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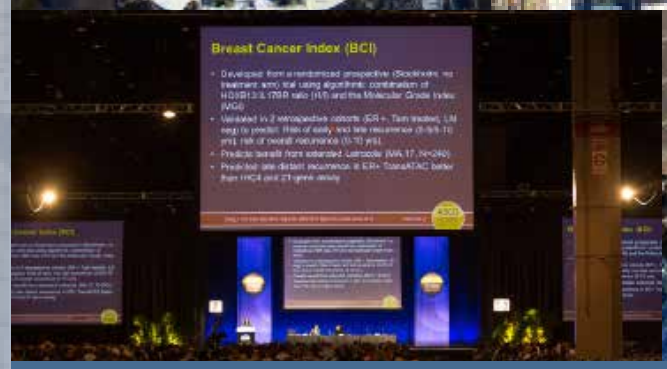

The median age of patients in the VISTA† trial was 71 years (range: 48-91).

Indication and Important Safety Information for VELCADE® (bortezomib)

INDICATION

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

CONTRAINDICATIONS

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

WARNINGS, PRECAUTIONS, AND DRUG INTERACTIONS

- **Peripheral neuropathy:** Manage with dose modification or discontinuation. Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.
- **Hypotension:** Use caution when treating patients taking antihypertensives, with a history of syncope, or with dehydration.
- **Cardiac toxicity:** Worsening of and development of cardiac failure have occurred. Closely monitor patients with existing heart disease or risk factors for heart disease.
- **Pulmonary toxicity:** Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms.
- **Posterior reversible encephalopathy syndrome:** Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.
- **Gastrointestinal toxicity:** Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement.
- **Thrombocytopenia or Neutropenia:** Monitor complete blood counts regularly throughout treatment.
- **Tumor lysis syndrome:** Closely monitor patients with high tumor burden.
- **Hepatic toxicity:** Monitor hepatic enzymes during treatment.

In treating multiple myeloma

What is the value of VELCADE® (bortezomib)?

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

IF YOU DEFINE VALUE AS AN OVERALL SURVIVAL ADVANTAGE:

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

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

IF YOU DEFINE VALUE AS DEFINED LENGTH OF THERAPY:

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

IF YOU DEFINE VALUE AS MEDICATION COST:

- Medication cost is an important factor when considering overall drug spend. The Wholesale Acquisition Cost for VELCADE is $1585 per 3.5-mg vial as of July 2014
- When determining the value of a prescription drug regimen, it may be worth considering medication cost, length of therapy, and dosing regimens. This list is not all-inclusive; there are additional factors to consider when determining value for a given regimen

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

ADVERSE REACTIONS

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

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

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

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

*Melphalan+prednisone.

† **VISTA TRIAL:** a randomized, open-label, international phase 3 trial (N=682) evaluating the efficacy and safety of VELCADE administered intravenously in combination with MP vs MP in previously untreated multiple myeloma. The primary endpoint was TTP. Secondary endpoints were CR, ORR, PFS, and overall survival. At a prespecified interim analysis (median follow-up 16.3 months), VELCADE+MP resulted in significantly superior results for TTP (median 20.7 months with VELCADE+MP vs 15.0 months with MP [$p=0.000002$]), PFS, overall survival, and ORR. Further enrollment was halted and patients receiving MP were offered VELCADE in addition. Updated analysis was performed.

VELCADE®
(bortezomib) FOR INJECTION

VELCADE®
(bortezomib) FOR INJECTION

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/m^2 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/m^2 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/m^2/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+melphalan and prednisone study in previously untreated multiple myeloma, the safety profile of VELCADE administered intravenously in combination with melphalan/prednisone is consistent with the known safety profiles of both VELCADE and melphalan/prednisone. The most commonly reported adverse reactions in this study (VELCADE+melphalan/prednisone vs melphalan/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 melphalan-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 melphalan 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.

Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Millennium Pharmaceuticals, Inc., Cambridge, MA 02139

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The 50th Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Chicago, May 30, 2014, to June 3, 2014, was as exciting an event as it promised to be. Innovations and advances in the technological and clinical disciplines, as well as policies and guidelines, were shared and discussed. Among all the headline-grabbers, immunooncology left its mark. Numerous posters and live sessions presented the latest data evaluating PD-1, PD-L1, and CTLA-4 inhibitors in diverse cancer types.

However, recent advances with some of the traditional oncology targets, such as the epidermal growth factor receptor (EGFR), were also quite encouraging. EGFR has proved a promising target in metastatic lung, colorectal, pancreatic, and head-and-neck cancers, and an increased understanding of resistance mechanisms has resulted in improved small-molecule inhibitors and antibodies that block the receptor. A session that saw participation from Pasi A. Janne, MD, PhD (Dana-Farber Cancer Institute), Lecia V. Sequist, MD, MPH (Massachusetts General Hospital), Gideon Michael Blumenthal, MD (Holy Cross Hospital), and Lawrence H. Schwartz, MD (Columbia University Medical Center), presented the progress report on targeting EGFR in patients harboring the T790M resistance mutation. Additionally, participants discussed the use of appropriate surrogate markers that can accelerate the pace of approval.

Policy discussions were prominent on the agenda as well, as faculty from the University of Chicago and Dana-Farber Cancer Institute discussed the influence of the Affordable Care Act (ACA) on healthcare. The 3 researchers presented patient-centric analyses and addressed the Act's impact on physicians providing care. "Each stakeholder—the provider, the payer, and the manufacturer—has a role to play in bringing about this payment reform," said Rena Conti, PhD, a health economist and assistant professor at the University of Chicago. As they discussed the implications of the current provisions of the ACA, it became obvious that the path ahead will be long and arduous.

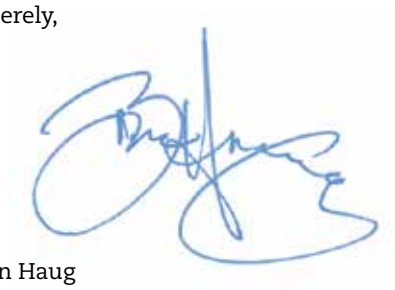
The value discussion in oncology has been making headlines, especially following the recent decision by WellPoint involving clinical pathways, incentivizing physicians to make treatment decisions based on payer-sponsored clinical regimens. Additionally, UnitedHealthcare recently published results from a cancer care payment model that was evaluated in collaboration with 5 medical oncology groups. The finding: the new model reduced medical costs by 34%.

This topic was the focus of various debates at the annual meeting as well, with each stakeholder presenting his or her perspective on what value of care meant. In the session titled "Overdiagnosis and Overtreatment in Cancer: Point/Counterpoint," physicians delved into defining overdiagnosis and overtreatment. The debate boiled down to laying down clear, cancer-specific, evidence-based guidelines and using decision-making tools to guide treatment. ASCO, for its part, has been promoting the Choosing Wisely campaign in cancer care, a list of tests and treatments that are commonly used even in the absence of evidence-based value. Efforts are also under way in Europe, where the European Society for Medical Oncology is developing a Magnitude of Benefit Scale for drugs, factoring in quality of life, overall survival, progression-free survival, and other variables.

Our coverage of the annual meeting also includes roundups of poster sessions on emerging cancer therapies, as well as studies evaluating the value of clinical pathways.

This special issue will provide our readers with many additional insights and updates on current research. As always, keep reading, and visit www.ajmc.com for information on faculty listings and discussion topics at our live meeting, Patient-Centered Oncology Care, to be held in Baltimore, November 13-14, 2014.

Sincerely,



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

EDITORIAL MISSION

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

Cancer Care in the United States: The Path Ahead

Surabhi Dangi-Garimella, PhD

The debate is global: how long can healthcare systems sustain the continually rising costs of care? Pharmaceutical and biotechnology companies are investing heavily in research to develop new molecules with improved efficacy and minimal adverse effects, novel drug delivery technologies, and diagnostic tests that can help personalize therapy as well as monitor response to therapy, especially in oncology.

Here's the big picture: a report by the Pharmaceutical Research and Manufacturers of America (PhRMA) published last year indicated that it takes an average of 10 to 15 years to develop 1 drug molecule.[1] Furthermore, drug development costs have experienced a steep rise over the past few decades: estimated at $140 million back in the 1970s, recent assessments reveal that the cost to develop 1 drug molecule now ranges from $1.3 to $11 billion.[1,2] R&D spending, meanwhile, has also seen a steady increase—PhRMA projected its average per member cost, which was $2 billion in 1980, to be $48.5 billion for 2012.[1] Like any other industry, the pharmaceutical sector seeks a return on its investments. So what does the spending translate into? Rising drug costs.

However, the discussion, especially in the oncology realm, is about whether the modest increase in benefit observed with some of the newer therapies—sometimes a few added weeks or months of life—justifies the cost (**Figure 1**). Back in 2012, Memorial Sloan Kettering Cancer Center took a stand and chose Avastin (which costs about $5000 per month) over Zaltrap (which costs about $11,000 per month) for treating patients with advanced metastatic colorectal cancer. Zaltrap, developed by Sanofi/Regeneron, was no more effective than Genentech's Avastin. Subsequently, Sanofi was forced to reduce the price of Zaltrap by 50% in the United States.[3]

There is no arguing that this tremendous investment in cancer care has paid dividends for patients. Since 1980, 83% of the improvement in the life expectancy of cancer patients has resulted from new treatments, which include novel medicines.[1] Innovative approaches such as RNAi, cancer vaccines, and immunotherapy (both monoclonal antibodies and the new immunooncology inhibitors) are transforming the therapeutic spectrum. Screening and early detection have improved outcomes, at least for certain cancer types. The National Breast and Cervical Cancer Early Detection Program (NBCCEDP), run by the CDC following a Congressional directive, provides screening and diagnostic services to low-income and uninsured women throughout the country. Since 1991, the program has diagnosed more than 62,121 cases of breast cancer, 3458 cases of invasive cervical cancer, and 163,548 premalignant cervical lesions. Early detection in these 2 cancer types have definitely proved beneficial.[4]

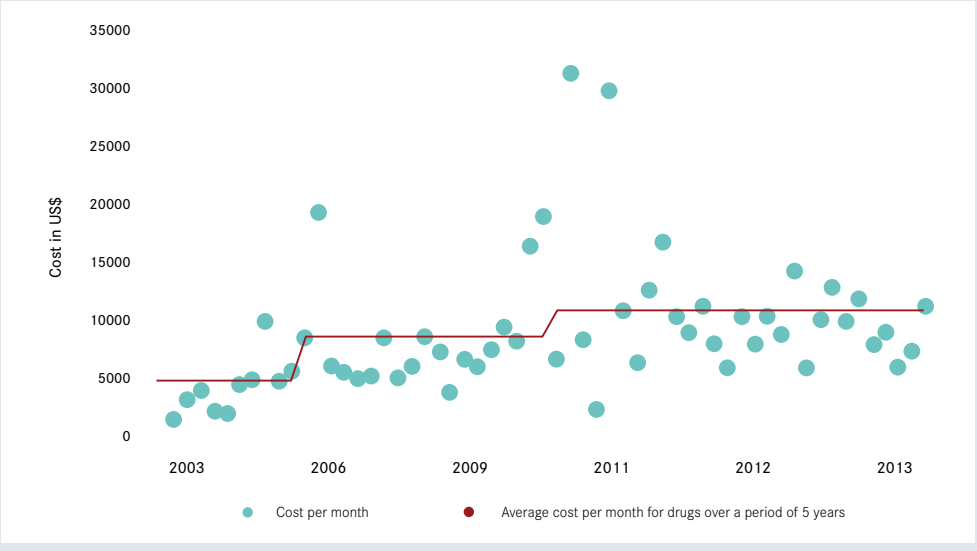
Drug development, of course, is just 1 variable in the equation of cancer care. Other treatment-associated costs, including doctor visits, hospitalization, and outpatient services such as laboratory tests, complete the picture.

The Affordable Care Act of 2010 supported the development of accountable care organizations (ACOs), with this objective: collaborative and coordinated care to improve quality, value, and health outcomes for patients. ACOs are expected to greatly impact Medicare spending. A feared potential drawback, however, is provider consolidation. This could drive up the cost of care, with the patient ultimately footing the bill (**Figure 2**).[5]

However, providers can play a significant role in reducing these costs, as was argued during the session "Cancer Overdiagnosis and Overtreatment, or Appropriate Attention to Early Disease?" on June 1, 2014, at the annual meeting of the American Society of Clinical Oncology (ASCO) **(see page SP285)**. To this end, ASCO's Value of Cancer Care Task Force developed a list of opportunities for physicians to improve the quality and value of care delivered, as part of the Choosing Wisely campaign.[6]

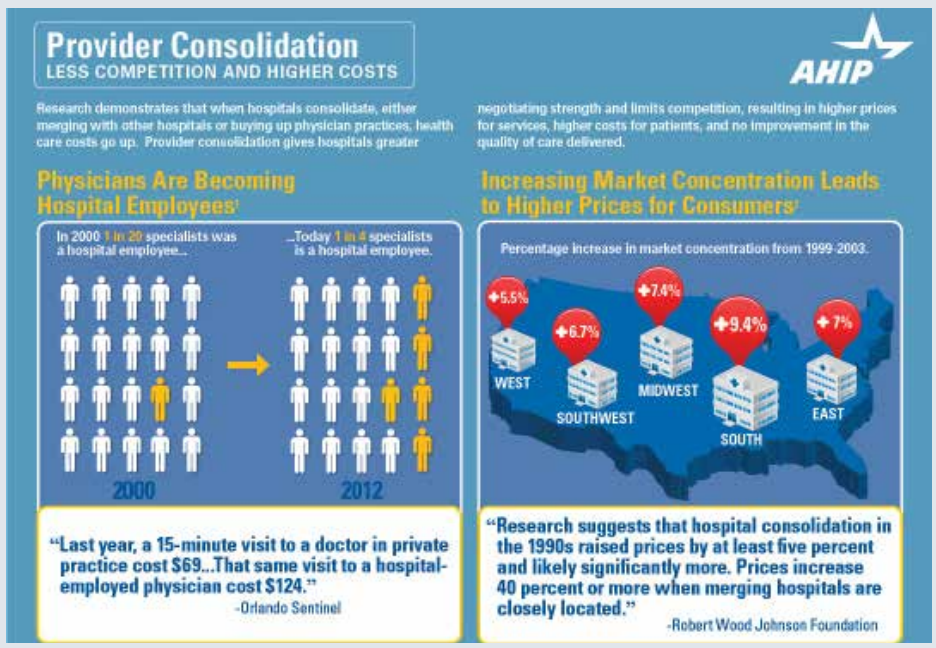
The debate will persist about choices made by physicians while treating an individual patient versus policies that govern the patient population as a whole. During a session that discussed the value of care **(see page SP359)**, Daniel P. Sulmasy, MD, PhD, professor of medicine and associate director at the MacLean Center for Clinical Medical Ethics at the University of Chicago, said, "Population medicine cannot be practiced at the bedside. The goal is to improve the life of an individual patient and not the population. Bedside rationing and providing financial incentives can threaten the integrity of medicine and also undermine the patient's trust." **EBO**

Figure 1. Cost per Month of Branded Oncology Drugs in the United States (2003-2013)



Source: Innovations in cancer care and implications for health systems. http://bit.ly/1rHF8tM. IMS Institute for Healthcare Informatics website. Published May 2014. Accessed July 11, 2014.

