Person-Centered Care: The New Business Case for Cancer

As a senior program officer for The John A. Hartford Foundation, **Amy Berman, BS, RN,** *has devoted her career to spreading the word about better ways to deliver healthcare. Three years ago, she became her own case study when she discovered she had inflammatory breast cancer, a rare form of the disease with poor odds of 5-year survival. Berman's story of embracing palliative care and an active life embodies the movement toward "person-centered" care that will become essential as the population with cancer ages.*

For **Amy Berman, BS, RN,** today's cancer care delivery system is a lot like the sound of 1 hand clapping: It can be out of sync and unproductive, because it fails to touch the patients it treats.

Creating a better system for delivering cancer care means creating a new *value* proposition, Berman said; it means making a new business case for cancer.

Berman, a senior program officer at The John A. Hartford Foundation, predicts that demographics will drive change. "We have 10,000 people turning 65 every day," she said, and this group is getting older. The sexy senior on the tennis court who takes a pill for high blood pressure is increasingly joined by the extremely old person, aged 85 years or above, who suffers from multiple chronic conditions or dementia. This latter group, Berman said, is accounting for more and more of today's cancer diagnoses.

Understanding the demographic realities is key to grasping—and avoiding—the 2 top cost drivers in cancer care, she said. First, the top cost driver of cancer care are treatments that don't meet patient goals. The second cost driver is a lack of community-based support services.

"We have a system that is perfectly designed for someone to show up in the emergency department (ED), where we don't want them to show up," Berman said. Improving the value proposition means working to keep people away from the ED, in part by trimming the twin pillars of runaway cost.

Berman presented the concept of the "triple aim," which she said refers to better health, better care, and lower costs. "Another way to look at value is gaining the same or better quality care at the same or lower cost. You want to *improve* quality as you *decrease* cost," she said. "That is the improvement of a value proposition."

Professionally, Berman's focus has been to find ways to avoid hospital readmissions. She has a nurse's eye and heart. But 3 years ago, the red spot that appeared on her right breast put Berman on the "patient" side of the table. Even before her test results came back, Berman knew what she was facing, and the look on her primary care physician's face only strengthened her suspicion of inflammatory breast cancer.

As Berman explained to the conference attendees, inflammatory breast cancer is a rare form of a common disease; its 5-year survival rates are only about 40%. Survival rates are so much worse than for most breast cancers that its patients drag down rates for breast cancer generally (where improvements in treatment have raised survival to 90%).

"Inflammatory breast cancer looks different—it's not a tumor or a lump that can be picked up early," Berman said. When it clumps up, it appears on the skin and looks like the peel of an orange.

Given her background, Berman spent the night before her biopsy reviewing the literature: Who was treating inflammatory breast cancer? Who has funding? Where are the best treatments being offered? What does the National Cancer Institute say about different approaches? Berman found an expert oncologist in her search and resolved to visit that person.

After her biopsy, there was more sobering news from a body scan: Her lower spine had a "hot spot" of activity—it could be an old surfing injury, but it could mean the cancer had already spread. Berman had a bone biopsy, and she traveled out of state with her 70-year-old mother in tow to see the specialist she had identified.

During their trip, she was walking with her mother when she received a call from her oncologist: the cancer was in her lower spine. At diagnosis, she was already at stage IV. Her 5-year survival prognosis was now 11%.

"It was raining out, and hearing those words, my mother and I dropped our umbrellas, and we hugged on the street and cried. We cried the whole way home, and it felt like the entire world was crying with us.

"It was absolutely devastating, but we stopped crying pretty quickly, and I'll tell you why. It is really important to know that for whatever time I have left, I didn't want to be spending it in tears—or not *doing*."

The next day she visited the specialist. The oncologist wanted aggressive treatment: a mastectomy, radiation, chemotherapy. Knowing the cancer was already in her spine, Berman asked, "Why?" The treatment would rob Berman of her ability to work, to write, to enjoy time with her family. It would compromise her immune system and leave her open to infections.

