SPECIAL ISSUE: HEALTHCARE GAPS

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RESEARCH & LEADERSHIP

Evidence-Based ONCOLOGY™

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ALSO IN THIS ISSUE

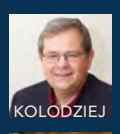
EMPHASIS ON THE ONCOLOGIST–PATIENT COMMUNICATION

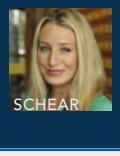
How effective is the communication between patients and their oncologists? Does it impact clinical outcomes? The National Coalition for Cancer Survivorship initiated focus groups to better understand the interaction between cancer patients and their oncologist. Read about what they discovered on SP515.

CANCER MOONSHOT

The Blue Ribbon Panel appointed by the National Cancer Institute to lead the White House Cancer Moonshot initiative recently released a preliminary report on how best to rapidly improve cancer care in the United States. *The American Journal of Managed Care®* sought insight from Daniel F. Hayes, MD, FASCO, 2016-2017 president of the American Society of Clinical Oncology, on the importance of these recommendations (SP520).

PANEL DISCUSSION


KOLODZIEJ


SCHEAR

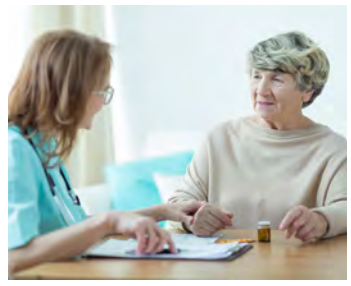
Communication and collaboration within the care team, patient–oncologist dialogue, and an upfront conversation on palliative care. Our expert panelists had this and more to discuss (SP523).

CARE COORDINATION

Making Oncologists Good Neighbors

Michael Kolodziej, MD

WHILE ACTIVELY TREATING CANCER PATIENTS FOR THEIR MALIGNANCIES, oncologists like to take full ownership of the medical care for their patients. Because so much of cancer care is highly specialized, this makes a lot of sense. But it is not unusual for lines of communication between doctors, doctors and patients, and doctors and family members to break down. Every oncologist has stories about missed handoffs. Every patient can recount, in excruciating detail, all the times their doctors did not make an important phone call. If we are aiming for the best patient outcome and the best patient experience, we aren't even close to hitting the mark. And to my knowledge, no one is taking ownership of this problem.



This lack of care coordination will become a crisis as care shifts to integrated delivery systems, like accountable care organizations (ACOs). The rationale behind these arrangements is that by forcing an organization to assume both clinical and financial responsibility, all of the interested parties will become engaged, as they will be at risk for a bad outcome. However, even a superficial analysis of how these programs are evolving reveals the obvious problem: specialists—who take care of the most complicated and most expensive (and, therefore, the most critical) patients—are marginalized. Additionally, under most models, an ACO does not exist without a panel of specialists. Layer on the often-strained relationships between hospital administrators and specialists, as well as those between primary care physicians (PCPs) and specialists, and the challenge gets even more acute. There is an expectation that in this "medical neighborhood," specialists will be good neighbors.

KEY POINTS

4 SCENARIOS IN NEED OF COORDINATION:

1. Streamlining patient referral
2. Managing patients with complex comorbidities
3. Optimizing end-of-life care
4. Transitioning to survivorship

Identifying the Greater Evil

Where is the need for coordination greatest? Although I specifically list 4 scenarios, I am sure there are many more:

1. Streamlining patient referral.

Referral for specialist care is a dysfunctional process. Bidirectional and accurate communication between the referring physician and

CONTINUED ON SP539

FERTILITY PRESERVATION

Multi-Level Approach to Addressing Iatrogenic Infertility

Aditi Narayan, MSW; Loyce Pace, MPH; and Rebekkah Schear, MIA

SARAH WAS 30 YEARS OLD WHEN SHE FIRST HEARD THE WORDS "You have breast cancer." Five years later, she was cancer-free, married, and making plans to start a family. Then she heard those dreaded words again: "You have cancer." As she and her husband dealt with the shock, she was informed that she would likely need to have her ovaries removed. They were heartbroken at the thought that she would not be able to have children biologically, until her oncologist told them about fertility preservation. However, they learned that in-vitro fertilization (IVF) cost an average of $10,000 and would not be covered by insurance.

Refusing to give up hope, Sarah called LIVE**STRONG** for help. Through LIVE**STRONG** Fertility, she was able to receive a discount on IVF and free stimulation medication. Today, Sarah lives with her husband and their beautiful daughter.

CONTINUED ON SP546

CARE DELIVERY

Enhancing Healthcare Delivery Research at the National Cancer Institute

Ann M. Geiger, PhD, MPH; Ashley W. Smith, PhD, MPH; Sarah C. Kobrin, PhD, MPH; and Stephen H. Taplin, MD

PRESIDENT OBAMA'S ANNOUNCEMENT OF THE CANCER MOONSHOT, including the recent release of the Blue Ribbon Panel Report[1] identifying potential research priorities, highlights that now is a time of great hope for cancer care.[2] Efforts to promote tobacco cessation and human papillomavirus (HPV) vaccination exemplify clinical opportunities to prevent cancer. Developments in cancer screening, specifically the fecal immunochemical test and low-dose computed tomography of the lung, increase the chances of early detection and treatment of cancer. Advances

CONTINUED ON SP553

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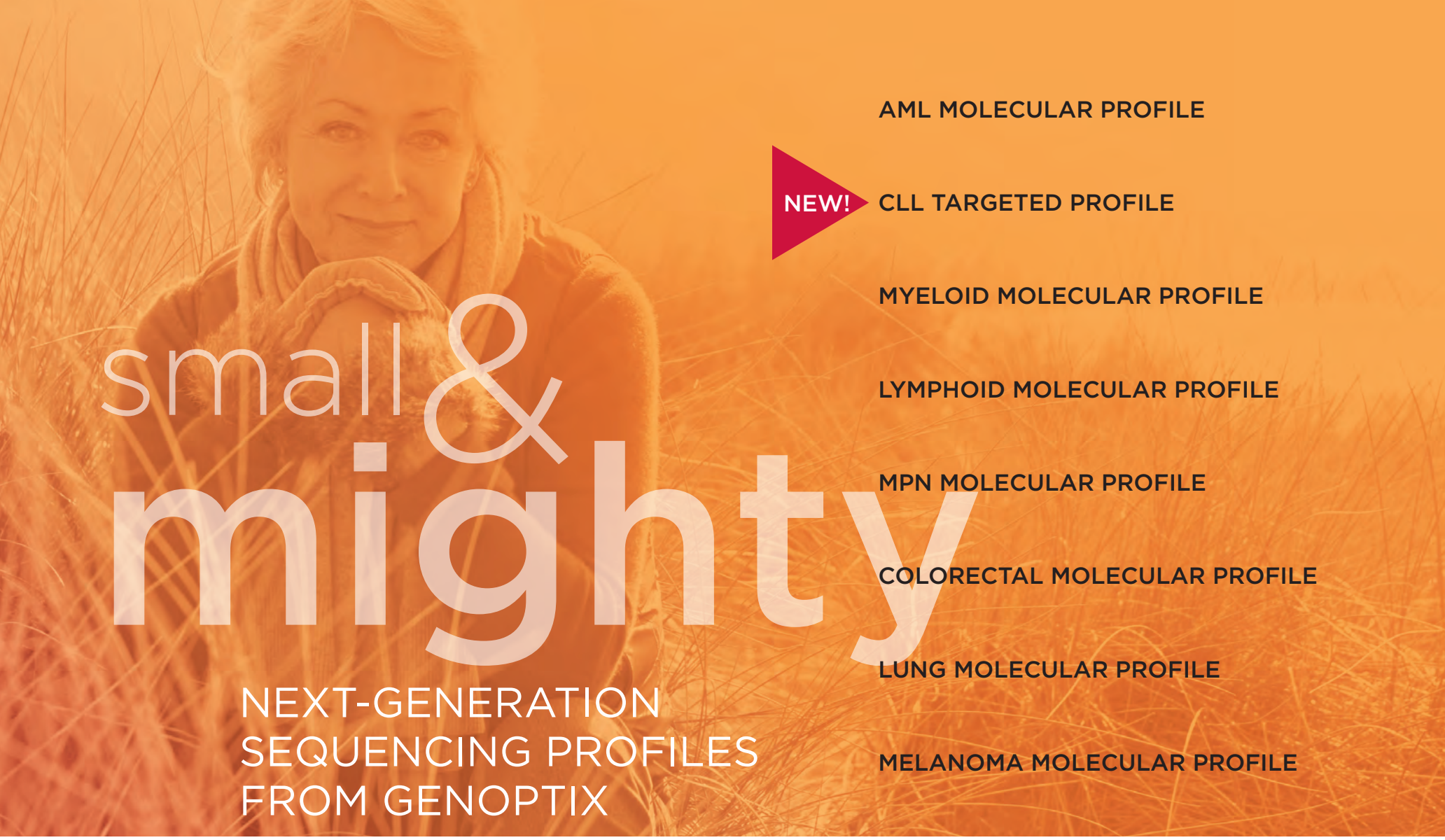

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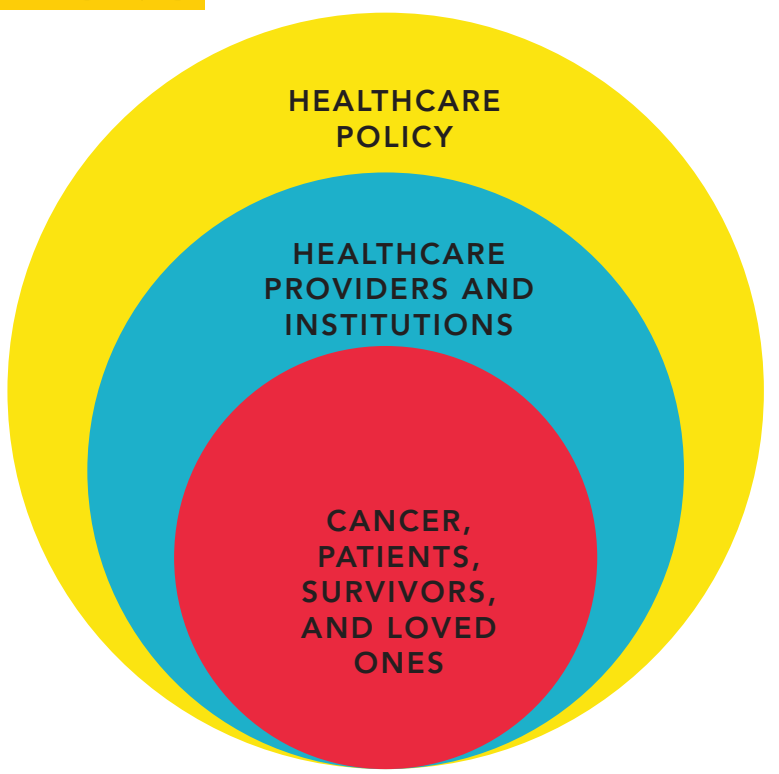
LIVESTRONG



SP546. Read about a program that uses a multi-pronged approach to address cancer and fertility.

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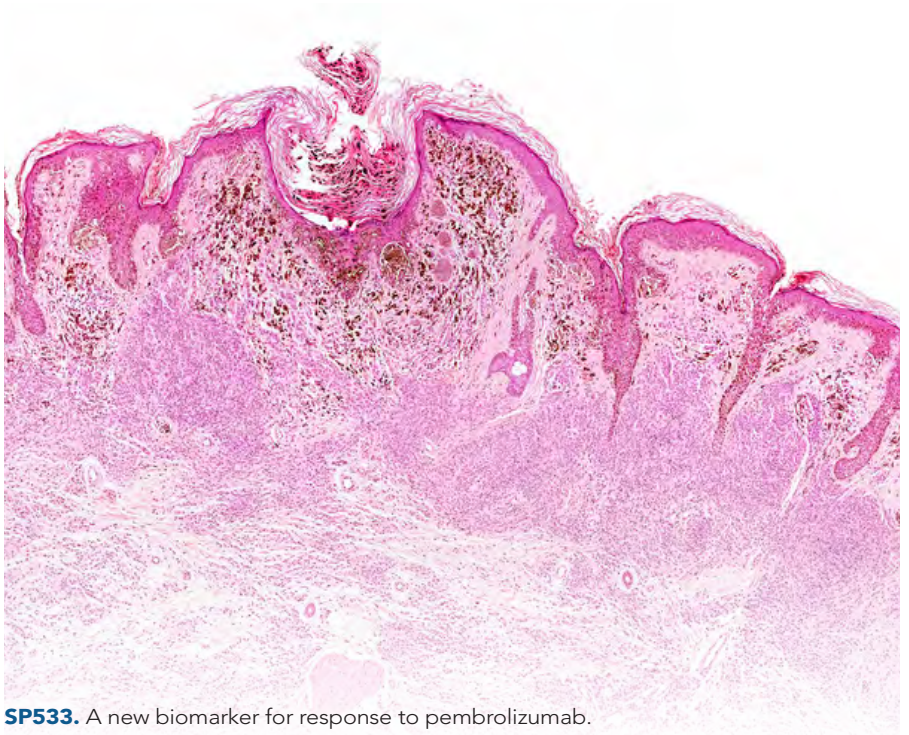

SP533. A new biomarker for response to pembrolizumab.

FROM THE CHAIRMAN

Patient-Centricity in Oncology—Where Are We Lacking?

MIKE HENNESSY, SR

FERTILITY PRESERVATION is a topic that may not be at the top of the agenda for physicians, but it might hold significant value for an adolescent or young adult cancer patient. The LIVE**STRONG** Foundation has spearheaded several research and policy efforts to understand this issue and has identified several barriers, including patient and physician education, cost, and institutional support. With this in mind, the foundation has developed a multi-pronged approach to address the concerns of patients and their families, physicians, and healthcare institutions and to push for changes in barriers due to healthcare policies.

Communication gaps complicate healthcare and can devastate the prognosis of a patient undergoing cancer treatment. Shared decisions on treatment are important, but can take on different meanings depending on what the patient might desire. Findings from patient–oncologist focus groups hosted by the National Coalition for Cancer Survivorship (NCCS) found that the patient may want to be the primary decision maker, might want the oncologist to direct treatment decisions, or expects the decision-making process to be a collaborative one.

A common concern among patients and families is the discussion on palliation, which stems from the misunderstanding—or the lack thereof—about what palliative care actually is. The NCCS focus groups drew attention to this topic. Patients said that palliation and hospice were never a part of their discussions of a treatment plan with their physicians; some patients went so far as to say that their doctor avoided the topic. Both Michael Kolodziej, MD, and Rebekkah Schear, MIA, who participated on a panel on care gaps hosted by *Evidence-Based Oncology*™ (see SP523), proposed that advance care planning and palliation should be addressed at the time of diagnosis and should not be a consideration only when all other options have failed. Dr Kolodziej recognized, however, that changing physician behavior on this front would be a challenge.

Finally, adapting these changes necessitates communication—among physicians, nurses, social workers, the patients, and their families. Interoperability should not be a term restricted to digital healthcare platforms; it should also be adopted by all stakeholders involved in making treatment decisions and supporting patients during the care journey.

The good news is that new models for healthcare delivery, as well as reimbursement, are being developed, which includes the Oncology Care Model by the Centers for Medicare & Medicaid Innovation, that try to learn from and address some of these gaps in oncology care.

As always, we appreciate your readership. You can hear more on these topics at our meeting, Patient-Centered Oncology Care® (http://www.ajmc.com/meetings/pcoc16), which is celebrating its 5th anniversary this year. Scheduled to be held in Baltimore on November 17-18, the meeting will provide insightful presentations and panel discussions, as well as opportunities for participants to present their research as posters. ◆

Sincerely,
Mike Hennessy, Sr
CHAIRMAN AND CEO

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- A 71% reduction in duration of severe neutropenia vs placebo (1.1 days vs 3.8 days, $p<0.0001$)[2]
  - Efficacy was evaluated in a multinational, multicenter, randomized, controlled, Phase III study of chemotherapy-naïve patients with high-risk breast cancer receiving doxorubicin (60 mg/m^2 IV bolus)/docetaxel (75 mg/m^2)[2]
- The safety of GRANIX was established in 3 Phase III trials, with 680 patients receiving chemotherapy for either breast cancer, lung cancer, or non-Hodgkin lymphoma (NHL)[2]
- Offering a presentation for self-administration

Indication

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

Important Safety Information

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

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

For more information, visit GRANIXhcp.com.

References: 1. This information is an estimate derived from the use of information under license from the following IMS Health Information Service: IMS National Sales Perspective, GRANIX micrograms by non-federal hospital channel February 2016. IMS expressly reserves all rights, including rights of copying, distribution, and republication (micrograms calculated as eaches x strength). **2.** GRANIX® (tbo-filgrastim) Injection Prescribing Information. North Wales, PA: Teva Pharmaceuticals; 2014.

TEVA Oncology

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

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

5.2 Acute Respiratory Distress Syndrome (ARDS)

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

5.3 Allergic Reactions

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

5.4 Use in Patients with Sickle Cell Disease

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

5.5 Capillary Leak Syndrome

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

5.6 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience

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

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

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

Leukocytosis

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

Additional Adverse Reactions

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

6.2 Immunogenicity

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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

Animal Data

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No case of overdose has been reported.

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GRX-40580 January 2015

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

Minding the Gaps and Filling the Chasms in Oncology


JOSEPH ALVARNAS, MD

IN 1999, THE INSTITUTE OF MEDICINE (IOM) report, Crossing the Quality Chasm: A New Health System for the 21st Century, described an ideal healthcare system as one that delivers safe, effective, patient-centered, efficient, timely, and equitable care.[1] On March 21, 2010, The Affordable Care Act (ACA) was signed into law by President Barack Obama. The ACA was a highly ambitious piece of legislation that sought to improve the effectiveness and safety of healthcare by reducing gaps in healthcare access and linking payments to improvements in healthcare quality outcomes. Important provisions of the law included a prohibition on the denial of coverage based upon preexisting conditions, the elimination of lifetime limits on insurance coverage, and the stipulation of standards for essential minimal coverage benefits (including cancer screening).[2] In many ways, the ACA attempted to enshrine the IOM's 6 aims of healthcare as important drivers of the ongoing evolution of American healthcare.

As we enter a time of extraordinary advances in cancer care, empowered by the rapid identification of new molecular targets and the increasing availability of targeted and immunotherapeutic agents, some of the optimism over these advances has been tempered by the growing realization of the challenges of delivering these cancer care solutions. Providers and healthcare systems are confronted with delivering increasingly complex cancer care more efficiently, effectively, and safely. Yet, ensuring that care is delivered equitably is particularly challenging and requires an understanding of the gaps that continue to exist in cancer care delivery. These include gaps in the care of adolescent and young adult patients, patients making the transition from pediatric to adult care systems, older patients, uninsured patients, patients whose linguistic and cultural attributes may impact care, patients from lower socioeconomic groups, and patients at the end of life. Gaps in care may include lack of access to specific treatments and technology, distress management, effective pain relief, and multidisciplinary treatment planning and coordination of care.[3-5]

Contributor's in this month's issue of *Evidence-Based Oncology*™ review some of the key gaps in cancer care and explore how they can be more effectively addressed. Researchers from LIVE**STRONG** evaluate the importance of assessing patients carefully for fertility preservation strategies and discuss how this should be performed as a routine part of cancer care planning. An article from the National Coalition for Cancer Survivorship emphasizes the importance of effective physician-patient communication and how best to address gaps in care planning and decision-making communication. Experts from the National Cancer Institute's Healthcare Delivery Research Program review the role of the Division of Cancer Control and Population Sciences in facilitating behavioral, epidemiologic, and other types of research intended to decrease cancer incidence, increase cancer survival, and improve the well-being of cancer patients, survivors, caregivers, and the community. Michael Kolodziej, MD, formerly with Aetna, reviews the importance of care coordination in ensuring effective longitudinal cancer care.

The rapidly expanding armamentarium of high-tech cancer care therapeutics and the growing focus on precision medicine solutions have deeply altered our perceptions of effective cancer care; however, the most important aspect of caring for patients affected by cancer begins with a personal focus on the patient before us. Although the quest for more effective technical solutions provides the basis for soaring rhetoric, the real-world healthcare needs, knowledge and access gaps to effective care, and the prosaic work of care coordination and goals of care planning represent some of the areas of greatest opportunity facing patients today. ◆

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POLICY

A Holistic Approach to Cancer Care: Focus on Collaboration

Surabhi Dangi-Garimella, PhD

COLLABORATION IS KEY TO THE SUCCESS of any business venture, and healthcare should be no exception. Yet time and again, we encounter gaps in patient care that stem from miscommunication or lack of communication among those involved in patient care, and this could result in decisions that lead to adverse outcomes.

The lack of cohesion highlights several aspects of the care delivery system:

- Fragmented care delivery
- Lack of interoperability between data systems used by healthcare clinics and academic centers
- Failure of communication among the following:
    - healthcare providers who participate in patient care
    - patient and provider
    - provider and family caregivers
- Gaps in care transitions, especially with survivor care (**FIGURE**)

Such disjointed care can yield questions that are left open for interpretation by physicians, radiologists, or nurse practitioners who may not be communicating with oncologists. The end result could vary from inappropriate treatment to a lack of adequate treatment—an unnecessary burden on healthcare costs. To address this, several different models have been developed for more seamless patient care.

Care Models

Role of Health Navigators

Support received from a nurse navigator can significantly improve the patient experience and reduce problems in care, according to a study published in the *Journal of Clinical Oncology*.[1] The trial enrolled newly diagnosed cancer patients and divided them into a control group that received usual care and an intervention group that received support from a nurse navigator for 4 months. Patients were assessed using several patient-reported outcomes measures at baseline, at 4 months, and at 12 months. Although there was no difference in the quality-of-life between the 2 groups, patients with lung cancer who received guidance from a nurse navigator had lower healthcare costs (average $6852).

COLLABORATION AMONG THE PATIENT'S CARE TEAM MEMBERS IS VITAL FOR IMPROVED CLINICAL OUTCOMES.