Figure 2. Impact of Provider Consolidation in ACOs[4]



Consolidation of healthcare practices and hospitals spells bad news for patients. As with any other industry, mergers entail monopoly, and could result in rising costs of care services.
ACO indicates accountable care organization.

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The EGF Receptor (EGFR) Continues to Be a Promising Target in NSCLC

The epidermal growth factor receptor (EGFR), one of the many receptor tyrosine kinases that are targeted in cancer treatment, is frequently overexpressed or mutated in cancer, resulting in cell proliferation, survival, invasion, metastasis, and tumor-induced neoangiogenesis.[1] The approach to targeting EGFR in cancer has included the use of small molecule tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, lapatinib, and afatinib, and monocloncal antibodies such as cetuximab, panitumumab, and matuzumab (**Figure**).[2]

Pasi A. Janne, MD, PhD

A session titled "Targeting EGFR: The Next 10 Years," held May 31, 2014, on the second day of the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO), provided a progress report on the successful targeting of the protein in non-small cell lung cancer (NSCLC).

The opening talk by Pasi A. Janne, MD, PhD, director of the Lowe Center for Thoracic Oncology at the Dana-Farber Cancer Institute and professor of medicine, Harvard Medical School, was titled "Clinical Activity of the Mutant-Selective EGFR Inhibitor AZD9291 in Patients With EGFR Inhibitor-Resistant NSCLC." Janne presented results from a phase 1, open-label, multicenter clinical trial with a selective, third-generation EGFR-TKI by AstraZeneca, AZD9291, that has been found to be effective against both EGFR-TKI–sensitizing and resistance (T790M) mutations in preclinical models.

The trial, conducted in 199 EGFR mutant (T790M+) NSCLC patients with acquired resistance to EGFR-TKIs, conducted a dose escalation and expansion study of oral AZD9291. Among all the evaluable patients, the confirmed+unconfirmed overall response rate (c+uORR) was 51% (91/177). Response Evaluation Criteria in Solid Tumors (RECIST) responses were observed at all dose levels and in brain metastases. Of 132 patients with centrally confirmed T790M, the c+uORR in 89 EGFR T790M+ patients was 64% (95% CI: 53%-74%), and in 43 EGFR T790M patients was 23% (95% CI: 12%-39%). The overall disease control rate in T790M+ patients was 96% (85 of 89). Among the 60 patients with a confirmed response, 97% (58 of 60) were ongoing at data cutoff and the longest duration of response was greater than 8 months. AZD9291 did not present any dose-limiting toxicities, maximum tolerated dose (MTD) was not defined, and the most common adverse events (AEs) were diarrhea, rash, and nausea. Very few grade 3 or higher AEs were observed in any of the cohorts. The overall response rate (ORR) was 53% and the overall disease control rate was 83%. A progression-free survival (PFS) benefit was observed in T790M+ patients. The results of this study have helped establish the dose for the phase 2 trials.

The phase 1 study demonstrated that T790M+ NSCLC patients with acquired resistance to EGFR-TKIs respond very well to AZD9291 and have a higher ORR compared with the EGFR T790M patients. Further clinical developments directed at the T790M+ patient population are ongoing.

The subsequent presentation was a dose-finding study for Clovis Oncology's CO-1686, a molecule that targets the EGFR T790M mutation in NSCLC patients, which recently received the FDA's "breakthrough therapy" designation.[3] Designed to target mutant EGFR, CO-1686 does not bind wild-type EGFR, thus increasing specificity and reducing adverse effects, which makes it eligible as first-line therapy in patients with activating EGFR mutations.[4] Clovis wants to develop CO-1686 as an oral treatment for NSCLC patients who have failed EGFR-directed therapy, such as Tarceva (Genentech) or Iressa (AstraZeneca), and have also developed the T790M mutation, which is the dominant resistance mechanism to Tarceva/Iressa.[4]

Lecia V. Sequist, MD, MPH

The results were presented by Lecia V. Sequist, MD, MPH, Massachusetts General Hospital. The first-in-human dose-finding study was conducted in 88 patients with EGFR-mutated advanced NSCLC. The formulation, a hydrogen bromide salt form of CO-1686, was administered to patients who were previously treated with EGFR TKI and had a tumor biopsy in screening for central EGFR genotyping. The patients had previously received a median of 3 therapies, with 40% having had more than 1 prior line of EGFR TKI. Related AEs, which were mild and observed in about 10% of patients, included nausea, fatigue, and hyperglycemia (managed with oral hypoglycemic agents such as metformin, with or without dose reduction). A recommended phase 2 dose of 750 mg twice a day was selected.

ORR was 58% in biopsy-proven, heavily pretreated, centrally confirmed T790M+ patients, and the responses deepened over time with longer follow-up. Median PFS was not reached at the time the data was presented, but was projected at more than 12 months. The trial also observed central nervous system responses with the drug.

Lawrence H. Schwartz, MD

CO-1686 proves promising in T790M+ EGFR mutant NSCLC patients, and the phase 1 study provided proof of concept that targeting the mutant form of EGFR can reduce AEs like diarrhea and rash. The phase 2/3 program initiated this year called TIGER (third generation inhibitor of mutant EGFR in lung cancer) is actively recruiting patients for 3 registration studies.

The subsequent presentation by Gideon Michael Blumenthal, MD, Holy Cross Hospital, who is also a clinical team lead with the FDA, was entitled "Overall Response Rate (ORR) as a Potential Surrogate for Progression-Free Survival (PFS): A Meta-Analysis of Metastatic Non-Small Cell Lung Cancer (mNSCLC) Trials Submitted to the FDA." There is an ongoing debate about the appropriate end points in clinical trials—they hold immense importance in oncology trials—and the FDA has guidelines for same.[5] The use of surrogate markers has stemmed from the accelerated drug approval process, whereby drug manufacturers often use surrogate end points to speed up drug launch, to save or extend lives. These surrogate end points include ORR, PFS, disease-free survival (DFS), time to progression (TTP), and patient-reported outcomes.[6]

Targeted therapies (TT) administered as single agents in molecularly defined mNSCLC subsets are yielding high ORRs. Additionally, large improvements in PFS with favorable benefit-to-risk ratio have served as the basis of drug approval in mNSCLC. However, the relationship of ORR with PFS or OS in mNSCLC is not established. The FDA conducted a meta-analysis using data from 15 mNSCLC trials that were submitted to the agency, which enrolled 12,534 patients, including 3 trials of TT in molecularly enriched populations with high

ORR. The estimated PFS hazard ratio (HR) and OS HR versus the estimated odds ratio (OR) of ORR on the log scale was calculated.

On a trial level, the meta-analysis of randomized, active-controlled trials indicated a strong correlation between ORR and PFS (R^2 = .89), especially for head-to-head trials, which means ORR could be an acceptable surrogate for PFS. A correlation between ORR or PFS and OS is not established and may be confounded by crossover in the TT trials. This might either be the result of a weak relation or no relation or a high crossover, under-power, or long post program survival, in the 3 small targeted therapy trials in the enriched population, which may confound the analysis. At the trial level, a TT in a molecularly defined subset of mNSCLC with a large magnitude of effect on ORR will likely have a large effect on PFS.

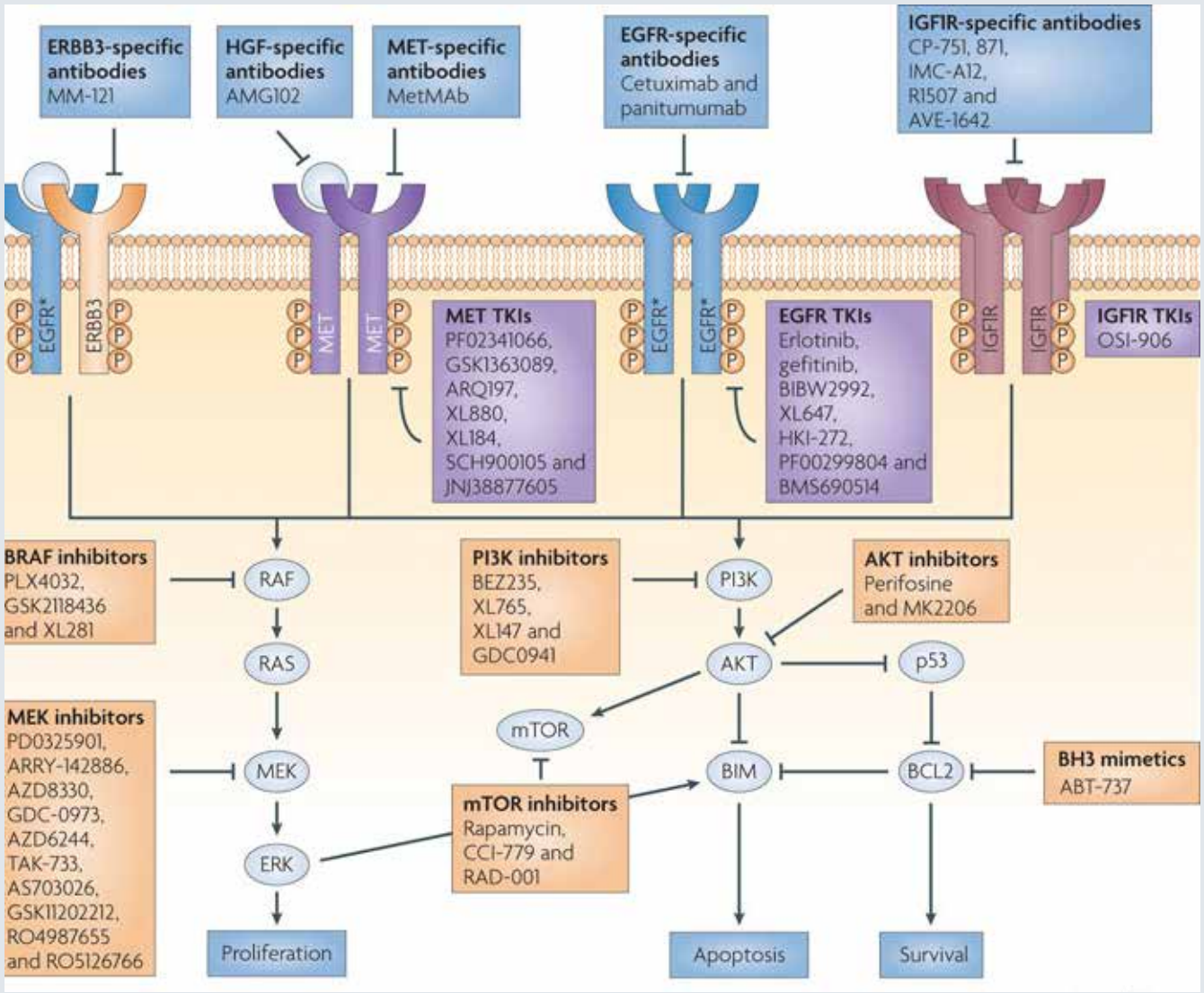
Lawrence H. Schwartz, MD, a diagnostic radiologist at Columbia University Medical Center and at NewYork-Presbyterian Hospital, concluded the session with his talk titled "Getting the Right Drug to the Right Patient Faster," wherein he provided his critique on the current treatment protocols that analyze response versus progression of disease.

"It's critical to distinguish response and progression as 2 distinct events," said Schwartz. Response rate is objective, measurable, and reproducible. Additionally, there's a long history—more than 30 years—of standardization and measurement of response. But the definition of response needs to be challenged and modified, he said. RR can be strongly correlated with median survival time, but the question remains—what is "optimal" RR?

Moving on to analyzing progression, Schwartz asked, "How accurate a gold standard is progression?" Alternate methods to assess response and progression to find effective therapies earlier are needed. To this end, the FNIH-sponsored VOL-PACT trial is under way, which considers an entire spectrum of metrics, not just RR. "The value proposition of these simulations is that combining metrics with imaging would provide much improved results," said Schwartz.

He concluded the session by saying that there is a need to combine smarter trials and smarter trial end points, including imaging, to derive optimal results and responses. **EBO**

Figure. Rational Drug Development in EGFR-Resistant NSCLC



EGFR indicates epidermal growth factor receptor; NSCLC, non-small cell lung cancer.
Source: Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nat Rev Cancer.* 2010;10(11):760-764.

CO-1686 proves promising in T790M+ EGFR mutant NSCLC patients—the phase 1 study provided proof of concept that trageting the mutant form of EGFR can reduce AEs like diarrhea and rash. The phase 2/3 program initiated this year called TIGER is actively recruiting patients for 3 registration studies.

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Promising Results in Leukemia From a BCL-2 Inhibitor

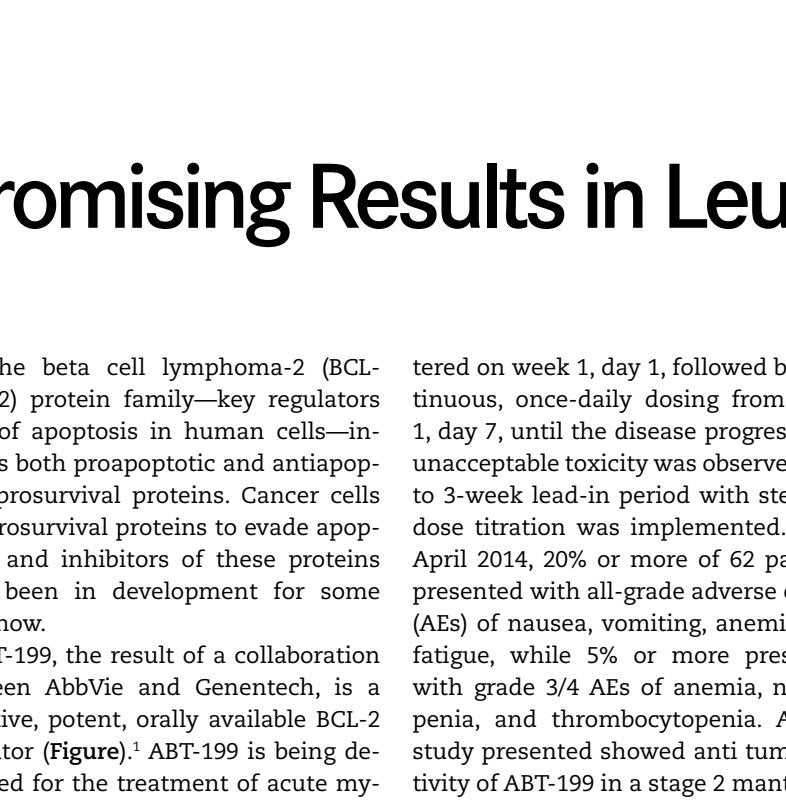
The beta cell lymphoma-2 (BCL-2) protein family—key regulators of apoptosis in human cells—includes both proapoptotic and antiapoptotic/prosurvival proteins. Cancer cells use prosurvival proteins to evade apoptosis, and inhibitors of these proteins have been in development for some time now.