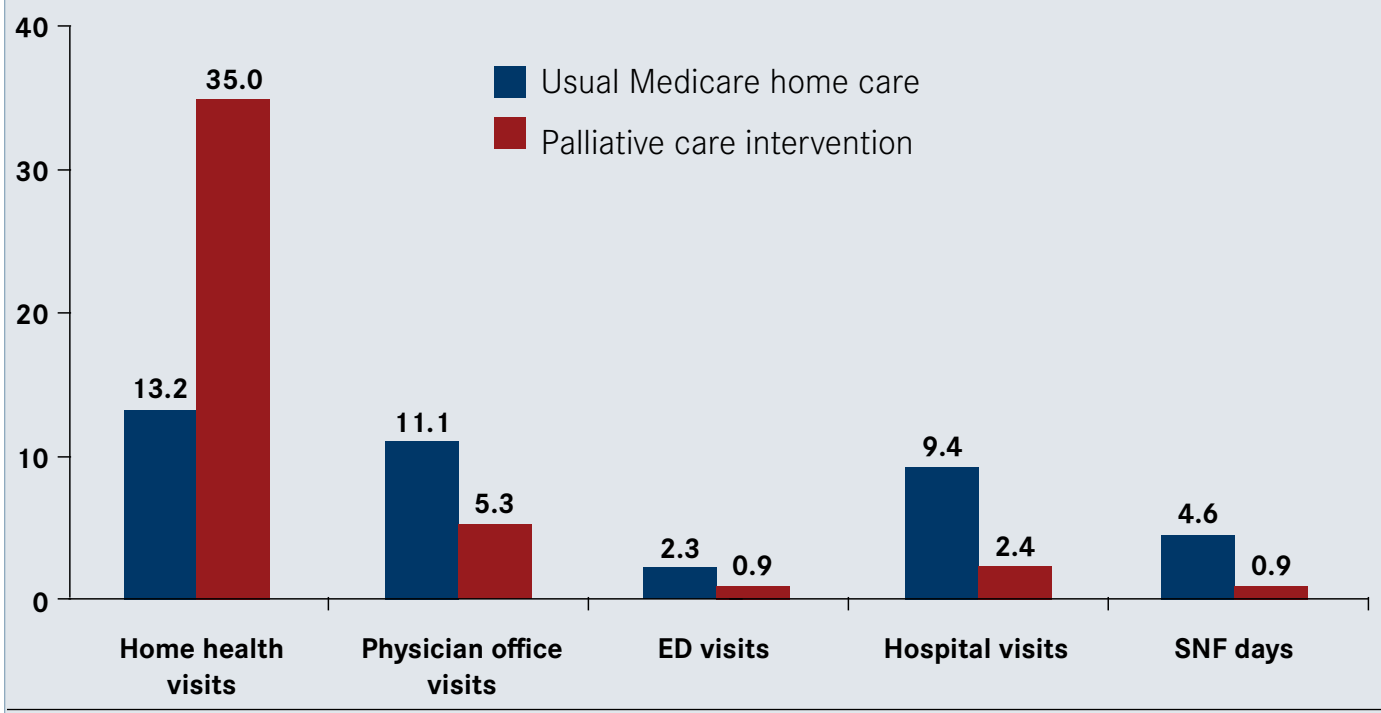
So Berman said, "No."

"I probably have saved my payer about $500,000," Berman told the gathering. More important, however, are the experiences Berman has gained: "I jet-skied to the Statue of Liberty this summer. I've climbed the Great Wall of China twice. I work, I play; I have a very good life, and I *am* getting treatment."

Berman has opted for palliative care, and lower-dose chemotherapy that holds her cancer in check. She takes an oral medication—a single pill—at night; once a month, she has an infusion to keep her bones strong.

The literature supports Berman's approach. "People actually do live longer when you focus on pain and symptoms and quality of life," she said, citing a study in the *New England Journal of Medicine* (**Figure**).[1] The question, asked Ber-

Figure. Palliative Care Shifts Care Out of Hospital to Home



ED indicates emergency department; SNF, skilled nursing facility.
Source: *NEJM*, 2010, Temel JS, Greer JA, Muzikansky A, et al.

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man, is why doesn't this happen more often?

"How can care be patient-centered when we don't discuss serious illness with patients?" she asked. "I don't think people are trying to do bad things, even that physician who would have suggested that I throw everything at it."

That physician, Berman said, laid out his plan before asking what her goals were—because that's the way he practiced medicine. Care that is truly patient-centered, she said, "Considers the patient's cultural traditions, their personal preferences, values, their family situation, and their lifestyle."

The value proposition, she said, comes when the patient gets all the information and is part of the decision, "because studies show that people actually choose less aggressive care when they understand the totality of their situation."

Cancer care has not done this historically. "Oncology chooses to look in a narrow way at the cancer, and we have to begin addressing the person."

Data show physicians often don't give patients the full story.[2] Yet the American Medical Association code of ethics, revised in 2006, states that they must. This is, as Berman put it, the "nut" of the issue in the rising cost of cancer care: physicians must start embracing palliative care, which Berman defined as that "layer of support" that can go alongside curative treatment, not just at the end of life. Palliative care exists for other ailments: congestive heart failure, dementia, and other conditions with pain. It also covers advance planning, or "the stuff that oncology typically does not want to do."

What the data show, Berman said, is that physicians want to do less just as informed patients do, but what happens instead is "liability-driven care."

