANION DIAGNOSTICS

The impact of a cultural shift to precision medicine may also be a factor in the breadth of immuno-oncology adoption. Immunohistochemical analysis following anti-PD-1 therapy in metastatic melanoma has shown higher response rates and improved progression-free survival in patients with at least 5% of tumor cells from a pretreatment metastatic lesion staining for membrane PD-L1 expression. In the study by Robert et al, melanoma patients were stratified according to tumor PD-L1 expression status. However, nivolumab showed substantial benefit even in patients with negative or indeterminate biomarkers.⁵ Will clinical pathways depend on biomarkers to select between anti-BRAF and anti-PD-1 therapy in patients with BRAF-mutated metastatic melanoma or to determine which patients might be better responders following anti-PD-1 therapy alone? Perhaps to choose the best combination therapy among the many potentially active ones that will be developed over the coming years? Due to the complex tumor-host relationship and multitude of variables that may influence outcome with respect to pharmacologic intervention, development of reliable and affordable predictive biomarkers will be difficult and require a substantial investment in resources. Findings of Robert et al have underscored the need to validate a prospective predictive biomarker in a randomized, controlled clinical trial.

COST

The unsustainable cost trend in health-care in general, and cancer care in particular, has often been blamed on the

rising cost of drug treatment. The last 10 oncology drugs that have come to market, including the immuno-oncology agents discussed herein, have price tags that exceed \$10,000 per month. Although the cost versus value can be debated, cost has increasingly become a factor in stakeholder adoption. Even when novel therapeutics are awarded Breakthrough Therapy designation or demonstrate cure (as in the case of the new class of hepatitis C drugs), cost has been at the forefront of stakeholder discussions. The potential scope of application, coupled with continued use as maintenance therapy in responders, likelihood of combination therapy, and effectiveness in transforming life-threatening diagnoses to chronic diseases magnify the price scrutiny of immuno-oncology agents. I believe that the parallels to hepatitis C agents cannot be overstated and that the recent market response should be viewed seriously, as 3 to 6 PD-1 pathway drugs will likely enter the market with similar indications and labeling in the next 2 years.

CONCLUSIONS

The foundation for immuno-oncology as an anticancer treatment was built upon the knowledge that tumor cells can use complex and overlapping mechanisms to avoid immune detection. As the evidence builds around the impressive clinical activity of PD-1 and PD-L1 antagonists in patients with a variety of cancers, the critical and foundational role of immune interventions in cancer treatment is no longer deniable. The success achieved to date was accomplished with agents directed against only 2 of the many potentially important immune targets. Rapid responses, durable tumor control, and long-term sur-

vival through harnessing the power of the immune system are now realities. Data with agents that block CTLA-4, PD-1, and other checkpoint proteins are affording a benchmark to measure the efficacy of future therapies while stimulating interest in alternative sequencing or smart combination approaches to further improve outcomes. The potential for broad antitumor activity agnostic to histology or complex genotype, rapid onset of response, the relatively low toxicity profile of PD-1 and PD-L1 antagonists, and possibility of T-cell memory resulting in durable responses differentiate this third generation of immuno-oncology agents from the preceding ones. We must remember, however, that these agents have toxicities, are enormously expensive, and are not currently curative. Informed stakeholders are likely to weigh all these factors carefully in their decision to adopt immuno-oncology drugs. **EBO**

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toxicity of anti-PD-1/PD-L1 agents, an exponential increase in their use in treatment regimens is inevitable. With the increased use of these agents as well as the relatively substantial costs, now is a good time to begin thinking about how best to use these agents to optimize value both for the individual patient and for healthcare system at large.

Moving forward, the following 3 actions are among those that could be taken to improve the value of these agents:

- Recognize both the patients who are most likely to benefit and those who are unlikely to benefit from the agent.
- Identify the optimal duration of therapy, which remains unknown.
- Determine the best sequence or combination in which to administer these agents.

UPFRONT IDENTIFICATION OF PATIENTS LIKELY TO BENEFIT

Many in the field are exploring either clinical or translational biomarkers that can reliably predict who will benefit from anti-PD-1/PD-L1 therapies. Initially, Topalian et al demonstrated that the lack of tumor expression of PDL-1 had a very strong negative predictive value, with 0 of 17 patients with PD-L1-negative tumors not responding to nivolumab (anti-PD-1).¹ In that same study, 9 of 25 (36%) patients with PD-L1-positive tumors did respond.¹ Subsequent studies have confirmed that while PD-L1-positive patients are more likely to achieve clinical benefit with anti-PD-1/PD-L1 agents, patients whose tumors are PD-L1-negative can also respond, albeit at a lower rate than patients with PD-L1-positive tumors.^{2,3} Specifically, Daud