ABT-199, the result of a collaboration between AbbVie and Genentech, is a selective, potent, orally available BCL-2 inhibitor (**Figure**).[1] ABT-199 is being developed for the treatment of acute myelogenous leukemia and chronic lymphocytic leukemia (CLL).

The following posters presented at the meeting provided the current status of this promising drug moiety.

1. ABT-199 in the treatment of diffuse B-cell and follicular lymphoma.[2]
The objectives of this phase 1 dose-escalation study included evaluation of safety, pharmacokinetics (PK), and preliminary efficacy in patients with relapsed/refractory non-Hodgkin's lymphoma (NHL). ABT-199 was administered on week 1, day 1, followed by continuous, once-daily dosing from week 1, day 7, until the disease progressed or unacceptable toxicity was observed. A 2- to 3-week lead-in period with stepwise dose titration was implemented. As of April 2014, 20% or more of 62 patients presented with all-grade adverse events (AEs) of nausea, vomiting, anemia, and fatigue, while 5% or more presented with grade 3/4 AEs of anemia, neutropenia, and thrombocytopenia. A case study presented showed anti tumor activity of ABT-199 in a stage 2 mantle cell lymphoma patient who had previously undergone 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, Oncovin, and prednisone) and 2 cycles of R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and IFRT (involved-field radiation therapy). A 6-week treatment with ABT-199 showed complete clinical resolution of node after 6 weeks. The overall response rate was 48% in the evaluated NHL patients. The authors are in the process of conducting biomarker studies with ABT-199.

Figure. Mechanism of Action of the Bcl-2 Inhibitor ABT-199



ABT-199 binds Bcl-2, resulting in free cytochrome-c and the subsequent in activation of caspases to promote apoptosis (cell death).

Bcl-2 indicates beta cell lymphoma-2. Source: Selective BCL-2 Inhibitor (GDC-0199/ABT-199). Genentech website. http://www.biooncology.com/pipeline-molecules/bcl-2. Accessed July 30, 2014.

2. Interim results from a phase 1b trial of ABT-199 plus rituximab in CLL.[3]
The objective of this trial was to assess the safety, pharmacokinetics (PK), and preliminary efficacy of ABT-199 with rituximab in patients with relapsed/refractory (R/R) CLL, and to determine a recommended phase 2 dose. The most common treatment-emergent AEs, observed in more than 25% patients, were neutropenia (43%), nausea (38%), and diarrhea (30%). The most common grade 3/4 AEs were neutropenia (43%), thrombocytopenia (16%), and anemia (11%). Two dose-limiting toxicities were observed with ABT-199 + rituximab: thrombocytopenia and hemophagocytic syndrome. The addition of rituximab to ABT-199 identified no new toxicities. The combination was active in R/R CLL with a substantial complete response (CR) rate. Best CR of 89% was observed in R/R patients and 39% achieved CR/CR with inadequate recovery (CRi). Absence of minimal residual disease was observed in 6 of 8 patients tested who had achieved CR/CRi, along with 5 patients who had a partial response. A fatal episode of tumor lysis syndrome (TLS) occurred during the ABT-199 lead-in period, but dosing modifications and increased monitoring prevented the occurrence of any further TLS events. Rituximab did not seem to influence ABT-199 exposure.

A phase 3 trial is ongoing in previously treated CLL patients, to evaluate ABT-199 plus rituximab versus bendamustine plus rituximab.[4]

3. Phase 1 study of ABT-199 in CLL and SLL patients: determine safety, PK, efficiency.[5]
The primary objectives of this phase 1 study were to evaluate the safety and PK and to determine the maximum tolerated dose and a recommended phase 2 dose of ABT-199 in patients with CLL and small lymphocytic leukemia (SLL). A secondary objective was to assess preliminary efficacy. Following early events of TLS, a weekly ramp-up period to the final cohort dose (150-1200 mg) was implemented. Patients are currently being enrolled in the safety expansion (SE) cohort. Most common AEs observed were diarrhea (37%), nausea (36%), neutropenia (35%), upper respiratory tract infection (29%), and fatigue (27%). Grade 3/4 AEs (≥3 patients) were neutropenia (32%), anemia (8%), TLS (8% including 1 G5), and febrile neutropenia, thrombocytopenia, hyperglycemia, and hypokalemia (6% each). Twenty-eight patients discontinued the study: 18 for disease progression, 8 for AEs, and 2 for other reasons. ABT-199 monotherapy was active in patients with R/R CLL with a 77% RR. Patients with high-risk CLL showed similar efficacy, with OR above 75%. ABT-199 monotherapy and combination therapy in CLL are currently enrolling. This includes a phase 3 trial evaluating the combination of ABT-199 and rituximab compared with bendamustine/rituximab in patients with relapsed CLL[4] and combination studies with bendamustine/rituximab and obinutuzumab in patients with relapsed CLL. **EBO**

ABT-199, the result of a collaboration between AbbVie and Genentech, is a selective, potent, orally available BCL-2 inhibitor. ABT-199 is being developed for the treatment of acute myelogenous leukemia and chronic lymphocytic leukemia (CLL).

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ACA and Cancer Care

Impact of the Affordable Care Act on Cancer Care

CO-1686 proves promising in T790M+ EGFR mutant NSCLC patients—the phase 1 study provided proof of concept that trageting the mutant form of EGFR can reduce AEs like diarrhea and rash. The phase 2/3 program initiated this year called TIGER is actively recruiting patients for 3 registration studies.

May 31, 2014, the second day at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO), ended with a session entitled "Health Care in America in 2014: Current and Future Implications of the Patient Protection and Affordable Care Act" (ACA). The presenters provided an overview of the recent and anticipated changes related to the ACA as well as its timeline. The panelists also explored how federal budget sequestration might affect reimbursement, Medicare, and funding of research and drug development.


Rena M. Conti, PhD

Rena M. Conti, PhD, a health economist and assistant professor in the section of hematology/oncology at the University of Chicago, opened the session with, "Bracing for the Future: Impact of Changes in Healthcare Policy on Drug Development." Healthcare spending in the United States is already 17.7% of current gross domestic product (GDP), and is projected to rise to 22% in 6 years, she said. About 1 of every 20 healthcare dollars is spent on cancer care, said Conti, although estimates vary among private insurers.

Conti affirmed that cancer care costs are rising faster than overall healthcare and cancer care is outpacing all other healthcare spending, with the current costs estimated at $125 billion. The ACA will increase that level of spending, and a population that is increasingly older will add to the financial burden.

So where is the problem? It manifests in the skirmish between the average value of new innovations and their application to individual patients. There result: although improvements in survival benefit are observed (due to various contributing factors such as improved screening techniques, treatment advances, and behavioral changes) (**Figure**), there is overuse and misuse of therapies. This is in addition to the off-label and unapproved use of drugs.

There is no argument that drug costs have seen a substantial increase, although the newer molecules have improved precision and thus response to therapy. But are these costs sustainable?

"So the fundamental question remains, how do we improve access and cost-effectiveness of these therapies while maintaining innovation?" asked Conti.

Conti laid out the political economy of reform. The cost of a drug is 2-pronged: if patients are well insured, they don't face very steep bills. Additionally, co-payment assistance is widely available for branded therapies. This, however, acts as a lever to inflate prices.

Consequently, physician practices face significant pressures to find deep discounts on acquisition prices of these therapies, and the 340B drug pricing program, which requires drug manufacturers to provide outpatient drugs to eligible healthcare organizations or covered entities at significantly reduced prices[1]—this Domino effect has resulted in a major consolidation of practices.

Conti highlighted the "how" of reform:

1. Change drug reimbursement policy: maintain the current system but make efforts to closely match reimbursements with acquisition costs.
2. Change the locus of risk bearing from physicians and hospitals to pharmacy benefit managers and insurers.
3. Change reimbursement models to include novel drugs.

Use of generic therapies is an obvious opportunity to exploit, she said. For example, Gleevec is going off-patent in 6 months, and replacing it with a generic will cause a drastic drop in drug price. "Each stakeholder—the provider, the payer, and the manufacturer—has a role to play in bringing about this payment reform," concluded Conti.

Lawrence N. Shulman, MD, chief of staff and senior vice president for medical affairs at Dana-Farber Cancer Institute, and associate professor, department of medicine, Harvard Medical School, presented his perspective on "The Impact of Accountable Care Organizations on Oncology Practice." He explained what accountable care organizations (ACOs) are and what can be done to best position oncologists in that environment.


Lawrence N. Shulman, MD

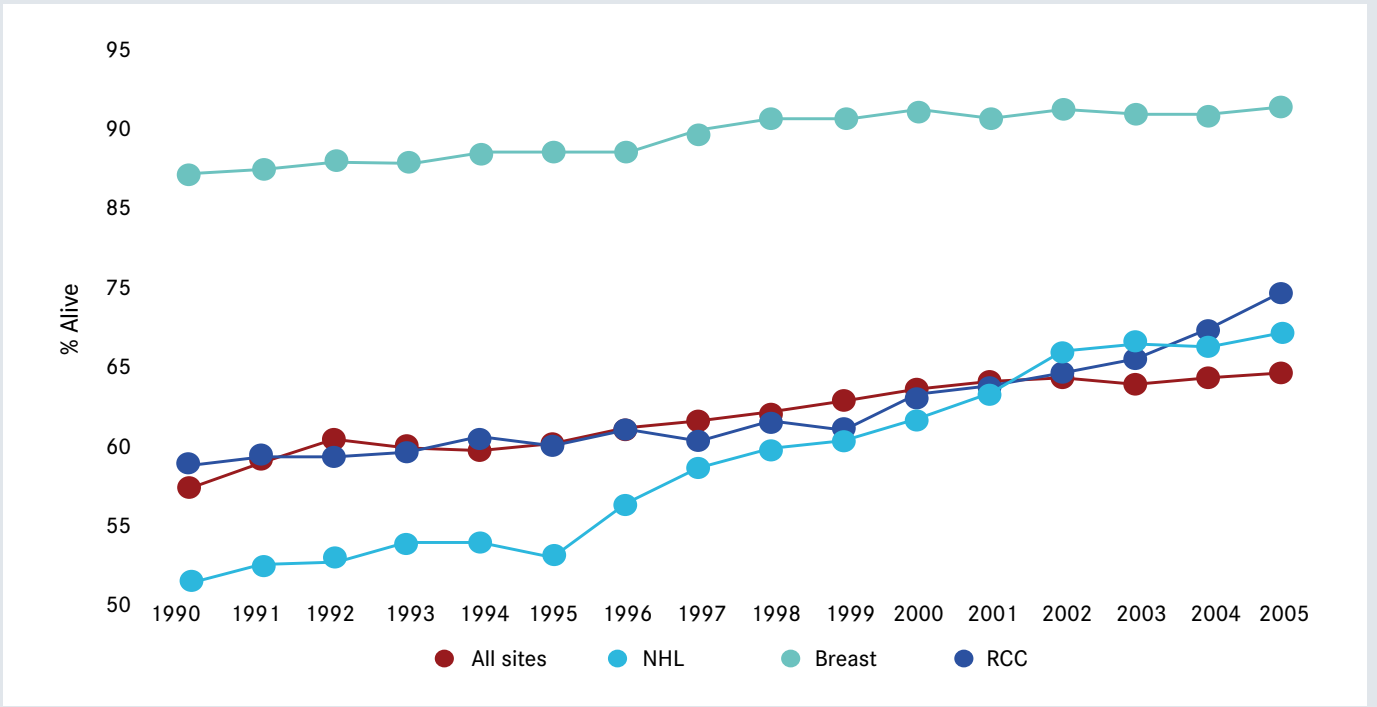
He started off with the CMS definition of an ACO.[2] ACOs are groups of doctors, hospitals, and other healthcare providers who come together voluntarily to deliver coordinated high-quality care to their Medicare patients.

The goal of coordinated care is to ensure that patients, especially the chronically ill, get the right care at the right time, while avoiding unnecessary duplication of services and preventing medical errors. When an ACO succeeds, both in delivering high-quality care and spending healthcare dollars more wisely, it will share in the savings it achieves for the Medicare program.

Shulman then delineated the characteristics of an ACO. Patients participate in an ACO if their primary care physician (PCP) is enrolled in it. Patients are not restricted to seeking care from predetermined providers, although PCPs may try to direct care. Although the payment is fee-for-service, the actual cost is still determined by CMS.

The question remains, though, "What do patients want? Access to treatment for best chance of survival, an improved quality of life, high

Figure. Five-Year Survival Rates in the United States by Year of Diagnosis



Source: Innovation in cancer care and implications for healthy systems: global oncology trend report. IMS Institute for Healthcare Informatics. Published May 2014. Accessed July 11, 2014.

quality of care delivered safely and efficiently, and of course affordable care," said Shulman. Payers are interested in high-quality care, at a reasonable cost, and they want affordable premiums that are acceptable to their clients. The third stakeholder in the equation, the oncologist, wants freedom to provide the best care, fair compensation, and freedom from administrative burdens to be better able to focus on care.

Shulman then said that cancer care is different with regard to ACOs. PCPs manage or co-manage patients with diabetes, heart failure, and other ailments with specialists, and influence the cost of care. But they cede care of the cancer patient to a specialist and so are out of the cost equation. However, PCPs would share the risk and benefit of ACO performance when employed by a hospital or by multi specialty practices.

Blase N. Polite, MD, MPP

The challenges with cost include noninformed decision making. Oncologists are not very good at measuring patient outcomes, managing cost of care, and factoring in cost of treatment during care. Much of what they do daily in the clinic only provides weak evidence to help decide between treatments. "But," emphasized Shulman, "that cost must be factored in when making treatment decisions." Pathways, he said, must include the total cost of care, and the oncologist must carefully evaluate the cost of imaging, the selection of a testing laboratory, and other factors, based on what is absolutely needed.

Shulman's concluding remarks were that pathway developers need to make tough decisions. Partnerships between providers and payers can control costs and improve care. "We should aspire to do these things with the patient in mind," said Shulman. "The current system is not patient centered."