She presented numbers for what drives up the cost of cancer care, as well as the 5 elements of the "Choosing Wisely" initiative produced by the American Society of Clinical Oncology.[3] They focus on symptom relief and palliative care, and are:

1. Do not give patients starting on a chemotherapy regimen that has a low or moderate risk of causing nausea and vomiting anti-emetic drugs intended for use with a regimen that has a high risk of causing nausea and vomiting.

2. Do not use combination chemotherapy (multiple drugs) instead of chemotherapy with 1 drug when treating an individual for metastatic breast cancer, unless the patient needs a rapid response to relieve tumor-related symptoms.

3. Avoid using PET or PET-CT scanning as part of routine follow-up care to monitor for a cancer recurrence in patients who have finished initial treatment to eliminate the cancer, unless there is high-level evidence that such imaging will change the outcome.

4. Do not perform prostate-specific antigen (PSA) testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live less than 10 years.

5. Do not use a targeted therapy intended for use against a specific genetic aberration unless a patient's tumor cells have a specific biomarker that predicts an effective response.

The Institute of Medicine's recent report, "Delivery High-Quality Cancer Care: Charting a New Course for a System in Crisis," reported the obvious: When cancer strikes older people, who have more than just cancer, "value" takes on new meaning, and it may not be the same thing for each person.

Amy Berman, BS, RN, at the Great Wall of China.

"The number 1 goal was to engage your patient, and you can read the reasoning behind it," Berman said. Starting palliative care—that "extra layer" of support—at the onset of a serious disease, rather than at the end of life, will bring cost savings and greater quality of life, she said.

Palliative care keeps people from showing up in the ED; patients may be able to resolve issues over the phone. It keeps people from ending up without advance directives. "For those of you who are in the managed care environment, in ACOs, working under new patient methodologies, you have the ability to offer it all to your patients," she said. "If you are in a capitated environment, you will benefit from this. It will reduce liability."

"This is everything that you want. It's everything that people like me want." **EBO**

References

1. Temel JS, Greer JA, Muzikansky A, et al. Palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363:733-774.

2. Seoane L, Bourgeois DA, Blais CM, Rome RB, Luminais, HH, Taylor, DE. Teaching palliative care in the intensive care unit: how to break the bad news. *Oschner J.* 2012;12(4):312-317.

3. Schnipper LE, Lyman GH, Blayney DW, et al. American Society of Clinical Oncology 2013 Top Five List in Oncology. *JCO.* 2013:4362-4370.

Patient-Centered Oncology Care: Real-World Perspectives

Will Shifts in Oncology Outpatient Points of Care Lead to More Profits or Savings?

To begin the session entitled "Oncology Practice in the Era of PCMHs and ACOs: Square Pegs or Round Holes?", **Peter B. Bach, MD, MAPP,** *outlined how new payment models are changing the settings of oncology practice. High drug costs and shifting reimbursement trends have pushed patients out of community settings and into hospitals. Rather than lament this shift, Bach suggests hospitals should be targeted for savings.*

Alterations in risk and incentives that have accompanied the healthcare system's move away from fee-for-service have had some unintended consequences. This can compromise the ability for stakeholders to achieve the goals intended by the reform, but can also create opportunities for new payment models to emerge, for care to improve, and for savings to be achieved, according to **Peter B. Bach, MD, MAPP,** director, Center for Health

Policy and Outcomes, Memorial Sloan-Kettering. Bach pointed out the shrinking network of community oncology outpatient care clinics, which has led to consolidations, hospital agreements, and acquisitions. As the provider networks grow, various risk scenarios are being explored that include care management fees, bundled payments, capitated risk, and integrated delivery through accountable care organizations (ACOs).

Bach noted that, although he believes bundled payments offer the best opportunities for savings and improved care, the marketplace may not be ready for this. Most stakeholders are more comfortable with a shared savings environment similar to what is seen in ACOs. In oncology, the trend is to try to achieve savings outside of the drugs. The data so far suggest that care through a patient-centered medical home (PCMH) can result in reduced hospitalizations and overall cost reductions. However, it remains to be seen whether these reductions can be sustained over time. "There's a lot of money spent on hospitalizations, a lot of money spent on imaging, advanced testing," he stated. Practicing physicians are in a position to redesign care and reduce these costs.

The consolidation has led to larger provider networks, such as hospitals, being in a better position to take on more risk, Bach said. "I think the general trend is to move risk, and to move it to the place where the discretionary decisions are made," he added. At the same time, the larger networks are also "garnering strong negotiating leverage with payers."

"So, this consolidation cuts both ways," Bach said. "They're ready to take on risk, but they're also getting to a point where they could be one of the few providers in the area, which allows them to extract much higher rates."