et al demonstrated that while patients with PD-L1-positive tumors did have better outcomes with pembrolizumab, those with PD-L1-negative tumors had a response rate of 4% and disease control rate of 17%.³ Furthermore, Herbst et al demonstrated that PD-L1 expression on the tumor-infiltrating lymphocytes, not the tumor, strongly correlated with improved outcomes in patients receiving Roche's anti-PD-L1 antibody (MPD-L3280A), while patients with PD-L1-negative or low PD-L1-expressing tumors also achieved a response rate of 13%.² Outside of tumor expression of PD-L1, at least 1 study demonstrated that baseline tumor size was the strongest independent predictor of benefit from pembrolizumab, with patients with lower tumor burdens much more likely to achieve clinical benefit than those with

larger tumors.⁴

In summary, further work is necessary to more reliably identify those who are more likely and less likely to benefit from anti-PD-1/PD-L1 agents. PD-L1 expression on either the tumor or tumor-infiltrating lymphocytes is helpful to enrich for patients who are more or less likely to respond, but the positive and negative predictive value is far from perfect. Given the enormous potential for anti-PD-1/PD-L1 agents to provide clinical benefit, withholding the drug from patients who have a reasonable chance to benefit would not be ethical. However, when considering value to the healthcare system, perhaps withholding these agents from those who are extremely unlikely to benefit would be the ideal goal.

PROVIDER PERSPECTIVE

Improving the Value of Immune-Based Therapies
(CONTINUED FROM COVER)

“Identifying the optimal duration of therapy in responders, as well as identifying markers that could reliably rule out pseudo-progression in non-responders, could significantly improve the overall value of PD-1/PD-L1 agents.”

—RICHARD W. JOSEPH, MD



Richard W. Joseph, MD

IDENTIFICATION OF OPTIMAL DURATION OF TREATMENT

A second key way to improve value of anti-PD-1/PD-L1 therapies is to determine the optimal duration of therapy for patients who are responding. For example, a hallmark of most successful immunotherapies, including the use of anti-PD-1/PD-L1 agents, is the ability to provide a durable remission and even a cure. While the therapy is still in its infancy, the median duration of response has not been reached in the majority of patients who achieved a clinical response to anti-PD-1/PD-L1 therapies, suggesting that many patients may respond indefinitely. Questions I am frequently asked by patients who are responding are, “How long do I need to stay on therapy?” or “What will happen if I stop therapy?” Unfortunately, we are currently lacking sci-

entific answers to these questions. Future studies that address the added benefit of continuing therapy after patients respond should help answer this question.

On the flip side, and due to the well-described phenomenon of pseudoprogression (or late responders), it is often challenging to determine when to stop using these agents in patients who are not responding following initial scans. For example, a small minority of patients (5%-10%) treated with both pembrolizumab and nivolumab experienced disease progression at initial restaging (12 weeks) but then went on to respond at a later time point.⁵ With that being said, pseudoprogression is relatively rare, and therefore continuing therapy in all patients who are not initially responding decreases the overall value of these agents. Further work to identify patients who are unlikely to be late responders would help limit the use of these agents and thereby provide additional value.

In summary, identifying the optimal duration of therapy in responders, as well as identifying markers that could reliably rule out pseudoprogression in patients who are not responding, could significantly improve the overall value of anti-PD-1/PD-L1 agents.

IDENTIFICATION OF THE PROPER SEQUENCE OF ANTI-PD-1/PD-L1 AGENTS IN THE COURSE OF THERAPY

At present, both pembrolizumab and nivolumab are FDA approved only in patients with metastatic melanoma who have previously progressed on ipilimumab, and if the patient's tumor harbored a mutation in BRAF, the patient must also progress on a BRAF inhibitor. However,

members of the National Comprehensive Cancer Network believe that anti-PD-1/PD-L1 agents should be considered in the frontline setting due to improved clinical efficacy and toxicity compared with ipilimumab.⁶ Furthermore, in a phase 3 study of previously untreated patients with metastatic melanoma, nivolumab demonstrated improved overall survival (OS) compared with those treated with dacarbazine, providing evidence that anti-PD-1 agents can and do provide OS benefit when given in the frontline setting.⁷ In addition, there are retrospective data, at least, that suggest that patients who are treatment-naïve have a smaller tumor burden and are perhaps more likely to benefit from these agents.⁴ Ongoing studies will further elucidate the benefit of anti-PD-1/PD-L1 agents in the frontline setting.