Another study used nurse navigators at imaging centers to identify women at greater risk of hereditary breast and ovarian cancer (HBOC) syndrome as a preliminary screening method. The study enrolled 1420 women (seeking imaging/screening or breast biopsy results) at 3 mammography and imaging centers to use the HBOC risk assessment tool coupled with a nurse navigator to identify who may be at risk for HBOC. As a result of the program, fewer women required HBOC education and evaluation and a greater number of women with positive biopsy results were found to be at risk for HBOC compared with similar studies. Knowing patients' risk of HBOC during biopsy helped direct clinical decisions on the kind of surgery that would be needed.[2]

Spectrum Health, a health system in Grand Rapids, Michigan, provides its patients access to an oncology nurse navigator, from prediagnosis through survivorship and end-of-life care. The navigator serves as the pillar of support for patients and their family members by offering the following[3]

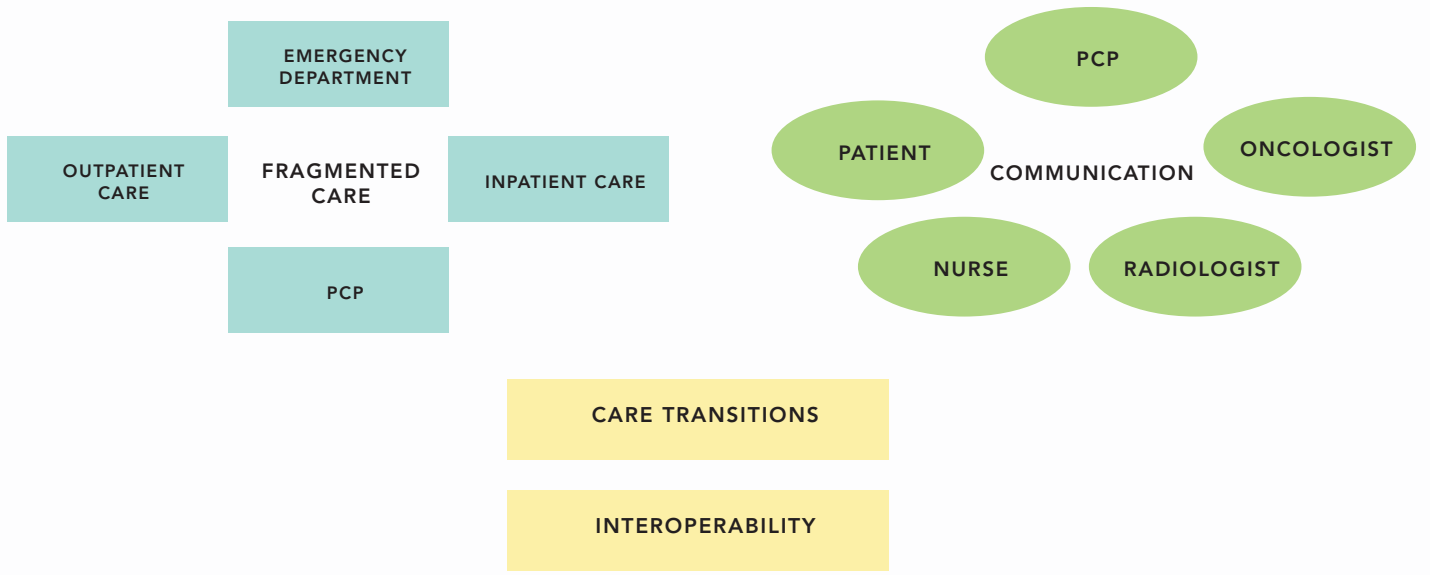
- Help navigating complex treatment by serving at the point of contact
- Education about disease process and treatment
- Psychosocial support
- Liaison between specialists and family physician
- Seamless care transitions by removing barriers to care
- Connections with services, including social work, nutrition counseling, genetics, research, pastoral care, physical and occupational therapy, and financial counseling

Patient and Caregiver Engagement: Self-Management and Patient-Reported Outcomes

Engaging patients in their own care is extremely important, as patients can be their own best advocates. Being aware of their condition and cognizant of the effects of various treatments, patients can be the focal point of contact for the providers integral to their care and can also provide input in terms of patient-reported outcomes.

Symptom management is the primary goal of patient engagement and the foundation of patient-centered care that can improve both outcomes and quality of life. Although information is crucial for patients to feel they are in control, with minimal interruptions of their daily activities, each person's inherent ability to manage these symptoms will vary within a population. To overcome this discrepancy, researchers have developed the Theory of Symptom Self-Management so clinical outcomes can be maximized via patient-friendly tools that allow the patient and the physician to

FIGURE. Problems in Oncology Care That Can Impact Clinical Outcomes



PCP indicates primary care physician.

collaborate on tailored, achievable, goal-oriented plans for symptom management.[4]

Family caregivers should be actively engaged in care management, and physicians must ensure communication with the patients' family members on all aspects of care—from diagnosis and treatment options through survivorship and end-of-life issues. The National Cancer Institute has developed a comprehensive guide that provides step-by step instructions for both physicians and patients on the role of a family caregiver in caring for cancer patients.[5]

Along the lines of patient involvement in their own care, a study conducted in the Urology Department at the University of North Carolina at Chapel Hill included patient values and preferences when developing treatment plans for patients with prostate cancer. Using a Web-based application equipped to provide education, preference measurement, and personalized decision analysis for newly diagnosed patients with prostate cancer, the researchers enrolled 109 men to complete the application prior to their consultation. The result was a significant reduction in decisional conflict (37%; $P<.0001$); further patient satisfaction with the process was high, as they felt more involved with, and responsible for, treatment decisions.[6]

The Medical Home Model

The medical home model—be it the patient-centered medical home (PCMH) or the oncology medical home (OMH)—is a proponent of team-based care. The OMH model has evolved from the PCMH, which promotes a physician-directed network of care that may be provided by other physicians, nonphysician providers, or allied ancillary health services. The first such model was commissioned by John Sprandio, MD, in 2010, when the National Committee for Quality Assurance recognized his 9-physician oncology practice as a PCMH.[7] The practice boasted a reduction in unnecessary resource use, including:

- 68% reduction in emergency department (ED) visits
- 51% reduction in hospital admissions for patients on chemotherapy
- 21% reduction in hospital length of stay

The clinic estimated that it saved insurance plans an average $1 million per physician per year when the paper was published in 2012.

Along the lines of the OMH is the Community Oncology Medical Home, the COME Home program, developed by Innovative Oncology Business Solutions, which was implemented in 7 oncology practices across the country using a grant sponsored by the Center for Medicare & Medicaid Innovation. The program uses triage nurses up front to direct patients when they call the clinic; this service is available 24/7. Additionally, the clinics have extended office hours through the week and they implement clinical pathways to ensure standardized treatment. COME Home practice sites have seen between a 23% and 28% reduction in ED visits.[8]

SYMPTOM MANAGEMENT IS THE PRIMARY GOAL OF PATIENT ENGAGEMENT AND THE FOUNDATION OF PATIENT-CENTERED CARE THAT CAN IMPROVE BOTH OUTCOMES AND QUALITY OF LIFE.

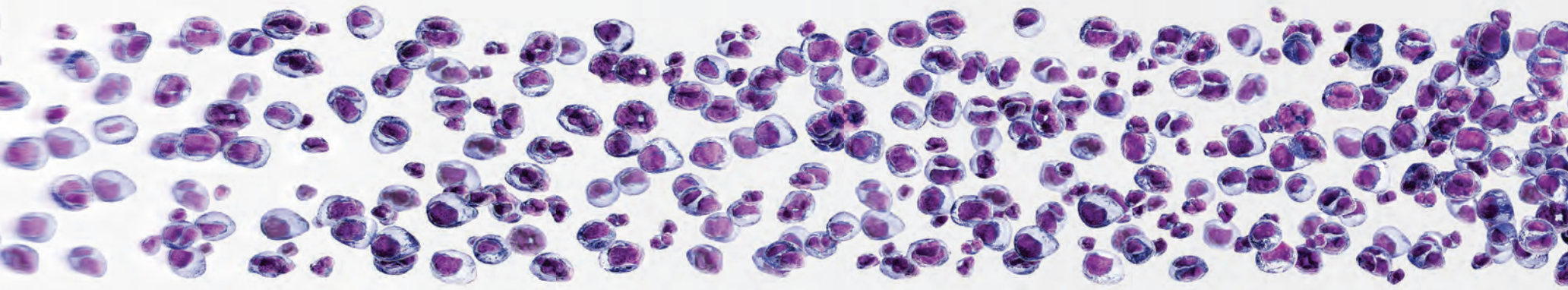
The PCMH seems an ideal model, but with provider shortages, especially oncology care providers, physician assistants (PAs) and nurse practitioners (NPs) could play an important role in team-based care to improve productivity. There are, however, several considerations to this role-sharing by nonphysician staff, and clinics would need to contemplate the following:[9]

- A clear delineation of provider roles to maximize efficacy
- A well-defined communication plan among team members
- A feedback loop to measure quality of care and cost-efficiency of the process
- Institutional credentialing and licensing may be different for PAs and NPs
- From the reimbursement point of view, productivity tracking should be accurate for billing purposes.

Building a transactive memory within, and between, teams of care providers, who might be a part of a single healthcare system or collaborating across healthcare systems, can significantly impact patient care and outcomes. The process requires 2 or more team representatives to develop a shared system for encoding, storing, and retrieving information, wherein each professional is responsible for retaining only part of the total information. The patient,

(continued on SP514)

When multiple myeloma relapses...



Superior PFS and deeper response shown in the ASPIRE* study

26.3 MONTHS

Median PFS†

- 26.3 months for KRd vs 17.6 months for Rd, two-sided $P = 0.0001$[1]

>3X INCREASED

Complete response or better (≥ CR)

- 32% for KRd vs 9% for Rd[1]

*ASPIRE = C**A**rfilzomib, Lenalidomide, and Dexametha**S**one versus Lenalidomide and Dexamethasone for the treatment of Pat**I**ents with **R**elapsed Multiple My**E**loma.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION

Cardiac Toxicities: New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of KYPROLIS administration.

- Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart KYPROLIS at 1 dose level reduction based on a benefit/risk assessment.
- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.
- Patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with KYPROLIS and remain under close follow-up.

Acute Renal Failure: Cases of acute renal failure and renal insufficiency adverse events (including renal failure) have occurred in patients receiving KYPROLIS. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome: Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred in patients receiving KYPROLIS. Patients with multiple myeloma and a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly. Withhold KYPROLIS until TLS is resolved.

Pulmonary Toxicity: Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving KYPROLIS. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension: Pulmonary arterial hypertension (PAH) was reported in patients treated with KYPROLIS. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart KYPROLIS based on a benefit/risk assessment.

Dyspnea: Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Hypertension: Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with KYPROLIS. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart KYPROLIS based on a benefit/risk assessment.

Venous Thrombosis: Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with KYPROLIS. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

- Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with KYPROLIS in combination with dexamethasone or lenalidomide plus dexamethasone.

Infusion Reactions: Infusion reactions, including life-threatening reactions, have occurred in patients receiving KYPROLIS. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms of an infusion reaction and to contact a physician immediately if they occur.

Thrombocytopenia: KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in patients receiving KYPROLIS. Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure: Cases of hepatic failure, including fatal cases, have been reported during treatment with KYPROLIS. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy: Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred in patients receiving KYPROLIS. Monitor for signs and symptoms of TTP/HUS. Discontinue KYPROLIS if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES): Cases of PRES have occurred in patients receiving KYPROLIS. PRES was formerly known as Reversible Posterior Leukoencephalopathy Syndrome. Consider a neuro-radiological imaging (MRI) for onset of visual or neurological symptoms. Discontinue KYPROLIS if PRES is suspected and evaluate. The safety of reinitiating KYPROLIS therapy in patients previously experiencing PRES is not known.

Embryo-fetal Toxicity: KYPROLIS can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals.

- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

- The most common adverse reactions occurring in at least 20% of patients treated with KYPROLIS in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information on adjacent pages.

ASPIRE: A phase 3, randomized, open-label, multicenter superiority study evaluated KYPROLIS in combination with lenalidomide and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. 792 patients were randomized in a 1:1 ratio (396 patients to KRd, 396 to Rd). Patients received their randomized study treatment in 28-day cycles until disease progression or unacceptable toxicity occurred. KYPROLIS was discontinued at 18 cycles unless disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Select secondary endpoints included overall survival, overall response rate (ORR), and duration of response.[1,2]

References: 1. KYPROLIS [prescribing information]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc., an Amgen Inc. subsidiary; 2016. **2.** Stewart AK, Rajkumar SV, Dimopoulos MA, et al; for the ASPIRE Investigators. *N Engl J Med.* 2015;372:142-152.

See more results at Kyprolis-HCP.com

ONYX® PHARMACEUTICALS
An Amgen subsidiary

USA-171-120751 February 2016 Printed in USA

Kyprolis™ (carfilzomib) for Injection

KYPROLIS® (carfilzomib) for injection, for intravenous use
Brief Summary of Prescribing Information.
Please see the KYPROLIS package insert for full prescribing information.

1. INDICATIONS AND USAGE

- Kyprolis is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- Kyprolis is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

2. DOSAGE AND ADMINISTRATION

2.1 Administration Precautions

Hydration - Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity and following the administration of Kyprolis with both oral and intravenous (IV) fluids, if needed. **Electrolyte monitoring -** Monitor serum potassium levels regularly during treatment with Kyprolis. **Premedications -** Premedicate with the recommended dose of dexamethasone for monotherapy or the recommended dose if on combination therapy. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles. **Administration -** Infuse over 10 or 30 minutes depending on the Kyprolis dose regimen. Do not administer as a bolus. Flush the IV line with normal saline or 5% dextrose injection, USP, immediately before and after Kyprolis administration. Do not mix Kyprolis with or administer as an infusion with other medicinal products. **Thromboprophylaxis -** Thromboprophylaxis is recommend for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. **Infection Prophylaxis -** Consider antiviral prophylaxis for patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Kyprolis. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Kyprolis, these events occurred throughout the course of Kyprolis therapy. Death due to cardiac arrest has occurred within one day of Kyprolis administration. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with lenalidomide and dexamethasone (KRd) versus lenalidomide/dexamethasone (Rd), the incidence of cardiac failure events was 6% in the KRd arm versus 4% in the Rd arm. In a randomized, open-label, multicenter trial of Kyprolis plus dexamethasone (Kd) versus bortezomib plus dexamethasone (Vd), the incidence of cardiac failure events was 8% in the Kd arm versus 3% in the Vd arm.

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Kyprolis for Grade 3 or 4 cardiac adverse events until recovery, consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment.

While adequate hydration is required prior to each dose in Cycle 1, all patients should also be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to patients < 75 years of age. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with Kyprolis and remain under close follow-up.

5.2 Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (including renal failure) have occurred in approximately 10% of patients treated with Kyprolis. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

5.3 Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis in Cycle 1, and in subsequent cycles as needed. Consider uric acid-lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, including interruption of Kyprolis until TLS is resolved.

5.4 Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in less than 1% of patients receiving Kyprolis. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue Kyprolis.

5.5 Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 1% of patients treated with Kyprolis and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline, and consider whether to restart Kyprolis based on a benefit/risk assessment.

5.6 Dyspnea

Dyspnea was reported in 28% of patients treated with Kyprolis and was Grade 3 or greater in 4% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Kyprolis based on a benefit/risk assessment.

5.7 Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with KRd versus Rd, the incidence of hypertension events was 16% in the KRd arm versus 8% in the Rd arm. In a randomized, open-label, multicenter trial of Kd versus Vd, the incidence of hypertension events was 26% in the Kd arm versus 10% in the Vd arm. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment.

5.8 Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating KRd versus Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm versus 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd versus Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm versus 2% in the Vd arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%.

Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with Kyprolis in combination with dexamethasone or lenalidomide plus dexamethasone.

5.9 Infusion Reactions

Infusion reactions, including life-threatening reactions, have occurred in patients receiving Kyprolis. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

5.10 Thrombocytopenia

Kyprolis causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 40% of patients in clinical trials with Kyprolis. Monitor platelet counts frequently during treatment with Kyprolis. Reduce or withhold dose as appropriate.

5.11 Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (< 1%) during treatment with Kyprolis. Kyprolis can cause increased serum transaminases. Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate.

5.12 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Kyprolis. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate. If the diagnosis of TTP/HUS is excluded, Kyprolis may be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known.

5.13 Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). Discontinue Kyprolis if PRES is suspected and evaluate. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

5.14 Embryo-Fetal Toxicity

Kyprolis can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. Males of reproductive potential should be advised to avoid fathering a child while being treated with Kyprolis. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6. ADVERSE REACTIONS

The following adverse reactions have been discussed above and can be found in the Warning and Precautions section of the prescribing information. They include Cardiac Toxicities, Acute Renal Failure, TLS, Pulmonary Toxicity, Pulmonary Hypertension, Dyspnea, Hypertension, Venous Thrombosis, Infusion Reactions, Thrombocytopenia, Hepatic Toxicity and Hepatic Failure, Thrombotic Microangiopathy, and PRES.

6.1 Clinical Trials Experience

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

Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm.

Deaths due to adverse reactions within 30 days of the last dose of any therapy in the KRd arm occurred in 27/392 (7%) patients compared with 27/389 (7%) patients who died due to adverse reactions within 30 days of the last dose of any Rd therapy. The most common cause of deaths occurring in patients (%) in the two arms (KRd versus Rd) included cardiac 10 (3%) versus 7 (2%), infection 9 (2%) versus 10 (3%), renal 0 (0%) versus 1 (< 1%), and other adverse reactions 9 (2%) versus 10 (3%). Serious adverse reactions were reported in 60% of the patients in the KRd arm and 54% of the patients in the Rd arm. The most common serious adverse reactions reported in the KRd arm as compared with the Rd arm were pneumonia (14% vs. 11%), respiratory tract infection (4% vs. 1.5%), pyrexia (4% vs. 2%), and pulmonary embolism (3% vs. 2%). Discontinuation due to any adverse reaction occurred in 26% in the KRd arm versus 25% in the Rd arm. Adverse reactions leading to discontinuation of Kyprolis occurred in 12% of patients and the most common reactions included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%).

Most Common Adverse Reactions (≥ 10% in the KRd Arm) Occurring in Cycles 1–12 (20/27 mg/m² Regimen in Combination with Lenalidomide and Dexamethasone)

	KRd Arm (N = 392), n (%)		Rd Arm (N = 389), n (%)	
Adverse Reactions by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	138 (35)	53 (14)	127 (33)	47 (12)
Neutropenia	124 (32)	104 (27)	115 (30)	89 (23)
Thrombocytopenia	100 (26)	58 (15)	75 (19)	39 (10)
Gastrointestinal Disorders				
Diarrhea	115 (29)	7 (2)	105 (27)	12 (3)
Constipation	68 (17)	0	53 (14)	1 (0)
Nausea	60 (15)	1 (0)	39 (10)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	109 (28)	21 (5)	104 (27)	20 (5)
Pyrexia	93 (24)	5 (1)	64 (17)	1 (0)
Edema peripheral	63 (16)	2 (1)	57 (15)	2 (1)
Asthenia	53 (14)	11 (3)	46 (12)	7 (2)
Infections and Infestations				
Upper respiratory tract infection	85 (22)	7 (2)	52 (13)	3 (1)
Nasopharyngitis	63 (16)	0	43 (11)	0
Bronchitis	54 (14)	5 (1)	39 (10)	2 (1)
Pneumonia[a]	54 (14)	35 (9)	43 (11)	27 (7)
Metabolism and Nutrition Disorders				
Hypokalemia	78 (20)	22 (6)	35 (9)	12 (3)
Hypocalcemia	55 (14)	10 (3)	39 (10)	5 (1)
Hyperglycemia	43 (11)	18 (5)	33 (9)	15 (4)

Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	88 (22)	3 (1)	73 (19)	3 (1)
Nervous System Disorders				
Peripheral neuropathies[b]	43 (11)	7 (2)	37 (10)	4 (1)
Psychiatric Disorders				
Insomnia	63 (16)	6 (2)	50 (13)	8 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	85 (22)	1 (0)	46 (12)	0
Dyspnea[c]	70 (18)	9 (2)	58 (15)	6 (2)
Skin and Subcutaneous Tissue Disorders				
Rash	45 (12)	5 (1)	53 (14)	5 (1)
Vascular Disorders				
Embolic and thrombotic events, venous[d]	49 (13)	16 (4)	22 (6)	9 (2)
Hypertension[e]	41 (11)	12 (3)	15 (4)	4 (1)

KRd = Kyprolis, lenalidomide, and low-dose dexamethasone; Rd = lenalidomide and low-dose dexamethasone.

[a] Pneumonia includes pneumonia and bronchopneumonia.

[b] Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Dyspnea includes dyspnea and dyspnea exertional.

[d] Embolic and thrombotic events, venous include deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.

[e] Hypertension includes hypertension, hypertensive crisis.

Grade 3–4 Laboratory Abnormalities (≥10%) in Cycles 1–12 (20/27 mg/m² Regimen in Combination with Lenalidomide and Dexamethasone)

Laboratory Abnormality	KRd (N = 392), n (%)	Rd (N = 389), n (%)
Decreased lymphocytes	182 (46)	119 (31)
Decreased absolute neutrophil count	152 (39)	140 (36)
Decreased phosphorus	122 (31)	106 (27)
Decreased platelets	101 (26)	59 (15)
Decreased total white blood cell count	97 (25)	71 (18)
Decreased hemoglobin	58 (15)	68 (18)
Decreased potassium	41 (11)	23 (6)

KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.

Safety Experience with Kyprolis in Combination with Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with dexamethasone was evaluated in an open-label, randomized trial of patients with relapsed multiple myeloma. Patients received treatment for a median duration of 40 weeks in the Kyprolis/dexamethasone (Kd) arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm.

Deaths due to adverse reactions within 30 days of last study treatment occurred in 22/463 (5%) patients in the Kd arm and 21/456 (5%) patients in the Vd arm. The causes of death occurring in patients (%) in the two arms (Kd vs. Vd) included cardiac 7 (2%) versus 5 (1%), infections 5 (1%) versus 8 (2%), disease progression 6 (1%) versus 4 (1%), pulmonary 3 (1%) versus 2 (< 1%), renal 1 (< 1%) versus 0 (0%), and other adverse events 2 (< 1%) versus 2 (< 1%). Serious adverse reactions were reported in 48% of the patients in the Kd arm and 36% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% vs. 9%). Discontinuation due to any adverse reaction occurred in 20% in the Kd arm versus 21% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 6, 1.3%) and peripheral neuropathy in the Vd arm (n = 19, 4.2%).

There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12. There were no new clinically relevant AEs that emerged in the later treatment cycles.