He presented data showing that the median introductory price for new oncology drugs has increased from about $100 per month in 1970 to about $10,000 per month in 2010. Due in part to the collapsing margins at the physician level, there has been a shift at the point of care from the physician office to the hospital outpatient department. "By site of service, there's a very strong trend. We used to say 80% of care was delivered in the community. It's now more proper probably to say it's about 60%," Bach said. This shift has been driven by the 340B drug discounts that allow hospitals to pay approximately 40% less than physician offices. The program was originally designed to target underserved populations, but about one-third of hospitals qualify for the discounts. "It's for outpatient drugs in the hospital, so only the hospitals can benefit from this through their outpatient departments, and this has caused a huge distortion in the marketplace."

The common belief is that cancer care costs more in the hospital outpatient setting than at the physician office. Bach pointed out that this is based on historic data. Also, the data are not adequately adjusted to reflect discounts or how sick the patients are. The increased purchasing power of the hospitals translates to more opportunities for savings. "So, we can look at the physician office and say OK, those margins are squeezed, people are going out of business. These hospitals have balance sheets and they're getting fantastic reimbursement," Bach said. "So, they're exactly the ones to target for (savings)." **EBO**

Care Reflects Patient Choice, but Having the Data Reflect "Consumerism" Is Another Matter

Cliff Goodman, PhD, *senior vice president and principal, The Lewis Group, moderated the panel discussion, "The Role of Consumerism in the Deliverability of Care." Panelists included* **Amy Berman, BS, RN,** *senior program officer, the John A. Hartford Foundation;* **Dennis Scanlon, PhD,** *professor, health policy and administration, Pennsylvania State University; and* **Manasi A. Tirodkar, PhD, MS,** *research scientist, National Committee for Quality Assurance.*

In her work with The John A. Hartford Foundation, **Amy Berman, BS, RN,** seeks opportunities for change. The fundamental shifts in the marketplace are about more than just looking at billing and point of service, Berman stated. There are real opportunities for working with patients to structure their goals of care and improve their outcomes.

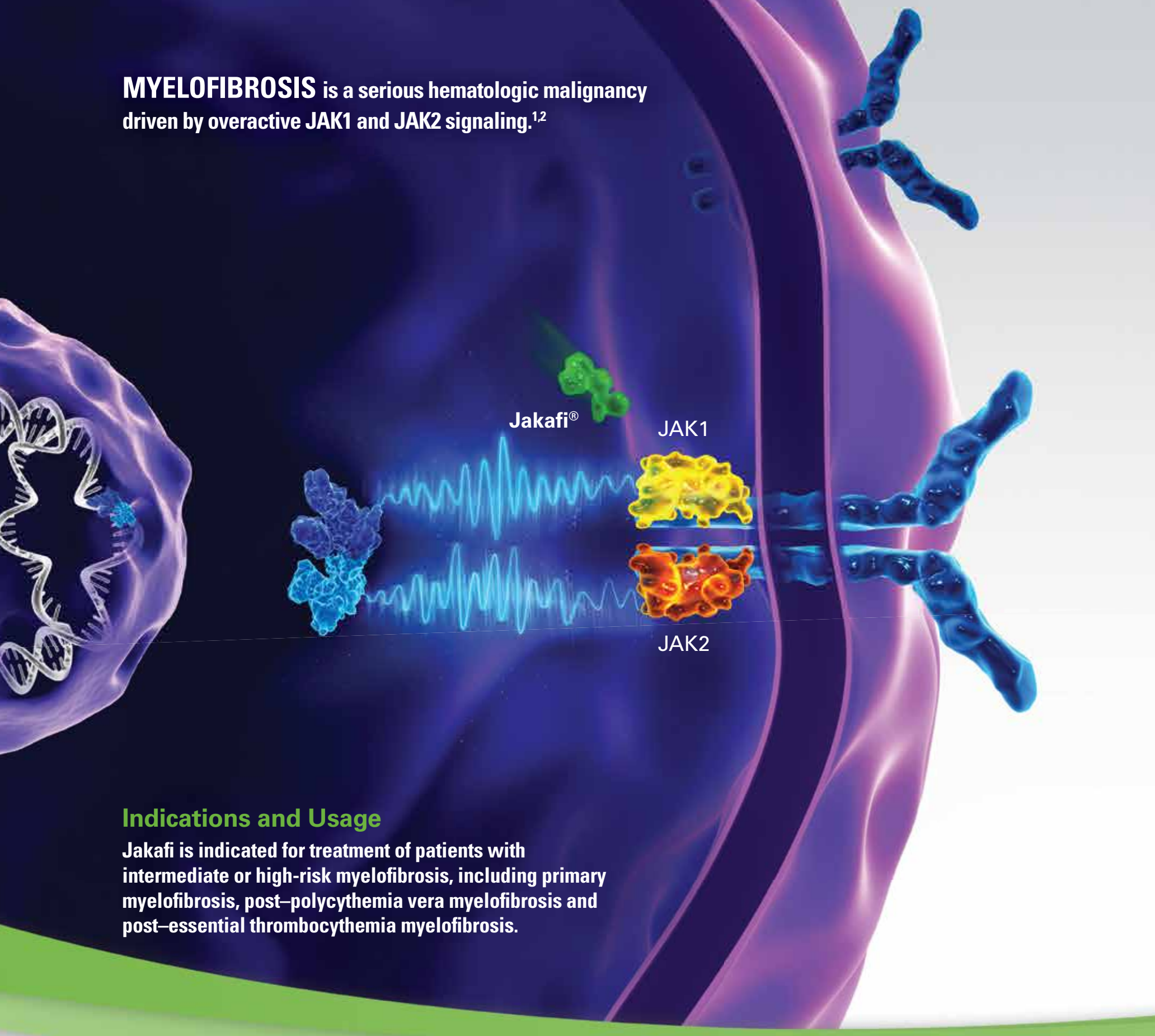
Cliff Goodman, PhD, asked Berman to elaborate on how the patient will be regarded in light of the "mega trends" in the healthcare system. "We certainly are in an environment where there are greater costs that are going to be put back on the individual, on the consumer," she said. There needs to be a greater emphasis on the value proposition at the point of service. Her question: "How does this really fit in terms of people cycling in and out of hospitals, which are really typically poorly designed for continuity?"