When discussing the value of anti-PD-1 agents, administration of anti-PD-1/PD-L1 molecules in the frontline could provide overall value to the healthcare system and to the individual. For example, anti-PD-1/PD-L1 agents given in the front line provide durable remissions, which could obviate the need for expensive and toxic future therapy. Fortunately, additional clinical studies testing these agents in the frontline setting are currently under way and will, it is hoped, provide more clues to where these agents are most effective.

CONCLUSIONS

Immunotherapies with anti-PD-1/PD-L1 agents have revolutionized care for patients with metastatic melanoma, and preliminary data suggest that these agents likely will revolutionize the care of patients with other malignancies as well. Given the predicted widespread use of these immune-modulating agents, combined with their high costs, continued efforts are necessary to optimize their efficacy and thus improve their value.

Specifically, improving our use of predictive biomarkers, further refining the optimal duration of therapy, and identifying the proper sequence of these agents will greatly enhance the value equation. Advanced clinical studies designed to address these questions are needed. **EBO**

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PATIENT PERSPECTIVE

Patient Cost-Sharing in Oncology and the Patient Access Network Foundation
(CONTINUED FROM COVER)

policy and market conditions, while trying to anticipate how future trends could impact its mission and operations. For example, after the Affordable Care Act (ACA) passed in 2010, PAN anticipated the change in the timing of when patients would need financial support; in particular, the start of manufacturers' discounts for brand name drugs, as well as other provisions that will close the Medicare Part D coverage gap by 2020.

Recently, PAN has been witnessing a growing need for patient financial assistance, as more Medicare Part D plans and commercial insurers are requiring a high percentage (25%-33%) of coinsurance for specialty drugs. While the higher coinsurance cost allows Part D enrollees to qualify for catastrophic coverage earlier in their treatment cycle, this benefit de-

sign change has the potential to limit access to and decrease adherence to current cancer therapies—and likely will have the same effect on new immuno-oncology therapies.

EVOLVING WITH MEDICAL PROGRESS

PAN continually evaluates trends in research and development (R&D), regulatory actions for therapies in the R&D pipeline, and government policy and market developments that affect patient access to important treatments for cancer, rare diseases, and chronic conditions. The foundation has followed—with great interest—the development of immunotherapy, a new paradigm in oncology care and an important therapeutic advance that complements current approaches using chemotherapy, small molecule-targeted

therapies, radiation, and surgery.

Immuno-oncology presents new challenges that span the regulatory spectrum: from FDA approval of therapies and related biomarkers to a broad range of challenges affecting patient access, including coverage decisions of government programs and private payers, and increased cost-sharing requirements for specialty drugs. Currently approved immuno-oncology therapies and those under development will fall in the specialty category.



Dan Klein

Biomarkers, a critical part of the immuno-oncology framework, play an important role in the development of more personalized approaches to drug therapies, and are increasingly included in national clinical guidelines and on FDA labels.¹ In the 10 years since the Human Genome Project ended, medications that include pharmacogenomic information on the FDA-approved label have doubled.² Characterizing biomarkers helps physicians identify positive or negative responders to a certain therapy.³ Because the cost burden for these tests may fall on patients, PAN may

need to expand the scope of its cancer funds to provide assistance for patients who face high out-of-pocket (OOP) costs for molecular testing.

ADDRESSING THE COST-SHARING BURDEN

In addition to the high cost-sharing burden associated with traditional, and more time-limited, types of cancer treatment, some newer oncology treatments are prescribed as maintenance therapies over lengthier periods of time. As a result, patients face increasing financial pressures long after the initial oncology treatment has ended.