Most Common Adverse Reactions (≥ 10% in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m² Regimen in Combination with Dexamethasone)

	Kd (N = 463), n (%)		Vd (N = 456), n (%)	
Adverse Reaction by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	160 (35)	57 (12)	112 (25)	43 (9)
Thrombocytopenia[a]	127 (27)	46 (10)	112 (25)	65 (14)
Gastrointestinal Disorders				
Diarrhea	111 (24)	14 (3)	150 (33)	26 (6)
Nausea	69 (15)	4 (1)	66 (15)	3 (1)
Constipation	58 (13)	1 (0)	109 (24)	6 (1)
Vomiting	45 (10)	5 (1)	32 (7)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	112 (24)	13 (3)	124 (27)	25 (6)
Pyrexia	102 (22)	9 (2)	52 (11)	3 (1)
Peripheral edema	75 (16)	3 (1)	73 (16)	3 (1)
Asthenia	71 (15)	9 (2)	66 (14)	13 (3)
Infections and Infestations				
Upper respiratory tract infection	66 (14)	4 (1)	54 (12)	3 (1)
Bronchitis	54 (12)	5 (1)	26 (6)	2 (0)
Nasopharyngitis	45 (10)	0 (0)	42 (9)	1 (0)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	66 (14)	1 (0)	22 (5)	3 (1)
Back pain	58 (13)	7 (2)	60 (13)	8 (2)
Nervous System Disorders				
Headache	68 (15)	4 (1)	38 (8)	2 (0)
Peripheral neuropathies[b]	54 (12)	7 (2)	167 (37)	23 (5)
Psychiatric Disorders				
Insomnia	103 (22)	5 (1)	113 (25)	10 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea[c]	123 (27)	23 (5)	66 (15)	8 (2)
Cough	77 (17)	0 (0)	55 (12)	1 (0)
Vascular Disorders				
Hypertension[d]	80 (17)	29 (6)	33 (7)	12 (3)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone.

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[b] Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Dyspnea includes dyspnea and dyspnea exertional.

[d] Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.

The event rate of ≥ Grade 2 peripheral neuropathy in the Kd arm was 6% (95% CI: 4, 8) versus 32% (95% CI: 28, 36) in the Vd arm.

Grade 3 and higher adverse reactions that occurred during Cycles 1-12 with a substantial difference (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.

6.2 Postmarketing Experience

The following additional adverse reactions were reported in the post-marketing experience with Kyprolis. 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: hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis.

7. DRUG INTERACTIONS

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Kyprolis can cause fetal harm based on findings from animal studies and the drug's mechanism of action. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. Males of reproductive potential should be advised to avoid fathering a child while being treated with Kyprolis. Consider the benefits and risks of Kyprolis and possible risks to the fetus when prescribing Kyprolis to a pregnant woman. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Kyprolis in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kyprolis and any potential adverse effects on the breastfed infant from Kyprolis or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Kyprolis can cause fetal harm. Advise female patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 30 days following completion of therapy. Advise male patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 90 days following completion of therapy.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 598 patients in clinical studies of Kyprolis monotherapy dosed at 20/27 mg/m² by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age. In a single-arm, multicenter clinical trial of Kyprolis monotherapy dosed at 20/27 mg/m² (N = 266), no overall differences in effectiveness were observed between older and younger patients.

Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 47% were 65 and over and 11% were 75 years and over. The incidence of serious adverse events was 50% in patients < 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

Of 463 patients treated with Kyprolis dosed at 20/56 mg/m² by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 50% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age. No overall differences in effectiveness were observed between older and younger patients.

8.6 Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. The pharmacokinetics and safety of Kyprolis were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic dialysis. In this study, the pharmacokinetics of Kyprolis was not influenced by the degree of baseline renal impairment, including the patients on dialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the drug should be administered after the dialysis procedure.

10. OVERDOSAGE

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.

There is no known specific antidote for Kyprolis overdosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions listed in the Adverse Reactions section.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.kyprolis.com or contact Amgen Medical Information at 1-800-772-6436.

This Brief Summary is based on the Kyprolis Prescribing Information v10, 01/16.

U.S. Patent Numbers: http://pat.amgen.com/kyprolis

CIGNA'S COLLABORATIVE CARE PROGRAM OFFERS FINANCIAL INCENTIVES, DATA, AND OPERATIONAL SUPPORT TO PARTICIPATING PRACTICES.

(continued from SP509)

meanwhile, functions as the unifying member of the teams and is central to successful care delivery.[10]

A Role for Insurers

Cigna, a health insurance service company, has developed its own Cigna Collaborative Care program modeled on the accountable care organization principle: it depends on a network of large and small health practices and hospitals, and needs a primary care component for the physicians to be responsible for the health of their patient population.[11] The fulcrum of this collaborative structure is a care coordinator who ensures patients seek appropriate screening and follow-up care, especially if they suffer from chronic conditions.[12]

This model has now been extended to cover cancer care practices. Cigna now provides support to participating practices—in the form of financial incentives, data, and operational support—so they can ensure patients:

- Have 24/7 access to a care provider
- Have a go-to registered nurse (RN) oncology care coordinator
- Are involved in treatment decisions with their oncologist
- Can provide feedback on quality metrics, such as palliative care assessment and distress screening

Participating clinics have access to the following resources:

1. Financial incentives, including a patient management fee and opportunity to partake of shared savings.
2. Cigna's patient database that will provide them with a daily inpatient admission report and a quarterly report on patient resource utilization.
3. Significant operational support that includes,
    a. An oncology nonclinical navigator who supports participating groups in the collaborative, acting as their single point of contact
    b. A case manager to support the RN
    c. A report on inpatient care within 24 hours
    d. A nationwide collaborative for participants to share and learn from best practices

According to the Advisory Board's report, Cigna has collaborated with 3 oncology practices to launch Cigna Collaborative Care:

- Virginia Cancer Institute, in Richmond, Virginia
- Regional Cancer Care Associates, in Hackensack, New Jersey
- Florida Cancer Specialists & Research Institute, in Fort Myers, Florida

Cigna announced in August that 3 other practices would be joining the Collaborative[13]:

- Northwest Georgia Oncology Centers, PC, in Atlanta, Georgia
- Oncology Consultants, in Houston, Texas
- Cedars-Sinai, in southern California

"We've had much success with our collaborative care arrangements for large primary care physician groups. Now we're applying that successful model—which includes a care coordinator employed by the medical practices and incentives that compensate physicians for the value of the care they deliver—to drive similar improvements in quality and cost of cancer treatment," said Bhuvana Sagar, MD, the Cigna medical director who provides clinical oversight for the company's oncology collaborative care arrangements, in the press release.

A similar such initiative has been launched by Highmark Inc. Called the Highmark Cancer Collaborative, Highmark, which is an independent licensee of the Blue Cross Blue Shield Association, has brought together the Alleghany Health Network Cancer Institute and the Johns Hopkins Kimmel Cancer Center to create and share best practices in cancer care. The Collaborative includes several different initiatives, all aimed to improve the standard of patient-centered care, such as:

- Implementing standardized treatment pathways
- Providing performance-based reimbursement for providers
- Improving patient access to care by removing unnecessary administrative barriers
- Offering second opinions for patients based on the complexity of their disease
- Arranging access to early-stage clinical trials

The patient-centric design of the model is obvious from the flexibility it offers to patients to seek care at alternative sites outside of the hospital if they are more convenient to patients and cost-effective.

"I believe we are unique in how we are integrating these components together, centered around our members. Above all, we want patients to have confidence that they're getting the best possible care," according to Ginny Calega, MD, vice president of strategic clinical solutions at Highmark, in a statement. The model will initially include Highmark members in western Pennsylvania, with plans to expand to other Highmark markets.[14] ◆

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Learning About Oncologist–Patient Communications by Speaking Directly With Each

Daniel Weber, MPM, and Shelley Fuld Nasso, MPP

THE IMPORTANCE OF DOCTOR–PATIENT COMMUNICATION IN GENERAL CLINICAL SETTINGS IS WELL ESTABLISHED. "Effective doctor–patient communication is a central clinical function in building a therapeutic doctor–patient relationship, which is the heart and art of medicine."[1] The impact of this communication goes even further. "Research has shown that effective patient–physician communication can improve a patient's health as quantifiably as many drugs—perhaps providing a partial explanation for the powerful placebo effect seen in clinical trials."[2] With the high levels of psychological stress, uncertainty, fear, and sense of helplessness associated with a cancer diagnosis, the National Coalition for Cancer Survivorship (NCCS) sought to learn more about this critical interaction specifically from cancer patients and oncologists.

Background

Three decades ago, a cancer experience was viewed differently than it is today. Someone diagnosed with the disease was simply and helplessly referred to as a "cancer victim" and was often treated accordingly. However, for a small group of individuals, many of whom had experienced a cancer journey themselves, the status quo was no longer acceptable. In 1986, this group—including recognized experts on employment and disability law, healthcare consumerism, and psychosocial and behavioral research—came together to create NCCS. The organization changed the culture in oncology, replacing "cancer victim" with "cancer survivor" and creating the concept of "survivorship." NCCS defined someone as a "survivor" from the time of diagnosis and for the balance of life, which is now the norm for the entire cancer community, including the National Cancer Institute.

Today, there are an estimated 15.5 million cancer survivors, with projections that nearly 1.7 million additional persons will be diagnosed with cancer this year alone.[3] By 2026, it is estimated that there will be 20.3 million cancer survivors in the United States.[3] Add to these figures the caregivers, family members, and friends of a cancer patient, and the number of individuals impacted by cancer is staggering—it affords relevance to the substantial investments in cancer research, primarily focused on treatments. However, with evidence indicating the importance of survivorship issues, including quality of life (QOL) during and after cancer treatment, it is critical that more effort and resources be devoted to improving doctor–patient communication, and ensuring shared decision making, so that treatment choices reflect the patient's goals and values.

NCCS-Initiated Focus Groups

One of the goals at NCCS is ensuring a shared decision-making process between patient and provider that includes a discussion of the specific diagnosis, prognosis, goals of care, treatment options (including the benefits and risks of each option), QOL, and patient preferences. To enhance our understanding of stakeholder perspectives on these issues and to identify the most effective approaches to improve communication and adoption of shared decision making, NCCS collaborated with Edge Research to conduct patient–oncologist focus groups. The scope of this research was qualitative in nature, intended to be descriptive rather than predictive. As such, statements and observations made regarding "patients" and "oncologists" in this paper refer only to those who took part in this study.

The research objectives included the following:

- Understand the attitudes, values, beliefs, and behaviors of cancer patients and providers regarding communication about diagnosis, treatment options, and goals.
- Understand the challenges of cancer care planning, including discussions on QOL, side effects, access/cost, and the impact of delivery location.
- Gather recommendations for what would improve patients-provider communication (eg, tools, practice structures, etc).

The oncologists participated in an in-person focus group with 9 participants of different ages and from different practice settings, including cancer centers, academic health centers, community hospitals, and private practice (FIGURE 1). Each participant works with large populations of Medicare patients.

FIGURE 1. Research Structure

ONCOLOGISTS	PATIENTS	
In-person focus group	**In-person focus group**	**5 individual interviews + 3 dyads (with patient and caregiver)**
• 9 participants • Mix of practice settings, including cancer centers, academic health centers, community hospitals, and private practice • Mix of ages **Location:** Baltimore	• 8 participants • Aged 65-75 years • Socioeconomic mix • Mainly cancer survivors (breast, prostate, and colon) • Diagnosed within past 3 years **Location:** Baltimore	• Aged 65-75 years • Socioeconomic mix • Advanced state/cancers with poorer prognosis (lung, metastatic, breast, ovarian, colon, and biliary duct) • Diagnosed within past 3 years **Location:** Virtual

The patients were split into 2 groups. The first was an in-person group of 8 participants, aged 65 to 75 years, representing a mix of socioeconomic backgrounds; they were primarily cancer survivors who had completed treatment and had been diagnosed within the past 3 years. The second group took part in a series of 8 in-depth interviews conducted virtually—5 with individual patients and 3 dyads with a patient and their caregiver. These patients had advanced cancers with poor prognosis. All focus groups and interviews were conducted in January and February of 2016.

NCCS NATIONAL COALITION FOR CANCER SURVIVORSHIP

WEBER

NASSO

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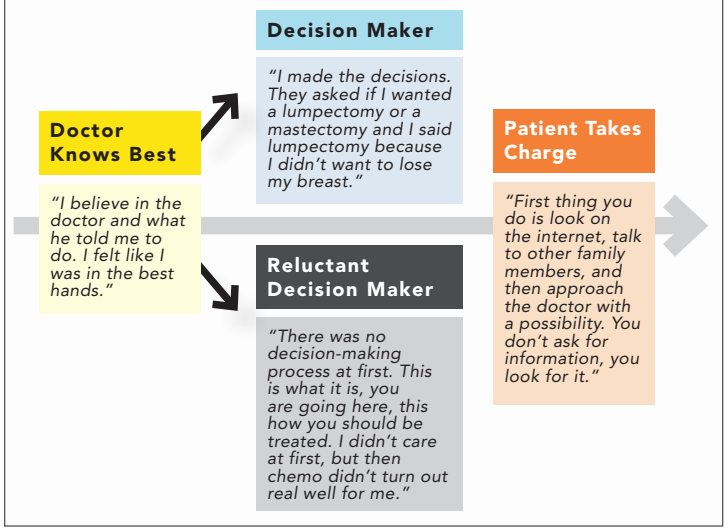
Research Findings

Patient Mindset

The conversations revealed a range of patient mindsets about the oncologist–patient relationship, falling on a spectrum from little patient involvement to a take-charge approach (FIGURE 2).

FIGURE 2. Patient Mindset



Treatable and early-stage patients fell predominately under the "decision maker" mindset and are an extension of the "doctor knows best" mentality. They want their doctor to steer the ship, but it's also important for them to feel like they have choices for their treatment options. Patients with advanced cancer and a poorer prognosis, however, had a wider spectrum of mindsets, whether based on personality (the take-charge patient) or on circumstance (the reluctant decision maker who is forced to assume a greater role in their care). To complicate this dynamic further, patients may shift from one mindset to another during their journey due to a variety of factors, including poor treatment and care, recurrence of disease, and fear of death. These mindsets, and how patients relate to the oncologist–patient relationship, must be considered when developing and implementing strategies for improvement.

Physician Mindset

Not surprisingly, physician mindsets showed a wide degree of variance, as well. Physicians shared that they value good outcomes for their patients, but they take different approaches toward achieving these outcomes. Some were more paternalistic in their interactions ("You can beat them over the head, but they may have very strong opinions about what they want. It's like being with your kids. Being a parent helps you be a good doctor,"), while others saw themselves as more of an interpreter or a guide through a decision-making process ("They are ultimately decision makers, but they [don't have enough information] to make decisions so we guide them"). One attribute that came through, and this was seen vividly during the discussion regarding care planning tools, was that many physicians felt as though they were losing control of how they practice their craft. They cited changes to drug costs, reimbursement, value-based care, use of electronic health records, quality measurement, and a general sense that they were losing autonomy of how they ran their practice or provided care.

THE PATIENT MINDSET AND HOW EACH RELATES TO THE ONCOLOGIST–PATIENT RELATIONSHIP MUST BE CONSIDERED WHEN DEVELOPING STRATEGIES FOR IMPROVEMENT.

With these variations in mindset, in addition to the historical oncologist–patient dynamic, it is no wonder that considerable disconnects in communication continue to exist. To be fair, both patients and oncologists agreed that trust and empathy (establishing a good rapport) were key elements to a beneficial oncologist–patient relationship. However, the similarities ended there, with disagreement on how to establish that trust and empathy. Whereas both groups said they believed in the goal of developing and wanting a partnership, the definitions for each group were highly variable (patient "buys in" to the oncologist's recommendations vs a true back and forth discussion). Further, the oncologists showed that they inherently believe in the value of good communication with their patients, but again, their definitions of "good" were highly variable and often at odds with patient values (see TABLE).

TABLE. Examples of Patient–Oncologist Disconnect

ONCOLOGIST	PATIENT
"I bought a nice 28-inch monitor that helps patients see exactly what I see on my end…it keeps them engaged"	"He didn't have a computer or clipboard in front of him. He looked into my eyes and made me feel so secure."
"My introduction is always the same. 'Hi, my name is Dr____. What can I do for you today?'"	"They always ask, 'What can I do for you today?' It's irritating! They should know."

In general, patients wanted to feel heard, but many also expressed a desire to feel comforted by the security of having a plan laid out for them. Several admitted that they were more comfortable taking their questions to a different member of the staff (ie, patient advocate, nurse, or social worker).

Shared Decisions and Patient Centricity

When discussing the oncologist–patient relationship, the terms "shared decision making" and "patient-centered care" are widely used, particularly in the patient advocacy community. However, when exploring this terminology with patients and oncologists, we found that understanding and interpretations varied wildly.

Oncologists' interpretations of the term "shared decision making" ranged from the need to secure patient buy-in for treatment success to having patients be active or contributing participants in their own care planning. Most saw some form of shared decision making as necessary for treatment, but differed on what this actually meant. A few of the doctors shared that they preferred the term "informed and shared decision making." Among patients, the definition depended on their mindset. Many of the patients said they wanted to be comforted and given direction in order to arrive at a decision they feel they own; at the very least, most wanted to feel like they were offered a choice.

Patient-centered care is gaining greater attention in the medical community. Yet, the oncologists in the focus group almost unanimously viewed the term as highly politicized and anti-physician. They believe the term provides additional evidence on how bureaucrats dictate physician performance. Oncologists responded negatively, and even resentfully, to the term, which they equated with 24-7 accessibility, a symbol of practice change that they considered unrealistic and unreasonable. For patients, while the term was largely unknown, it garnered associations around greater access to support services and good customer service (many equated it with a cancer center, a relationship with nurse or patient advocate, or a support group). When patients were asked if they had actually experienced receiving patient-centered care, the responses were mixed (ie, "It doesn't exist!" vs "This is my cancer center").

The disconnect between doctors and patients around communication and decision making extends to discussions around treatment planning and QOL goals. These are discussions that patients don't seem to be having with their doctors, resulting in poor communication around needs and expectations for QOL and symptom management.

For example, discussion around palliative care reinforced the common misunderstanding that palliative care is only provided at the end of life. Regardless of the stage, most patients were not familiar with the term and associated it with hospice care—a topic many do not feel ready to discuss. Pain and discomfort, however, were a pervasive part of the patient journey. Indeed, thinking about worst-case scenario/end of life was something many were fearful of, although some patients with more advanced disease were more open to these types of discussions. Patients do not remember physicians bringing up palliative care or hospice as part of the discussion on treatment, and some patients were frustrated that their doctors avoid the topic. As other surveys have shown, the concept of palliative care is well received when it is explained to patients. Unfortunately, the terminology is the problem.

Although they are not necessarily proactive in their care planning, all participating patients valued being prepared for their visits. Patients admitted they had a hard time remembering information they receive at appointments, and oncologists concurred that the Medicare population was usually less prepared and could only absorb a certain amount of information. As such, patients saw the usefulness of care planning tools in helping them remember and track important information for their care and symptom management; however, these would need to be tailored to patient needs and preferences. For example, the ability to track symptoms or keep a record of their chemotherapy treatments was especially appealing for patients in treatment (hard to remember during "chemo fog"), but they found a vast treatment plan too overwhelming. They felt such tools should to be made available by a doctor or nurse in a paper format, as well ("People over 60 [years] need a clipboard"), and should be referenced during appointments.

Conversely, the oncologists resented any additional paperwork, claiming that patients would not use these types of care planning tools, and thus ultimately dismissed their usefulness. One quote from a doctor summed it up: "All this paperwork is going to be left behind. If a patient is interested in this information, they're going to have it already."

Implications and Next Steps

This small study is a step forward in exploring these important issues further via direct interaction with patients and oncologists. We interviewed a range of patients who reinforced that cancer is complicated and it is difficult to design one-size-fits-all strategies. Based on individual mindsets, certain subsets of patients are more receptive to tools and strategies to help them manage their care and communicate with their doctors than others. That said, patients who want their doctors to take the lead are not a lost audience and also require various levels of assistance—many of these patients acknowledge the need for help in retaining information, tracking side effects, and acquiring additional guidance when making decisions.

The Medicare patient mindset appears to be influenced by a variety of factors that merit further exploration, including socioeconomic status, care delivery setting, and disease severity. Additional qualitative and quantitative research among Medicare patients across these groups could help further elucidate the types of patient mindsets and yield added insights into finding what tools and strategies are most useful to specific types of patients.

The Impact of Payment and Delivery Reforms

Our study clearly showed that the oncologists felt an increasing loss of control due to a variety of factors, including changes in payment models and care delivery. This is compounded by new pressures from being evaluated on performance metrics. It is in this environment that we must recognize and seek to understand the ongoing disconnect between doctor and patient, and more importantly, how best to make improvements through additional help with soft skills (ie, patient communication). These added pressures also provide some insights on their reactions to care planning tools—one that is easy to use and does not burden their already busy schedules (ie, they will resent filling out more paperwork, and they expect respect and reimbursement for their time). Continuing medical education was not considered a viable option for the oncologists in the focus group.

From the NCCS perspective, what is at stake is far too important not to pursue every possibility. As Travaline et al state, "The physician who can communicate bad news in a direct and compassionate way will not only help the patient cope, but will also strengthen the therapeutic relationship, so that it endures and further extends the healing process."[2]

Additional qualitative and quantitative research with oncologists would identify who is open to education and training around communication and use of tools, in addition to identifying less politicized language that can be used to discuss shared goals. The results from this small focus group already suggest that there are differences in oncologists' attitudes and values by age, years in practice, and practice settings. These questions need to be explored further with a larger sample of oncologists.

There was some consensus among participants that Medicare patients and oncologists are not always best equipped to talk to each other. Future research projects could delve into increasing the engagement of intermediaries such as nurse practitioners, patient advocates, and other mid-level providers, along with informal caregivers (family members and friends). Although caregiver perceptions were preliminarily explored through the dyad approach, it would be helpful to talk to them as a separate audience who may not only have a different mindset, but be more receptive to tools and strategies. Also, given their key role as patient advocates and intermediaries between patients and oncologists, it would also be important to explore questions around improving communication and patient-centered care with nurses, social workers, patient navigators, etc. Looking to those outside of the traditional oncologist–patient relationship may offer additional solutions for improving shared decision making and, ultimately, patient care. ◆

OUR RESULTS SUGGEST DIFFERENCES IN ONCOLOGISTS' ATTITUDES AND VALUES, BY AGE, YEARS IN PRACTICE, AND PRACTICE SETTINGS.