Dennis Scanlon, PhD, stated that future research should explore areas surrounding patients' emotional and family support, their level of understanding regarding their conditions and risks, and how well those risks and treatment options have been communicated. "At the end of the day, we need to bring it all together to understand how do we redesign the care delivery system and provide financial and nonfinancial incentives to redesign it." He added that both good and bad reasons for variation in care exist, which raises the level of complexity. However, data are not currently being collected to reflect the variability inherent in incorporating patient preferences. Scanlon asked, "How do we adjust that outcome based on patient preferences and clinical evidence and acknowledge that the outcome may vary, depending on not

(continued on SP75)

Cliff Goodman, PhD, asked for comments about how patients' desires can be reflected in data on quality.

MYELOFIBROSIS is a serious hematologic malignancy driven by overactive JAK1 and JAK2 signaling.[1,2]



Indications and Usage

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

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects, with the most frequent being thrombocytopenia and anemia. 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
- Thrombocytopenia was generally reversible and was usually managed 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. Withhold Jakafi until recovery
- The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache
- Serious bacterial, mycobacterial, fungal and viral infections may occur. Active serious infections should have resolved before starting Jakafi. Observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment

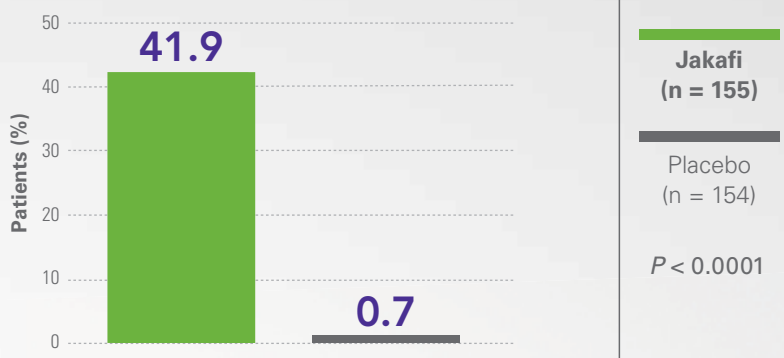
Incyte

The first and only FDA-approved drug treatment for intermediate or high-risk **MYELOFIBROSIS**[3,4]

Target the JAK pathway—treat the disease

Jakafi inhibits both JAK1 and JAK2 signaling, an underlying mechanism of disease, and significantly improves splenomegaly and symptoms[4,5]

COMFORT-I: Percentage of patients with ≥35% reduction in spleen volume from baseline to Week 24[4,5,a]



COMFORT-I: Percentage of patients with ≥50% improvement in TSS at Week 24[4,5,a,b]

COMFORT-I = COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment (I); TSS = Total Symptom Score.

- Efficacy was seen with Jakafi in both *JAK2*V617F-positive and *JAK2*V617F-negative patients, relative to placebo[6,7]

Consider Jakafi upon diagnosis for your patients with intermediate-1, intermediate-2 or high-risk myelofibrosis

JAK = Janus kinase.