How oncology practices will fit into and interact with ACOs is not very clear yet. Oncology practices should play an active role in the control of cancer care costs to fit into the quality metrics of care.

"Healthcare Reform 101: Summary of the Recent and Planned Changes Related to the Patient Protection and Affordable Care Act" was presented by Blase N. Polite, MD, MPP. Polite, an assistant professor of medicine in the section of hematology/oncology at the University of Chicago and chair of the ASCO Government Relations Committee, offered an overview of the impact of the PPACA on patients and providers.

Polite discussed ASCO's policy on Medicaid expansion, which has been the source of controversy in some states due to the US Supreme Court ruling that upheld ACA but allowed states to opt out of extending Medicaid to Americans in the low-income tier just above the poverty level. ASCO's policy, Polite said, is that "All states should expand their Medicaid program to provide coverage, at least for individuals with incomes below the poverty level, or should come up with an alternate strategy that provides comprehensive subsidized health coverage that ensures, among other benefits, access to high-quality cancer care, measured by cancer-specific quality metrics, delivered by a cancer specialist."

The suggested changes are:

- expand the list of cancer risk syndromes covered
- clarify that follow-up testing should be covered without cost sharing
- clarify that coverage for risk-reducing surgeries is covered

The clinical trial provisions under ACA state that health plans cannot:

- deny an individual participation in a clinical trial
- deny, limit, or impose additional conditions on the individual associated with participation in a trial
- discriminate against the individual for participation in a trial

However, these provisions are not yet backed by strong regulations. They do not apply to Medicaid patients or those covered by "grandfathered" health plans, and they do not allow out-of-network coverage. Polite emphasized that oncologists need to monitor the implementation of these policies by health plans.

Polite concluded by saying that the ACA-implemented provisions are good news for cancer patients overall, although there are a few concerns with regard to coverage and penalties on physicians caring for the poorest and sickest patients. **EBO**

"Oncologists are not very good at measuring patient outcomes, managing cost of care, and factoring in cost of treatment during care. That cost must be factored in when making treatment decisions. Pathways must include the total cost of care, and the oncologist must carefully evaluate the cost."

—Lawrence N. Shulman, MD

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The Oncologist Defines Value of Care

Earlier this year, the American Society of Clinical Oncology (ASCO) brought together the pharmaceutical industry, payers, providers, and patient advocacy groups to initiate a conversation on the challenges of defining value in cancer care. Annual costs in cancer care are escalating with no end in sight; estimated at $125 billion in 2010, treating cancer patients is predicted to cost the United States a staggering $175 billion in 2020.[1] While the cost of newly improved drug molecules and drug delivery systems accounts for a significant part of these totals, several other factors contribute. Quality improvement measures (such as QOPI) and participation in the Choosing Wisely campaign adopted by ASCO can help develop and promote high-quality, evidence-based care.

Healthcare providers play an extremely important role in choosing the right treatment and care option without compromising the quality of care. On the second day of the 50th Annual Meeting of ASCO, "The Value of Cancer Care and the Professional and Ethical Obligations of the Practicing Oncologist: A Debate" delved into the ethical issues raised by the economic reality of the rising costs of cancer care for the practicing oncologist. The presenters discussed the potential conflict between costs and value in cancer care, as well as affordability issues and how they may come into conflict with respecting the patient's individual wishes and needs.

The 3 physicians who participated in this session co-authored an article that was published online by ASCO: Value of Cancer Care: Ethical Considerations for the Practicing Oncologist.[2]

Beverly Moy, MD, MPH, clinical director of the breast oncology program at the Massachusetts General Hospital, Harvard Medical School, opened the discussion with her talk, "'Value' and 'Values' in Cancer Care: Can We Balance Our Duties to Patients and Society?" Moy began with an example of a 32-year-old woman with HER2+ breast cancer without metastatic disease. The dilemma in this case was, in addition to adjuvant chemotherapy and trastuzumab, could she be administered pertuzumab? Pertuzumab is priced at $4890 to $6000 per cycle.

Pertuzumab was granted accelerated approval by the FDA as neoadjuvant therapy for HER2+ early-stage breast cancer; however, there are no data demonstrating improved overall survival or event-free survival. Additionally, no data demonstrating its efficacy in the adjuvant setting are available.

Another example was of a 38-year-old woma, with ALK+ lung cancer. She had stage T2aN1 non-small cell lung cancer (NSCLC) with ALK rearrangement but no metastasis. The dilemma with this patient: Is there a role for crizotinib in the adjuvant setting? Crizotinib, which costs $9200 to $12,000 per month, improves response rate and progression-free survival with ALK rearrangements, but there are no data on adjuvant treatment.

The cost of cancer care is skyrocketing. The National Institutes of Health estimated the total cost for cancer care for the year 2009 at $216.6 billion, and cancer therapy takes up 5% to 11% of the national healthcare budget. Asked Moy, "Where is the major spending? Technology and drugs account for most of the costs, and chemotherapy takes up a major chunk of the drug cost." Moy went on to emphasize that practicing oncologists are the gatekeepers of chemotherapy and patient care, and so in some way are responsible for the cost. Six of the 8 drugs approved by the FDA in 2013 cost $10,000 per month. Alarmingly, most of these failed to show improved survival, and even if they did, the results were modest. "Where's the value? The response to this question will vary based on the stakeholder who's asked. There's no consensus," said Moy.

Moy ended her talk by echoing the thoughts that were expressed in the value session on the first day of the meeting—no consensus has yet been reached in defining value.

"The ethical dilemma arises because the oncologist's duty is split between the patient and the society, and choosing a side is extremely difficult. The cost of this dilemma—patient deprivation of life-saving therapy."

Reshma Jagsi, MD, DPhil

Daniel P. Sulmasy, MD, PhD, professor of medicine and associate director at the MacLean Center for Clinical Medical Ethics at the University of Chicago, took the stage next to discuss "Advocating for the individual patient's good should be the oncologist's priority." His research interests include end-of-life decision making, ethics education, and spirituality in medicine.[3]

As the speaker before him, Sulmasy began the discussion by stating that costs in oncology have spun out of control, and oncologists are responsible for controlling the costs. However, he argued that this cost control cannot be implemented at the patient's bedside. Economics and public policy do not control bedside medicine—it's about treating an individual patient and not the population. In the art of medicine, the individual patient is of interest: "Will this drug be useful to this patient under a particular circumstance?" However, science is concerned with population effects and not an individual patient. Clinical medicine is a blend of both, he said—it involves science directed to an individual patient.

Daniel P. Sulmasy, MD, PhD

"Population medicine cannot be practiced at the bedside. The goal is to improve the life of an individual patient and not the population," said Sulmasy. Medicine has historically been treated as a business. However, given the necessity of access to medicine, it should be considered a public good and not a business. Patients should trust that the physicians are practicing medicine to improve their lives.

The question that arises, therefore, is: How can we control healthcare costs without compromising on quality?

"Bedside rationing and providing financial incentives can threaten the integrity of medicine," said Sulmasy. "They also undermine the patients trust: is the CT scan ordered to increase personal income or do I really need it? Additionally, financial incentives disrupt the balance between the professional, the state, and the market."

In the absence of transparent and universally applicable rules, treatment will become unpredictable and idiosyncratic, and it will not achieve the goals of those who are advocating it.

So the big question is: How can costs be contained in a morally appropriate manner, and what's the oncologists role? "Diagnostic elegance and therapeutic parsimony are the call of the hour. Diagnostic elegance translates into using only those tests necessary to diagnose a patient, while therapeutic parsimony means using adequate treatment, not overtreatment."

The session was wrapped up by Reshma Jagsi, MD, DPhil, associate professor of radiation oncology, University of Michigan. Jagsi's clinical practice and research are focused on breast cancer, but she is also actively involved in social, political, and ethical aspects of medical care. In her talk, "The Oncologist's Duty to Society," Jagsi stated that physicians have a moral duty to society and they have a privileged professional role. They have an obligation to serve not only their individual patient, but also the society in general.

It has been proved that healthcare spending crowds out other spending in social services that are essential to promote health. Additionally, the rising cost of care limits access by limiting the affordability of care. Rationing is no longer an issue of whether, but how. Resources are finite and allocation must happen. "Physicians owe it to society to help ensure that resources are allocated in a way that is congruent with broad moral intuitions, as well as to reduce waste to maximize the value of our interventions," said Jagsi.

She affirmed that physicians must be stewards to lead an evidence-based assessment of value, including studies to identify situations of overdiagnosis and overtreatment in healthcare. Eliminating waste is absolutely essential, and it could be initiated at the level of the easy low-hanging fruit. For example, a shorter course of radiotherapy for preventing bone metastases or for adjuvant treatment of breast cancer. Embracing such an approach could reduce cost and improve outcome as well. Another easy fruit to pick is utilizing cheaper therapy with the same outcomes. Jagsi believes it's not just about financial incentives—oncologists are a little nervous about adopting cost-saving changes when

they lack a clear understanding. An example of a more difficult decision to make would involve a patient who is unlikely to benefit from a treatment with high costs for society, but who demands to be administered the drug. This would create a conflict for the provider, who would have to balance his obligation to society with obligation to his patient.

The Choosing Wisely campaign by the American Board of Internal Medicine is engaging professional societies like ASCO to obtain therapeutic parsimony and diagnostic elegance. ASCO in turn has issued top 5 lists of opportunities to improve the quality and value of care.

Jagsi left the audience with the following words of wisdom from Howard Brody, MD, PhD, director of the Institute for the Medical Humanities:

"The myth that physicians are innocent bystanders merely watching healthcare costs zoom out of control cannot be sustained."

Her own final thoughts were, "We must eliminate the cases of obvious waste, and we must be leaders in engaging our society in public deliberation over what constitutes meaningful benefit and value in healthcare." **EBO**

Beverly Moy, MD, MPH

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Velcade: A Progress Report in Various Cancers

Velcade (bortezomib), developed by Millenium Pharmaceuticals Inc, is a proteasome inhibitor (**Figure**) currently approved for the treatment of multiple myeloma and relapsed mantle cell lymphoma.[1] Several abstracts, presented on May 31, 2014, and June 1, 2014, at the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago set forth data from trials that are under way to evaluate bortezomib for other indications.

Bortezomib and rituximab in the treatment of iNHL[2]

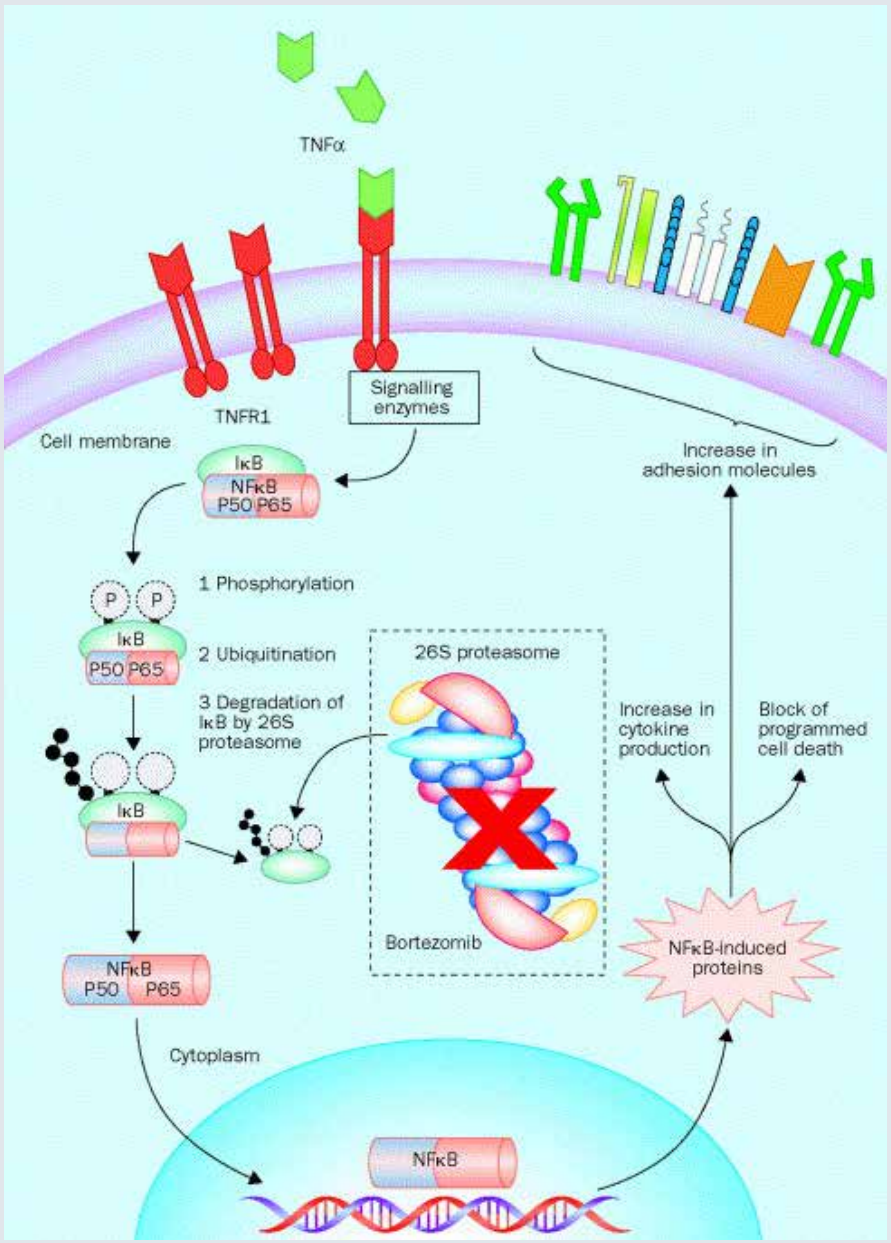
This study, conducted at multiple trial centers and led by clinicians at Northwestern University, Chicago, was designed to assess the tolerability of bortezomib and rituximab in patients with high tumor burden (HTB) non-Hodgkin's lymphoma. Treatment in this multicenter phase 2 study consisted of 3 induction cycles of bortezomib and rituximab, followed by an abbreviated consolidation. All outcomes were analyzed by intent to treat. All 42 patients enrolled in the trial were evaluable. The therapy was well tolerated, with few grade 3/4 toxicities and minimal neurotoxicity. Grade 3 adverse events (AE) included fever, infusion reaction, infection, cardiac, fatigue, diarrhea, hypokalemia, and bowel obstruction; the only grade 4 AEs were neutropenia and thrombocytopenia. Overall response rate (ORR) at the end of therapy was 70%, with a 40% complete remission (CR) rate (follicular lymphoma [FL]: ORR 76%, CR 44%). At a median follow-up of 50 months, 4-year progression-free survival (PFS) was 44%, with 4-year overall survival (OS) of 87% (FL: 44% and 97%, respectively). Interestingly, 4-year OS was superior for FL compared with non-FL histologies (97% vs 43%, respectively, $P = .003$). Altogether, bortezomib/rituximab is a targeted therapeutic regimen that was very well tolerated and resulted in long-term survival rates comparable to prior HTB FL rituximab/chemotherapy series.