DISCLOSURES

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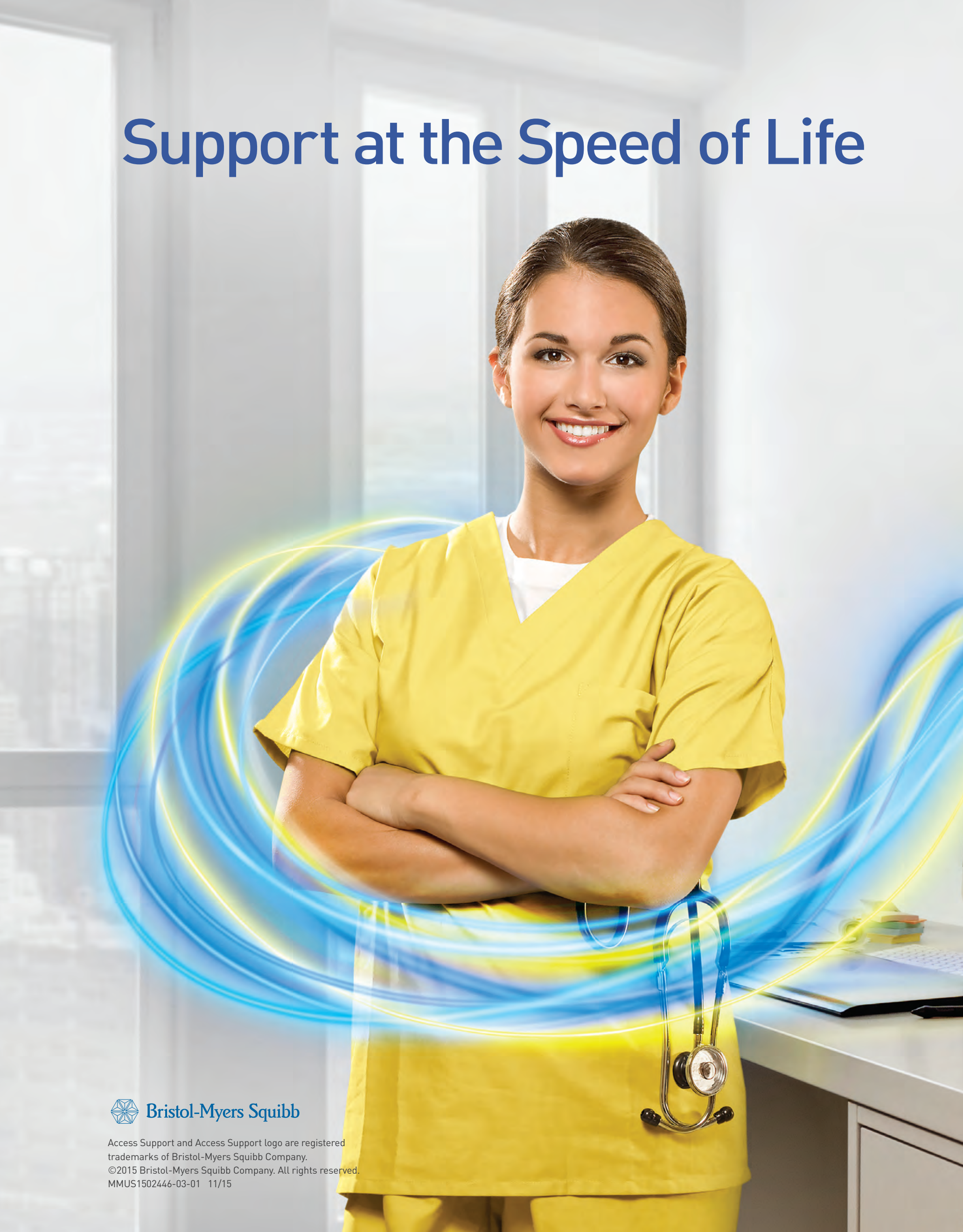

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ASCO President Dr Daniel F. Hayes Applauds Recommendations for Cancer Moonshot

Surabhi Dangi-Garimella, PhD

HAYES

THE BLUE RIBBON PANEL (BRP)—a committee of scientific experts, patient advocates, and representatives from the pharmaceutical industry, appointed by the National Cancer Institute (NCI) to lead the White House Cancer Moonshot initiative—released a preliminary report[1] with important recommendations that can support faster, more precise treatments for patients diagnosed with cancer, with potential for much improved outcomes. *The American Journal of Managed Care*® reached out to Daniel F. Hayes, MD, FASCO, 2016-2017 president of the American Society of Clinical Oncology (ASCO), to understand his perception of how these recommendations would impact cancer care in the United States.

AJMC®: **One of the suggestions of the BRP is to better link databases to assimilate patient information across systems, with the potential to recruit patients to participate on trials. Since interoperability remains a significant challenge for our healthcare system, do you foresee this as a more long-term recommendation?**

HAYES: Widespread interoperability for sharing electronic health information is critical for optimal cancer care. It's incredible that we have a standardized method for streaming TV shows, but not for taking care of sick patients. I'm pleased that the Panel included this recommendation in the report. Frankly, this is the kind of innovation that we cannot put on the long-term track. The cancer community—the entire medical community, actually—needs to put our full support behind interoperability so that it is achieved more quickly. The American public does not suffer lack of access and interoperability when it comes to other potentially sensitive information (eg, financial information). We should expect no less when it comes to the medical information needed to stay healthy and treat illness, especially a serious diagnosis like cancer. This is the kind of innovation that the Moonshot requires. ASCO is fully supportive of this transformative idea.

"LARGE CANCER INSTITUTIONS MAY [BE] USING MULTIPLE ELECTRONIC HEALTH RECORD SYSTEMS THAT DO NOT TALK ACROSS DEPARTMENTS."

—Daniel F. Hayes, MD, FASCO

AJMC®: **How are individual clinics and smaller practices adopting interoperability?**

HAYES: There are 2 issues embedded in this question: 1) the adoption of electronic health records (EHRs) and 2) interoperability among them. Individual clinics and smaller practices are having a *very* difficult time, especially with the first. The problem isn't isolated to just small practices, however. Even large, internationally recognized cancer institutions may be in a situation where they're using multiple electronic records systems that do not talk across clinics and departments—whether they are across town, in different states, or right next door to one another. This is a major concern in oncology, where we routinely work with patients going to multiple medical providers across the continuum of care, eg, radiation therapy, surgery, chemotherapy, imaging, pathology, etc. Gaining access to medical information and seamlessly integrating and analyzing it for patients across multiple providers takes more effort than it should.

Because of this, ASCO has called on Congress to address this issue directly. ASCO issued the following 4 recommendations, which should be part of the Moonshot initiative:

- Congress should enact legislation as quickly as possible to ensure widespread interoperability is achieved.
- Congress should pass legislation to remove barriers to interoperability, especially information blocking.
- Policy makers should ensure that cancer patients, oncologists, and other oncology providers do not bear the costs of achieving interoperable EHRs and of companies refraining from information blocking.
- Federal officials should work with ASCO and other stakeholders to ensure that healthcare providers have the information necessary to be prudent purchasers and users of health information technology systems.

We are pleased that the BRP included the idea of a National Cancer Data Ecosystem. ASCO is building this with CancerLinQ and working with patient organizations and our colleagues across the medical professions to integrate data.

AJMC®: **Although pediatric cancers have received specific recommendations from the panel to improve clinical outcomes, geriatric cancers have not. Your thoughts on that?**

HAYES: You raise a very important point. It is admirable that the BRP recognized unique issues facing children with cancer, which ASCO supports. We also need to put focus on older adults with cancer because oncology clinicians face tremendous challenges in meeting their cancer care needs.

Patients over 65 make up 60% of those diagnosed with cancer and 70% of cancer deaths. ASCO issued a statement in October 2015 that includes recommendations on improving the evidence base for treating older adults with cancer.[2] ASCO's Moonshot recommendations to the NCI BRP included many items from the statement, including broadening eligibility criteria to facilitate greater participation of older adults in research, conducting pragmatic trials that focus on broader patient populations, and conducting research with real-world data.

Many of the Moonshot initiative's recommendations are likely to improve care for older patients, even if the specific recommendations are much broader. As efforts are made to implement these recommendations, however, it will be important to ensure that they consider the needs of geriatric patients.

Examples of the Panel's recommendations that have the potential to improve care for older adults:

- The network for patient engagement has the potential to increase older adults' participation in clinical trials by matching patients based on the tumor profile to appropriate trials.
- The National Cancer Data Ecosystem for Sharing and Analysis could provide data on older adults from real-world settings,

which would complement research from randomized clinical trials that often exclude older adults.
- The focus on research into symptom management is particularly relevant to older adults because this population often places great value on endpoints other than overall survival (eg, functional independence).

AJMC®: With the rapid rise in the number of oral anticancer agents, monitoring patient adherence can prove to be a significant challenge that ultimately impacts patient outcomes. Do you think the panel should have proposed ways to improve patient adherence to treatment? How can we address this issue in cancer patients?

HAYES: Orally administered anticancer agents allow many patients to undergo treatment outside of a hospital or doctor's office and go about their daily lives with minimal disruption, providing significant advantages over more traditional intravenous (IV) or injected medications.

Patient adherence to oral anticancer agents can pose a significant challenge, because obviously, medicines don't work in the bottle—they only work in the patient! Poor adherence leads to reduced rates of response, more complications from the cancer, and increased medical costs. Among the many barriers to oral cancer therapy adherence, cost is a significant barrier. Some health plans impose significantly higher cost-sharing requirements on patients who receive oral anticancer medications. (Cancer medications delivered by IV are covered under the medical benefit provision, while cancer drugs taken orally are often covered under the outpatient prescription drug benefit.)

To address this issue, ASCO has continued to advocate for states and the federal government to pass legislation that ensures patients can access oral cancer drugs under the same general cost-sharing rules as other cancer drugs.

In addition to cost, side effects and forgetfulness in everyday life can lead to poor adherence and persistence with oral medications. In this regard, ASCO's recommendations to the NCI highlighted the need to enhance our patient-reported outcomes (PRO) measurement tools so that we can determine what toxicities patients are actually experiencing—financial, physical, or psychosocial. NCI and the oncology community have made a huge investment in developing a PRO tool that measures the common toxicity criteria in cancer clinical trials (PRO-CTCAE). We are pleased that the BRP recognized the value of the PRO-CTCAE. However, ASCO further strongly recommends that the NCI invest in:

1. Implementing the PRO-CTCAE, which will require investment in enhancing the way we conduct trials to regularly capture toxicity information from trial participants.
2. Enhancement of the PRO-CTCAE to incorporate additional factors that patients may consider when making a treatment decision, in addition to the "important medical and clinical conditions" already included in the PRO-CTCAE.

Although various methods for measuring and improving adherence are available, additional research is needed to identify optimal methods that will work across diverse practice settings. Indeed, ASCO has supported such trials through our Conquer Cancer Foundation grants system. Other organizations, including NCI, are doing so as well, but we need more resources to address this critical issue.

AJMC®: As we transition toward precision healthcare, there is no dearth of diagnostic tests or molecular data on tumors. However, interpretation of this data seems to be a significant hurdle. Does the report address this issue?

HAYES: Several sections of the report include provisions that would help advance our understanding of diagnostic testing and molecular profiling data:
- Network for direct patient engagement: making testing accessible and enabling data sharing and participation in molecularly driven clinical trials
- Fusion oncoproteins in pediatric cancer: improving understanding of the role of oncoproteins in pediatric cancers and identifying therapeutic targets
- Retrospective analysis of biospecimens from patients treated with standard of care: we may discover molecular biomarkers for response or resistance
- Generation of human tumor atlases: documenting genetic lesions and cellular interactions that guide the development of each tumor as it evolves from a precancerous lesion to advanced cancer

Many of these recommendations build on important work that the NCI is already engaged in, such as genomic testing and investigation of molecularly driven therapies in the adult and pediatric MATCH trials and Lung-MAP trial, biospecimen banking and analysis through the National Clinical Trials Network and the Cooperative Groups before it, the Exceptional Responders Programs, and The Cancer Genome Atlas (TCGA) that advanced basic science understanding of common tumors.

ASCO has, over the last 3 decades, provided evidence-based guidelines for using tumor biomarker tests to direct patient care, and we have helped establish criteria for doing so. Because we believe that "a bad tumor biomarker test is as bad as a bad drug," we have recently supported an analysis of increasing the value of tumor biomarker tests performed by the National Academy of Medicine (formerly the Institute of Medicine).

In our recommendations to the BRP, ASCO also discussed the need to better understand molecular testing through the Coverage with Data Development mechanism, as well as leveraging clinical trials, like ASCO's TAPUR study,[3] to test whether drugs used for a molecular target in one cancer are effective for the same target in other cancers, and using learning healthcare systems like CancerLinQ to accumulate and analyze data on testing and associated therapies.

The question you raise also points to the importance of a strong, definitive role for the FDA in premarket regulation of testing that is used to indicate precision therapies. In an era when we are using targeted drugs (especially drugs that may work only if the target is present), it is vital that we understand the safety and efficacy of the test that indicates whether a tumor has the target.

AJMC®: Do you think we need greater emphasis on cancer prevention research?

HAYES: Yes, absolutely. We were really pleased to see the BRP's focus on improving prevention research within its report to the NCI. The panel specifically highlighted people at higher risk for cancer, because of their family history, and the need to implement screening. ASCO also believes it is important to advance research related to behavioral changes and socioeconomic factors that influence population health behaviors that prevent people from doing what we know works to prevent cancer, such as energy balance and obesity prevention and treatment.

"AMONG THE MANY BARRIERS TO ORAL CANCER THERAPY ADHERENCE, COST IS A SIGNIFICANT BARRIER."

—Daniel F. Hayes, MD, FASCO

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AJMC®: **While on one hand imaging technologies accelerate cancer diagnosis, unnecessary imaging can result in overdiagnosis. Do you think integrating information across multiple testing platforms is the way forward, rather than interpreting individual tests that may present just a part of the picture? Who should be responsible to assimilate this data, which may exist in silos: the oncologist or the primary care physician?**

HAYES: There are multiple answers to this question. The first component regards ordering of diagnostic tests. We support development of evidence-based oncologic pathways and guidelines to help physicians make good decisions for their patients. Indeed, we have a very active guidelines program that is widely respected, and we have recently published criteria for determining the quality of clinical pathways. Although we support physician autonomy in caring for his/her patient, we are convinced that these guidelines and pathways can help guide appropriate diagnostic test ordering and reduce unnecessary imaging.

We agree that multiple physicians caring for 1 patient can result in inconsistent care. As cancer has become increasingly complex and multimodal in its treatment, having multiple providers, each with specialized expertise, is often necessary and important. That said, multiple physicians caring for 1 patient can result in inconsistent care if such care is not coordinated. As we've noted, ASCO has been advocating for action by policy makers to promote the interoperability of electronic health data across multiple information technology systems. At this time, the patient plays an important role in helping to assemble data, but the healthcare system has an obligation to meet this demand.

AJMC®: **What is your realistic estimate of the impact the recommendations will have on improving cancer outcomes? Where in cancer care do you expect to see the biggest strides?**

HAYES: The panel's thoughtful work makes an important contribution to the Cancer Moonshot initiative. We will be eager to see how the Cancer Moonshot Task Force and Vice President Joe Biden move ahead with their reports. The recommendations could significantly expedite our nation's progress against cancer, if Congress provides the crucial additional funding to support the Cancer Moonshot initiative. ASCO is heavily engaged in the discussion as the work proceeds.

We are pleased the panel also sent recommendations to the Task Force for policy changes related to cancer research and care delivery. ASCO is working closely with the Vice President's office to advance policy and regulatory changes that will help streamline research, standardize regulatory requirements, and enable public–private partnerships to extend the Moonshot initiative. Sometimes being innovative requires finding the straight line through a process that can get lost in the endless loops of bureaucracy. We are optimistic that the Moonshot initiative will provide a shot in the arm to move our already impressive anticancer efforts forward, and we advocate for a sustained program to support the research and care delivery that is needed to maintain them. ◆

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SIDEBAR

Panel Delivers Recommendations for the Cancer Moonshot

SURABHI DANGI-GARIMELLA, PHD

IMPROVING PATIENT ENGAGEMENT, developing a cancer immunotherapy clinical trial network, and providing support to manage patient-reported symptoms—these are among recommendations from an exclusive committee appointed to lead the White House's Cancer Moonshot initiative. The Blue Ribbon Panel is a mix of scientific experts in biology, immunology, genomics, diagnostics, bioinformatics, and cancer prevention and treatment. Representatives from cancer advocacy groups and the pharmaceutical and biotechnology industries are also represented on this team.

In its preliminary report,[1] the panel has underscored the importance of collaboration and integration across the healthcare system, merging science, technology, advocacy, and social science to strengthen existing infrastructure and build new bridges. Under the combined leadership of Tyler Jacks, PhD, from Massachusetts Institute of Technology; Elizabeth Jaffee, MD, from Johns Hopkins University; and Dinah Singer, PhD, from the National Cancer Institute, the panel provides recommendations to the National Cancer Advisory Board on scientific opportunities that could accelerate the Cancer Moonshot initiative.

Seven working groups, each with a similar diverse composition, listed 2 to 3 significant research opportunities in the following areas:

- Clinical trials
- Enhanced data sharing
- Cancer immunology
- Implementation science
- Pediatric cancer
- Precision prevention and early detection
- Tumor evolution and progression

With the objective of improving various aspects of these 7 areas, the following specific recommendations were made:

1. Direct patient engagement to allow opportunity for comprehensive tumor profiling. Gathering patient data through linked databases will improve "precision" care and match patients with appropriate clinical trials.
2. Develop a national cancer immunotherapy clinical trial network to improve cure rates and eventually develop vaccines to prevent cancer.
3. Create a National Cancer Data Ecosystem to gather, share, and connect datasets to facilitate discovery and improve patient outcomes.
4. Increase understanding of fusion oncoproteins that result from chromosomal translocations; these are responsible for several pediatric cancers and demand new therapeutic approaches.
5. Provide additional support for personalized care research in the field of symptom management throughout the cancer care continuum; this will improve patient quality of life and subsequently improve treatment adherence.
6. Focus on implementation science to develop cohesive strategies that include the patients, caregivers, and family members; healthcare providers and health systems; and the community as a whole. The committee recommended directing prevention and screening efforts toward human papillomavirus vaccination, colorectal cancer screening, and tobacco control, as well as identifying individuals genetically predisposed to cancer.
7. Create a human tumor atlas that documents genetic lesions and cellular interactions that map tumor development to help prevent cancer, identify new therapies, and avoid resistance development to existing treatments.
8. Enable development of new cancer technologies, such as implantable microdosing devices in tumors, new patient-derived tumor models, advanced imaging technologies, and computational platforms for data integration.

The working groups also made some policy recommendations including coverage and reimbursement, patient consent, fragmented care delivery, and barriers to data sharing. The report provided health policy groups with evidence that can further their lobbying efforts to Congress to fund the Cancer Moonshot initiative.

"They needed to see a plan," Jon Retzlaff, MBA, MPA, managing director of Science Policy and Government Affairs at the American Association for Cancer Research, told *STAT news*.[2] "Now it's something that we can take to Capitol Hill. Here are projects that can be funded and should be funded and will help us get to where we need to go."

A final comprehensive report, which will help establish a cancer research agenda in the nation, is expected by the end of 2016. ◆

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PANEL DISCUSSION

Filling the "Donut Hole" in Oncology Care With Collaboration and Navigation

Surabhi Dangi-Garimella, PhD

HEALTHCARE, OF LATE, HAS SEEN A LOT OF MOVEMENT toward improved care delivery and reimbursement, with several experimental models being tested in the field by CMS and private health plans. The emphasis is on collaboration and communication: data sharing and team-based care can offer providers a multidimensional view of the patient and improve outcomes.

To discuss this progress and what is currently lacking in care practices in oncology, *The American Journal of Managed Care*® invited Rebekkah Schear, MIA, director of mission delivery at the LIVE**STRONG** Foundation, and Michael Kolodziej, MD, former national medical director of oncology strategies at Aetna and currently the national medical director of Managed Care Strategy at Flatiron Health. The telepanel was moderated by Joseph Alvarnas, MD, editor-in-chief of *Evidence-Based Oncology*™. Alvarnas is associate clinical professor and director of medical quality, risk, and regulatory management, City of Hope, Duarte, California.

The panel began with Alvarnas asking participants to define what patient-centeredness and shared decision making mean in oncology care. Patient-centeredness is the new paradigm for care delivery, as reflected by major shifts in policy and practice, Schear said. Considering how complex cancer care is, patient-centeredness is all the more important. "Reports have come out in 2013 that list 6 core elements of what delivery of cancer care should look like moving forward and how patient-centeredness, shared decision making, coordination of care, a learning healthcare system, all of these things, are sort of embedded in what that might look like," she said. Although this is being implemented, she believes there's room for improvement.

What about the potential for information overload? How can patients and their caregivers be effectively engaged in care planning without inundating them with details?

Kolodziej explained that oncologists have faith in their patient-education ability and including them in treatment decisions. Payers, however, do not have much insight into how well this is being implemented by oncologists, but he agreed with Schear that there are shortcomings to the process. "The biggest shortcoming really boils down to the fact that when a newly-diagnosed patient comes into your office with, or without, supportive family members or friends, there is just such a knowledge gradient and it's a loaded conversation. It's very hard to process it," Kolodziej said.

Despite a few unsuccessful attempts, Kolodziej thinks we are currently at a point where there is some bit of standardization of communication systems for use between the members of the team of providers who are caring for the patient. In his opinion, the Oncology Care Model (OCM), which requires a documented care plan based on the Institute of Medicine's 13-point Care Management Plan, exemplifies this.[1] The "major component there is the first dialogue with the patient regarding the treatment plan and expectations from treatment."

The OCM wants providers to give patients access to all the information that they might need to understand their care plan, once the patients have adjusted to the shock of being diagnosed with cancer. "Because it's something that we think the patient will need to come back to frequently in order to totally get the entire picture of the complexity and the enormity of the care they're going to receive," Kolodziej said.