- Progressive multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

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

[a]As studied in COMFORT-I, a randomized, double-blind, placebo-controlled phase III study with 309 total patients. The primary endpoint was the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to Week 24. A secondary endpoint was the proportion of subjects with a ≥50% reduction in TSS from baseline to Week 24.[4,5]

[b]TSS was captured by a daily patient diary (MFSAF v2.0). TSS encompasses debilitating symptoms of myelofibrosis: abdominal discomfort, early satiety, pain under left ribs, pruritus, night sweats and bone/muscle pain. Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60. At baseline, mean TSS was 18.0 in the Jakafi group and 16.5 in the placebo group.[4,5]

References: 1. Tefferi A. *Blood*. 2011;117:3494-3504. **2.** Verstovsek S, et al. *N Engl J Med*. 2010;363:1117-1127. **3.** Deisseroth A, et al. *Clin Cancer Res*. 2012;18:3212-3217. **4.** Jakafi Prescribing Information. Incyte Corporation. **5.** Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. **6.** Verstovsek S, et al. *N Engl J Med*. 2012;366(suppl):1-38. **7.** Verstovsek S, et al. *Br J Haematol*. 2013;161:508-516.

Jakafi®
ruxolitinib (tablets)

Jakafi®
ruxolitinib (tablets)

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

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

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.2) in Full Prescribing Information, and Adverse Reactions*]. 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. Withhold Jakafi until recovery [*see Adverse Reactions*]. 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 (2.2) in Full Prescribing Information, and Adverse Reactions*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections may occur. Active serious infections should have resolved before starting therapy with Jakafi. Observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly. *PML* Progressive multifocal leukoencephalopathy (PML) has been reported 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*].

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Myelosuppression [*see Warnings and Precautions*]; • Risk of Infection [*see Warnings and Precautions*] **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with myelofibrosis in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 88.7% of patients treated for more than 6 months and 24.6% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In a double-blind, randomized, placebo-controlled study of Jakafi, 155 patients were treated with Jakafi. The most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11.0% of patients treated with Jakafi and 10.6% of patients treated with placebo. Following interruption or discontinuation of Jakafi, symptoms of myelofibrosis generally return to pretreatment levels over a period of approximately 1 week. There have been isolated cases of patients discontinuing Jakafi during acute intercurrent illnesses after which the patient's clinical course continued to worsen; however, it has not been established whether discontinuation of therapy contributed to the clinical course in these patients. When discontinuing therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered [*see Dosage and Administration (2.9) in Full Prescribing Information*]. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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

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

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

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

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

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

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

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

DRUG INTERACTIONS Drugs That Inhibit or Induce Cytochrome P450 Enzymes Ruxolitinib is predominantly metabolized by CYP3A4. **Strong CYP3A4 inhibitors:** The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, with Jakafi administration (10 mg single dose) following ketoconazole 200 mg twice daily for four days, compared to receiving Jakafi alone in healthy subjects. The half-life was also prolonged from 3.7 to 6.0 hours with concurrent use of ketoconazole. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding ruxolitinib AUC following concurrent administration with ketoconazole. When administering Jakafi with strong CYP3A4 inhibitors a dose reduction is recommended [*see Dosage and Administration (2.7) in Full Prescribing Information*]. Patients should be closely monitored and the dose titrated based on safety and efficacy. **Mild or moderate CYP3A4 inhibitors:** There was an 8% and 27% increase in the C_{max} and AUC of ruxolitinib, respectively, with Jakafi administration (10 mg single dose) following erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to receiving Jakafi alone in healthy subjects. The change in the pharmacodynamic marker, pSTAT3 inhibition was consistent with the corresponding exposure information. No dose adjustment is recommended when Jakafi is coadministered with mild or moderate CYP3A4 inhibitors (eg, erythromycin). **CYP3A4 inducers:** The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, with Jakafi administration (50 mg single dose) following rifampin 600 mg once daily for 10 days, compared to receiving Jakafi alone in healthy subjects. In addition, the relative exposure to ruxolitinib's active metabolites increased approximately 100%. This increase may partially explain the reported disproportionate 10% reduction in the pharmacodynamic marker pSTAT3 inhibition. No dose adjustment is recommended when Jakafi is coadministered with a CYP3A4 inducer. Patients should be closely monitored and the dose titrated based on safety and efficacy.

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

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only the clinical situation, but the patient's preferences?"

Goodman asked **Manasi A. Tirodkar, PhD, MS,** to comment on whether a pathway currently exists for creating quality measures that take patient preferences into account.

"We have been looking at potential measures of shared decision making," Tirokdar said. "Part of the problem is that data simply don't exist." She noted that this issue is primarily on the provider side due to limitations with electronic health records, claims, and other standard forms of data collection. The NCQA is looking into patient-reported outcomes that reflect the shared decision making.