Replacing vincristine with bortezomib in R-CHOP regimen in treating mantel cell lymphoma[3]

R-CHOP—rituximab, cyclophosphamide, doxorubicin (Hydroxydaunomycin), vincristine sulfate (Oncovin), prednisone—is standard therapy for newly diagnosed, bone-marrow transplant (BMT)-ineligible mantle cell lymphoma (MCL) patients. Bortezomib is approved in the United States for relapsed MCL. This study, registered as a collaborative trial between Millennium Pharmaceuticals and Johnson & Johnson Pharmaceuticals, evaluated whether replacing vincristine with bortezomib in R-CHOP improves outcomes in newly diagnosed, BMT-ineligible MCL patients. Adults with treatment-naïve, measurable stage 2 through 4 MCL and ECOG PS 0 to 2 were randomized to VR-CAP (velcade, rituximab, cyclophosphamide, doxorubicin, prednisone) or R-CHOP. The primary end point was PFS and secondary end points included time to progression, time to next treatment, OS, response by modified international lymphoma workshop response criteria (LWRC), and safety. Of the 487 patients, 244 were ran-

Replacing vincristine with bortezomib significantly prolonged PFS and consistently improved secondary efficacy end points in newly diagnosed, BMT-ineligible MCL patients, with additional but manageable toxicity.

Figure. Mechanism of Action of the Proteasome Inhibitor Bortezomib



Phosphorylation and degradation of IκB releases NFκB, which then translocates into the nucleus to prevent apoptosis (cell death) and the expression of adhesion molecules that promote cancer cell invasion and metastasis. Bortezomib binds the 26S proteasome, which inhibits degradation of IκB and maintains NFκB in the cytoplasm.

IκB indicates inhibitor of kappaB; NFκB, nuclear factor kappaB; TNFR1, tumor necrosis factor receptor 1; TNFα, tumor necrosis factor α.
Source: Bruno B, Rotta M, Giaccone L, et al. New drugs for treatment of multiple myeloma. *Lancet Oncol*. 2004;5(7):430-442.

domized to the R-CHOP arm and 244 to the VR-CAP arm, and were administered a median of 6 cycles. After 40 months median follow-up (298 PFS events), median PFS was 14.4 months (R-CHOP) vs 24.7 months (VR-CAP). Rates of grade 3 or higher AEs were 85% (R-CHOP) versus 93% (VR-CAP), serious AEs were 30% versus 38%, discontinuations due to AEs 7% versus 9%, and on-treatment drug-related deaths 3% versus 2%. This trial showed that VR-CAP significantly prolonged PFS and consistently improved secondary efficacy end points versus R-CHOP in newly diagnosed, BMT-ineligible MCL patients, with additional but manageable toxicity.

Phase 3 trial for myeloma comparing different iMiDs[4]

Treatment with immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) has dramatically increased response rates and survival for myeloma patients over the last decade, with triple drug combinations proving more effective than double or single agents. This trial, Myeloma XI—a collaborative study between the University of Leeds, Celgene Corportation, and Merck Sharp and Dohme Corporation—was a phase 3 randomized trial for newly diagnosed patients of all ages, which compared induction treatment with cyclophosphamide/lenalidomide/dexamethasone (CRD) to cyclophosphamide/thalidomide/dexamethasone (CTD), given to maximum response or intolerance. To evaluate the role of pretransplant consolidation with a proteasome inhibitor, patients achieving less than a very good partial response (VGPR) were randomized to additional cyclophosphamide/bortezomib/dexamethasone (CVD) versus no treatment. Fit patients went on to receive melphalan + autologous stem cell transplant. Of the 1939 patients analyzed, 1104 were on the intensive pathway arm (540 CRD vs 564 CTD) and 835 were on the nonintensive arm (411 CRDa vs 424 CTDa); 274 patients received additional bortezomib. The preplanned intent-to-treat analysis of combined CR+VGPR rates presented a significant difference between CRD and CTD treatment on multivariate analysis in favor of CRD, with odds ratio of 1.27 (95% CI 1.06-1.52, P = .009). Additional bortezomib therapy—for those with a suboptimal response—upgraded response in 51% of the patients, demonstrating that PI therapy can be effective in patients intrinsically resistant to IMiDs. Treatment with both IMiDs was well tolerated. The trial demonstrated an important difference in response between the IMiDs thalidomide, and lenalidomide; however, further follow-up is required to see whether this translates into prolonged PFS and OS. **EBO**

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Overdiagnosis and Overtreatment: The Cancer Paradigm

Some experts argue that overdiagnosis (OD) and overtreatment (OT) of cancer is common and increasingly costly. Others argue that current cure rates are high because of the screening processes that are in place. Both viewpoints were debated during the session "Overdiagnosis and Overtreatment in Cancer: Point/Counterpoint," conducted on June 1, 2014, the third day of the annual meeting of the American Society of Clinical Oncology (ASCO) held in Chicago.

"Cancer overdiagnosis and overtreatment, or appropriate attention to early disease?" was the question posed by Barbara L. Smith, MD, PhD, director of the breast program at Massachusetts General Hospital, codirector of the Gillette Center for Women's Cancers, and associate professor of surgery at Harvard Medical School. So far, the goals of cancer care have been minimizing mortality, prolonging life, reducing morbidity of treatment, preventing primary cancers, and providing access to quality care for all. Of late, the discussion has widened to include cost effectiveness and avoiding excess treatment.

"For several years now, death rates from cancer have seen a dip and cancer incidence rates have plateaued—an indicator that the strategy is working. The cornerstones of success of modern care include earlier detection, improved treatments (multimodality care op-

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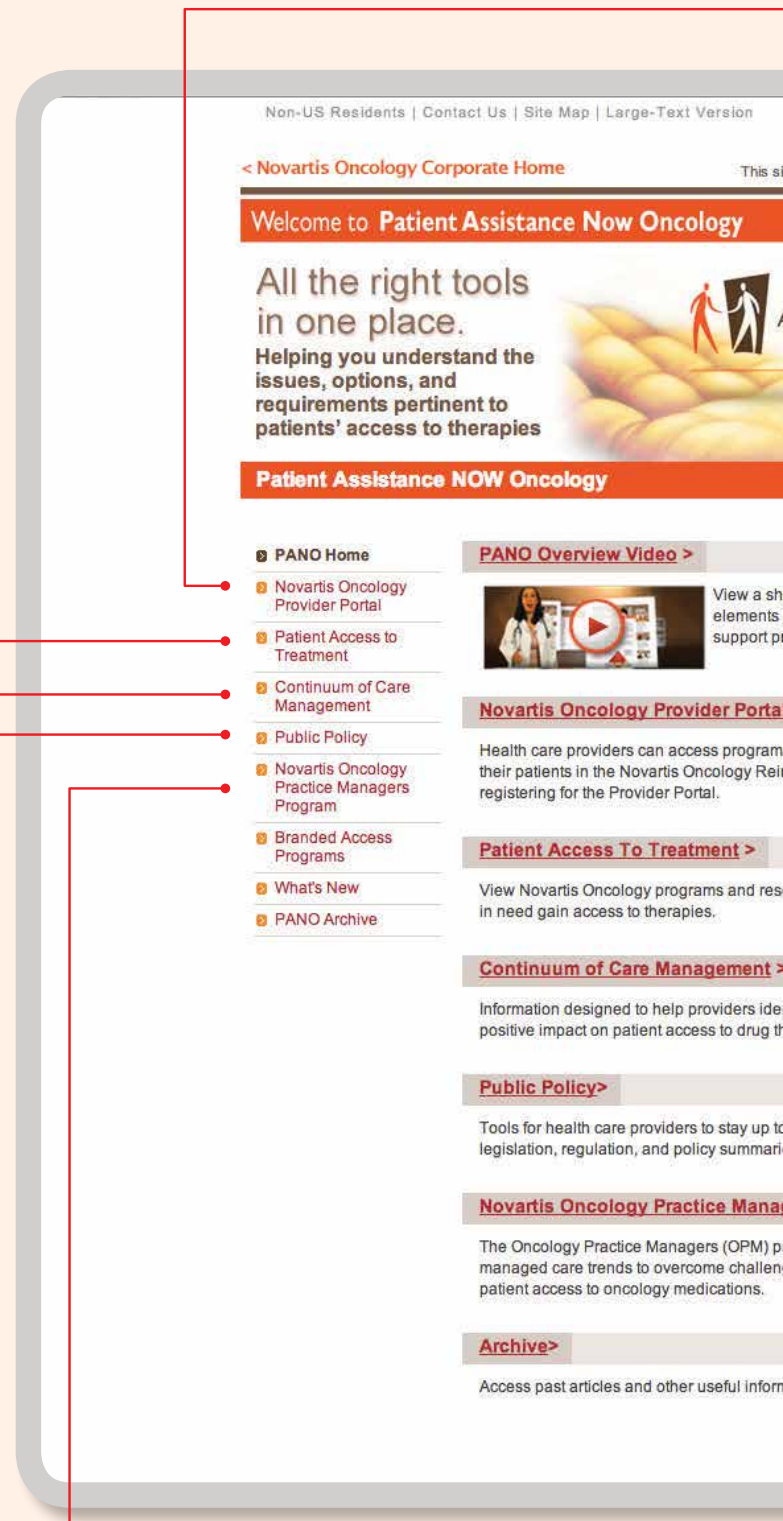

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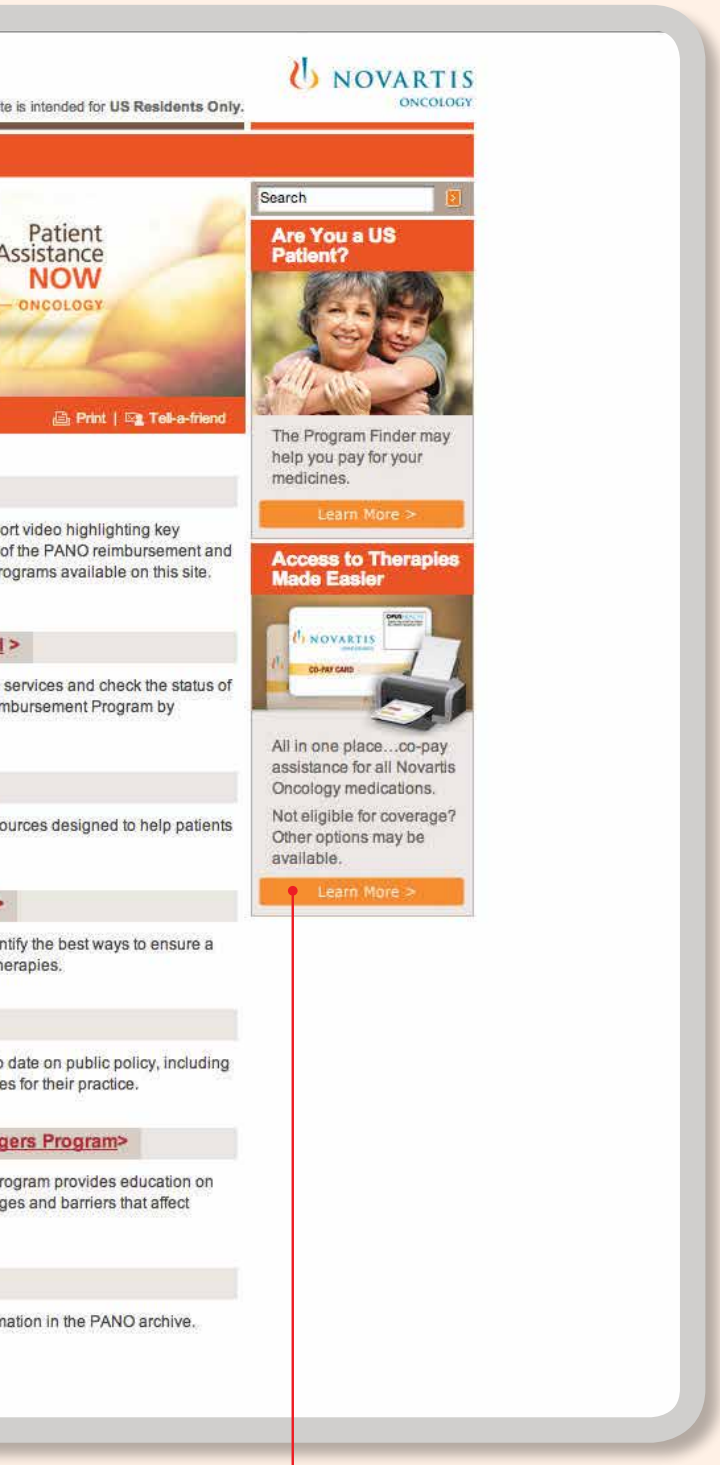

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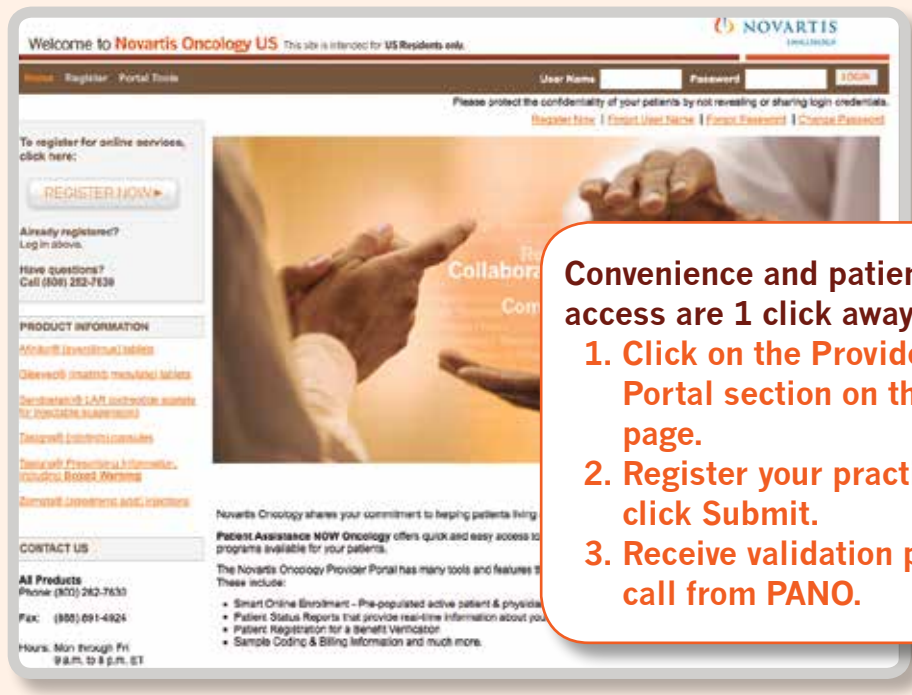

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tions), a combination of early detection and better treatment, and also improvement in overall population health. Healthier patients can work through the toughest treatments," said Smith.