Cancer Care Plan: Documentation and Communication

Alvarnas asked Kolodziej to comment on the importance of documenting the treatment plan for cancer patients, an objective of the Planning Actively for Cancer Treatment or PACT Act.[2] Kolodziej emphasized that documentation and processes of care, especially for emergency department visits and inpatient stay, are very important for both the patient and caregiver to understand how care will be managed. Another dimension to this pertains to healthcare reform and integrated care, where poor communication among physicians has been well documented. "A standard means of communication among multiple care management teams is important, especially for Medicare patients," Kolodziej added.

Documenting treatment plans creates functionality for patients, particularly post treatment, Schear said. It can help patients and their families find a path of continuity as they adjust to the "new normal" of survivorship. Its important, she added, that all providers, particularly the primary care providers (PCPs), be aware and integrate the patient's current treatment with reference to what they have gone through for their cancer care.

A 2015 survey by LIVE**STRONG** among cancer patients and survivors found that only 29% of surveyed patients had a written summary of their treatment plan and only 17% said they had difficult care plans. More than three-fourths of survey respondents agreed that their care plans were "incredibly useful." Schear noted that patients also use the treatment plan to understand their susceptibility to other cancers in the future and the need for additional testing.

Alvarnas emphasized that assuming that patients and their caregivers can navigate all the information they have been provided would be a misstep. Patients with cancer receive care from multiple providers, and care coordination across the board of experts is vital. "Who should lead the coordination of care? How do we align economic incentives to reward that level of coordination?" Alvarnas asked.

Schear agreed with Alvarnas that although there have been big strides on ideas for care coordination, implementation barriers exist. Patients often encounter a lack of communication between providers who might be part of different healthcare systems. What


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becomes obvious is the lack of harmony within their team of PCPs, social workers, psychosocial counselors, oncologists, surgeons, and other nonclinical support. "I think that ultimately, there has to be a marriage between an informatics-enabled cancer care system with both face-to-face provision of care and knowing that patient navigators are going to be able to support [coordination] and implementation," Schear said. She added that reimbursement policies for navigators, care managers, and their services is a necessary and important amendment. "Changing this policy is possibly the most significant barrier to increasing the implementation of patient-centered cancer care," and it can help tackle the challenges of interoperability, she said.

Kolodziej's concurred with Schear. In his opinion, navigator services mandated by the OCM for Medicare beneficiaries in participating practices is the high-touch way; high-tech solutions, he said, will be necessary for efficient implementation. He believes that fragmented information technology (IT) highways are at the root of existing problems in oncology. Whereas healthcare IT platforms may not be compatible, information exchange and interoperability form the crux of accountable care organizations (ACOs), Kolodziej said. What will hurt an ACO is lack of effective communication with all the involved parties, "because there will be duplication of services, inefficiencies that will lead to higher cost of care and poor outcomes."

Kolodziej believes that interoperability will help develop Health Insurance Portability and Accountability Act (HIPAA)-compliant health information exchanges that can also include the patient in the conversation. He anticipates a much bigger role for the care provider in the process, in extracting the information and conveying just the right amount to facilitate dialogue.

Developing an Ideal Patient Portal

So how soon can patients and the healthcare system anticipate a technological fix to the existing problem of interoperability? Schear listed several existing patient-friendly apps, such as Open Notes, My Blue Health, and Patients Know Best, which ensure patients have access to their health information and a line of communication with their care provider. She also highlighted the importance of wearable devices that share patient information with care provider(s). She cautioned, however, that use of these platforms should be restricted for the most important conversations with their care providers.

However, considering HIPAA restrictions on information sharing, Schear would like to see policy changes keep pace with technological advances so patients have the ability to access and share their personal health data while simultaneously protecting it. Kolodziej agreed that the evolution of HIPAA is inevitable, and Alvarnas noted a role for patient advocacy groups like LIVE**STRONG** in the process.

"I THINK THE KIND OF CONNECTEDNESS AND ENGAGEMENT THAT IS COMING TO HEALTHCARE. WE SHOULD ALL APPLAUD IT."

—Michael Kolodziej, MD

What does an ideal patient portal look like? Schear appreciates the advantages of using the EPIC health IT platform—the flexibility to update information and communicate with your provider. What's missing, she said, is the holistic perspective—considering the health of the patient in its entirety. "We are people with emotional, social, spiritual, philosophical, and family-oriented needs and values and wants. There has to be a way for all of that to be reflected both in assessments with our providers, when we're meeting with them on an ongoing basis, and also in these patient portals, so that any time any of your providers are logging in and taking a peek at what you have going on, they get the whole story of who you are," Schear said.

Schear and Kolodziej concurred that the patient portal should provide a more patient-centric view to those who access it. Kolodziej added that although these portals were initially developed to fulfill meaningful use criteria, they are evolving to keep up with the changes within healthcare. Alvarnas pointed out that the healthcare journey is not binary. "It's not 'cure or not cure.' There's a lot more to caring for someone that may involve acknowledging issues of distress, anxiety, interfamilial difficulties, and also the fact that some patients can't be cured." He asked the panelists to address issues of quality of life, palliation, and helping patients achieve their goals of care.

Schear believes that advance care planning (ACP) and palliation should be addressed right at the outset, from the time of diagnosis, and should not be a consideration only when all options have failed. This screams for a navigator and a mechanism that allows care teams to be aware of the patient's needs and values. It also calls for participation by both the patients and their family members in treatment decisions, palliation, and decisions on end of life (EOL) care.

Schear stressed that providers need to make the time for clear, patient-centered communication that involves discussions on every aspect of care—from diagnosis to survivorship. Providers should also support patients as they decipher the impact of their disease and its treatment. Schear believes that an important aspect of providing care is for the physician to understand the patient's concerns and expectations of their care. This can lead to a shared understanding and development of solutions during treatment. "I think building that shared understanding is the critical backbone to being able, from a patient-centered perspective, to have these very critical conversations around quality of life, treatment plans, and palliation, and then when it comes to it, hospice and some of those more difficult decisions," Schear said.

Appreciating the Value of Care

How can we bring all of these considerations into perspective when trying to value them for reimbursement purposes? Kolodziej said that he's not really concerned with how the healthcare system and physicians would be financially rewarded for bringing about these changes. His concern is with ensuring physicians change their behavior.

Value-based reimbursement, Kolodziej said, which incorporates execution of ACP, EOL care, and palliative care, will generate healthcare savings and improve patient outcomes and satisfaction. "But how do we get doctors to do it?" he asked. It's how we get them to do what everybody knows is the right thing to do that's important, he added. He explained that while at Aetna, he tried to merge behavioral health resources so practices could improve their care strategy for patients. "I'm a little more worried about how we execute the kind of culture change that needs to happen in order for this to really be realized, to the advantage in the short term," Kolodziej added. Physicians, he believes, will soon realize how important this is in changing the way care is delivered.

The onus for behavioral and culture change is not the primary responsibility of the providers, according to Schear. Patients and families need to be educated on this, as well. Palliation, for example, is highly misunderstood and stigmatized—patients and their families need to look beyond their preconceived notions to understand how palliation can assist pain management and improve quality of life throughout the cancer care journey. "Patient education around this issue is absolutely critical. De-stigmatizing the idea of palliative care and removing the fear around the idea that you can still be in active treatment and you can work on improving your quality of life. You could [also] have those discussions with your providers," Schear added.

So who should be the go-to person to navigate the patient and their family through this process? The navigator may not neces-

sarily be one person. The function of a care navigator—communication, coordination of care, hand-offs, and serving as the patient touch point—should be the responsibility of the entire team that is caring for the patient, Kolodziej said. "The captain of the team is the oncologist, but in fact, every member of the team has a critical role and equally shares in both success and failure of the care delivery model," he specified.

The Patient-Oncologist Disconnect

A study published in *JAMA Oncology* found that patient–oncologist discordance was common among the cases studied, and patients were unaware that their opinions differed from their physician's.[3] While patients may be more optimistic about their prognosis, the oncologist may not. That's a disconnect that needs to be closed.

Schear narrated the story of a friend whose family could not agree on her mother's treatment plan, especially when deciding on her transition from active treatment to hospice. Schear proposed that an expert, like a social worker or an oncology nurse navigator, could help family members come together and guide them through the decision-making process under these circumstances. "I think, again, finding ways to have these open dialogues in a diffused environment is really important."

Kolodziej said that as he looks at this now as an outsider who's been there, he realizes how certain aspects of care are managed very poorly or not handled at the right time. "We do it when we're facing a crisis typically. That's not when you get the most responsive, receptive, constructive dialogue necessarily going." The entire treatment plan should be addressed right up front, with consideration for opinions of the family.

Reiterating the need for handling hospice and EOL care the right way, he said, "I am cautiously optimistic that there will be such an appetite among the patient community and the provider community for a good solution; that we will, in fact, find a way to do this much better than we're doing it right now."

When asked about the CMS proposal to pay physicians for ACP with patients and their families,[4] Kolodziej said he does not believe it will help. Deeming it as a continuous journey, he said paying for a documented 15-minute conversation on ACP will not achieve much. "But I understand that if nothing more, it does give physicians the feeling that there is a value among the payer universe behind this activity. I understand the symbolic significance of it," but he does not believe it will change the status quo.

The discussion then moved on to gaps in survivorship care and preparing patients for their life "after" cancer. Schear shared results of a LIVE**STRONG** survey from several years ago that found that a majority of patients had at least 1 posttreatment physical, emotional, or practical concern. However, 29% said they did not receive care for their physical concerns, nearly 50% voiced lack of follow-up care for their emotional concerns, and one-third did not get follow-up care for practical concerns. Less than half of the patients reported having conversations on fertility preservation and fertility risk with their provider.

Alvarnas asked Kolodziej whether adult cancer care can be modeled based on pediatric survivorship care and if it's possible to align incentives. Kolodziej said that a lot remains unknown with chemotherapy agents. He cited examples of his patients with breast cancer from 2 decades ago who were concerned about cardiac effects post treatment with Adriamycin or Herceptin—drugs known to be cardiotoxic. He said he was at a loss for information because not much was known back then about survivorship care. While the situation is improving, wellness recommendations for survivors continue to lack structure, he said.

Kolodziej drew attention to the fact that survivorship care involves a significant contribution from the patient's PCP, especially considering that many are not very confident with managing cancer survivors. "Most [PCPs] are not really that interested necessarily in taking their cancer survivors back because they're petrified that they're going to do something wrong. They're just horrified," Kolodziej said. He emphasized the importance of continued communication between the oncologist and the PCP throughout the care continuum, from diagnosis through survivorship. He believes oncologists should provide PCPs with recommendations that can promote wellness and improve patient QOL.

Alvarnas agreed that while oncologists want their patients to return to primary care, they also seek confidence that the patient's PCP is "well-positioned to ensure that issues related to cancer care are addressed equitably and in a timely fashion." Would healthcare reform impact any of this? Will value-based models push for a more integrated and ideal care delivery for these patients?

Schear thinks that the OCM is a good start and the outcomes will become clear over time. However, she does expect to see a positive impact on navigation care planning, with the patient at the center of the process. "We are moving from "an illness-centered perspective toward a person-centered perspective," Schear said. Kolodziej said that he's very satisfied that healthcare reform mandates co-payment–free cancer screening and has eliminated restrictions based on preexisting conditions. He, too, is looking forward to learning what implementation of the OCM will do, as data would be scrutinized for quality and process improvement while keeping the patient front and center. "The idea that you do things because this is the way we do things, and the patient's kind of peripheral to all this, that's disappearing," he added.

"The idea of patient centeredness isn't necessarily a means to the end. It's not a route to the point," said Schear. Reiterating the need to evolve our care systems to lend holistic support to patients, she added that it's a long journey and she's happy that we are well on our way.

Transformation using technology in healthcare will not be instantaneous Kolodziej said, but it can dramatically improve every aspect of care delivery and care coordination. "I think the kind of connectedness and engagement that is coming to healthcare. We should all applaud it." ◆

"FINDING WAYS TO HAVE OPEN DIALOGUES [BETWEEN THE ONCOLOGIST AND PATIENT] IN A DIFFUSED ENVIRONMENT IS REALLY IMPORTANT."
–Rebekkah Schear, MIA

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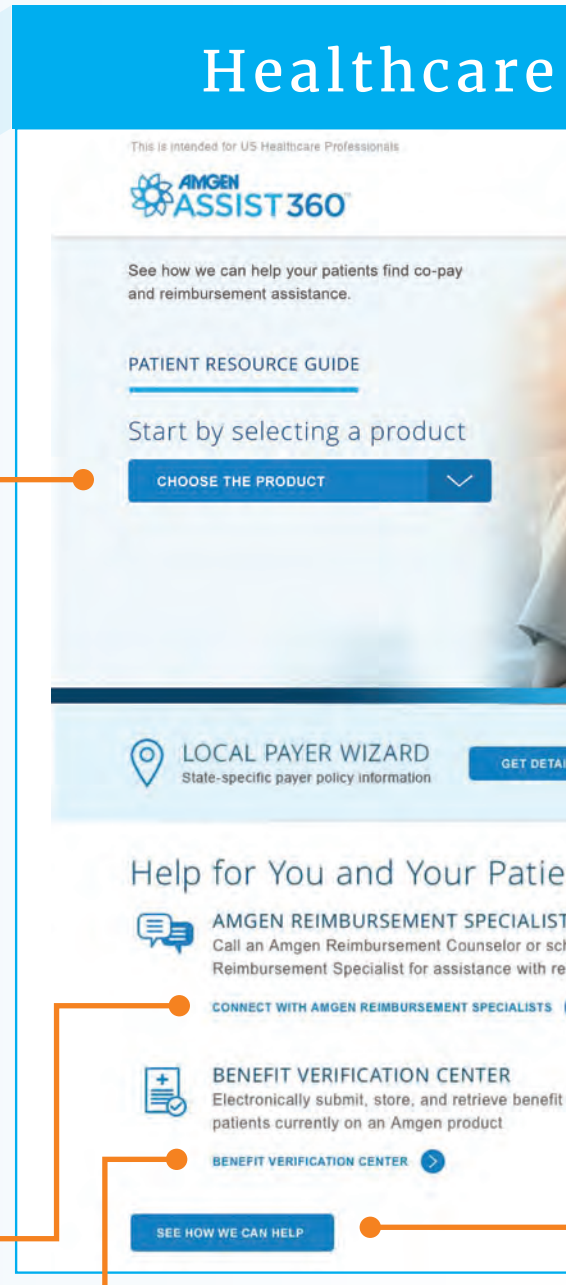

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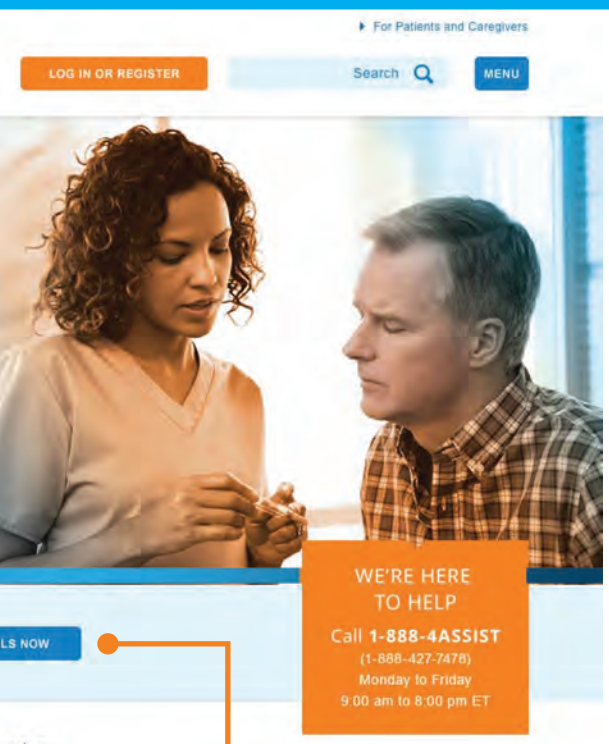

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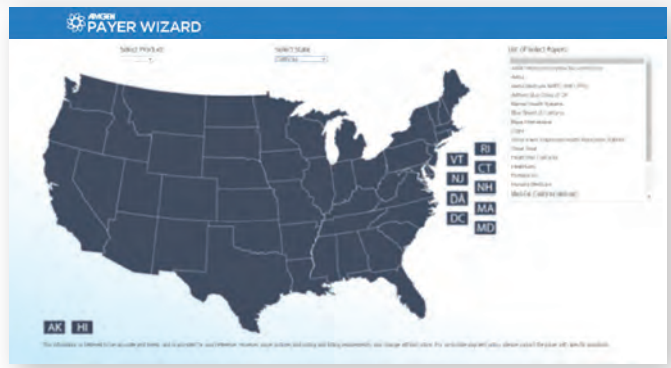

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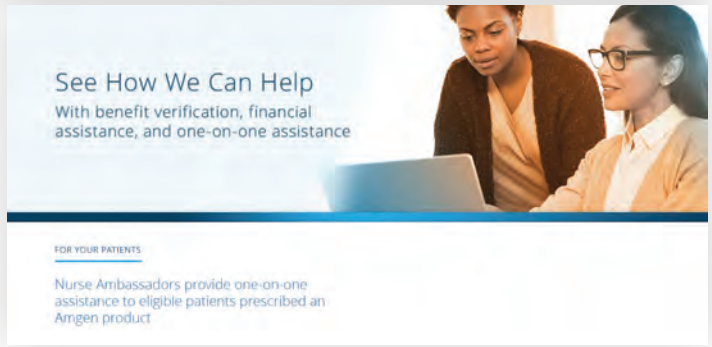

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Produced by Nicole Beagin and Laura Joszt

Lidia Fonseca Explains How Data Analytics Improves Patient Outcomes

How can the use of data analytics improve patient outcomes?

I think a couple of ways, actually. One, by bringing the information together, by making it actionable. There's a couple of major outcomes that are going to result from this. Number 1, I spoke about that shift from treating the sick to keeping people well—it'll enable us, actually, by running those data diagnostics that we can intervene sooner. If you think about employers that insure their employees and if you look at their metrics, it tends to be that a small percentage of their employees with chronic conditions are the ones that drive the lion's share of healthcare spending.

So, one of the long-term outcomes of this data diagnostics is that we can identify risk sooner. For example, if somebody is prediabetic, you take certain actions versus when you're diabetic or if you're in a late stage of diabetes. And so, by being able to intervene sooner, number 1, we can improve the quality of life of patients because we actually have the ability to intervene and stave off chronic conditions. So the one long-term effect is that we can improve the quality of life for the individual.

The second effect is that we identify risk and we can intervene, and we can actually take actions to keep a patient on track and manage their health over time. And then, I think the other major long-term effect is that by doing this and intervening, and managing risk and actually taking action sooner, it will take costs out of the healthcare system, as well. But again, more importantly, improving the quality of life for the patient, improving the outcomes themselves because we made better clinical decisions, and then really taking costs out of the system and becoming more efficient.

Dr Andrew Pecora Discusses Socioeconomic Disparities and Payment Reform

Do alternative payment models that are based on value consider the impact of the socioeconomic status of the patients being served?

It's a complex question because socioeconomic impact, it's not a unidirectional issue. So, on the one hand, people who are less fortunate socioeconomically, they have a number of challenges that go beyond the disease they have. Can they get to the doctor's office because they don't own a car? Can they miss work because they need to work to pay to live? Do they live in an environment that's a healthy environment, where they're getting good fresh food? All of those things impact. That's one issue.

Compliance to prescribed therapy is another. It's very hard sometimes, particularly with serious illness, when you have a family to deal with, you have a job, you don't feel good, and then you have medications that are very expensive and you have to take them in a frequency that is a challenge to you. If you're in a lower socioeconomic group, that may be a problem.

So, when you think about payment reform, what is it trying to do? It's on a different level than that issue. the issue is that it's a zero-sum game. Despite the fact we're the most prosperous nation on Earth, we can't afford to sustain the growth in healthcare expenditures. Everyone agrees with that, and the problem we have right now is that the pace of acceleration is increasing in regard to discovery, and discovery, every new discovery, drives more expense. So you have more discovery, more expense, people living longer because of these wonderful new drugs but costing more, and we can't afford that.

The point we're coming to, which would be a crisis point, is at some point, we'd have to ration care. And then, regardless of your socioeconomic status—you could be rich, you could be poor—if the government or payers can't afford to pay for the medicines, well, then you're not going to get them. And, so, I think it's a 2-tiered issue on the personal level, on the human level. There are challenges that payment reform might, in part, disproportionately impact someone who doesn't have the means of someone who does. But on the bigger level, if that patient, regardless of their means, needs a certain medication and we can't afford to give it to them, that's a whole other problem.

Stephen Nuckolls Emphasizes Importance of Care Coordinators in an ACO

Coastal Carolina Quality Care has a lot of care coordinators embedded into the ACO. What is the importance of that?

We feel like care coordination is one of the central parts of our organization. It helps us with patient engagement, and with developing strategies to get them involved. One of the main ways to get patients involved in their care is to let them know what they need to do. And, many times, for especially our frail and elderly patients, they need more contact than our physicians alone can do.

So, we set up different regimens and protocols, and our care coordinators call them and follow up to see how well they're doing, to see if they're having problems either getting their medications or taking their meds or have questions about them. We also are a little more directive in asking, "Have you done this and are you doing your exercise regimen?'" And many times, it's just following up to see how they do and showing them how much we care that really makes a difference.

Rocco Perla Explains the Importance of Patient-Centered Reform Conversations

How have social needs interventions risen to the top of the reform agenda in the last 6 months?

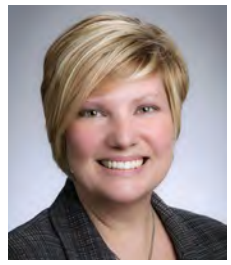
So, first, I think the health system needs to come together and view itself more broadly. Payers, providers, and the public health sector need to share accountability and leadership. So, I think, traditionally, what we've seen is that they've each taken a piece of the healthcare puzzle and tried to figure it out on their own. If those pieces aren't brought together, we'll only be marginally impactful.

Second, we need to think about putting the patient at the center of everything we do. I mentioned a couple of times that we're in a historic period with so much activity in health reform, but we can actually lose the forest for the trees. We talk about payment models as a primary driver of thinking about new ways to deliver care, but it's not—the payment models are in service of the patient. And if we keep the patient at the center of everything we do, and engineer the payment structures and the delivery structures around the patient, we can never go wrong. So, I think making sure we have our true north established is going to be our guiding light.

And then, lastly, let's look to who's already doing this well. We've been working with a number of really innovative health systems like Kaiser Permanente, for example, is one of our integrated delivery system partners and they're doing amazing work. They're really trailblazers in this space, and others can look to them as an example for how to do this. I think if we kind of put that together and focus on execution, I think we could make some serious headway.