Scanlon stated that it is important to be able to gather information about discussions between the patient and provider as well as the regimen and outcome. "We need some detail about that interaction, about discussions about risk, about discussions about treatment options, whether patients feel that their views were considered, and also how healthcare was organized and delivered," he said. Tirodkar noted that decision aids are available to help standardize these discussions. However, they are based on a single treatment decision. Also, patients typically do some of their own research.

Incorporating patient decision making and providing the appropriate setting to help patients get the information they need is very complex, Scanlon said.

Goodman asked the panel, "How would each of you propose to enhance the role of the informed patient/consumer in rocky economic conditions?"

Berman said that although there are many challenges with measuring the various aspects of patient-centered care, "Consumerism has arrived." What is known, she said, is that patients need a diagnosis, a prognosis as to the likely course of the disease, and choices about their care. "What's the benefit now, what's the longer-term benefit, and cost?" With this information, the patient has the appropriate context and will receive better care in the process.

Tirodkar added that patients need help navigating the system. "It could be a nurse navigator, a patient navigator, or a care coordinator," she said. "There are various different people that can fulfill that role (who) can also provide that information on finances and navigating payer systems and reimbursement." **EBO**

When Making Decisions in Cancer Care, Patients Want to Know: How Will I Feel?

*How patients feel during treatment for cancer can have a lot to do with outcomes—and with the cost of care. In "Incorporating Patient-Centered Outcomes in Clinical Trials," **Ethan Basch, MD,** associate professor and director, Cancer Outcomes Research Program at the University of North Carolina, Chapel Hill, discussed the need for standardization of data, so newly diagnosed patients can learn how treatment has affected other people like them.*

Patient-reported outcomes are increasingly being incorporated in clinical trials, and they are finding their way into comparative effectiveness research (CER) as well as clinical practice decision making. "Patients wish to know what the experiences of people like them were in similar contexts previously, either within trial contexts or real-world or non-trial contexts," said **Ethan Basch, MD**. Having this information is helpful for estimating the comparative effectiveness among treatments for various stakeholders, including payers.

For example, the American Society of Clinical Oncology (ASCO) guidelines for antiemetics recommended the inclusion of patient-reported nausea in future clinical studies. Although vomiting is important clinically because of the risk for dehydration, "It turns out that what patients care about is nausea because that's what they are at home experiencing, and it's actually much more prevalent and often more severe."

Clinical trials have a long history of including patient-reported outcomes such as quality of life, symptoms, and functional status. In the context of delivery, however, "We start to think about treatment preferences, shared decision making, effectiveness, understanding of goals of care, and satisfaction." Patient-reported outcomes should be meaningful and actionable to people who are making a choice. Researchers should also engage patients throughout the process. According to Basch, before outcomes measures can be developed, qualitative research should be conducted in the target population "to understand the concepts, the experiences, the symptoms, and the other outcomes that are important and meaningful to them, particularly toward making decisions."

Payers should care about patient-reported outcomes because patients' healthcare utilization is impacted by how they are feeling. "There's growing evidence to suggest that improving how people feel decreases utilization, particularly office visits, support of medication use, and referrals." Patient-reported outcomes are also important in the context of cost-utility analyses, he said.

The Center for Medical Technology Policy issued an effectiveness guidance that recommends specific measures be used within oncology. This includes anorexia, anxiety, constipation, depression, diarrhea, dyspnea, fatigue, insomnia, nausea, pain, neuropathy, and vomiting. "These are felt to be important cross-cutting symptoms that should be assessed across trials, not only because they are important to people and will render information that will assist people in making decisions about the best treatment, but because these will also allow us to compare across products in order to understand their comparative impact on the patient experience," Basch said.

The National Quality Forum is developing a pathway to test patient-reported outcomes in performance measures. ASCO has created a work group to develop patient-reported outcome performance measures that are specific to oncology, including symptoms as well as metrics around shared decision making and decision quality.

> ***Patient-reported outcomes should be meaningful and actionable to people who are making a choice. Researchers should also engage patients throughout the process.***
>
> **—Ethan Basch, MD**

Basch noted that, whereas regulators are more interested in very context-specific measurements, payers are looking at PROs in terms of comparative value and reimbursement. Observational and retrospective data are more acceptable to payers than to regulators. "Often-

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times in the regulatory context, unfortunately, this is considered supportive of other data, whereas in the context of care delivery, this may actually become one of the most important indicators of value."