Barbara L. Smith, MD, PhD

Smith questioned whether diminishing returns could be resulting in overkill. "Are cancer patients being administered more treatment than needed?" More importantly, can comparable success be achieved with lighter treatment?

She provided an example of the increasing use of bilateral mastectomy in early-stage breast cancer. The numbers were at 3% back in 1998 but are up to 18% in 2007. The question to pose: Is it necessary? Patients want the procedure for peace of mind—to reduce their chances of recurrence. But what about the oncologist?

This is a challenge being discussed across a spectrum of disease states such as hypertension and cholesterol. Some of the questions that oncologists need to ask include:

- What is the optimal way to screen (sensitivity/specificity goals, cost, and limitations of diagnostic technologies)?
- What should the threshold for treatment be?
- What are the morbidity and mortality goals?

An ideal example is that of the recent debate about using the Papanicolaou (Pap) test cytology versus human papillomavirus (HPV) DNA testing. Pap has proved successful in reducing cervical mortality, but the role of HPV in disease has been recognized, and recently the cobas test was approved as a primary HPV screen.

The sensitivity of the screening is ideal—the problem lies in the fact that 10% of patients who are Pap-positive have precancerous lesions, but some cancers are HPV-negative. Additionally, there may be cancer-independent transient HPV infections that could result in false-positive results. Only 10% of women with high-risk HPV develop persistent infection. The result: unnecessary colposcopies and biopsies following HPV testing.

However, a recent study showed that patients are the ones who want screening and would even overrule their physician in wanting to be screened.

Can improved treatment reduce the need for screening? Not yet, said Smith. We still cannot reliably distinguish between patients with indolent and aggressive cancer. "Cost is the elephant in the room—an unsustainable and sensitive topic that comes up with death panels, rationing, etc," she said.

The other elephant in the room is liability for malpractice. Delays in diagnosis are common claims in malpractice lawsuits, and variations in guidelines (eg, annual vs biennial screening for breast cancer) can increase a physician's exposure to such litigations.

What will it take to change practice? A change in physician perspective and a change in patient expectations may be the answer. Additionally, cost constraints need to be modified, guidelines need to be standardized, and medicolegal issues need to be addressed.

Smith concluded by saying that implementing small changes can lead to the bigger goals of:

- stretching screening intervals
- tweaking thresholds for intervention
- reducing cost of treatment

"Cost is the elephant in the room—an unsustainable and sensitive topic that comes up with death panels, rationing, etc. The other elephant in the room is liability for malpractice. Delays in diagnosis are common claims in malpractice lawsuits, and variations in guidelines can increase a physician's exposure to such litigations."

—Barbara L. Smith, MD, PhD

Rinaa S. Punglia, MD, MPH, associate professor, Department of Radiation Oncology, Harvard Medical School, presented "The Case Against Overdiagnosis and Overtreatment of Cancer."


Rina S. Punglia, MD, MPH

OD/OT are inherent in breast cancer screening, and OD is central to the mammography debate in breast cancer. "OD usually leads to OT. A treatment does not necessarily alter outcomes," said Punglia.

The solution to this problem, she believes, lies in informed decision making (IDM), which is made possible by opening a dialogue. Decision to screen can lead to false positives, but also to early diagnosis and improved outcomes. IDM can be used to reduce OT.

For example, ductal carcinoma in situ (DCIS) has historically been treated with mastectomy, but that approach may be too drastic. Today, patients undergo breast preservation surgery, which can leave patients at risk for a second breast event in the preserved breast, but can be followed with radiation therapy (RT). Meaningful outcomes for a patient after RT include recurrence, treatment of recurrence, and breast preservation. However, on the downside, RT can be expensive.

So how does one decide if a patient receives RT? DCIS overestimates a patient's risk of recurdrence, and making a decision is difficult for patients. Therefore, individual decision making is key—lay the options down and help patients make the right choice. Punglia shared knowledge on a decision-making tool being actively used at Dana-Farber (www.onlineDeCISion.org), which helps patients and providers alike.

The final viewpoint in this debate, "The Case for Overdiagnosis and Overtreatment of Cancer," was presented by Laura Esserman, MD, MBA, director, Carol Franc Buck Breast Care Center; and coleader, breast oncology program, UCSF Helen Diller Family Comprehensive Cancer Center.

In March 2012, the National Cancer Institute convened a workshop to generate ideas for a research agenda around OD. According to Esserman, a critical shift in philosophy is needed to explain that the previous approach of OD saves lives.

The old paradigm of cancer was of inexorable progression—or of every patient having the same rate of disease progression. That has changed, and we know today that it is far from true. Oncologists recognize that there is variable progression in patients and that there are IDLE (indolent lesions of epithelial origin) lesions that may not affect mortality. Therefore, understanding the biology of the cancer is extremely important.

Although the spectrum of disease has been realized and understood, the definition of cancer has not evolved. If a patient thinks "cancer," they think they will die if they are not treated.

"A very important question is: what do you know, when do you know, and how do you act on what you know?" said Esserman.

The need of the time is a new approach to cancer treatment rather than arguments on 30-year-old guidelines, Esserman emphasized. However, it is extremely important to understand outcomes before changing guidelines. "Increased detection saves lives" is way too simple: the concept is much more complex, she said.

Recognizing and gaining an improved understanding of IDLE disease is important said Esserman—for example, does a tumor with little potential for metastasis and with little chance of progression or death require aggressive treatment? "IDLE tumor gene signatures could help define ultra-low–risk tumors. This could be validated in various cohorts and used to stratify patients with high- and low-risk tumors," according to Esserman.

Esserman closed her argument by recommending that a better-tailored definition replace the word "cancer," companion diagnostics be coupled with treatment, and observational registries be created to identify IDLE disease. **EBO**

The Global Perspective on Value in Cancer Care

On June 1, 2014, the penultimate day of the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO), the discussion on value in cancer care was rekindled, but this time on a global scale. The session, "ASCO/European CanCer Organisation (ECCO) Joint Session: Value and Cancer Care," saw participation from physicians and economists from around the world, with individual perspectives on defining value and the programs being developed to address the issue. Regulatory approval does not guarantee patient access to efficient therapies. So where lies the problem?

Elisabeth De Vries, MD, PhD

The first talk was "ESMO-EONS: Value and the Exchange Between Physicians, Nurses, and Patients" by Elisabeth De Vries, MD, PhD, University Medical Center Groningen, Netherlands, a member of the Magnitude of Clinical Benefit Scale task force.

De Vries began with an overview on cancer drug use in Europe, and discussed how the cancer drug development process is influenced by the European Society for Medical Oncology (ESMO).

Similar to what has been demonstrated in the United States, the 5-year relative cancer survival rate in Europe increased between 1999 and 2007. However, the cost of treatment is only burgeoning.

So what is the relevance of the cost of cancer drugs? Using imatinib as an example, De Vries presented a pricing plot that showed that the drug costs the most in the United States, but costs substantially less in Europe and other countries elsewhere around the globe.

She went on to state that there are differences in access to relevantly new anticancer drugs in Europe–differences in price, differences in healthcare costs, and differences in time to access following approval by the European Medicines Agency (EMA). These disparities are associated with various issues, one of which is the cost of the drug and reimbursement.

Among European nations, a 1.8-fold difference in the cost of trastuzumab has been identified. Additionally, a difference in time to availability after EMA approval has been observed. The bottom line: the lack of timely access to anticancer drugs can result in major disparities in cancer outcomes.

With the hope of standardizing policies and easing patient access to novel treatments, ESMO is developing the Magnitude of Clinical Benefit Scale. How will the scale be used? EMA-approved drugs will be scaled by the task force, and drugs with the highest value will then be promoted.

Various factors that contribute to the scale include quality of life (QOL), overall survival (OS), progression-free survival (PFS), prognosis of condition, toxicity, hazard ratio, long-term survival, and rate of response. These factors will be used to determine the magnitude of clinical benefit. "We did not factor costs into the equation due to the heterogeneity that exists across Europe," clarified De Vries. "We believe the ESMO scale will be constantly evolving with the availability of increasing efficacy and toxicity data as the treatment is used by the wider population."

The scales, she noted, are distinct for curative versus palliative settings. PFS, for example, can never qualify for a grade 4 score as a primary end point, but could be a secondary end point to be considered concurrent with OS, toxicity, and QOL.

The major heterogeneity in drug price and access across Europe can result in inequality in optimal care. The ESMO scale grades drugs to determine the ideal drugs that should be immediately accessible to patients across Europe.[1] The task force plans to develop and further mature this grading scale by collaborating with sister societies to generate as much data as possible to improve patient access.

Richard Sullivan, MD, PhD

Next on the panel was Richard Sullivan, MD, PhD, Kings Health Partners Integrated Cancer Centre, London, England, who discussed "Cancer Care in Cost-Restrained Healthcare Systems." Sullivan, who is also a part of the team that is developing the ESMO scale, conducts a research program whose focus extends from the sociopolitical policy of global cancer (OncoPolicy) to the development of public health systems in high-risk conflict areas focusing on DR Congo, Afghanistan, and Libya. In OncoPolicy, he recently led the first major Lancet Oncology Commission that examined the affordability of cancer in high-income countries.[2]

"All healthcare systems are struggling to deliver affordable and equitable cancer care," said Sullivan. Cancer care operates as a complex adaptive system, and unlike other normal systems:

- it is non-linear, dynamic, and can even appear chaotic;
- individuals who comprise the system behave according to social and structural norms rather than the needs of the system;
- goals and behaviors are often in conflict; and
- there is no single point of control.

"Our global economic systems have become 'addicted' to the returns generated by cancer care and treatment," pointed out Sullivan. Income equality is worsening globally, and we need to gain a better handle on value and equitability. Research has shown that three-fifths of the global population has less than 5% of global wealth. How can that provide equitable cancer care?

Additionally, the cancer research portfolio is extremely narrow when it comes to drug discovery and fundamental biology. The sheer volumes and pace of outputs is outstripping the ability of policy makers. "It's harder to make cost-effective and rational decisions to provide or make available efficient therapy to the population as a whole," said Sullivan.

Cancer care systems are framed by behaviors and cultures that are not coterminous with affordability and equity. Patients can have very high expectations from their cancer treatment. Therefore, "How we frame the debate becomes as important as the content of the debate," proclaimed Sullivan.

Identifying sites for fiscal controls and sustainability mechanisms is an uphill battle, and recognizing problem areas to adapt cost-effectiveness is very hard. This is even more difficult in developing nations like India, where 67% of out-of-pocket expenditure with financial hardship and 21% catastrophic expenditure has been documented with cancer care, according to Sullivan.

Most of our societies are reaching limits on affordability or what we are willing to pay. How do we then get value-based pricing?

Balancing costs and benefits with toxicity of new technologies needs consideration. New, extremely efficient drugs (such as the developing immunooncology molecules) could be the stepping stone in this setting.

"Value-based pricing without universality or universal healthcare does not work," concluded Sullivan. "Reform can never stop, as exogenous factors emerge and societal demands and values change."

The final presentation in the session, by Lowell E. Schnipper, MD, Beth Israel Deaconess Medical Center, discussed "American Perspective on Globally Defining Value in Cancer Care."

The United States spends a lot more on healthcare than a lot of European nations, and the data are spotty.

"Why do we emphasize value?" asked Schnipper.

Drug price is a part of the high cost of cancer care, but not the only problem by any means. Outside the United States, clinical aspects are used for assessment first, and then the results are applied for price negotiation.

He reiterated that the physician has an active role to play in value determination and cost regulation, and ASCO is making efforts to help define value in cancer care with the long-term goal of integrating these suggestions in the clinic.

His final thoughts were that the value model must also be adaptable for early disease settings, which is ongoing.

The closing remarks were provided by Clifford Hudis, MD, Memorial Sloan Kettering, and the immediate past president of ASCO. "We are entirely dependent on industry for both innovation and cash flow. But we want to develop a dialogue and generate communication when it comes to drug costs." **EBO**

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Clinical Pathway Adherence and Barriers to Coverage

The health services research poster session held in the afternoon on June 1, 2014, the penultimate day of the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, presented varying perspectives on issues that determine patient care decisions. This is an important discussion, especially in light of the recent report by *The Wall Street Journal* on WellPoint's effort to promote oncologist adherence to standardized treatment guidelines.[1] WellPoint has begun its initiative to offer oncologists a $350 per month payment for every patient who is on 1 of the insurer's recommended regimens.

1. Cancer cost evaluation in chemotherapy-naïve patients treated under a payer-sponsored pathway program[2]

With the cost of cancer care in the United States projected to exceed $173 billion by 2020, clinical pathways can help curb spending by reducing unnecessary and costly treatment variations while improving patient outcomes. Cardinal Health Specialty Solutions evaluated cost savings of a payer-sponsored pathway program for patients with cancer receiving their first chemotherapy intervention. A large payer for the Mid-Atlantic region of the United States collaborated with its community oncology provider network to create a 3-year pathway program, managed by Cardinal Health, for chemo-naïve patients with breast cancer (BC), colorectal cancer (CRC), and lung cancer. All drug costs were standardized to average sales price effective in the last quarter of the program year, and participating physicians received financial incentives. The study included a total of 453 patients, and savings relative to projected cost per patient, per year for pathway cohorts were $21,106 for CRC and $2964 for lung cancer. For BC, the cost increased by $9271. Overall mean cost per patient, adjusted for trastuzumab use (29% study vs 21% control), decreased 5% ($1698 per patient per year) for an aggregate savings of $750,436. The study concluded that voluntary pathway participation can lower drug cost of common malignancies even in first-line treatment. The approach of limiting pathway inclusion to chemotherapy-naïve patients will provide the greatest clarity of pathway impact throughout the duration of illness.