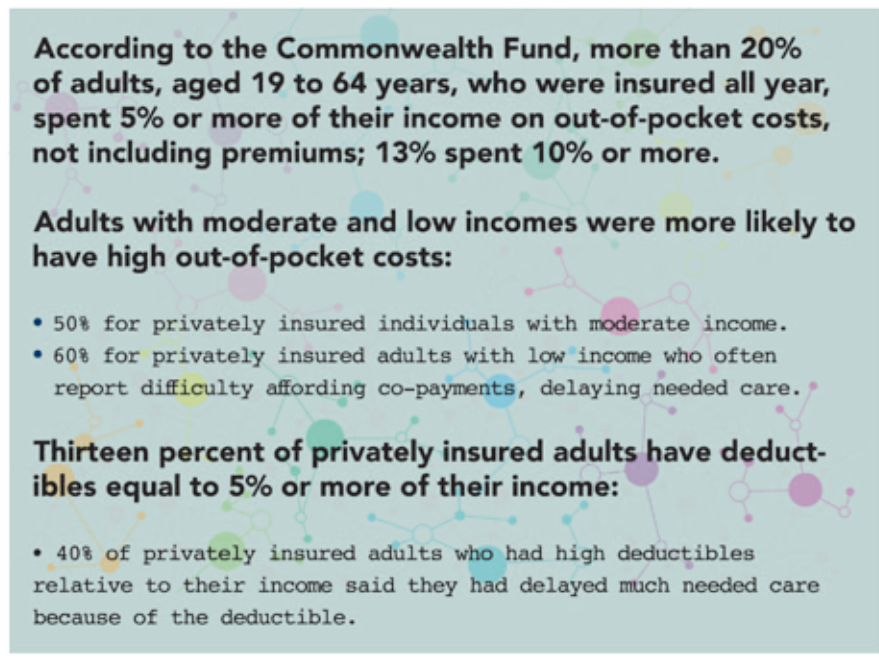
PAN provides vital assistance to help patients who might otherwise forgo critical therapies prescribed by their physicians. Researchers have quantified the importance of financial assistance by linking patients' adherence to prescribed treatment to their ability to pay their cost-sharing amounts. Significant evidence has demonstrated the inverse relationship between patient adherence to a prescribed treatment and the level of financial hardship that a cost-sharing percentage represents, based on their income. A study from Prime Therapeutics found that 1 in 6 cancer patients with high OOP costs abandon their medication at the pharmacy. In fact, patients with OOP costs greater than \$200 were at least 3 times more likely to not fill their prescriptions than those with OOP costs of \$100 or less.⁴ By providing financial grants to cover some or all of a patient's cost-sharing amounts, PAN is able to eliminate or reduce cost-sharing as a barrier to that patient's ability to initiate and adhere to important therapies, including those in the immuno-oncology group.

UNDERSCORING THE ISSUE OF UNDER-INSURANCE

The magnitude of underinsurance as a barrier to cancer care is increasing as the level of health coverage increases (see Figure for more details). The tax subsidies for coverage obtained through the state and federal marketplaces authorized by the ACA are benchmarked to the premium for a defined Silver plan, which has an actuarial value of 70%; that is, 30% of the average annual costs for the covered group, including the high coinsurance rates applied to specialty drugs, will be paid out of patients' own pockets. The trends in the marketplaces are consistent with those of employer health plans, the leading source of private health insurance coverage.

For example, for 2015, most exchange plans have set the maximum out-of-pocket (MOOP) cost limit lower than the maximum of \$6600 for individual plans and \$13,200 for plans offered to families. The average deductible for Silver plans, which accounted for about two-thirds of 2014 marketplace enrollment, increased by 7% for 2015 to \$2658 (or 45% of the MOOP cost limit). The average deductible

FIGURE. Out-of-Pocket Healthcare Costs in the United States



Source: Collins SR, Rasmussen PW, Doty MW, Beutel S. Too high a price: out-of-pocket health care costs in the United States: findings from the Commonwealth Fund health care affordability tracking survey. The Commonwealth Fund website. http://www.commonwealthfund.org/~media/files/publications/issue-brief/2014/nov/1784_collins_too_high_a_price_out_of_pocket_tb_v2.pdf. Published November 2014. Accessed January 13, 2015.

for Bronze plans increased to \$5249 (or 82% of the MOOP cost limit).⁵

More than half of the individuals helped by PAN had incomes at or below 200% of the federal poverty level. The majority of patients (85%) who have been helped by PAN also are Medicare beneficiaries who cannot afford therapies,⁶ some of which may be covered as a Part B benefit or a Part D benefit. The other 15% are insured by a private health plan.

LOOKING FORWARD

As a charitable organization, PAN is guided by a board of directors that provides overall policy direction to staff regarding the Foundation's operations. Most of PAN's revenue is in the form of donations from interested stakeholders, primarily specialty drug manufacturers. Most of PAN's expenses are associated with the cost-sharing grants that it provides to patients, along with the necessary administrative costs required to meet the needs of patients in a responsible manner, consistent with all of the regulatory requirements of charitable foundations that provide financial assistance to underinsured patients.

PAN has continually evolved its programs to respond to the changing needs created by new therapeutic approaches, such as immuno-oncology; legislative changes, such as the ACA provisions that provide health coverage for millions of Americans; and the Medicare Part D changes, including closing the coverage gap and regulatory review of Part D plans' use of specialty cost-sharing tiers.

The Foundation appreciates the role that *Evidence-Based Oncology* plays in encouraging discussions between providers, payers, and patients on the quality

and cost of cancer care. PAN welcomes the chance to participate in discussions about how the new paradigm represented by immuno-oncology will impact the need for the patient financial assistance that PAN provides and how to broaden the range of resources required to provide this important resource for patients. **EBO**

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