Karin VanZant Explains How CareSource Fills the Gaps in Coordinated Care

When Medicaid beneficiaries are working with multiple organizations and case managers, how do you get all of these entities to work together and coordinate?



From my own personal experience in 20 years of working in this industry, it's amazing the number of programs that are really out there. I think that all of the programs are very well intentioned. They definitely are meeting some kind of a need, but the amount of coordination, or even collaboration between them, is very limited.

So, that's the space that we've decided to fill. Instead of offering our own job training programs or our own housing programs, how do we sit in a space alongside our members, bring all of the resources to the table that they're already involved with, and get everybody on a consistent plan? I can tell you that most of our community providers have been very open to this response. There have been a few that have been a little leery about a health insurance Medicaid plan getting into this space—but [they are convinced] once we're able to talk through how we want to share information, how we want to share successes, but mostly how we all have a mission to help this person.

And I talk about Mrs Smith all the time, her and her 2 kids, and how are we all really pulling together around Mrs Smith and her 2 kids so that she could actually leave the life of subsidy and have a much higher quality of life and prosperity. And when we can put our focus on Mrs Smith and her kids, instead of on what our rules are and our program or what our agency's mission is or what my paycheck is tied to, we can get much, much further in helping that family.

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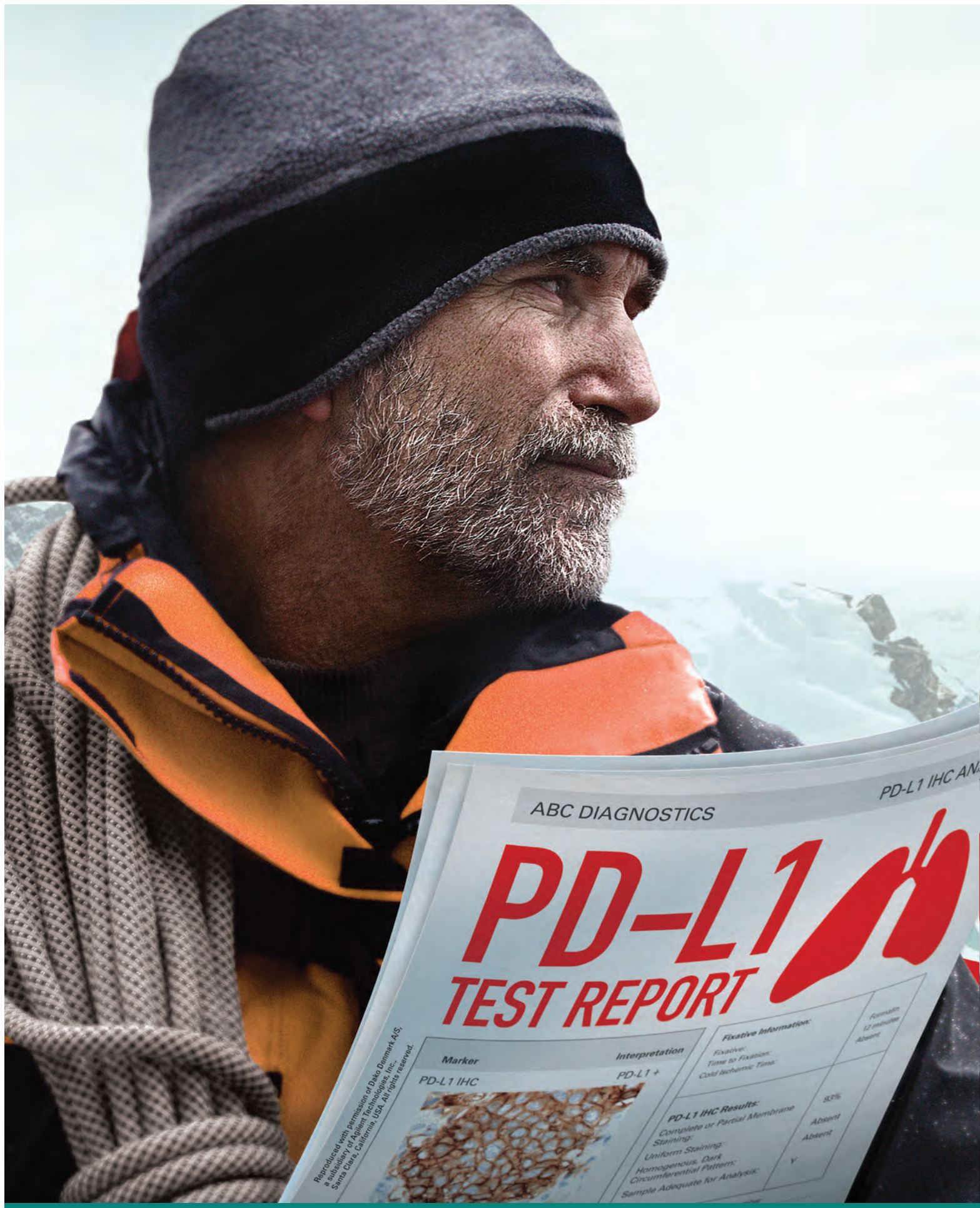
Obesity: A Growing Burden for Cancer Survivors

Priyam Vora

PATIENTS WITH A HISTORY OF CANCER were more likely to suffer from obesity than the general population, according to new research studying the incidence of obesity in cancer survivors. This incidence was even greater in patients who were survivors of colorectal and breast cancers.

The study from Columbia University's Mailman School of Public Health was designed to compare rates of obesity among cancer survivors and adults without a history of cancer. By examining the trend in obesity prevalence among cancer survivors in the and comparing the trends with those of adults without a history »



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of cancer, the study is a first of its kind to be held in the United States. The autors have published their findings in the *Journal of Clinical Oncology*.[1]

Prevalence of Obesity for Cancer Survivors

The researchers used a population-based nationally representative sample of 538,969 noninstitutionalized US adults with or without a history of cancer. All participants were between the ages of 18 and 85 years. They had also participated in annual cross-sectional National Health Interview Surveys from 1997 to 2014.

For standardization purposes, obesity was defined as body mass index ≥30 kg/m^2 for non-Asians and body mass index ≥27.5 kg/m2 for Asians. »

NCHS Report: Rising Survivorship in Pediatric Cancers, Brain Cancer Leading Cause of Death

Surabhi Dangi-Garimella, PhD

THERE WAS A STEADY DECLINE in death rates among children and adolescent patients diagnosed with cancer, without gender or racial disparity, between 1999 and 2014, according to a new report released by the National Vital Statistics System of the National Center for Health Statistics. A significant finding of the report is that brain cancer has replaced leukemia as the leading cause of cancer-related death.

BRAIN CANCER HAS REPLACED LEUKEMIA AS THE LEADING CAUSE OF CANCER-RELATED DEATH AMONG CHILDREN AND ADOLESCENT PATIENTS.

Pediatric cancers have seen a steady decline in mortality over the past decade, despite a slow increase in incidence of certain cancer types. For the current report, the researchers evaluated cancer death rates for children aged 1 to 19 years for the period between 1999 and 2014. They compared death rates for both male and females, as well as white and black children and adolescents. The following are key findings from the report for that period:

- A steady decline in the cancer death rate in the United States, for children and adolescents aged 1 to 19 years: from 2.85 to 2.28 deaths per 100,000, a 20% decline.
  - The death rate for females was 22% lower in 2014 (1.98) compared with 1999 (2.54)
  - The death rate for males was 18% lower in 2014 (2.57) compared with 1999 (3.15)
- In 2014, the cancer death rate for males aged 1 to 19 years was 30% higher than for females.
- The decline in the death rate for the entire period was consistent across genders and between black and white children and adolescents:
  - The cancer death rate for white children and adolescents was 17% lower in 2014 (2.36) than in 1999 (2.85), and it was 23% lower for those who were black (3.01 in 1999 vs 2.32 in 2014).
- For adolescents aged 15 to 19 years, the cancer deaths dropped by 22% between 1999 (3.71) and 2014 (2.9), although they had the highest cancer death rates in 1999, 2006, and 2014.
- At the beginning of the study period, children younger than 4 years had a 10% higher cancer death rate (2.72) compared with children 5 to 9 years of age (2.47). Data from 2014, however, found no significant difference in the death rates across age groups from 1 to 14 years.
- Over the 5-year period of analysis, brain cancer replaced leukemia as the leading cause of death in children aged 1 to 19 years, with 30% of cancer deaths in 2014 alone.
  - Brain cancer and leukemia combined remained the leading causes of cancer deaths in the 1-to-19 age group during the study period (53.4% in 1999 vs 54.8% in 2014).
  - Other tumor sites responsible for higher mortality in this age group included bone and articular cartilage, thyroid and endocrine glands, and mesothelial and soft tissue—these top 5 sites accounted for more than 80% of cancer deaths in this age group in 2014. ◆

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The key results were as follows:

- A total of 32,447 cancer survivors were identified.
- The most common cancer diagnoses were breast cancer (6948 patients), prostate cancer (3984 patients), and colorectal cancer (2546 patients).
- During the study period, the prevalence of obesity increased for both cancer survivors and adults without a history of cancer (from 22.4% to 31.7% in cancer survivors and from 20.9% to 29.5% in adults without a history of cancer).
- The annual increase in obesity prevalence was higher in adults with a history of cancer compared with those without a history.
- Populations with the highest rates of increasing obesity were colorectal cancer survivors followed by breast cancer survivors.
- African American survivors of all 3 cancers were particularly affected.

Obesity a Growing Health Burden

"Our study identified characteristics of cancer survivors at the highest risk of obesity, which are important patient populations in which oncology care providers should focus their efforts," said Heather Greenlee, MD, PhD, assistant professor of epidemiology at the Mailman School and lead researcher.

Patients with a history of cancer may have battled their biggest health issue, but often they are left with the side effects of the illness. The study highlights the strong link between the incidence of obesity and history of cancer. If targeted properly, these patients can be selectively and pro-actively treated for weight management and physical training in order to prevent the increasing obesity trends in cancer survivors.

"These results suggest that obesity is a growing public health burden for cancer survivors, which requires targeted interventions, including weight management efforts to stave off the increasing obesity trends we are seeing in cancer survivors," noted Greenlee. ◆

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Intervention Improved Oncologist-Patient Communication, Not QOL or Hospice Use

Surabhi Dangi-Garimella, PhD

TO QUANTIFY THE IMPACT OF PATIENT-CENTERED communication between an oncologist and a patient on the quality of care, patient's quality of life (QOL), and the need for making informed decisions, a global interventional study was designed and conducted at centers across the United States and in Australia. The Values and Options in Cancer Care (VOICE) study evaluated the impact of 2 interventions on the outcomes listed above in patients with advanced cancer.

Participating oncologists, whose baseline communication patterns had been assessed, were randomized to receive individual communication training via patient instructors if they were in the intervention arm. Patients and their caregivers were randomized to receive an individualized coaching session with follow-up telephone calls. Participant enrollment was between August 2012 and June 2014, with follow-up through October 2015.

Enrolled patients (265) were being treated for nonhematologic cancers (stage III or IV) and had a poorer prognosis. Inpatients and hospice patients were excluded. Patients agreed to an audio recording of their office visits and pre-visit and postvisit questionnaires. They were provided in-office physician training sessions (2) and a 1-hour patient and caregiver coaching session, and up to 3 follow-up phone calls. The training sessions focused on 4 main domains of patient-centered communication:

- Disease course
- Prognosis
- Treatment decisions
- End-of-life care

The primary outcome was a combination of patient-centered communication measured from audio recordings of the first visit after patient coaching or enrollment (control group). The trial also measured the following secondary outcomes: the patient–physician relationship, shared understanding of prognosis, QOL, and aggressive treatment and hospice use in the last 30 days of life.

The final analysis, with data from 38 oncologists and 265 patients, found that the interventional strategy resulted in clinically and statistically significant improvement in the primary physician–patient communication (adjusted intervention effect, 0.34; 95% CI, 0.06-0.62; $P = .02$). The authors write that paired communication training involving patients and oncologists achieves patient-centered care in advanced cancer by engaging patients in consultations, responding to their emotions, and providing information on prognosis and chosen treatments. Secondary outcomes were not influenced by the intervention. The authors explain that cancer patients reported stable QOL during the entire course of disease, up until the last few months.

Since the current intervention did not impact QOL, they discuss adjusting the timing of the intervention in future studies, hoping to impact QOL trajectories. The authors also suggest training office personnel to develop skill sets to coach patients to address logistical and methodological difficulties. Since healthcare utilization was the same between the 2 cohorts, the authors recommend addressing physician attributes and institutional norms in the context of aggressive interventions and hospice in patients with advanced cancer. ◆

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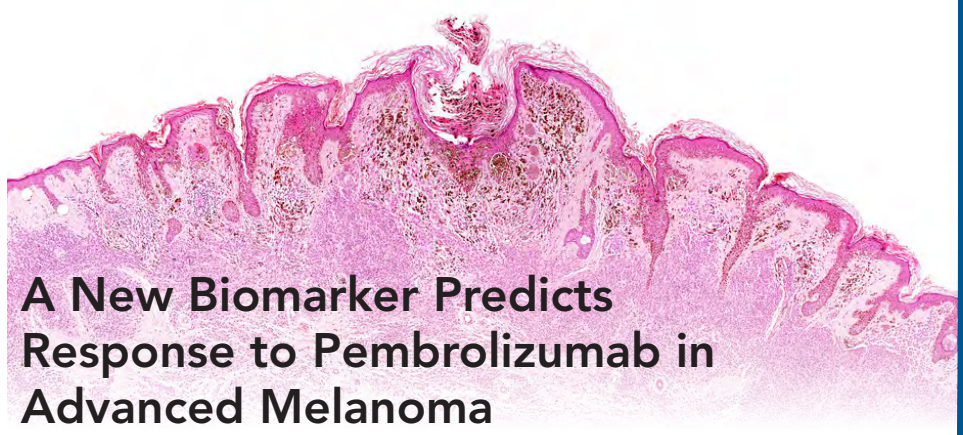

A New Biomarker Predicts Response to Pembrolizumab in Advanced Melanoma

Surabhi Dangi-Garimella, PhD

PREDICTIVE BIOMARKERS—those that can ascertain the success of a treatment—can be very useful in deciding early on if a patient should continue on a treatment plan. Now, a new study by researchers at the Perelman School of Medicine at the University of Pennsylvania has identified such a biomarker in stage IV patients with melanoma being treated with the immunotherapy pembrolizumab (Keytruda).

"WE WERE EXCITED TO FIND THAT PATIENTS WITH A BALANCE IN FAVOR OF THE IMMUNE RESPONSE COMPARED TO TUMOR BURDEN WERE MORE LIKELY TO HAVE CLINICAL BENEFIT."

–Alexander Huang, MD

In their study presented at the CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival, the authors found that the ratio of a subset of immune cells in the blood to the tumor burden correlated with clinical response. "We set out to investigate whether we could monitor and predict a patient's response to pembrolizumab by tracking the effect of pembrolizumab on immune cells in blood samples from the patients," said lead author Alexander Huang, MD, clinical fellow in the Division of Hematology/Oncology and Institute for Immunology at Perelman.

The researchers monitored 29 patients with advanced stage IV melanoma by analyzing immune cells in their blood that was collected before and at 3, 6, 9, and 12 weeks after initiating treatment with pembrolizumab. The authors were primarily interested in following the proliferation of exhausted phenotype CD8+ T cells, which have high levels of programmed death ligand-1 (PD-L1) on their cell surface. These cells are so named because they are no longer capable of inhibiting tumor cells. Pembrolizumab can reinvigorate exhausted phenotype CD8+ T cells, which can be measured by their proliferative capacity.

The authors identified increased proliferation of exhausted phenotype CD8+ T cells in 78% of patients, post treatment. When they calculated the ratio of exhausted phenotype CD8+ T cell reinvigoration to pretreatment tumor burden, a correlation with clinical response was noted. Using this calculation, a clinical response was observed in 38% patients. In one cohort, half the patients with a clinical response exceeding 1.94 were alive at 11-months post treatment with pembrolizumab. In another cohort, 75% of patients with a ratio greater than 1.94 were alive a 2-years post treatment. "We were excited to find that patients with a balance in favor of the immune response compared to tumor burden were more likely to have clinical benefit," Huang said, adding that their findings need validation in a larger study. ◆

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UnitedHealth Formulary to Support Generic and Biosimilar Drugs

Surabhi Dangi-Garimella, PhD

BASAGLAR, BIOSIMILAR TO LANTUS; Zarxio, biosimilar to Neupogen; and generic imatinib mesylate (Gleevec) will replace their respective reference products on UnitedHealth's formulary in 2017. The health plan's proposal follows similar such exclusions that were released by major pharmacy benefit managers, Express Scripts and CVS Health, about a month back.[1]

A presentation on the UnitedHealth website provides an update to its pharmacy benefits and prescription drug lists (PDLs) and explains the various aspects of the company's PDL decision-making process. With a focus on specialty medications, the company shares statistics on specialty medications: they represent 1% to 2% of utilization but more than 36% of UnitedHealth's costs.

The following are some of the PDL changes announced:

TABLE. Changes in UnitedHealth's 2017 Formulary

CATEGORY	DRUG	CHANGE
DIABETES	LANTUS	EXCLUDED
	BASAGLAR	TIER 1
	LEVEMIR	TIER 2
MULTIPLE SCLEROSIS	PLEGRIDY	WILL BE COVERED
	AUBAGIO	STEP THERAPY NOT REQUIRED
	GILENYA	STEP THERAPY NOT REQUIRED
PAIN MANAGEMENT	OXYCONTIN	EXCLUDED
	BUTRANS	EXCLUDED
	SUMAVEL DOSEPRO	EXCLUDED
	XTAMPZA ER	TIER 3
NEUTROPENIA	NEUPOGEN	EXCLUDED
	ZARXIO	REPLACES NEUPOGEN
CANCER	SPRYCEL	EXCLUDED
	GLEEVEC	EXCLUDED
	IMATINIB	REPLACES GLEEVEC
	TASIGNA	STEP THERAPY; STEP 1 MEDICATION: IMATINIB

"Branded biologic exclusions could extend into other categories, such as inflammation or oncology," they told investors, according to *FiercePharma*.[2] Ronny Gal, with Bernstein, predicted payer support will definitely help boost the biosimilar market.

The company has also taken a significant policy stand by excluding 2 pain drugs, OxyContin and Butrans, from the PDL citing "aggressive drug marketing of opioids." This will also help them comply with changes announced by the CDC in March 2016, which includes modifying the prior-authorization criteria. Gal noted, "[W]e are seeing commercial payers making more aggressive steps to control formulary costs," but believes that these changes are being made at a significantly faster rate than what analysts had expected. ◆

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Improved Design, Access, and Transparency of Trials Essential for Success of Cancer Moonshot

Surabhi Dangi-Garimella, PhD

THE NATIONAL CANCER INSTITUTE (NCI)'S Cancer Moonshot initiative received yet another boost following Vice President Joe Biden's announcement of several activities to accelerate the pace of oncology clinical research.[1] The announcement, which comes less than 2 weeks after the Blue Ribbon Panel made its recommendations to the National Cancer Advisory Board,[2] will hopefully improve participation in clinical trials, irrespective of where the trial is being conducted. "These steps will improve the safety, accessibility, and impact of our clinical research system" to help researchers around the globe develop new strategies against cancer, Biden said.

The following are some of the announcements:

1. **Redesign of cancer clinical trial information made available by the NCI.**
   A collaboration between the NCI and the White House Presidential Innovation Fellows has resulted in a new user-friendly cancer clinical trial website, trials.cancer.gov, which provides information on NCI-supported trials. The website provides a new application programming interface (API) to allow researchers and patient groups to tailor information in real time and identify relevant ongoing trials. This is expected to ease new patient recruitment and ensure easy access to trial information.

2. **FDA to announce efforts for new clinical trial designs.**
   A series of efforts to garner the collective input from researchers across government and private industry will be announce by the FDA, to allow design of smarter and efficient trials. Tactics include sharing control groups across studies that use different drugs for the same indication and smarter patient selection. This can accelerate the pace of studies, control costs, and help bring products to market faster for increased access.

3. **HHS announcement of final rule for clinical trial registration and results reporting.**
   HHS will release a final rule on requirements for clinical trial registration and reporting of trial results on the ClinicalTrials.gov website. This is expected to improve transparency and streamline access to trial information for all products (drugs and devices) that are yet to be FDA-approved. Detailed access to such information will let patients make informed decisions on participation in a trial and will prevent duplication of unsafe or unnecessary trials.

4. **Increasing usability of ClinicalTrials.gov.**
   To make ClinicalTrials.gov more user-friendly and accessible, the National Institutes of Health is working with technical experts to make it easier for patients to research and identify relevant interventions and clinical trials. ◆

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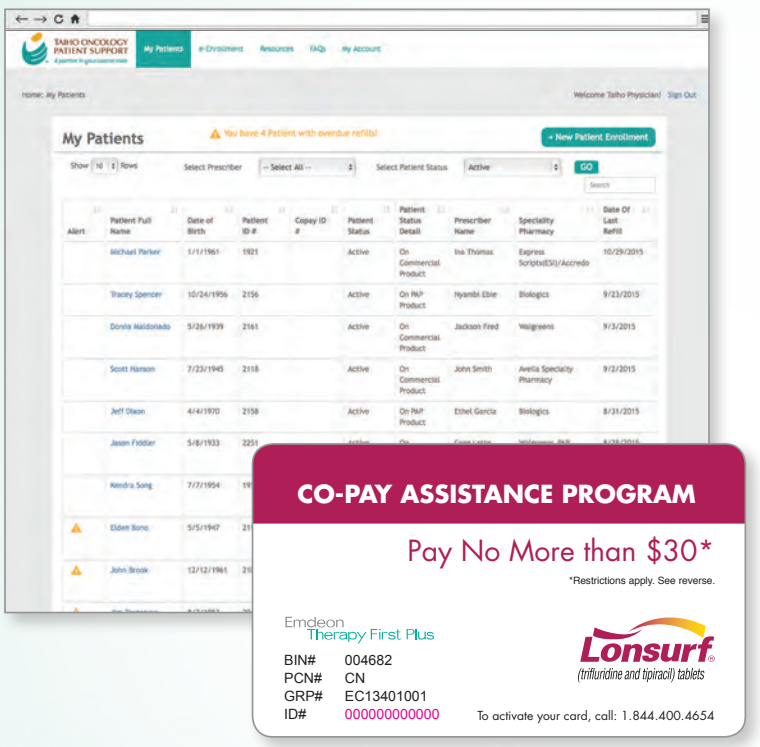

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Lonsurf® (trifluridine and tipiracil) tablets

TAIHO ONCOLOGY

Lonsurf®

(trifluridine and tipiracil) tablets

Indication

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild type, an anti-EGFR therapy.