2. Barriers to insurance coverage of next-generation tumor sequencing by US payers[3]

Next-generation tumor sequencing (NGTS) panels are increasingly being used in the clinical setting, but are not formally covered by payers in the United States. Lack of consistent coverage policy may impact access and adoption. The current study aimed to identify considerations used by payers for NGTS coverage decisions. Semistructured interviews with senior executives of 7 large national and 3 regional plans in the United States, covering more than 125 million members, found that most payers (80%) believe NGTS has a potential to transform cancer care, but all (100%) report barriers to coverage. The current policy stems from the lack of exhaustive data validation. (1) 70% of payers wanted evidence for 1 target and 1 cancer type at a time, rather than a bundle. (2) 80% of payers may predicate coverage policy for NGTS based on the validity of included targets, and also on outcomes from therapies informed by NGTS, with 30% requiring phase 3 evidence for each new marker/drug indication. (3) 70% of payers wanted additional clarification and increased evidence that NGTS is "medically necessary" and not "experimental or investigational." Therefore, payers may not cover panels that include novel targets. (4) Payers cite challenges in assessing accuracy and value of bioinformatics required to implement NGTS. Nearly three-fourths of payers did not believe that bioinformatics should be reimbursed. Based on this study, the authors concluded that NGTS does not fit the current payer coverage and evidence framework and thus faces potential barriers to access. The entry of this rapidly evolving technology into clinical practice requires ongoing dialogue among payers, providers, and policy makers to develop an innovative road map to coverage and reimbursement.

The study (by Cardinal Health) concluded that voluntary pathway participation can lower drug cost of common malignancies even in first-line treatment. The approach of limiting pathway inclusion to chemo-naïve patients will provide the greatest clarity of pathway impact throughout the duration of illness.

3. Enhancing pathway adherence in a quality initiative for breast cancer[4]

The H. Lee Moffitt Cancer Center and Research Institute (MCC) in Tampa, Florida, has developed and implemented clinical pathways across disease-focused programs. This collaborative study between MCC and QURE Healthcare performed a series of measurements of adherence to evidence-based clinical pathways, which included subsequent educational feedback on performance. Using Clinical Performance and Value (CPV) vignettes, a validated in-silico simulation measurement tool, they evaluated breast cancer (BC) clinical pathway adherence every 4 months. Eighteen providers completed 2 BC cases each, at months 1, 5, and 9. Clinicians received confidential individualized feedback for each case, with quantitative feedback benchmarked to their peers and qualitative individual feedback with suggestions on how they could improve pathway adherence. Baseline measurement revealed wide variance levels of adherence to pathways across the clinician cohort. With serial measurement and feedback, mean computer percentage value scores increased significantly from 55.4% at round 1 to 68.8% at round 3 ($P < .01$). Particularly, chemotherapy pathway compliance increased from 40% to 65%, appropriate diagnostic work from 31% to 93%, and surgery pathway compliance from 69% to 86%. The authors concluded that adherence to clinical pathways can be improved with a serial measurement and feedback tool. Future studies are planned to link these changes to utilization and costs. Consistent feedback at the individual and group level engages and aligns providers around pathways and common practice standards. **EBO**

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THE AMERICAN JOURNAL OF MANAGED CARE®

Achieving Value in Cancer Care—the Case of Low- and Middle-Income Countries

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By the year 2030, the number of new cancer cases worldwide is projected to rise to 21.3 million annually, up from the estimated 12.7 million cancer cases currently diagnosed.[1] Of the 21.3 million new cases every year, approximately 70% will be from low- and middle-income countries (LMICs), many of which lack the healthcare programs required to effectively manage their current cancer burden, much less that predicted for 2030.[2,3] Moreover, the ratio of mortality to incidence will continue to be significantly higher in LMICs (64% to 75%) than in high-income countries (46%).[4]

A significant feature of the demographic transition in LMIC countries is the change in disease epidemiology; the result is a dual burden of cancer in the presence of communicable and noncommunicable diseases.[5] A consequence of infectious diseases as well as westernized lifestyles, this "cancer transition" has contributed to a higher average burden of cancer (in terms of disability-adjusted life-years [DALYs] lost) in these low-resource settings compared with high-resource regions.[2] This is largely due to premature mortality (years of life lost), which stems from advanced disease at presentation and variable access to cancer care.[6,7]

Improvements in prevention, screening, early diagnosis, and treatment have led to reductions in mortality from cancer in high-income countries, following significant economic investment. However, many countries have reached a plateau, with increased financial investment no longer an assurance of improved outcomes.[8,9]

Richard Sullivan, MD, PhD

In LMICs, the costs of managing such chronic health issues and their risk factors are stretching the already fragile health services infrastructure, or, in many cases, generating a catastrophic impact on health costs and personal finances.[10,11] Many health programs focus solely on communicable diseases through vertical interventions, with little strategic planning for chronic diseases. Cancer treatment in particular is highly challenging and quite distinct from all other service provision planning. The lack of coordination between the plethora of public and private institutions, as well as uncontrolled private enterprise, has contributed to wastage of healthcare resources, gaps in coverage, and wide variations in quality as a result of varying modalities of financing, affiliation, and healthcare delivery.[12]

How Can We Achieve Value in the Management of Cancer?

Research

Despite the burden of cancer in LMICs, only a fraction (2.7%) of global sector investment in cancer research is spent on R&D directly relevant to LMICs.[13] Research efforts should be focused to meet the unique challenges of cancer care in LMICs and should enable cost-effective treatment pathways with highly significant outcomes.[14] This is not just about creativity—rather, greater emphasis must be placed on achieving equivalent or superior outcomes using prevailing treatments and technology, intermittently or for shorter duration. This will include practices of care that encourage shorter in-patient stays and less extensive use of expensive cancer medicines. LMIC countries need to be encouraged to choose a leadership role in value-based research, but currently, the economic incentives for this are limited, especially where fee-for-service financing of healthcare predominates. With regard to radiation technologies, brachytherapy, hypofractionated radiotherapy (reduced number of treatment sessions whilst maintaining effective dose), and combination therapy (with chemotherapy agents) provide potentially cost-effective options for radical treatment and palliation.[15-17]

Prevention

LMICs cannot sustain pursuing a high-income –country model of cancer management. Their priority should instead be prevention and adequate financing of public systems. Public health campaigns need to focus on prevalent risk factors such as obesity, sedentary lifestyles, and smoking. Taxation has been advocated as an integral component of antitobacco policy,[18] and food advertising regulation, school-based educational initiatives, and pricing policies on foods have all been considered as ways to tackle obesity.[19]

Infectious agents such as *Helicobacter pylori,* human papilloma virus, and hepatitis B virus are mediators of gastric cancer, cervical cancer, and hepatocellular carcinoma, respectively.[20] These cancers require multimodality management, including radiotherapy, surgery, and chemotherapy. Although expensive, the diseases are potentially preventable through modulation of the causative agent. Vaccinations have been developed for the human papilloma virus, which can significantly reduce the risk of developing a malignancy,[21] and are being rolled out in LMICs such as Rwanda.[22] However, primary prevention with vaccination or screening programs will not necessarily be cost-effective in all countries. Instead, programs such as visual inspection with acetic acid for cervical cancer can prove cost-effective in the diagnosis of early-stage cancers.[23]

Funding of Healthcare

The structure of the healthcare system will have a direct impact on the ability of individuals and their families to access healthcare, and can potentially widen inequities in outcomes. Inability to pay for specialist diagnostic and treatment services can result in late presentation, diagnosis, and inadequate treatment for cancer care.[24,25] It can also lead to catastrophic or impoverishing health expenditures due to a lack of financial protection afforded by the healthcare system.[26] Families may sacrifice expenditure on basic necessities such as food and housing to finance care for chronic disease. Therefore, universal healthcare coverage is essential for ensuring that vulnerable populations are protected from the financial cost of ill health, and the fee for treatment should be determined based on their ability to pay rather than the risk of ill health. However, out-of-pocket payments remain high in many LMICs.[27] Countries such as Mexico have introduced social insurance schemes to ensure risk pooling and protect from the destabilizing effects and financial implications of ill health, and Mexico is considered a model for other LMICs, especially in the face of the epidemiological transition.[28]

Avoiding the Zero-Sum Game

It is essential, given the competing healthcare demands resulting from the epidemiological transition in LMICs, to avoid a zero-sum game (where the loss equals the gain). Management of communicable diseases such as HIV/AIDS and malaria have focused on vertical interventions.[29-31] However, research into biomedical and behavioral interventions show that no single strategy is effective and that what is required is a compre-

hensive, multilevel, intersectoral, and culturally sensitive series of interventions that engages both the general population and groups at elevated risk.[32]

Interventions acting on structural factors would provide a horizontal integrated approach. If coordinated effectively and focused on issues such as education, employment, poverty, and healthcare access, these interventions could reduce the incidence and facilitate the effective management of cancer as well as reduce the incidence of other debilitating diseases, contributing to an improvement in overall population health and the achievement of Millennium Development Goals.[13,33,34]

The Institute of Medicine states, "Cancer is such a prevalent set of conditions and so costly, it magnifies what we know to be true about the totality of the healthcare system. It exposes all of its strengths and weaknesses."[35] While this is true, a horizontal approach takes into account the social determinants of health, which has roots in the economic, political, legal, and cultural environment of a country.[36,37] The impact of these factors in predisposing populations to risk of disease and outcomes from cancer care is as important as the strengthening of health services.

Manpower

Manpower shortages result in long waiting times, inequities in access, and elevated healthcare costs.[4,38] The western model has largely focused on oncologists being split into 2 categories: medical oncologists, responsible for delivery of systemic anticancer therapies, and radiation oncologists, who deliver radiation therapies, including brachytherapy. Given the shortage of specialty oncologists in LMICs, greater consideration should be given to clinical oncology specialization in LMICs to address these shortages. Clinical oncologists are trained to deliver both systemic and radiation therapies. This is particularly relevant in LMICs, where the disease burden with higher rates of cervical, oesophageal, and prostate cancer necessitates multimodality treatment.[39-41] A dual-training approach provides a flexible workforce, reduces the number of consultations an individual requires, and potentially ensures greater efficiency in resource consumption. There is also an urgent need to address the chronic shortage and up-skilling of surgeons to tackle cancer.[42,43] In many LMICs, cancer specialization will not be cost-effective and new general cancer surgical training models will need to be implemented.

Conclusion

To conclude, value-based strategies are essential in LMICs to develop efficient, sustainable cancer care programs to meet the projected rise in cancer incidence. A high-income country model is not feasible or appropriate in LMICs. However, through an appreciation of the structural factors which predispose and potentiate cancer—as well as affect access, quality, and affordability of cancer care—high-value, cost-effective strategies can be developed. Critically, most LMICs do not have sufficient funds allocated to develop basic cancer care systems or to develop and implement models that would avoid high patient expenditures. Additionally, LMICs should assign funds to adequately compensate cancer healthcare professionals in the public sector. **EBO**

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In Conversation With ASCO President Peter Paul Yu

Produced by Nicole Beagin

On August 13, 2014, Peter P. Yu, MD, FASCO, the 2014–2015 president of the American Society of Clinical Oncology (ASCO), sat down with *The American Journal of Managed Care* at their headquarters in Alexandria, VA, to discuss some of the "value" prospects that ASCO has brought to the table when discussing cancer care.

Peter Paul Yu, MD

American Journal of Managed Care: **How is ASCO defining value in cancer care?**

Peter Yu, MD: "Value" is important to talk about in cancer care as it feeds into concerns regarding both the sustainability of and access to cancer care. ASCO's initial framework for evaluating value in oncology is defined by three key components: clinical benefit, toxicity, and cost.

American Journal of Managed Care: **How is ASCO helping both providers and patients navigate today's changing healthcare landscape?**

Dr Yu: The cancer patient is bombarded during a time of high emotional stress. There are a lot of discussions occurring within a short period of time—treatment options, side effects to anticipate, prognosis, etc. Layering it with a discussion of cost of care makes it even harder on the patient. Yet if these conversations with the provider do not happen before treatment begins, patients will surely realize the cost burden after the fact: the cost of care, the co-pays, and the unaffordability of it all. This can impact the success of therapies, compliance, and other issues. ASCO is endeavoring to develop a framework that can form the basis to initiate the value discussion. The approach is to look at different kinds of cancer treatments, assess their clinical benefit in terms of quality of life and survival, the economic cost, and the toxicity cost, in a way that can be compared with alternative treatments. This can help compare different regimens on a relative basis without trying to rank-order treatment, based on a single value judgment. We want to establish a basis to conduct a discussion on choosing treatment options, not to restrict patient or physician choice. Outlooks, of course, will vary—for some patients, certain side effects may be intolerable, while others may accept any degree of side effects as long as there is a significant survival benefit. So it's not possible to state a single right answer for every patient—that's for the doctor and the patient to decide together. But if we can provide a basis for having a consistent discussion across patients and providers, it'd be a significant benefit.

American Journal of Managed Care: **Can you elaborate on the Choosing Wisely campaign and the role that ASCO seeks to play?**

Dr Yu: It's the first part of a broader effort across the house of medicine to discourage use of therapies or diagnostic tests that have no proven value. This is an effort across medicine to foster a culture for doctors to evaluate the downstream consequences of the things we order. A generation ago, most oncologists ignored the broader considerations of treatment decisions; they did not believe it to be their responsibility. They thought, "My job as a patients advocate is to do everything I can to have the patient survive a day longer—end of story. Anything else is not my responsibility." They also believed it was unethical for a physician to consider both financial and clinical toxicity cost." However, with medical events triggering a quarter of US personal bankruptcies, most physicians today recognize that it's their responsibility to discuss the relative value of the treatments that they are recommending to their patients. We would like to instill a sense that we need to be mindful of this conversation.

American Journal of Managed Care: **Can you provide us an overview of CancerLinQ?**

Dr Yu: We are rapidly moving to a world of digital heath. All aspects of our lives are captured electronically in a way that can speed communication, enhance coordination of care and allow discovery of patterns of care that can speak to quality and best outcomes. It's often hard to gauge correlation from a small patient sample—the disease is complex as is the patient, and a small sample size will have a lot of bias. Physicians are often biased from personal experience as well. However, when we aggregate results from across thousands of patients, we can gain insights or trends on patterns that may not be visible from a smaller number of patients or an individual doctor's experience. Consider the example of side effects or toxicities. When the FDA approves a drug, there's been a solid evidence-base to the decision which is founded on clinical trial data. Post-approval, patient exposure now increases by a 1000-fold and you could learn things that were perhaps missed in smaller trials. CancerLinQ will allow us to amass, aggregate and analyze data and learn from it. This information, when returned to the doctor at point-of-care, will allow physicians to make choices based on rapidly available information that can improve treatment decisions.

American Journal of Managed Care: **Were there any barriers with CancerLinQ? How does ASCO plan to take stewardship of the information?**

Dr Yu: There are a lot of issues in all aspects of modern life—electronic data, security, identity theft, etc., which we hear about in the press all the time. Add on top of that our special sensitivity to, and need for, privacy of data in healthcare. HIPAA is a set of laws governing the use and distribution, as well as obligations for privacy and security around, personal health data. However the greatest barrier to overcome is resistance to sharing data. Both the economic and the learning benefit of health data are more fully realized when we share our data sets and make them available. ASCO has set up a data governance structure to ensure that patient data is secure and that data analytics are performed only in de-identified data sets by ASCO staff. Raw data are not released.