Some of the challenges for the future include developing appropriate measures and standardizing them. Also, data gathering, cost, and infrastructure are challenges. "There's been quite a bit of movement recently to integrate patient-reported outcomes into electronic health records (EHRs)," he said. "A patient comes in, they self-report on their experience. That information lives on the EHR. It is used for clinical care, it's aggregated for quality assessment, it's aggregated for effectiveness research, and ultimately, perhaps even for use in the regulatory context."

Basch concluded by emphasizing the importance of incorporating the patient perspective in effectiveness research as well as in clinical practice quality assessment. "I would argue that we have an incomplete picture of the impact of treatments on patients without this information," he said. "In oncology, our drugs are highly toxic and in the advanced and metastatic setting, our benefits can be meager, and I think understanding the impact on how patients feel is an important piece of understanding the value of a product." **EBO**

Cancer Patients Need Better Information, and Payers Should Demand They Receive It

Cliff Goodman, PhD, *moderated a panel discussion on the "Implications of Healthcare Reform: 'No' Will Be Heard." Participating were* **A. Mark Fendrick, MD,** *professor, department of health management and policy, University of Michigan;* **John L. Fox, MD, MHA,** *senior medical director and associate vice president, medical affairs, Priority Health; and* **Ira M. Klein, MD, MBA, FACP,** *chief of staff, Office of the Chief Medical Officer, Aetna, Inc.*

Payers should demand that patient preferences be considered, and that patients be provided the help they need to make decisions, according to **John L. Fox, MD, MHA.** Payers do not want to be interposed between patients and providers. Patients, Fox said, should be "afforded the opportunity to make their choices known and to have their choices respected."

Ira Klein, MD, MBA, FACP, said that most cancer patients do not fully understand their prognosis or their treatment options. Patients, he said, "should have access to a little bit more understanding about what is going to happen to them from the beginning, the middle, and the end—whether it's incurable disease, long-term survivorship, or mid-term remission."

Fox cited examples in which patients were unaware of their prognoses. One study showed that 81% of patients receiving chemotherapy for incurable metastatic colorectal cancer thought that they were getting curative chemotherapy. Another study found that 69% of patients who had incurable metastatic non-small cell lung cancer thought they were getting curative chemotherapy. When patients are fully informed, they "tend to be less aggressive than their physicians" regarding their care.

A. Mark Fendrick, MD, said that the topic is not really about saying "no" but about shifting the discussion and altering the reimbursement to reflect the value of the treatment. In what he referred to as "nuance care," the greater the treatment value, the lower the cost should be. For example, if the cure rate is 90% with a given agent, it should cost the patient less than if the patient stands to extend his or her life by a few months.

Cliff Goodman, PhD, posted a question to the panel: "How equipped are oncologists to actually listen to what the patient said—if it's a 'no,' for example—and proceed accordingly?"

Fox pointed out that oncologists say they want to talk to their patients and want to know their goals of care and their preferences, but they don't have good systems in place to have this conversation.

Some organizations are beginning to "create systems of care within practices so it becomes the routine." Fox added that the time spent should be billable. "We can't say this has value and then not reward that behavior." His organization has a billable code for "advanced care planning," he said.

Klein noted that, on the provider side, his organization has "pay-for-value" arrangements with physicians so that they are encouraged to look beyond simply following the standard of care for each patient. On the patient side, "We're looking at ways to have patients be more engaged (and) not be a passenger in the journey. That's really hard to do."

> *"The main issue is that most benefit designs in public and private plans basically have a one-size-fits-all system…"*
>
> **—A. Mark Fendrick, MD**
> University of Michigan

Goodman asked the panel to comment on the impact of healthcare reform on patient decision making. Klein said that reform within the context of an already fragmented system may have negative consequences. "You will have changing networks, changing copayments, changing coinsurances," he said. "If people don't have a way to make their way through the system and understand what they're going to pay, what they're paying for, it will be a degradation in the care that we have today."

"We need to remove any barriers that exist to ensuring that patients have an opportunity to express their goals of care," Fox insisted. "Ultimately, we'll drive down the cost of care if the evidence is correct, if we are more in tune with what the patients want, and we create systems of care that ensure that those voices are heard."

Fendrick stated that the Affordable Care Act (ACA) has provisions that ensure that certain cancer screenings, such as mammograms for women over the age of 40 years, are available at no cost to patients. "The main issue is that most benefit designs in public and private plans basically have a one-size-fits-all system; all doctor visits cost the same; all drugs in the tier of the formulary cost the same; (and) every diagnostic test costs the patients the same out of pocket."

Fox said that one of the challenges with nuance care is that it would be difficult to explain to people and also to implement. "There may be drugs that are more effective in one cancer versus another, and yet for us to be able to say, for one indication you're going to pay more, in another indication you're going to pay less, would be challenging." **EBO**