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breast-feed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older who received LONSURF.

Renal Impairment: Patients with moderate renal impairment may require dose modifications for increased toxicity. No patients with severe renal impairment were enrolled in Study 1.

Hepatic Impairment: Patients with moderate or severe hepatic impairment were not enrolled in Study 1.

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%).

Additional Important Adverse Drug Reactions: The following occurred more frequently in LONSURF-treated patients compared to placebo: infections (27% vs 15%) and pulmonary emboli (2% vs 0%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: Laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).

Please see brief summary of Prescribing Information on the following pages.

Learn more at LONSURFhcp.com

TAIHO ONCOLOGY

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

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

1 INDICATIONS AND USAGE
LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Myelosuppression
In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery resume LONSURF at a reduced dose. *[see Dosage and Administration (2.2) in the full Prescribing Information]*

5.2 Embryo-Fetal Toxicity
Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m^2 twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full Prescribing Information]*

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

The data described below are from Study 1, a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received LONSURF as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of LONSURF therapy was 12.7 weeks.

The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In Study 1, 3.6% of patients discontinued LONSURF for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 1 Per Patient Incidence of Adverse Drug Reactions (≥5%) in Study 1 Occurring More Commonly (>2%) than in Patients Receiving Placebo.

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades	Grades 3-4*	All Grades	Grades 3-4*
Gastrointestinal disorders				
Nausea	48%	2%	24%	1%
Diarrhea	32%	3%	12%	<1%
Vomiting	28%	2%	14%	<1%
Abdominal pain	21%	2%	18%	4%
Stomatitis	8%	<1%	6%	0%
General disorders and administration site conditions				
Asthenia/fatigue	52%	7%	35%	9%
Pyrexia	19%	1%	14%	<1%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	29%	5%
Nervous system disorders				
Dysgeusia	7%	0%	2%	0%
Skin and subcutaneous tissue disorders				
Alopecia	7%	0%	1%	0%

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Table 2 Laboratory Test Abnormalities

Laboratory Parameter	LONSURF (N=533*)			Placebo (N=265*)		
	Grade†			Grade†		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia‡	77	18	N/A#	33	3	N/A
Neutropenia	67	27	11	1	0	0
Thrombocytopenia	42	5	1	8	<1	<1

*% based on number of patients with post-baseline samples, which may be less than 533 (LONSURF) or 265 (placebo)
† Common Terminology Criteria for Adverse Events (CTCAE), v4.03
‡ Anemia: No Grade 4 definition for these laboratory parameters in CTCAE, v4.03
# One Grade 4 anemia adverse reaction based on clinical criteria was reported

In Study 1, infections occurred more frequently in LONSURF-treated patients (27%) compared to those receiving placebo (15%). The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% versus 2%), and urinary tract infections (4% versus 2%).

In Study 1, pulmonary emboli occurred more frequently in LONSURF-treatment patients (2%) compared to no patients on placebo.

Additional Clinical Experience
Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

7 DRUG INTERACTIONS
No pharmacokinetic drug-drug interaction studies have been conducted with LONSURF.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on animal data and its mechanism of action, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. [see *Data*] There are no available data on LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifuridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Contraception

Females

LONSURF can cause fetal harm when administered to a pregnant woman. *[*see *Use in Specific Populations (8.1)]*

Advise females of reproductive potential to use effective contraception during treatment.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose. *[*see *Nonclinical Toxicology (13.1) in the full Prescribing Information]*

8.4 Pediatric Use

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

Animal Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

In Study 1, 533 patients received LONSURF; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of LONSURF based on age.

Patients 65 years of age or older who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.

In Study 1, patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 178).

No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ Grade 3 adverse events in either the LONSURF or placebo groups.

10 OVERDOSAGE

The highest dose of LONSURF administered in clinical studies was 180 mg/m^2 per day.

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Myelosuppression:

Advise the patient to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests. *[*see *Warnings and Precautions (5.1)]*

Gastrointestinal toxicity:

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain. *[*see *Adverse Reactions (6.1)]*

Administration Instructions:

Advise the patient that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dose. Advise the patient of the importance of reading prescription labels carefully and taking the appropriate number of tablets.

Advise the patient to take LONSURF within 1 hour after eating their morning and evening meals. *[*see *Dosage and Administration (2.1) in the full Prescribing Information]*

Advise the patient that anyone else who handles their medication should wear gloves. *[*see *References (15) in the full Prescribing Information]*

Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[*see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.3)]*

Lactation:

Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. *[*see *Use in Specific Populations (8.2)]*

TAIHO ONCOLOGY, INC.

Making Oncologists Good Neighbors

Michael Kolodziej, MD

continued from cover

the oncologist is key and works better than giving the patient a stack of papers with the kernels of truth buried deep. A methodology for electronic triage would be a really useful tool. Let's give patients access to all electronic communication relevant to their case. Interestingly, many virtual second opinion programs do just this, following completion of a virtual case report form. Currently, it is a manual process, but it doesn't have to be.

For patients that do require the consultant's care, a navigator can be a priceless (and, ultimately, deeply loved and appreciated) partner for the patient on the care journey. And remember that in an integrated network, there will be a strong disincentive to referral as consultants consume resources. So good communication as to why consultation is not required will be just as important. The result: ACO savings, transparent evaluation, potentially better quality of care, and happier patients.

2. Managing patients with complex comorbidities.

These patients pose major challenges for the oncologist for several reasons:

- They take up a lot of the healthcare provider's time
- They frequently suffer complications
- The oncologist is ill-suited to manage some of the medical problems

The current default—referral back to the PCP or another specialist—is highly inefficient, often inconvenient (and sometimes costly) for the patient, and invariably accompanied by poor communication of the clinical ask. This is certainly a cause of unnecessary hospitalizations, and it certainly makes patients deeply unhappy. The easy target is the darn doctor...if only they would just get on the phone. But that has always been the solution, and it hasn't worked very well. The solution here is probably adoption of a care team mentality. There is little doubt that a skilled nurse practitioner can facilitate the hand-off of these complicated patients on both ends of the transaction. Again, an electronic solution would make things so much better.

3. Optimizing end-of-life care.

Advanced care planning discussions are very difficult and not particularly enjoyable for many. Evidence shows that many oncologists do not do a very good job with this,[1] even though they steadfastly maintain that they "own" these discussions and become irate if someone else has the audacity to intervene. Now, with the evidence that palliative care providers significantly improve patient care at the end of life, there is need for facilitating their access to these patients (and, with that, the need to coordinate care).

Besides the obvious need for oncologists to "get over" their territorialism, effective integration of these providers into the care team will unquestionably improve the quality of care throughout the care continuum and likely reduce costs. There is no doubt that if oncologists do not solve this problem, the integrated delivery system will do it for them—and patients will like it (or so the data say).[1] Do not forget that the PCPs also need to be kept in the loop. For many patients, these doctors manage families across generations and enjoy tremendous trust and respect. Again, an electronic solution appears needed.

KOLODZIEJ

4. Transitioning to survivorship.

Finally, it is not unfair to say that survivorship care is a mess. It is the epitome of a nonstandardized, nonevidence-based mélange, and this may be the single area most in need of improvement in coordination of care. Oncologic elitism has made it very difficult for most PCPs to re-assume the care of their cancer survivors, and this uneasiness is readily perceived by patients who interpret it as incompetence. If they only knew the truth!

Oncologists are expensive, and they do not do a very good job of providing primary care. Studies have shown that survivors expect their oncologists to assume responsibility for health maintenance (especially cancer screening), yet they rarely do (in fact, they do not consider themselves responsible).[2] An appropriate care transition would probably be in everyone's best interest, but it rarely happens. ACOs, however, will demand it. Interestingly, part of the Institute of Medicine's (now the National Academy of Medicine) 13-point care plan, which is now required as part of the Center for Medicare & Medicaid Innovation's Oncology Care Model, is a survivorship plan. Pity is, no one knows what to put there. In addition to the establishment of evidence-based standards, a methodology to document and communicate these recommendations to patients, and the rest of the care team, is needed.

[SURVIVORSHIP CARE] IS THE EPITOME OF A NONSTANDARDIZED, NONEVIDENCE-BASED MÉLANGE AND AN AREA MOST IN NEED OF IMPROVED CARE COORDINATION.

Oncologists will not disagree with these gaps—we see the impact of these care gaps every day. What most oncologists do not realize is that healthcare reform will require solutions, and fast. One could argue that people are not "hurt" by these gaps, that there is no evidence they impact outcomes. Patients, however, sure do not like them, and if they negatively impact the financial outcomes of an integrated delivery system, they will not be tolerated. Healthcare reform is doing oncology a favor by forcing it to do the right thing.

Where Do We Start?

A good place would be interoperability. The Cancer Moonshot initiative identifies it as a priority (although not a major one); in my opinion, it would be fine if we spent every last Moonshot

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DOCUMENTING AND COMMUNICATING EVIDENCE-BASED STANDARD OF CARE TO PATIENTS AND THE CARE TEAM IS IMPORTANT.

dollar on just this problem. For integrated delivery systems where all the doctors are employed, all working on the same dysfunctional electronic health record, perhaps this is not the issue. But in oncology, despite the migration of oncology practices to hospital ownership, more than half of the care is still being delivered by independent community oncologists. So, these bridges need to be built.

The next step is to adopt a team approach to care management. This doesn't mean assigning people new jobs. It means convincing every clinician, every clerical staff member, every person that touches a patient, that they are vital to the best patient experience. And if they are vital, they should be treated with respect. Aspirational? Perhaps. But we are all patients-in-waiting, and it is only fair to ask what we would expect if the care were being delivered to us. We have healthcare reform to thank for moving us in the right direction. ◆

DISCLOSURES

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SIDEBAR

PanCAN's Precision Medicine Trial Designed for Collaboration and Personalized Care

SURABHI DANGI-GARIMELLA, PHD

WITH THE ANNOUNCEMENT OF PRECISION PROMISE, the Pancreatic Cancer Action Network (PanCAN) seeks to transform outcomes for pancreatic cancer patients with the goal set to double survival by 2020. The trial is focused on boosting the dismal clinical trial-enrollment rate and using a personalized approach to care.[1]

The PanCAN trial will evaluate the molecular nature of the patient's tumor to mark mutations and direct the patient to the most suitable sub-study arm of the trial—reflecting the principles of the NCI-MATCH (National Cancer Institute Molecular Analysis for Therapy Choice) and TAPUR (Targeted Agent and Profiling Utilization Registry) trials. The PanCAN trial offers patients the flexibility to move between arms based on their response to therapy without having to wait between different clinical trials.

"Instead of looking for the right patient for a clinical trial, we are designing the right clinical trial for each patient," said Julie Fleshman, JD, MBA, president and chief executive officer of PanCAN, when announcing the initiative.
The following 12 sites, selected via a competitive peer-reviewed process, will begin enrolling trial participants in the Clinical Trial Consortium:

1. Dana Farber/Harvard Cancer Center
2. Memorial Sloan Kettering Cancer Center
3. University of Pennsylvania
4. University of Florida
5. Washington University
6. University of Michigan
7. University of Chicago
8. Virginia Mason
9. Fred Hutchison Cancer Research Center/Seattle Cancer Care Alliance/University of Washington
10. University of California, San Francisco
11. Cedars-Sinai
12. University of California, San Diego

The Consortium includes 5 working groups, comprised of leading researchers with expertise in specific aspects of pancreatic cancer:

1. DNA damage repair working group
2. Stromal disruption working group
3. Immunotherapy working group
4. Supportive care working group
5. Industry working group

Under the umbrella of Precision Promise, data collected from all 12 sites will be collated and analyzed together for efficient and timely dissemination of trial data. The trial will initially have a 3-pronged approach toward the disease: DNA damage repair, stromal disruption, and immunotherapy; however, it has been designed to add new arms and sub-studies based on novel research findings.

With an initial commitment of $35 million over the first 4 years—excluding drug costs—the trial expects to enroll thousands of participants starting spring 2017. ◆

REFERENCE

Precision Promise: Revolutionizing treatment for every pancreatic cancer patient. Pancreatic Cancer Action Network website. https://www.pancan.org/research/precision-promise/. Accessed October 4, 2016.

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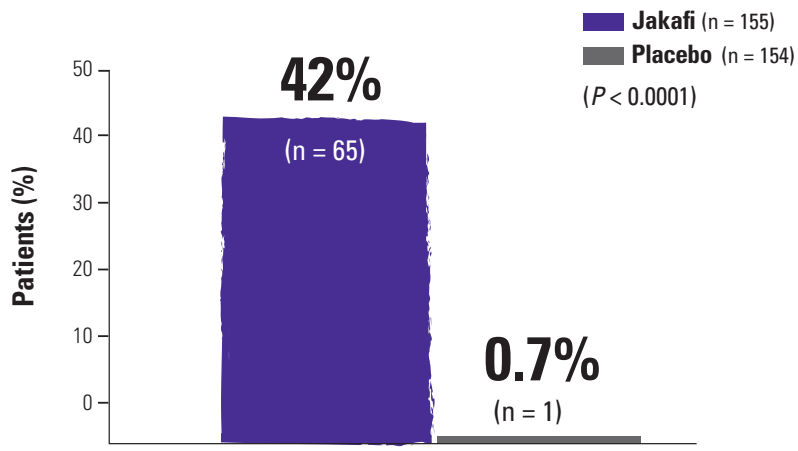
FDA APPROVED FOR INTERMEDIATE OR HIGH-RISK MYELOFIBROSIS

Significantly more patients with intermediate-2–risk or high-risk myelofibrosis receiving Jakafi® (ruxolitinib) achieved the primary end point compared with placebo (COMFORT-I*) or best available therapy† (COMFORT-II‡)[1-3]

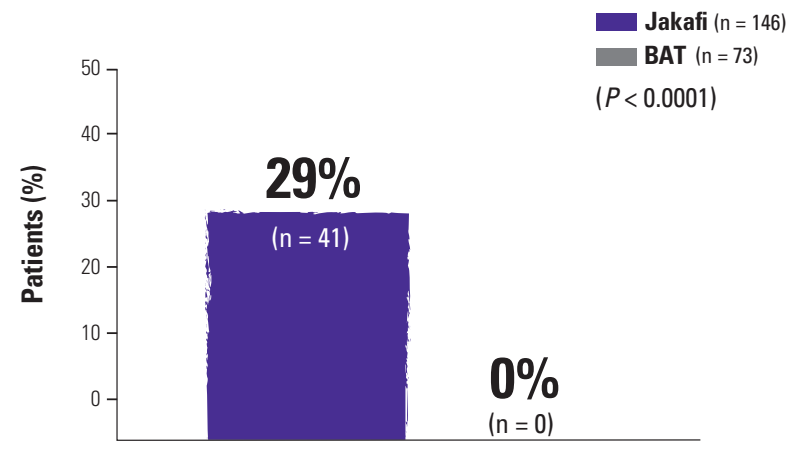
- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 24 as measured by CT or MRI[1,2]

COMFORT-I Primary End Point: Spleen Volume Reduction at Week 24[1,2]



- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI[1,3]

COMFORT-II Primary End Point: Spleen Volume Reduction at Week 48[1,3]



BAT, best available therapy.

* COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk and high-risk myelofibrosis.[1,2]

† Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.[4]

‡ COMFORT-II (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk and high-risk myelofibrosis.[1,3]

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

Incyte

Jakafi® ruxolitinib (tablets)

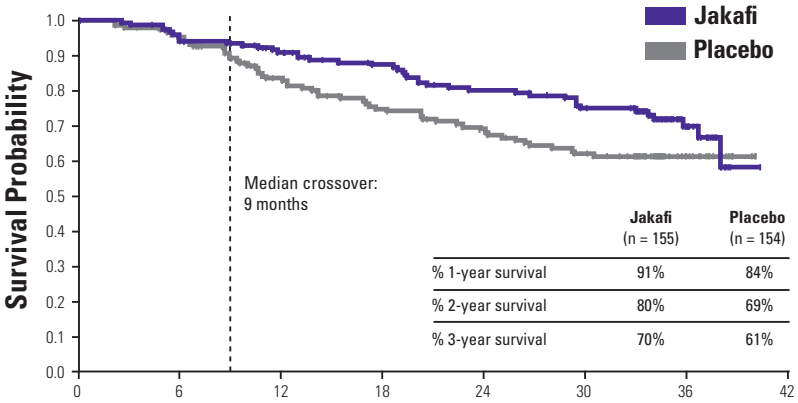
Indications and Usage

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

Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II[1]

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo[1]
- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy[1]

COMFORT-I Overall Survival: Kaplan-Meier Curves by Treatment Group[1]

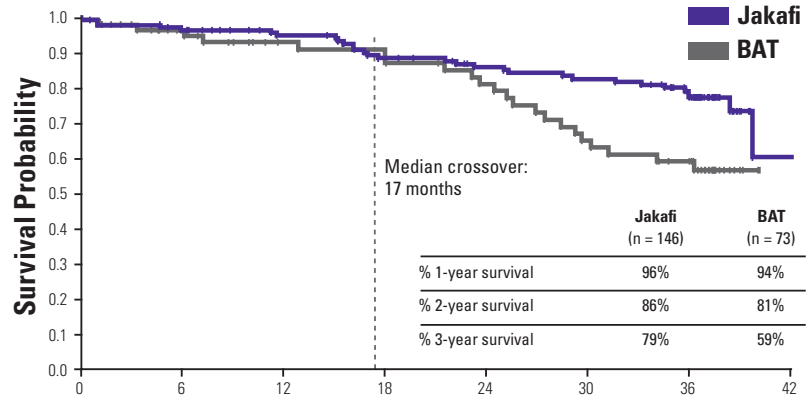


	Jakafi (n = 155)	Placebo (n = 154)
% 1-year survival	91%	84%
% 2-year survival	80%	69%
% 3-year survival	70%	61%

Number of patients at risk

Jakafi	155	145	134	122	111	102	29	0
Placebo	154	142	117	101	92	82	32	0

COMFORT-II Overall Survival: Kaplan-Meier Curves by Treatment Group[1]



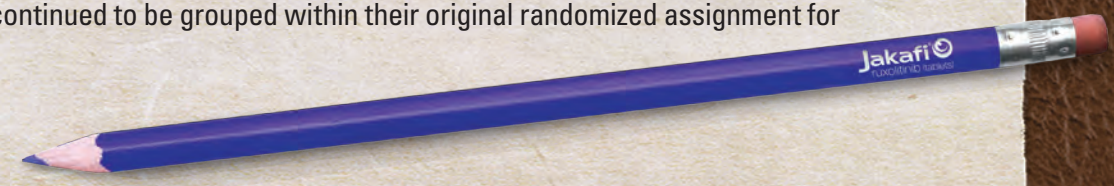
	Jakafi (n = 146)	BAT (n = 73)
% 1-year survival	96%	94%
% 2-year survival	86%	81%
% 3-year survival	79%	59%

Number of patients at risk

Jakafi	146	135	126	115	107	104	33	0
BAT	73	58	50	47	42	33	9	0

BAT, best available therapy.

- Because of progression-driven events or at the physician's discretion, patients randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II) who crossed over to receive Jakafi continued to be grouped within their original randomized assignment for analysis purposes[4]



- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

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

To learn more about Jakafi, visit **Jakafi.com/HCP**.

References: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799-807. **3.** Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012;366(9):787-798. **4.** Data on file. Incyte Corporation. Wilmington, DE.

Jakafi®
ruxolitinib (tablets)

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

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *PML* Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Clinical Trials Experience in Myelofibrosis** The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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

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

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

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

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

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

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

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

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

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

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

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

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

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

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

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

USE IN SPECIFIC POPULATIONS Pregnancy Pregnancy Category C: *Risk Summary* There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Nursing Mothers** It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. **Geriatric Use** Of the total number of patients with myelofibrosis in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended [*see Dosage and Administration (2.4) in Full Prescribing Information*]. **Hepatic Impairment** The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and hepatic impairment [*see Dosage and Administration (2.4) in Full Prescribing Information*].

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

Revised: March 2016 RUX-1778a

FERTILITY PRESERVATION

LIVESTRONG

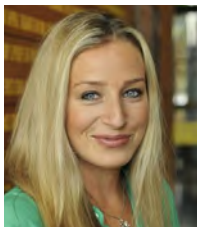
Multi-Level Approach to Addressing Iatrogenic Infertility

Aditi Narayan, MSW; Loyce Pace, MPH; and Rebekkah Schear, MIA

continued from cover

NARAYAN

PACE



SCHEAR

Each year, 150,000 Americans, like Sarah, will be diagnosed with cancer during their reproductive years, of which 40% to 80% of women and 35% to 70% of men will be at risk for reproductive compromise. However, less than 50% report being informed of potential risks to their fertility by their healthcare team.[1] Few healthcare providers follow the clinical practice guidelines from the American Society of Clinical Oncology on fertility preservation. Multiple barriers, however, often prevent them from broaching the topic with patients, including:

- Insufficient information on fertility preservation techniques and their impact on cancer
- Concerns about the patient's ability to afford costly preservation procedures
- Concerns with the often urgent treatment timeline
- Lack of internal institutional support

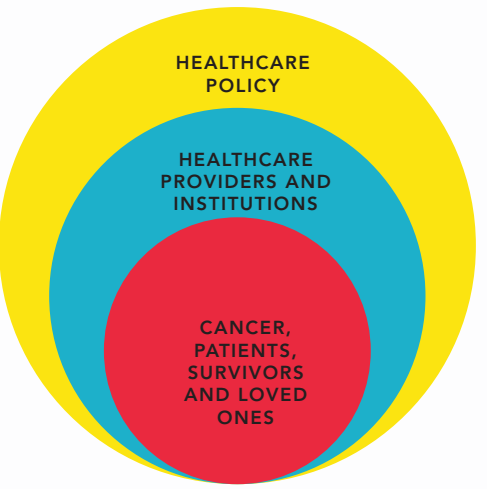
Although some individuals may be able to preserve their fertility post treatment, patients are encouraged to make the choice pre-treatment to access the full range of preservation options, including egg or embryo freezing and sperm banking.[2,3] However, as Sarah experienced, fertility preservation is often extremely expensive, costing an average of $10,000 for women and $1000 for men. Additionally, most insurance companies do not cover fertility preservation for individuals at risk of iatrogenic infertility, leaving the full financial burden on patients who are likely already overwhelmed with the rising costs of cancer care.[2]

A multi-faceted approach to solution generation is required in order to fully address this issue for patients and healthcare providers. There is a proven need for further education on, and affordable access to, fertility preservation resources for patients, along with further education for healthcare providers about the impact of cancer on fertility and the skills needed to address the risks with patients.[4] Additionally, cancer institutions should aim to implement systematic programs to address patients and healthcare professionals' needs related to cancer and fertility. A 3-level approach that focuses on patient and family care, education, and resources for healthcare providers, as well as streamlined programs within cancer care institutions, will help ensure that the unique fertility needs of adolescent and young adult cancer patients and survivors will be addressed and routinely included as part of cancer care.