American Journal of Managed Care: **Could you discuss some of the cost barriers of cancer therapies.**

Dr Yu: We feel cost should be linked to the value. Common sense dictates that when something is more valuable, we pay more for it and vice versa. But costs of drugs and pricing of new therapeutics in the market don't necessarily have any bearing to actual clinical benefit. ASCO believes we need to tie clinical benefit, toxicity and cost together in terms of defining value. It is the basis of our value-framework to determine the true value of a therapeutic. ASCO, of course, will not participate in pricing decisions, but if a doctor and a patient feel that a drug has high value in that patient's case, they'll use it even if expensive. However, if they decide that there's another regimen that's equally effective but less costly, the discussion should entail using the less costly drug.

We are also looking at clinically-meaningful benefit for new therapies. ASCO's March policy statement addressed what constitutes a meaningful benefit in survival in the opinion of four expert panels that evaluated the treatment of diseases such as triple-negative breast cancer and pancreatic cancer. Starting by defining what current standard of care treatments deliver in improved survival, the panel debated what improvement in survival beyond this would be considered a meaningful step forward. Estimates ranged from 2 to 6 months based on baseline treatment and 20% or more in actual survival improvement. The objective was not about providing recommendations to the FDA for approval; rather, it was to raise the bar and expectations that clinical research trials aim for improvements if they want to establish a new standard of care. When the industry develops a new drug, it should target a certain improvement level in the drugs being developed.

American Journal of Managed Care: **What is the value of speaking at meetings such as *AJMC's* Patient Centered Oncology Care, which will be held on November 13-14, in Baltimore, and where you'll be delivering a keynote?**

Dr Yu: We have a complex ecosystem in healthcare—and that complexity means multiple stakeholders who are often not together at the same table having the same conversations. We need to engage all stakeholders in the system. In January, ASCO convened a summit that brought together payers—both private and Medicare—the pharmaceutical industry, patient advocates, and provider groups, to talk about value and to come to an agreement that we are all responsible for improving value of care. We need to reduce the cost of conducting research; the regulatory burdens, which add to cost of care delivery, should be moderated; payers need to pay for things that are high-value, which in turn should reduce copays; and physicians need to choose wisely. Essentially, the entire healthcare system needs to contribute to the conversation. So the value of speaking at a conference like *AJMC's* Patient Centered Oncology Care is that it's a diverse group of stakeholders—a wider audience—and that's where this conversation has to take place. **EBO**

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

2.2 Dose Modification

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

Recommended dose delays

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

Recommended dose reductions

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

Table 1 Recommended Dose Reductions

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

ANC = absolute neutrophil count.

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

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

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

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

5.2 Peripheral Neuropathy

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

5.3 Embryo-Fetal Toxicity

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

5.4 QT Prolongation

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

• Neutropenia • Peripheral neuropathy • QT interval prolongation

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

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

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

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

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

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

Table 2 (cont'd)

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

[a]Based upon laboratory data.

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

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

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

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

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

Less Common Adverse Reactions: The following additional adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group: **Eye Disorders:** increased lacrimation; **Gastrointestinal Disorders:** dyspepsia, abdominal pain, stomatitis, dry mouth; **General Disorders and Administration Site Conditions:** peripheral edema; **Infections and Infestations:** upper respiratory tract infection; **Metabolism and Nutrition Disorders:** hypokalemia; **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, muscular weakness; **Nervous System Disorders:** dysgeusia, dizziness; **Psychiatric Disorders:** insomnia, depression; **Skin and Subcutaneous Tissue Disorders:** rash.

6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval of HALAVEN. 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. **Blood and Lymphatic System Disorders:** lymphopenia; **Gastrointestinal Disorders:** pancreatitis; **Hepatobiliary Disorders:** hepatitis; **Immune System Disorders:** drug hypersensitivity; **Infections and Infestations:** pneumonia, sepsis/neutropenic sepsis; **Metabolism and Nutrition Disorders:** hypomagnesemia, dehydration; **Respiratory, thoracic, and mediastinal disorders:** interstitial lung disease; **Psychiatric Disorders:** anxiety; **Skin and Subcutaneous Tissue Disorders:** pruritus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category D

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

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

There is no known antidote for HALAVEN overdose.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Hepatic Impairment

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

Renal Impairment

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

12.6 Cardiac Electrophysiology

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies have not been conducted with eribulin mesylate.

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

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

IN MBC, ONCOLOGISTS ARE CONSISTENTLY

EXTENDING THE CONTINUUM OF MEANINGFUL CARE[1-3]

With MBC treatment potentially extending to 6 lines and beyond, third-line chemotherapy can still be early in the fight for some patients[2]

MBC=metastatic breast cancer.

Indication

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

Important Safety Information

Neutropenia

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

Peripheral Neuropathy

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

Pregnancy Category D

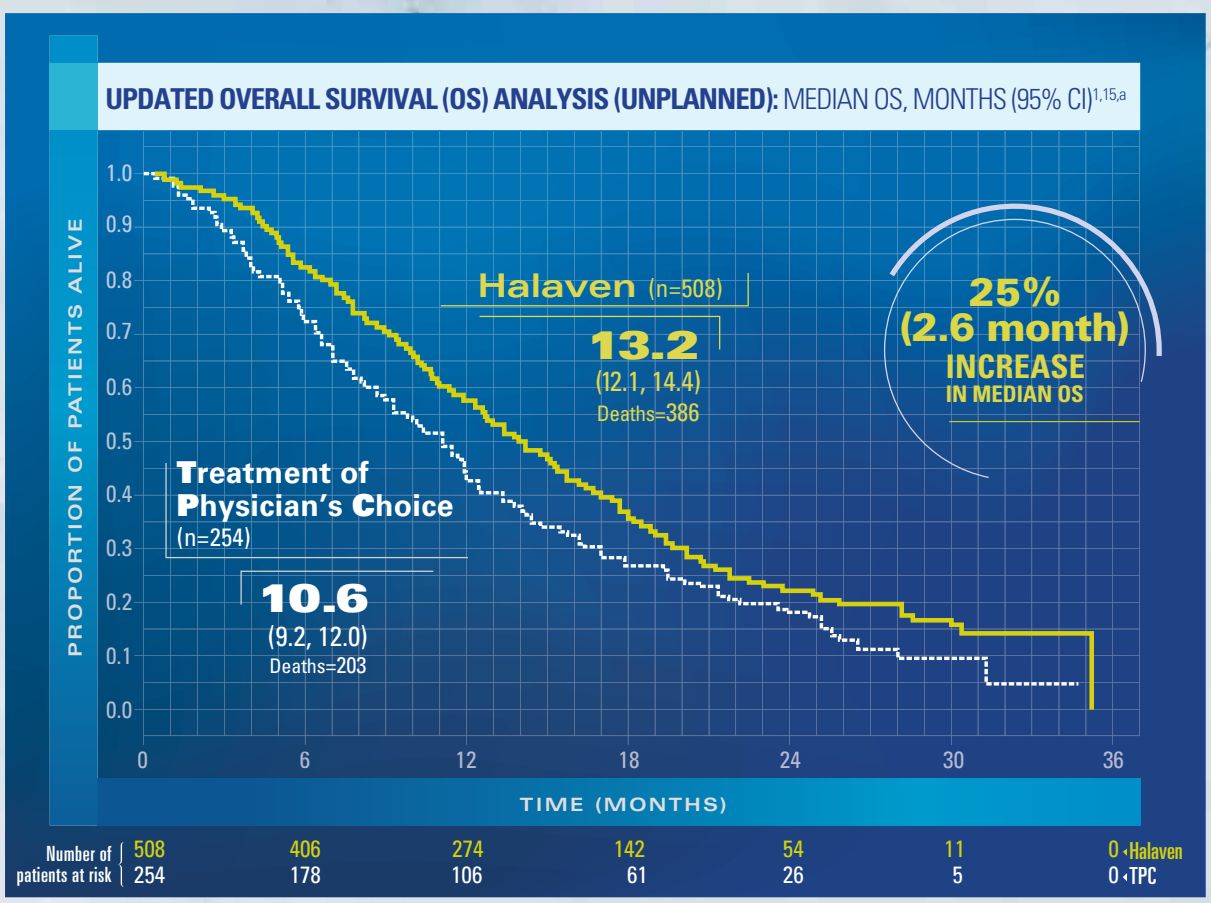
- Halaven is expected to cause fetal harm when administered to a pregnant woman and patients should be advised of these risks

QT Prolongation

- In an uncontrolled ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no prolongation on Day 1. ECG monitoring is recommended for patients with congestive heart failure; bradyarrhythmias;

GIVE YOUR PATIENTS AN OPPORTUNITY FOR MORE LIFE

The FIRST and ONLY single agent that significantly extended OVERALL SURVIVAL in third-line MBC[7-14]



Results from an updated, unplanned survival analysis of the Phase III, randomized, open-label, multicenter, multinational Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389 (Eribulin) (EMBRACE) trial of Halaven versus Treatment of Physician's Choice (TPC) in patients with MBC (N=762), conducted when 77% of events (deaths) had been observed. The primary endpoint was OS. Patients were randomized (2:1) to receive either Halaven 1.4 mg/m^2 intravenously for 2 to 5 minutes on Days 1 and 8 of a 21-day cycle, or any single-agent therapy, selected prior to randomization. At baseline, all patients had received ≥2 prior chemotherapeutic regimens for metastatic disease and demonstrated disease progression within 6 months of their last chemotherapeutic regimen. All patients received prior anthracycline- and taxane-based chemotherapy, unless contraindicated. Therapies in the TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxanes [included paclitaxel, docetaxel, nab-paclitaxel, and ixabepilone], 9% anthracyclines, 10% other chemotherapy), and 3% hormonal therapy.

CI=confidence interval.
[a]Conducted in the intent-to-treat population.

The updated OS analysis was consistent with the primary analysis[7]

- The primary analysis, conducted when ~50% of events (deaths) had been observed, demonstrated a median OS for Halaven vs TPC of 13.1 months (95% CI: 11.8, 14.3) vs 10.6 months (95% CI: 9.3, 12.5), hazard ratio=0.81 (95% CI: 0.66, 0.99) (*P*=0.041)[7,15]

concomitant use of drugs that prolong QT interval, including Class Ia and III antiarrhythmics; and electrolyte abnormalities

- Correct hypokalemia or hypomagnesemia prior to initiating Halaven and monitor electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome

Hepatic and Renal Impairment

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

Most Common Adverse Reactions

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

References: 1. Dufresne A, et al. *Breast Cancer Res Treat*. 2008;107(2):275-279. **2.** Planchat E, et al. *Breast*. 2011;20(6):574-578. **3.** Ray S, et al. In: *J Clin Oncol*. San Francisco, CA: ASCO Breast Cancer Symposium; 2012. Abstract 116. **4.** Cardoso F, et al. *Ann Oncol*. 2002;13(2):197-207. **5.** Seah DS, et al. Poster presented at: 2012 ASCO Annual Meeting; June 1–5, 2012; Chicago, IL. Abstract 6089. **6.** Lin NU, et al. *Lancet*. 2011;377(9769):878-880. **7.** Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2013. **8.** Saad ED, et al. *J Clin Oncol*. 2010;28(11):1958-1962. **9.** Slamon DJ, et al. *N Engl J Med*. 2001;344(11):783-792. **10.** Geyer CE, et al. *N Engl J Med*. 2006;355(26):2733-2743. **11.** von Minckwitz G, et al. *J Clin Oncol*. 2009;27(12):1999-2006. **12.** Miller K, et al. *N Engl J Med*. 2007;357(26):2666-2676. **13.** Robert NJ, et al. *J Clin Oncol*. 2011;29(10):1252-1260. **14.** Sparano JA, et al. *J Clin Oncol*. 2010;28(20):3256-3263. **15.** Cortes J, et al. *Lancet*. 2011;377(9769):914-923.

Please see accompanying brief summary of Halaven full Prescribing Information.

Visit **www.halaven.com/hcp.aspx**

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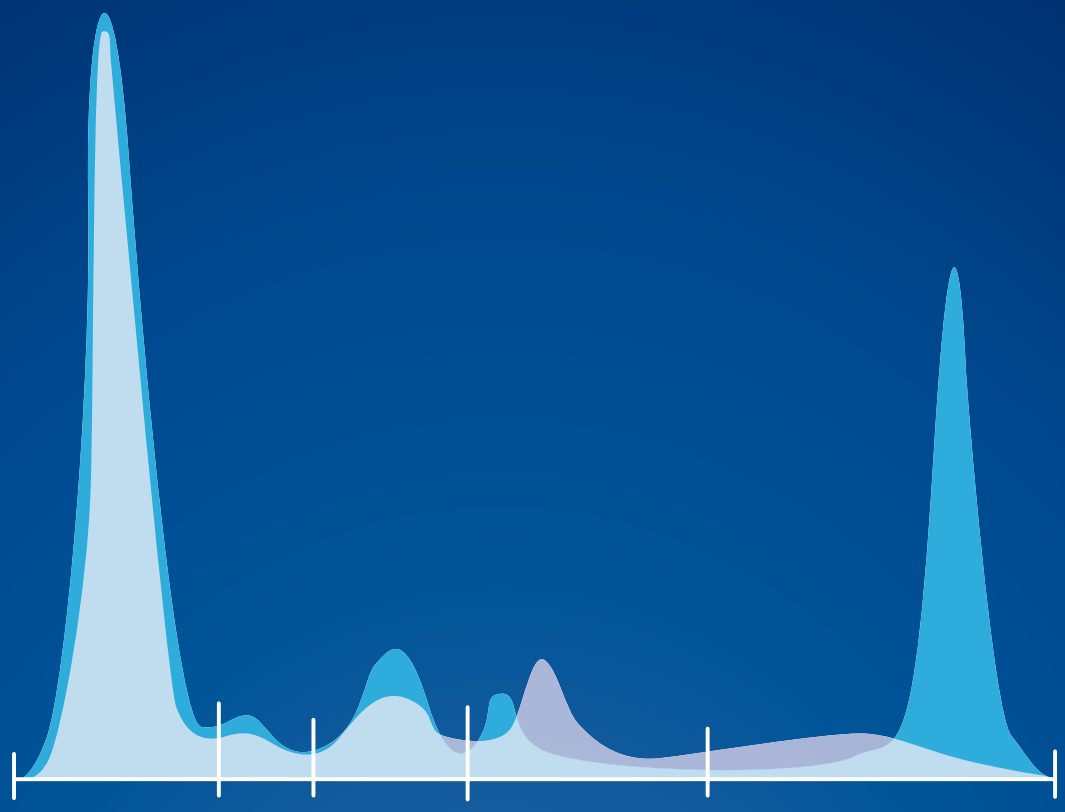

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