Patients, Survivors, and Loved Ones

LIVE**STRONG** provides educational resources for patients and survivors in need of information about the impact of cancer treatment on fertility. Our Fertility Risk tool[5] informs individuals of infertility risks based on cancer type, and the Family-Building Options[6] tool informs individuals of family-building options based on treatment type. Additionally, patients and survivors can access discounted preservation services at over 550 clinics nationwide, and female patients and survivors can access free stimulation medication through LIVE**STRONG**'s partnership with EMD Serono.

FIGURE. LIVE**STRONG** Fertility Model



The LIVE**STRONG** Foundation's programmatic effort is an example of using a multi-pronged approach to address cancer and fertility.

Healthcare Providers and Institutions

LIVE**STRONG** recognized the gap in education on cancer and fertility for health professionals and created a dynamic online training to address this.[7] The 60-minute training is designed for healthcare professionals to understand the impact of cancer on fertility and to improve their ability to conduct cancer-related fertility discussions with patients. The training includes a simulated conversation with patients and their primary caregivers, and also offers 1 continuing education unit to Texas residents.

LIVE**STRONG** understands that in order to ensure iatrogenic infertility is systematically addressed at cancer clinics and hospitals across the United States, there needs to be a change at the institutional level. With this goal in mind, LIVE**STRONG** developed a guide for cancer institutions to implement a systematic approach to addressing cancer and fertility.

The LIVE**STRONG** Fertility Recommended Practices Toolkit: Implementing a Systematic Approach to Cancer and Fertility,[7] outlines 7 key practices to creating and implementing a cancer and fertility program within institutions. Additionally, the toolkit is an acknowledgement of the institutional barriers many health organizations experience when adding new services and is designed to act as a guide in helping institutions identify and discuss the barriers to building a program. The 7 recommended practices include:

- Institutional commitment: developing a formal policy, guideline, or standard, with administration endorsement for the program.

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*Rebekkah Schear, MIA, is director of mission delivery at the LIVE**STRONG** Foundation.*

- Institutional ownership: ensuring there is an internal champion and dedicated staff for the program.
- Professional education: providing education and referral resources to appropriate staff, including physicians, nurses, and social workers.
- Patient resources: providing printed educational and referral materials for patients, along with information about other supportive resources.
- Patient notification process: developing a method for delivering appropriate timely information to at-risk patients and instituting formal documentation policies.
- Referral process: thoroughly identifying all fertility service providers in the area and developing a formal method for patient referral to ensure success of the process.
- Evaluation measures: developing quantitative and qualitative evaluation measures to continuously improve the process for both patients and staff.

All of the practices listed above are required in order to successfully create and implement a cancer and fertility program. In addition to developing the toolkit, LIVE**STRONG** provides presentations that health professionals can use to make an institutional case for support.

Dealing with cancer is an emotionally, physically, and financially overwhelming experience. Everyone at risk for iatrogenic infertility should be informed of their risks and have the right to choose whether they want to have a biological family in the future. The healthcare community must ensure that providers have the support they need to appropriately address this issue with patients: education, institutional support, and referral resources.

EVERYONE AT RISK FOR IATROGENIC INFERTILITY SHOULD BE INFORMED OF THEIR RISKS AND HAVE THE RIGHT TO CHOOSE IF THEY WANT TO HAVE A BIOLOGICAL FAMILY IN THE FUTURE.

Policy Change

While LIVE**STRONG** Fertility supports the needs of more than 1000 individuals and couples every year, change is required at a systemic level to reach more survivors in need of fertility preservation services. In 2010, LIVE**STRONG** launched a fertility policy initiative that targeted insurance companies. The goal was to expand coverage for fertility preservation services in the event that infertility was due to cancer treatment. (Traditionally, fertility services are treated as elective and not medically necessary, similar to cosmetic surgery). We developed a case for support[8] that presented a cost analysis of covering infertility services for the small subset of beneficiaries diagnosed with cancer who would likely take advantage of this benefit. In addition to minimal costs for the companies themselves, coverage of infertility services would also reduce the burden on patients to explore and pay for these options during an already stressful time post diagnosis. Knowing that affordable fertility preservation is an option, despite iatrogenic treatment, might also improve treatment decision making and subsequent health outcomes for patients.

We approached a number of major insurance companies to consider making changes to their coverage regulations and practices. We also met with many large employers, including Fortune 500 companies, about adjusting their employer-sponsored packages to include a fertility benefit for cancer survivors. In the end, many

SOURCE: LIVE**STRONG**

organizations were receptive to our outreach, and we estimate close to 3 million lives were covered between 2011 and 2013 for cancer-related fertility preservation as a result of our efforts.

LIVE**STRONG** has helped more than 7000 men and women save over $30 million in fertility preservation and medication costs. There is no denying the importance of this service among adolescent and young adult cancer patients and survivors. Fertility preservation should be affordable for patients and covered by insurance companies. No individual should have to worry about being able to afford to conceive a family tomorrow while fighting for their life today. ◆

DISCLOSURES

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8. Research library. LIVE**STRONG** website. https://d1un1nybq8gi3x.cloudfront.net/sites/default/files/what-we-do/reports/LIVE**STRONG**-Benefit-Case-Study-2011.pdf. Accessed September 12, 2016.

NEW DATA: IMBRUVICA® EXTENDED OVERALL SURVIVAL VS CHLORAMBUCIL IN FRONTLINE CLL/SLL

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)[1]
- CLL/SLL with 17p deletion[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

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

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

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 5% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4% to 13%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (eg, high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

pharmacyclics® An AbbVie Company

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil (N=269) in frontline CLL/SLL patients ≥65 years[1]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended overall survival vs chlorambucil

Statistically significant reduction in risk of death[1]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

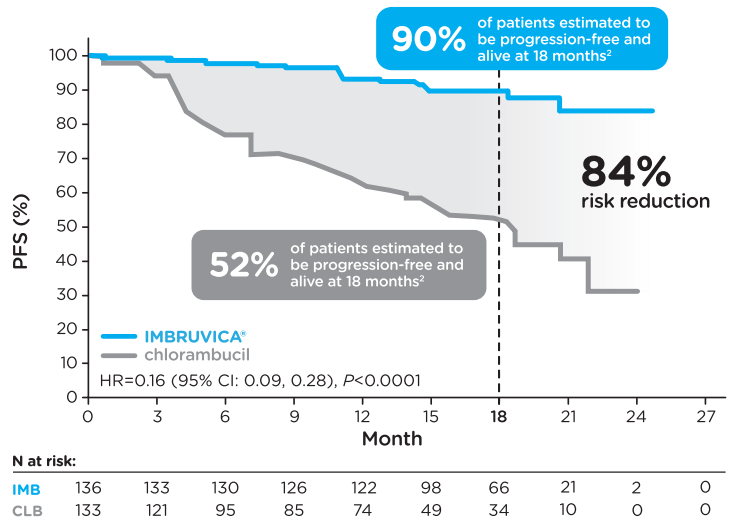
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OVERALL SURVIVAL (OS)

- Median follow-up was 28 months[1]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil



PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (PFS)

- Median follow-up was 18 months[2]
- IMBRUVICA® median PFS not reached[1]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[1]
- PFS was assessed by an Independent Review Committee (IRC) per revised International Workshop on CLL (IWCLL) criteria[1]

Adverse reactions ≥20% across CLL/SLL registration studies[1]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia* (64%), thrombocytopenia* (63%), diarrhea (43%), anemia* (41%), musculoskeletal pain (30%), rash (29%), nausea (29%), bruising (29%), fatigue (27%), hemorrhage (21%), and pyrexia (21%).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

The most common Grade 3 or 4 non-hematologic adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

Approximately 6% (CLL/SLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse reactions.

Approximately 4%-10% (CLL/SLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse reactions. Most frequent adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each) in CLL/SLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

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

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see the Brief Summary on the following pages.

References: 1. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2016. **2.** Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information].*

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

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

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

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

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

Monitor complete blood counts monthly.

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

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

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

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

* Based on laboratory measurements and adverse reactions

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

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

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

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

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

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 2

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

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

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

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

* Based on laboratory measurements per IWCLL criteria.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0

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Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients in Study 3 (continued)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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

Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients in Study 4

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

Waldenström's Macroglobulinemia: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial that included 63 patients with previously treated WM.

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

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

Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

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

* Based on laboratory measurements.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 63%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 15%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 12 days (range, 0 to 627), of Grade 2 was 37 days (range, 1 to 667) and of Grade 3 was 71 days (range, 3 to 627). Of the patients who reported diarrhea, 83% had complete resolution, 1% had partial improvement and 16% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 88 days (range, 1 to 414 days). Of the patients with visual disturbance, 64% had complete resolution and 36% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 281 days).

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary disorders: hepatic failure (includes multiple terms)

Respiratory disorders: interstitial lung disease (includes multiple terms)

Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*

Skin and subcutaneous tissue disorders: anaphylactic shock, angioedema, urticaria

DRUG INTERACTIONS

CYP3A Inhibitors: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations *[see Data]*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception:

Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

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

Geriatric Use: Of the 839 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA *[see Clinical Studies (14.2) in Full Prescribing Information]*.

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function.

The safety of IMBRUVICA has not been evaluated in cancer patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh class B and C) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

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

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions]*.
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions]*.
- *Atrial fibrillation:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions]*.
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions]*.
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions]*.
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions]*.
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions]*.
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions]*.
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent *http://www.imbruvica.com*

PRC-02067

CARE DELIVERY

Enhancing Healthcare Delivery Research at the National Cancer Institute

Ann M. Geiger, MPH, PhD; Ashley W. Smith, PhD, MPH; Sarah C. Kobrin, PhD, MPH; and Stephen H. Taplin, MD

continued from cover

in understanding the drivers of tumor growth and the immune response to tumor cells have resulted in entirely new classes of drugs. Improvements in the measurement and management of cancer- and treatment-related symptoms offer opportunities to improve patients' and survivors' health-related quality of life. The Cancer Moonshot goal of accomplishing in 5 years what would otherwise take 10 will, hopefully, accelerate scientific progress.

Realizing the full public health impact of these advances will require their routine implementation in healthcare delivery. Cancer care spans prevention and screening, diagnosis and acute treatment, and long-term follow-up and end-of life care. The clinicians providing care may, at various points, include physicians, advanced practice nurses, physician assistants, and others. These clinicians may be trained in primary care, surgery, medical oncology, radiation oncology, nursing, palliative care, psychology, or other disciplines. However, substantial variability exists in efforts to achieve patient engagement and coordinate care. The lack of electronic health record interoperability makes it difficult to ensure accurate and timely communication among clinicians and between clinicians and patients. New models, like patient-centered medical homes and accountable care organizations, are altering the practice context. In addition, financial pressures are mounting, in the form of out-of-pocket costs for patients and shifts from fee-for-service to bundled reimbursement for clinicians. A National Academy of Medicine panel recently summarized these challenges by describing cancer care as a "system in crisis."[3]

Historically, the National Cancer Institute (NCI) has been the predominant funder of bench, clinical, and population-based cancer research in the United States. The NCI also supports research resources, such as national networks, to collect data on cancer patients and to conduct clinical trials in both academic and community settings. Nearly 70 NCI-designated and -funded cancer centers provide additional research infrastructure. The Division of Cancer Control and Population Sciences facilitates behavioral, epidemiologic, and other types of research intended to decrease cancer incidence, increase cancer survival, and improve the well-being of cancer patients, survivors, caregivers, and the community. The purpose of this manuscript is to outline recent Division efforts to enhance research on the delivery of cancer care.

Formation of the Healthcare Delivery Research Program

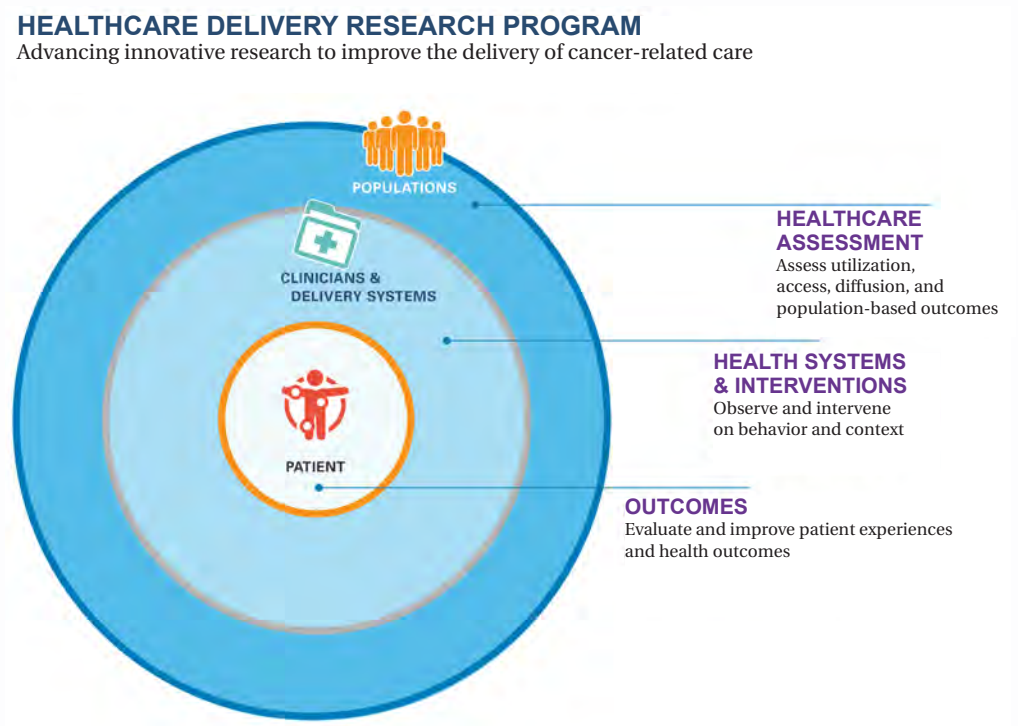
The need for empirical evidence to address cancer care challenges has been increasingly apparent to leadership and staff of the NCI's Division of Cancer Control and Population Sciences. In 2014, leadership began discussing the possibility of centralizing relevant Division efforts in order to facilitate the development of new initiatives and increase the internal and external visibility of this important area.

As a result of these discussions, the Healthcare Delivery Research Program was created in January 2015.

The phrase "healthcare delivery research" was intended to describe all efforts aimed at creating generalizable knowledge about approaches to improving cancer care in both oncology and noncancer settings. Healthcare delivery research was also intended to incorporate scientific contributions from traditional health services researchers and scientists whose primary work in other fields may be applicable to cancer care. Staff defined the vision of the program as "optimal health outcomes for individual, families, and communities affected by cancer." This vision statement highlights healthcare delivery research, not as an end, but as a means to achieve the ultimate outcome of improved health for individuals and populations. The stated mission of advancing innovative research to improve the delivery of cancer-related care emphasizes the need to develop new strategies to address emerging challenges.

The mission of the Healthcare Delivery Research Program is carried out by 3 subgroups known as Branches (FIGURE). The primary mission of the Outcomes Research Branch is to evaluate and improve patient experiences and health outcomes, with particular attention to symptom and function measurement and management. The Health Systems and Interventions Branch observes and intervenes on contextual factors that influence care delivery, such as the function of healthcare teams and use of health information technology. The Healthcare Assessment Research Branch focuses on population-level questions related to access, utilization, diffusion, and outcomes. The following

FIGURE. Expected Impact of the Healthcare Delivery Research Program

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subsections describe these branches and their activities in more detail.

Outcomes Research Branch

The Outcomes Research Branch funds research that seeks to understand the health of cancer patients and survivors, and their caregivers and family members, with the ultimate goal of improving patient and survivor health and well-being. Of key interest is research that focuses on patient-reported outcomes such as anxiety, physical function, and social well-being; cancer-related symptoms such as pain and fatigue; and patient-generated health data—such as information collected through mobile devices or sensors of an individual's physical state. Another priority is the evaluation and delivery of quality cancer care, particularly patient-centeredness and patient engagement, including satisfaction and experiences with medical care.

The Outcomes Research Branch also focuses on the development and implementation of outcomes measures for research and clinical use, as well the creation of novel data resources for research use. Work relevant to outcomes measures includes coordinating an initiative to integrate and make publicly available National Institutes of Health-funded measures designed to capture patient-centered assessments of health, function, life satisfaction, and other factors.[4] This branch also facilitated the development of a measurement system designed to examine patient-reported adverse events in oncology clinical trials that supplements standard reporting by clinicians.[5] Other key initiatives include the first publicly available linkage of cancer registry and health-related quality of life data.[6] A second resource linking cancer registry and quality of care data is anticipated to be available later this year. In addition to informing research, work supported by the Outcomes Research Branch has the potential to inform drug approval processes and quality metrics.

Health Systems and Interventions Research Branch

The Health Systems and Interventions Research Branch funds a growing portfolio of research that seeks to understand how processes and outcomes of care are influenced by multilevel contextual factors related to clinicians, practice settings, delivery systems, insurance, and policy. A majority of currently funded studies focus on identifying nonpatient factors that include clinician behavior and organizational structure, which can be targets of interventions aimed at improving care. Expanding support for the development and evaluation of interventions targeting those factors—including improving measurement of organizational characteristics—is a strong interest. For example, this branch encourages shared decision-making research that addresses clinician and organizational structures rather than focusing solely on the patient. Similarly, the branch is interested in how the structure and function of health care teams influence care delivery, particularly when there is a transition from primary to oncology care or between oncology specialties. Research seeking to use health information technology to improve healthcare delivery is an area of growing emphasis.

Members of the Health Systems and Research Branch are engaged in a number of efforts to facilitate research on contextual factors in healthcare. For example, the branch developed a partnership with the American Society of Clinical Oncology to improve healthcare team functioning, which has included a workshop and a series of forthcoming manuscripts that will provide a foundation for future research.[7] The branch provides ongoing leadership for an innovative initiative to provide NCI-designated cancer centers, with funding to support community-based work improving HPV vaccination rates.[8] Similarly, the branch partners with a network of outside investigators to identify and address problems in the follow-up of abnormal screening tests.[9] Finally, the branch is working collaboratively with other NCI colleagues to expand implantation science in such areas as shared decision making.[10,11]

Healthcare Assessment Research Branch

The Healthcare Assessment Research Branch supports research focused on demographic, social, economic, and health-system factors as they relate to access to, and provision of, cancer care at the population level rather than the individual level. Of particular interest is research on patterns of care, outcomes of healthcare services, and healthcare disparities. The branch also supports research examining the financial burden of cancer care on cancer patients, survivors, caregivers, and families, including direct (eg, co-pays and indebtedness) and indirect (eg, employment and time) costs. Policy research, such as that into reimbursement strategies and behavioral economics, is of interest as it relates to patient outcomes. Studies supported by this branch often involve population-based data linkages or research networks that are a source of information on patients, clinicians, practice settings, and insurance coverage.

The Healthcare Assessment Research Branch manages several research resources that facilitate the work of external scientists or reporting on national cancer control trends. A data linkage of national cancer registry and Medicare claims data has been widely used to explore cancer etiology, treatment patterns, and survivorship issues.[12] Similarly, the addition of cancer-relevant questions to a national survey of individual spending on healthcare has provided insights into the financial burden of cancer.[13] The branch also works with other federal partners to coordinate the cancer portion of a national survey of individual health that is used to monitor prevention behaviors, screening rates, and other aspects of cancer control.[14] Finally, the branch conducts patterns-of-care studies designed to assess the diffusion of, and possible disparities in, the use of new therapies.[15]

Future Directions

Staff across the Healthcare Delivery Research Program are engaged in several efforts to expand cancer care delivery. Funding opportunities have been developed to encourage work in emerging areas such as caregiving,[16] de-implementation,[17] treatment disparities,[18] and system strategies to promote HPV vaccination.[19] Program staff are using innovative grant-making mechanisms like the Small Business Innovation Research Program, which currently seeks applications for digital platforms to support cancer caregiving[20] and informatics tools to measure cancer care coordination.[21] Efforts to enhance current initiatives are ongoing, including a plan to renew funding for a network that focuses on improving cancer screening processes[22] and promotion of cancer care delivery research within a network of community-based cancer practices historically focused on clinical trials.[23] Several proposals for funding opportunities are moving through the NCI development and approval processes.

The program also convenes workshops to explore areas that may benefit from new funding opportunities or research resources,

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most recently on cancer caregiving; consequences of shared decision making; designing delivery systems and information technology interfaces with the user in mind; employment issues experienced by cancer patients and survivors; and new opportunities for data linkages. In addition, the program partnered with a nonfederal organization to hold the national conference, "Cancer Care Delivery in a Rapidly Changing Healthcare System."[24] Staff also participate in national scientific meetings and engage with the research and clinical communities in many settings.

Conclusion

The Healthcare Delivery Research Program at NCI was formed to address the need for empirical evidence to support challenges in cancer prevention, screening, diagnosis, treatment, survivorship, and end-of-life care. The program currently includes 3 components with complementary interests:

- Patient experiences and health outcomes
- Delivery system context
- Access, utilization, and outcomes at the population level

This structure and the activities described above may be modified in the future as the program responds to evolving research priorities of the Division and NCI. Continuous growth of the program will occur under the guidance of its first permanent leader, Paul Jacobsen, PhD, who joined NCI in September 2016. Over the next few years, program staff will continue to work toward meeting the mission of advancing innovative research to improve cancer care in service to the ultimate vision of optimal health outcomes for individual, families, and communities affected by cancer. ◆

DISCLOSURES

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